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Graphical Arrays of Chemical-Specific Health Effect Reference Values for Inhalation Exposures

Includes Errata Sheet created on 4/6/2010

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Table or Figure	Page	Erratum
	133	Changed "values" to "value," deleted "and OSHA," and added "OSHA PEL" before "ACGIH " in the first sentence of the second paragraph. Added the following sentence at the end of the second paragraph: "It should also be noted that the original documentaion for the OSHA PEL cited it as a Ceiling Value (OSHA, 1996, 192249) but OSHA later clarified in a memo that the value was a time-weighted average (OSHA, 1996, 598129)"
Figure 2.15	133	Replaced Figure 2.15
Table 2.15	137	Replaced "OSHA-Ceiling" with "OSHA-PEL (TWA)" in the first column of Table 2.15. Replaced "10 min" with "8 hr TWA" in the second column. Added reference in last column.
	140	Added reference "OSHA (1996). Mercury vapor. Retrieved 11-JUN-09, from http://www.osha.gov/SLTC/healthguidelines/mercuryvapor/recognition.html. 192249 OSHA (1996). PEL (permissible exposure limit) for inorganic mercury is a time-weighted average, not a ceiling (Sept 3, 1996), with June 2, 2005 correction. Retrieved 06-APR-10, from http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=INTERPRETATIONS&p_id=23866. 598129

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ACRONYMS

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
BEI	Biological Exposure Indices
BMC	Benchmark Concentration
BMCL	Benchmark Concentration Limit
BMD	Benchmark Dose
BMDL	Benchmark Dose Level
CASRN	CAS Registry Number
CDC	Centers for Disease Control
ERPG	Emergency Response Planning Guideline
GPL	General Population Limit
HEAST	Health Effects Assessment Summary Tables
IARC	International Agency for Research on Cancer
IDLH	Immediately Dangerous to Life or Health
IRIS	Integrated Risk Information System
LC	Lethal Concentration
LD	Lethal Dose
LOAEL	Lowest Observed Adverse Effect Level
MRL	Minimal Risk Level
NAC	National Advisory Committee
NIOSH	National Institute for Occupational Safety and Health
NOAEL	No Observed Adverse Effect Level
NR	Not Reported
OSHA	Occupational Safety and Health Administration
PEL	Permissible Exposure Limit
POD	Point of Departure
ppm	parts per million
REL	Recommended Exposure Limit
RfC	Reference Concentration
STEL	Short Term Exposure Limit
TEEL	Temporary Emergency Exposure Limit
TLV	Threshold Limit Value
TSD	Technical Support Document
TWA	Time-weighted Average
UF	Uncertainty Factor
WHO	World Health Organization
WPL	Worker Protection Limit

SECTION 1:
INTRODUCTION

1.1. Purpose

The purpose of this document is to provide graphical arrays that compare human inhalation health effect reference values (e.g., RfCs (Reference Concentrations), AEGLs (Acute Exposure Guideline Levels) for specific chemicals across durations, populations (e.g., general public vs. healthy workers), and intended use (e.g., general public vs. emergency response vs. repeated occupational exposure vs. occupational ceiling values). A number of program offices within the Agency, as well as other Federal, State, and International agencies, have a need for these types of arrays to be readily available (See Appendix A). These arrays are intended to assist risk assessors, decision makers (risk managers), toxicologists, and may be useful in communication with the general public. Clients of this project have indicated that the graphical data arrays will be most useful in communicating the risks and relevant information to non-toxicologists. The data arrays will also be useful for clients in selecting action levels during response situations. Specifically, the data arrays could serve to support the Office of Emergency Management and Office of Water in exercises that prepare responders for emergency situations. Additionally, the Office of Air and Radiation has indicated that the data arrays will improve risk communication among risk managers and with the general public in assessments of hazardous air pollutants (HAPs) emitted from industrial sources. The 24 data arrays presented below have been refined to present the most relevant information regarding the available inhalation reference values and are in response to client need.

1.2. Overview

This document provides a brief summary of the types of available inhalation health effect reference value systems, the purpose and population for which the various types of health effect reference values were designed to be applied, and some rudimentary comparisons between reference values on a chemical-specific basis. This summary presents only information regarding the inhalation health effect reference values, providing key background information relevant to how the values were derived, and where appropriate, highlighting some considerations on the use of individual values. An earlier, more general discussion can be found in a review article by Woodall (2005, 088790) which compares reference values, especially for acute exposure durations, and the different types of reference values developed for specific purposes. This document builds upon that earlier work and expands the scope to include the health effect reference values derived for longer durations up to chronic (potentially lifetime) exposures.

Inhalation reference values are developed by various Federal, State, or professional organizations and are derived from data drawn from the epidemiologic and toxicological literature. Standard uncertainty factors are often used in the derivation of these reference values to ensure that they are protective of the population for which they were intended and to account for unknown differences between the population studied and the population to be protected. Other adjustments may also be applied to account for differences in duration of exposure or other variables or to account for known or unknown information. Additionally, more rigorous

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Note: Hyperlinks to the reference citations throughout this document will take you to the NCEA HERO database (Health and Environmental Research Online) at http://epa.gov/hero. HERO is a database of scientific literature used by U.S. EPA in the process of developing science assessments.

analytical methods (e.g., benchmark dose) have been developed and may be applied to arrive at a starting basis or point of departure (POD) differently than simply choosing a no-effect or effect level from the exposure concentrations tested in a study.

Table 1-1, below, provides a quick introduction to the health effect reference value systems available for chemical exposures in general; however, not all systems are specifically represented. The Emergency Response values are shown with light red shading, the Occupational values with light tan shading, and the General Public values are shown with light green shading. More detail on each of the available reference value systems and the values derived within them is provided in Section 1.5.

Chemical-specific inhalation reference value arrays for 24 chemicals are presented in Section 2. For each chemical, a brief description is provided with details on the chemical properties and uses, as well as a discussion of the available reference values. Graphical arrays for each chemical include inhalation reference values for Emergency Response, Occupational, and General Public values. The reference value arrays are accompanied by a table with additional information regarding the derivation of the reference values.

The first arrays comparing inhalation reference values were developed in support of a draft document developed by an interagency work group dealing with chemical decontamination and focused on chemical warfare agents. Later arrays were developed on an as-needed basis for additional chemicals, and as a result, the format changed over time to incorporate the needs of various programs. The final list of 24 chemicals included in this document took advantage of this previous work; no other priority or implied importance was placed on this list of chemicals.

Table 1.1. General descriptions of the health effect reference values.

Reference Value	Definition	Originating Organization	Level of Review
Emergency Response[2]			
AEGL Acute Exposure Guideline Level	Three severity levels (10-min up to 8-hrs) (NRC, 2001, 192042) 1 = Mild, reversible effects; 2 = Irreversible effects or impairs ability to escape; 3 = Lethal	National Advisory Committee for AEGLs (NAC/AEGL)	• Federal Advisory Committee Peer Review • Public Comment • NAS Panel Review
ERPG Emergency Response and Planning Guidelines	Three severity levels (one-hour only) (AIHA, 2002, 192051) 1 = Mild, transient effects; 2 = Irreversible effects or impairs ability to escape; 3 = Lethal	American Industrial Hygiene Association (AIHA)	Expert Panel Review
TEEL Temporary Emergency Exposure Limits	Four severity levels (one-hour only) (DOE, 2008, 192182) 0 = No adverse health effects; 1 = Mild, transient effects; 2 = Irreversible effects or impairs ability to escape; 3 = Life threatening health effects or death	Department of Energy Subcommittee on Consequence Assessment and Protective Actions (SCAPA)	Internal Process Review

[2] Emergency Response reference values are developed using an assumption of a rare, "once-in-a-lifetime" exposure scenario, which is a key consideration when comparing these refernce values to any Occupational or General Public reference values. These values are designed for coverage of the general public, including susceptible (e.g., children) but not hyper-susceptible individuals.

Reference Value	Definition	Originating Organization	Level of Review
Occupational			
IDLH Immediately Dangerous to Life and Health	A situation "that poses a threat of exposure to airborne contaminants when that exposure is likely to cause death or immediate or delayed permanent adverse health effects or prevent escape from such an environment." Exposure durations of 30 minutes or less. (NIOSH, 1994, 192183)	National Institute for Occupational Safety and Health (NIOSH)	Public Comment Period
TLV Threshold Limit Value	"Determinations made by a voluntary body of independent knowledgeable individuals that represent the opinion of the scientific community that has reviewed the data described in the Documentation. Exposure at or below the level of the TLV® or BEI® does not create an unreasonable risk of disease or injury." Exposure durations usually based on an 8-hour time weighted average (TWA) or short duration ceiling value. (ACGIH, 2007, 192024)	American Conference of Governmental Industrial Hygienists (ACGIH)	Expert Panel Review
PEL Permissible Exposure Limit	"PELs are regulatory limits on the amount or concentration of a substance in the air. They may also contain a skin designation. OSHA PELs are based on an 8-hour time weighted average (TWA) exposure." (OSHA, 2006, 192276)	Occupational Safety and Health Administration (OSHA)	Federal Register
REL Recommended Exposure Limit	"NIOSH develops and periodically revises recommended exposure limits (RELs) for hazardous substances or conditions in the workplace." Usually developed for 8- or 10-hour TWAs. (NIOSH, 2006, 192177)	NIOSH	Public Comment Period
CDC WPL Worker Population Limit	"An airborne exposure limit designed to protect workers. It is expressed as a time-weighted average (TWA) for exposure over an 8-hour work shift." (CDC, 2003, 192190; CDC, 2004, 192193)	Centers for Disease Control and Prevention (CDC)	Federal Register, Public Meeting and Public Comment Period
STEL Short-Term Exposure Limit	An excursion level above the relevant TWA exposure limit for a specified period of time, usually 15 or 30 minutes. (NIOSH, 2006, 192177)	ACGIH	Expert Panel Review
		NIOSH	Public Comment Period
		OSHA	Federal Register
		Others	
Ceiling	"Level of exposure that should not be exceeded at any time." (NIOSH, 2006, 192177)	ACGIH	Expert Panel Review
		NIOSH	Public Comment Period
		OSHA	Federal Register
		Others	

Reference Value	Definition	Originating Organization	Level of Review
General Public			
RfC Reference Concentration	"An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure estimate to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory or systemic effects)." Developed for continuous chronic exposure scenarios. (EPA, 2009, 192196)	Environmental Protection Agency (EPA)	• Agency Work Group Review • Public Comment • Interagency Consultation/ Discussion • External Peer Review
MRL Minimal Risk Level	"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. These substance specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites." Developed for acute (1-14 days), intermediate (15-365 days), and chronic (>365 days) durations. (ATSDR, 2009, 192154)	Agency for Toxic Substance and Disease Registry (ATSDR)	• Expert Panel Review • Public Comment Period
CA-REL Reference Exposure Level	"The concentration level at or below which no adverse health effects are anticipated for a specified exposure duration is termed the reference exposure level (REL). RELs are based on the most sensitive, relevant, adverse health effect reported in the medical and toxicological literature. RELs are designed to protect the most sensitive individuals in the population by the inclusion of margins of safety. Since margins of safety are incorporated to address data gaps and uncertainties, exceeding the REL does not automatically indicate an adverse health impact." Acute 1-hour and/or 8-hour values, and chronic duration values, developed based on available data. (OEHHA, 2008, 192197)	Office of Environmental Health Hazard Assessment (OEHHA), State of California	External Peer Review

Reference Value	Definition	Originating Organization	Level of Review
CDC GPL General Population Limit	"An airborne exposure limit designed to protect the general public." Developed for continuous exposures for up to several years. (CDC, 2003, 192190)	CDC	Federal Register, Public Meeting and Public Comment Period
WHO Air Quality Guideline	"The primary aim of these guidelines is to provide a basis for protecting public health from adverse effects of air pollution and for eliminating, or reducing to a minimum, those contaminants of air that are known or likely to be hazardous to human health and wellbeing." Developed for continous chronic exposure scenarios. (WHO, 2000, 180143)	World Health Organization	Internal Peer Review

1.2.1 Document Organization

This review is organized in two major sections. Section 1 is this introductory section that provides the background information on the various reference value systems, purposes and limitations of the derived health effect reference values, and additional chemical-specific information. Section 2 provides summaries on the available inhalation health effect reference values on a chemical-by-chemical basis, also providing the details of the derivation of these reference values. The key element of each summary is a graphical array that compares the available reference values for each specific chemical. Tables are also provided as a companion to each chemical-specific array and provide more details related to the derivation of the reference values and the purposes for which they are designed. A similar shading scheme as was applied in Table 1-1 is also used in these chemical specific tables.

In the graphical array of each chemical-specific reference value summary, those values that were designed for use in an occupational setting are shown with an asterisk in the legend noting that caution and expert judgment be exercised prior to applying these values to the general public. This caution is provided to clearly state that the occupational values are designed for application to a presumed healthy work force of prime working age (e.g., 18 – 65 years of age, working 40 hours/week). Although some susceptibilities (e.g., pregnancy in female workers) may be a consideration, many other potential susceptibilities are not taken into account (e.g., greater susceptibility in children) that would apply to the general population.

Similarly, caution should be exercised in applying the Emergency Response values (AEGL and ERPG values) in that they are designed with an assumption that exposures are limited to a short duration (less than 8-hours) and that such exposures would occur on an extremely rare basis (i.e., once-in-a-lifetime). The Emergency Response values may not be adequately protective for exposures that would occur for a longer duration or in situations where increases of exposures for a short duration may be more routinely experienced (e.g., weekly). These Emergency Response values are developed as frank effect levels and not as indicators of safe exposure. If exceeded, these values may indicate cause for concern.

Additional introductory material is provided below on duration and uncertainty factors to aid in describing aspects that should be considered in choosing an appropriate reference value by a user of this document.

1.3. Reference Value Derivation

In general, two types of health-based reference values may be available: reference values in units of concentration that may be used as is – this is usually the case for inhalation noncancer reference values; and reference values that are expressed in terms of dose (e.g., milligrams per kilograms of body weight per day) and concentrations in different media that will need to be derived based on assumptions of level of exposure using risk-based calculations. All reference values described in this document are reported in units of concentration, preferably as milligrams per cubic meter (mg/m^3).

Derivation of a reference value involves a number of steps, which are listed below. All of these steps are applied only after a thorough evaluation of the available toxicological data for the chemical has been conducted to determine the appropriate endpoint for the reference value.

- Determination of the Point of Departure (POD)

Dosimetry Adjustments: Calculation of the Human Equivalent Concentration (HEC)
Duration Extrapolations

- Application of Uncertainty Factors

The final reference value is the result of application of adjustments HEC (Human Equivalent Concentration) and duration extrapolations to the POD to arrive at a value (e.g., $NOAEL_{HEC}$) which is then divided by the composite (i.e., total) uncertainty factor (Total UF). All of the elements that go into this derivation have been captured in the tables for the specific chemicals in Section 2 of this document.

1.3.1 Point of Departure (POD)

The POD is an estimate of the exposure concentration at the threshold of the chosen adverse effect. The chosen effect will be appropriate to the reference value being derived. The approach to estimate a predetermined effect level is based on the best available exposure-response model and the model used would be determined largely by the availability of data. More data is necessary to apply the benchmark concentration (BMC) approach, which is described in full elsewhere (http://www.epa.gov/ncea/bmds/), than is required for use of the no observable adverse effect level (NOAEL) or lowest observable adverse effect level (LOAEL). Each approach has certain strengths and weaknesses and, depending on the data that are available, one or more could be applied. In general, preference is given to models that use more exposure-response information (e.g., BMC), but this is a decision based on the nature of the studies, amount of data available to model, the agreement between the results of the models, and the size of the confidence bounds for the applicable models. When data permit, a comparative analysis among these approaches may be undertaken and is recommended to aid in the quantitative analysis of uncertainty.

For the BMC approach, the critical decision is the designation of a specific adverse effect (or risk) level. The BMCL (benchmark concentration limit), the POD for the BMC approach, is the 95% lower confidence bound on the concentration corresponding to the BMR, and the choice varies between the various procedures. The BMCL is used like the NOAEL and implies that the effect (or risk) level in the BMC approach is close to the onset of an adverse effect.

1.3.2 Dosimetry Adjustments

The approach taken for performing dosimetry adjustments on study results from inhalation exposures in laboratory animals to derive exposure concentrations that are relevant to humans is termed the HEC. The HEC can be determined for all exposures to inhaled agents, both gases and particles, through the use of available valid models.

To accommodate species differences in inhaled dose, dosimetric adjustments are made to exposure concentrations used in experimental animal studies to yield an HEC. The intention of dosimetric adjustment is to provide an estimate of internal dose at the target tissue (or area of effect) in the test species produced by a given external concentration; the corresponding external concentration for humans that produces that same internal dose is the HEC.

The general equation for the calculation of an HEC as developed and presented in the RfC Method Document (U.S. EPA, 1994, 192307) is through application of a DAF to the exposure concentration of an animal inhalation exposure, as shown in the equation below:

$$\text{Exposure Concentration in animals } (mg/m^3) \times \text{DAF} = \text{HEC}$$

Procedures are included for the entire respiratory tract, for any of its regions, or for the whole body (referred to as systemic or extrarespiratory) in response to a reactive/water-soluble gas, an insoluble/nonreactive gas, a gas of intermediate reactivity/solubility, and particles. The procedures are intended to be applied in a hierarchy ranging from optimal to default procedures. An example of an optimized instance would be where sufficient data relating to dosimetry are available and integrated into a useful PBPK model to estimate an HEC from any given exposure of any laboratory species. To accommodate cases most often available (i.e., where dosimetric information is marginal) default procedures using various surrogate procedures and assumptions are also available in the RfC Method document.

1.3.3 Duration Extrapolation

In many cases, the data available for the derivation of a reference value comes from studies with an exposure duration other than what is desired. For example, an acute reference value for one hour is needed but all the study data comes from observations at 4 hours. In such cases, calculations are needed to estimate the concentration at the desired duration that would cause the same level of effect at the observed duration.

The magnitude of response to a toxic chemical exposure by inhalation is often dependent on both the concentration and the duration of the exposure. The internal dose of a chemical at the site in the body where toxicity occurs also determines the magnitude of the response. A more detailed discussion on these issues is provided in a review article (Woodall et al., 2009, 194213).

For the purposes of this document, three approaches to duration extrapolation are described: (1) use of standard uncertainty factors (see below) when going from subchronic durations to chronic durations; (2) use of a concentration by time relationship ($C^n \times T$) – described more fully below; and (3) use of physiologically-based pharmacokinetic (PBPK) models to estimate the internal dose at the site in the body of toxic injury.

Response has often been related to the product of concentration (C) and duration of exposure or time (T). Haber's relationship (Haber, 1924, 059334) suggests that this product is a constant (i.e., $C \times T = k$. Although widely viewed as an overgeneralization, this assumption is regularly used as a default assumption. A more general version of this model advanced by ten Berge et al. (1986, 025664) is expressed as $C^n \times T^b = k$, with n and b being empirically derived, and have been determined for a series of chemicals with values ranging from 0.8 to 3.5 . The analysis based on lethality data by ten Berge indicates that few chemicals would be expected to show a value of $n < 1$, suggesting that, at least for severe effects, a value of $n = 1$ would be a reasonable default for time frames longer than the observed data. In the absence of information to extrapolate to shorter durations, the default assumption applied in the AEGL SOPs (NRC, 2001, 192042) is to use a value of $n = 3$.

1.3.4 Uncertainty and Variability

Organizations that develop reference values use an approach that is intended not to underestimate risk in the face of uncertainty and variability. When there are gaps in the available information, uncertainty factors (UFs) are applied to derive reference values that are intended to be protective against appreciable risk of deleterious effects. UFs are commonly standard values[3] (e.g., factors of 10 or 3), used in the absence of compound-specific data. However, when data are available, uncertainty factors may also be developed using compound-specific information.

EPA, as an example, begins the development of reference values by evaluating all of the available relevant peer-reviewed literature to determine noncancer endpoints of concern, evaluating the quality, strengths and limitations of the available studies. EPA typically chooses the relevant endpoint that occurs at the lowest dose, often using statistical modeling of the available data, and then determines the appropriate point of departure (POD) for derivation of the toxicity value. A POD is determined by (in order of preference): (1) a statistical estimation using the benchmark dose (BMD) approach; (2) use of the dose or concentration at which the toxic response was not significantly elevated (no observed adverse effect level – NOAEL); or (3) use of the lowest observed adverse effect level (LOAEL).

A series of downward adjustments using uncertainty factors is then applied to the POD to estimate the reference value (U.S. EPA, 2002, 088824; U.S. EPA, 2004, 192199). While collectively termed "uncertainty factors", these factors account for a number of different quantitative considerations when utilizing observed animal (usually rodent) or human toxicity data in a risk assessment. The uncertainty factors are to account for: (1) extrapolating from experimental animal data to humans (i.e., interspecies differences); (2) variation in susceptibility among the members of the human population (i.e., inter-individual variability); (3) extrapolating from data obtained in a study with less-than-lifetime exposure (i.e., subchronic to chronic exposure); (4) extrapolating from a LOAEL in the absence of a NOAEL; and (5) when the database is incomplete or there are problems with applicability of available studies. When scientifically sound, peer-reviewed assessment-specific data are not available, default adjustment values are selected for the individual uncertainty factors. For each type of uncertainty (when relevant to the assessment), EPA typically applies an uncertainty factor value of 10 or 3 with the cumulative uncertainty factor value leading to a downward adjustment of 10-3,000 fold from the selected POD. If an extrapolation step or adjustment is not relevant to an assessment (e.g., if applying human toxicity data and an interspecies extrapolation is not required) the associated uncertainty factor is not used. The major adjustment steps are described in greater detail below.

1.4. Duration

There is considerable variation in how organizations define the length of time associated with different exposure durations. The definitions from the Environmental Protection Agency's (EPA's) Risk Assessment Forum (U.S. EPA, 2002, 088824) have been adopted for use in this document:

[3] According to the NRC report *Science and Judgment in Risk Assessment* (NRC, 1994) "(Default) options are generic approaches, based on general scientific knowledge and policy judgment, that are applied to various elements of the risk-assessment process when the correct scientific model is unknown or uncertain." The 1983 NRC report *Risk Assessment in the Federal Government: Managing the Process* defined the standard option as "the option chosen on the basis of risk assessment policy that appears to be the best choice in the absence of data to the contrary" (NRC, 1983a, p. 63).

Acute exposure/duration: Exposure by the oral, dermal, or inhalation route for 24 hours or less;
Short-term exposure/duration: Repeated exposure by the oral, dermal, or inhalation route for more than 24 hours, up to 30 days;
Subchronic exposure/duration: Repeated exposure by the oral, dermal, or inhalation route for more than 30 days, up to approximately 10 percent of the life span in humans (greater than 30 days but less than 90 days in typically used laboratory animal species); and
Chronic exposure/duration: Repeated exposure by the oral, dermal, or inhalation route for more than approximately 10 percent of the life span in humans (greater than 90 days to 2 years in typically used laboratory animal species).

1.5. Available Health Effect Reference Values

The following is a descriptive list of health-based reference values that may be useful to risk assessors and decision-makers dealing with hazardous chemicals. This list is organized by three general categories of reference values: (1) Emergency Response Values; (2) Occupational Values; and (3) General Public Values. The applicability of each of these types of reference values is also provided to help guide their appropriate use.

1.5.1 Emergency Response Reference Values

Emergency response values are designed for use in situations where there is a danger to the general public from short duration exposure to high concentrations with potential serious health effect consequences. This theme is repeated in each of the descriptions for the individual reference value systems described below. They are designed with assumptions that exposures will be extremely rare (e.g., once-in-a-lifetime). They are useful in determining a course of action in planning for or to guide immediate reaction to a catastrophic release (i.e., evacuation or shelter-in-place), but should not be misconstrued to also be levels indicating safety for any repeat exposure (e.g., to indicate it is safe to reoccupy an affected area). For example, tier 2 levels are thresholds for irreversible effects and tier 3 levels are thresholds for lethality.

1.5.1.1 Acute Exposure Guideline Levels (AEGLs) – U.S. Environmental Protection Agency

The AEGLs are developed through an EPA Federal Advisory Committee and reviewed and published by the National Research Council, as specified in the Standing Operating Procedures (SOP) document (2001, 192042). The development process includes an open peer-review and public participation.

The SOP document states that AEGLs “represent threshold exposure limits for the general public and are applicable to emergency exposures ranging from 10 min to 8 h.” The intended application of AEGL values is “for conducting various risk assessments to aid in the development of emergency preparedness and prevention plans, as well as real-time emergency response actions, for accidental chemical releases at fixed facilities and from transport carriers.” The SOP document lays out the purpose and objectives of AEGLs by stating that “the primary purpose of the AEGL program and the NAC/AEGL Committee is to develop guideline levels for once-in-a-lifetime, short-term exposures to airborne concentrations of acutely toxic, high-priority

chemicals." Three health effect levels are developed for 10- and 30-minute and 1-, 4-, and 8-hour exposures, resulting in as many as 15 different AEGL concentration values for a specific chemical. These values are intended to protect the general public and include consideration of sensitive and susceptible persons, including sensitive subpopulations, but not hyper-sensitive or hyper-susceptible persons. The three AEGL health effect levels are defined below.

AEGL-1: The airborne concentration of a substance above which it is predicted that the general population, including susceptible persons, could experience notable discomfort, irritation, or certain asymptomatic, non-sensory effects. However, the effects are non-disabling and are transient and reversible upon cessation of exposure.

AEGL-2: The airborne concentration of a substance above which it is predicted that the general population, including susceptible persons, could experience irreversible or other serious, long-lasting health effects or impaired ability to escape.

AEGL-3: The airborne concentration of a substance above which it is predicted that the general population, including susceptible persons, could experience life-threatening health effects or death.

The AEGLs are based primarily on acute toxicology data for vapor exposures, not subchronic or chronic exposure data. The AEGL values include uncertainty factors to account for variability in biological response in the human population. For carcinogens, the chemical-specific Technical Support Document (TSD) includes an evaluation of the degree of excess cancer risks anticipated for one-time exposure at the various AEGL levels (typically less than 1 in 1000). However, cancer as an endpoint is not used to set AEGL values. The guidance does not consider or evaluate the effects that could result from repeated exposures.

AEGLs are not regulatory values, and the AEGL Committee does not provide specific guidance on their implementation or use. Instead, choices made regarding how and/or which AEGL value to use for various response decisions, such as evacuating or sheltering-in-place, are typically left up to the Federal, State, Tribal or local officials responding to the incident. However, it is highly recommended that the expert scientific judgment of qualified toxicologists and/or hazard assessors be sought to help inform chemical- and site-specific decisions.

For each set of AEGLs for a chemical, an associated TSD describes the toxicological derivation of the values (http://www.epa.gov/oppt/aegl/). Because the AEGL TSD contains a comprehensive review of all identified acute toxicology data on the subject chemical and the basis for the development of the AEGL values, these documents may also have general use as toxicological references in situations involving an acute exposure scenario that goes beyond the intended purpose of the AEGLs. Planners and risk managers should seek the advice of qualified scientific expertise (toxicologists and/or risk assessors) who are familiar with the TSDs for specific chemicals in order to understand the basis for the AEGL values prior to using these values outside of their stated purpose.

Where to find AEGLs

- Specific AEGL values and final Technical Support Documents can be found at: www.epa.gov/oppt/aegl

1.5.1.2. Emergency Response Planning Guidelines (ERPGs) – American Industrial Hygiene Association

The ERPGs are developed by the American Industrial Hygiene Association (AIHA) and are intended for emergency planning and response operations (similar to AEGLs), but ERPGs are only based on a 1-hour exposure duration (AIHA, 2002, 192051). ERPGs are intended to protect the general population, but not particularly sensitive persons. They are reviewed at regular intervals as new information becomes available. Definitions of the three levels of ERPG values are as follows.

ERPG-1: The maximum airborne concentration below which it is believed nearly all persons could be exposed for up to 1 hour without experiencing more than mild, transient adverse health effects or without perceiving a clearly defined objectionable odor.

ERPG-2: The maximum airborne concentration below which it is believed nearly all persons could be exposed for up to 1 hour without experiencing or developing irreversible or other serious health effects or symptoms that could impair a person's ability to take protective action.

ERPG-3: The maximum airborne concentration below which it is believed nearly all persons could be exposed for up to 1 hour without experiencing or developing life-threatening health effects.

Where to find ERPGs

- ERPGs for various chemicals can be found at: http://www.aiha.org/1documents/Committees/ERP-erpglevels.pdf
- Documentation for the individual ERPGs is available for purchase from AIHA.

1.5.1.3. Temporary Emergency Exposure Limits (TEELs) – U.S. Department of Energy

The U.S. Department of Energy (DOE) has published TEELs for about 1,200 chemicals (DOE, 2008, 192182). TEELs adopt AEGLs and then ERPGs as their primary hierarchy for publication of values, but they also present values obtained by other methods for use when AEGLs or ERPGs are not available. Although the TEEL methodology has been peer-reviewed and peer-reviewed studies are used in developing TEELs, the values derived by these other methods are not currently peer-reviewed. In the absence of AEGL and ERPG values, TEELs are based on the correlation between acute data (e.g., lethal concentration, LD_{50}, LC_{LO}, etc.) and existing values (e.g., IDLH, STEL, TLVs and various levels of existing ERPGs). DOE thus provides a methodology for combining hierarchy- and toxicity-based TEELs into procedure-derived TEELs to facilitate its use by anyone requiring concentration limits for chemicals. TEEL values, like the ERPGs, are based on a 1-hour exposure duration. The various TEEL definitions are as follows.

TEEL-0: The threshold concentration below which most persons will experience no appreciable risk of health effects.

TEEL-1: The maximum concentration in air below which it is believed nearly all persons could be exposed without experiencing other than mild transient adverse health effects or perceiving a clearly defined objectionable odor.

TEEL-2: The maximum concentration in air below which it is believed nearly all persons could be exposed without experiencing or developing irreversible or other serious health effects or symptoms that could impair their abilities to take protective action.
TEEL-3: The maximum concentration in air below which it is believed nearly all persons could be exposed without experiencing or developing life-threatening health effects.

Where to find TEEL Values

- TEEL values for various substances can be found at: http://www.hss.energy.gov/healthsafety/wshp/chem_safety/teel.html

1.5.2 Occupational Reference Values

Occupational reference values are designed to protect the worker population from exposures over the course of a normal work-day and work-week for a typical career (e.g., 8 hours per day, 5 days per week, for several years). Protection for this type of exposure scenario is typically accomplished using a time-weighted average (TWA) approach. In addition to the TWA for normal average exposures over an extended period of time, short-term exposure limits (STELs) and/or ceiling values are also developed to protect workers from shorter-duration excursions to the average that may be a concern for worker safety but would be lost in a multi-hour average value. Occupational values are also often derived with an assumption that the population is a healthy cohort of working age (e.g., 18-65 years old) and is less likely to include susceptible subpopulations. In addition to consideration of health effects, occupational guidelines and standards often also consider the technical feasibility of reliably monitoring and reporting for a specific concentration, and some trade-offs (work practices, length of time at a task, etc.) may be used to compensate for these monitoring and reporting considerations.

1.5.2.1. Occupational Exposure Limits – Various Sources and Organizations

Several considerations apply to the selection of appropriate occupational exposure limits; they include both a maximum concentration of a chemical in air and a well-defined exposure duration. The range of available limits include: (1) 8- to 10-hour time-weighed average (TWA) limits; (2) ceiling values, which are concentrations that should not be exceeded at anytime during an 8-hour workday; and (3) short-term exposure limits (STELs), which are generally 15-min exposure limits that should not be exceeded during the course of a workday. The ceiling and STEL values are assigned to substances that exert toxic effects over a short period of time.

Chemicals may have one or more of these values. For example, the U.S. Department of Labor, Occupational Safety and Health Administration (OSHA) has assigned carbon disulfide both a ceiling value and a TWA. In this case, neither the ceiling value nor the TWA should be exceeded. A worker may experience multiple peak exposures during the work shift; however, none of these peaks may exceed the ceiling value. In addition, the average of these peaks and other total exposures over the entire work shift may not exceed the TWA value.

The STEL, ceiling, and TWA values are concentrations to which workers may be safely exposed daily, throughout their entire working life (up to 40 years). They are designed to protect healthy adults. It is, however, important to note that not all workers will be protected from adverse health effects even though their exposures are maintained below these levels. Some may experience adverse health effects because of personal susceptibility, a preexisting medical

condition, and/or hypersensitivity (allergy). The occupational reference values are not intended for application to community exposure or the general public.

The primary sources of occupational exposure values for the workplace are (1) NIOSH Recommended Exposure Limits (RELs) (NIOSH, 2006, 192177), (2) the American Conference of Governmental Industrial Hygienists' (ACGIH) Threshold Limit Values (TLVs) and Biologic Exposure Indices (BEIs) (2007, 192024), and (3) OSHA's Permissible Exposure Limits (PELs), which include TWA, ceiling and STEL values (OSHA, 2006, 192276; OSHA, 2006, 192291). The OSHA PELs are legally enforceable exposure limits, whereas the NIOSH RELs and the ACGIH TLVs and BEIs are recommended guidelines.

Additionally, the Centers for Disease Control and Prevention (CDC) has recommended exposure limits for workers to protect against potential exposure to the chemical warfare agents GA (tabun), GB (sarin), VX, L (lewisite), and HD (sulfur mustard) (CDC, 2003, 192190; CDC, 2004, 192193). These Worker Protection Limits (WPLs) are intended for use among workers involved in chemical weapons disposal. Similar to other occupational reference values, these worker population limits for chemical warfare agents are described in terms of 8-hour TWAs and STEL values and are applicable to long-term, routine work in dismantling chemical weapons. The CDC also developed General Population Limits (GPLs) which are described below.

Where to Find Occupational Exposure Limits

- NIOSH RELs can be found at: www.cdc.gov/niosh/npg/npg.html
- The ACGIH TLVs are published annually in the *Threshold Limit Values for Chemical Substances and Physical Agents & Biological Exposure Indices*. Additional information on the ACGIH TLVs can be found at www.acgih.org/home.htm
- OSHA PELs are listed at www.osha.gov/SLTC/pel/index.html
- Information on the CDC airborne exposure limits for chemical warfare agents can be found at: http://www.cdc.gov/nceh/demil/reports/reports.htm.

1.5.2.2. Immediately Dangerous to Life or Health (IDLH) Concentrations – National Institute for Occupational Safety and Health

IDLH concentrations are published by NIOSH (NIOSH, 1996, 192195), which defines an IDLH condition as a situation "that poses a threat of exposure to airborne contaminants when that exposure is likely to cause death or immediate or delayed permanent adverse health effects or prevent escape from such an environment." Furthermore, the stated purpose of establishing an IDLH concentration is to "ensure that the worker can escape from a given contaminated environment in the event of failure of the respiratory protection equipment." IDLH concentrations were based on the effects that might occur as a consequence of a 30-min exposure. However, the 30-min period was not meant to imply that workers should stay in the work environment any longer than necessary following the failure of respiratory protection equipment.

Where to find IDLH Values

- The methodology for deriving IDLH concentrations and the actual values for nearly 400 substances can be found at: www.cdc.gov/niosh/idlh/idlh-1.html

The NIOSH respirator selection logic uses an IDLH as one of several respirator selection criteria. Under the NIOSH respirator decision logic, *highly reliable* respirators (i.e., the most protective respirators) would be selected for emergency situations, fire fighting, exposure to carcinogens, entry into oxygen-deficient atmospheres, entry into atmospheres that contain a substance at a concentration greater than 2,000 times the NIOSH REL or OSHA PEL, and for entry into IDLH conditions. These highly reliable respirators include either a self-contained breathing apparatus (SCBA) that has a full face piece and is operated in a pressure-demand or other positive-pressure mode, or a supplied-air respirator that has a full face piece in combination with an auxiliary SCBA, both operated in a pressure-demand or other positive-pressure mode.

1.5.3 General Public Reference Values

The general public reference values are set to protect almost all susceptible subpopulations and tend to over-estimate rather than under-estimate potential risks from exposures. Although the Emergency Response values are also applicable to the general public, they are derived for more specific purposes, with attendant assumptions of frank effects and rare "once-in-a-lifetime" exposure scenarios. The acute values derived for the general population tend to incorporate the potential for a repeat exposure for a similar duration (e.g., one-hour) as an uncertainty rather than the assumption of a rare event occurring, as was discussed for the emergency response values, and including more protection for susceptible subpopulations than are typical for the occupational values. The general public values are therefore likely to be the best guidance values for determining safe levels of exposure for reoccupancy of a site following clean-up or remediation.

1.5.3.1. Integrated Risk Information System (IRIS) – U.S. Environmental Protection Agency

The Integrated Risk Information System (IRIS), prepared and maintained by EPA, is an electronic database containing information on human health effects that may result from exposure to various chemicals in the environment (EPA, 2009, 192196). IRIS contains descriptive and quantitative information and includes oral reference doses (RfDs) and inhalation reference concentrations (RfCs) for chronic noncarcinogenic health effects and oral slope factors (CSFs) and inhalation unit risks (IURs) for carcinogenic effects. RfDs are usually provided in units of mg/kg-day and RfCs in units of mg/m^3. CSFs are usually provided in units of $(mg/kg\text{-}day)^{-1}$ and IURs are provided in $(ug/m^3)^{-1}$. RfDs, CSFs and IURs (dose-based reference values) are not directly comparable to environmental concentrations. However, mathematical models

using appropriate exposure parameters can be applied to convert these dose-based reference values into concentration-based reference values.

EPA IRIS values represent the Agency's consensus for chronic toxicity values. Many other Federal and State agencies also make IRIS their preferred source of these dose-based reference values. IRIS assessments are externally peer-reviewed before they are released as final assessments.

Reference Doses (RfDs) and Inhalation Reference Concentrations (RfCs): RfDs and RfCs are generally defined as an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. RfDs and RfCs can be derived from a NOAEL, a LOAEL, or a BMD, with standard or data-derived uncertainty factors generally applied to reflect limitations of the data used.

Oral/Cancer Slope Factors (CSF): The Cancer Slope Factor (CSF) is defined as a plausible upper bound on the increased cancer risk from a lifetime exposure to an agent. This estimate is usually expressed as a dose in units of proportion (of a population) affected per mg/kg-day.

Inhalation Unit Risk Values (IUR): IURs are defined as the upper-bound excess lifetime cancer risk estimated to result from repeated exposure to an agent at a concentration of 1 µg/m^3 in air. The interpretation of inhalation unit risk would be as follows: if unit risk = 2 x 10^{-6} per µg/m^3, 2 excess cancer cases (upper bound estimate) are expected to develop per 1,000,000 people if exposed daily for a lifetime to 1 µg of the chemical in 1 cubic meter of air.

Where to find IRIS Values

- IRIS values and background information can be accessed at: http://cfpub.epa.gov/ncea/iris/index.cfm.

1.5.3.2. Acute, Intermediate and Chronic Minimum Risk Levels (MRLs) – Agency for Toxic Substances and Disease Registry

The Agency for Toxic Substances and Disease Registry (ATSDR) has developed MRLs in response to mandates under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), as amended by the Superfund Amendments and Reauthorization Act (ATSDR, 2009, 192154).

An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncarcinogenic health effects over a specified duration of exposure. These values are not regulatory numbers, but are used by ATSDR health assessors and others to identify contaminants and potential health effects that may be of concern at hazardous waste sites.

MRLs are set below levels that, based on current information, have the potential to cause adverse health effects in the persons most sensitive to such substance-induced effects. Most MRLs contain some degree of uncertainty because of the lack of precise toxicological information on persons who might be most sensitive (e.g., infants, elderly, and the nutritionally or immunologically compromised) to the effects of hazardous substances. In deriving MRLs, ATSDR employs uncertainty factors and modifying factors to account for uncertainty in

derivation of human health toxicity values. ATSDR states that exposure to a level above the MRL does not necessarily mean that adverse health effects will occur.

Where to Find MRLs:

- Background information and documentation for ATSDR MRLs are publicly available in the toxicological profile information sheet at: http://www.atsdr.cdc.gov/toxpro2.html
- MRL values for various chemicals can be found at: http://www.atsdr.cdc.gov/mrls/index.html

MRLs are derived for exposure durations of 1 to 14 days via the oral and inhalation routes of exposure. While ATSDR refers to this duration as acute, it corresponds to the EPA/IRIS short-term exposure scenario described previously. In addition, ATSDR derives oral and inhalation MRLs for longer-term exposure durations: intermediate (>14 to 364 days) and chronic (365 days and longer). MRLs receive extensive internal and external peer-review.

1.5.3.3. California Reference Exposure Levels (CA-RELs) – State of California Environmental Protection Agency, Office of Environmental Health Hazard Assessment

The California EPA (CalEPA) Office of Environmental Health Hazard Assessment (OEHHA) has published reviews of the acute health effects for 51 chemical contaminants and 80 chronic Reference Exposure Levels (CA-RELs)[4] for individual chemicals based on the most sensitive adverse health effect (OEHHA, 2008, 192197). The CA-RELs have a heavy emphasis on the utilization of available human data, with two-thirds of the acute CA-RELs based on observed human health outcomes. The final values incorporate uncertainty factors similar to those used in deriving RfCs for chronic exposures. OEHHA derives acute (1-hour) and chronic inhalation CA-RELs for hazardous airborne substances and has recently begun developing 8-hour values.

The acute CA-RELs represent an exposure that is not likely to cause adverse effects in a human population, including sensitive subgroups, exposed to that concentration for 1 hour on an intermittent basis (OEHHA, 1999, 192198; OEHHA, 2008, 192197). Chronic CA-RELs are concentrations or doses at or below which adverse health effects are not likely to occur. A central assumption is that a population threshold exists below which adverse effects will not occur in a population; however, such a threshold is not observable and can only be estimated. Areas of uncertainty in estimating effects among a diverse human population exposed continuously over a lifetime are addressed using extrapolation and uncertainty factors.

OEHHA's Toxicity Criteria Database provides peer-reviewed toxicity reference values that address both cancer and non-cancer effects.

Where to find CA-RELs:

[4] The CA-RELs are distinct from the NIOSH occupational RELs (Recommended Exposure Limits).

- Acute CalEPA REL values can be found at: http://www.oehha.ca.gov/air/acute_rels/acuterel.html#download
- Chronic CalEPA REL values can be found at: http://www.oehha.ca.gov/air/chronic_rels/index.html
- A complete list of CalEPA toxicity values, including RELs, is available on the CalEPA website at: http://www.oehha.ca.gov/risk/chemicalDB//index.asp

1.5.3.4. General Population Limits (GPLs) for Chemical Warfare Agents (CWAs) – Centers for Disease Control and Prevention

CDC recommends GPLs, which are long-term (lifetime) exposure limits for several chemical warfare agents in air, applicable to populations surrounding chemical weapons disposal sites. GPLs have been developed for GA (tabun), GB (sarin), VX, HD (sulfur mustard), and L (lewisite). These values were developed specifically for CWA facilities where large amounts of agent are handled, processed and stored continuously in bulk. These values are closely related to the Worker Population Limits (WPLs) described in the section on occupational values.

For More Information on GPLs:

- http://www.cdc.gov/nceh/demil/files/Federal%20Register%20Reprint%20-%20October%209.pdf
- http://www.cdc.gov/nceh/demil/files/Federal%20Register%20Mustard%20AEL%205_2004.pdf

1.5.3.5. World Health Organization (WHO) Air Quality Guidelines for Europe

The WHO Air Quality Guidelines for Europe were developed by the Regional Office for Europe of the WHO (WHO, 2000, 180143). The primary aim of the WHO Air Quality guidelines is to provide "*a uniform basis for the protection of public health and of ecosystems from adverse effects of air pollution, and to eliminate or reduce to a minimum exposure to those pollutants that are known or are likely to be hazardous. The guidelines are based on the scientific knowledge available at the time of their development. They have the character of recommendations, and it is not intended or recommended that they simply be adopted as standards.*" There are guidelines developed for 16 organic compounds, 12 inorganic pollutants, and 4 pollutants considered "criteria pollutants" by the U.S. EPA (particulate matter, ozone and other photochemical oxidants, nitrogen dioxide and sulfur dioxide).

1.5.3.6. Other Peer-Reviewed Values or Concentration Levels

A number of other peer-reviewed published values are in existence but have not been incorporated here. For example, the National Research Council (NRC)/National Academies (NAS) has reviewed and published RfDs for oral exposures to six chemical warfare agents (GA, GB, GD, VX, sulfur mustard, lewisite) and a CSF for sulfur mustard. This report is available at: http://www.nap.edu/books/0309065984/html/1.html. Other special use reference value systems have also been developed, such as the Spacecraft Maximum Allowable Concentration (NRC, 2008, 194182) and others, but those are not included here.

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SECTION 2:
CHEMICAL-SPECIFIC REFERENCE VALUE ARRAYS

This section summarizes the available health effects reference values for inhalation exposures for 24 chemical compounds. For each chemical, a brief description is provided with details on the chemical properties and uses, as well as a discussion of the available reference values. Graphical arrays for each chemical include inhalation reference values for Emergency Response, Occupational, and General Public values. The reference value arrays are accompanied by a table with additional information regarding the derivation of the reference values.

Reference Value Arrays – The arrays were developed to show all available values across the different categories of reference values (Emergency Response, Occupational, and General Public), across all durations (acute – less than 24 hours, short-term – 1 to 30 days, subchronic – over 30 days up to several years, and chronic – up to a lifetime), and severity of effect (lethality down to no presumed adverse effect). The x-axis on the arrays represents hours of duration on a logarithmic scale to allow readable inclusion of all durations on a single array. The y-axis also shows a logarithmic scale for exposure concentration in units of milligrams per cubic meter (mg/m^3).

Standard shapes to denote related types of values and colors to denote severity of effect were used as noted below.

Shapes:

- Diamonds and Triangles for Emergency Response values[5]
- Circles for Occupational values
- Squares for General Public values

Colors

- Red for defining lethality threshold values
- Gold for Irreversible/Serious effects
- Blue for Reversible/Mild effects
- Green for values deemed without any adverse effects

Some variation in the use of colors was applied to differentiate between the occupational values, which were all for similar severity levels[6].

Derivation Details for Reference Values – Detailed information was compiled into tables to provide the key information necessary for understanding the derivation and potential application of the reference values shown in the graphical arrays. These tables are critical accompaniments to the graphical arrays. Information included in the tables include final derived health effect reference values, the critical health effect(s) for which the values were derived, the critical study and details on the study (species, duration of exposure, etc.), the point of departure (POD) used,

[5] Two shapes were used for the Emergency Response values due to the fact that all three varieties of values include three severity levels, which are best represented by shading differences, whereas shapes more clearly depict a different source for values.

[6] Color/shading instead of shape differences were chosen for the Occupational values because all values typically were for the same severity level, yet there were often multiple values available for the same chemical from a variety of sources.

any adjustments to the observations in the study in deriving the POD, uncertainty factors used, and finally any other important considerations not otherwise captured on derivation of the reference value.

The 24 chemicals presented in this section, shown in the table below, were chosen based on an inventory of existing arrays and those chemicals classified as a priority by clients identified as primary users of the final document. Table 2.1 is a summary of the inhalation reference values available for each chemical. An “X” indicates an available inhalation reference value for a chemical, whereas a lack of an “X” indicates that no inhalation reference value is available for that chemical.

Table 2-1. Summary of Available Inhalation Reference Values for 24 Chemicals

	Emergency Response			Occupational							General Public				
	AEGL	ERPG	TEEL	IDLH	TLV	PEL	REL	CDC WPL	STEL	Ceiling	RfC	MRL	CA-REL	CDC GPL	WHO Air Quality Guideline
Acrolein	X	X		X		X	X		X	X	X	X	X		
Ammonia	X	X		X	X	X	X		X		X	X	X		
Arsine (SA)*	X	X		X	X	X				X	X		X		
Chlorine*	X	X		X	X				X	X	X	X	X		
Chromium VI			X	X	X	X	X				X	X	X		
Cyanogen Chloride*		X								X					
Etyhlene Glycol Methyl Ether			X	X	X	X	X				X		X		
Ethylene Oxide	X	X		X	X	X	X			X		X	X		
Formaldehyde	X	X		X		X	X		X	X		X	X		X
Soman (GD) + Cyclosarin (GF)*	X			X					X						
Hydrogen Cyanaide (AC)*	X	X		X		X			X	X	X		X		
Hydrogen Fluoride	X	X		X	X	X	X		X			X	X		
Hydrogen Sulfide	X	X		X	X				X	X					
Lewisite (L)*	X							X						X	
Mercury	X	X		X	X		X			X	X	X	X		
Methylene Chloride	X	X		X	X	X			X			X	X		X
Percholoroetyhlene	X	X		X	X	X	X		X	X		X	X		
Phosgene (CG)*	X	X		X	X	X	X			X	X		X		
Phosphine*	X	X		X	X	X	X		X		X		X		
Sarin (GB)*	X			X				X	X					X	
Styrene	X	X		X	X	X	X		X	X	X	X	X		X
Sulfur Mustard (HD)*	X			X				X	X			X		X	
Tabun (GA)*	X			X				X	X					X	
VX*	X			X				X	X					X	

* indicates a chemical warfare agent

2.1 Chemical-Specific Reference Values for Acrolein (CASRN 107-02-8)

Acrolein is a colorless or yellowish liquid at ambient temperature and pressure and has an acrid, pungent odor and is highly irritating to mucous membranes, especially the upper respiratory tract and eyes. The odor threshold is <0.1 ppm (Beauchamp RO et al., 1985, 007387). It is used as an intermediate in the production of acrylic acid; it is also used as an herbicide, algicide, and slimicide; in the cross-linking of protein collagen in leather tanning; as a fixative of histological samples; in the production of perfumes; and in military poison gas mixtures. The largest sources of human exposure to acrolein are from incomplete combustion of organic materials (such as in urban fires and forest fires), tobacco smoke, and the burning of fat-containing foods (Beauchamp RO et al., 1985, 007387). Additional information on the nature of acrolein and detailed summaries of health effects can be found in the AEGL Technical Support Document (NAC/AEGL, 2006, 192187), the ATSDR Toxicological Profile (ATSDR, 2007, 192118), the IRIS Toxicological Review (U.S. EPA, 2003, 192239), the OHHEA REL documentation (OEHHA, 2008, 192315), and other sources and is not repeated here.

As can be inferred from Figure 2.1, the occupational values for ceiling exposures and for the time-weighted averages (TWAs) are generally very similar to the emergency response values. As shown for the AEGL values and described in the Technical Support Document (2006, 192187), a clear concentration by time ($C^n \times t = k$) relationship[7] exists for lethality (AEGL-3), where n = 1.2, derived from lethality data in rats exposed to acrolein from 1 to 4 hours; however, concentration alone is the determinant for irritation (AEGL-1) and the AEGL-2 was developed using a mixed approach to avoid values for 4 and 8 hours that were similar or lower than the AEGL-1 values. Two data sets were used in deriving the AEGL-3 with one point used for 10-min, 30-min and 1-hr AEGL-3 derivation from 1 hour and a separate 4-hour data point used for 4-hr and 8-hr AEGL-3 derivation.

The relatively more health protective nature of the California REL (CA-REL), ATSDR MRL and, EPA RfC values is also readily apparent for all durations. The chronic reference values used studies with similar points of departure (Dorman et al., 2008, 180108; Feron et al., 1978, 007381) and differences in final values related to dose extrapolation, derivation methods and application of uncertainty factors (see Table 2.1). The intermediate duration ATSDR MRL and the chronic duration EPA RfC both used adjustments for duration of exposure and differences in ventilation rates between humans and rats to derive a human equivalent concentration (HEC) of the lowest observable adverse effect level (LOAEL).

The NIOSH values are derived by a weight of evidence approach and no particular study was identified as the basis for the values. Following 60 seconds of exposure to 5.5 ppm, intense irritation and marked lacrimation was noted (Henderson and Haggard, 1943, 010318). Additionally, the background document cited slight eye irritation after 1 minute and profuse lacrimation after 4 minutes following exposures to 1.8 ppm (NRC, 1981, 192157). In studies with human volunteers, those exposed for 5 minutes to concentrations of 2 to 2.3 ppm produced severe eye irritation (Darley et al., 1960, 015690), and a 10-minute exposure at 8 ppm and a 5-minute exposure at 1.2 ppm elicited extreme eye irritation described as "only just tolerable" (Sim and Pattle, 1957, 071236).

[7] Where C = concentration, t = time, n is an empirically derived value from observed data, and k = a constant This relationship was originally developed by Haber (Haber, 1924) and later revised by ten Berge (ten Berge et al., 1986).

Overall, there is a full set of reference values for acrolein available. The database for this chemical is quite well defined. The most critical issues are related to the nature of the C x t relationship and how it changes along the severity gradient and in moving from very short (acute) to longer durations.

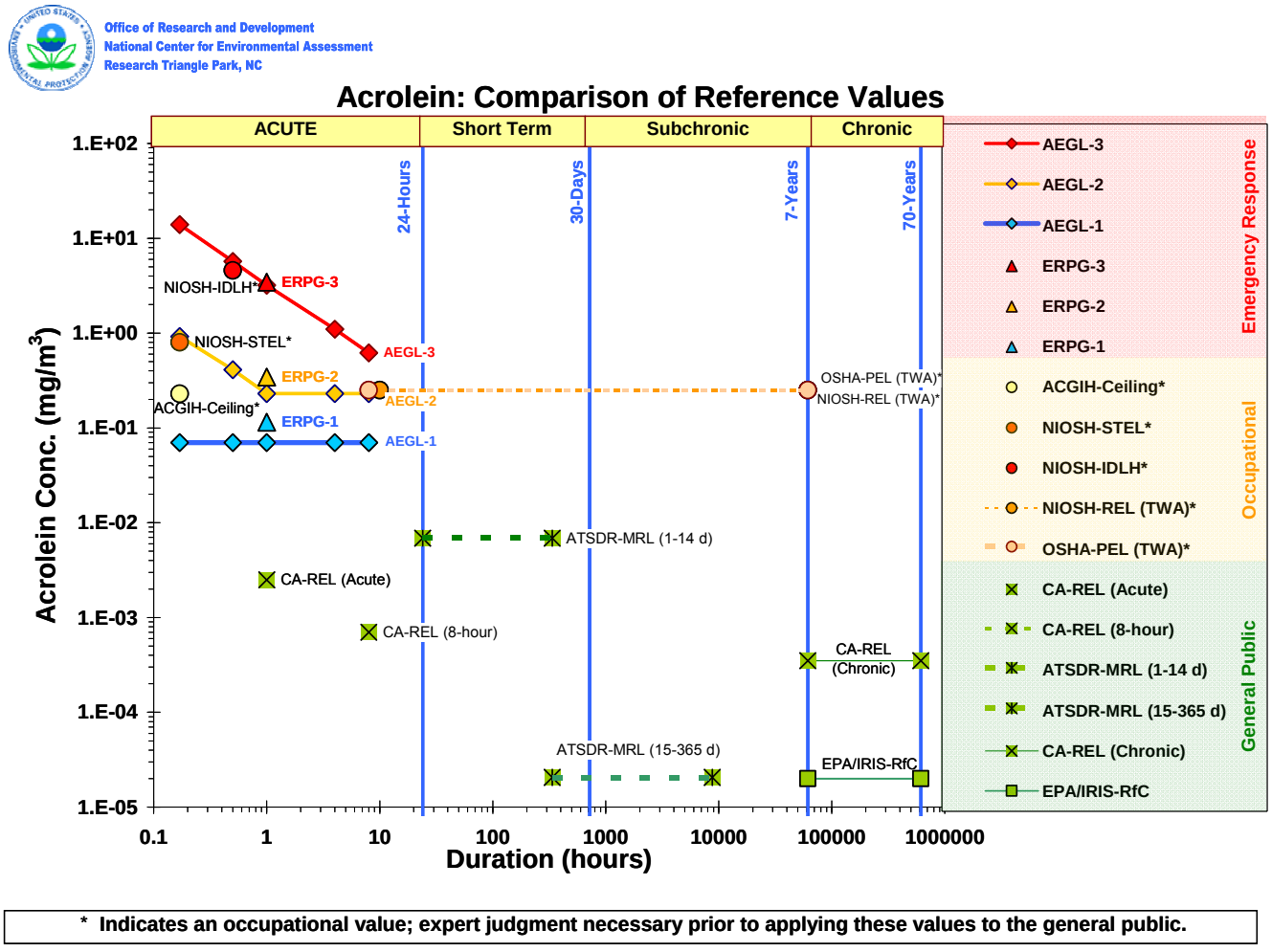

Figure 2.1. Comparison of Available Health Effect Reference Values for Inhalation Exposure to Acrolein

Table 2.1. Details on derivation of the specific inhalation health effect reference values for acrolein.

Reference Value Type / Name		Duration	Reference Value (mg/m^3)	Reference Value (ppm)	Health Effect	Point of Departure		Uncertainty Factors	Notes on Derivation	Review Status
Emergency Response[1]	**AEGL-3**	10 min	14	6.2	Concentration causing no death in rats for a 1-hour exposure (10-min, 30-min, 1-hr) (Ballantyne et al., 1989, 007753)	14 ppm (1 hour)	LC_{01}	Total UF = 9 UF_A = 3 UF_H = 3	Duration adjusted via $C^n \times t = k$ where n = 1.2	Proposed (NAC/AEGL, 2006, 192187)
		30 min	5.7	2.5						
		1 hr	3.2	1.4						
		4 hr	1.1	0.48	Concentration causing no death in rats for a 4-hour exposure (4-hr, 8-hr) (Ballantyne et al., 1989, 007753)	4.8 ppm (4 hour)	LC_{01}			
		8 hr	0.62	0.27						
	AEGL-2	10 min	0.92	0.44	10-25% decrease in respiratory rate and sensory irritation in healthy humans (Weber-Tschopp et al., 1977, 007797)	0.3 ppm	NOAEL	Total UF = 3 UF_H = 3	Duration adjusted as AEGL-3 to 1 hour, then flat-lined	
		30 min	0.41	0.18						
		1 hr	0.23	0.10						
		4 hr	0.23	0.10						
		8 hr	0.23	0.10						
	AEGL-1	10 min	0.07	0.03	Eye irritation and "annoyance"/ discomfort in healthy humans (Weber-Tschopp et al., 1977, 007797)	0.09 ppm	Threshold for effects		No duration adjustment	
		30 min	0.07	0.03						
		1 hr	0.07	0.03						
		4 hr	0.07	0.03						
		8 hr	0.07	0.03						
	ERPG-3	1 hr	3.4	1.5	Irritation (Albin, 1962, 007452; Carpenter et al., 1949, 094685; Kruysse, 1971, 192236; Pattle et al., 1956, 072271)	8-25 ppm (4-6 hr)	LC_{50}	NR		Final (AIHA, 2002, 192060)
	ERPG-2	1 hr	0.34	0.15	Eye and respiratory irritation (Albin, 1962, 007452; NRC, 1981, 192157)	0.5 ppm	NR	NR		

[1] Emergency Response reference values are developed using an assumption of a rare, "once-in-a-lifetime" exposure scenario, which is a key consideration when comparing these refernce values to any Occupational or General Public reference values.

Reference Value Type / Name		Duration	Reference Value (mg/m^3)	Reference Value (ppm)	Health Effect	Point of Departure		Uncertainty Factors	Notes on Derivation	Review Status
	ERPG-1	1 hr	0.12	0.05	Mild, transient eye and respiratory irritation (American Industrial Hygiene, 1968, 192027; NRC, 1981, 192157)	0.1 ppm	NR	NR		
Occupational	**Ceiling-ACGIH***	Any	0.23	0.1	Mucous membrane irritation, pulmonary edema (Beauchamp RO et al., 1985, 007387; Henderson and Haggard, 1943, 010318; Lyon et al., 1970, 007468; Prentiss, 1937, 015303; Schaper, 1993, 180252)	0.22 ppm (animal)	LOAEL	NR		Final (ACGIH, 2007, 192024)
						0.25 ppm (human)	LOAEL			
						6 ppm (mouse)	RD_{50}			
	NIOSH-STEL*	15 min	0.8	0.3	Intense irritation and marked lacrimation (Henderson and Haggard, 1943, 010318; Sim and Pattle, 1957, 071236) (Darley et al., 1960, 015690; NRC, 1981, 192157)	NR	NR	NR		Final (NIOSH, 1996, 192195)
	NIOSH-IDLH*	30 min	4.6	2		2 ppm	Effect Level	NR		
	NIOSH-REL (TWA)*	10 hr (TWA)	0.25	0.1	NR	NR	NR	NR		Final (NIOSH, 2006, 192177)
	OSHA-PEL*	8 hr (TWA)	0.25	0.1		NR	NR	NR		

Reference Value Type / Name		Duration	Reference Value (mg/m^3)	Reference Value (ppm)	Health Effect	Point of Departure		Uncertainty Factors	Notes on Derivation	Review Status
General Public	**CA-REL (Acute)**	1 hr	0.25	0.1	Subjective ocular irritation in humans (Darley et al., 1960, 015690)	0.06 ppm	LOAEL	Total UF = 60 UF_L = 6 UF_H = 10		Final (OEHHA, 2008, 192315)
	CA-REL (8-hr)	8 hr	0.0007	0.0003	Lesions in respiratory epithelium (Dorman et al., 2008, 180108)	0.2 ppm 0.6 ppm	NOAEL LOAEL	Total UF = 200 $UF_s = 10^{1/2}$ UF_A: TK = 2, TD = $10^{1/2}$ UF_H = 10		
	ATSDR-MRL (1-14 d)	1 - 14 d	0.007	0.003	Decrease in respiratory rate, nose and throat irritation (Weber-Tschopp et al., 1977, 007797)	0.3 ppm	LOAEL	Total UF = 100 UF_L = 10 UF_H = 10		Final (ATSDR, 2007, 192118)
	ATSDR-MRL (15 – 365 d)	15 d – 1 yr	0.00009	0.00004	Nasal epithelial metaplasia in rats (Feron et al., 1978, 007381)	0.012 ppm	$LOAEL_{HEC}$	Total UF = 300 UF_L = 10 UF_A = 3 UF_H = 10		
	CA-REL (Chronic)	Chronic	3.5×10^{-4}	1.5×10^{-5}	Lesions in respiratory epithelium (Dorman et al., 2008, 180108)	0.2 ppm 0.6 ppm	NOAEL LOAEL	Total UF = 60 UF_L = 6 UF_H = 10		Final (OEHHA, 2008, 192315)
	RfC (IRIS)	Chronic	2×10^{-5}	8.7×10^{-6}	Slight nasal effects (Feron et al., 1978, 007381)	0.02 mg/m^3	$LOAEL_{HEC}$	Total UF = 1000 UF_A = 3 UF_H = 10 UF_S = 10 UF_L = 3		Final (U.S. EPA, 2003, 192239)

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2.2 Chemical-Specific Reference Values for Ammonia (CASRN 7664–41-7)

Ammonia is a colorless, corrosive, alkaline gas with a sharp, intensely irritating odor. Its odor threshold is around 5 ppm. It is lighter than air and easily liquefied by pressure. Ammonia is used as a compressed gas and in aqueous solutions. It is used in household cleaning products, in fertilizers, and as a refrigerant. Ammonia is very water soluble, forming ammonium hydroxide and heat when it contacts moist surfaces, often resulting in immediate damage (severe irritation and burns) to the eyes, skin and mucous membranes of the oral cavity and respiratory tract. More details on the chemical nature and toxicity from exposure to ammonia are available from other sources (AIHA, 2002, 192093; NAC/AEGL, 2002, 192201; U.S. EPA, 1991, 192219)) and are not repeated here.

Inhalation health effect reference values for ammonia are displayed graphically in Figure 2.2. Details available on the derivation of these values, including key effects, studies, adjustments, and uncertainty factors (UFs) are shown in Table 2.2.

The Emergency Response (AEGL and ERPG) values for ammonia are in close agreement with one another for all severity levels, and also closely follow the occupational guidelines. The most obvious exception is that the NIOSH IDLH value is somewhat lower than the AEGL-3 value for 30 minutes; these values are often in close agreement. More details are provided in the derivation of the AEGL values than for the ERPGs, as shown in Table 2.2. Time scaling was performed in the derivation of the AEGL-3 values, using the $C^n \times t$ relationship described by ten Berge (1986, 025664), where n = 2. Duration extrapolations were also performed in deriving AEGL-2 values for 30 minutes, one hour and four hours from two hour observations (Verberk, 1977, 008111); however, the 30 minute value was adopted as the 10 minute value because to do otherwise may have lead to values that would impair the ability to escape, and the 4 hour value was adopted as the 8 hour value because the severity for irritation rating changed very little from 30 minutes to 2 hours and is not expected to change for exposures up to 8 hours. AEGL-1 values were held constant across durations, as specified in the Standing Operating Procedures for the AEGLs (NRC, 2001, 192042) when considering mild irritation effects.

The NIOSH Occupational values are derived by a weight of evidence approach and no particular study was identified as the basis for the values. The maximum short exposure tolerance is reported as 300 to 500 ppm for 30 minutes to 1 hour (Henderson and Haggard, 1943, 010318). Subjects exposed to 500 ppm for 30 minutes experienced moderate to severe irritation and a change in respiration rate (Silverman et al., 1946, 063013). Fewer details were provided for all of the other occupational values, hence the majority of the derivation fields in Table 2.2 show not reported (NR).

For the General Population values, acute values were derived by the State of California (OEHHA, 2008, 192240) for 1 hour exposures and by ATSDR for an Acute Mimimal Exposure Level (MRL) with exposures from 1 – 14 days (ATSDR, 2004, 192116). The acute California Reference Exposure Level (CA-REL) was developed based on observations from several studies at various durations and concentrations, which were adjusted to a standard 1-hour duration using the $C^n \times t$ formula, where n = 4.6 [which varies from the value of n used in the AEGL derivations and in studies with ammonia (ten Berge et al., 1986, 025664)]. A benchmark concentration (BMC) analysis was conducted to calculate the 95% lower confidence limit for a 5% response ($BMCL_{05}$) for the endpoint of eye and respiratory irritation to arrive at a point of departure (POD) of 13.6 ppm, which was then divided by an uncertainty factor of 3 to derive a

final one hour CA-REL of 4.5 ppm (3.2 mg/m^3). The acute MRL was based on an observed LOAEL of 50 ppm, with no adjustments made for duration and application of uncertainty factors for use of a LOAEL (UF_L = 3) and for inter-individual variability (UF_H = 10).

Three chronic General Public values – CA-REL, ATSDR MRL, and EPA/IRIS RfC – were derived, all using the same study (Holness et al., 1989, 008181). The differences in the derived values were due to variations in the uncertainty factors used and in operational methods (e.g., when and where in the derivation process rounding and units conversions were applied). Even with those considerations taken into account, the chronic ATSDR MRL seemed to arrive at values that were not in keeping with the stated derivation procedure outlined in Appendix A of the Toxicological Profile for ammonia (ATSDR, 2004, 192116).

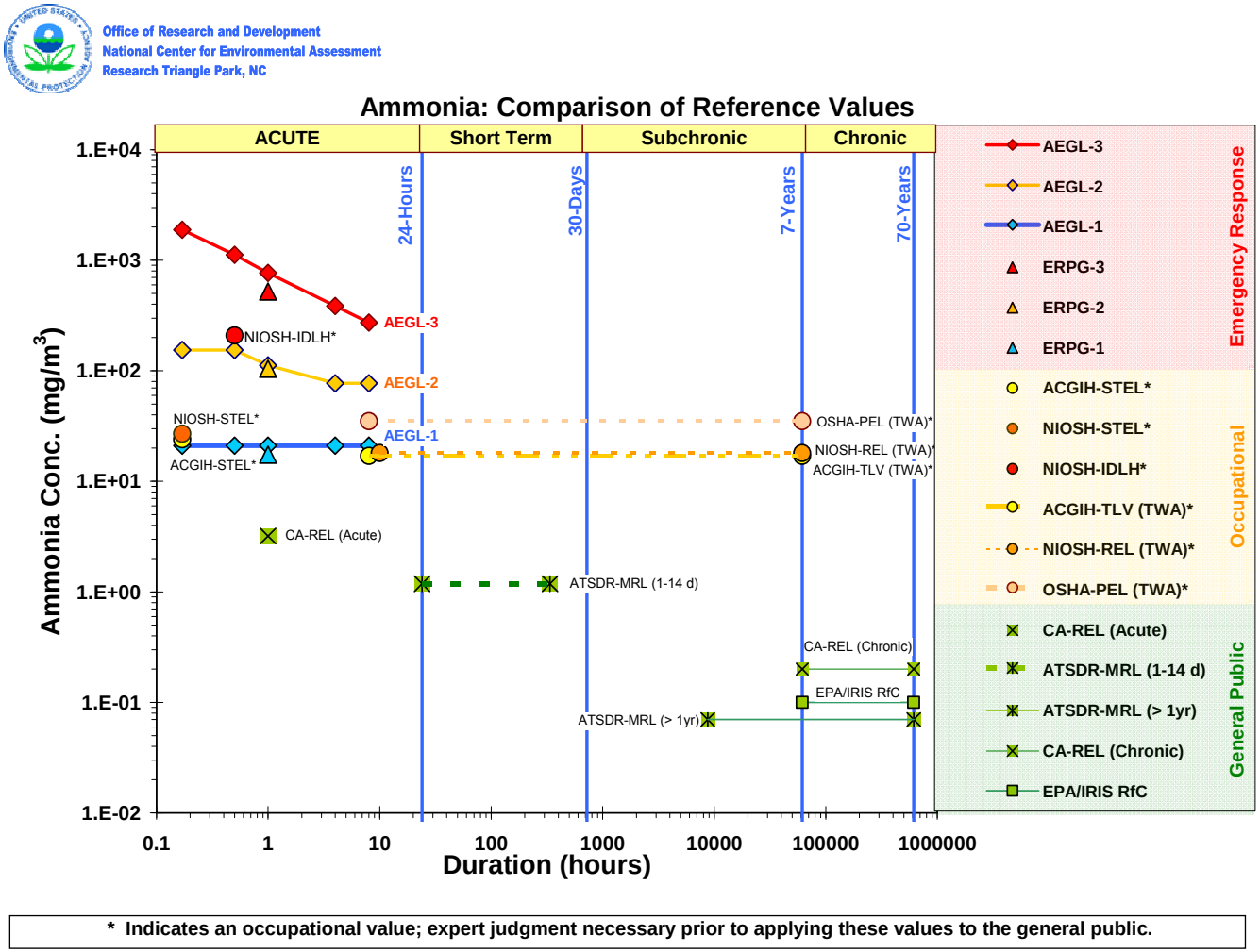

Figure 2.2. Comparison of Available Health Effect Reference Values for Inhalation Exposure to Ammonia

Table 2.2. Details on derivation of the specific inhalation health effect reference values for ammonia.

Reference Value Type / Name		Duration	Reference Value (mg/m^3)	Reference Value (ppm)	Health Effect	Point of Departure	Uncertainty Factors	Notes on Derivation	Review Status
Emergency Response[1]	**AEGL-3**	10 min	1900	2700	Lethality in mice (Kapeghian et al., 1982, 008040; MacEwen and Vernot, 1972, 041949)	3,219 ppm $BMDL_{05}$ 3,278 ppm (4 hours)	Total UF = 3 UF_A = 1 UF_H = 3	Time scaling using C^n x t where n = 2 (ten Berge et al., 1986, 025664)	Final (NAC/AEGL, 2002, 192201)
		30 min	1100	1600					
		1 hr	770	1100					
		4 hr	385	550					
		8 hr	273	390					
	AEGL-2	10 min	154	220	Respiratory tract and eye irritation to humans exposed to 110 ppm for 2 hr (Verberk, 1977, 008111)	110 ppm (2 hours) Threshold for effects	Total UF = 1	Time scaling using C^n x t where n = 2 (ten Berge et al., 1986, 025664)	
		30 min	154	220					
		1 hr	113	160					
		4 hr	77	110					
		8 hr	77	110					
	AEGL-1	10 min	21	30	Faint or no irritation to humans (MacEwen and Vernot, 1972, 041949)	30 ppm (10 min) Threshold for effects		No time scaling.	
		30 min	21	30					
		1 hr	21	30					
		4 hr	21	30					
		8 hr	21	30					

[1] Emergency Response reference values are developed using an assumption of a rare, "once-in-a-lifetime" exposure scenario, which is a key consideration when comparing these refernce values to any Occupational or General Public reference values.

Reference Value Type / Name		Duration	Reference Value (mg/m^3)	Reference Value (ppm)	Health Effect	Point of Departure		Uncertainty Factors	Notes on Derivation	Review Status
Emergency Response[2]	**ERPG-3**	1 hr	525	754	1-hr median lethal concentrations in the rat from 7340 to 16600 ppm and from 4230 to 4840 in the mouse, also causing eye, nasal, and respiratory irritation (ACGIH, 1986, 192014; Appelman et al., 1982, 007955; Industrial Bio-test Laboratories, 1973, 061664; Kapeghian et al., 1982, 008040; MacEwen et al., 1970, 064655; Silverman et al., 1949, 008092; Verberk, 1977, 008111; Weatherby, 1952, 008121)	NR	NR	NR		Final (AIHA, 2002, 192093)
	ERPG-2	1 hr	105	151	Slight eye irritation in humans exposed to 100 pm for 5 weeks; no changes in respiratory function in humans exposed to 140 ppm for 2 hr (Ferguson et al., 1977, 008010; Industrial Bio-test Laboratories, 1973, 061664; Verberk, 1977, 008111; Weatherby, 1952, 008121)	NR	NR	NR		

[2] Emergency Response reference values are developed using an assumption of a rare, "once-in-a-lifetime" exposure scenario, which is a key consideration when comparing these reference values to any Occupational or General Public reference values.

Reference Value Type / Name		Duration	Reference Value (mg/m^3)	Reference Value (ppm)	Health Effect	Point of Departure		Uncertainty Factors	Notes on Derivation	Review Status
	ERPG-1	1 hr	17.5	25	Mild odor perception and mild irritation (Ferguson et al., 1977, 008010; Industrial Bio-test Laboratories, 1973, 061664; MacEwen et al., 1970, 064655; Pierce, 1994, 180261)	25 ppm	NR	NR		
Occupational	**ACGIH TLV-TWA***	Any	17	25	Eye and respiratory irritation in humans (Stombaugh et al., 1969, 008097)	NR	NR	NR		Final (ACGIH, 2007, 192024)
	ACGIH TLV-STEL*	15 min	24	35	Acute sensory effects (Stombaugh et al., 1969, 008097)	NR	NR	NR		
	OSHA-PEL (TWA)*	8 hr TWA	35	50	NR	NR	NR	NR		Final (NIOSH, 2006, 192177)
	NIOSH-REL (TWA)*	10 hr TWA	18	25		NR	NR	NR		
	NIOSH-STEL*	15 min	27	35	Acute inhalation toxicity data in humans	NR	NR	NR		Final (NIOSH, 1996, 192195)
	NIOSH-IDLH*	< 30 min	210	300						

Reference Value Type / Name		Duration	Reference Value (mg/m^3)	Reference Value (ppm)	Health Effect	Point of Departure	Uncertainty Factors	Notes on Derivation	Review Status
General Public	**CA-REL (Acute)**	1 hr	3.2	4.6	Eye and respiratory irritation in humans (Industrial Bio-test Laboratories, 1973, 061664; MacEwen et al., 1970, 064655; Silverman et al., 1949, 008092; Verberk, 1977, 008111)	13.6 ppm $BMCL_{05}$	Total UF = 3 UF_A = 1 UF_H = 3	BMC analysis performed on duration adjusted observations using $C^n \times T$, where n=4.6.	Final (OEHHA, 2008, 192317)
	ATSDR-MRL (1-14 d)	1 - 14 days	1.2	1.7	Eye, nose, and throat irritation in humans (Verberk, 1977, 008111)	50 ppm LOAEL	Total UF = 30 UF_L = 3 UF_H = 10		Final (ATSDR, 2004, 192116)

Reference Value Type / Name		Duration	Reference Value (mg/m^3)	Reference Value (ppm)	Health Effect	Point of Departure	Uncertainty Factors	Notes on Derivation	Review Status
General Public	**ATSDR-MRL (> 1yr)**	Chronic	0.07	0.1	No significant alterations in lung function in chronically exposed workers (Holness et al., 1989, 008181)	3.0 ppm $NOAEL_{HEC}$ (9.2 ppm × 8/24 × 5/7)	Total UF = 30 UF_H = 10 MF = 3	Duration adjustments accounting for work schedule applied (8hr/24hr, and 5d/7d).	Final (ATSDR, 2004, 192116)
	Chronic RfC (IRIS)	Chronic	0.1	0.14	Decreased pulmonary function or changes in human subjective syptomatology (Holness et al., 1989, 008181)	2.3 mg/m^3 $NOAEL_{HEC}$ (Based on 6.4 mg/m^3 [9.2 ppm] observed × 5/7 × 10/20)	Total UF = 30 UF_H = 10 UF_{DB} = 3	HEC Adjustments based on 5 day/wk and 10 m^3/day occupational breathing rate vs. 20 m^3/d human average	Final (U.S. EPA, 1991, 192219)
	CA-REL (Chronic)	Chronic	0.2	0.29	Pulmonary function, eye, skin, and respiratory symptoms of irritation (Broderson et al., 1976, 007975; Holness et al., 1989, 008181)	3 ppm $NOAEL_{HEC}$ (Based on 9.2 ppm observed × 5/7 × 10/20, rounded to 3 ppm then converted to 2 mg/m^3)	Total UF = 10 UF_H = 10	Same HEC adjustments as the IRIS RfC, but rounding to 3 ppm as the POD then converting to mg/m^3 before applying UFs.	Final (OEHHA, 2000, 192318)

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2.3. Chemical-Specific Reference Values for Arsine (CASRN 7784-42-1)

Arsine is a colorless, extremely flammable gas with a mild, garlic-like odor (NLM, 2005, 192329). The gas is heavier than air and accumulates close to the surface, which makes distant ignition possible in the presence of flame or spark. Arsine is extensively used in the semiconductor industry for epitaxial growth of gallium arsenide, as a doping agent for silicon based solid state electronic devices and the manufacture of light emitting diodes. In humans, arsine is absorbed via the lungs and mucosal surface of the respiratory tract. After exposure, the concentration of arsine increases rapidly in blood, whereas the distribution to the liver, kidneys and other organs is much slower. In humans, arsine is metabolized to trivalent and pentavalent arsenic. Trivalent arsenic is methylated to monomethylarsonate and dimethylarsinate. Arsine metabolites are mainly excreted via urine. Arsine in humans (and other mammals) induces hemolysis with an increase in plasma hemoglobin, iron and potassium and subsequent anemia and kidney damage. Myocardial and pulmonary failures are other causes of death. IARC (IARC, 1987, 192133) lists arsenic and arsenic compounds as "*carcinogenic to humans*," hence many of the reference values for arsine consider cancer as well as noncancer endpoints. More details on the chemical nature and toxicity of arsine are available elsewhere (AIHA, 2002, 192087; American Industrial Hygiene, 1965, 192026; NAC/AEGL, 2000, 192321; U.S. EPA, 1994, 192320); (NLM, 2005, 192329) and are not repeated here.

Inhalation health effect reference values for arsine are displayed graphically in Figure 2.3. Details available on the derivation of these values, including key effects, studies, adjustments, and uncertainty factors (UFs) are shown in Table 2.3.

The Emergency Response reference values , both the AEGLs and ERPGs, depend on a single study in mice (Peterson and Bhattacharyya, 1985, 067598) for deriving level 2 values (irreversible adverse health effects) and level 3 values (severe effects leading to potentially lethality). Neither the AEGL nor ERPG committees developed level 1 values due to a lack of a margin seemingly inconsequential exposures and lethal exposures, making it inappropriate to develop AEGL-1 or ERPG-1 values.

The NIOSH Occupational values are derived by a weight of evidence approach and no particular study was identified as the basis for the values. The recommended exposure level (REL) consists of only a ceiling value (a REL time-weighted average value was not established), and was based on concern for potential carcinogenicity. For establishing the IDLH value, several studies were noted for symptoms indicative of poisoning were noted after a few hours of exposure to concentrations of 3 to 10 ppm (Henderson and Haggard, 1943, 010318). Additionally, a one hour exposure to 1 to 10 ppm may be dangerous (American Industrial Hygiene, 1965, 192026), while 6 to 30 ppm is the maximum concentration that can be inhaled in 1 hour without serious consequences (Henderson and Haggard, 1943, 010318). Minimal disabling exposures were reported to be 1,543 ppm for 2 minutes and 62 ppm for 30 minutes (Gates et al., 1946, 192214). The lowest LC_{Lo} of 25 ppm in humans (Teitelbaum and Kier, 1969, 068668), however, seems to be the pivotal study in derivation of the IDLH, as noted in the documentation (NIOSH, 1996, 192331).

The ACGIH-TLV TWA Occupational value was not based on consideration of cancer effects, with ACGIH noting in their documentation (2007, 192024) that "there are no human or animal data that show arsine to be carcinogenic." The key effects noted in that documentation

focused on an occupational study in battery formation work (Landrigan et al., 1982, 005485), with other supporting studies also noted.

The General Public values include a set of newly revised Reference Exposure Levels from the State of California (CA-RELs) for acute (1-hour), 8-hour and chronic durations (OEHHA, 2008, 192332). The 1-hour acute value was based on equivalents of arsenic (As) from inhalation exposure to arsenic trioxide (As_2O_3) in a developmental study in mice (Nagymajtenyi et al., 1985, 062165). The 8-hour CA-REL was determined to be equivalent to the chronic CA-REL, which was in turn based on developmental neurotoxicity in children from exposure to inorganic arsenic at the parts per billion (ppb) level in drinking water (Tsai et al., 2003, 180240; Wasserman et al., 2004, 180230). The values shown in Table 2.3 for the 8-hour and chronic CA-RELs are based on milligrams of arsenic per cubic meter, however, the parts per million (ppm) units were converted to arsine in the Technical Support Document (OEHHA, 2008, 192332).

The U.S. EPA's IRIS Program developed a chronic inhalation RfC (U.S. EPA, 1994, 192320) based on hemolysis, abnormal red blood cell morphology and increased spleen weight in both rats and mice (Blair et al., 1990, 067664; Blair et al., 1990, 067665; Hong et al., 1989, 067671). Adjustments were made to account for the 6 hour per day and 5 days per week exposures, reducing the no observed adverse effect level (NOAEL) in rodents of 0.08 mg/m^3 to a human equivalent concentration of the NOAEL ($NOAEL_{HEC}$) of 0.014 mg/m^3. Uncertainty factors applied included: (1) 10 to account for sensitive populations; (2) a factor of 3 to account for interspecies extrapolation (default dosimetry adjustments and large species differences not expected for direct hemolytic effects); and (3) a composite factor of 10 to account for both subchronic duration extrapolation and database deficiencies, specifically the lack of a two-generation reproductive study. A reduced uncertainty factor for subchronic-to-chronic duration is applied because the principal studies do not suggest that duration of exposure is a key determinant of the critical effects (14- and 28-day exposures caused similar hematologic effects as 90-day exposures in all three species tested). The final result is a chronic RfC value of 5×10^{-5} mg/m^3.

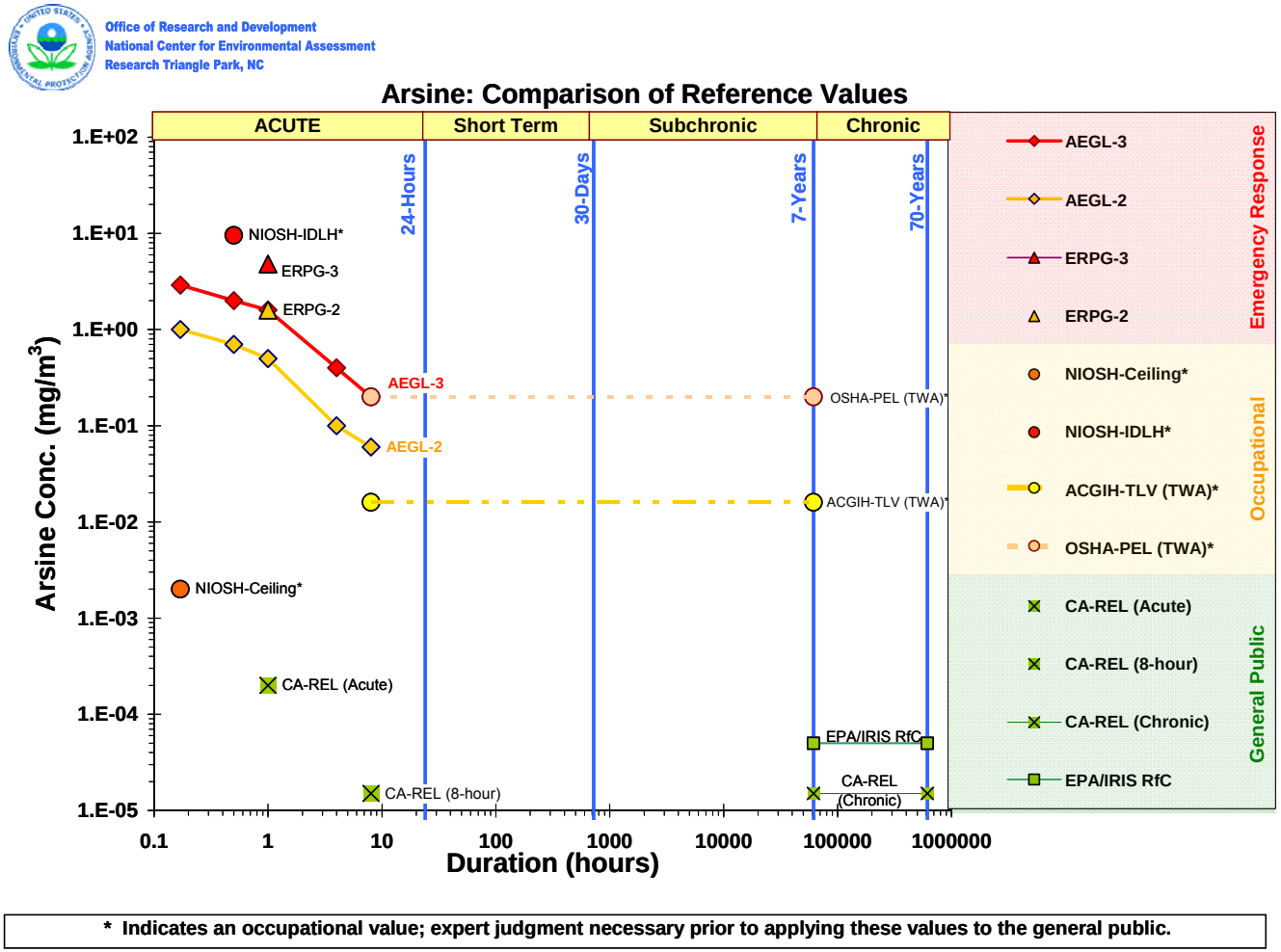

Figure 2.3. Comparison of Available Health Effect Reference Values for Inhalation Exposure to Arsine

Table 2.3. Details on derivation of the specific inhalation health effect reference values for arsine.

Reference Value Type / Name		Duration	Reference Value (mg/m^3)	Reference Value (ppm)	Health Effect	Point of Departure		Uncertainty Factors	Notes on Derivation	Review Status
Emergency Response[1]	**AEGL-3**	10 min	2.9	0.91	Hemolysis and lethality in mice (Peterson and Bhattacharyya, 1985, 067598)	15 ppm (1 hour)	Threshold for lethality in mice	Total UF = 30 UF_A = 10 UF_H = 3	Time scaling using $C^n \times t$ with default values of n: 3 for shorter and 1 for longer durations. (NRC, 2001, 192042)	Final (NAC/AEGL, 2000, 192321)
		30 min	2.0	0.63						
		1 hr	1.6	0.50						
		4 hr	0.40	0.13						
		8 hr	0.20	0.060						
	AEGL-2	10 min	0.96	0.3	Absence of significant hemolysis in mice exposed for 1 h (1985, 067598)	5 ppm (1 hour)	NOEL	Total UF = 30 UF_A = 10 UF_H = 3		
		30 min	0.7	0.21						
		1 hr	0.5	0.17						
		4 hr	0.1	0.04						
		8 hr	0.06	0.02						
	ERPG-3	1 hr	4.8	1.5	Hemolysis and lethality in mice (1985, 067598)	15 ppm (1 hour)	No lethality or hemolysis in mice	NR	Although UFs were not reported in the ERPG document, it may be assumed a total UF of 10 was applied.	Final (AIHA, 2002, 192087)
	ERPG-2	1 hr	1.6	0.5	Absence of significant hemolysis in mice exposed for 1 h (1985, 067598)	5 ppm (1 hour)	Below the threshold for hemolysis	NR		

[1] Emergency Response reference values are developed using an assumption of a rare, "once-in-a-lifetime" exposure scenario, which is a key consideration when comparing these reference values to any Occupational or General Public reference values.

Reference Value Type / Name		Duration	Reference Value (mg/m^3)	Reference Value (ppm)	Health Effect	Point of Departure		Uncertainty Factors	Notes on Derivation	Review Status
Occupational	**NIOSH-Ceiling***	15 min	2×10^{-3}	6.3×10^{-4}	Potential carcinogen	NR		NR		Final (ATSDR, 2006, 192117)
	OSHA-PEL*	8 hr TWA	0.2	0.05	NR	NR	NR	NR	Based on previous ACGIH-TLV	
	NIOSH-IDLH*	30 min	9.6	3	Human acute inhalation toxicity (Teitelbaum and Kier, 1969, 068668)	25 ppm	LC_{Lo}	NR		Final (NIOSH, 1996, 192331)
	ACGIH – TLV (TWA)*	8 hour TWA	0.016	0.005	Peripheral nervous system; vascular system; kidney and liver damage	0.049 mg/m^3 (Landrigan et al., 1982, 005485)	NOAEL	NR	UFs not reported, but Total UF = 3 inferred.	Final (ACGIH, 2007, 192024)
General Public	**CA-REL (Acute)**	1 hr	2×10^{-4} (Based on mg As)	6.5×10^{-5} (Arsine)	Decreased fetal weight in mice (Nagymajtenyi et al., 1985, 062165)	0.197 mg As/m^3	LOAEL	Total UF = 1000 UF_L = 10 UF_A: 10 TK= 3 TD = 3 UF_H: 10 TK = 3 TD = 3	Derivations based on molar equivalents of arsenic (As) from inhalation of As_2O_3.	Final (OEHHA, 2008, 192332)
	CA-REL (8-hr)	8 hr	1.5×10^{-5} (Based on mg As)	5.0×10^{-6} (Arsine)	Decrease in intellectual function, neurobehavioral development in human children (Tsai et al., 2003, 180240; Wasserman et al., 2004, 180230)	0.00023 mg As/m^3	LOAEL	Total UF = 30 UF_L = 3 UF_H: 10 TK = 3 TD = 3	Derivations based on molar equivalents of inorganic arsenic (As) in drinking water.	
	CA-REL (Chronic)	Chronic	1.5×10^{-5} (Based on mg As)	5.0×10^{-6} (Arsine)		0.00023 mg As/m^3	LOAEL			
	Chronic RfC (IRIS)	Chronic	5×10^{-5}	2.2×10^{-5}	Increased hemolysis, increased spleen weight	0.014 mg/m^3 (0.08 mg/m^3 × 6/24 × 5/7)	$NOAEL_{HEC}$	Total UF = 300 UF_H = 10 UF_A = 3 UF_S = 10	Adjustments made to NOAEL to account for 6 hours/day and	Final (U.S. EPA, 1994, 192320)

Reference Value Type / Name		Duration	Reference Value (mg/m^3)	Reference Value (ppm)	Health Effect	Point of Departure	Uncertainty Factors	Notes on Derivation	Review Status
					(Blair et al., 1990, 067664; Blair et al., 1990, 067665; Hong et al., 1989, 067671)			5 days/wk in key study.	

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2.4. Chemical-Specific Reference Values for Chlorine (CASRN 7782-50-5)

Chlorine (Cl_2) is a greenish-yellow, highly reactive halogen gas with a pungent, suffocating odor. Like other halogens, chlorine exists in the diatomic state in nature. The vapor is heavier than air and will form a cloud in low-lying areas adjacent to the vicinity of a spill, potentially flowing into valleys under low wind conditions. Chlorine is extremely reactive and rapidly combines with both inorganic and organic substances, potentially reacting explosively or forming explosive compounds with many common substances such as acetylene, ether, turpentine, ammonia, fuel gas, hydrogen and finely divided metals. Chlorine is used in the manufacture of a wide variety of chemicals, as a bleaching agent in industrial and household products, and as a biocide in water and waste treatment plants. It has been used as a chemical warfare agent in World War I (Heller, 1984, 192322) and other more recent conflicts (Multi-National, 2007, 192323). Additional details are provided from multiple other sources (AIHA, 2002, 192059; ATSDR, 2007, 192119; NRC, 2004, 192142) on the chemical nature of and the health effects from exposure to chlorine gas, and is not repeated here.

Inhalation health effect reference values for chlorine are displayed graphically in Figure 2.4. Details available on the derivation of these values, including key effects, studies, adjustments, and uncertainty factors (UFs) are shown in Table 2.4.

The Emergency Response reference values (AEGLs and ERPGs) were developed for all three severity categories (level 1 for mild transient effects; level 2 for irreversible effects or impairment of ability to escape; and level 3 for potentially lethal effects). The one-hour AEGLs and the ERPGs are in relatively close proximity to one another, with the ERPG-3 being somewhat lower than the corresponding one-hour AEGL-3. The nature of this difference is difficult to assess because fewer details are provided for the derivation of the ERPGs than is provided for the AEGLs.

The NIOSH Occupational reference values are derived by a weight of evidence approach and no particular study was identified as the basis for the values. Intense coughing fits were reported with exposure to 30 ppm, while exposure to 40 to 60 ppm for 30 minutes to one hour may cause serious damage (ILO, 1971, 192324). Exposure to 34 to 51 ppm has been reported to be lethal when subjects were exposed for one to 1.5 hours (Freitag, 1941, 194017)It has also been reported that exposure to 14 to 21 ppm for 30 minutes to one hour is dangerous (NPIRI, 1983, 192325).

Two acute General Public reference values are available for chlorine – an acute CA-REL and an acute ATSDR MRL. Both use the same study (Anglen, 1981, 010298) as the basis for the POD and perform time scaling, but using two different approaches. ATSDR (ATSDR, 2007, 192119) uses the 8-hour observations from the study and performs what amounts to application of Haber's "rule" [$C \times t = k$; (Haber, 1924, 059334)] by multiplying the NOAEL by 8/24 to account for the 8-hour exposure to arrive at a 24 hour POD. OEHHA (OEHHA, 1999, 192221) uses the $C^n \times t = k$ formula with a value of $n = 2$, but reports that a 30-minute time point was used as the starting point for the extrapolation to 1 hour while the study report notes observations from exposures of 4 or 8 hours only. The end results are acute reference values that are identical for both 1-hour (CA-REL) and 24-hour (ATSDR) durations.

Other General Public reference values include both intermediate (14 to 365 days) and chronic (> 1 year) duration ATSDR MRLs, as well as a chronic CA-REL (durations up to a

lifetime). All of these longer duration reference values include adjustments for the experimental exposure schedule (i.e., consideration of hours per day and days per week during exposure) and differences in respiratory surface area and breathing rates between the experimental animals and humans through the use of the regional gas dose ratio (RGDR). Details on the calculation of the RGDR are not provided here and the reader is directed to the ATSDR Toxicological Profile (2007, 192119) and the OEHHA Technical Support Document (1999, 192221) for chlorine.

The rather large and comprehensive data base of health effect data in several experimental animal models and in human studies, coupled with the ubiquitous nature of chlorine in commerce led to the development of a fairly comprehensive set of inhalation health effect reference values across all types of values (emergency response, occupational, and general public), severity of effects (presumptively safe, mild, severe, and lethal), and durations (acute, short-term, subchronic, and chronic timeframes). There also seems to be some strong concordance among the values, based on consideration of the nature and purpose of the different values. The lowest level emergency response values (AEGL-1 and ERPG-1) which were designed for once-in-a-lifetime types of exposure scenarios are in the same range of exposure levels as the ceiling and TWA occupational values. There is also a clear stair-step decrease in the general public reference values as duration increases, based largely on the empirical evidence that health effects accumulate from longer duration exposures to low level concentrations of chlorine.

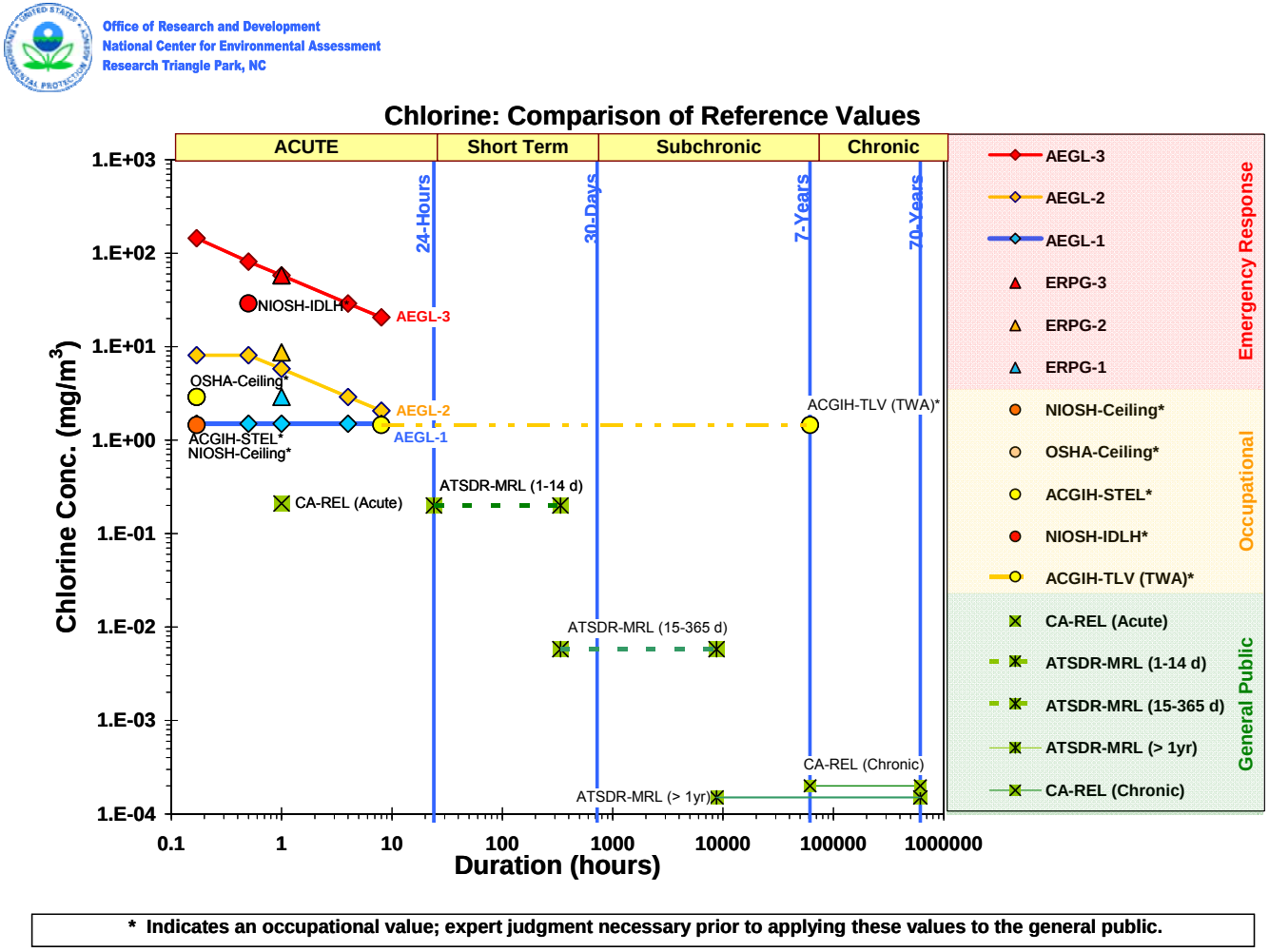

Figure 2.4. Comparison of Available Health Effect Reference Values for Inhalation Exposure to Chlorine

Table 3.5. Details on derivation of the specific inhalation health effect reference values for chlorine.

Reference Value Type / Name		Duration	Reference Value (mg/m^3)	Reference Value (ppm)	Health Effect	Point of Departure		Uncertainty Factors	Notes on Derivation	Review Status
Emergency Response[1]	**AEGL-3**	10 min	145	50	Lethality (MacEwen and Vernot, 1972, 041949; Zwart and Wouterson, 1988, 010507)	200 ppm (1 hour)	Estimated mean of nonlethal values for the rat and mouse	Total UF = 10 UF_A = 3 UF_H = 3	Time scaling: $C^n \times t = k$ where n = 2, derived empirically.	Final (NRC, 2004, 192142)
		30 min	81	28						
		1 hr	58	20						
		4 hr	29	10						
		8 hr	21	7.1						
	AEGL-2	10 min	8.1	2.8	Sensory irritation and transient changes in pulmonary function measurements (D'Alessandro et al., 1996, 081056; Rotman et al., 1983, 064252)	1 ppm (4 hours)	NOAEL for AEGL-2 effects	Total UF = 1 (susceptible human)		
		30 min	8.1	2.8						
		1 hr	5.8	2						
		4 hr	2.9	1						
		8 hr	2.0	0.7						
	AEGL-1	10 min	1.5	0.5	Notable irritation and significant changes in pulmonary function parameters (Anglen, 1981, 010298; D'Alessandro et al., 1996, 081056; Rotman et al., 1983, 064252; Shusterman et al., 1998, 085870)	0.5 ppm (4 hours)	NOAEL for AEGL-1 effects	Total UF = 1 (susceptible human)	No time scaling	
		30 min	1.5	0.5						
		1 hr	1.5	0.5						
		4 hr	1.5	0.5						
		8 hr	1.5	0.5						
	ERPG-3	1 hr	58	20	Lethality (Schlagbauer and Henschler, 1967, 010243; Withers and Lees, 1985, 010258; 1985, 010259)	NR	NR	NR		Final (AIHA, 2002, 192059)

[1] Emergency Response reference values are developed using an assumption of a rare, "once-in-a-lifetime" exposure scenario, which is a key consideration when comparing these reference values to any Occupational or General Public reference values.

Reference Value Type / Name		Duration	Reference Value (mg/m^3)	Reference Value (ppm)	Health Effect	Point of Departure		Uncertainty Factors	Notes on Derivation	Review Status
	ERPG-2	1 hr	8.7	3	Slight irritation and discomfort (Barrow et al., 1979, 064226; Zeilhaus, 1970, 180139)	NR	NR	NR		
	ERPG-1	1 hr	3	1	Slight transient effects (Gerrity et al., 1990, 012098; Rotman et al., 1983, 064252)	NR	NR	NR		
Occupational	**OSHA-Ceiling (TWA) ***	15 min	3	1	Irritation and pulmonary function decline	NR	NR	NR		Final (OSHA, 1989, 192326)
	NIOSH Ceiling*	15 min	1.5	0.5	Pulmonary and ocular effects	NR	NR	NR		Final (NIOSH, 1976, 192334)
	NIOSH-IDLH (<30 min) *	30 min	29	10	Acute inhalation toxicity data in humans	NR	NR	NR		Final (NIOSH, 1996, 192333)
	ACGIH TLV-STEL*	15 min	2.9	1	Eye and mucous membrane irritation (Anglen, 1981, 010298; Rotman et al., 1983, 064252; Rupp and Henschler, 1967, 064253)	NR	NR	NR		Final (ACGIH, 2007, 192024)
	ACGIH TLV-TWA*	8 hr TWA	1.5	0.5		NR	NR	NR		
General Public	**CA-REL (Acute)**	1 hr	0.21	0.07	Itching or burning of throat in humans (Anglen, 1981, 010298)	0.71 ppm (1 ppm at 30 min scaled to 1 hour)	NOAEL	Total UF = 10 UF_H = 10	Time scaling using $C^n \times t = k$ where n = 2	Final (OEHHA, 1999, 192221)
	ATSDR- MRL (Acute)	1 - 14 d	0.2	0.07	Sensory irritation and pulmonary function in humans (Anglen, 1981,	0.2 ppm (0.5 ppm × 8/24)	$NOAEL_{ADJ}$	Total UF = 3 UF_H = 3	Adjusted for 8 hour exposure duration	Draft (ATSDR, 2007, 192119)

Reference Value Type / Name	Duration	Reference Value (mg/m^3)	Reference Value (ppm)	Health Effect	Point of Departure	Uncertainty Factors	Notes on Derivation	Review Status
				010298)				
ATSDR- MRL (Intermediate)	15 d - 1 yr	5.8×10^{-3}	2×10^{-3}	Tracheal lesions in rats (Kutzman, 1983, 094919)	0.14 ppm (0.5 ppm × 6/24 × 5/7 × 1.41) $LOAEL_{HEC}$	Total UF = 60 $UF_L = 3$ $UF_A = 2$ $UF_H = 10$	Adjusted for 6 hr/d; 5 d/wk; and RGDR = 1.41	
ATSDR- MRL (Chronic)	> 1yr	1.5×10^{-4}	5×10^{-5}	Nasal lesions in monkeys (Klonne et al., 1987, 094918)	1.36 ppb (20 ppb × 6/24 × 5/7 × 0.34) $BMCL_{10[HEC]}$	Total UF = 30 $UF_A = 3$ $UF_H = 10$	Adjusted for 6 hr/d; 5 d/wk; and RGDR = 0.34	
CA-REL (Chronic)	Chronic	2×10^{-4}	6.9×10^{-5}	Upper respiratory epithelial lesions in rats (Wolf et al., 1995, 076612)	2.4 ppb (140 ppb × 6/24 × 3/7 × 0.16) $BMC_{05\text{-}HEC}$ (LOAEL = 0.4 ppm; BMC_{05} = 0.14 ppm)	Total UF = 30 $UF_A = 3$ $UF_H = 10$	Adjustments to BMC_{05} for 3 d/wk; 6 h/d and RGDR = 0.16	Final (OEHHA, 2000, 192223)

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2.5. Chemical-Specific Reference Values for Chromium VI (CASRN 18540-29-9)

Chromium is a naturally occurring element present in the earth's crust. Chromium VI [Cr(VI); Cr^{6+}] is one of three valence states of the chromium metal ion (II, III, or VI), and is the most toxic form. Chromium(III) is an essential trace nutrient required for normal energy metabolism. Cr(VI) is usually found as either water-soluble or insoluble chromate compounds (ACGIH, 2001, 192015). Water-soluble chromates include potassium chromate (K_2CrO_4) and dichromate ($K_2Cr_2O_7$), sodium chromate ($NaCrO_4$) and dichromate ($Na_2Cr_2O_7$), ammonium chromate ($(NH_4)_2CrO_7$), and chromium trioxide (chromic acid; CrO_3). Insoluble chromates include all other Cr(VI) compounds not listed as water-soluble.

The higher toxic potency of Cr(VI) compared to Cr(III) is complex (ATSDR, 2008, 192121). Cr(VI) enters cells by facilitated uptake, whereas Cr(III) crosses cell membranes by simple diffusion; thus, cellular uptake of Cr(VI) is more effective than of Cr(III). Furthermore, in biological systems, reduction of Cr(VI) to Cr(III) results in the generation of free radicals, which can form complexes with intracellular targets. Health effects of chromium compounds can vary with route of exposure, with certain effects specific for the portal of entry. Respiratory effects are associated with inhalation of chromium compounds, but not with oral and dermal exposures, and gastrointestinal effects are primarily associated with oral exposure. However, effects of chromium are not limited to the portal of entry, with hematological, immunological, and reproductive systems also identified as targets for chromium. In addition, results of occupational exposure studies and chronic duration animal studies indicate that inhalation and oral exposures to Cr(VI) compounds are associated with respiratory and gastrointestinal system cancers, respectively. Cr(VI) in both water-soluble and insoluble forms have been designated as known human carcinogens via inhalation (IARC, 1990, 192135), Classification A1 - Confirmed Human Carcinogen. More information on the toxic potential and chemical nature of chromium compounds and Cr(VI) can be found from other sources (ATSDR, 2008, 192121; IARC, 1990, 192135; U.S. EPA, 1998, 192335) and the reader is directed to consult them for additional details.

The remainder of this discussion focuses on the available inhalation health effect reference values for Cr(VI). Reference values for Cr(VI) are arrayed graphically across duration and severity level across all types of values (Emergency Response, Occupational, and General Public) in Figure 2.5. Additional details on the derivation of those reference values are shown in Table 2.5, including whatever information is available on the health effect used as the basis for the value, the concentration used as the point of departure for protection against those effects, any adjustments for duration of exposure or other considerations (e.g., animal to human or occupational to continuous exposures), and application of uncertainty factors. One of the complicating factors in discussing the available reference values for Cr(VI) is due to the issue of speciation. This includes the differences between the various valence states of chromium, as well as subcategories within the various Cr(VI) compounds; these include variations such as the water-soluble and insoluble dichotomy, and acid mists and aerosols versus particulates. All of the reference values shown in this summary are for Cr(VI), and are based on chromium content (i.e., chromium compounds such as chromium trioxide are based on the equivalents of chromium). Variations based on subcategories of Cr(VI) are noted in the column "Notes on Derivation" in Table 2.5.

The only Emergency Response reference values derived for chromium and chromium compounds were the TEELs. The TEEL values shown are based on the chromium content for the compound chromium trioxide. Very little information is available currently on the derivation of the TEELs for individual compounds, although the methods for developing TEELs are available (DOE, 2008, 192182). The TEEL values shown in this summary are for chromic acid, which is reported as Cr(VI). Values for a number of other individual Cr(VI) compounds are also included in the table of TEEL values.

The Occupational reference values include IDLH and TWA values from ACGIH, NIOSH and OSHA. All of the TWA values are based on concerns for cancer potential from repeated exposures. ACGIH-TLV values were derived separately for water-soluble versus insoluble Cr(VI) compounds, with the concentration values for water-soluble Cr(VI) being a factor of five higher than those for the insoluble. All of the other occupational values were derived based on exposure to chromic acid but are expressed in units of milligrams chromium per cubic meter. There is a notable difference between the levels for the IDLH and TWA values which is due predominantly to the cancer concern for the TWA values versus frank noncancer toxicity used in the derivation of the IDLH value.

The General Public reference values for Cr(VI) are numerous and complicated due to values developed for different Cr(VI) species. The only acute duration value included in this summary is one Effects Screening Level (ESL) developed by the Texas Commission on Environmental Quality (2009, 180241), and was developed for all Cr(VI) compounds. Very little detail was readily available for the derivation of the acute TX-ESL value. Although a chronic TX-ESL is also available, it is not included in this review due to the numerous, more-rigorously-reviewed chronic values already available.

ATSDR developed two intermediate duration MRL values for Cr(VI), one for acid mists and aerosols, and another for particulates. These are the only subchronic general public reference values available. The intermediate MRL is identical to the chronic MRL for acid mists and aerosols and is discussed in more detail with the other chronic values below. The MRL developed for particulate Cr(VI) was set at approximately two orders of magnitude higher than the MRL for acid mists and aerosols. A similar pattern emerges in comparing the EPA/IRIS RfC values derived for those same species [acid mists and aerosols versus particulate Cr(VI)], with a similar spread in concentrations. The chronic CA-REL values were developed using a slightly different split in Cr(VI) species by developing values for only the water-soluble species, but discriminating between chromium trioxide and all other water-soluble Cr(VI) species.

The same study and very similar approaches were taken with both the intermediate MRL and chronic RfC values for particulate Cr(VI): both used the same BMC analysis performed by the researchers (Malsch et al., 1994, 192336) as the basis for deriving a point of departure (POD), and both used HEC adjustments using a Regional Deposited Dose Ratio (RDDR) factor; however, the RDDR values were not the same and resulted in very different POD values. A similar approach was also taken with the chronic CA-REL for particulate Cr(VI), which used the same data set (Glaser et al., 1990, 004286) but instead performing their own BMC analysis to derive a $BMCL_{05}$ versus the previously derived $BMCL_{10}$ (Malsch et al., 1994, 192336), then used an RDDR factor more closely in keeping with the EPA derivation. The uncertainty factors applied between these three values for particulate Cr(VI) were also similar, with an added factor of 3 applied to the chronic RfC and CA-REL values to account for use of a subchronic study.

The same study (Lindberg and Hedenstierna, 1983, 063710) was used for all three chronic values (MRL, RfC and CA-REL) developed for acid mists and aerosols, as well as the

intermediate MRL which is the same as the chronic MRL for Cr(VI) acid mists and aerosols. The resulting reference values vary based on the application of different uncertainty factors (UFs) and on variations on adjustments for exposure duration in the key study to continuous exposure. As noted in Table 2.5, both the CA-REL and RfC for acid mists and aerosols used not only the same study, but also arrived at the same POD using identical adjustments to the occupational LOAEL to arrive at a continuous LOAEL ($LOAEL_c$). The major difference between these values was in the application of uncertainty factors. OEHHA used a factor of 10 for the subchronic to chronic (UF_S) and EPA applied a factor of 3. Another difference was the use of a composite (total) UF of 90 for the derivation of the RfC, when in other cases this would have been expressed as a factor of 100; this was not well described in the IRIS Toxicological Review for Chromium (U.S. EPA, 1998, 192335). The intermediate and chronic MRL values for chromic acid mists and aerosols used a total uncertainty factor of 100 (10 for use of a LOAEL and 10 for inter-individual variability), but used a duration adjustment for use of an occupational study (8 hours per 24 hour day; effectively a factor of 1/3) instead of using differences in occupational versus average continuous breathing rates (10 m^3 per day versus 20 m^3 per day; effectively a factor of 1/2), as was used in the CA-REL and RfC derivations.

The coverage of reference values for Cr(IV) is somewhat complicated by the use of different forms of the chromate compounds, both from different classifications of which compounds apply to a particular reference value, as well as the physical state of the emissions (e.g., particulate versus acid mist or aerosol). The issue of speciation and which reference value applies in a given scenario (in lieu of having accurate information) may be addressed by the use of the most health protective (lowest concentration) reference value for the particular type of application being considered.

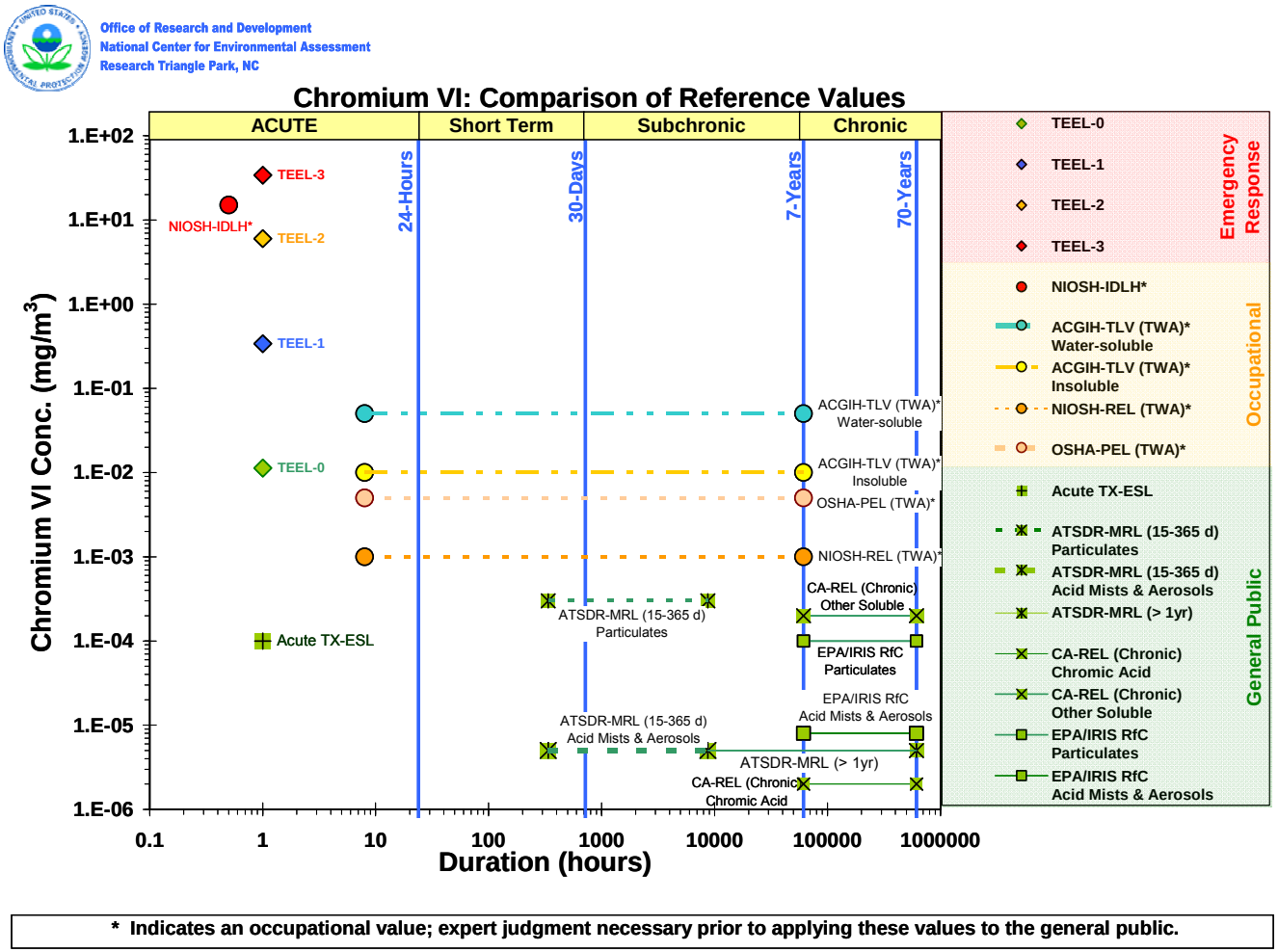

Figure 2.5. Comparison of Available Health Effect Reference Values for Inhalation Exposure to Chromium VI

Table 2.5. Details on derivation of the specific inhalation health effect reference values for chromium VI.

Reference Value Type / Name		Duration	Reference Value (mg/m^3)	Reference Value (ppm)	Health Effect	Point of Departure		Uncertainty Factors	Notes on Derivation	Review Status
Emergency Response[1]	**TEEL - 0**	1 hr	0.0113	1.2×10^{-3}	NR	NR	NR	NR		Final (DOE, 2008, 192182)
	TEEL - 1	1 hr	0.339	7.3×10^{-3}		NR	NR	NR		
	TEEL - 2	1 hr	6.0	0.01		NR	NR	NR		
	TEEL - 3	1 hr	34	3.7		NR	NR	NR		

[1] Emergency Response reference values are developed using an assumption of a rare, "once-in-a-lifetime" exposure scenario, which is a key consideration when comparing these reference values to any Occupational or General Public reference values.

	Reference Value Type / Name	Duration	Reference Value (mg/m^3)	Reference Value (ppm)	Health Effect	Point of Departure		Uncertainty Factors	Notes on Derivation	Review Status
Occupational	**NIOSH-IDLH (<30 min) ***	< 30 min	15	3.7	Cough, headache, dyspnea, substernal pain (ILO, 1971, 192324; Seiler et al., 1988, 191789)	NR	NR	NR	Based on exposure to chromic acid mist.	Final (NIOSH, 1996, 192338)
	ACGIH TLV-TWA*	8 hr TWA	0.05	0.01	Cancer; liver; kidney	NR	NR	NR	**Water-soluble Cr(VI)**	Final (ACGIH, 2001, 192015)
			0.01	0.005	Cancer; irritation	NR	NR	NR	**Insoluble Cr(VI)**	
	NIOSH-REL (TWA)*	10 hr TWA	1×10^{-3}	2.5×10^{-4}	Cancer (NIOSH, 1975, 192337)	NR	NR	NR	Based on exposure to chromic acid mist.	Final (NIOSH, 2006, 192177)
	OSHA-PEL (TWA) *	8 hr TWA	5×10^{-3}	1.2×10^{-3}	Cancer	NR	NR	NR		Final (OSHA, 2006, 192188)
General Public	**Acute TX-ESL**	1 h	1×10^{-4}	2.5×10^{-5}	NR	NR	NR	NR	**All Cr(VI) compounds**	Under review (Texas Commission on Environmental, 2009, 180241)
	ATSDR- MRL (15-365 d)	15 d – 1 yr	3×10^{-4}	1.4×10^{-4}	Lactate dehydrogenase (LDH) in bronchoalveolar lavage fluid (BALF) (Malsch et al., 1994, 192336)	10 µg/m^3 (16 µg/m^3 × 0.63)	$BMCL_{10}$ (HEC)	Total UF = 30 UF_A = 3 UF_H = 10	**Cr(VI) particulates**; HEC adjusted for RDDR[2] = 0.63	Draft (ATSDR, 2008, 192121)

[2] RDDR = regional deposited dose ratio, for differences between humans and experimental animals

Reference Value Type / Name	Duration	Reference Value (mg/m^3)	Reference Value (ppm)	Health Effect	Point of Departure		Uncertainty Factors	Notes on Derivation	Review Status
ATSDR- MRL (< 1 yr)	Chronic	5 x 10^{-6}	1.2 x 10^{-6}	Upper respiratory effects (Lindberg and Hedenstierna, 1983, 063710)	0.5 µg/m^3 (2 µg/m^3 × 8/24 × 5/7)	$LOAEL_{ADJ}$	Total UF = 100 UF_L = 10 UF_H = 10	**Acid mists and aerosols;** Adjusted for 8h/d and 5d/wk	
CA-REL (Chronic)	Chronic	2 x 10^{-4}	4.9 x 10^{-5}	Broncho-alveolar hyperplasia in rats (Glaser et al., 1990, 004286)	24.47 µg/m^3 (12.5 µg/m^3 × 22/24 × 2.143)	BMC_{05} (HEC)	Total UF = 100 UF_S = 3 UF_A = 3 UF_H = 10	**Cr(VI) particulates;** Adjusted for 22h/d and RDDR^2 = 2.143.	Final
		2 x 10^{-6}	4.9 x 10^{-7}	Nasal septum atrophy, lung toxicity (Lindberg and Hedenstierna, 1983, 063710)	0.68 µg/m^3 (1.9 µg/m^3 × 10/20 × 5/7)	LOAELc[3]	Total UF = 300 UF_L = 3 UF_S = 10 UF_H = 10	**Acid mists and aerosols;** Adjusted for (5 d/week) and breathing rate (10 vs 20 m^3/d)	Final (OEHHA, 2001, 192226)
Chronic RfC (IRIS)	Chronic	8 x 10^{-6}	2 x 10^{-6}				Total UF = 90 UF_L = 3 UF_S = 3 UF_H = 10		Final (U.S. EPA, 1998, 192335)
		1 x 10^{-4}	4.7 x 10^{-5}	LDH in BALF (Malsch et al., 1994, 192336)	34 µg/m^3 (16 µg/m^3 × 2.16)	$BMCL_{10}$ (HEC)	Total UF = 100 UF_A = 3 UF_S = 3 UF_H = 10	**Cr(VI) particulates;** Adjusted for RDDR^2 = 2.16	

[3] LOAELc = LOAEL for continuous exposure

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2.6 Chemical-Specific Reference Values for Cyanogen Chloride (CASRN 506-77-4)

Cyanogen chloride (CK; CNCl) is a highly volatile and toxic chemical asphyxiant that interferes with the ability of the body to use oxygen (NIOSH, 2008, 192339). CK is a chemical warfare agent but is also used commercially in chemical synthesis and fumigation. Exposure to CK can be rapidly fatal. It has whole-body (systemic) effects, particularly affecting those organ systems most sensitive to low oxygen levels: the central nervous system (brain), the cardiovascular system (heart and blood vessels), and the pulmonary system (lungs). CK has strong irritant and choking effects. Its vapors are extremely irritating and corrosive.

Very few inhalation health effect reference values are available for CK. These are displayed graphically in Figure 2.6, with the details available on the derivation of those values shown in Table 2.6.

ERPG values for Emergency Response were derived based on a weight of evidence approach, noting that "*exposures above the 4 ppm level might cause severe respiratory irritation and possibly edema*" (AIHA, 2002, 192086) in the derivation of the ERPG-3 level, and the ERPG-2 level was based in part on a report that 0.7 ppm was unbearable to workers. The resulting values of 4.0 and 0.4 ppm for the ERPG-3 and ERPG-2, respectively, were designed to be protective of susceptible subpopulations in the general population for a single exposure.

The only Occupational values (NIOSH Ceiling and ACGIH Ceiling) are for short (<15 minute) exposures only, and are for the same exposure level – 0.3 ppm (0.75 mg/m^3). Very little detail in the derivation of either value was provided, and was consistent with the literature reviewed for the ERPGs.

A calculation error was made in the NIOSH Pocket Guide (NIOSH, 2006, 192177), reporting that 0.3 ppm converts to 0.6 mg/m^3, that has since been propagated in other documents (USACHPPM, 2006, 192030). Using the conversion factor shown in the NIOSH Pocket guide of 1 ppm = 2.52 mg/m^3, a value of 0.75 mg/m^3 is derived.

No General Public values were found for cyanogen chloride.

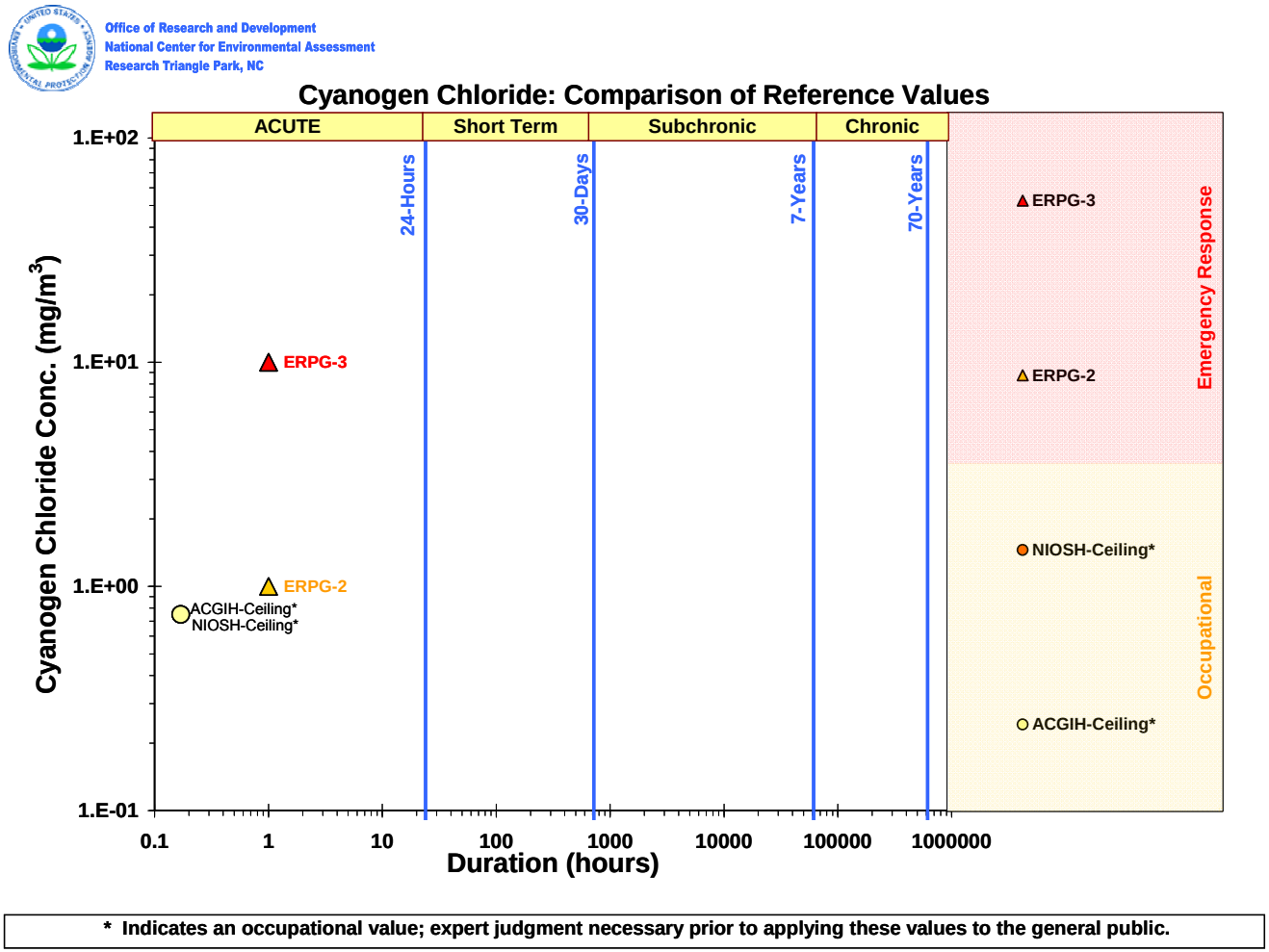

Figure 2.6. Presentation of the Available Health Effect Reference Values for Inhalation Exposure to Cyanogen Chloride

Table 2.6. Details on derivation of the specific inhalation health effect reference values for cyanogen chloride.

Reference Value Type / Name		Duration	Reference Value (mg/m^3)	Reference Value (ppm)	Health Effect	Point of Departure		Uncertainty Factors	Notes on Derivation	Review Status
Emergency Response[1]	**ERPG-3**	1 hr	10	4	Lethality; severe respiratory irritation and pulmonary edema (Moore and Gates, 1946, 192165)	120 ppm 48 ppm	LC_{50} (30 min) LC_{01} (6 hr)	NR		Final (AIHA, 2002, 192086)
	ERPG-2	1 hr	1	0.4	Severe eye and respiratory irritation in humans (Michigan Department of Health, 1986, 192340)	0.7 ppm	NR	NR		
Occupational	**NIOSH–Ceiling***	15 min	0.75	0.3	NR	NR	NR	NR		Final (NIOSH, 2006, 192177)
	ACGIH–Ceiling*	Any	0.75	0.3	Irritation, cellular metabolic interference (ACGIH, 2007, 192024)	NR	NR	NR		Final (ACGIH, 2007, 192024)

[1] Emergency Response reference values are developed using an assumption of a rare, "once-in-a-lifetime" exposure scenario, which is a key consideration when comparing these reference values to any Occupational or General Public reference values.

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2.7 Chemical-Specific Reference Values for Ethylene Glycol Monomethyl Ether (EGME) (CASRN 109-86-4)

EGME (Ethylene Glycol Monomethyl Ether; 2-methoxyethanol, methyl cellosolve; $CH_3OCH_2CH_2OH$) is a colorless liquid with a mild, pleasant odor. It has several commercial uses, including as a solvent for cellulose acetate; in dyeing leather; and as antifreeze in jet fuel. EGME is most toxic when inhaled, and is irritating to the eyes, nose, and throat; exposure may also cause headache, nausea, vomiting, and disorientation. Additional information on the nature of EGME and detailed summaries of health effects can be found in the IRIS Toxicological Review (U.S. EPA, 1991, 192218) the CA-REL documentation (OEHHA, 2000, 192222), (OEHHA, 2008, 192341), and other sources and is not repeated here.

Available inhalation health effect reference values for EGME are arrayed graphically in Figure 2.7. Details available on the derivation of these values, including key effects, studies, adjustments, and uncertainty factors (UFs) are shown in Table 2.7.

The only available Emergency Response reference values are provided by the Department of Energy (DOE) in the 1-hour TEEL values for EGME (level 0 for no adverse effects; level 1 for mild transient effects; level 2 for irreversible effects or impairment of ability to escape; and level 3 for potentially lethal effects). No details on the derivation of chemical-specific TEELs are provided.

The Occupational values for EGME focus more on repeated exposures, and vary over three orders of magnitude. The time-weighted average (TWA) NIOSH REL and ACGIH TLV values are equivalent, while the OSHA PEL is set at a considerably higher concentration. No ceiling or STEL values are available. NIOSH developed an IDLH of 200 ppm based on a factor of 2000 times the NIOSH REL of 0.1 ppm instead of the value of 400 ppm that would have been the independently derived basis. The factor of 2000 is an assigned protection factor for respirators; only the "most reliable" respirators are recommended above 2000 times the NIOSH REL (NIOSH, 1996, 192342). EGME is readily absorbed through the skin in amounts sufficient to elicit systemic toxicity, therefore, the “skin” notation is appropriately applied to all the occupational values (ACGIH, 2006, 192016).

There are both acute and chronic General Public reference values available for EGME. The acute CA-REL was based on developmental effects, which OEHHA deems to be a severe adverse effect level, and no mild adverse effect level was established. Also, no time scaling was applied to the 6-hour observations in deriving the acute CA-REL, hence the final value was for a 6-hour duration. The chronic EPA/IRIS RfC and CA-REL values were derived from the same study (Miller et al., 1983, 180119) and arrived at the same POD of 17 mg/m^3 (5.4 ppm), which was derived by adjustments to the observed NOAEL (30 ppm; 93 mg/m^3) at 6 hours per day, 5 days per week. The differences in the chronic General Public values are due to variation in the application of uncertainty factors.

EGME lacks a peer-reviewed set of Emergency Response values, and Occupational ceiling or short-term exposure limits. This is indicative that EGME has few immediately observable adverse health effects, and that most effects are due to an accumulation of effects from repeated exposures.

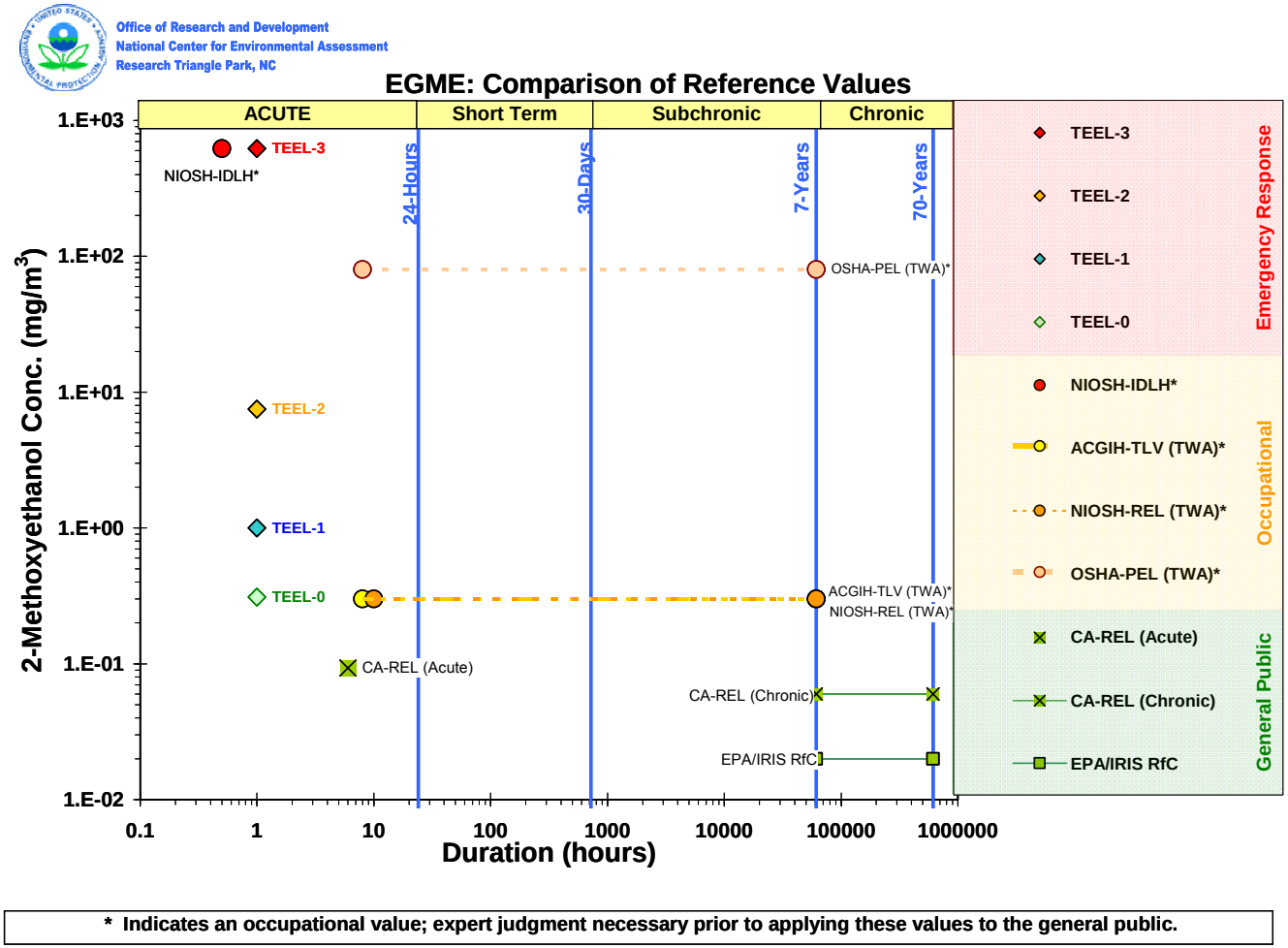

Figure 2.7. Comparison of Available Health Effect Reference Values for Inhalation Exposure to EGME

Table 2.7. Details on derivation of the specific inhalation health effect reference values for EGME.

Reference Value Type / Name		Duration	Reference Value (mg/m^3)	Reference Value (ppm)	Health Effect	Point of Departure		Uncertainty Factors	Notes on Derivation	Review Status
Emergency Response[1]	**TEEL-0**	1 hour	0.3	0.1	NR	NR	NR	NR		Final (DOE, 2008, 192182)
	TEEL-1	1 hour	1	0.35		NR	NR	NR		
	TEEL-2	1 hour	7.5	2.5		NR	NR	NR		
	TEEL-3	1 hour	622	200		NR	NR	NR		

[1] Emergency Response reference values are developed using an assumption of a rare, "once-in-a-lifetime" exposure scenario, which is a key consideration when comparing these reference values to any Occupational or General Public reference values.

Reference Value Type / Name		Duration	Reference Value (mg/m^3)	Reference Value (ppm)	Health Effect	Point of Departure		Uncertainty Factors	Notes on Derivation	Review Status
Occupational	**NIOSH-IDLH (<30 min) ***	< 30 minutes	622	200	Acute inhalation toxicity data (Union Carbide, 1969, 180239)	NR	NR	NR	2000 times NIOSH REL value	Final (NIOSH, 1996, 192342)
	ACGIH TLV-TWA*	8 hour TWA	0.3	0.1	Hematologic and reproductive toxicity (Hanley Jr et al., 1984, 180288; Hanley Jr et al., 1984, 180112; Nelson et al., 1984, 031878; Shih et al., 2003, 180246)	NR	NR	NR		Final (ACGIH, 2006, 192016)
	NIOSH-REL (TWA)*	10 hour TWA	0.3	0.1	NR	NR	NR	NR		Final (NIOSH, 2006, 192177)
	OSHA-PEL (TWA) *	8 hour TWA	80	25	NR	NR	NR	NR		Final (OSHA, 2006, 192188)

Reference Value Type / Name		Duration	Reference Value (mg/m^3)	Reference Value (ppm)	Health Effect	Point of Departure	Uncertainty Factors	Notes on Derivation	Review Status
General Public	**CA-REL (Acute)**	6 hour	0.09	0.03	Gross soft tissue and skeletal teratogenic effects and significantly decreased fetal body weights in rabbits (Hanley Jr et al., 1984, 180288)	3 ppm NOAEL	Total UF = 100 UF_A = 10 UF_H = 10	NOTE: CA-REL was developed for 6-hours and for "severe adverse effects"	Final (OEHHA, 2008, 192341)
	CA-REL (Chronic)	Chronic	0.06	0.02	Testicular effects (Miller et al., 1983, 180119)	5.4 ppm ($NOAEL_{HEC}$) (30 ppm x 6/24 x 5/7)	Total UF = 300 UF_S = 10 UF_A = 3 UF_H = 10	Adjusted NOAEL = 30 ppm (93 mg/m^3) for 6 hr/d ; and 5 d/wk	Final (OEHHA, 2000, 192222)
	Chronic RfC (IRIS)	Chronic	0.02	0.006		17 mg/m^3 ($NOAEL_{HEC}$) (93 mg/m^3 x 6/24 x 5/7)	Total UF = 1000 UF_S = 10 UF_H = 10 UF_D = 10		Final (U.S. EPA, 1991, 192218)

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2.8 Chemical-Specific Reference Values for Ethylene Oxide (CASRN 75-21-8)

Ethylene oxide (EtO; C_2H_4O) is a colorless, sweet smelling gas that is highly reactive at room temperature and pressure. It is rapidly absorbed in the lungs and is irritating to the eyes, respiratory tract, and skin; exposure to high concentrations may cause severe eye damage including corneal injury and cataracts. EtO can also cause dermal irritation. EtO is used commercially as a fumigant, sterilizer, disinfectant, and insecticide; and as an intermediate in the production of many industrial chemicals (HSDB, 2009, 192343). EtO is listed as carcinogenic in humans (Group 1) by IARC (IARC, 2008, 192126). Additional details are provided from multiple other sources (Agency for Toxic Substances and Disease, 1990, 018341; IARC, 2008, 192126; NAC/AEGL, 2008, 192205; OEHHA, 2000, 192224) on the chemical nature of and the health effects from exposure to ethylene oxide, and are not repeated here.

Available inhalation health effect reference values for EtO are displayed graphically in Figure 2.8. Details available on the derivation of these values, including key effects, studies, adjustments, and uncertainty factors (UFs) are shown in Table 2.8.

Emergency Response values (AEGLs and ERPGs) were developed for the two most severe categories (level 2 for irreversible effects or impairment of ability to escape; and level 3 for potentially lethal effects). A level 1 (mild transient effects) AEGL value is not available, as the lowest concentration causing irritation is above the AEGL-2 levels. As shown in Figure 2.8, the AEGL-2 and ERPG-2 values are very similar. The ERPG-3 value is higher than the corresponding 1-hr AEGL-3, however both are derived from the same study (Jacobson et al., 1956, 061930). The lack of detailed derivation information for the ERPGs precludes a more critical analysis of the differences between these Emergency Response values. Time scaling was applied to the AEGL-2 and -3 values using a $C^n \times t = k$ relationship where n = 1.2, which was derived from rat lethality data.

Several Occupational reference values are available for ethylene oxide. The NIOSH IDLH Occupational values are derived by a weight of evidence approach and no particular study was identified as the basis for the values. The NIOSH and OSHA ceiling values are equivalent, as are the time weighted average (TWA) OSHA PEL and ACGIH TLV. All of the Occupational values note the carcinogenic potential for EtO, as well as the potential for effects from dermal absorption and dermal effects ("skin" designation).

The availability of General Public reference values for ethylene oxide is limited. Currently, only an intermediate ATSDR MRL and a chronic CA-REL value exist. Both values use a NOAEL as the point of departure, which is then adjusted for exposures occurring 6 hours per day, 5 days per week. The chronic CA-REL was based on a subchronic study of neurotoxic effects in rats (Snellings et al., 1984, 018265), and the intermediate MRL was based on renal lesions in mice (NTP, 1987, 192179).

Inhalation health effect reference values for EtO are available across all three types of values (Emergency Response, Occupational and General Public). Coverage is relatively poor, however, for General Public values and the lowest severity of Emergency Response values. No acute value for the General Public is currently available, and coupled with the lack of Emergency Response values for the lowest severity level indicates a weak warning potential for irreversible effects. The TWA Occupational values are at relatively low concentrations in comparison to the Emergency Response values, and this is likely due to the concern for the potential for cancer

from repeated exposures. All of the Occupational values were established prior to the 2008 publication of the latest IARC Monograph on EtO (IARC, 2008, 192126).

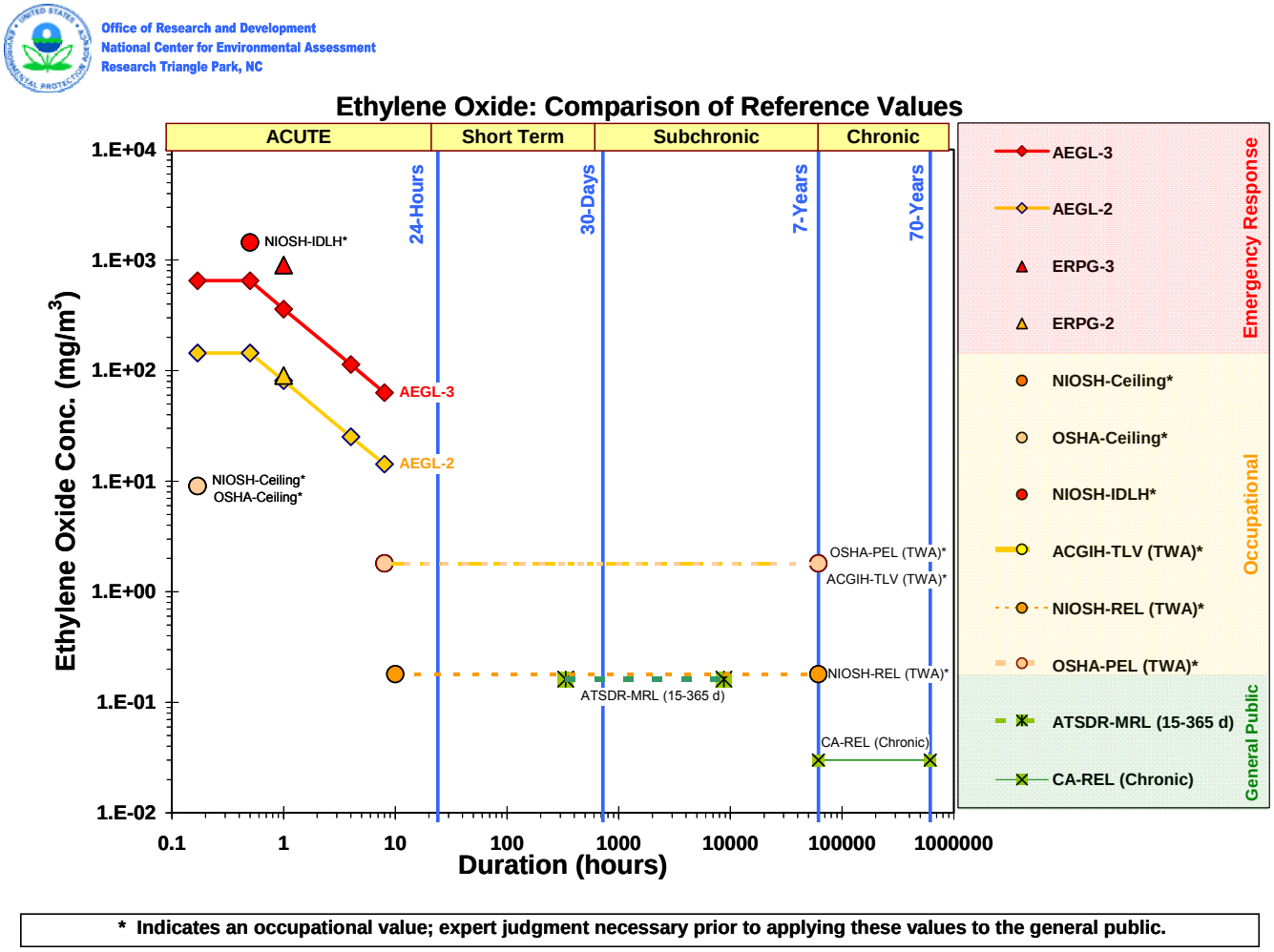

Figure 2.8. Comparison of Available Health Effect Reference Values for Inhalation Exposure to Ethylene Oxide

Table 2.8. Details on derivation of the specific inhalation health effect reference values for ethylene oxide.

Reference Value Type / Name		Duration	Reference Value (mg/m^3)	Reference Value (ppm)	Health Effect	Point of Departure	Uncertainty Factors	Notes on Derivation	Review Status
Emergency Response[1]	**AEGL-3**	10 min	648	360	Lethality in rats (Jacobson et al., 1956, 061930)	628 ppm (LC_{01}) (4 hrs)	Total UF = 10 UF_A = 3 UF_H = 3	Time scaling: $C^n \times t = k$ where n = 1.2, derived empirically	Interim (NAC/AEGL, 2008, 192205)
		30 min	648	360					
		1 hr	360	200					
		4 hr	113	63					
		8 hr	63	35					
	AEGL-2	10 min	144	80	Neurotoxicity in rats (Mandella, 1997, 088809; Snellings et al., 1982, 018541)	100 ppm (NOAEL) (6 hrs)	Total UF = 10 UF_A = 3 UF_H = 3		
		30 min	144	80					
		1 hr	81	45					
		4 hr	25	14					
		8 hr	14	7.9					
	ERPG-3	1 hr	900	500	Lethality in rodents (Jacobson et al., 1956, 061930)	533 ppm (LOAEL)	NR		Final (AIHA, 2002, 192064)

[1] Emergency Response reference values are developed using an assumption of a rare, "once-in-a-lifetime" exposure scenario, which is a key consideration when comparing these reference values to any Occupational or General Public reference values.

	ERPG-2	1 hr	90	50	Reproductive and developmental effects in rats (Hardin et al., 1983, 061926; Snellings et al., 1982, 018541)	100 ppm	NOAEL	NR		

Reference Value Type / Name		Duration	Reference Value		Health Effect	Point of Departure		Uncertainty Factors	Notes on Derivation	Review Status
			(mg/m^3)	(ppm)						
Occupational	**NIOSH-Ceiling***	10 min per day	9	5	NR	NR	NR	NR		Final (NIOSH, 2006, 192177)
	NIOSH-REL (TWA)*	10 hr TWA	0.18	0.1						
	NIOSH-IDLH*	< 30 min	1.4×10^3	800	Acute inhalation toxicity data in humans	NR	NR	NR		Final (NIOSH, 1996, 192280)
	OSHA-PEL (TWA) *	8 hr TWA	1.8	1	NR	NR	NR	NR		Final (OSHA, 2006, 192276)
	OSHA-Ceiling*	<15 min	9	5						
	ACGIH–TLV (TWA)*	8 hr TWA	1.8	0.1	Reproductive and hematological effects, cancer (Karelova et al., 1987, 192282)	NR	NR	NR		Final (ACGIH, 2001, 192015)
General Public	**ATSDR-MRL (15 – 365 days)**	15 d – 1 yr	0.16	0.09	Renal lesions (NTP, 1987, 192179)	8.9 ppm (50 ppm x 6/24 x 5/7)	$NOAEL_{ADJ}$	Total UF = 100 UF_A = 10 UF_H = 10	Adjustments for 6 hr/d; 5 d/wk	Final (Agency for Toxic Substances and Disease, 1990, 018341)
	CA-REL (Chronic)	Chronic	0.03	0.018	Impaired neurological function (Snellings et al., 1984, 018265)	1.79 ppm (10 ppm x 6/24 x 5/7)	$NOAEL_{HEC}$	Total UF = 100 UF_s = 3 UF_A = 3 UF_H = 10	Adjustments for 6 hr/d; 5 d/wk; and RGDR = 1.0	Final (OEHHA, 2000, 192224)

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2.9 Chemical-Specific Reference Values for Formaldehyde (CASRN 50-00-0)

Formaldehyde (CH_2O) is a colorless flammable gas with a pungent, suffocating odor. It is ubiquitous in the ambient environment (a constituent of smog), in indoor air (homes that contain urea-formaldehyde foam insulation, particle board construction, carpeting, etc.), and at industrial sites (NAC/AEGL, 2008, 192206). Formaldehyde is a constituent of many foods and is a normal metabolite in the human body. Much more detail can be found on the toxicological effects and chemical nature of formaldehyde in other sources (AIHA, 1978, 192033; Agency for Toxic Substances and Disease Registry, 1999, 093087; NAC/AEGL, 2008, 192206; NICNAS, 2006, 192040; NIOSH, 1976, 192344; NIOSH, 1996, 192345; OEHHA, 2008, 192346), and is not repeated here. The remainder of the discussion in this document focuses on the development and use of the available inhalation health effect reference values for formaldehyde.

The primary effect during acute and short term inhalation exposure to formaldehyde is irritation to the eyes, nose and throat (OEHHA, 2008, 192346). Prolonged low-level exposures are associated with allergic sensitization, respiratory symptoms (coughing, wheezing and shortness of breath), changes in respiratory tissues, and decreases in lung function. Long-term, moderate-level exposures have been found to be carcinogenic in the respiratory tract of experimental animals.

Figure 2.9 provides a graphical array of the available inhalation health effect reference values for formaldehyde. Types of reference values (Emergency Response, Occupational and General Public), levels of severity of effect (e.g., AEGL and ERPG levels 1, 2 and 3), and across duration categories (acute, short-term, subchronic, and chronic) are all provided in this array. Additional details on the basis and derivation of the individual reference values is provided in Table 2.9.

Emergency Response reference values for formaldehyde include both AEGL and ERPG values. The AEGL values for formaldehyde are largely in agreement with those of the ERPGs, with the ERPG-3 being somewhat lower than and the ERPG-1 being somewhat higher than the corresponding one-hour AEGL values. The AEGL program also developed an estimate of the concentration at which there is a level of distinct odor awareness at 3.6 ppm, although it is also noted that most individuals will notice but not necessarily be able to identify the distinct, pungent odor of formaldehyde at the AEGL-1. According to the AEGL SOPs (NRC, 2001, 192042), unless data provide a reason to do otherwise, low level irritation is assumed to be more concentration-dependent and therefore there is no time scaling across the 10-minute to 8-hour duration span for those values – most commonly applied to the AEGL-1. In the case of formaldehyde, there was no time scaling for the AEGL-1 or for the AEGL-2 due to the endpoint of eye and nose irritation to which adaptation occurs.

There is quite a large range in the Occupational reference values, with more than an order of magnitude range between the lowest ceiling value (NIOSH Ceiling) and the highest STEL (OSHA STEL), and a similar spread between the TWA values. The occupational values from Australia are also included in this array of values, which are somewhat in the middle of the range of both the short-term and TWA values. In the discussions supporting the occupational values, one of the considerations that likely drive these disparities is the weight given to the cancer potential from repeated long-term exposures to formaldehyde. As often found with other chemicals, details on the basis and derivation of the occupational values for formaldehyde are

somewhat lacking and it can be surmised that a weight of evidence approach was used in establishing the values.

A full set of formaldehyde reference values for the General Public are also available, with values developed for every duration category. The ATSDR developed formaldehyde MRLs for all of their duration categories (acute, 1-14 days; intermediate, 15 days to one year; and chronic, greater than one year). These values do not consider cancer potential and show a fairly shallow stair step decrease in concentration when going from the acute to chronic values, with the smallest step down in going from the acute to intermediate values. The CA-RELs also step down concentrations from short- to long-term durations of exposure, but with the largest decrease between the one-hour acute and 8-hour value – the chronic CA-REL is the same as the 8-hour value. An additional general public value is the WHO Air Quality Guideline, which was developed for a 30 minute exposure. The WHO value is in line with what might be expected in a progression when going from an eight-hour, to a one-hour CA-REL, to a 30-minute WHO Guideline. Although copious details were provided on the basis and derivation of the CA-REL and ATSDR MRL values, only a weight of evidence (WOE) approach could be discerned as the basis for the WHO value.

IARC (2006) had a finding that "formaldehyde is carcinogenic to humans (Group 1)" based on "sufficient evidence in humans for the carcinogenicity of formaldehyde" and "sufficient evidence in experimental animals for the carcinogenicity of formaldehyde."

Overall, the coverage of reference values for formaldehyde was quite good across all categories (types of value, severity of effect, and duration). This is tempered; however, with the uneven comparability between the occupational reference values and the acute and short-term general public values. There was fair concordance between the ATSDR and CA-REL chronic values. There is a large and deep set of data on formaldehyde that included a substantial amount of data from human exposures, which lead to the use of relatively low uncertainty factors for those reference values which reported UFs.

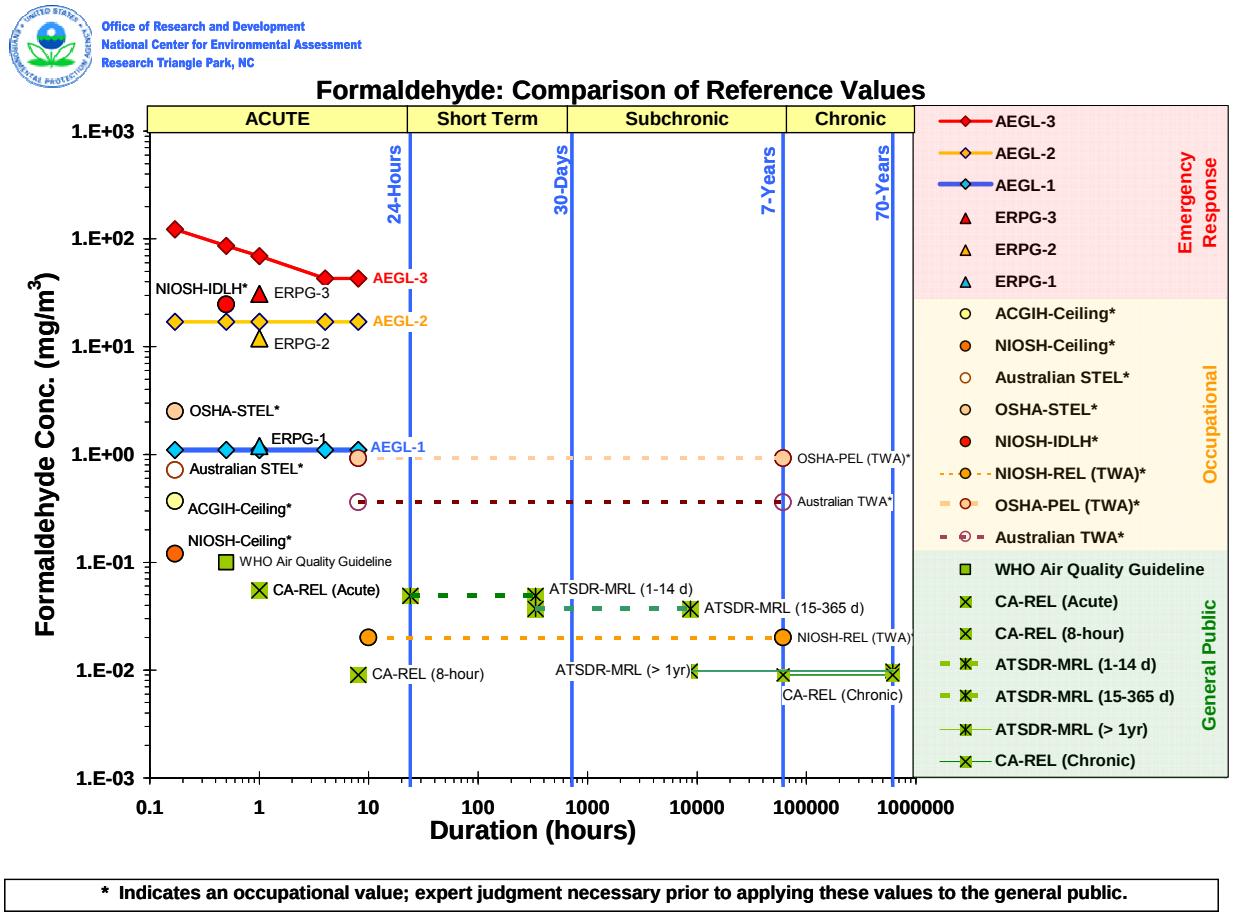

Figure 2.9. Comparison of Available Health Effect Reference Values for Inhalation Exposure to Formaldehyde

Table 2.9. Details on derivation of the specific inhalation health effect reference values for formaldehyde.

Reference Value Type / Name		Duration	Reference Value (mg/m^3)	Reference Value (ppm)	Health Effect	Point of Departure		Uncertainty Factors	Notes on Derivation	Review Status
Emergency Response[1]	**AEGL-3**	10 min	123	100	Lethality (Nagorny et al., 1979, 193928)	350 ppm (4 hr)	LC_{01}	Total UF = 10 UF_A = 3 UF_H = 3	Time scaling: $C^n \times t = k$ where n = 3 for shorter and n = 1 for longer durations	Interim (NAC/AEGL, 2008, 192206)
		30 min	86	70						
		1 hr	69	56						
		4 hr	43	35						
		8 hr	43	35						
	AEGL-2	10 min	17	14	Nose and eye irritation, lacrimation (Sim and Pattle, 1957, 071236)	13.8 ppm	Threshold for effects	Total UF = 1 (human data)	Time scaling not applied	
		30 min	17	14						
		1 hr	17	14						
		4 hr	17	14						
		8 hr	17	14						
	AEGL-1	10 min	1.1	0.9	Eye irritation (Bender et al., 1983, 180100)	0.9 ppm	NOAEL	Total UF = 1 (human data)	Time scaling not applied	
		30 min	1.1	0.9						
		1 hr	1.1	0.9						
		4 hr	1.1	0.9						
		8 hr	1.1	0.9						
	ERPG-3	1 hr	30.7	25	Severe respiratory irritation, pulmonary edema, and death possible for humans	≥ 25 ppm (1 hr)	Threshold for effects	NR		Final (AIHA, 2002, 192056)
	ERPG-2	1 hr	12	10	Eye, nasal, and throat irritation	10 ppm	Threshold for effects	NR		
	ERPG-1	1 hr	1.2	1.0	Detectable objectionable odor	1 ppm	Threshold for effects	NR		

[1] Emergency Response reference values are developed using an assumption of a rare, "once-in-a-lifetime" exposure scenario, which is a key consideration when comparing these reference values to any Occupational or General Public reference values.

Reference Value Type / Name		Duration	Reference Value (mg/m^3)	Reference Value (ppm)	Health Effect	Point of Departure		Uncertainty Factors	Notes on Derivation	Review Status
Occupational	**ACGIH–Ceiling***	Any	0.37	0.3	Respiratory and eye irritation; cancer	NR	Threshold for effects	NR		Final (ACGIH, 2007, 192024)
	NIOSH–Ceiling*	15 min	0.12	0.10	See NIOSH REL (TWA), below	NR	NR	NR		Final (NIOSH, 1976, 192344)
	Australian STEL*	10 min	0.72	0.59	NR	NR	NR	NR		Proposed (NICNAS, 2006, 192040)
	Australian TWA*	8 hr TWA	0.36	0.29		NR	NR	NR		
	OSHA-PEL (TWA) *	8 hr TWA	0.92	0.75	Respiratory and eye irritation, and cancer potential	NR	NR	NR		Final (OSHA, 1992, 192349)
	OSHA-STEL*	10 min	2.46	2.0						
	NIOSH-IDLH*	< 30 min	24.6	20	• Upper airway irritation, increased nasal and lower airway resistance • chronic pulmonary obstruction (Eastman Kodak Company, 1963, 192350; IARC, 1982, 192124; National Research, 1981, 026996)	0.1 to 25 ppm	Threshold for effects	NR		Final (NIOSH, 1996, 192345)
	NIOSH-REL (TWA)*	10 hr TWA	0.0197	0.016		5 to 30 ppm		NR		Final (NIOSH, 1976, 192344)

Reference Value Type / Name		Duration	Reference Value (mg/m^3)	Reference Value (ppm)	Health Effect	Point of Departure		Uncertainty Factors	Notes on Derivation	Review Status
General Public	**WHO Air Quality Guideline**	30 min	0.1	0.081	Nose and throat irritation in humans	0.1 mg/m^3	WOE	NR	Weight of evidence approach	Final (WHO, 2000, 180143)
	CA-REL (Acute)	1 hr	0.055	0.05	Mild and moderate eye irritation in humans (Kulle et al., 1987, 023225)	0.44 ppm	$BMCL_{05}$ (Log-probit)	Total UF = 10 UF_H : 10 TK = 1, TD = 10		Final (OEHHA, 2008, 192346)
	CA-REL (8-hr)	8 hr	9×10^{-3}	7.3×10^{-3}	Nasal obstruction and discomfort, lower airway discomfort, eye irritation (Wilhelmsson and Holmstrom, 1992, 180138)	0.09 mg/m^3	NOAEL (8 hr)			
	ATSDR-MRL (1-14 d)	1 - 14 d	0.05	0.04	Nasal and eye irritation (Pazdrak et al., 1993, 006631)	0.4 ppm	LOAEL	Total UF = 10 UF_L = 3 UF_H = 3		Final (Agency for Toxic Substances and Disease Registry, 1999, 093087)
	ATSDR-MRL (15-365 d)	15 d – 1 yr	0.037	0.03	Naso-pharyngeal irritation and nasal epithelium lesions in monkeys (Rusch et al., 1983, 063803)	0.98 ppm	NOAEL	Total UF = 30 UF_A = 3 UF_H = 10		
	ATSDR-MRL (> 1yr)	Chronic	9.8×10^{-3}	8×10^{-3}	Eye and respiratory tract irritation (Holmstrom et al., 1989, 003564)	0.24 ppm	LOAEL	Total UF = 30 UF_L = 3 UF_H = 10		
	CA-REL (Chronic)	Chronic	9×10^{-3}	7.3×10^{-3}	Nasal obstruction and discomfort, lower airway discomfort, eye irritation (Wilhelmsson and Holmstrom, 1992, 180138)	0.09 mg/m^3	NOAEL	Total UF = 10 UF_H : 10 TK = 1, TD = 10		Final (OEHHA, 2008, 192346)

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2.10 Chemical-Specific Reference Values for Soman (Agent GD) and Cyclosarin (Agent GF) (CASRN 96-64-0 and 329-99-7)

Soman (Agent GD; pinacolyl methylphosphonofluoridate; CAS Registry No. 96-64-0) and Cyclosarin (Agent GF; O-cyclohexylmethyl-fluorophosphonate; CAS Registry No. 329-99-7) are organophosphate (OP) nerve agents that have been specifically designed and formulated to cause death, major injuries, or incapacitation to enemy forces in wartime. The term "nerve" agent refers to its anti-cholinesterase properties. Nerve agents are particularly effective in a military sense because of their potency. Detailed descriptions of nerve agent toxicity as well as the physical nature of this chemical agent can be found in the AEGL Technical Support Document (NAC/AEGL, 2003, 192304), and are not repeated here.

There are only two sources of health effect reference values for the chemical warfare agents GD and GF: the National Advisory Committee for Acute Exposure Guideline Levels (2003, 192304) and the US Army (CDC, 2002, 192175). Both organizations determined that these agents were equally toxic, on a mg/m^3 basis, and derived values that were the same for both agents. The same limited set of data was used for deriving values for GD and GF; however, the dataset for GB was the most robust of all of the nerve agents for which values were derived, and the relative potency of the nerve agents Tabun (GA), GD, GF, and VX to Sarin (GB) was used to derive values for those other nerve agents.

The only Emergency Response reference values available for GD and GF are the AEGLs. AEGL-3 values for GD and GF were derived based on a calculated lethality at the one percent level (LC_{01}) in female rats using observations at 10-, 30-, 60-, 240-, and 360-minutes. Studies showing miosis (pinpoint pupils) in female rats (Mioduszewski et al., 2002, 192189) and visual acuity effects in humans (Baker and Sedgewick, 1996, 180099) were the basis for the AEGL-1 and AEGL-2, respectively. For the AEGL-1, a UF_A of 1 was used based on the observation that miosis response to GB vapors is similar across mammalian species.

A Federal Register Notices published by the Centers for Disease Control and Prevention (CDC, 2002, 192175) documents the Airborne Exposure Levels proposed by the US Army for application to the agents GA, GB, GD, GF, and VX, for the protection of workers at chemical weapon decommissioning facilities and the general population living near those facilities. The CDC determined that due to the fact that GD and GF were "*not part of the U.S. stockpile, and neither transportation nor open-air testing is being considered for these agents*," that they would not adopt values for those agents as part of the program for those applications; however, the U.S. Army has since used those proposed values in their guidance documents (USACHPPM, 2003, 192131).

The Airborne Exposure Level values for GD and GF include a General Population Limit (GPL), a Worker Population Limit (WPL), as well as a Short-term Exposure Limit (STEL) and Immediately Dangerous to Life and Health (IDLH) occupational values. The GPL and WPL values for GB were based on exposures of 20 minutes per day for 4 days per week and were adjusted to derive a Lowest Observable Adverse Effect Level Human Equivalent Concentration ($LOAEL_{HEC}$) for 24 hour and 8 hour time weighted averages (TWAs), respectively. Fewer details were provided in the derivation of the STEL and IDLH values, and it is assumed that a weight of evidence approach was used in their derivation.

The resulting GD and GF values for both the AEGL and the CDC are shown in Figure 2.10 and Table 2.10. More recent research by the U.S. Army provides additional data that may lead to further revision of both sets of values (Dabisch et al., 2008, 192038).

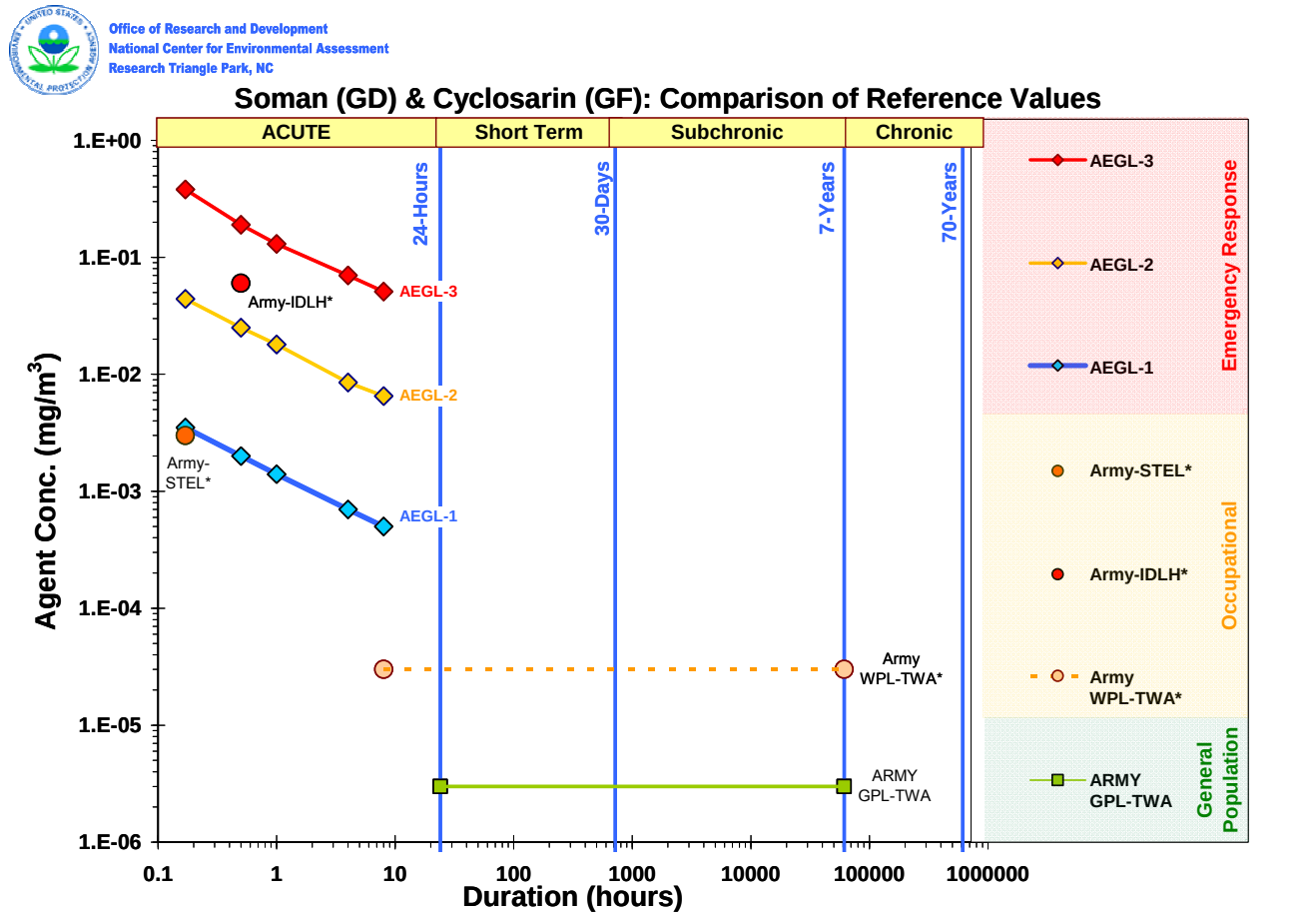

Figure 2.10. Comparison of Available Health Effect Reference Values for Inhalation Exposure to Soman (GD) and Cyclosarin (GF)

Table 2.10. Details on derivation of the specific inhalation health effect reference values for GD and GF.

Reference Value Type / Name		Duration	Reference Value[1] (mg/m^3)	Reference Value[1] (ppm)	Health Effect	Point of Departure		Uncertainty Factors	Notes on Derivation	Review Status
Emergency Response[2]	**AEGL-3**	10 min	0.38	0.049	Lethality (Aas et al., 1985, 180091; Anthony et al., 2002, 192037; Mioduszewski et al., 2000, 192305; Mioduszewski et al., 2001, 192306; Mioduszewski et al., 2002, 180121)	11.54 mg/m^3	LC_{01} (female rats)	Total UF = 30 UF_A = 3 UF_H = 10	Potencies of GD and GF are equal to that of GB for lethality	Final (NAC/AEGL, 2003, 192304)
		30 min	0.19	0.025		5.84 mg/m^3				
		1 hr	0.13	0.017		4.01 mg/m^3				
		4 hr	0.07	9.1×10^{-3}		2.09 mg/m^3				
		8 hr	0.051	6.6×10^{-3}		1.76 mg/m^3 (6 hr)				
	AEGL-2	10 min	0.044	5.7×10^{-3}	Miosis, dyspnea, photophobia, and inhibition of RBC-ChE seen in humans (Baker and Sedgewick, 1996, 180099)	0.5 mg/m^3 (30 min)	Sub-clinical effects	Total UF= 10 UF_A = 1 UF_H = 10	Potencies of GD and GF are approximately twice that of GB and GA for AEGL-2 effects	
		30 min	0.025	3.3×10^{-3}						
		1 hr	0.018	2.2×10^{-3}						
		4 hr	8.5×10^{-3}	1.2×10^{-3}						
		8 hr	6.5×10^{-3}	8.5×10^{-4}						
	AEGL-1	10 min	3.5×10^{-3}	4.6×10^{-4}	Induction of miosis in female rat (Harvey, 1952, 192174; Johns, 1952, 192313; Mioduszewski et al., 2002, 192189; van Helden et al., 2001, 180238)	Range of 0.01-0.48 mg/m^3 at 10 min, 60 min, and 240 min	EC_{50} for miosis	Total UF= 10 UF_A = 1 UF_H = 10	Potencies of GD and GF are approximately twice the potency of agents GB and GA for AEGL-1 effects	
		30 min	2.0×10^{-3}	2.6×10^{-4}						
		1 hr	1.4×10^{-3}	1.8×10^{-4}						
		4 hr	7.0×10^{-4}	9.1×10^{-5}						
		8 hr	5.0×10^{-4}	6.5×10^{-5}						

[1] Reference values for GD and GF were derived on a mg/ m^3 equivalance. The values shown in units of parts per million (ppm) were those reported in the AEGL Technical Support Document, with the values for GD shown first (top). Values in ppm were not derived for the values used by the Army (CDC, 2002).

[2] Emergency Response reference values are developed using an assumption of a rare, "once-in-a-lifetime" exposure scenario, which is a key consideration when comparing these reference values to any Occupational or General Public reference values.

Reference Value Type / Name		Duration	Reference Value[1] (mg/m^3)	Reference Value[1] (ppm)	Health Effect	Point of Departure		Uncertainty Factors	Notes on Derivation	Review Status
Occupational	**Army IDLH***	30 min	0.05	NR	NR	NR	NR	NR		Final (CDC, 2002, 192175; NAC/AEGL, 2003, 192304; USACHPPM, 2003, 192131)
	Army STEL*	15 min	1 x 10^{-3}	NR						
	Army WPL-TWA*	8 hr TWA	3 x 10^{-5}	NR	Miosis (McKee and Woolcott, 1949, 192172)	0.06 mg/m^3 (20 min/d, for 4 days)[3]	$LOAEL_{HEC}$	Total UF = 30 UF_S = 10 UF_L = 3	Values derived based on relative potency to Agent GB (Sarin), with GD and GF twice as potent as GB on a mg/m^3 basis. Adjusted for duration and breathing rate – details not provided.	
General Population	**Army GPL-TWA***	24 hr TWA	1 x 10^{-6}	NR				Total UF = 300 UF_L = 3 UF_S = 10 UF_H = 10		

[3] The POD value shown is that for GB (Sarin), details on the adjustments for duration and breathing rate were not provided.

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2.11 Chemical-Specific Reference Values for Hydrogen Cyanide (CASRN 74-90-8)

Hydrogen cyanide (HCN) is a colorless, rapidly acting, highly poisonous gas or liquid that has an odor of bitter almonds. Most HCN is used as an intermediate at the site of production. Major uses include the manufacture of nylons, plastics, and fumigants (NRC, 2002, 192138). The acute dose-effect curve in humans is steep (NLM, 2008, 192348). HCN is well absorbed via the gastrointestinal tract or skin, and rapidly absorbed via the respiratory tract. HCN is rapidly and ubiquitously distributed throughout the body, with the highest levels typically found in the liver, lungs, blood, and brain; however, there is no accumulation following chronic or repeated exposure. Approximately 80% of absorbed HCN is metabolized to thiocyanate in the liver and excreted in the urine. Additional information on the nature of HCN and detailed summaries of health effects can be found in other sources (NLM, 2008, 192348; NRC, 2002, 192138; U.S. EPA, 1994, 192351) and is not repeated here.

Figure 2.11 presents a graphical array of the available inhalation health effect reference values for HCN. Details are provided in Table 2.11, including the key effects, studies, adjustments, uncertainty factors (UFs), and other information useful in reconstructing the derivation of these reference values.

The Emergency Response values (AEGLs and ERPGs) are in close agreement to one another, although the ERPG levels 2 and 3 are slightly elevated in comparison to the comparable AEGLs. An AEGL-1 was derived, but the ERPG committee did not believe the available information allowed for derivation of an ERPG-1. The time scaling performed in deriving the AEGL-3 and AEGL-2 values utilized the data from the respective key studies to calculate separate slope factors (value of n) to be applied in the $C^n \times t$ formula, as outlined in the AEGL Standing Operating Procedures (SOPs) (NRC, 2001, 192042). The data in support of the AEGL-1 values, however, did allow for calculation of a separate duration slope factor, and the default n value of 3 was applied to the 8 hour data to derive values for shorter durations, also as outlined in the AEGL SOPs. Additional details used in deriving the AEGLs are provided in the Technical Support Document for HCN (NRC, 2002, 192138). The details provided in the ERPG documentation (AIHA, 2002, 192063) indicated that a weight of evidence approach was applied for both the ERPG-2 and ERPG-3 values, with a route equivalent adjustment from intravenous injection to inhalation exposure performed for the ERPG-2 (details not provided).

Details on derivation were also lacking for most of the Occupational reference values, with most of the more detailed documentation (ACGIH, 2007, 192024; NIOSH, 2006, 192177) indicating that a weight of evidence approach was taken. The OSHA PEL value was based on a previously available ACGIH TLV (TWA) value that has since been replaced.

Both of the chronic General Public reference values used the same point of departure from the same study, and performed the same human equivalent concentration (HEC) adjustments; the differences in the values are due solely to application of different uncertainty factors. The acute CA-REL was based on a study with observations at 30 minutes, and to adjust to the one hour target application of the classic Haber's rule (ten Berge et al., 1986, 025664) was applied using a straight $C \times t$ relationship (see discussion on AEGL values, above), which is in keeping with the recommendations from the NRC in deriving AEGL values (2001, 192042).

Overall, the slate of inhalation reference values for HCN should provide adequate information for most foreseeable applications. No obvious gaps are evident.

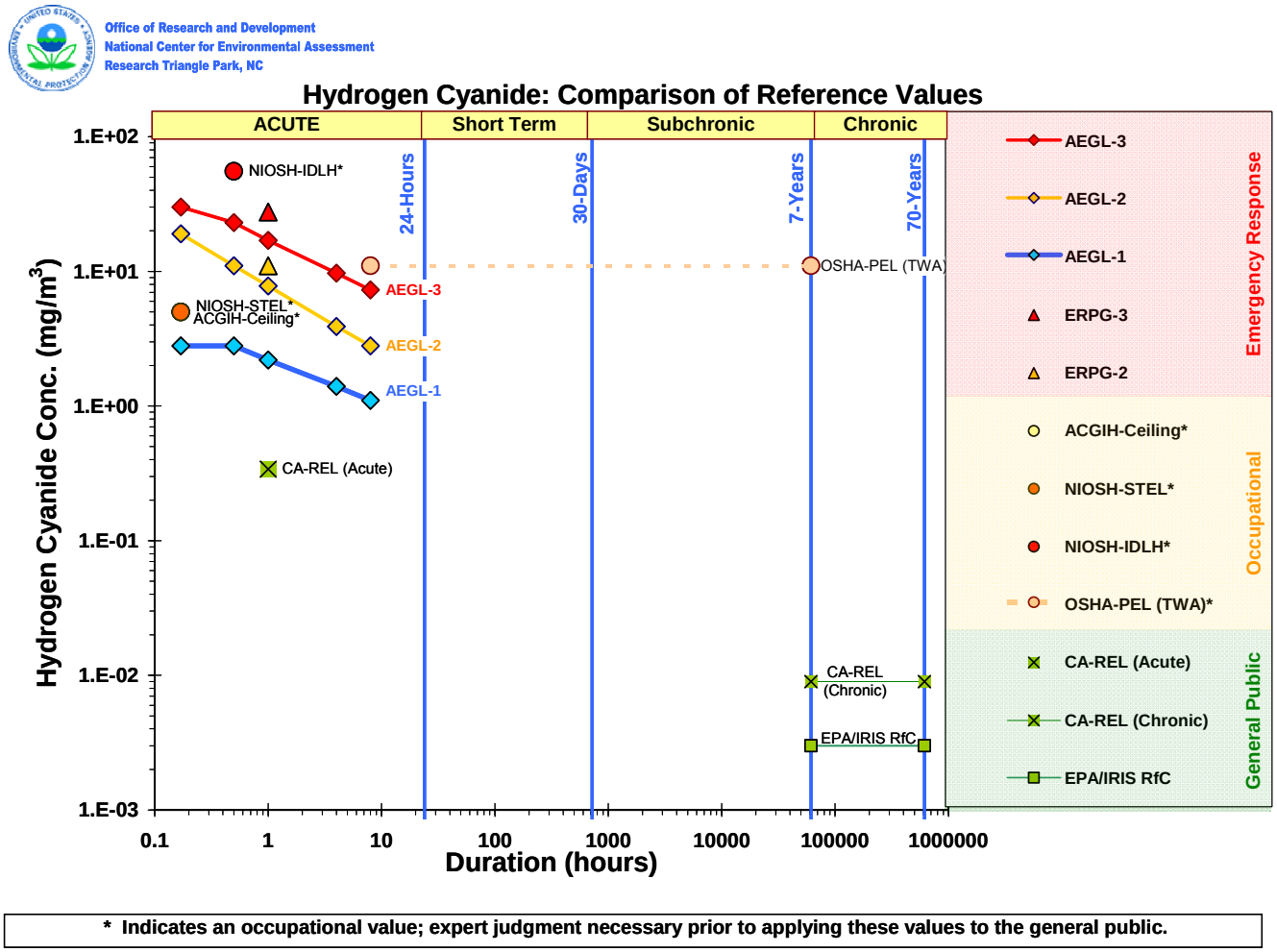

Figure 2.11. Presntation of Available Health Effect Reference Values for Inhalation Exposure to Hydrogen Cyanide

Table 2.11. Details on derivation of the specific inhalation health effect reference values for hydrogen cyanide.

Reference Value Type / Name		Duration	Reference Value (mg/m^3)	Reference Value (ppm)	Health Effect	Point of Departure	Uncertainty Factors	Notes on Derivation	Review Status
Emergency Response[1]	**AEGL-3**	10 min	30	27	Lethality in rats (DuPont, 1981, 192211)	138 ppm (LC_{01}) (15 min) 127 ppm (30 min) 88 ppm (60 min)	Total UF = 6 UF_A = 2 UF_H = 3	Time scaling: $C^n \times t = k$ where n = 2.6, derived from the key study.	Final (NRC, 2002, 192138)
		30 min	23	21					
		1 hr	17	15					
		4 hr	9.7	8.8					
		8 hr	7.3	6.6					
	AEGL-2	10 min	19	17	Slight CNS depression in monkeys (Purser et al., 1984, 094953)	60 ppm (30 min) NOAEL	Total UF = 6 UF_A = 2 UF_H = 3	Time scaling: $C^n \times t = k$ where n = 2, derived from the effect level data in key study.	
		30 min	11	10					
		1 hr	7.8	7.1					
		4 hr	3.9	3.5					
		8 hr	2.8	2.5					
	AEGL-1	10 min	2.8	2.5	Absence of severe health effects (El Ghawabi et al., 1975, 064697; Hardy et al., 1950, 180113) (Grabois, 1954, 192212)(Maehly and Swensson, 1970, 193929); (Leeser et al., 1990, 192352)	1 ppm (8 hour) NOAEL	None, as 1 ppm is the lowest NOAEL for a chronic occupational study (Leeser et al., 1990)	Time scaling: $C^n \times t = k$ where n = 3, protective for extrapolating from an 8 hr exposure	
		30 min	2.8	2.5					
		1 hr	2.2	2					
		4 hr	1.4	1.3					
		8 hr	1.1	1					
	ERPG-3	1 hr	28	25	Only transient effects with exposures to 45-50 ppm	NR NR	NR		Final (AIHA, 2002, 192063)

[1] Emergency Response reference values are developed using an assumption of a rare, "once-in-a-lifetime" exposure scenario, which is a key consideration when comparing these reference values to any Occupational or General Public reference values.

Reference Value Type / Name		Duration	Reference Value (mg/m^3)	Reference Value (ppm)	Health Effect	Point of Departure		Uncertainty Factors	Notes on Derivation	Review Status
					(Flury and Zernik, 1931, 059306; Lehmann, 1903, 192353; Parmenter, 1926, 180125)					
	ERPG-2	1 hr	11	10	No severe effects in humans with intravenous sodium cyanide (0.11 mg/kg) (Wexler et al., 1947, 180224)	10 ppm (route to route equiv-alent)	NOAEL	NR		
Occupational	**ACGIH–Ceiling***	Any	5	4.7	Throat irritation, headache, thyroid enlargement (El Ghawabi et al., 1975, 064697; NIOSH, 1997, 192347; Wolfsie and Shaffer, 1959, 180140)	NR	NR	NR		Final (ACGIH, 2007, 192024)
	OSHA-PEL (TWA) *	8 hr TWA	11	10	NR	NR	NR	NR	Based on previous ACGIH-TLV	Final (NIOSH, 2006, 192177))
	NIOSH-STEL*	10 min	5	4.7	Lethal or life-threatening health effects (Flury and Zernik, 1931, 059306)	45 - 54 ppm (30 min-1 hr)	NOAEL	NR		Final (NIOSH, 1996, 192356)
	NIOSH-IDLH (<30 min) *	< 30 min	55	50			NR	NR		
General Public	**CA-REL (Acute)**	1 hr	0.34	0.3	CNS depression/ incapacitation in monkeys (Purser, 1984, 064725; Purser et al., 1984, 094953)	34 mg/m^3 ($68\ mg/m^3$ x 30/60 min)	$NOAEL_{ADJ}$	Total UF = 100 UF_A = 10 UF_H = 10	Time scaling from 30 min to 1 hr using straight C × t	Final (OEHHA, 2008, 192355)

Reference Value Type / Name		Duration	Reference Value		Health Effect	Point of Departure		Uncertainty Factors	Notes on Derivation	Review Status
			(mg/m^3)	(ppm)						
	CA-REL (Chronic)	Chronic	9×10^{-3}	8.1×10^{-3}	CNS effects, thyroid enlargement, hematological disorders in humans (El Ghawabi et al., 1975, 064697)	2.5 mg/m^3 (7.1 mg/m^3 × 10/20 × 5/7)	$LOAEL_{HEC}$	Total UF = 300 $UF_L = 10$ $UF_S = 3$ $UF_H = 10$	Adjustments for breathing rate 10 m^3 (worker) vs. 20 m^3 (avg) breathing rate, and 5 day/wk schedule	Final (OEHHA, 2000, 192354)
	Chronic RfC (IRIS)	Chronic	3×10^{-3}	2.7×10^{-3}	CNS symptoms and thyroid effects in humans (El Ghawabi et al., 1975, 064697)	2.5 mg/m^3 (7.1 mg/m^3 × 10/20 × 5/7)	$LOAEL_{HEC}$	Total UF = 1000 $UF_H = 10$ $UF_L = 10$ $UF_{DB} = 3$ $UF_S = 3$		Final (U.S. EPA, 1994, 192351)

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2.12 Chemical-Specific Reference Values for Hydrogen Fluoride (CASRN 7664-39-3)

Hydrogen fluoride (HF) is a colorless, corrosive gas or liquid with a strong, irritating odor. It is used commercially in the production of herbicides, aluminum, plastics, fluorescent light bulbs, and pharmaceuticals; as a catalyst in the petroleum alkylation process; and in the production of fluorocarbons which are used broadly as refrigerants. The largest sources of human exposure to HF are from aluminum production plants, phosphate fertilizer plants, and the combustion of fluoride containing materials, notably coal. Chemical, steel, magnesium, and brick production processes also emit HF. Hydrogen fluoride is designated a hazardous air pollutant (HAP) under the Clean Air Act Amendments of 1990. Additional information on the nature of HF and detailed summaries of health effects can be found in the AEGL TSD (NRC, 2004, 192143), the ATSDR Toxicological Profile (ATSDR, 2003, 192114), the OEHHA REL documentation (OEHHA, 2003, 192228; OEHHA, 2008, 192290), and other sources and is not repeated here.

Hydrogen fluoride has a relatively complete range of inhalation health effect reference values, which are displayed graphically in Figure 2.12. Details available on the derivation of these values, including key effects, studies, adjustments, and uncertainty factors (UFs) are shown in Table 2.12.

Emergency Response AEGL and ERPG values were developed for all three severity levels (level 1 for mild transient effects; level 2 for irreversible effects or impairment of ability to escape; and level 3 for potentially lethal effects). ERPG values were not only derived for one hour durations, as customary, but 10 minute values were also developed in an addendum (AIHA, 2002, 192090). As shown in Figure 2.12, the one hour and 10 minute AEGL-3 values are very similar to the corresponding ERPG-3 values, while the ERPG-2 values are slightly lower and the ERPG-1 values are slightly higher than the corresponding AEGL values. The nature of this difference is difficult to assess because fewer details are provided for the derivation of the ERPGs than is provided for the AEGLs. Time-scaling was applied to both the AEGL-2 and AEGL-3 values using a $C^n \times t = k$ relationship where n = 2 [derived from empirical data on lethality, see the AEGL TSD for details (NRC, 2004, 192143)] for durations up to 1-hr. The 8-hr AEGL-2 and AEGL-3 values were set equal to the 4-hr values to avoid inconsistencies with study data.

The NIOSH IDLH Occupational values are derived by a weight of evidence approach. Observations that 50 ppm may be fatal when inhaled for a period of 30 to 60 minutes (Deichmann and Gerarde, 1969, 009221), and studies with human volunteers exposed to concentrations as high as 4.7 ppm for 6 hours per day for 10 to 50 days being tolerated without severe adverse effects (Largent, 1961, 066345) served to bracket the recommended value of 25 ppm. As displayed in Figure 2.12, all of the time-weighted average (TWA) Occupational values (the ACGIH TLV, OSHA PEL, and NIOSH REL) for HF are equivalent. In contrast, the ACGIH and NIOSH ceiling values diverge by a factor of 3, with the NIOSH value being higher; however, the level of detail provided in the support documents was not adequate to assess the basis for these differences.

Two acute General Public reference values are available for HF – an acute CA-REL and an acute ATSDR MRL. Both organizations use the same study (Lund et al., 1997, 180115) to derive their reference values with the major differences in derivation of values relating to the determination of the point of departure (POD) and the application of UFs. OEHHA determined that the high end of the range of exposures was a NOAEL and applied a total UF of 10 for inter-individual variability. ATSDR determined that the midpoint of the same range of exposures was a minimal LOAEL and applied an additional UF of 3 to account for that. The chronic CA-REL was derived from a subchronic occupational study that was adjusted to account for exposure occurring 8 hours per day, 5 days per week, which is effectively implying that Haber's rule ($C \times t = k$) applies in these types of adjustments. An UF of 10 was applied for inter-individual variability to arrive at a final chronic CA-REL.

In looking across the entire collection of HF reference values, there is a strong concordance seen within the emergency response and occupational values, especially in looking at the three TWA occupational values, which all have the same value. The acute MRL is nearly identical to the chronic CA-REL, despite the difference in duration, while the acute CA-REL is an order of magnitude higher concentration than the acute MRL. Differences in the determination of the POD and application of UFs are largely responsible for these differences in the general public values. It should be noted, however, that the acute and chronic CA-REL values are consistent with one another in derivation and are in general keeping with expectations for differences across durations.

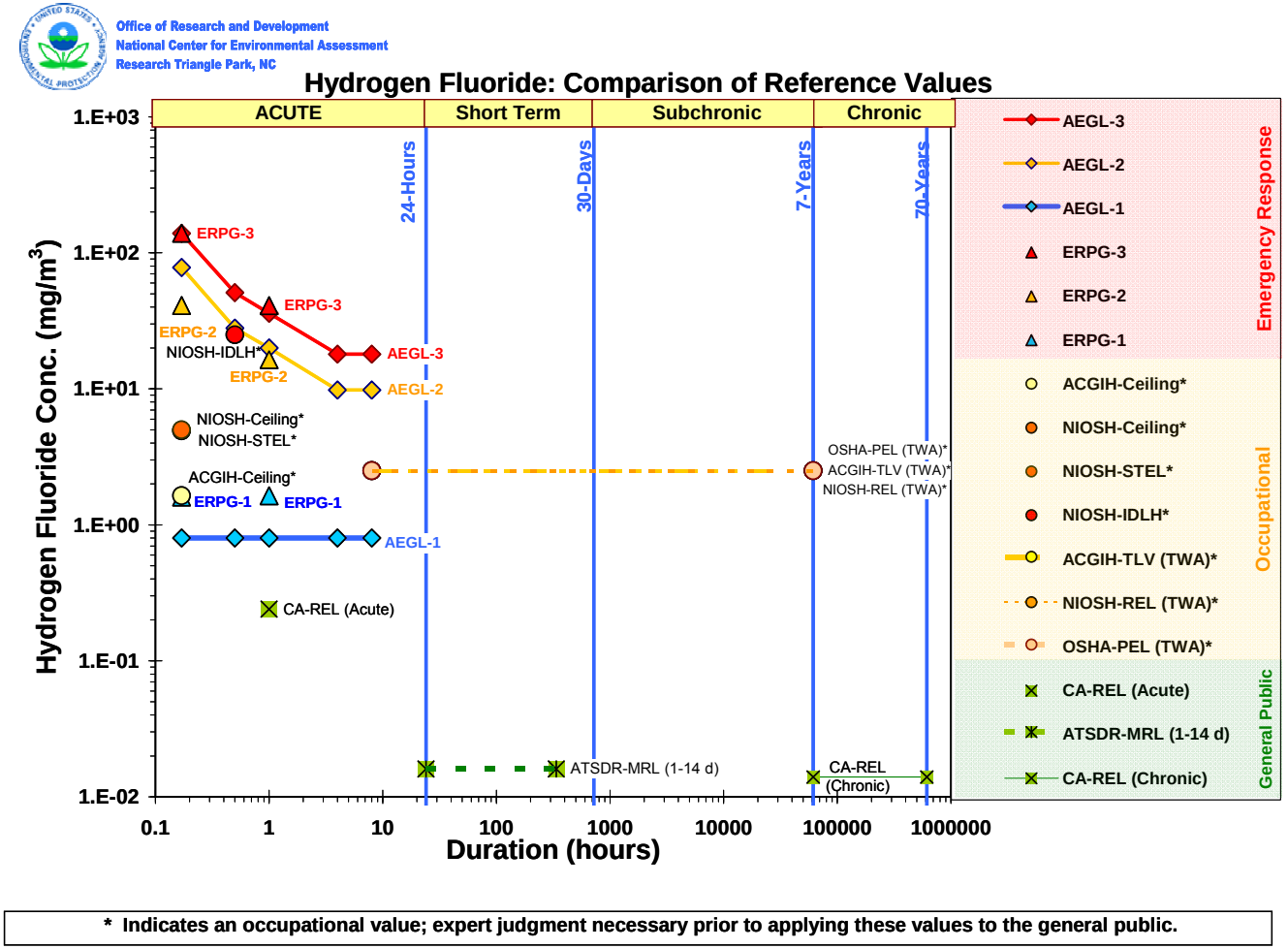

Figure 2.12. Comparison of Available Health Effect Reference Values for Inhalation Exposure to Hydrogen Fluoride

Table 2.12. Details on derivation of the specific inhalation health effect reference values for hydrogen fluoride.

Reference Value Type / Name		Duration	Reference Value (mg/m^3)	Reference Value (ppm)	Health Effect	Point of Departure		Uncertainty Factors	Notes on Derivation	Review Status
Emergency Response[1]	**AEGL-3**	10 min	140	170	Lethality (Dalbey, 1996, 192191; Dalbey et al., 1998, 180105; Wohlslagel et al., 1976, 019571)	1,764 ppm (10 min)	Minimal LOAEL	Total UF = 10 UF_A = 3 UF_H = 3	Time Scaling: $C^n \times t = k$ where n = 2 to 4 hrs; 8 hr AEGL-3 value equal to 4-h value	Interim (NAC/AEGL, 2004, 192285)
		30 min	51	62						
		1 hr	36	44		263 ppm (1 hour)	NOAEL	Total UF = 3 UF_A = 1 UF_H = 3		
		4 hr	18	22						
		8 hr	18	22						
	AEGL-2	10 min	78	95	Pulmonary effects Blinking, sneezing, coughing, eye and nasal irritation in dogs (Dalbey, 1996, 192191; Dalbey et al., 1998, 180105; Rosenholtz et al., 1963, 019861)	950 ppm (10 min)	NOAEL for lethality	Total UF = 10 UF_A = 3 UF_H = 3	Time Scaling: $C^n \times t = k$ where n = 2 to 4 hrs; 8 hr AEGL-2 value equal to 4-h value	
		30 min	28	34						
		1 hr	20	24		243 ppm (1 hour)	Threshold for AEGL-2 effects			
		4 hr	9.8	12						
		8 hr	9.8	12						
	AEGL-1	10 min	0.8	1	Pulmonary inflammation, sensory irritation (Lund et al., 1997, 180115; Lund et al., 1999, 180265)	3 ppm (1 hour)	Sub-threshold	Total UF = 3 UF_H = 3	Time scaling not applied	
		30 min	0.8	1						
		1 hr	0.8	1						
		4 hr	0.8	1						
		8 hr	0.8	1						
	ERPG-3	1 hr	41	50	Lethality (Prince, 1989, 080118; Valentine and Makovec,	WOE	WOE	NR	Weight of evidence approach	Final (AIHA, 2002, 192067; AIHA, 2002,

[1] Emergency Response reference values are developed using an assumption of a rare, "once-in-a-lifetime" exposure scenario, which is a key consideration when comparing these reference values to any Occupational or General Public reference values.

Reference Value Type / Name	Duration	Reference Value (mg/m^3)	Reference Value (ppm)	Health Effect	Point of Departure	Uncertainty Factors	Notes on Derivation	Review Status
				1993, 192192; Wohlslagel et al., 1976, 019571)				192090)
	10 min	140	170	Lethality (Dalbey, 1996, 192191; Dalbey et al., 1998, 180105)	1700 ppm (LC_{01}) (10 min)	NR	A total UF = 10 can be deduced.	
ERPG-2	1 hr	16	20	Threshold for nonlethal effects for animals exposed to 260-1300 ppm (Machle and Evans, 1940, 180116; Machle et al., 1933, 180118)	20 ppm NOAEL	NR		Final (AIHA, 2002, 192067; AIHA, 2002, 192090)
	10 min	41	50	Respiratory tract irritation (Darmer KI et al., 1972, 010495; Lewis and Hext, 1990, 192287)	50 ppm (RD_{50})	NR		
ERPG-1	1 hr	1.6	2	Exposure of humans to 1.4 ppm was not irritating and exposure to 2.7-4.7 caused slight irritation (Lindberg, 1968, 192288)	2 ppm NR	NR		
	10 min	1.6	2	Exposure of humans to 4.6 ppm for 6 hr caused only reversible irritation (Largent, 1961, 066345)		NR		

Reference Value Type / Name		Duration	Reference Value		Health Effect	Point of Departure		Uncertainty Factors	Notes on Derivation	Review Status
			(mg/m^3)	(ppm)						
Occupational	**ACGIH–Ceiling***	Any	1.6	2	Lung damage (Lund et al., 1997, 180115; Lund et al., 1999, 180265)	NR	NR	NR		Final (ACGIH, 2007, 192024)
	ACGIH TLV-TWA*	8 hr TWA	0.4	0.5		NR	NR	NR		
	NIOSH-IDLH*	30 min	25	30	Acute inhalation toxicity data in humans	50 ppm (30 – 60 min) 4.7 ppm (6 h/d, 10 to 50 d)	Fatal Threshold (Deichmann and Gerarde, 1969, 009221) NOAEL (Largent, 1961, 066345)	NR		Final (NIOSH, 1996, 192289)
	NIOSH-Ceiling*	15 min	5	6	Pulmonary effects; irritation (NIOSH, 1976, 192167)	NR	NR	NR		Final (NIOSH, 2006, 192177)
	NIOSH REL-TWA*	8 hr	2.5	3		NR	NR	NR		
	OSHA-PEL*	8 hr	2.5	3	NR	NR	NR	NR		Final (OSHA, 2006, 192276)
General Public	**CA-REL (Acute)**	1 hr	0.24	0.3	Upper respiratory tract membrane irritation in humans (Lund et al., 1997, 180115)	2.4 mg/m^3 (1 hr; high end of range)	NOAEL	Total UF = 10 UF_H = 10		Final (OEHHA, 2008, 192290)
	ATSDR-MRL (1-14 d)	1 - 14 d	0.016	0.02		0.5 ppm (1 hr; mid-point of range)	LOAEL	Total UF = 30 UF_L = 3 UF_H = 10	Minimal LOAEL	Final (ATSDR, 2003, 192114)
	CA-REL (chronic)	Chronic	0.014	0.017	Increased bone density (skeletal fluorosis) (Derryberry et al., 1963, 066269)	0.14 mg/m^3 (0.39 mg/m^3 x 10/20 x 5/7)	$BMC_{05\text{-}HEC}$ (0.39 mg/m^3)	Total UF = 10 UF_H = 10	Adjustments for 8h/day; 5 d/wk	Final (OEHHA, 2003, 192228)

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2.13 Chemical-Specific Reference Values for Hydrogen Sulfide (CASRN 7783-06-4)

Hydrogen sulfide (H_2S) is a flammable, colorless gas that has a sweet taste and a rotten egg odor (HSDB, 2006, **192357**). The presence of H_2S is detectable at low concentrations, but its odor may be undetectable at high concentrations. The majority of hydrogen sulfide present in the environment is produced by natural sources, although several anthropogenic sources exist as well. It is used in the production of elemental sulfur and sulfuric acid; in the purification of nickel and manganese; and as a component of inorganic sulfides, used in dyes, pesticides, polymers, leather, and plastic additives. The largest source of human exposure to H_2S is through the inhalation of polluted ambient air. Additional information on the nature of hydrogen sulfide and detailed summaries of health effects can be found in a number of sources, including the AEGL TSD (NAC/AEGL, 2002, **192202**), the ATSDR Toxicological Profile (ATSDR, 2006, **192117**), the IRIS Toxicological Review (U.S. EPA, 2003, **192242**), the OEHHA REL documentation (OEHHA, 2008, **192243**), and is not repeated here.

Hydrogen sulfide has a rather full range of available inhalation health effect reference values, as shown in Figure 2.13. Additional details are provided in Table 2.13 on the derivation of the available reference values, including the basis, point of departure (POD), time scaling, and uncertainty factors (UFs).

Emergency Response reference values (AEGLs and ERPGs) were developed for all three severity categories (level 1 for mild transient effects; level 2 for irreversible effects or impairment of ability to escape; and level 3 for potentially lethal effects). The 1-hr AEGL-2 and AEGL-3 values are largely in agreement with the corresponding ERPG values, with the ERPG-3 value being slightly higher than the AEGL-3 value and near the same concentration as the occupational IDLH value. The AEGL-3 and AEGL-2 values were scaled based on the equation $C^n \times t = k$, where n = 4.4, which was derived from experimental observations in lethality studies. A higher value of n indicates a predominance of concentration rather than duration of exposure in the C × t relationship, and is more commonly observed for irritant chemicals. The ERPG-1 and AEGL-1 values occur at much lower concentrations than the other severity level values, with the ERPG-1 being at the lowest concentration of all of the Emergency Response values for H_2S. Both sets of level-1 values are for low-level, subjective symptoms; the AEGL-1 was based on reported headaches in exercising asthmatics that were otherwise asymptomatic and the ERPG-1 was based on objectionable odor. The AEGL TSD also includes the estimation of a separate level of odor awareness (LOA) of 0.01 ppm; the AEGL program bases all of its values on health effect endpoints (NRC, 2001, 192042), whereas the ERPG program includes objectionable odors as a criterion for level-1 effects.

The Occupational values typically provide less information on their derivation and are likely derived by a weight of evidence approach, with no particular study identified as the basis for the values. The NIOSH IDLH documentation (NIOSH, 1996, **192241**) noted the following evidence in human and occupational studies: 170 to 300 ppm as the maximum concentration that can be endured for one hour without serious effects (Henderson and Haggard, 1943, **010318**); olfactory fatigue noted with exposure to 100 ppm (Poda, 1966, **020850**); and in a very early study (Yant, 1930, **020748**) concentrations of 50 to 100 ppm cause mild conjunctivitis and respiratory irritation after one hour of exposure, 500 to 700 ppm may be dangerous with 30 minutes to one hour of exposure, exposure to 700 to 1,000 ppm results in unconsciousness,

cessation of respiration, and death, and exposure to 1,000 to 2,000 pm results in unconsciousness, cessation of respiration, and death in a few minutes.

A large set of General Public reference values are available for H_2S, including acute, intermediate, and chronic values. Acute values include those developed by ATSDR and California's Office of Environmental Health Hazard Assessment (OEHHA). An intermediate ATSDR value, covering exposure durations between 15 days and 1 year, and chronic CA-REL and EPA/IRIS RfC values were also developed for hydrogen sulfide; all three are adjusted using time scaling to account for exposure occurring 6 hours per day and either 5 or 6 days per week. The RfC and intermediate MRL reference values cite the same study (Brenneman et al., 2000, 012535) and use an equivalent point of departure. A WHO Air Quality Guideline (WHO, 2000, 180143) value for 24 hours is available, as is a 30-minute value for odor annoyance set at 7 $\mu g/m^3$ (not included in figure or table).

Overall, the coverage of reference values for hydrogen sulfide is more heavily weighted to values available for acute exposures. As noted in a number of the supporting documents for the reference values, it is likely the chronic effects are due to an accumulation of effects from repeated short term increases in exposure (NIOSH, 1977, 192166)(CARB, 1984, 192168), 192168)(AIHA, 2002, 192061; ATSDR, 2006, 192117; NIOSH, 1996, 192241; U.S. EPA, 2003, 192242). Regardless, there are inhalation health effect reference values for hydrogen sulfide that span all durations, including values for effects ranging from odor annoyance to lethality, and coverage of all three types of reference values (Emergency Response, Occupational and General Public).

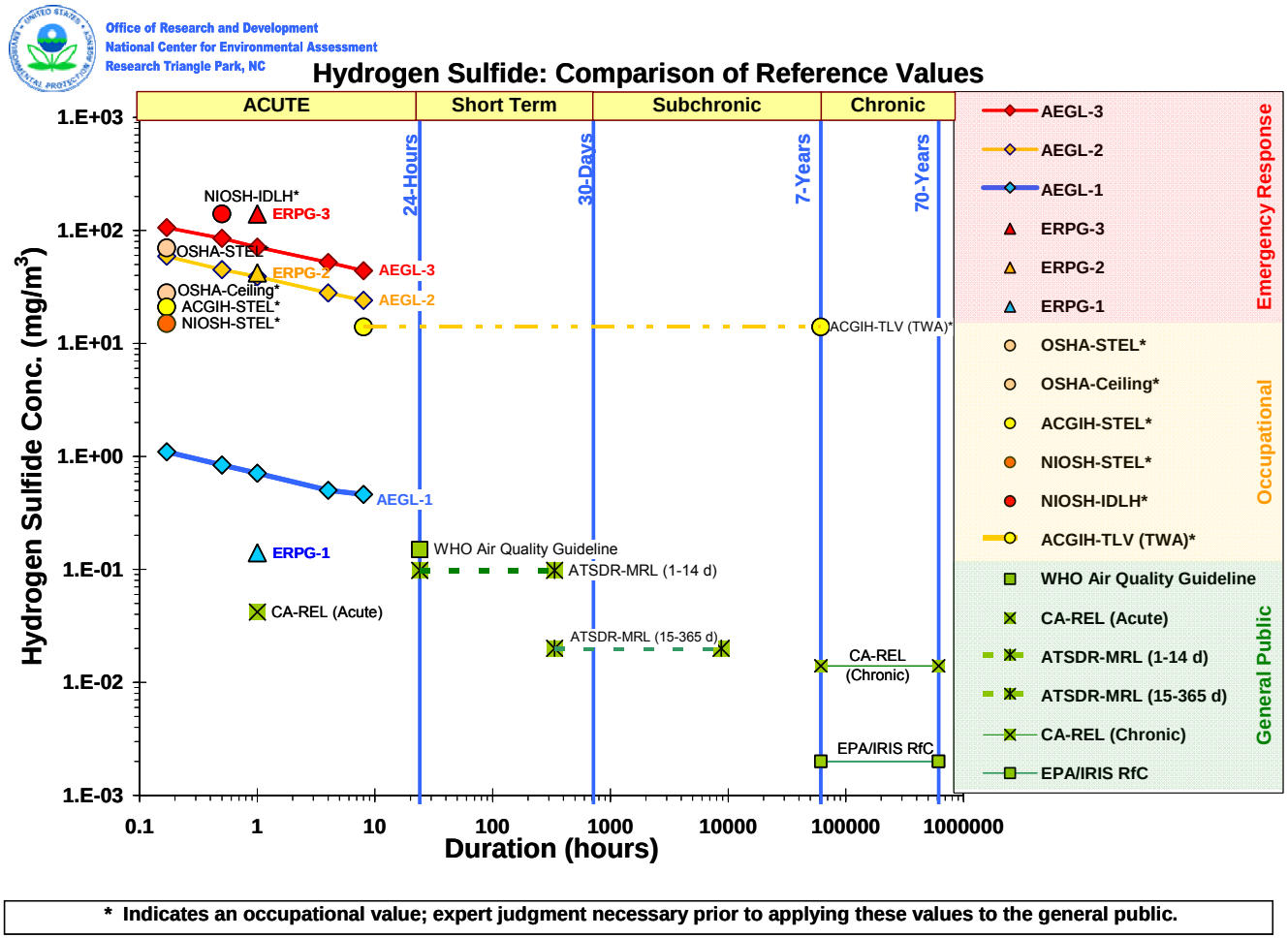

Figure 2.13. Comparison of Available Health Effect Reference Values for Inhalation Exposure to Hydrogen Sulfide

Table 2.13. Details on derivation of the specific inhalation health effect reference values for hydrogen sulfide.

Reference Value Type / Name		Duration	Reference Value		Health Effect	Point of Departure	Uncertainty Factors	Notes on Derivation	Review Status
			(mg/m^3)	(ppm)					
Emergency Response[1]	**AEGL-3**	10 min	106	76	Lethality (MacEwen and Vernot, 1972, 041949)	504 ppm (1 h) Highest concentration on causing no death in rats	Total UF = 10 UF_A = 3 UF_H = 3	Time scaling: $C^n \times t = k$ where n = 4.4	Interim (NAC/AEGL, 2002, 192202)
		30 min	85	61					
		1 hr	71	51					
		4 hr	52	37.3					
		8 hr	44	31.6					
	AEGL-2	10 min	59	42.3	Gross lung pathology, minor perivascular edema, increased protein and LDH in lung lavage fluid; pulmonary alveolar marcrophage viability (Green et al., 1991, 021128; Khan et al., 1991, 021080)	200 ppm NEL	Total UF = 10 UF_A = 3 UF_H = 3		
		30 min	45	32.3					
		1 hr	39	28					
		4 hr	28	20.1					
		8 hr	24	17.2					
	AEGL-1	10 min	1.1	0.75	Headache in human asthmatics (Jappinen et al., 1990, 021082)	2 ppm NR	Total UF = 1		
		30 min	0.84	0.6					
		1 hr	0.71	0.51					
		4 hr	0.5	0.36					
		8 hr	0.46	0.33					

[1] Emergency Response reference values are developed using an assumption of a rare, "once-in-a-lifetime" exposure scenario, which is a key consideration when comparing these reference values to any Occupational or General Public reference values.

Reference Value Type / Name		Duration	Reference Value (mg/m^3)	Reference Value (ppm)	Health Effect	Point of Departure		Uncertainty Factors	Notes on Derivation	Review Status
Emergency Response	**ERPG-3**	1 hr	140	100	Unconsciousness and decreased blood pressure in humans exposed to 230 ppm for 20 min; Conjunctivitis and respiratory tract irritation in humans exposed to 200-300 ppm for 1 hr; LC_{50} of 712 ppm for 1 hr exposure for animals (CIIT, 1983, 192169)	712 ppm	LC_{50}	NR		Final (AIHA, 2002, 192061)
	ERPG-2	1 hr	42	30	No lethality in rats exposed to 45 ppm for 4 hr; unconsciousness and cardiac irregularities in rabbits exposed to 72 ppm for 1.5 hr (Kosmider et al., 1967, 061830; Rogers and Ferin, 1981, 020893)	45 ppm 72 ppm	NR	NR		
	ERPG-1	1 hr	0.14	0.1	Distinct objectionable odor (Clayton and Clayton FE, 1982, 034134)	.03 ppm	NR	NR		

Reference Value Type / Name		Duration	Reference Value		Health Effect	Point of Departure		Uncertainty Factors	Notes on Derivation	Review Status
			(mg/m^3)	(ppm)						
Occupational	**ACGIH TLV-TWA***	8 hr TWA	14	10	Sudden death, eye irritation, neurasthenic symptoms, CNS damage (Ahlborg, 1951, 061803; NIOSH, 1977, 192166)	NR	NR	NR		Final (ACGIH, 2007, 192024)
	ACGIH TLV-STEL*	15 min	21	15		NR	NR	NR		
	OSHA Ceiling*	Any time	28	20	NR	NR	NR	NR		Final (OSHA, 2006, 192291)
	OSHA-STEL*	10 min[2]	70	50						
	NIOSH Ceiling*	10 min	15	10	Acute inhalation toxicity data in humans (NIOSH, 1977, 192166)	NR	NR	NR		Final (NIOSH, 2006, 192177)
	NIOSH–STEL*	15 min	15	10						
	NIOSH-IDLH*	< 30 min	140	100	Acute inhalation toxicity data in humans (see discussion)	NR	NR	NR		Final (NIOSH, 1996, 192241)

[2] 10 minutes. once only if no other measured exposure occurs (OSHA, 2006).

Reference Value Type / Name		Duration	Reference Value		Health Effect	Point of Departure		Uncertainty Factors	Notes on Derivation	Review Status
			(mg/m^3)	(ppm)						
General Public	**WHO Air Quality Guideline**	24 hr	0.15	0.11	Eye irritation	15 mg/m^3	LOAEL	Total UF = 100		Final (WHO, 2000, 180143)
	CA-REL (Acute)	1 hr	0.04	0.03	Headache and nausea in humans (California state department of public, 1969, 192292)(CARB, 1984, 192168); (Amoore, 1985, 192034; Reynolds and Kamper, 1984, 192170)	0.03 ppm	LOAEL (Mid point of range for odor detection)	Total UF = 1	Odor LOAEL endpoint	Final (OEHHA, 2008, 192243)
	ATSDR-MRL (1-14 d)	1 - 14 d	0.1	0.07	Lung effects in humans (Jappinen et al., 1990, 021082)	0.07 ppm	LOAEL	Total UF = 30 UF_L = 3 UF_H =3 UF_{DB} = 3		Final (ATSDR, 2006, 192117)
	ATSDR-MRL (15-365 d)	15 d – 1 yr	0.02	0.02	Olfactory neuron loss and basal cell hyperplasia (Brenneman et al., 2000, 012535)	0.46 ppm (10 ppm x 6/24 x 7/7 x 0.184)	NOAE L_{HEC}	Total UF = 30 UF_A = 3 UF_H = 10	Adjusted for 6 hr/d; 7 d/wk; and RGDR=0.184	
	CA-REL (Chronic)	Chronic	0.01	7.2×10^{-3}	Histopathological inflammatory changes in nasal mucosa in mice (CIIT, 1983, 192169)	0.85 ppm (30.5 ppm x 6/24 x 5/7 x 0.16)	NOAE L_{HEC}	Total UF = 100 UF_L = 1 UF_S = 3 UF_A = 3 UF_H = 10	Adjusted for 6 hr/d; 5 d/wk; and RGDR=0.16	Final (OEHHA, 2000, 192244)
	Chronic RfC (IRIS)	Chronic	2×10^{-3}	1.4×10^{-3}	Nasal tract lesions in rat (Brenneman et al., 2000, 012535)	0.64 mg/m^3 (13.9 mg/m3 x 6/24 x 7/7 x 0.184)	NOAE L_{HEC}	Total UF = 300 UF_A = 3 UF_H = 10 UF_S = 10	Adjusted for 6 hr/d; 7 d/wk; RGDR=0.184	Final (U.S. EPA, 2003, 192242)

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2.14 Chemical-Specific Reference Values for Lewisite

LEWISITE L-1 (CAS Reg. No. 541-25-3)
$ClCH=CHAsCl_2$
LEWISITE L-2 (CAS Reg. No. 40334-69-8)
$(ClCH=CH)_2$ AsCl
LEWISITE L-3 (CAS Reg. No. 40334-70-1)
$(ClCH=CH)_3$ As

Lewisite is the name applied to a group of organic arsenical compounds with vesicant properties. The only purpose for the Lewisite compounds is as chemical weapon agents. Lewiste-1 (L-1; 2-chlorovinyldichloroarsine) is the main product, with Lewisite-2 [L-2; *bis*-(2-chlorovinyl)chloroarsine] and lewisite-3 [L-3; *tris*-(2-19 chlorovinyl)arsine] formed as byproducts in the production of L-1. L-1 can exist as a trans-isomer or a cis-isomer; in aqueous solutions, the cis isomer undergoes photoconversion to the trans-isomer. Pure Lewisite is a colorless, odorless oily liquid; however, the synthesized agent is an amber to dark brown liquid with a geranium-like odor (Munro et al., 1999, 026185). Lewisite causes local corrosive damage and may cause systemic poisoning after absorption through skin or mucous membranes. Exposure to Lewisite causes almost immediate irritation and burning sensation of the eyes, skin, upper respiratory tract, and lungs. Death may result from direct pulmonary damage or circulatory failure due to fluid loss and arrhythmia. Death that occurs within 24 hours of exposure is likely due to pulmonary damage (NAC/AEGL, 2007, 192203). A detailed description of Lewisite toxicity as well as the physical nature of this group of chemical agents can be found in the AEGL Technical Support Document (NAC/AEGL, 2007, 192203), with additional details available in the U.S. National Response Team Quick Reference Guide (NRT, 2008, 192160), and are not repeated here.

There are only two sources of health effect reference values for the chemical warfare agent Lewisite: the National Advisory Committee for Acute Exposure Guideline Levels (NAC/AEGL, 2007, 192203) and the Center for Disease Control and Prevention (CDC, 1988, 192173). Both organizations used the same limited set of data for deriving values for Lewisite.

The Emergency Response values for Lewisite are comprised of the AEGLs. AEGL-3 values for Lewisite were derived based on an estimate of the lethality at the one percent level (LC_{01}) in dogs using one-third of the LC_{50} observations at 7.5-, 15-, 30-, 60-, and 240-minutes. No data was available other than the unclassified report on dogs (Armstrong, 1923, 192132) used in derivation of the AEGL-3 values, therefore, AEGL-2 values were derived by simply dividing the AEGL-3 values by 3. No values for AEGL-1 were derived based on the lack of information.

A Federal Register Notice published by the Centers for Disease Control and Prevention (CDC, 1988, 192173) provided final recommendations for Airborne Exposure Levels proposed by the US Army for application to Lewisite as well as the agents Tabun (GA), Sarin (GB), VX, and the Sulfur Mustards (H, HD, HT) for the protection of workers at chemical weapon decommissioning facilities and the general population living near those facilities.

The Airborne Exposure Level values for Lewisite include a General Population Limit (GPL), and a Worker Population Limit (WPL). No details were provided in the derivation of these values and it is assumed that a weight of evidence approach was used in their derivation.

The resulting Lewisite values for both the AEGL and US Army are shown in Figure 2.14 and Table 2.14.

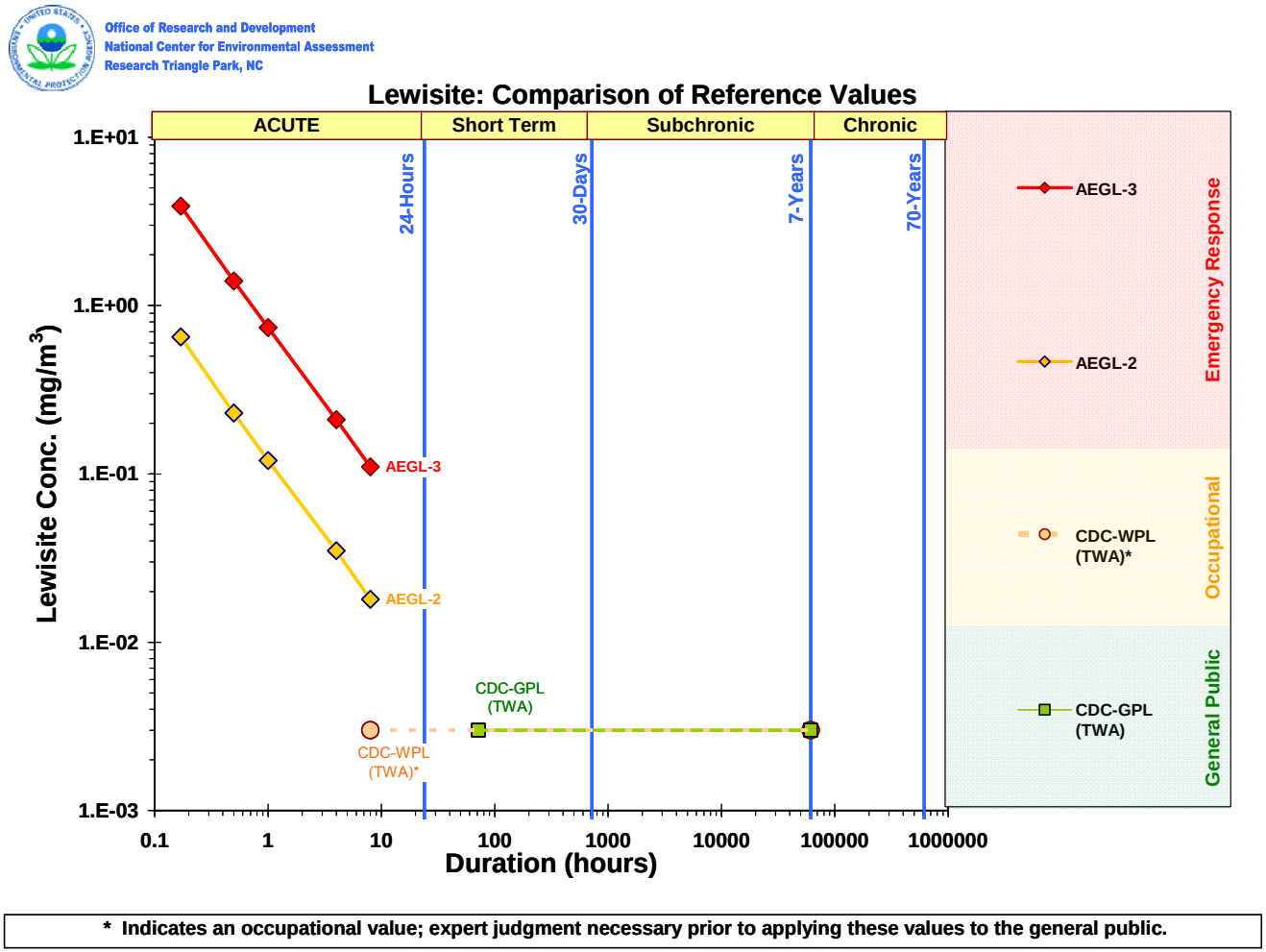

Figure 2.14. Comparison of Available Health Effect Reference Values for Inhalation Exposure to Lewisite

Table 2.14. Details on derivation of the specific inhalation health effect reference values for lewisite.

Reference Value Type / Name		Duration	Reference Value[1] (mg/m^3)	Reference Value[1] (ppm)	Health Effect	Point of Departure		Uncertainty Factors	Notes on Derivation	Review Status
Emergency Response[2]	**AEGL-3**	10 min	3.9	NA	Lethality (Armstrong, 1923, 192132)	38.7 mg/m^3	LC_{01}	Total UF = 10 UF_A = 3 UF_H =3	Estimates of LC_{01} values were derived by dividing time-specific LC_{50} values by 3. AEGL-3 values for L-1 adopted as AEGL-3 values for mixture of L-1, L-2, and L-3	Final (NAC/AEGL, 2007, 192203)
		30 min	1.4	NA		14.0 mg/m^3				
		1 hr	0.74	NA		7.4 mg/m^3				
		4 hr	0.21	NA		2.1 mg/m^3				
		8 hr	0.11	NA		1.1 mg/m^3				
	AEGL-2	10 min	0.65	NA	Ocular effects including blinking and lacrimation, sneezing, excessive nasal secretion (Armstrong, 1923, 192132)	1/3 of AEGL-3	Estimated threshold for irreversible effects		1/3 of the AEGL-3 values for Lewisite-1; considered threshold for the inability to escape AEGL-2 values for L-1 adopted as AEGL-2 values for mixture of L-1, L-2, and L-3	
		30 min	0.23	NA						
		1 hr	0.12	NA						
		4 hr	0.035	NA						
		8 hr	0.018	NA						

[1] Values in units of parts per million (ppm) were not provided for this group of agents, but were only reported in units of mg/m^3.
[2] Emergency Response reference values are developed using an assumption of a rare, "once-in-a-lifetime" exposure scenario, which is a key consideration when comparing these reference values to any Occupational or General Public reference values.

Reference Value Type / Name		Duration	Reference Value[1] (mg/m^3)	Reference Value[1] (ppm)	Health Effect	Point of Departure		Uncertainty Factors	Notes on Derivation	Review Status
Occupational	**CDC- WPL (TWA)***	8 hours	0.003	NR	Immediate, severe irritation to respiratory system, eyes and skin	NR	NR	NR		Final (CDC, 1988, 192173)
General Public	**CDC-GPL (TWA)**	72 Hours	0.003	NR		NR	NR	NR		

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2.15 Chemical-Specific Reference Values for Elemental Mercury Vapor (CASRN 7439-97-6)

Elemental mercury vapor (Hg^0) is a colorless, odorless gas generated from elemental mercury or inorganic mercury compounds such as mercuric chloride (NAC/AEGL, 2008, 192208). Under ambient conditions, mercury is a silver-white, liquid metal. Metallic mercury is non-flammable and only slightly volatile (vapor pressure of 0.002 mm). Elemental mercury vapor is more soluble in plasma, whole blood, and hemoglobin than in distilled water, where it dissolves only slightly (HSDB, 2005, 192178). Elemental mercury vapor is readily absorbed by the lung, with up to 80% of inhaled Hg^0 absorbed by the lung, and can readily pass through exposed skin. The central nervous system is the critical organ for mercury vapor exposure, with the kidney being more affected by divalent mercury (Hg^{2+}), which is produced by catalases in red blood cells following exposure to Hg^0. Acute inhalation exposure to mercury vapor may be followed by chest pains, dyspnea (shortness of breath), coughing, hemoptysis (bloody sputum), and sometimes interstitial pneumonitis (inflammation of the connective tissues in the lung) leading to death. Short term exposures (1-30 days) have given rise to psychotic reactions characterized by delerium, hallucinations, and suicidal tendencies. Occupational exposure has resulted in irritation and excitability as the principal feature of a broad ranging functional disturbance and has long been associated with the development of proteinuria (i.e., excess protein in urine, indicating effects upon kidney function). More details on the chemical nature and toxicity from exposure to Hg^0 are available from multiple sources (HSDB, 2005, 192178; NAC/AEGL, 2008, 192208) and is not repeated here.

As noted in Figure 2.15, the occupational value for ceiling exposures from NIOSH and for the time-weighted average occupational values (OSHA PEL, ACGIH TLV and NIOSH REL) are much lower than the emergency response values (AEGL-2 and ERPG-2). This is due in large part to the repeated exposures expected in the occupational setting and the persistence of absorbed mercury to remain in the body, and for low-level effects to accumulate with repeated exposures. In pharmacokinetic terms, the toxicity to Hg^0 is more related to the accumulation of dose over time (i.e., area under the curve – AUC) than with peak exposures. The NIOSH IDLH value is essentially equivalent to the 30 minute AEGL-3 value. It should also be noted that the original documentation for the OSHA PEL cited it as a Ceiling value (OSHA, 1996, 192249) but OSHA later clarified in a memo that the value was a time-weighted average (OSHA, 1996, 598129).

It is also important to note that neither AEGL-1 nor ERPG-1 was developed due to a lack of effects at the severity level for Hg^0 or any warning properties (e.g., odor). The lack of AEGL-1 or ERPG-1 values does not imply that no adverse health effects occur at exposure levels below the AEGL-2 or ERPG-2, but based on the assumptions applied during their development, no "irreversible adverse effects or impairment of ability to escape" would be expected to be seen from a single, rare (i.e., "once-in-a-lifetime") exposure to Hg^0 at lower exposure levels.

The relatively more health protective nature of the California REL (CA-REL) values is also readily apparent for both the acute and chronic durations. It should also be noted that all of the chronic reference values use essentially the same data set and have values that are in strong agreement with one another, with differences related more to derivation methods and application of uncertainty factors, as shown in Table 2.15.

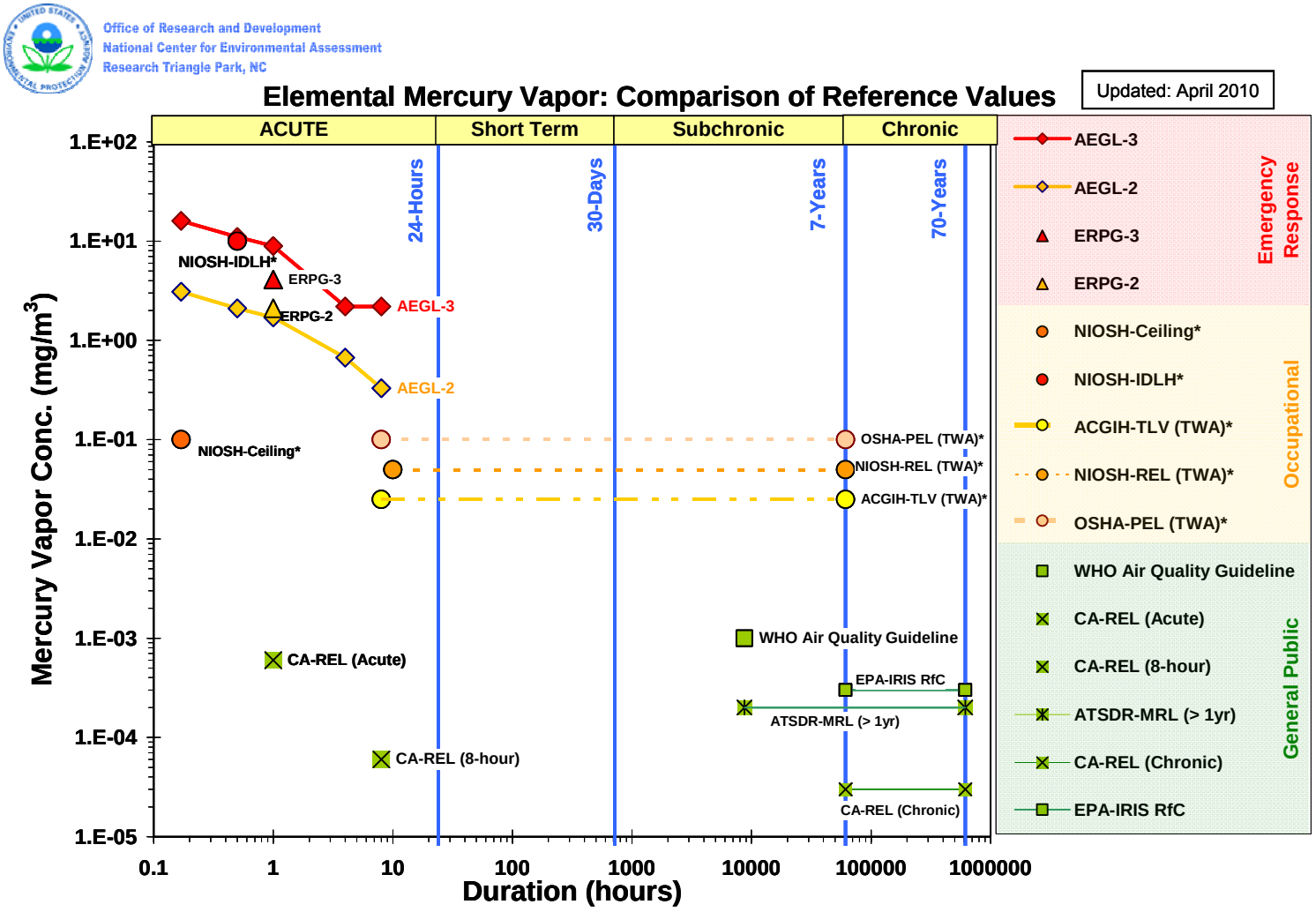

Figure 2.15. Comparison of Available Health Effect Reference Values for Inhalation Exposure to Elemental Mercury Vapor (Hg^0)

Table 2.15. Details on derivation of the specific inhalation health effect reference values for elemental mercury vapor.

Reference Value Type / Name		Duration	Reference Value (mg/m^3)	Reference Value (ppm)	Health Effect	Point of Departure		Uncertainty Factors	Notes on Derivation	Review Status
Emergency Response[1]	**AEGL-3**	10 min	16	2.0	No lethality (Livardjani et al., 1991, 019910)	26.7 mg/m^3 (1 hour)	No deaths; lung lesions	Total UF = 3 UF_A = 1 UF_H = 3	C^n x t = k where n = 3 for shorter and n = 1 for longer durations (NRC, 2001, 192042). The 8-hour value was set equal to the 4-hour value.	Proposed (NAC/AEGL, 2008, 192208)
		30 min	11	1.3						
		1 hr	8.9	1.1						
		4 hr	2.2	2.7		27.0 mg/m^3 (2 hours)	Lethality in 20/32 rats			
		8 hr	2.2	2.7						
	AEGL-2	10 min	3.1	0.38	Fetal toxicity and developmental effects in rats (Morgan et al., 2002, 192099)	4 mg/m^3 (2 hr/day, 10 day exposure)	NOAEL for fetal toxicity	Total UF = 3 UF_A = 1 UF_H = 3	Time scaling using C^n x t = k, same as in AEGL-3.	
		30 min	2.1	0.26						
		1 hr	1.7	0.21						
		4 hr	0.67	0.087						
		8 hr	0.33	0.040						
	ERPG-3	1 hr	4.10E+00	5.00E-01	Brain, kidney, and lung damage (Asano et al., 2000, 180282; Ashe et al., 1953, 019952; Beliles et al., 1968, 180283; Eto et al., 1999, 180285; Kurisaki et al., 1999, 192246;	NR	NR	NR		Final (AIHA, 2002, 192096)

[1] Emergency Response reference values are developed using an assumption of a rare, "once-in-a-lifetime" exposure scenario, which is a key consideration when comparing these reference values to any Occupational or General Public reference values.

Reference Value Type / Name		Duration	Reference Value (mg/m^3)	Reference Value (ppm)	Health Effect	Point of Departure		Uncertainty Factors	Notes on Derivation	Review Status
					Livardjani et al., 1991, 019910; Tennant et al., 1961, 180242)					
	ERPG-2	1 hr	2.05E+00	2.50E-01	Lung lesions, mercury intoxication (Fraser et al., 1934, 180287; Kishi et al., 1978, 020079; Livardjani et al., 1991, 019910)	NR	NR	NR		
Occupational	**ACGIH TLV-TWA***	8 hr TWA	2.50E-02	3.05E-03	Neurological effects (Roels et al., 1985, 180254)	50 ug/g creatinine	biological threshold for effects	NR		Final (ACGIH, 2007, 192024)
	OSHA-PEL (TWA)*	8 hr TWA	1.00E-01	1.22E-02	NR	NR	NR	NR	Value established in 1971.	Final (OSHA, 1996, 192249) (OSHA, 1996, 598129)
	NIOSH-Ceiling*	10 min	1.00E-01	1.22E-02	NR	NR	NR	NR		Final (NIOSH, 2006, 192177)
	NIOSH-REL (TWA)*	10 hr TWA	5.00E-02	6.09E-03	NR	NR	NR	NR		
	NIOSH-IDLH*	30 min	1.00E+01	1.22E+00	Damage to kidneys, lungs, and colon in animals (Ashe et al., 1953, 019952)	28.8 mg/m^3 (4 h)	NR	NR		Final (NIOSH, 1996, 192257)

Reference Value Type / Name		Duration	Reference Value		Health Effect	Point of Departure		Uncertainty Factors	Notes on Derivation	Review Status
			(mg/m^3)	(ppm)						
General Public	**CA-REL (Acute)**	1 hr	6.00E-04	7.31E-05	CNS disturbances in offspring of exposed mice (Danielsson et al., 1993, 180106)	1.8 mg/m^3 (1 hr/day, gestational days 11-14)	LOAEL	Total UF = 3000 UF_L = 10 UF_A: 30 TK = 3 TD = 10 UF_H: 10 TK = 3 TD = 3		Final (OEHHA, 2008, 192259)
	CA-REL (8-hr)	8 hr	6.00E-05	7.31E-06	Neurotoxicity and decreased EEG activity in humans (Fawer et al., 1983, 019897; Ngim et al., 1992, 019916; Piikivi, 1989, 019918; Piikivi and Hanninen, 1989, 061838; Piikivi and Tolonen, 1989, 019920)	18 $\mu g/m^3$ (25 $\mu g/m^3$ x 5/7)	$LOAEL_{HEC}$ (8 hr/d, 5 d/wk, 13.7 – 15.6 work years)	Total UF = 300 UF_L = 10 UF_H: 30 TK = 3 TD = 10	POD adjusted to account for 5 d/wk exposures. Factor of 10 for UF_H TD to account for susceptibility of children.	
	CA-REL (Chronic)	Chronic	3.00E-05	3.66E-06	Neurotoxicity and decreased EEG activity in humans (Fawer et al., 1983, 019897; Ngim et al., 1992, 019916; Piikivi, 1989, 019918; Piikivi and Hanninen, 1989, 061838; Piikivi and Tolonen, 1989, 019920)	9 $\mu g/m^3$ (25 $\mu g/m^3$ x 10/20 x 5/7)	$LOAEL_{HEC}$ (8 hr/d, 5 d/wk, 13.7 – 15.6 work years)	Total UF = 300 UF_L = 10 UF_H: 30 TK = 3 TD = 10	Adjusted to account for 5 d/wk exposures and respiratory rate of workers over general population (10/20 m^3). Factor of 10 for UF_H TD to account for susceptibility of children.	Final (OEHHA, 2008, 192259)
	ATSDR- MRL	Chronic	2.00E-04	2.44E-05	Increased	0.0062	$LOAEL_{HEC}$	Total UF = 30	Adjusted to	Final

Reference Value Type / Name		Duration	Reference Value (mg/m^3)	Reference Value (ppm)	Health Effect	Point of Departure		Uncertainty Factors	Notes on Derivation	Review Status
	(> 1yr)				frequency of tremors (Fawer et al., 1983, 019897)	mg/m^3 (0.026 mg/m^3 x 8/24 x 5/7)	(8 hr/d, 5 d/wk, 13.7 – 15.6 work years)	UF_L = 3 UF_A = 1 UF_H = 10	account for 5 d/wk and 8 hr/d work schedule.	(ATSDR, 1999, 192112)
	WHO Air Quality Guideline*	1 yr	1.00E-03	1.22E-04	Renal effects (WHO, 2000, 180143)	15-30 ug/m^3	LOAEL	NR		Final (WHO, 2000, 180143)
	Chronic RfC (IRIS)	Chronic	3.00E-04	3.66E-05	Hand tremor, memory disturbance, autonomic dysfunction in humans (Fawer et al., 1983, 019897; Liang et al., 1993, 192164; Ngim et al., 1992, 019916)	0.009 mg/m^3 (0.026 mg/m^3 x 10/20 x 5/7)	$LOAEL_{HEC}$ (8 hr/d, 5 d/wk, 13.7 – 15.6 work years)	Total UF = 30 UF_H = 10 UF_{DB} = 3	Adjusted to account for 5 d/wk exposures and respiratory rate of workers over general population (10/20 m^3).	Final (U.S. EPA, 1995, 192216)

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2.16 Chemical-Specific Reference Values for Methylene Chloride (CASRN 75-09-2)

Methylene chloride (MeCl, dichloromethane; CH_2Cl_2) is a colorless liquid with a mild sweet odor. It is a halogenated hydrocarbon that does not occur naturally in the environment. It is used as a solvent in paint strippers and removers; as a propellant in aerosols; as an extraction solvent for food (e.g., decaffeination of coffee); as a process solvent in the manufacture of drugs, pharmaceuticals, and film coatings; as a metal cleaning and finishing solvent; in electronics manufacturing; and as an agent in urethane foam blowing. MeCl is a high-production volume chemical with U.S. production of 229,000 tons in 1988 and total production in Western Europe ranging from 331,500 tons in 1986 to 254,200 tons in 1991. Due to its rapid evaporation, the primary route of exposure to MeCl is through the inhalation of contaminated ambient air, which at low concentrations may cause dizziness, nausea, and a decreased reaction time, while at higher concentrations may lead to unconsciousness and death. MeCl forms carbon dioxide as a metabolic byproduct leading to formation of carboxyhemoglobin (COHb). COHb formation is one of the primary mechanisms for toxicity at high exposure concentrations to MeCl. IARC determined that MeCl is "*possibly carcinogenic to humans (Group 2B)*" (IARC, 1999, 192122). Additional information on the nature of MeCl and detailed summaries of health effects can be found in the AEGL TSD (NAC/AEGL, 2008, 192207), the ATSDR Toxicological Profile (ATSDR, 2000, 192113), the OEHHA REL documentation (OEHHA, 2000, 192225; OEHHA, 2008, 192263), from IARC (1999, 192122), and other sources.

Methylene chloride has a relatively broad range of inhalation health effect reference values across all types of values (Emergency Response, Occupational, and General Public), levels of severity and durations. The available reference values are arrayed graphically in Figure 2.16. Details available on the derivation of these values, including key effects, critical studies, time scaling and other adjustments, and application of uncertainty factors (UFs) are shown in Table 2.16.

Emergency Response reference values (AEGLs and ERPGs) were developed for all three severity categories (level 1 for mild transient effects; level 2 for irreversible effects or impairment of ability to escape; and level 3 for potentially lethal effects). At all severity levels, the ERPG values are lower than the corresponding AEGL values, with the largest difference occurring between the AEGL-3 and ERPG-3. Time scaling was applied to all AEGL values using a PBPK model, while the basis varied between severity levels and time intervals. The AEGL-3 reference values for all time intervals were scaled based on the maximum MeCl concentration in the brain except for the 8-hr value, which was based on COHb formation. The 10- and 30-minute AEGL-2 values were scaled based on the maximum MeCl concentration in the brain, while the 1-, 4-, and 8-hr values were based on COHb formation. The AEGL-1 reference values for all time intervals were scaled based on maximum MeCl concentration in the brain, and values for 4- and 8-hours were not derived as the derived values would be at concentrations greater than the corresponding AEGL-2 values.

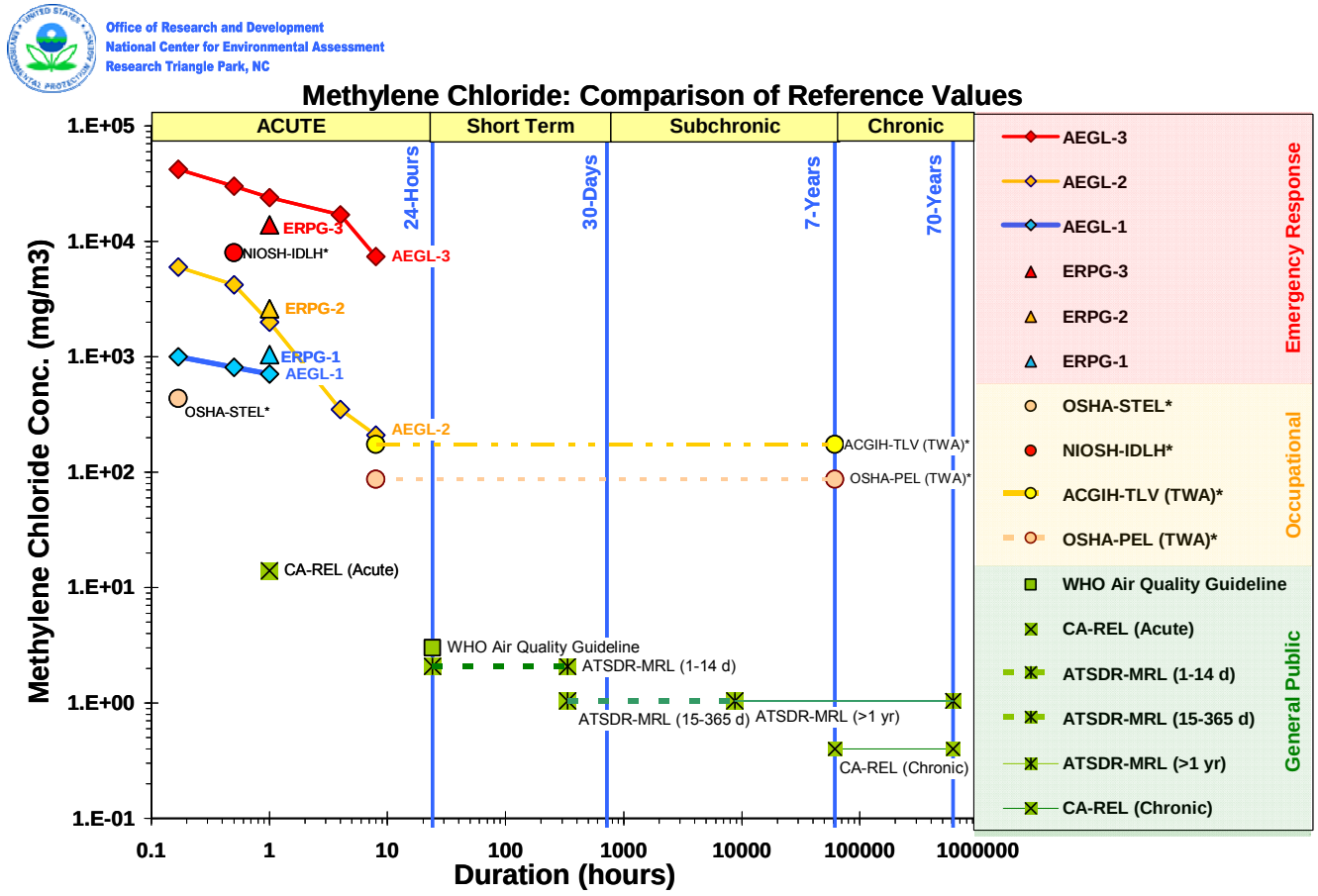
Several Occupational reference values for MeCl are available for time-weighted averages (TWAs) as well as short-term excursions. The NIOSH IDLH value was based on the results of a study in which exposure to 2,300 ppm of methylene chloride for 1-hr produced no feeling of dizziness in human subjects (Sax, 1975, 018750). Additional Occupational values include OSHA STEL and PEL values and an ACGIH TLV TWA reference value. The

Occupational TWA values – the OSHA PEL and ACGIH TLV – are in close accord with one another, with the OSHA value being at a two times lower concentration than the ACGIH TLV. The ACGIH-TLV provides some details on derivation, with a statement that "*a safety factor of four should be adequate to account for interindividual differences in sensitivity and the fact that a LOAEL rather than a NOAEL was identified in a human study*" (2007, 192024).

A wide range of General Public reference values are available for MeCl. ATSDR has developed MRLs for all of their duration categories (acute, 1-14 days; intermediate, 15 days to 1 year; and chronic, greater than 1 year). The acute (1-14 day) MRL was based on neurological effects (decreased critical flicker frequency and auditory vigilance performance), whereas both the intermediate (15 days to 1 year) and chronic (one year or longer) duration MRLs were both based on effects on the liver. Time scaling was applied to the acute MRL by using a PBPK model, with uncertainty factors applied for inter-individual variability ($UF_H = 10$) and for use of a LOAEL ($UF_L = 10$) in a human study. Essentially no adjustments were made to the NOAEL of 25 ppm from a rat study as the basis for the intermediate MRL; the ratio between blood:gas partition coefficients for rats and humans was set equal to one, and the exposure was continuous for 14 weeks; only uncertainty factors were applied. Adjustments for exposure schedule only were made to the chronic rat study used as the basis for the chronic MRL. Acute and chronic CA-REL reference values, as well as a World Health Organization (WHO) value are available for methylene chloride.

In looking across the available inhalation health effect reference values for MeCl, a consistent stair-step decrease in concentration as duration of exposure increases can be seen across the General Public values. There is strong concordance between the 24-hour WHO value and the acute ATSRD MRL, and between the chronic MRL and the chronic CA-REL.

It is important to note that the AEGL-1 values stop at one hour. This may be important if exposures at or near the 1-hour AEGL persist for longer durations, as the steep concentration by time ($C \times t$) relationship for AEGL-2 levels transect the extrapolation of the AEGL-1 to longer durations. The AEGL-2 effect for MeCl is based on a clinically significant increase in the potential to trigger angina (chest pain) in patients with coronary artery disease when blood COHb levels reach 4% (NAC/AEGL, 2008, 192207), which is more severe than the slight CNS effects (light-headedness and difficulty with enunciation) for the AEGL-1.



*** Indicates an occupational value; expert judgment necessary prior to applying these values to the general public.**

Figure 2.16. Comparison of Available Health Effect Reference Values for Inhalation Exposure to Methylene Chloride

Table 2.16. Details on derivation of the specific inhalation health effect reference values for methylene chloride.

Reference Value Type / Name		Duration	Reference Value (mg/m^3)	Reference Value (ppm)	Health Effect	Point of Departure		Uncertainty Factors	Notes on Derivation	Review Status
Emergency Response[1]	**AEGL-3**	10 min	4.2×10^4	12,000	CNS effects, maximum additional COHb level of 15 % in humans (Haskell Laboratory, 1982, 192293; NAC/AEGL, 2008, 192294)	3.01 mM in blood	Maximum target MeCl level (PBPK)	Total UF = 1 $UF_A = 1$	Time scaling based on maximum MeCl concentration in brain (10 min, 30 min, 1 h, and 4 h values) or COHb formation (8 h values) using PBPK-model	Interim (NAC/AEGL, 2008, 192207)
		30 min	3×10^4	8,500						
		1 hr	2.4×10^4	6,900						
		4 hr	1.7×10^4	4,900						
		8 hr	7.4×10^3	2,100						
	AEGL-2	10 min	6×10^3	1.7×10^3	Absence of CNS effects, maximum additional COHb level of 4 % in humans (NAC/AEGL, 2008, 192294; Winneke, 1974, 180142)	0.137 mM in blood		Total UF = 1 $UF_H = 1$		
		30 min	4.2×10^3	1.2×10^3						
		1 hr	2×10^3	580						
		4 hr	350	101						
		8 hr	210	60.5						
	AEGL-1	10 min	1×10^3	288	Absence of slight CNS effects (Stewart et al., 1972, 029071)	0.063 mM in blood		Total UF = 3 $UF_H = 3$	Time scaling based on maximum MeCl concentration in brain using PBPK-model	
		30 min	810	230						
		1 hr	710	204						
		4 hr	NR	NR						
		8 hr	NR	NR						
	ERPG-3	1 hr	1.4×10^4	4×10^3	Absence of lethality or life-threatening health effects	NR	NR	NR		Final (AIHA, 2002, 192066)
	ERPG-2	1 hr	2.6×10^3	750	Dizziness, sedation effects (Stewart et al., 1972, 029071)	NR	NR	NR		

[1] Emergency Response reference values are developed using an assumption of a rare, "once-in-a-lifetime" exposure scenario, which is a key consideration when comparing these reference values to any Occupational or General Public reference values.

	Reference Value Type / Name	Duration	Reference Value (mg/m^3)	Reference Value (ppm)	Health Effect	Point of Departure		Uncertainty Factors	Notes on Derivation	Review Status
	ERPG-1	1 hr	1042	300	NR[2]	NR	NR	NR		
Occupational	**ACGIH TLV-TWA***	8 hr TWA	174	50	CNS Depression in humans (Putz et al., 1979, 023137; Winneke, 1974, 180142)	200 ppm	LOAEL	Total UF = 4		Final (ACGIH, 2007, 192024)
	NIOSH-IDLH*	30 min	8×10^3	2.3×10^3	Acute inhalation toxicity in humans (Sax, 1975, 018750)	2,300 ppm (1 hr)	Absence of effects	NR		Final (NIOSH, 1996, 192295)
	OSHA-PEL (TWA) *	8 hr TWA	87	25	NR	NR	NR	NR		Final (OSHA, 2006, 192276)
	OSHA-STEL*	< 15 min	434	125						

[2] Reference pending

Reference Value Type / Name		Duration	Reference Value		Health Effect	Point of Departure	Uncertainty Factors	Notes on Derivation	Review Status
			(mg/m^3)	(ppm)					
General Public	**WHO Air Quality Guideline**	24 hr	3	0.86	Production of COHb	NR NR	NR		Final (WHO, 2000, 180143)
		1 week TWA	0.45	0.13					
	CA-REL (Acute)	1 hour	14	4	Impaired performance on dual-task and auditory vigilance tests (Putz et al., 1979, 023137)	240 ppm (195 ppm observed at 90 min) LOAEL	Total UF = 60 UF_L = 6 UF_A = 1 UF_H = 10	1-h concentration extrapolated from 90 minute duration using C^n x t = k where n=2	Final (OEHHA, 2008, 192263)
	ATSDR-MRL (1-14 d)	1 – 14 d	2.1	0.6	Neurological effects in humans (Reitz et al., 1997, 192184; Winneke, 1974, 180142)	60 ppm (300 ppm observed LOAEL) $LOAEL_{ADJ}$	Total UF = 100 UF_L = 10 UF_H = 10	LOAEL adjusted for 24-hr exposure scenario using Reitz et al. (1997, 192184) PBPK model	Final (ATSDR, 2000, 192113)
	ATSDR-MRL (15 – 365 d)	15 d – 1 yr	1.04	0.3	Hepatic effects in rats (Haun et al., 1972, 029036)	25 ppm (25 x 1.0) $NOAEL_{HEC}$	Total UF = 100 UF_L = 3 UF_A = 3 UF_H = 10	Blood:gas partition coefficient for rat of 19.4 and for human of 8.94; ratio = 1, was used	
	ATSDR-MRL (> 1yr)	Chronic	1.04	0.3	Liver histopathology in female rats (Nitschke et al., 1988, 029244)	8.92 ppm (50 ppm x 6/24 x 5/7 x 1.0) $NOAEL_{HEC}$	Total UF = 30 UF_A = 3 UF_H = 10	Blood:gas partition ratio = 1 (See above); adjusted for 6 hr/day, 5 day/week	
	CA-REL (Chronic)	Chronic	0.4	0.12	Elevated carboxyhemoglobin levels (>2%) (DiVincenzo and Kaplan, 1981, 029026)	14 ppm (40 ppm x 10/20 x 5/7) LOAEL	Total UF = 100 UFL = 10 UFA = 1 UFH = 10	Adjusted for 8 hr/day; 5 day/week	Final (OEHHA, 2000, 192225)

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2.17 Chemical-Specific Reference Values for Perchloroethylene (CASRN 127-18-4)

Perchloroethylene (Perc, ethylene tetrachloride, tetrachloroethylene; C_2Cl_4) is a synthetic liquid chemical with a sharp, sweet odor that is detectable at concentrations of 1 ppm or greater. It is a volatile compound and thus the potential for exposure is greatest through the inhalation of contaminated air, which can result in dizziness, loss of consciousness, confusion, nausea, and death. Skin irritation may also occur with repeated exposure. Perchloroethylene is used primarily as a chemical intermediate; other uses include as a metal cleaner, a degreasing agent, and a solvent in dry cleaning. IARC found that perchloroethylene "*is probably carcinogenic to humans (Group 2A)*" (IARC, 1995, 192123). Additional information on the nature of perchloroethylene and detailed summaries of health effects can be found in the AEGL TSD (NAC/AEGL, 2001, 192200), the ATSDR Toxicological Profile (1997, 192111), the OEHHA REL documentation (CARB, 1991, 192266; CARB, 1991, 192269; OEHHA, 2008, 192171), as well as other sources and is not repeated here.

Perchloroethylene has a relatively complete set of inhalation health effect reference values, as shown in Figure 2.17. Additional details are provided in Table 2.17 on the derivation of the available reference values, including the basis, point of departure (POD), time scaling, and uncertainty factors (UFs).

Emergency Response reference values (AEGLs and ERPGs) were developed for all three severity categories (level 1 for mild transient effects; level 2 for irreversible effects or impairment of ability to escape; and level 3 for potentially lethal effects). The ERPG-3 and ERPG-1 values are higher than the corresponding 1-hour AEGL values, while the ERPG-2 value is slightly lower than the AEGL-2. All three AEGL values have time scaling applied following a $C^n \times t = k$ relationship with n = 2. Perchloroethylene AEGL-1 values were based on a human study in which exposure to 75-80 ppm for 1-4 minutes caused slight eye irritation (Stewart et al., 1961, 094466), with the 10- and 30-minute values set equal to each other. In the case of the AEGL-2 value, the 10- and 30-minute values were set equal to the 1-hour value as a human study showed that exposure to 600 ppm for 10 minutes caused significant health effects including irritation, dizziness, and numbness (Rowe et al., 1952, 058210). The 10-minute AEGL-3 value was set equal to the 30-minute AEGL-3 because it was considered inappropriate to scale from a time period of 4 hours to 10 minutes.

There is a relatively complete set of Occupational reference values available for perchloroethylene, including values developed by NIOSH, OSHA, ACGIH, and Australia's National Industrial Chemicals Notification and Assessment Scheme (NICNAS). The NIOSH IDLH Occupational values are derived by a weight of evidence (WOE) approach and no particular study was identified as the basis for the values**.** It has been reported that exposure to 2,000 ppm of perchloroethylene caused slight narcosis in 5 minutes; 9,301,185 ppm caused irritation of the eyes and throat, and marked dizziness after 2 minutes; 1,000 ppm caused slight drunkenness, but no narcosis after 95 minutes; 513,690 ppm caused eye, throat, and nose irritation, dizziness, loss of inhibition, and some incoordination after 10 minutes; 500 ppm for 2 hours caused slight discomfort; 206,356 ppm for 2 hours caused headache, burning of the eyes, sinus congestion, impaired coordination, and nausea; 206,235 ppm for 20 to 30 minutes caused eye irritation, sinus congestion, dizziness, and sleepiness; and 106 ppm caused only slight eye irritation (Negherbon, 1959, 192186; Rowe et al., 1952, 058210). As shown in Figure 2.17, the

Australian STEL (not labeled) and TWA values are slightly higher than the ACGIH STEL and TLV values but lower than the OSHA values.

ATSDR and the California OEHHA have published both acute and chronic General Public reference values for perchloroethylene. Time scaling was applied to the acute CA-REL value using a $C^n \times t = k$ relationship, where n = 2. The acute ATSDR MRL value was adjusted to extrapolate from intermittent exposure to exposure occurring 4 hours per day, while the chronic MRL was adjusted to account for exposure occurring 8 hours per day, 5 days per week. Contrary to most OEHHA-derived values, there is a lack of supporting information on the derivation of the chronic CA-REL value for perchloroethylene.

There is good coverage across types of inhalation health effect reference values, severity of effects, and durations for perchloroethylene. All of the General Public reference values are below the Emergency Response and Occupational values, as would be expected, and the values decrease in exposure concentration with increasing duration. Cancer is mentioned as a concern for this compound for all of the Occupational reference values as well as in the chronic CA-REL.

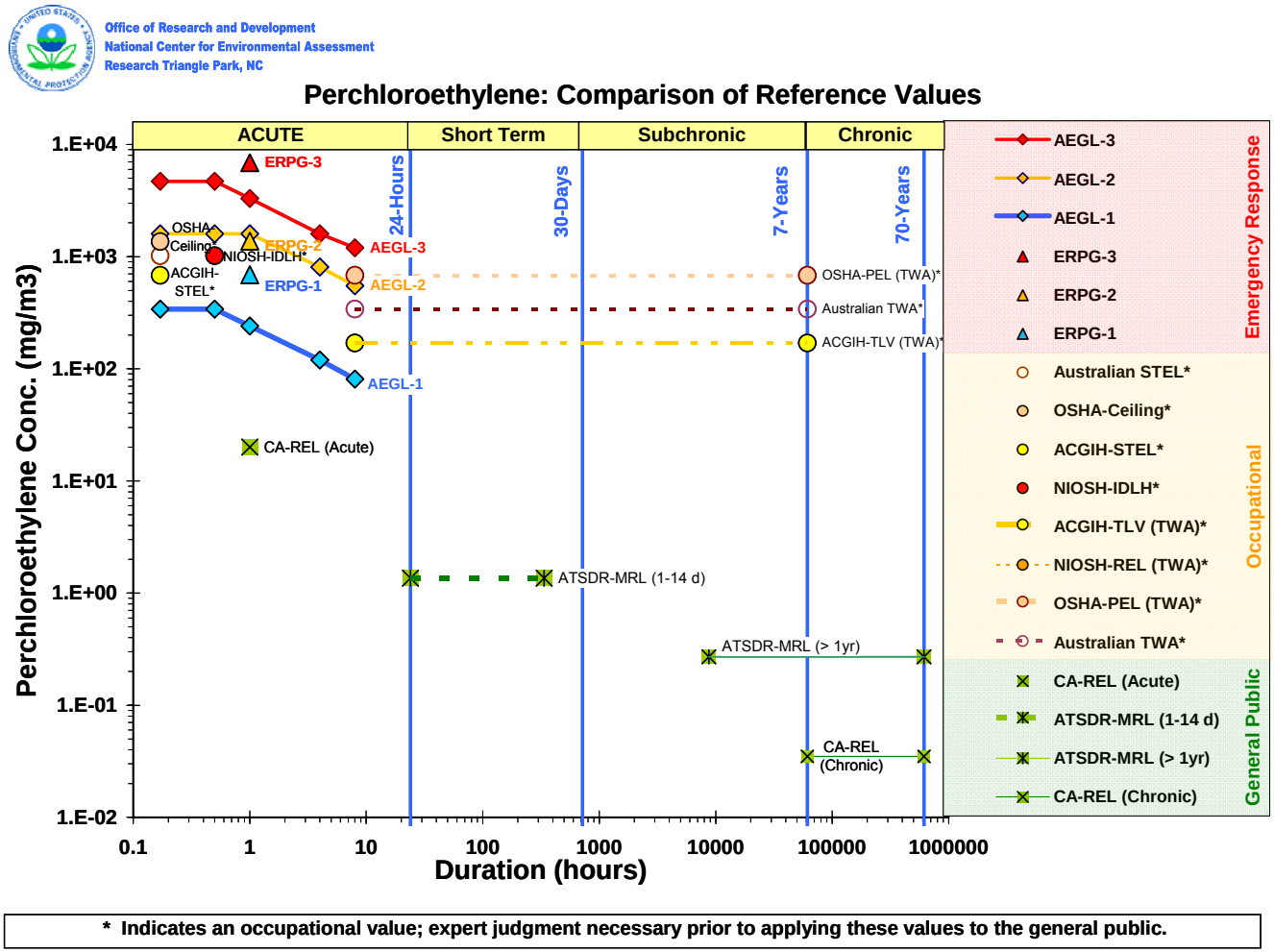

Figure 2.17. Comparison of Available Health Effect Reference Values for Inhalation Exposure to Perchloroethylene

Table 2.17. Details on derivation of the specific inhalation health effect reference values for perchloroethylene.

Reference Value Type / Name		Duration	Reference Value (mg/m^3)	Reference Value (ppm)	Health Effect	Point of Departure		Uncertainty Factors	Notes on Derivation	Review Status
Emergency Response[1]	**AEGL-3**	10 min	4700	690	Lethality (Friberg et al., 1953, 058329; NTP, 1986, 192272)	2450 ppm for 4 hrs (mice), 2445 ppm for 4 hrs (rats)	NOAEL	Total UF = 10 UF_A = 3 UF_H = 3	Time scaling: C^n x t = k where n = 2; 10 min equal to 30-min value	Interim (NAC/AEGL, 2001, 192200)
		30 min	4700	690						
		1 hr	3300	490						
		4 hr	1600	240						
		8 hr	1200	170						
	AEGL-2	10 min	1600	330	Ataxia (Goldberg et al., 1964, 058035)	1150 ppm (4 hr/d, 5 d/week for 2 weeks	NOAEL	Total UF = 10 UF_A = 3 UF_H = 3	Time scaling: C^n x t = k where n = 2; 10 and 30 min values equal to 1-hr value	
		30 min	1600	330						
		1 hr	1600	230						
		4 hr	810	120						
		8 hr	550	81						
	AEGL-1	10 min	340	50	Eye irritation (Rowe et al., 1952, 058210)	106 ppm (1 hr)	NR	Total UF = 3 UF_H = 3	Time scaling: C^n x t = k where n = 2; 10 min equal to 30-min value	
		30 min	340	50						
		1 hr	240	35						
		4 hr	120	18						
		8 hr	81	12						
	ERPG-3	1 hr	6781	1000	Lethality (Carpenter, 1937, 058185; Hake and Stewart, 1977, 058147; Rowe et al., 1952, 058210)	1000 ppm	Reportedly well tolerated in humans	NR		Final (AIHA, 2002, 192079)
	ERPG-2	1 hr	1356	200	CNS effects (Rowe et al., 1952, 058210)	NR	NR	NR		

[1] Emergency Response reference values are developed using an assumption of a rare, "once-in-a-lifetime" exposure scenario, which is a key consideration when comparing these reference values to any Occupational or General Public reference values.

Reference Value Type / Name		Duration	Reference Value (mg/m^3)	Reference Value (ppm)	Health Effect	Point of Departure		Uncertainty Factors	Notes on Derivation	Review Status
	ERPG-1	1 hr	678	100	Detectable odor (American Industrial Hygiene Association, 1989, 192018; Rowe et al., 1952, 058210; Stewart et al., 1970, 003141)	100 ppm (1 hr)	NR	NR		
Occupational	**ACGIH TLV-TWA***	8 hour TWA	170	25	Headache, dizziness, sleepiness, incoordination (ATSDR, 1997, 192111; Hake and Stewart, 1977, 058147; Rowe et al., 1952, 058210; Stewart et al., 1970, 003141)	NR	NR	NR		Final (ACGIH, 2007, 192024)
	ACGIH TLV-STEL*	15 min	680	101	Anesthetic-like effects (ACGIH, 2007, 192024)	NR	NR	NR		
	OSHA-PEL (TWA) *	8 hr TWA	680	100	NR	NR	NR	NR		(OSHA, 2006, 192276)
	OSHA-Ceiling*	Any 5 min period	1360	200						
	NIOSH-IDLH (<30 min) *	< 30 min	1020	150	Acute inhalation toxicity data in humans	NR	NR	NR		Final (NIOSH, 1996, 192296)
	NIOSH-STEL (TWA)*	15 min	678	100						

Reference Value Type / Name		Duration	Reference Value (mg/m^3)	Reference Value (ppm)	Health Effect	Point of Departure		Uncertainty Factors	Notes on Derivation	Review Status
	Australian TWA*	8 hr TWA	340	50	NR	NR	NR	NR		Final (NICNAS, 2006, 192040)
	Australian STEL*	15 min	1020	150						

Reference Value Type / Name		Duration	Reference Value (mg/m^3)	Reference Value (ppm)	Health Effect	Point of Departure		Uncertainty Factors	Notes on Derivation	Review Status
General Public	**CA-REL (Acute)**	1 hr	20	2.9	CNS effects, headache, eye, nose and throat irritation (Stewart et al., 1970, 003141)	1200 mg/m^3 (700 mg/m^3 observed)	$LOAEL_{ADJ}$	Total UF = 60 UF_L = 6 UF_H = 10	LOAEL based on 3 hr exposure extrapolated to 1 hr exposure via C^n x t = k where n = 2	Final (OEHHA, 2008, 192171)
	ATSDR-MRL (1-14 d)	1 - 14 days	1.36	0.2	Increase in VEP latencies in humans (Altmann et al., 1992, 180098)	1.67 ppm (10 ppm x 4/24)	NOAEL	Total = 10 UF_H = 10	Adjusted for 4 hr/d to extrapolate from intermittent exposure	Final (ATSDR, 1997, 192111)
	CA-REL (Chronic)	Chronic	0.035	5×10^{-3}	Kidney; alimentary system (liver); Cancer	NR	NR	NR		Final (CARB, 1991, 192269)
	ATSDR-MRL (> 1yr)	Chronic	0.27	0.04	Increased reaction time in humans (Ferroni et al., 1992, 066305)	3.57 ppm (15 ppm x 8/24 x 5/7)	LOAEL	Total UF = 100 UF_L = 10 UF_H = 10	Adjusted for 8 hr/day; 5 d/week	Final (ATSDR, 1997, 192111)

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2.18 Chemical-Specific Reference Values for Phosgene (CASRN 75-44-5)

Phosgene (Agent CG; $COCl_2$) is a colorless gas at ambient temperature and pressure, with an odor reminiscent of newly-mown hay, reportedly detectable at 0.9 ppm (Amoore and Hautala, 1983, **028918**). Phosgene was formerly used as a chemical warfare agent. It is manufactured from a reaction of carbon monoxide and chlorine gas in the presence of activated charcoal, and is used in the production of dyestuffs, isocyanates, carbonic acid esters (polycarbonates), acid chlorides, insecticides, and pharmaceutical chemicals. Manufacture of phosgene is approximately 1 million tons per year in the United States. Additional details on the chemical nature of phosgene and its potential for toxic effects are covered more fully elsewhere (AIHA, 2002, **192095**; NRC, 2002, **192139**; U.S. EPA, 2005,). The remainder of this discussion focuses on the generally available inhalation health effect reference values for phosgene.

Inhalation health effect reference values for phosgene are displayed graphically in Figure 2.18. Details available on the derivation of these values, including key effects, studies, adjustments, and uncertainty factors (UFs) are shown in Table 2.18.

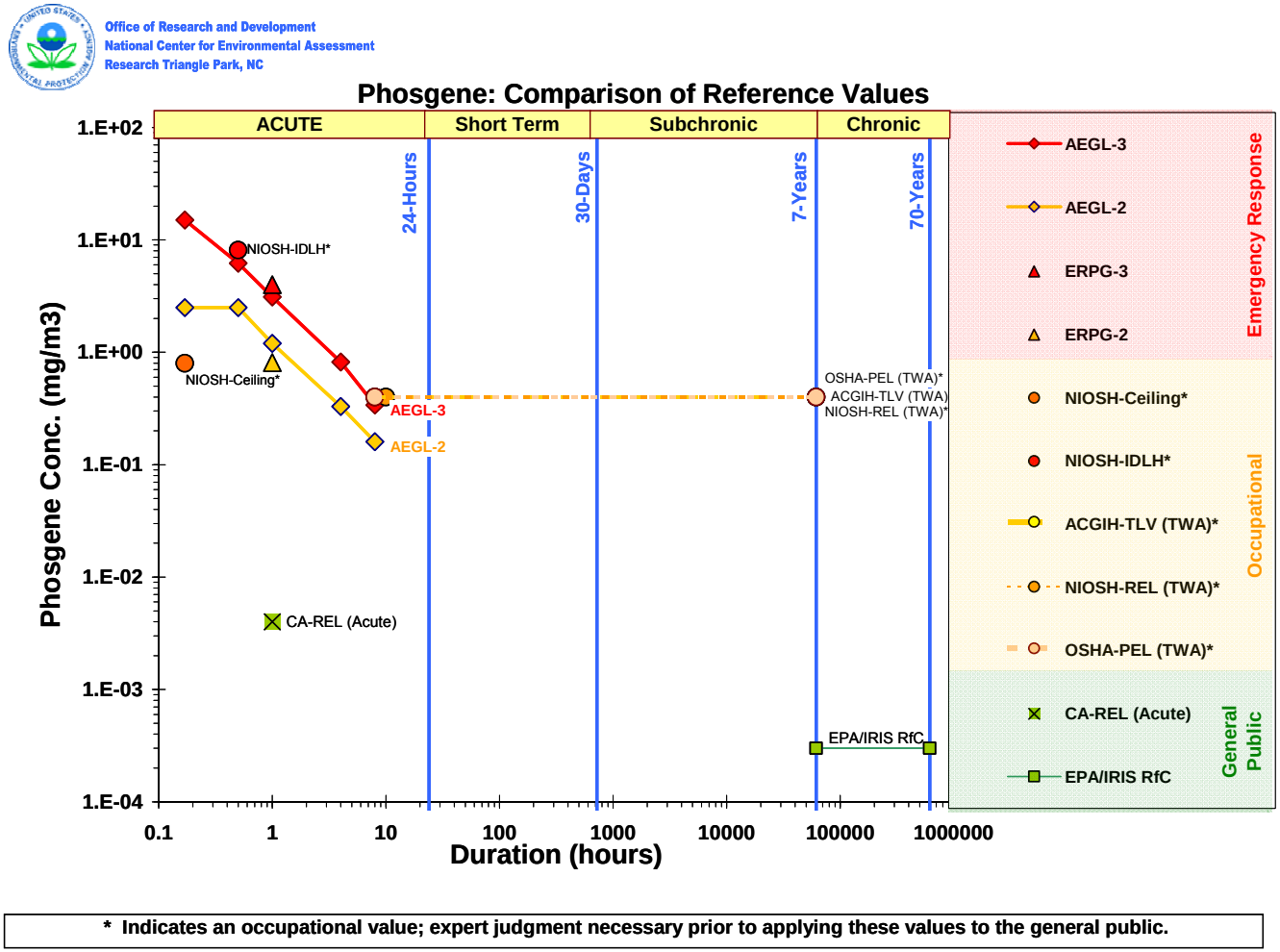
Emergency Response values have been developed for AEGLs and ERPGs at severity levels 2 (irreversible adverse effects or impairment of escape) and 3 (threshold for lethality), but no level 1 values were derived due to the lack of warning properties (e.g., odor detection) or mild effect levels at exposures below the AEGL-2 or ERPG-2. The one-hour AEGL values at both severity levels are in fairly close agreement with the corresponding ERPGs, even though the documents cite different key studies as the basis for the derived values. The time scaling used in the AEGLs applied a duration slope factor of one (n = 1 in the $C^n \times t$ equation). This is in keeping with the observations from the seminal work that led to Haber's "rule" (Haber, 1924, **059334**) and verified in more recent studies (Zwart et al., 1990, **021153**; ten Berge et al., 1986, **025664**).

The NIOSH Occupational values are derived by a weight of evidence approach and no particular study was identified as the basis for the values. A concentration of 5 ppm for 30 minutes was reported to be probably lethal for exposures of 30 minutes (Jacobs, 1967, **192298**). Gross et al. (1965, **061915**) indicated that exposure to concentrations as low as 0.5 ppm for 2 hours caused definite pathological changes in the lungs of rats; the investigators believed some abnormalities were present 3 months after rats had been exposed at 2 ppm for 80 minutes. An IDLH of 2 ppm is used for phosgene to prevent irreversible adverse health effects. It has been calculated that based on acute toxicity data in humans, the lethal dose for a 30 minute exposure would be about 17 ppm (Diller, 1978, **061910**). It has also been stated that exposure to 25 ppm for 30 to 60 minutes is dangerous and that brief exposure to 50 ppm may be rapidly fatal (Henderson and Haggard, 1943, **010318**). Studies also report that 5 ppm is probably lethal for a 30 minute exposure (Jacobs, 1967, **192298**). The occupational time-weighted average (TWA) reference values – the ACGIH TLV, NIOSH REL, and OSHA PEL – all being identical to one another, with the ACGIH documentation (2007, **192024**) providing the most background on the basis for the value.

The General Public reference values include both an acute (1-hour) CA-REL and a chronic EPA/IRIS RfC. The acute CA-REL value is based on a NOAEL for histological changes in the lung and did not apply any adjustments other than those implied in the uncertainty factors. The chronic RfC did apply the Regional gas dose ratio (RGDR) used in derivation of an HEC for gases [details available in the Toxicological Review for Phosgene (U.S. EPA, 2005, 192297)], as

well as adjustments for the 6 hour per day exposure schedule used with the experimental animals (rats) in the key studies (Kodavanti et al., 1997, 083623; Selgrade et al., 1995, 180126).

There is fair coverage across types of inhalation health effect reference values, severity of effects, and durations for phosgene. The greatest gap is for reference values for the general public in the short-term and subchronic durations.



* Indicates an occupational value; expert judgment necessary prior to applying these values to the general public.

Figure 2.18. Comparison of Available Health Effect Reference Values for Inhalation Exposure to Phosgene

Table 2.18. Details on derivation of the specific inhalation health effect reference values for phosgene.

Reference Value Type / Name		Duration	Reference Value (mg/m^3)	Reference Value (ppm)	Health Effect	Point of Departure		Uncertainty Factors	Notes on Derivation	Review Status
Emergency Response[1]	**AEGL-3**	10 min	15	3.6	Lethality (Zwart et al., 1990, 021153)	36 ppm	LC_{01}	Total UF = 10 UF_A = 3 UF_H = 3	Time scaling: $C^n \times t = k$ where n = 1. Haber's Law ($C \times t = k$) was originally derived from phosgene data (Haber, 1924, 059334).	Final (NAC/AEGL, 2002, 192299)
		30 min	6.2	1.5		15 ppm	LC_{01}			
		1 hr	3.1	0.75						
		4 hr	0.82	0.2						
		8 hr	0.34	0.09						
	AEGL-2	10 min	2.5	0.6	Chemical pneumonia (Gross et al., 1965, 061915)	2 ppm (90 min)	NR	Total UF = 10 UF_A = 3 UF_H = 3		
		30 min	2.5	0.6						
		1 hr	1.2	0.3						
		4 hr	0.33	0.08						
		8 hr	0.16	0.04						
	ERPG-3	1 hr	4	1	Pulmonary edema and lethality (Diller et al., 1985, 059296; Rinehart and Hatch, 1964, 061919)	1 ppm	NR	NR		Final (AIHA, 2002, 192095)

[1] Emergency Response reference values are developed using an assumption of a rare, "once-in-a-lifetime" exposure scenario, which is a key consideration when comparing these reference values to any Occupational or General Public reference values.

Reference Value Type / Name		Duration	Reference Value (mg/m^3)	Reference Value (ppm)	Health Effect	Point of Departure		Uncertainty Factors	Notes on Derivation	Review Status
	ERPG-2	1 hr	0.81	0.2	Pulmonary effects (Currie et al., 1985, 059289; Frosolono and Currie, 1985, 059308; Gross et al., 1965, 061915; Mautone et al., 1985, 059413; Rinehart and Hatch, 1964, 061919)	0.2 ppm	NR	NR		

Reference Value Type / Name		Duration	Reference Value (mg/m^3)	Reference Value (ppm)	Health Effect	Point of Departure		Uncertainty Factors	Notes on Derivation	Review Status
Occupational	**ACGIH TLV-TWA***	Any	0.4	0.1	Pulmonary irritation (Cameron et al., 1942, 059386; Diller, 1978, 061910; Henschler and Laux, 1960, 059321; Underhill, 1920, 059389)	NR	NR	NR		Final (ACGIH, 2007, 192024)
	OSHA-PEL (TWA) *	8 hr TWA	0.4	0.1	NR	NR	NR	NR		
	NIOSH–Ceiling*	15 min	0.8	0.2	NR	NR	NR	NR		Final (NIOSH, 2006, 192177)
	NIOSH-IDLH*	< 30 min	8.1	2	Acute inhalation toxicity data in humans	NR	NR	NR		Final (NIOSH, 1996, 192300)
	NIOSH-REL (TWA)*	10 hr TWA	0.4	0.1	NR	NR	NR	NR		Final (NIOSH, 2006, 192177)

Reference Value Type / Name		Duration	Reference Value (mg/m^3)	Reference Value (ppm)	Health Effect	Point of Departure		Uncertainty Factors	Notes on Derivation	Review Status
General Public	**CA-REL (Acute)**	1 hr	4×10^{-3}	1×10^{-3}	Histologic changes in lungs in rats (Diller et al., 1985, 059296)	0.1 ppm	NOAEL (1 hr) LOAEL (4 hr)	Total UF = 100 $UF_A = 10$ $UF_H = 10$		Final (OEHHA, 2008, 192301)
	Chronic RfC (IRIS)	8 hr	3×10^{-4}	7.4×10^{-5}	Increase in lung displacement volume, chronic lung damage, impaired resistance to bacterial infection in rats (Kodavanti et al., 1997, 083623; Selgrade et al., 1995, 180126)	0.03 mg/m^3 (0.73 mg/m^3 × 6/24 ×1.51)	$BMCL_{10}$ (HEC)	Total UF = 300 $UF_H = 10$ $UF_A = 3$ $UF_S = 3$ $UF_L = 3$	Adjustments for duration (6hr/day) and differences in animal to human respiratory systems (RGDR = 1.51)	Final (U.S. EPA, 2005, 192297)

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2.19 Chemical-Specific Reference Values for Phosphine (CASRN 7803-51-2)

Phosphine (PH_3) is a colorless gas used as a fumigant against insects and rodents in stored grain (NAC/AEGL, 2008, 192209). Paper sachets containing aluminum phosphide are added to grain and the grain is then sealed. The aluminum phosphide reacts with moisture in the grain to produce the phosphine gas. Phosphine is also used as a doping agent to treat silicon crystals in the semiconductor industry and is a byproduct of metallurgical reactions. Pure phosphine is odorless at concentrations up to 200 ppm. Additional, chemical-specific details and toxicological summaries are available from other sources (AIHA, 2002, 192088; NAC/AEGL, 2008, 192209; OEHHA, 2002, 192227; U.S. EPA, 1995, 192217) and are not repeated here.

Inhalation health effect reference values for phosphine are displayed graphically in Figure 2.19. Details available on the derivation of these values, including key effects, studies, adjustments, and uncertainty factors (UFs) are shown in Table 2.19.

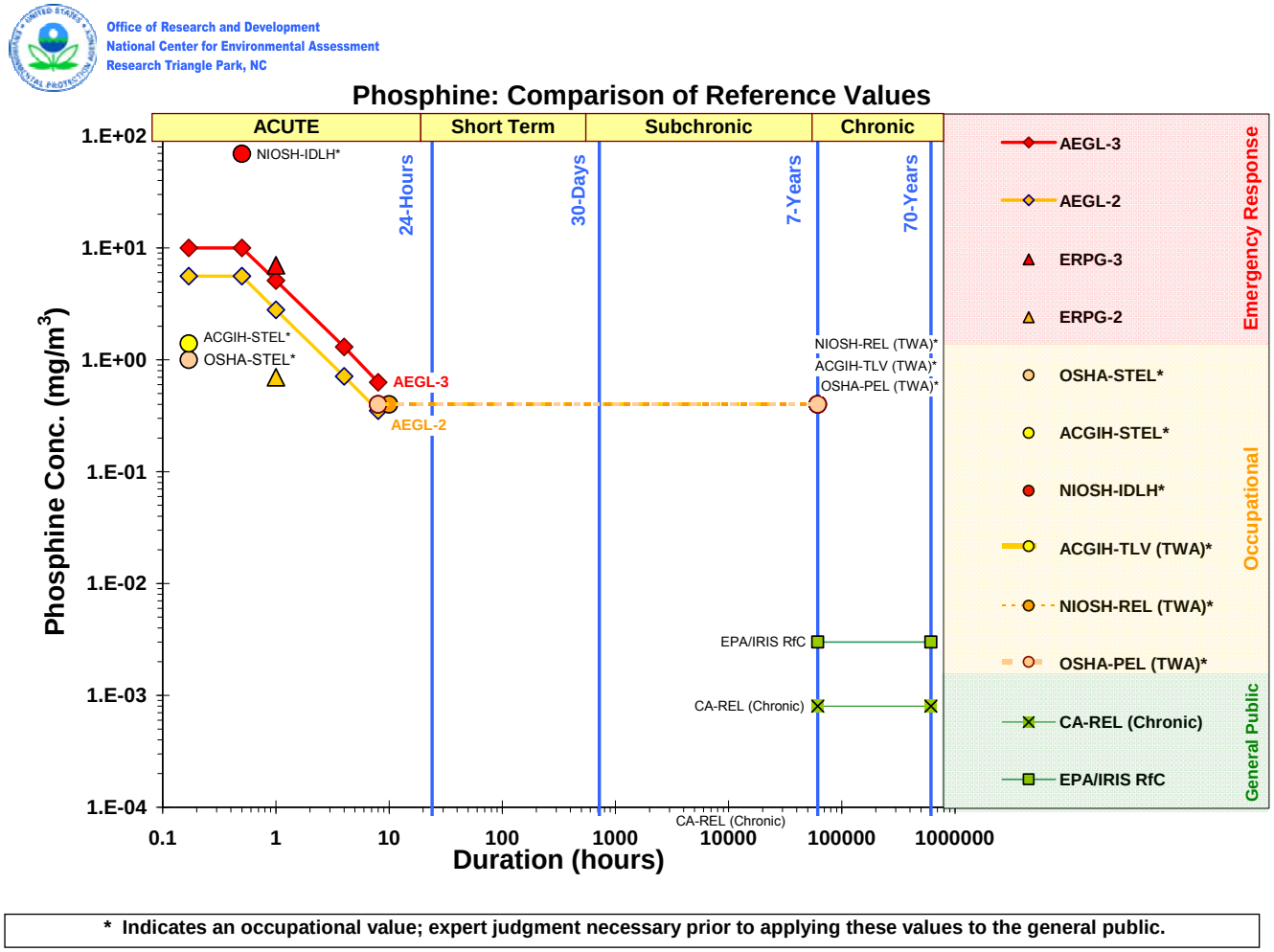
The Emergency Response reference values (AEGLs and ERPGs) for phosphine were derived for severity level 2 (irreversible effects or impairment of escape) and level 3 (severe effects with potential lethality), but not for level 1 as the toxicity at lower concentrations could not be characterized and awareness (e.g., odor detection) occurs at concentrations above the AEGL-2 and ERPG-2. Chemical-specific data on lethality were available to allow calculation of the duration slope factor [value of n in the $C^n \times t$ formula (ten Berge et al., 1986, 025664)] of n = 1 which was used in extrapolating from 6-hour data for both the AEGL-2 and AEGL-3. The 30-minute values were adopted as the 10-minute values as cited in the AEGL SOPs (NRC, 2001, 192042), where extrapolations across durations from observations greater than or equal to four hours to shorter durations is limited to the 30-minute value to avoid extending the extrapolation too far. The AEGL-3 and ERPG-3 are in close accord with one another; however, the 1-hour AEGL-2 is a factor of four higher than the corresponding ERPG-2.

Most of the Occupational reference values are based on a single occupational study (Jones et al., 1964, 095137), with several studies providing additional support (Henderson and Haggard, 1943, 010318; Misra et al., 1988, 066895). Details on the derivation for all of the occupational values are sparse, and indications are that a weight of evidence (WOE) approach was used in arriving at the published values, with the best documentation provided for the NIOSH IDLH and ACGIH TLV values (ACGIH, 2007, 192024; NIOSH, 1996, 192302). The ACGIH TLV documentation noted that although the values are protective of gastrointestinal, respiratory and central nervous system effects, that there is some potential for chronic phosphorus poisoning from phosphine exposure (ACGIH, 2007, 192024)

The chronic General Public reference values – the Chronic CA-REL and EPA/IRIS RfC – both used the same key study (Barbosa et al., 1994, 062969) and performed similar adjustments to arrive at the human equivalent concentration (HEC). Differences in the calculated values were due to variation in the uncertainty factors applied and to methodological differences (i.e., the point in the process where unit conversions and rounding of values were applied). No reference values for less than

lifetime exposure durations were developed for exposure of the general population to phosphine.

Overall coverage for the types of exposures anticipated for phosphine is good. Addition of an acute and other less-than-lifetime general public reference values would help to complete the collection of available inhalation health effect reference values for phosphine.



* Indicates an occupational value; expert judgment necessary prior to applying these values to the general public.

Figure 2.19. Comparison of Available Health Effect Reference Values for Inhalation Exposure to Phosphine

Table 2.19. Details on derivation of the specific inhalation health effect reference values for phosphine.

Reference Value Type / Name		Duration	Reference Value (mg/m^3)	Reference Value (ppm)	Health Effect	Point of Departure		Uncertainty Factors	Notes on Derivation	Review Status
Emergency Response[1]	**AEGL-3**	10 min	10	7.2	Lethality (Newton, 1991, 192039)	18 ppm (6 hrs)	NR	Total UF = 30 UF_A = 3 UF_H = 10	Time Scaling: C^n x t = k where n = 1; derived empirically from rat lethality data. 10 min values adopted from 30 minutes as per SOPs (NRC, 2001, 192042)	Final (NAC/AEGL, 2008, 192209)
		30 min	10	7.2						
		1 hr	5.1	3.6						
		4 hr	1.3	0.90						
		8 hr	0.63	0.45						
	AEGL-2	10 min	5.6	4.0	Red mucoid nasal discharge seen in rats from exposure for 6 hr (Newton et al., 1993, 180123)	10 ppm (6 hrs)	NR	Total UF = 30 UF_A = 3 UF_H = 10		
		30 min	5.6	4.0						
		1 hr	2.8	2.0						
		4 hr	0.71	0.50						
		8 hr	0.35	0.25						
	ERPG-3	1 hr	7	5	4-hr lethal concentration in animals between 11 and 40 ppm; no lethality in rats exposed repeatedly to 5 ppm (Muller, 1940, 193931)(Kligerman et al., 1994, 180291; Muthu et al., 1980, 066897; Newton et al., 1993, 180123; Waritz and Brown, 1975, 065707)	11-40 ppm	WOE	NR	Weight of evidence approach; details on derivation not provided	Final (AIHA, 2002, 192088)

[1] Emergency Response reference values are developed using an assumption of a rare, "once-in-a-lifetime" exposure scenario, which is a key consideration when comparing these reference values to any Occupational or General Public reference values.

Reference Value Type / Name		Duration	Reference Value (mg/m^3)	Reference Value (ppm)	Health Effect	Point of Departure		Uncertainty Factors	Notes on Derivation	Review Status
	ERPG-2	1 hr	0.7	0.5	Reversible, mild-to-moderate respiratory and CNS effects in humans exposed to 1 ppm for 1-3 hrs (Misra et al., 1988, 066895)	1 ppm (<2-3 hrs) 2 ppm (10 mins)	LOAEL NOAEL	NR		
Occupational	**ACGIH TLV-TWA***	8 hr TWA	0.42	0.3	Respiratory, gastrointestinal, and CNS symptoms (Jones et al., 1964, 095137)	NR	NR	NR		Final (ACGIH, 2007, 192024)
	ACGIH TLV-STEL*	15 min	1.4	1		NR	NR	NR		
	OSHA-PEL (TWA) *	8 hr TWA	0.4	0.3	Systemic toxicity	NR	NR	NR		Final (OSHA, 1989, 192303)
	NIOSH–REL (TWA)*	10 hr TWA	0.4	0.3	Acute inhalation toxicity in humans (Jones et al., 1964, 095137)	NR	NR	NR		Final (NIOSH, 2006, 192177)
	NIOSH-IDLH (<30 min) *	30 min	70	50		1,000 ppm (5 min)	LC_{Lo}	NR		Final (NIOSH, 1996, 192302)
	NIOSH-STEL*	15 min	1	1		NR	NR	NR		
Publi	**CA-REL (Chronic)**	Chronic	8×10^{-4}	6×10^{-4}	Decreased body weight, increase in relative organ weights, increase in micronuclei in mice	0.178 ppm (1 ppm x 6/24 x 5/7)	$NOAEL_{HEC}$	Total UF = 300 $UF_S = 3$ $UF_A = 10$ $UF_H = 10$	Adjustments for 6 hr/day, and 5 day/wk animal exposure	Final (OEHHA, 2002, 192227)

Reference Value Type / Name		Duration	Reference Value		Health Effect	Point of Departure		Uncertainty Factors	Notes on Derivation	Review Status
			(mg/m^3)	(ppm)						
	Chronic RfC (IRIS)	Chronic	3×10^{-4}	2×10^{-4}	(Barbosa et al., 1994, 062969)	0.25 mg/m^3 (1.4 mg/m^3 x 6/24 x 5/7)	$NOAEL_{HEC}$	Total UF = 1000 UF_H = 10 UF_S = 10 UF_D = 3 UF_A = 3	schedule	Final (U.S. EPA, 1995, 192217)

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2.20. Chemical-Specific Reference Values for Sarin (GB) (CASRN 107-44-8)

Sarin (Agent GB; isopropyl methylphosphonofluoridate) is one of several organophosphate (OP) nerve agents that have been specifically designed and formulated to cause death, major injuries, or incapacitation to enemy forces in wartime. The term "nerve" agent refers to its anti-cholinesterase properties. Nerve agents are particularly effective in a military sense because of their potency. Detailed descriptions of nerve agent toxicity as well as the physical nature of this chemical agent can be found in the AEGL Technical Support Document (NAC/AEGL, 2003, 192304), and is not repeated here.

There are only two sources of health effect reference values for the chemical warfare agent GB: the National Advisory Committee for Acute Exposure Guideline Levels (2003, 192304) and the Centers for Disease Control and Prevention (CDC, 2003, 192190). Both organizations used the same limited set of data for deriving values for GB. The dataset for GB was the most robust of all of the nerve agents, therefore, the relative potency of GB was used to derive values for the nerve agents Tabun (GA) and Agent VX.

AEGL-3 values for GB were derived based on a calculated lethality at the one percent level (LC_{01}) in female rats using observations at 10-, 30-, 60-, 240-, and 360-minutes (see Table 2.20). Studies showing miosis (pinpoint pupils) in female rats (Mioduszewski et al., 2000, 192305) and visual acuity effects in humans (Baker and Sedgewick, 1996, 180099) were the basis for the AEGL-1 and AEGL-2, respectively. For the AEGL-1, a UF_A of 1 was used based on the observation that miosis response to GB vapors is similar across mammalian species.

A series of Federal Register Notices published by the Centers for Disease Control and Prevention (CDC, 1988, 192173; CDC, 2002, 192175; CDC, 2003, 192190; CDC, 2004, 192193) document the Airborne Exposure Levels designed for application to the agents Tabun (GA), Sarin (GB), VX, Mustard Agent (H, HD, T) and Lewisite (L) for the protection of workers at chemical weapon decommissioning facilities and the general population living near those facilities. The first set of recommendations (CDC, 1988, 192173) were applied for over 14 years, and over the intervening years there was no apparent impact to human health; however, to be consistent with more recent risk assessment practice a reevaluation using the conventional risk assessment methods for inhalation exposures developed by the Environmental Protection Agency (U.S. EPA, 1994, 192307) was conducted and a set of revised values were published in the Federal Register (CDC, 2003, 192190) for the agents GA, GB and VX.

The Airborne Exposure Level values for GB included a General Population Limit (GPL), a Worker Population Limit (WPL), as well as a Short-term Exposure Limit (STEL) and Immediately Dangerous to Life and Health (IDLH) occupational values (CDC, 2003, 192190). The GPL and WPL values for GB were based on exposures of 20 minutes per day for 4 days per week and were adjusted to derive a Lowest Observable Adverse Effect Level Human Equivalent Concentration ($LOAEL_{HEC}$) for 24 hour and 8 hour time weighted averages (TWAs), respectively. Fewer details were provided regarding the derivation of the STEL and IDLH values, and it is assumed that a weight of evidence approach was used in their derivation.

The resulting values for both the AEGL and CDC are shown in Figure 2.20 and Table 2.20. More recent research by the U.S. Army provides additional data that may lead to further revision of both sets of values (Hulet et al., 2006, 192144).

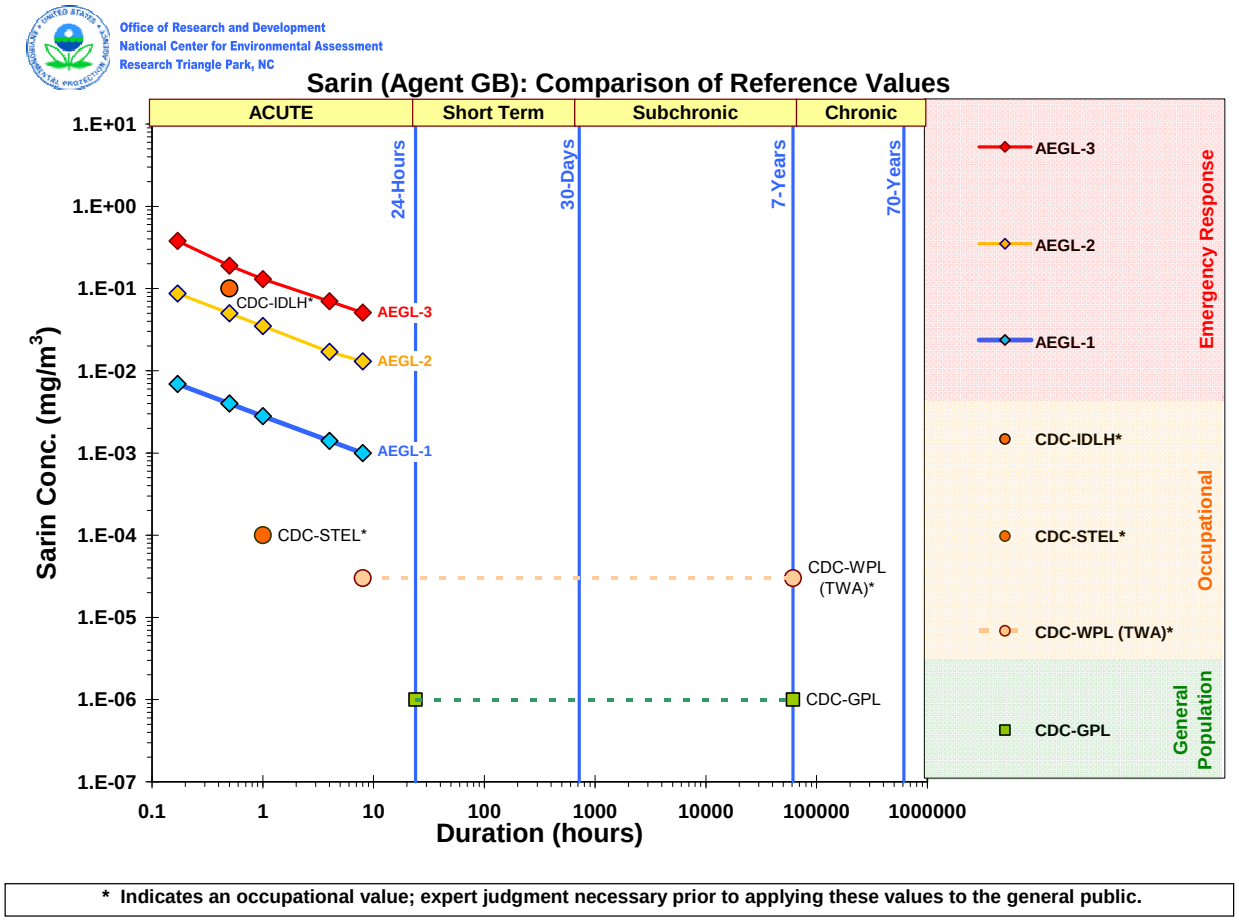

Figure 2.20. Comparison of Available Health Effect Reference Values for Inhalation Exposure to Sarin (GB).

Table 2.20. Details on derivation of the specific inhalation health effect reference values for Sarin (GB).

Reference Value Type / Name		Duration	Reference Value (mg/m^3)	Reference Value (ppm)	Health Effect	Point of Departure		Uncertainty Factors	Notes on Derivation	Review Status
Emergency Response[1]	AEGL-3	10 min	0.38	0.064	Lethality (Mioduszewski et al., 2000, 192305; Mioduszewski et al., 2001, 192306; Mioduszewski et al., 2002, 180121)	11.54 mg/m^3	LC_{01}	Total UF = 30 UF_A = 3 UF_H = 10	Discrete LC_{01} values were derived at each duration for use as AEGL-3 PODs. Time scaling using C^n x t where n = 2.	Final (NAC/AEGL, 2003, 192304)
		30 min	0.19	0.032		5.84 mg/m^3				
		1 hr	0.13	0.022		4.01 mg/m^3				
		4 hr	0.070	0.012		2.09 mg/m^3				
		8 hr	0.051	0.0087		1.76 mg/m^3 (6 hr)				
	AEGL-2	10 min	0.087	0.015	Miosis, dyspnea, photophobia, inhibition of RBC-ChE seen in humans (Baker and Sedgewick, 1996, 180099)	0.5 mg/m^3 (30 min)	Sub-clinical effects	Total UF = 10 UF_A = 1 UF_H = 10		
		30 min	0.050	0.0085						
		1 hr	0.035	0.0060						
		4 hr	0.017	0.0029						
		8 hr	0.013	0.0022						
	AEGL-1	10 min	0.0069	1.2×10^{-3}	Induction of miosis in female rat (Mioduszewski et al., 2002, 192189)	Range of 0.01-0.48 mg/m^3 at 10 min, 60 min, and 240 min	EC_{50}	Total UF = 10 UF_A = 1 UF_H = 10		
		30 min	0.0040	6.8×10^{-4}						
		1 hr	0.0028	4.8×10^{-4}						
		4 hr	0.0014	2.4×10^{-4}						
		8 hr	0.0010	1.7×10^{-4}						
Occupational	CDC-WPL (TWA)*	8 hr TWA	3×10^{-5}	5.2×10^{-6}	Miosis (McKee and Woolcott, 1949, 192172)	0.06 mg/m^3 (20 min/d, for 4 days)	$LOAEL_{HEC}$	Total UF = 30 UF_L = 3 UF_S = 10	Adjusted for duration and breathing rate, details not provided.	Final (CDC, 2003, 192190)

[1] Emergency Response reference values are developed using an assumption of a rare, "once-in-a-lifetime" exposure scenario, which is a key consideration when comparing these reference values to any Occupational or General Public reference values.

Reference Value Type / Name		Duration	Reference Value		Health Effect	Point of Departure	Uncertainty Factors	Notes on Derivation	Review Status
			(mg/m^3)	(ppm)					
	CDC-IDLH*	30 min	0.1	1.7×10^{-2}	NR	NR NR	NR		
	CDC-STEL*	15 min (up to 4x per day)	1×10^{-4}	1.7×10^{-5}	NR	NR NR	NR		
General Population	**CDC GPL**	24 hour	1×10^{-6}	1.7×10^{-7}	Miosis (McKee and Woolcott, 1949, 192172)	0.06 mg/m^3 $LOAEL_{HEC}$ (20 min/d, for 4 d/wk)	Total UF = 300 $UF_L = 3$ $UF_S = 10$ $UF_H = 10$	Adjusted for duration and breathing rate, details not provided.	Final (CDC, 2003, 192190)

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2.21. Chemical-Specific Reference Values for Styrene (CASRN 100-42-5)

Styrene (C_8H_8) is a colorless or slightly yellow, viscous liquid (NAC/AEGL, 2008, 192210). Pure styrene has a pungent, slightly sweetish odor; however, oxidation may lead to the formation of peroxides, certain aldehydes and ketones giving a sharp, penetrating, disagreeable odor. When emitted into the air, its half-life is estimated to be about 2 hours, and chemical transformation products include benzaldehyde and formaldehyde, both of which are odorous air pollutants. Owing to its volatility, low flash point, and the range of explosive limits in air (lower: 1.1 %, upper: 6.3 % v/v), styrene poses an acute fire and explosion hazard. Due to its tendency to polymerize at room temperature in the presence of oxygen and to oxidize on exposure to light and air, styrene is normally stabilized by the addition of tertiary butylcatechol (4-tert-butylbenzene-1,2-diol) as an inhibitor.

Styrene is predominantly used for the production of polymers (polystyrene, copolymers of styrene with acrylonitrile and/or butadiene) that are widely used in latex paints and coatings, synthetic rubbers, polyesters and styrene-alkyd coatings. Styrene is a high production volume (HPV) chemical with a worldwide production of 17,945 tonnes in 1998. Styrene also occurs in many agricultural products and foods, however, it is not clear whether styrene is naturally produced within plants (IARC, 2002, 192043).

Due to its ubiquitous use and a wealth of available health effects data, styrene has a rather full range of available inhalation health effect reference values, as shown in Figure 2.21. Additional details are provided in Table 2.21 on the derivation of the available reference values, including the basis, point of departure (POD), time scaling, etc.

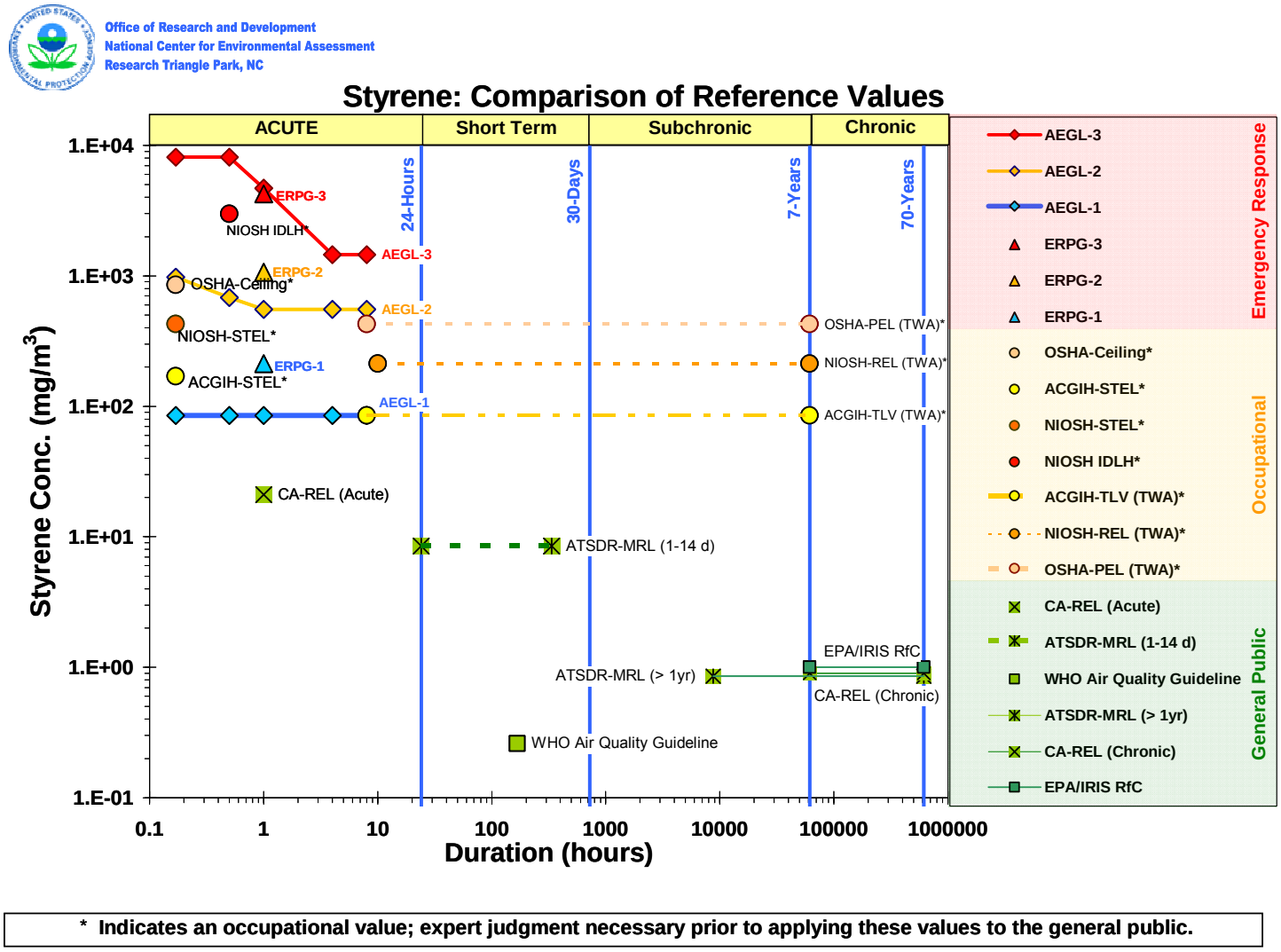
The Emergency Response reference values include both AEGLs and ERPGs. [**NOTE:** The AEGL-3 value for 1-hour is equal to 10% of the lower explosive limit (LEL) for styrene, and the 10-minute and 30-minute AEGL-3 values are greater than 10% of the LEL.] In keeping with the AEGL SOPs (NRC, 2001, 192042), the 10-minute AEGL-3 is equal to the 30-minute AEGL-3 due to the 4-hour duration of the POD. Additionally, the 8-hour AEGL-3 was kept equal to the 4-hour AEGL-3 because toxicokinetic data indicate that there is little increase of internal dose after four hours of exposure, and the lower 8-hour values derived by the default approach would generate calculated exposure levels not supported by toxicological data for humans (NAC/AEGL, 2008, 192210). Using a similar toxicokinetic basis, it was determined that no increases in internal dose would result from exposures to durations longer than one hour at the 1-hour AEGL-2 concentration, therefore no time scaling was performed for longer durations. Time scaling was not performed for the AEGL-1 based on observations that irritation did not increase with increased time at any exposure level. In derivation of the AEGL-2 values, the POD was noted as a NOAEL in the AEGL TSD, even though the effect was a LOAEL for CNS depression; the effect was interpreted to not be above a level that could impede the ability to escape, and therefore less than the AEGL-2 effect level. Similarly, in deriving the ERPG-2 it was noted that loss of balance in humans resulted from exposure to 200 ppm or more for 1-3 hours – indicative of a LOAEL for CNS depression but deemed a NOAEL for ERPG-2 effects (AIHA, 2002, 192065). The ERPG-3 and corresponding one-hour AEGL-3 values are quite similar in exposure concentrations derived, whereas the ERPG-2 and ERPG-1 values are at somewhat higher concentrations when compared to their corresponding AEGL values.

Occupational values for styrene include time-weighted average (TWA) and ceiling values developed by ACGIH, NIOSH and OSHA, as well as a NIOSH IDLH value. All the available

background documentation provided a fairly good discussion of the evidence surrounding the decision on establishment of the value, but was not explicit in defining a POD and application of uncertainty factors or other adjustments to a POD. There was half an order of magnitude difference between the lowest occupational reference values – ACGIH TLV-TWA and STEL – and the corresponding OSHA values, with the NIOSH values falling between. The reasons for this variation cannot be easily discerned based on the rather limited information available on the decisions that went into establishing each of these values.

Styrene reference values for the General Public include one developed for acute duration from the State of California (1-hour value CA-REL); two values for short-term durations from ATSDR (acute MRL – 1 to 14 days), and the World Health Organization (WHO; weekly average Air Quality Guideline); and values for chronic durations developed by California, ATSDR, and the US EPA. The WHO values are by far set at the lowest exposure concentration when compared to any other value, regardless of duration. The WHO value was derived from the lowest end of the range of occupational values showing subclinical effects on color vision (Chia et al., 1994, 010974; Eguchi et al., 1995, 010998; Fallas et al., 1992, 067341; Gobba and Cavalleri, 1993, 011026; Gobba et al., 1991, 005830) at 107 mg/m^3 and was then adjusted to approximate continuous exposure from the occupational studies by use of a factor of 4.2 (5/7 × 8/24; assuming a straight C × t time scaling relationship) and application of uncertainty factors (10 for interindividual variability and 10 for use of a LOAEL instead of a NOAEL). All of the chronic duration General Public reference values for styrene are within a narrow band of exposure concentrations, with all either derived from the same study on neurobehavioral effects (Mutti et al., 1984, 073490) or using a meta-analysis that includes that study plus others for the same endpoint (Benignus et al., 2005, 180102). As can be seen in Figure 2.21, the resulting chronic General Public reference values eclipse one another when plotted together.

As noted previously in this discussion, there is a fairly complete coverage of values for styrene, with a high level of concordance between the chronic reference values developed for the General Public and amongst the Emergency Response values. The Occupational values, however, varied quite a bit between the different organizations developing those values.



* Indicates an occupational value; expert judgment necessary prior to applying these values to the general public.

Figure 2.21. Comparison of Available Health Effect Reference Values for Inhalation Exposure to Styrene

Table 2.21. Details on derivation of the specific inhalation health effect reference values for styrene.

Reference Value Type / Name		Duration	Reference Value (mg/m^3)	Reference Value (ppm)	Health Effect	Point of Departure	Uncertainty Factors	Notes on Derivation	Review Status
Emergency Response[1]	**AEGL-3**	10 min	8090	1900[2]	Lethality in female rats (BASF, 1979, 053665)	3400 ppm (4 hrs) BMDL$_{05}$	Total UF = 10 UF_A = 3 UF_H = 3	Time scaling: $C^n \times t = k$ where n=1.2 for scaling to 30 min and 1 hr; 4-hr value adopted as 8-hr value	Interim (NAC/AEGL, 2008, 192210)
		30 min	8090	19002					
		1 hr	4700	11002					
		4 hr	1450	340					
		8 hr	1450	340					
	AEGL-2	10 min	980	230	CNS depression (Stewart et al., 1968, 073530)	376 ppm (1 hr) LOAEL[3]	Total UF = 3 UF_H = 3	Time scaling: $C^n \times t = k$ where n = 3 to 1 hour, then flat-lined	
		30 min	680	160					
		1 hr	550	130					
		4 hr	550	130					
		8 hr	550	130					
	AEGL-1	10 min	85	20	Slight irritation/ subjective discomfort, CNS effects (Seeber et al., 2002, 053685)	20 ppm (3 hrs) NOAEL	None	No time scaling	
		30 min	85	20					
		1 hr	85	20					
		4 hr	85	20					
		8 hr	85	20					
	ERPG-3	1 hr	4260	1000	Eye and nose irritation and CNS depression in humans (Carpenter et al., 1944, 094758)	800 ppm NOAEL for Lethality	NR		Final (AIHA, 2002, 192065)

[1] Emergency Response reference values are developed using an assumption of a rare, "once-in-a-lifetime" exposure scenario, which is a key consideration when comparing these reference values to any Occupational or General Public reference values.
[2] The lower explosive limit (LEL) of styrene in air is 1.1 % (11,000 ppm). The AEGL-3 value for 10 minutes, 30 minutes and 1 hour are equal or higher than 1/10 of the LEL. Therefore, safety considerations against hazard of explosion must be taken into account.
[3] Although the level cited (376 ppm) was noted as a LOAEL for CNS depression in the study (Stewart et al., 1968), it was cited as a NOAEL for AEGL-2 effects (NAC/AEGL, 2008).

Reference Value Type / Name		Duration	Reference Value		Health Effect	Point of Departure		Uncertainty Factors	Notes on Derivation	Review Status
			(mg/m^3)	(ppm)						
	ERPG-2	1 hr	1100	250	Nose, eye, and throat irritation, headache, and nausea in humans (Oltramare et al., 1974, 073640)	200 ppm	NOAEL for ERPG-2 effects	NR		Final (AIHA, 2002, 192065)
	ERPG-1	1 hr	213	50	Mild-to-moderate odor perception (Stewart et al., 1968, 073530; Wolf et al., 1956, 062279)	50 ppm	NOAEL for Irritation	NR		
Occupational	**ACGIH TLV-TWA***	8 hr TWA	85	20	NR (Barale, 1991, 010949; Edling and Ekberg, 1985, 064271; Kohn, 1978, 073466)	NR	NR	NR		Final (ACGIH, 2007, 192024)
	ACGIH TLV-STEL*	15 min	170	40		NR	NR	NR		
	NIOSH-IDLH*	30 min	3×10^3	700	Signs of neurologic impairment; (Stewart et al., 1968, 073530)	376 ppm (7 hr)	NR	NR	Effects also noted at 200-700ppm in occupational settings (Benignus et al., 2005, 180102)	Final (NIOSH, 1996, 192308)
	OSHA Ceiling*	< 15 min (4x/day)	852	200	NR	NR	NR	NR		Final (OSHA, 2006, 192276)
	OSHA-PEL (TWA)*	8 hr TWA	426	100	NR	NR	NR	NR		
	NIOSH-REL (TWA)*	10 hr TWA	213	50	NR	NR	NR	NR		Final (NIOSH, 2006, 192177)
	NIOSH-STEL*	15 min	426	100	NR	NR	NR	NR		

Reference Value Type / Name		Duration	Reference Value		Health Effect	Point of Departure		Uncertainty Factors	Notes on Derivation	Review Status
			(mg/m^3)	(ppm)						
General Public	**CA-REL (Acute)**	1 hr	21	5.1	Eye and throat irritation in humans (Stewart et al., 1968, 073530)	51 ppm	NOAEL	Total UF = 10 UF_H = 10	No time scaling	Final (OEHHA, 2008, 192309)
	ATSDR-MRL (Acute)	1 – 14 d	8.5	2	Lack of alterations in tests of simple reaction time, choice reaction time, or attention (Seeber et al., 2004, 180249)	20 ppm	NOAEL	Total UF = 10 UF_H = 10	No time scaling	Draft (ATSDR, 2007, 192120)
	WHO Air Quality Guideline	Weekly average	0.26	0.06	Neurological development impairments	25.5 mg/m^3 (107 mg/m^3 ÷ 4.2)	$NOAEL_{ADJ}$	Total UF = 100 UF_H = 10 UF_L = 10	Adjusted from occupational to continuous by factor of 4.2	Final (WHO, 2000, 180143)
	Chronic RfC (IRIS)	Chronic	1	0.24	CNS effects in humans (Mutti et al., 1984, 073490)	34 mg/m^3 (94 mg/m^3 x 5/7 x 10/20)	$NOAEL_{HEC}$	Total UF = 30 UF_{DB} = 3 UF_H = 3 UF_S = 3	Adjusted for 5 d/wk; and 10 m^3/d (worker) vs. 20 m^3/d (avg) breathing rates	Final (U.S. EPA, 1993, 192310)
	ATSDR-MRL (> 1yr)	Chronic	0.85	0.2	Increases in choice reaction time and decrease in color perception in humans (Benignus et al., 2005, 180102)	20 ppm	LOAEL	Total UF = 100 UF_L = 10 UF_H = 10	No time scaling	Draft (ATSDR, 2007, 192120)
	CA-REL (Chronic)	Chronic	0.9	0.2	Effects to central nervous system (Mutti et al., 1984, 073490)	0.61 ppm (1.7 ppm x 10/20 x 5/7)	$BMC_{05\text{-}HEC}$	Total UF = 3 UF_H = 3	Adjusted BMC_{05} for 5 d/wk; and 10 m^3/d (worker) vs. 20 m^3/d (avg) breathing rates	Final (OEHHA, 2000, 192311)

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2.22. Chemical-Specific Reference Values for Sulfur Mustard (CASRN 505-60-2)

Sulfur mustard (Agent HD, mustard gas, bis[2-chloroethyl]sulfide; $C_4H_8Cl_2S$) is a thick, colorless, and odorless synthetic organic liquid produced for use as a chemical weapon in World Wars I and II. It is a blister agent that can cause severe eye and skin irritation, as well as bronchitis and respiratory disease upon inhalation. Sulfur mustard has been designated as a Group 1 human carcinogen by the IARC (IARC, 1987, 192134). Detailed descriptions of toxicity as well as the physical nature of this chemical agent can be found in other sources (ATSDR, 2003, 192115; CDC, 2003, 192194; CDC, 2004, 192193; NRC, 2003, 192141; NRT, 2009, 192158) and are not repeated here.

Inhalation health effect reference values for sulfur mustard are arrayed graphically in Figure 2.22. Details available on the derivation of these values, including key effects, studies, adjustments, and uncertainty factors (UFs) are shown in Table 2.22.

A full set of Emergency Response AEGL values are available for sulfur mustard. The AEGL values were time scaled via the $C^n \times t = k$ formula. The value of n for the AEGL-3 reference value was set to either 3 for shorter (< 1 hour) and 1 for longer (> 1 hour) time periods, due to the absence of chemical-specific lethality data (NRC, 2003, 192141). The value of n = 1 was applied to derivation of the AEGL-1 and AEGL-2 values, based on analysis of mild ocular irritation (Anderson, 1942, 192035; Guild et al., 1941, 192161), with both values derived from the same study (Anderson, 1942, 192035), but using different PODs.

The only Occupational reference values developed for sulfur mustard were designed specifically in relation to airborne exposure limits (AELs) for disposal of chemical warfare agents (CDC, 2003, 192194; CDC, 2004, 192193), and CDC admonishes the reader that these values "*reflect realistic risk management provisions associated with chemical demilitarization and do not necessarily apply to other purposes*." These AELs include an 8-hour Worker Protection Limit (WPL), time-weighted average (TWA); along with a short-term exposure limit (STEL) and an immediately dangerous to life and health (IDLH) value. Minimal information on the derivation of these values was provided.

A General Public reference value was also developed by CDC (2003, 192194; 2004, 192193) as AELs for chemical demilitarization, with the same caveat on applicability to other purposes. The CDC general population limit (CDC-GPL) is a 12-hour TWA value for up to a lifetime chronic exposure (NRT, 2009, 192158). As with the Occupational AELs, very little detail was provided on the derivation of the CDC-GPL; no information on key study, POD, duration adjustments and application of uncertainty factors were provided. ATSDR published sulfur mustard MRLs for both acute (1-14 days) and intermediate (15 days to 1 year) durations. Duration adjustments were applied to both the acute and intermediate ATSDR MRL values, with adjustments in the acute MRL accounting for exposures of 8 hours per day, and in the intermediate MRL to account for 24 hours per day, 5 days per week exposures. All other details on derivation were provided in the Sulfur Mustard Toxicological Profile (ATSDR, 2003, 192115), which is summarized in Table 2.22. As can be seen in Figure 2.22 and

Table 2.22, the CDC GPL and the ATSDR intermediate MRL are both set at 2×10^{-5} mg/m^3, indicating good concordance between these two independently-derived reference values.

Overall, there is fair coverage on inhalation health effect reference values for sulfur mustard. As noted previously, the AELs were derived by CDC for the purposes of chemical demilitarization, and may not be applicable for other purposes; therefore, as with the Occupational values, the AELs should only be used with expert judgment.

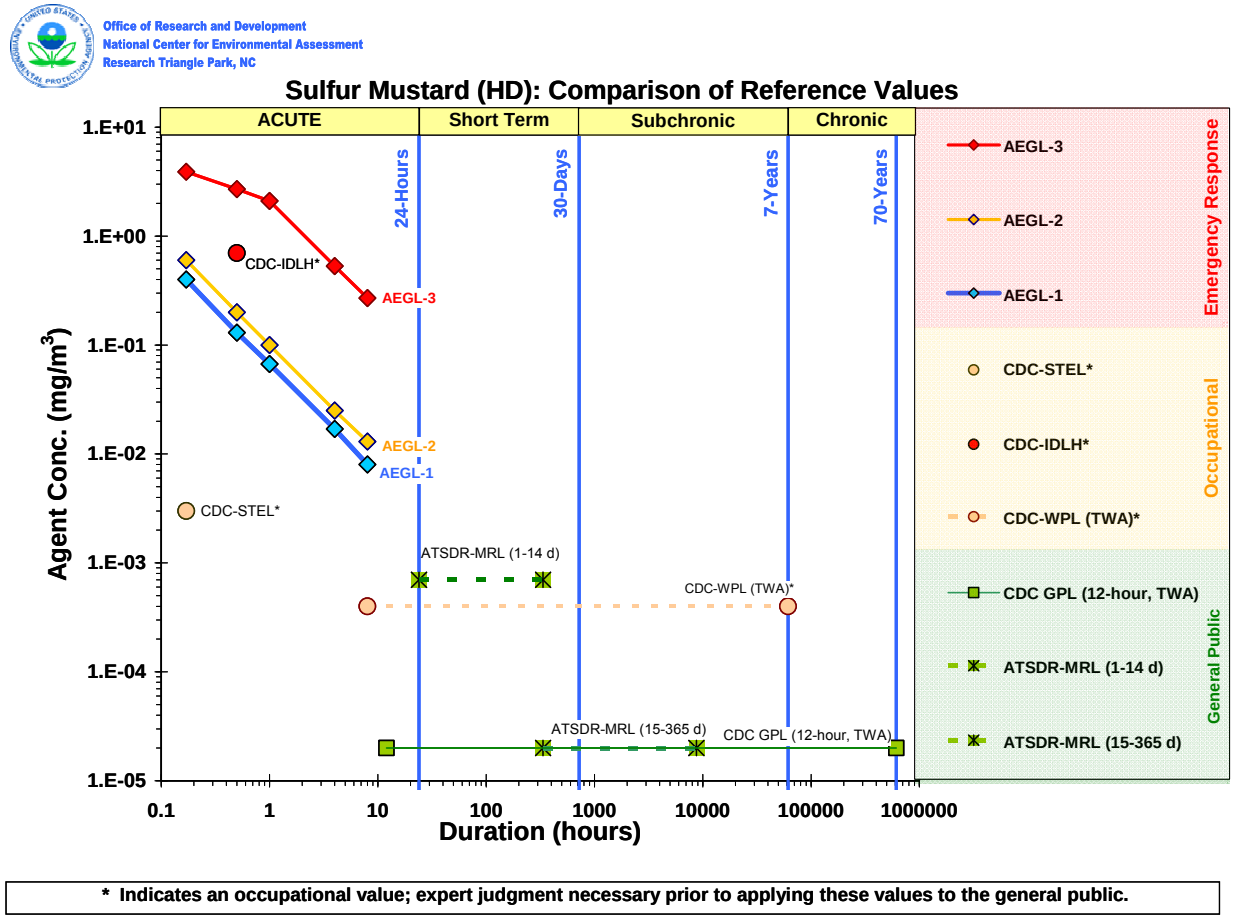

Figure 2.22. Comparison of Available Health Effect Reference Values for Inhalation Exposure to Sulfur Mustard

Table 2.22. Details on derivation of the specific inhalation health effect reference values for sulfur mustard.

Reference Value Type / Name		Duration	Reference Value (mg/m^3)	Reference Value (ppm)	Health Effect	Point of Departure	Uncertainty Factors	Notes on Derivation	Review Status
Emergency Response[1]	**AEGL-3**	10 min	3.9	0.59	Lethality estimate in mice (Kumar and, 1998, 180292)	21.2 mg/m^3 (1 h) ½ of the 1-h LC_{50}	Total UF = 10 UF_A = 3 UF_H = 3	Time scaling: $C^n \times t = k$ where n = 3 for shorter and n = 1 for longer durations	Final (NRC, 2003, 192141)
		30 min	2.7	0.41					
		1 hr	2.1	0.32					
		4 hr	0.53	0.08					
		8 hr	0.27	0.04					
	AEGL-2	10 min	0.60	0.09	Conjunctivitis, edema, photophobia, and eye irritation in human volunteers (Anderson, 1942, 192035)	60 mg min/m^3 Threshold for effects	Total UF = 3 UF_H = 3	Time scaling: $C^n \times t = k$ where n = 1	
		30 min	0.20	0.03					
		1 hr	0.10	0.02					
		4 hr	0.025	4×10^{-3}					
		8 hr	0.013	2×10^{-3}					
	AEGL-1	10 min	0.40	0.06	Conjunctival injection with minor discomfort in human volunteers (Anderson, 1942, 192035)	12 mg min/m^3 Threshold for effects	Total UF = 3 UF_H = 3	Time scaling: $C^n \times t = k$ where n = 1	
		30 min	0.13	0.02					
		1 hr	0.067	0.01					
		4 hr	0.017	3×10^{-3}					
		8 hr	8×10^{-3}	1×10^{-3}					

[1] Emergency Response reference values are developed using an assumption of a rare, "once-in-a-lifetime" exposure scenario, which is a key consideration when comparing these reference values to any Occupational or General Public reference values.

Reference Value Type / Name		Duration	Reference Value (mg/m^3)	Reference Value (ppm)	Health Effect	Point of Departure		Uncertainty Factors	Notes on Derivation	Review Status
Occupational	**CDC-STEL**	15 min	3×10^{-3}	4.6×10^{-4}	Irritation; ocular effects	NR	NR	NR		Final (CDC, 2003, 192194; CDC, 2004, 192193)
	CDC-IDLH	30 min	0.7	0.11	Lethality	NR	NR	NR		
	CDC WPL (TWA)*	8 hr TWA	4×10^{-4}	6.2×10^{-5}	Cancer; irritation; ocular effects	NR	NR	NR		
General Public	**CDC GPL (TWA)**	24 hr TWA, 7 d/wk for a lifetime	2×10^{-5}	3.1×10^{-6}		NR	NR	Total UF = 300		
	ATSDR-MRL (Acute)	1 – 14 d	7×10^{-4}	1.1×10^{-4}	Ocular effects (Guild et al., 1941, 192161)	0.02 mg/m^3 (0.06 mg/m^3 x 8/24)	$LOAEL_{ADJ}$	Total UF = 30 $UF_L = 3$ $UF_H = 10$	Adjusted for 8 hr/day	Final (ATSDR, 2003, 192115)
	ATSDR-MRL (15-365 d)	15 d – 1 yr	2×10^{-5}	3.1×10^{-6}	Ocular effects in dogs (McNamara et al., 1975, 192163)	0.0007 mg/m^3 (0.001 mg/m^3 x 5/7)	$NOAEL_{ADJ}$	Total UF = 30 $UF_H = 10$ $UF_A = 3$	Adjusted for 24 hr/d; 5 d/week	

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2.23. Chemical-Specific Reference Values for Tabun (GA) (CASRN 77-81-6)

Tabun (Agent GA; dimethylamidocyanoethylphosphate) is one of several organophosphate (OP) nerve agents that have been specifically designed and formulated to cause death, major injuries, or incapacitation to enemy forces in wartime. The term "nerve" agent refers to its anti-cholinesterase properties. Nerve agents are particularly effective in a military sense because of their potency. Detailed descriptions of nerve agent toxicity as well as the physical nature of this chemical agent can be found in the AEGL Techniucal Support Document (NAC/AEGL, 2003, 192304), and is not repeated here.

There are only two sources of health effect reference values for the chemical warfare agent GA: the National Advisory Committee for Acute Exposure Guideline Levels (NAC/AEGL, 2003, 192304) and the Centers for Disease Control and Prevention (CDC, 2003, 192190). Both organizations used the same limited set of data for deriving values for GA; however, the dataset for Sarin (GB) was the most robust of all of the nerve agents for which values were derived, and the relative potency of the nerve agents GA and Agent VX to GB was used to derive values for those other nerve agents.

AEGL-3 values for GA were derived based on the observation that GA appears to possess one half the toxic potency of GB; the calculated lethality at the one percent level (LC_{01}) in female rats using observations at 10-, 30-, 60-, 240-, and 360-minutes for GB was therefore doubled to derive values for GA, with all other factors remaining the same. The toxic potency of GA was deemed to be equal to GB for AEGL-1 [miosis – pinpoint pupils – in female rats (Mioduszewski et al., 2002, 192189)] and AEGL-2 effects [visual acuity effects in humans (Baker and Sedgewick, 1996, 180099)]; therefore the AEGL-1 and AEGL-2 values derived for GB were adopted as AEGL values for GA, with all other factors and conditions likewise adopted.

A series of Federal Register Notices published by the Centers for Disease Control and Prevention (CDC, 1988, 192173; CDC, 2002, 192175; CDC, 2003, 192190; CDC, 2004, 192193) document the Airborne Exposure Levels designed for application to the agents Tabun (GA), Sarin (GB), VX, Mustard Agent (H, HD, T) and Lewisite (L) for the protection of workers at chemical weapon decommissioning facilities and the general population living near those facilities. The first set of recommendations (CDC, 1988, 192173) were applied for over 14 years, and over the intervening years there was no apparent impact to human health; however, to maintain to be consistent with more recent risk assessment practice a reevaluation using the conventional risk assessment methods for inhalation exposures developed by the Environmental Protection Agency (U.S. EPA, 1994, 192307) was conducted and a set of revised values were published in the Federal Register (CDC, 2003, 192190) for the agents GA, GB and VX.

The Airborne Exposure Level values for GA were determined to be equal to those derived for GB, and included a General Population Limit (GPL), a Worker Population Limit (WPL), as well as a Short-term Exposure Limit (STEL) and Immediately Dangerous to Life and Health (IDLH) occupational values (CDC, 2003, 192190). The GPL and WPL values for GB (and hence GA) were based on exposures of 20 minutes per day for 4 days per week and were adjusted to derive a Lowest Observable Adverse Effect Level Human Equivalent Concentration ($LOAEL_{HEC}$) for 24 hour and 8 hour time weighted averages (TWAs), respectively. Fewer details were provided in the derivation of the STEL and IDLH values, and it is assumed that a weight of evidence approach was used in their derivation.

The resulting values for both the AEGL and CDC are shown in Figure 2.23 and Table 2.23, with the details on derivation for GA being identical to those developed for GB. More recent research by the U.S. Army provides additional data that may lead to further revision of both sets of values (Hulet et al., 2006, 192144).

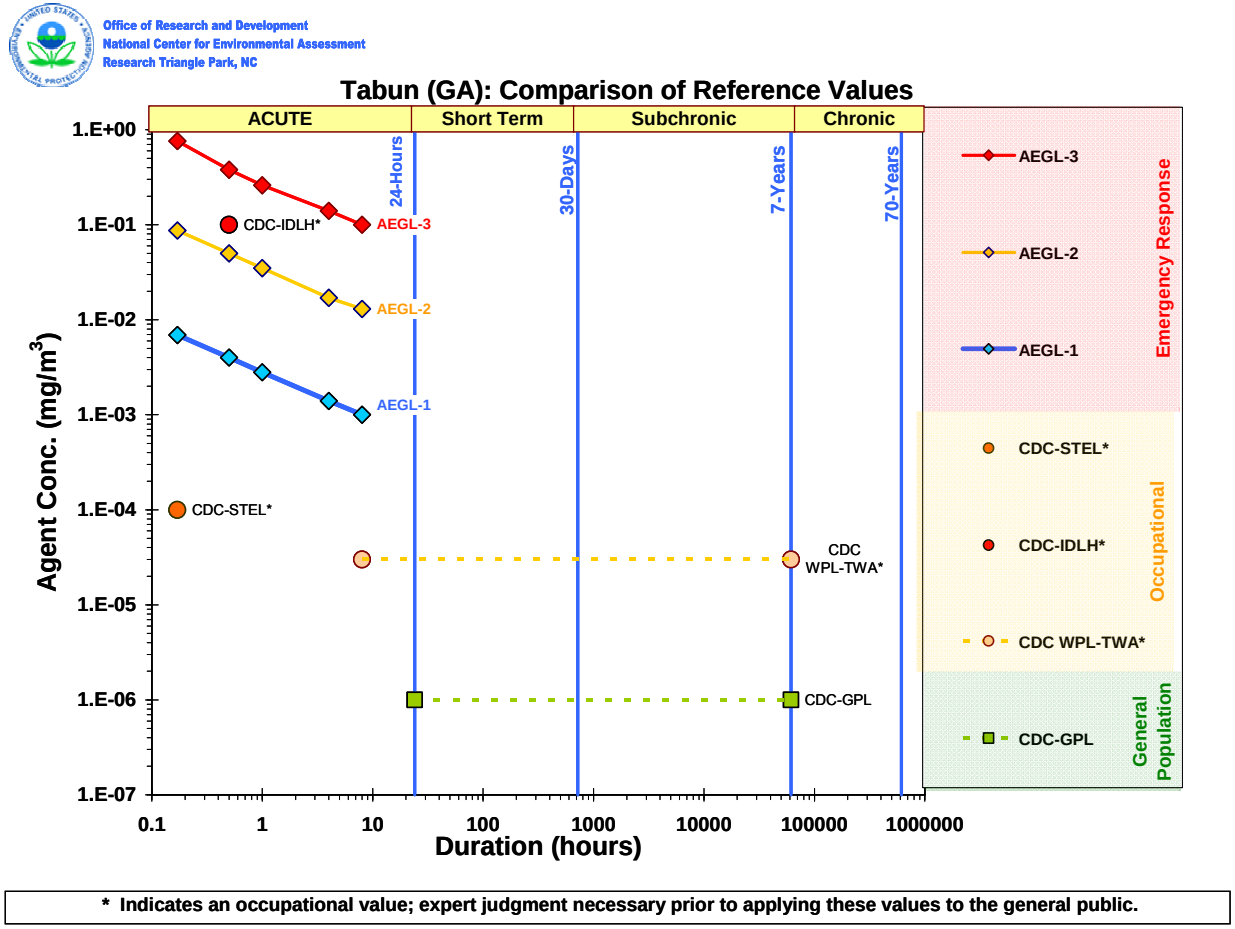

Figure 2.23. Comparison of Available Health Effect Reference Values for Inhalation Exposure to Tabun (GA)

Table 2.23. Details on derivation of the specific inhalation health effect reference values for Tabun (GA).

Reference Value Type / Name		Duration	Reference Value (mg/m^3)	Reference Value (ppm)	Health Effect	Point of Departure		Uncertainty Factors	Notes on Derivation	Review Status
Emergency Response[1]	**AEGL-3**	10 min	7.60E-01	1.15E-01	Lethality (Mioduszewski et al., 2000, 192305; Mioduszewski et al., 2001, 192306; Mioduszewski et al., 2002, 180121)	11.54 mg/m^3	LC_{01} (female rats)	Total UF = 30 UF_A = 3 UF_H = 10	Potency of GA is approximately 1/2 that of GB for lethality.	Final (NAC/AEGL, 2003, 192304)
		30 min	3.80E-01	5.73E-02		5.84 mg/m^3				
		1 hr	2.60E-01	3.92E-02		4.01 mg/m^3				
		4 hr	1.40E-01	2.11E-02		2.09 mg/m^3				
		8 hr	1.00E-01	1.51E-02		1.76 mg/m^3 (6 hr)				
	AEGL-2	10 min	8.70E-02	1.31E-02	Miosis, dyspnea, photophobia, inhibition of RBC-ChE seen in humans (Baker and Sedgewick, 1996, 180099)	0.5 mg/m^3 (30 min)	Sub-clinical effects	Total UF = 10 UF_A = 1 UF_H = 10	Potency of GA is equal to that of GB for AEGL-2 effects	
		30 min	5.00E-02	7.54E-03						
		1 hr	3.50E-02	5.28E-03						
		4 hr	1.70E-02	2.56E-03						
		8 hr	1.30E-02	1.96E-03						
	AEGL-1	10 min	6.90E-03	1.04E-03	Induction of miosis in female rat (Harvey, 1952, 192174; Johns, 1952, 192313; Mioduszewski et al., 2002, 192189; van Helden et al., 2001, 180238)	Range of 0.01-0.48 mg/m^3 at 10 min, 60 min, and 240 min	EC_{50}	Total UF = 10 UF_A = 1 UF_H = 10	Potency of GA is equal to that of GB for AEGL-1 effects, EC_{50} for miosis in rats	
		30 min	4.00E-03	6.03E-04						
		1 hr	2.80E-03	4.22E-04						
		4 hr	1.40E-03	2.11E-04						
		8 hr	1.00E-03	1.51E-04						

[1] Emergency Response reference values are developed using an assumption of a rare, "once-in-a-lifetime" exposure scenario, which is a key consideration when comparing these reference values to any Occupational or General Public reference values.

Reference Value Type / Name		Duration	Reference Value (mg/m^3)	Reference Value (ppm)	Health Effect	Point of Departure		Uncertainty Factors	Notes on Derivation	Review Status
Occupational	**CDC-WPL (TWA)***	8 hr TWA	3×10^{-5}	5.2×10^{-6}	Miosis (McKee and Woolcott, 1949, 192172)	0.06 mg/m^3 (20 min/d, for 4 days)	$LOAEL_{HEC}$	Total UF = 30 $UF_L = 3$ $UF_S = 10$	Adjusted for duration and breathing rate, details not provided.	Final (CDC, 2003, 192190)
	CDC-IDLH*	30 min	0.1	1.7×10^{-2}	NR	NR	NR	NR		
	CDC-STEL*	15 min (up to 4x per day)	1×10^{-4}	1.7×10^{-5}	NR	NR	NR	NR		
General Population	**CDC GPL**	24 hour	1×10^{-6}	1.7×10^{-7}	Miosis (McKee and Woolcott, 1949, 192172)	0.06 mg/m^3 (20 min/d, for 4 d/wk)	$LOAEL_{HEC}$	Total UF = 300 $UF_L = 3$ $UF_S = 10$ $UF_H = 10$	Adjusted for duration and breathing rate, details not provided.	

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2.24. Chemical-Specific Reference Values for Agent VX (CASRN 50782-69-9)

Agent VX (S-(diisopropyl aminoethyl) methyl phosphonothiolate, O-ethyl ester)) is one of several organophosphate (OP) nerve agents have been specifically designed and formulated to cause death, major injuries, or incapacitation to enemy forces in wartime. The term "nerve" agent refers to its anti-cholinesterase properties. Nerve agents are particularly effective in a military sense because of their potency. Detailed descriptions of nerve agent toxicity as well as the physical nature of this chemical agent can be found in the AEGL Technical Support Document (NAC/AEGL, 2003, 192304), and are not repeated here.

Agent VX is a persistent compound, deliberately formulated for low volatility; it is designed to contaminate surfaces and remain unchanged for long periods of time. VX can also be absorbed percutaneously, although all of the reference values described below are based on vapors. Since VX has a low vapor pressure, monitoring for VX presence in air is not likely to be an effective determinant in designating an area free of contamination; surface sampling should be the critical method for determining levels of contamination or presence of this compound.

There are only two sources of health effect reference values for the chemical warfare agent VX: the National Advisory Committee for Acute Exposure Guideline Levels (NRC, 2003, 192140) and the Centers for Disease Control and Prevention (CDC, 2003, 192190). Both organizations used the same limited set of data and relied on deriving values for VX based on the relative potency to sarin (GB).

The only Emergency Response values for VX are the AEGLs (NRC, 2003, 192140). Two studies (Grob and Harvey, 1958, 180110; Sidell and Groff, 1974, 180129)indicated that VX was four times more potent than sarin (GB), and this evidence was used as the basis to estimate the potency of VX (Mioduszewski et al., 2002, 180121). The adjusted value was used as the point of departure (POD) for deriving AEGL-3 values for VX. Similarly, a factor of four was used to account for the relative toxicity in deriving values based on sarin studies showing miosis (pupil dilation) (Mioduszewski et al., 2002, 192189) and visual acuity effects (Baker and Sedgewick, 1996, 180099) for the AEGL-1 and AEGL-2, respectively.

A series of Federal Register Notices published by the Centers for Disease Control and Prevention (CDC, 1988, 192173; CDC, 2002, 192175; CDC, 2003, 192190; CDC, 2004, 192193) document the Airborne Exposure Levels designed for application to the agents Tabun (GA), Sarin (GB), VX, Mustard Agent (H, HD, T) and Lewisite (L) for the protection of workers at chemical weapon decommissioning facilities and the general population living near those facilities The first set of recommendations (CDC, 1988, 192173) were applied for over 14 years, and over the intervening years there was no apparent impact to human health; however, to be consistent with more recent risk assessment practice a reevaluation using the conventional risk assessment methods for inhalation exposures developed by the Environmental Protection Agency (U.S. EPA, 1994, 192307) and used by other agencies was conducted and a set of revised values were published in the Federal Register (CDC, 2003, 192190) for the agents GA, GB and VX.

The approach to developing the CDC Airborne Exposure Levels for VX was quite similar to the approach taken in the development of the AEGL values (NRC, 2003, 192140) in that the relative potency of sarin to VX was used as the basis for applying the more robust database for sarin. In deriving values for VX, an assumption of a 12 fold increase in toxic potency of VX over GB was applied, along with application of a modifying factor of 3 for the sparse VX data set; there was no explanation provided on why a factor of 12 instead of 4 (as in the AEGL

derivation). Values were derived for a General Population Limit (GPL), a Worker Population Limit (WPL), as well as a Short-term Exposure Limit (STEL) and Immediately Dangerous to Life and Health (IDLH) occupational values. Adjustments were made, however, to the GPL value to accommodate the detection limit for monitoring. The resulting values for both the AEGL and CDC are shown in Figure 2.24 and Table 2.24. More recent research by the U.S. Army provides additional data that may lead to further revision of both sets of values (Benton et al., 2005, 192358; Benton et al., 2006, 192360).

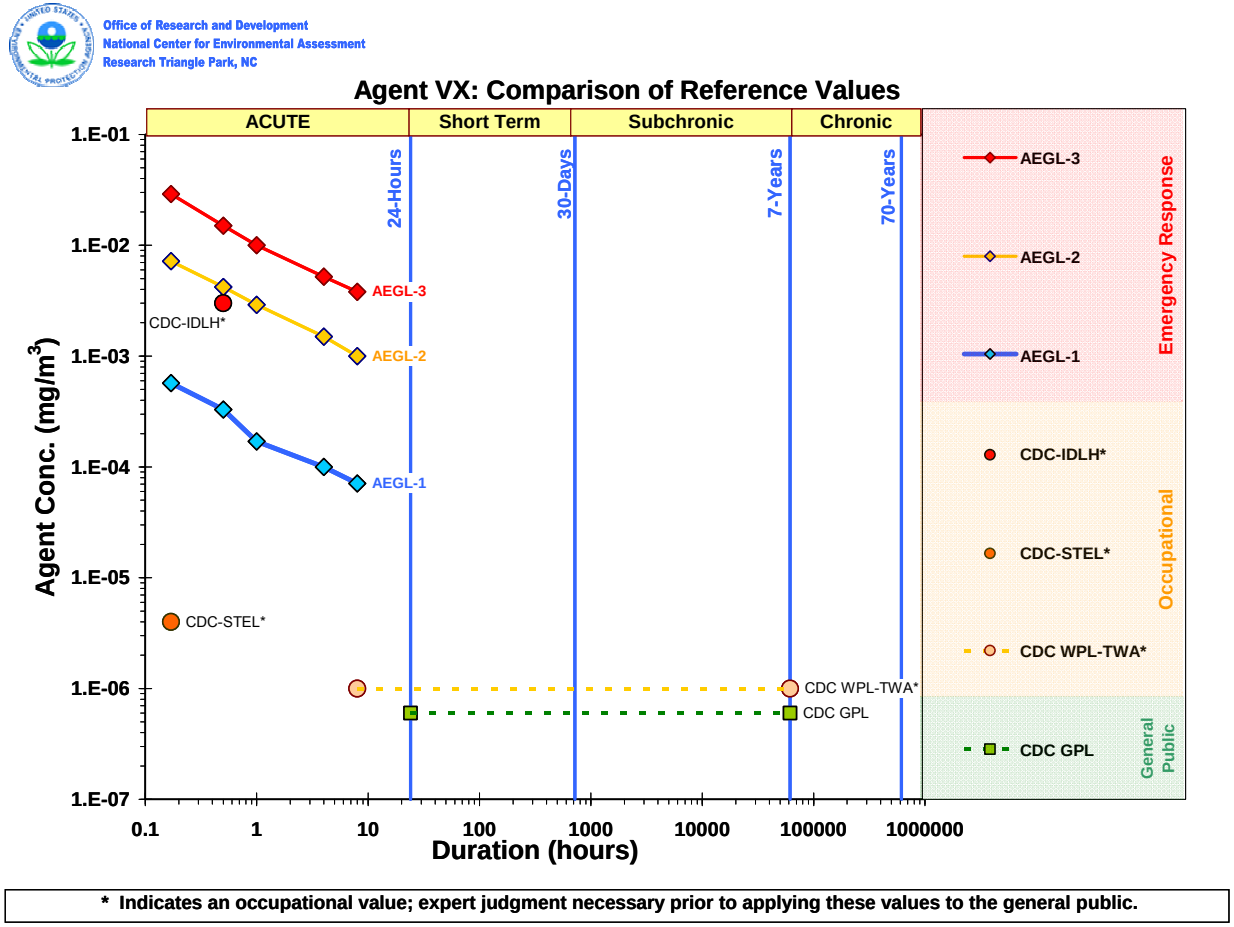

Figure 2.24. Comparison of Available Health Effect Reference Values for Inhalation Exposure to Agent VX

Table 2.24. Details on derivation of the specific inhalation health effect reference values for agent VX.

Reference Value Type / Name		Duration	Reference Value (mg/m^3)	Reference Value (ppm)	Health Effect	Point of Departure		Uncertainty Factors	Notes on Derivation	Review Status
Emergency Response[1]	AEGL-3	10 min	2.90E-02	2.65E-03	Lethality in rats (Mioduszewski et al., 2002, 180121)	1.46 mg/m^3 (6 hour)	LC_{01}	Total UF = 100 UF_A = 3 UF_H = 10 MF = 3 (sparse VX dataset)	Potency of agent VX is approximately 4 times that of agent GB (sarin) for AEGL-3 effects (Grob & Harvey, 1958; Sidell & Groff, 1974)and relative potency was used throughout; AEGL values are estimates for VX vapor exposures only.	Final (NRC, 2003, 192140)
		30 min	1.50E-02	1.37E-03						
		1 hr	1.00E-02	9.14E-04						
		4 hr	5.20E-03	4.75E-04						
		8 hr	3.80E-03	3.47E-04						
	AEGL-2	10 min	7.20E-03	6.58E-04	Miosis, dyspnea, photophobia, inhibition of RBC-ChE seen in humans (Baker and Sedgewick, 1996, 180099)	0.125 mg/m^3 (30 min)	LOAEL for sub-clinical effects	Total UF = 30 UF_A = 1 UF_H = 10 MF = 3 (sparse VX dataset)		
		30 min	4.20E-03	3.84E-04						
		1 hr	2.90E-03	2.65E-04						
		4 hr	1.50E-03	1.37E-04						
		8 hr	1.00E-03	9.14E-05						
	AEGL-1	10 min	5.70E-04	5.21E-05	Induction of miosis by sarin in female rat (Mioduszewski et al., 2002, 192189)	0.017 mg/m^3 (10 min)	EC_{50}	Total UF = 30 UF_A = 1 UF_H = 10 MF = 3 (sparse VX dataset)		
		30 min	3.30E-04	3.02E-05						
		1 hr	1.70E-04	1.55E-05		0.005 mg/m^3 (1 hour)				
		4 hr	1.00E-04	9.14E-06		0.003 mg/m^3 (4 hour)				
		8 hr	7.10E-05	6.49E-06						

[1] Emergency Response reference values are developed using an assumption of a rare, "once-in-a-lifetime" exposure scenario, which is a key consideration when comparing these reference values to any Occupational or General Public reference values.

Reference Value Type / Name		Duration	Reference Value (mg/m^3)	Reference Value (ppm)	Health Effect	Point of Departure		Uncertainty Factors	Notes on Derivation	Review Status
Occupational	**CDC WPL TWA***	8 hr TWA	1.00E-06	9.14E-08	Miosis (McKee and Woolcott, 1949, 192172)	0.06 mg/m^3 (20-min/day, 4 days/week)	LOAEL (Sarin)	Total UF = 100 UF_L = 3 UF_H = 10 MF = 3	Assumes VX is 12x potency of sarin (GB). Adjustements for duration, breathing rates, and detection limits.	Final (CDC, 2003, 192190)
	CDC-STEL*	<15 min, once/day	1.00E-05	9.14E-07						
	CDC-IDLH (<30 min) *	30 min	3.00E-03	2.74E-04				NR		
General Population	**CDC GPL**	24 hour	6.00E-07	5.48E-08				Total UF = 1000 UF_L = 3 UF_H = 10 UF_S = 10 MF = 3		

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APPENDIX A:
SUMMARY OF THE CLIENT WORKSHOP FOR REFERENCE VALUE ARRAYS

Workshop Summary

George Woodall, NCEA-RTP

This document provides a summary of a workshop that gathered a number of client programs together to discuss the development of reference value arrays. This workshop was conducted as a combination telephone and web-based conference, with voice communication conducted via a telephone conference line and visual presentations presented via the EPA Science Portal Web Conferencing capabilities.

Background

The U.S. EPA's National Center for Environmental Assessment (NCEA) has undertaken a project to standardize the development of graphical arrays that compare inhalation health effect reference values (e.g., RfCs, AEGLs) across durations, populations (e.g., general public vs. healthy workers), and intended use (e.g., general public vs. emergency response vs. repeated occupational vs. occupational ceiling values). A number of program offices within the Agency, as well as other Federal and State agencies, have an interest in having these types of arrays available. The eventual users of these arrays and accompanying documentation includes risk assessment professionals, decision makers (risk managers), and the general public. Accompanying explanatory text will need to be provided with all arrays to provide an adequate foundation for understanding the arrays, to enable an appropriate comparison of the displayed reference values, and to clearly indicate that the various reference values are not "one-size-fits-all." Tables will also be provided that include the numerical values, along with the details on derivation of the values (i.e., critical study[ies], point of departure [POD], uncertainty factors [UF], duration extrapolations, etc). The intent is to have finished, reviewed arrays available to the public via the NCEA internet site.

Examples of these comparative arrays, accompanying tables, and the plans for this project were discussed at the web-based workshop of representatives from client organizations. The agenda is shown below.

Workshop Agenda

- Introductions
- Goals for the Workshop
- Background and Context on Array Development
- Review of Existing Arrays and Summaries
- Supporting Information
    - Context for comparing the available health effect reference values
    - Data to include in accompanying tables
    - Other elements to include?

- Programmatic Needs and Applications
  - How can these arrays best support clients?
  - What elements are most useful? What might be a distraction?
  - What are some of the potential issues? Can they be addressed?
  - Do arrays need to be tailored for different client needs?
- Decisions on Elements and Format of Arrays
  - Add Point of departure for each value?
  - Include Cancer risk values? How best to do so?
- Conclusions and Next Steps
  - Current Project Schedule
  - Is there a desire for continued Client Input?
  - Which chemicals should be considered for the next phase?

Phase 1 of the Project Plan

- Perform an inventory of existing arrays (January 26, 2009)
  1. Currently 23 arrays are in various stages of completion, utilizing varying formats
- Determine priority list of chemicals for which arrays should be developed (January 31, 2009)
  1. Cross reference lists from OAQPS, NHSRC, DHS and others.
  2. Develop draft list
  3. Review with client Offices/Agencies in web-based workshop (see below)
- Review existing arrays for completeness (QC) and accuracy (QA), and comparing formats to determine most appropriate for final template to be used with all arrays (February 27, 2009)
  1. Review within NCEA
  2. Review with client Program Offices and Agencies in a web-based workshop (may delay finish date, depending on ability to schedule)
  3. Determine final template(s)
- Work to revise and finalize currently available arrays to conform to final template(s), with priority given to arrays for the general public (April 30, 2009)
- Develop additional general public arrays to meet APM (May 30, 2009)
- Perform quality control checks and peer review of all chemical-specific array products prior to posting

<u>Example Arrays and Supporting Materials</u>

The arrays themselves are the focal point for a broader discussion of the available inhalation health effect reference values for a specific chemical. The most fully developed package of array, introductory discussion, and supporting tables and text is provided in the summary for mercury (Appendix B).

In addition to the more complete example using mercury, two representations of the arrays developed for the chemical phosgene are shown below to illustrate how the representation of the arrays have changed over time. Figure A-1 shows one of the earliest examples of array development for the chemical phosgene. Note that only the acute reference values are represented here, the x-axis is not formatted logarithmically, and the

long-term or chronic values are merely segregated to be longer than 24-hours. In Figure A-2 more of the available reference values are displayed (including provisional values), along with formatting that allows a more inclusive set of values across all durations via the use of logarithmic scaling on the x-axis (denoted in hours).

Supporting Information

One of the basic requirements in providing the information represented in the arrays credibly, is to include a foundational discussion of the nature, appropriate application, and limitations for each type of reference value. This includes information that is taken from a previously published paper[42] where these issues were discussed, with explanatory text and a table such as shown in Table 1-1.

In addition to the introductory information, more detailed information regarding the specific reference values such as the study used as the basis for the derived reference value, the uncertainty factors applied to the study NOAEL/LOAEL or other indicator of toxic effect (e.g. BMDL), adjustments such as calculation of a human equivalent concentration from an animal study, and extrapolations across durations. [NOTE: Examples of the tables providing such information are shown in the tables included with the individual, chemical-specific summaries in Section 2 of this document.]

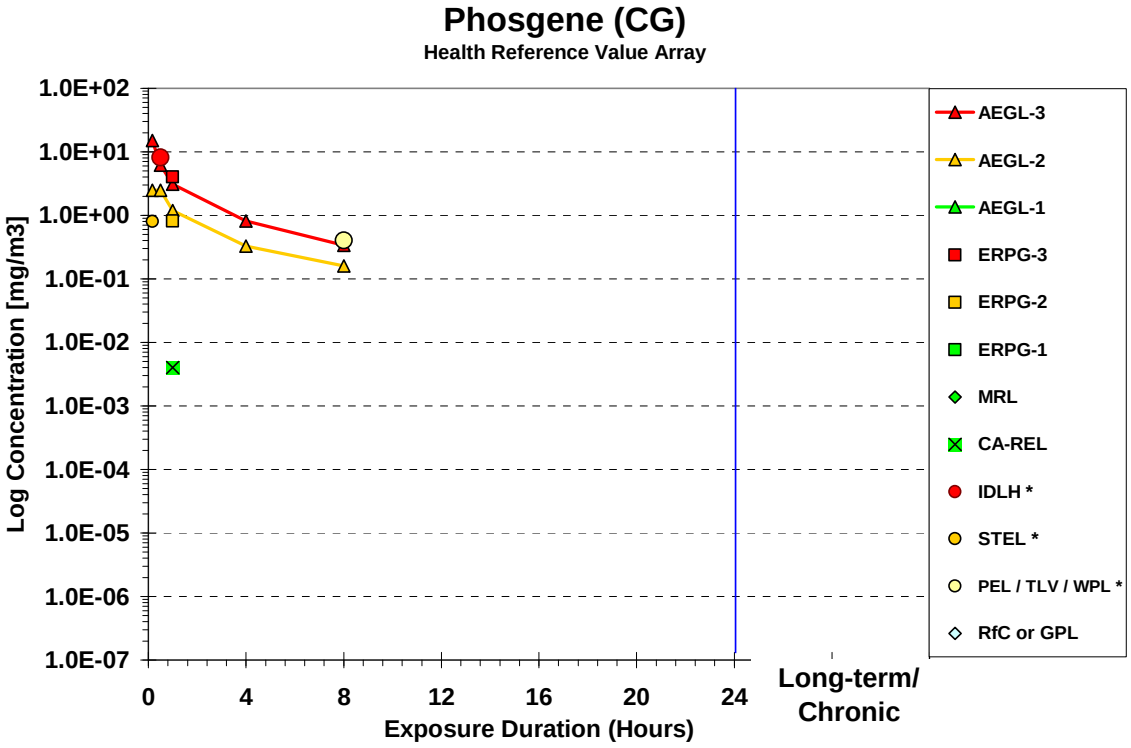

Figure A-1. First generation array example for phosgene.

[42] Woodall, GM (2005) Acute health reference values: Overview, perspective, and current forecast of needs. Journal of Toxicology and Environmental Health, Part A, 68:901-926

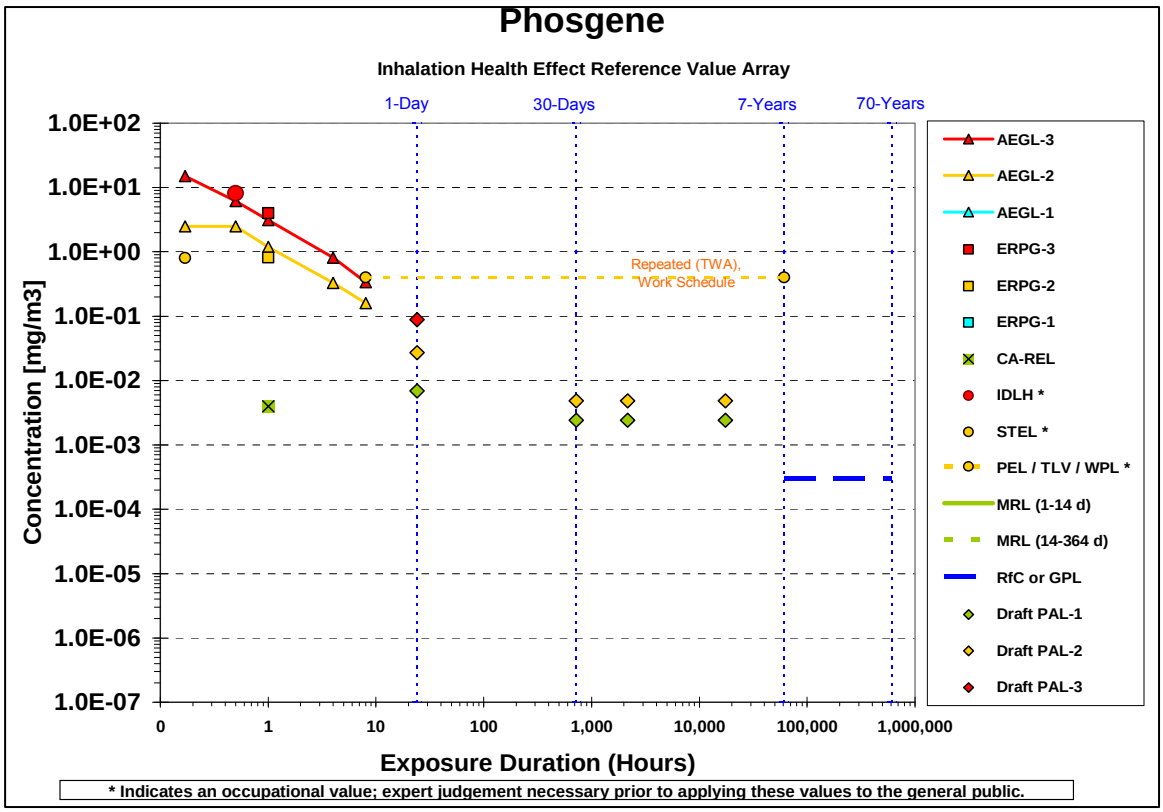

Figure A-2. Later version of the comparative array of inhalation health effect reference values for phosgene.

Regarding the supporting information, a number of questions were posed for the participants to consider and respond to following the meeting. Those questions are listed below.

- Is there an adequate foundation for understanding the arrays?
- Do the arrays enable an appropriate comparison of reference values?
- Is it clear that the Reference Values are not "one-size-fits-all?"

Programmatic Needs and Applications

An additional set of questions were posed to the participants regarding the needs for and application of the arrays by their respective programs. Those questions along with some of the discussion are provided below.

- How can these arrays best support Program Offices and other clients?
- What elements are most useful? What might be a distraction?
- Do arrays need to be tailored for different client needs?
    - Provisional values (PALs, and PPRTVs) are developed for a select Program Office Need. Should they be included in "Public View" versions of arrays?
    - Should there be "For Official Use Only" versions of the arrays?

In development of the final draft, selected participants were asked to respond to the following questions:

- What is your need for the graphical arrays?
- What are you going to be using the graphical data arrays for?

The responses are quoted below:

- Office of Air Quality Planning and Standards – "1. We need the graphical data arrays to improve risk communication (with both our own risk managers and the public) in our assessments of hazardous air pollutants emitted from industrial sources. 2. That's what we're going to be using them for.
- National Homeland Security Research Center – "I see their value in emergency response or remedial actions - therefore, less for current use (for me) and more for potential future use. Graphical representations such as the data arrays are excellent tools when trying to communicate confusing sets of numbers to non-toxicologists. If I were still a Regional Toxicologist, I would use them for risk communication with community groups. If I had them during the hurricane Katrina response, they would have been useful when selecting action levels. I have used them during table-top exercises when acting either in the Environmental Unit or as a Subject Matter Expert for selecting action levels and communicating the reason for my selection to the Incident Command."

Decisions on Elements, Format and Appearance of Arrays

The latest versions of the arrays have attempted to use standard shapes to denote related types of values.

- Diamonds and Triangles for emergency response values
- Circles for Occupational values
- Squares for General Public values

Standard colors have also been used to denote severity as well as different systems of reference values (e.g., to differentiate among several occupational values).

- Red for defining lethality threshold values
- Gold for Irreversible/Serious effects
- Blue for Reversible/Mild effects
- Green for values deemed without any adverse effects

There was general agreement on using standards that are the same across arrays, so that as these are used, they become familiar (e.g., the lack of a type of value would stand out). The IDLH values are colored red; the other occupational values are shown in shades ranging from gold to orange to yellow. Since the only occupational values that have a readily understandable severity rating on them are the IDLH values, it was planned to keep the shapes all circles for the occupational values and have the different color shadings consistent for each type of occupational value (i.e., OSHA, NIOSH, ACGIH, etc). On a related note, there was discussion of using hatching patterns or other ways to distinguish between values for those who may be unable to distinguish colors or when printing to a black and white printer.

A separate set of issues discussed the format for posting on the web. A set of questions were provided to the participants in the workshop for consideration and response after the meeting.

- How best should the arrays and accompanying text be presented?
- Is the Mercury Summary a good Template?
- The introductory material and accompanying tables need to be linked (somehow) with the arrays; are there any suggestions on accomplishing that goal?

The level of peer review (ranging from none to e.g., NAS review) would also be very useful to include in the supporting tables. Not mentioned in the meeting, but used in some applications, would be the level of confidence in the value and/or database. This is used in the IRIS values where ratings of high, medium or low are provided. It should be noted, however, that numerical values of total UFs and confidence levels are typically inversely related.

Discussion also touched upon whether a standard range of concentrations be used across all arrays or to have the range reflect the range of concentrations for the specific chemical. The advantage of the former is that it would make it easier to do cross-chemical comparisons of toxicity. The counter argument is that all values would not be spread out for easy comparisons within a chemical array. There was general agreement that arrays should have both a standard y-axis for cross-chemical comparisons, and a more focused array for comparing values for a single chemical (i.e., both types of arrays would be developed). One related suggestion was to use a Map and Map Inset approach on the web site.

Labeling and shading of array legends to highlight the types of values (e.g., emergency response vs. occupational vs. protective) was also mentioned as an enhancement to the arrays.

Conclusions and Next Steps

A request was made that the participants access the Environmental Science Connector Project Page (http://oaspub.epa.gov/portal/page/portal/ESConnector/CNTR_ESC/ESCHOME/MYWO

RKBENCH?escSelectedProjectId=24396) to help address some of the questions raised in the workshop.

Mention was made of having a "protected" PDF version of the summaries such that the array could not be copied and pasted by itself. The suggestion was also made to create links to the source/supporting documents and doing "map insets" on the standardized arrays to expand the details out for better within-chemical comparisons of values. Also,the addition of cancer unit risks for inhalation and cancer slope factors for the oral route at varying exposure levels will also be investigated, as will some of the recommendations for more interactive arrays that would allow popups, dropdowns, etc. with detailed information for specific reference values by clicking on the appropriate portions of the arrays.

An update on progress is expected to be posted using the ESC Project page for the client programs to be able to keep abreast of developments. Reciprocally, the project team is hopeful that the representatives from the programs will provide useful input to the project using that resource.

List of Workshop Participants

- William Ashman, Battelle, Contractor to Department of Homeland Security
- Deborah McKean, US EPA, National Homeland Security Research Center
- Michele Burgess, US EPA, Office of Solid Waste and Emergency Response
- Sarah Mazur, US EPA, Office of Science Policy
- Deborah Burgin, ATSDR
- Jayne Michaud, US EPA, Office of Solid Waste and Emergency Response
- Ernest Falke, US EPA, Office of Pollution Prevention and Toxic Substances
- Stan Durkee, US EPA, Office of Science Policy
- John Lipscomb, US EPA, National Center for Environmental Assessment
- John Vandenberg, US EPA, National Center for Environmental Assessment
- Debra Walsh, US EPA, National Center for Environmental Assessment
- Jess Rowland, US EPA, Office of Pollution Prevention and Toxic Substances
- Schatzi Fitz-James, US EPA, Office Emergency Management
- Roy Smith, US EPA, Office of Air Quality Planning and Standards

APPENDIX B: PROCEDURES FOR DEVELOPING ARRAYS OF HEALTH EFFECT REFERENCE VALUES

September 2009

Standardized procedures were used to identify source materials, extract and process relevant information, incorporate the information into Reference Value Arrays, and document the results. This set of procedures is anticipated to evolve as the process for developing these arrays becomes more automated and database-oriented. Additionally, it is anticipated that changes to format and customized options for variations on the reference value arrays will need to be accommodated based on client input.

This version begins with use of the best available electronic source for this information at this time (the Air Toxics Health Effects Database or ATHED) and a Microsoft Excel template for manipulating the data and rendering a graphical array of the values. It is anticipated that ATHED will eventually be linked into or become a part of the Health and Environmental Research Online (HERO) database, a data management resource being developed by NCEA-RTP. It would be through HERO that a more automated mechanism for the development and updating of reference value arrays would be created.

The remainder of this document describes the process used to develop reference value arrays and the supporting summary document. This process includes the use of ATHED, original technical support documents and other reference materials describing the derivation and use of the various reference values included in the arrays, a template for developing two variations of the arrays developed in MS-Excel™, and a template of the summary document developed in MS-Word™. The process is described below as the steps taken in the process of developing the data arrays and supporting documentation.

Step 1: Query ATHED

ATHED is a database developed in MS-Access™ and the 2009 version was used in this process (ATHED2009.mdb); however, the database is not at present available on-line. A separate Access file (Link2ATHED2009.mdb) was developed that links to the data tables in ATHED for the various purposes of querying and performing QC on the database without cluttering up the original database. A series of queries were developed within that linked database to standardize the units for the various values, and to create a cross-tabulation that is most useful for creating an array using the Excel template. All queries are provided in SQL format in Appendix A to this procedures document.

The first in the series of queries (RefValue-Std) performed the following: (1) developed an ordering for exposure durations with acute, followed by subchronic, then chronic; (2) standardized the "origin" field from ATHED; (3) converted the IDLH/10 back to IDLH values; (4) reported the values in original units and converted from ppm to mg/m^3 and vice versa; and (5) converted all durations into hours, including an assumption of 613,200 hours (70 years) and 61,320 hours (7 years) as the upper limits for chronic and subchronic values, respectively.

The next query (RefValue-Std_Crosstab) took the output from the first query and put into a cross-tabulation more amenable to use in Excel. This array also formatted several fields (e.g., duration hours) to make them consistent and more well ordered. The query also limited the selection of reference values to only be those for the inhalation route, and for chemicals limited to the 24 identified for the current work effort. The results from this query were copied into the Excel template as the initial basis for array development.

Step 2: Verification of ATHED Data

As the data were taken from the ATHED output, they were verified by comparison to the most updated versions of the source materials from the originating organization responsible for each of the reference values. If there was a discrepancy, it was noted in the spreadsheet by a yellow highlight and text in red font. This was done to help facilitate QC of ATHED and support the upcoming update to that database.

Step 3: Development of the Reference Value Arrays

Once the data were verified and the values input into the "Plot Data" tab in the Excel file, a draft of the array using a standard y-axis for concentrations of exposure ranging from 10^{-7} to 10^{5} mg/m^3 was developed. This array, labeled the "Comparison Array," was then manipulated to include labels for certain reference values and to adjust the labeling of the legend to match the reference value to its appropriate type (i.e., Emergency Response, Occupational, or General Public).

The more critical array for the development of summary documents is found in the tab labeled "Chemical-specific Array." In this array the range of concentrations is limited to display only the range applicable to the specific chemical and to more clearly enable the user to distinguish between reference values in close proximity to one another on the array.

Hiding rows in the spreadsheet labeled Plot Data where a type of reference value is not available removes the label from legend in both of the arrays. Additionally, changes in the labels may be performed to reflect chemical-specific values not generally found for most chemicals. For example, many of the chemical warfare agents have IDLH and/or TWA values developed by the Army instead of one of the occupational health agencies/organizations.

Once all of the appropriate labels have been hidden or revised, work may be needed to add, format, or move the labels included in the array proper to avoid overlapping text and other issues that make the labels unreadable or otherwise unclear. Additionally, formatted, semi-transparent colored boxes with labels have been added to the legend to segregate the emergency response, occupational, and general public values from one another and to help identify which are in each category. The boundaries of these colored boxes need to be manipulated based on the changes made to the Plot Data spreadsheet.

Step 4: Export the Final Array

Once all of the manipulations of the array have been finalized and all the formatting changes have been performed, the array area is highlighted and pasted into a formatted PowerPoint file (ChemicalSpecificArrays.ppt) where additional formatting

changes are performed and final branding labels are added. The most reliable way to paste the array into the PowerPoint file is by using the pull-down "Edit" menu item, selecting "Paste Special" and choosing to paste as an "Enhanced Metafile." Adjustments are made to ensure that the array fits into the slide by dragging the top left and top right corners to the edges of the slide. At this point, selecting "select all" from the pull-down "Edit" menu item will select all elements on the slide. A right click on the mouse brings up an options menu, and "Save as picture" should be selected to save the final array as an enhanced metafile. The final array for that chemical is now available for inclusion into the summary document.

Step 5: Develop the Summary Document

This step actually consists of several sub-steps and can be done in parallel with the development of the graphical array. The introductory section of the summary document is generally the same for each array and briefly describes the differences between the categories of reference values (emergency response, occupational, and general public), the durations for which each type of value is derived, and some discussion of the populations and purposes for which the various reference values were derived. Included in this introductory material is Table 1-1, which provides some of these details in an organized fashion.

Summary tables are provided as a direct companion to the individual, chemical-specific graphical arrays with many of the details that are important for a thorough comparison between the reference values but are not easily included in a graphical format. These details include the numerical concentration in both mg/m^3 and ppm, the duration for each value, the critical endpoint on which the value was based, identification of the study(ies) from which the point of departure was taken, the uncertainty factors used, and any other details relevant to derivation of the final reference value (e.g., use of adjustments or extrapolations, such as for duration).

A final discussion section is provided to help lead the reader through a comparison of the available reference values for the specific chemical, and to point out any particular variation in the derivation of the values from usual procedures. As much as possible, an objective tone is maintained and judgment on the merits of the use of one value over another is avoided, with the exception that caution is urged to use the derived values within the context for which they developed.

APPENDIX C: QUERIES OF ATHED

RefValue-Std

```
SELECT tblBenchmarks.Benchmark_ID, tblBenchmarks.CAS_No,
tblChemical_Info.Chemical_Name, tblChemical_Info.Sortable_Name,
tblChemical_Info.Molecular_Weight, tblBenchmarks.Exposure_Route,
IIf([exposure_Type]="acute",1,IIf([exposure_Type]="subchronic",2,IIf([exposure_Type]="chron
ic",3,Null))) AS ExpTypeOrder, tblBenchmarks.Exposure_Type,
IIf(InStr([Data_Source],"AEGL")>0,"NAC/AEGL",IIf(InStr([Data_Source],"ERPG")>0,"AIHA/
ERPG",IIf(InStr([Data_Source],"ATSDR")>0,"ATSDR",IIf(InStr([Data_Source],"CAL")>0,"C
AL",[Data_Source])))) AS RefValOrigin, RefValueType.RefValueType,
IIf([tblBenchmarks].[Benchmark_Type]="ID/10","IDLH",IIf([tblBenchmarks].[Benchmark_Typ
e]="STEL",Trim([Data_Source]) & "-STEL",[tblBenchmarks].[Benchmark_Type])) AS
Benchmark_Type,
IIf(tblBenchmarks.Benchmark_Type="ID/10",tblBenchmarks.Benchmark_Value*10,tblBenchm
arks.Benchmark_Value) AS Benchmark_Value, tblBenchmarks.Benchmark_Units,
IIf(UCase([Benchmark_Units])="PPM",[Benchmark_Value],IIf([Exposure_Route]="inhalation",
IIf([Benchmark_Units]="mg/cu
m",(24.45*[Benchmark_Value])/[Molecular_Weight],IIf([Benchmark_Units]="ug/cu
m",((24.45*[Benchmark_Value])/[Molecular_Weight])/1000,Null)))) AS Std_ppm,
IIf(UCase([Benchmark_Units])="mg/cu
m",[Benchmark_Value],IIf([Exposure_Route]="inhalation",IIf(UCase([Benchmark_Units])="PP
M",([Benchmark_Value]*[Molecular_Weight])/24.45,IIf([Benchmark_Units]="ug/cu
m",[Benchmark_Value]/1000,Null)))) AS [Std_mg/m3],
Val(IIf([Exposure_Type]="chronic",613200,IIf([Exposure_Type]="subchronic",61320,IIf([Expo
sure_Type]="acute",IIf([AvgTime] Is Not
Null,IIf([AvgTime_Units]="min",Round([AvgTime]/60,2),[AvgTime]),1))))) AS [Duration-hrs],
tblBenchmarks.AvgTime, tblBenchmarks.AvgTime_Units, tblBenchmarks.Benchmark_Date,
tblBenchmarks.Benchmark_Confidence, tblBenchmarks.Cancer, tblBenchmarks.Cancer_sites,
tblBenchmarks.Weight_of_Evidence, tblBenchmarks.HEC, tblBenchmarks.UF_cumulative,
tblBenchmarks.UF_interspecies, tblBenchmarks.UF_intraspecies, tblBenchmarks.UF__LOAEL,
tblBenchmarks.UF_subchronic, tblBenchmarks.UF_database, tblBenchmarks.UF_other,
tblBenchmarks.Modifying_Factor
FROM [APM-125] LEFT JOIN (RefValueType RIGHT JOIN (tblBenchmarks LEFT JOIN
tblChemical_Info ON tblBenchmarks.CAS_No = tblChemical_Info.CAS_No) ON
RefValueType.Type_ID = tblBenchmarks.Benchmark_Type) ON [APM-125].CAS_No =
tblBenchmarks.CAS_No
WHERE (((tblBenchmarks.CAS_No)<>""))
ORDER BY tblChemical_Info.Sortable_Name, tblBenchmarks.Exposure_Route,
IIf([exposure_Type]="acute",1,IIf([exposure_Type]="subchronic",2,IIf([exposure_Type]="chron
ic",3,Null))), RefValueType.RefValueType,
IIf([tblBenchmarks].[Benchmark_Type]="ID/10","IDLH",IIf([tblBenchmarks].[Benchmark_Typ
e]="STEL",Trim([Data_Source]) & "-STEL",[tblBenchmarks].[Benchmark_Type]));
```

RefValue-Std_Crosstab

```
TRANSFORM Avg([RefValue-Std].[Std_mg/m3]) AS [AvgOfStd_mg/m3]
SELECT [RefValue-Std].CAS_No, [RefValue-Std].Chemical_Name, [RefValue-
Std].ExpTypeOrder, [RefValue-Std].RefValueType, [RefValue-Std].Exposure_Route,
[RefValue-Std].Exposure_Type, [RefValue-Std].RefValOrigin, [RefValue-
Std].Benchmark_Type
FROM [RefValue-Std] INNER JOIN [APM-125] ON [RefValue-Std].CAS_No = [APM-
125].CAS_No
WHERE ((([RefValue-Std].Exposure_Route)="inhalation"))
GROUP BY [RefValue-Std].CAS_No, [RefValue-Std].Chemical_Name, [RefValue-
Std].ExpTypeOrder, [RefValue-Std].RefValueType, [RefValue-Std].Exposure_Route,
[RefValue-Std].Exposure_Type, [RefValue-Std].RefValOrigin, [RefValue-
Std].Benchmark_Type
ORDER BY [RefValue-Std].CAS_No, [RefValue-Std].ExpTypeOrder, [RefValue-
Std].RefValueType, [RefValue-Std].Benchmark_Type
PIVOT Format([Duration-hrs],"000000.00");
```