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EPA at 50 Progress for a Stronger Future

Overview of Regulatory Standards and Guideline Reference Values



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RATE Risk Assessment Training & Experience

Disclaimer:
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Overview

- Terminology and Key Concepts
- Standards vs. Guidelines
- Description of three major exposure contexts
  - Emergency response and planning
  - Occupational
  - General public
- Comparisons Across Values: Reference Value Arrays

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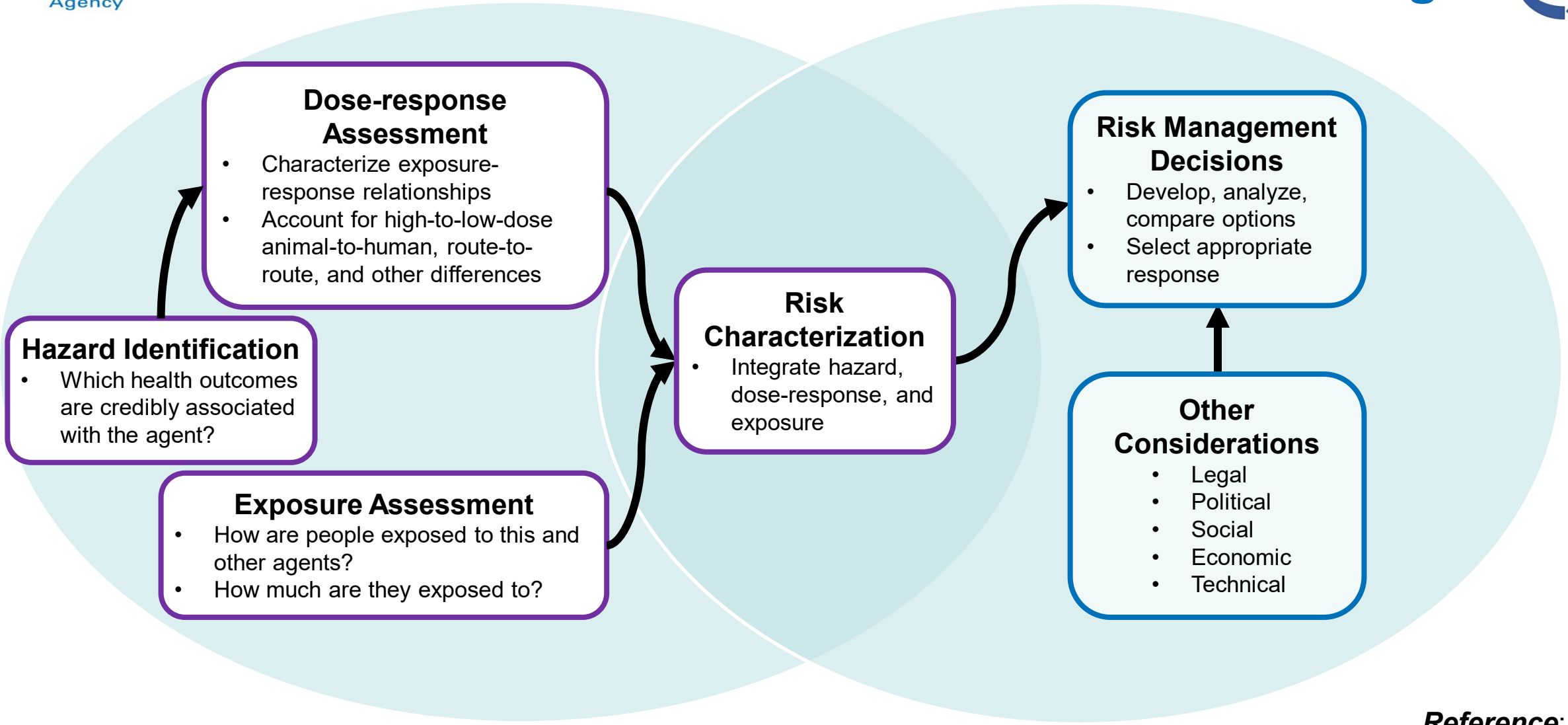
TERMINOLOGY AND KEY CONCEPTS

NRC Risk Assessment Paradigm



Reference:
NRC "Red Book"

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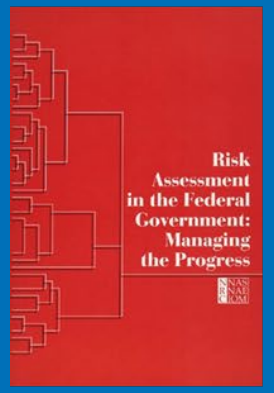
THE RISK ASSESSMENT PARADIGM
AS ESTABLISHED BY THE NATIONAL RESEARCH COUNCIL (NRC)



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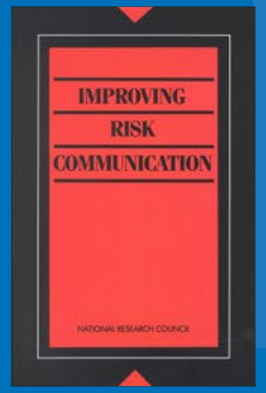
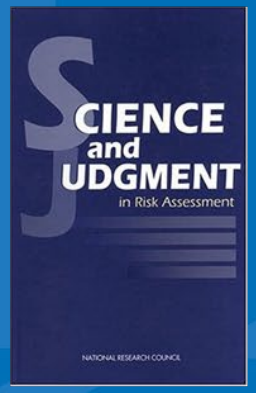


1989



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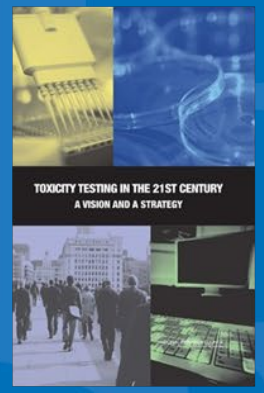
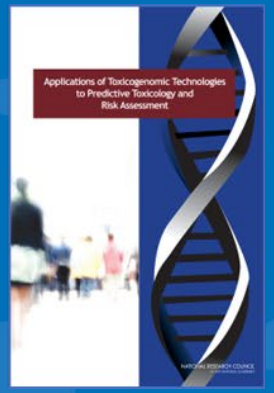


2007



2007

2009

2012

2017

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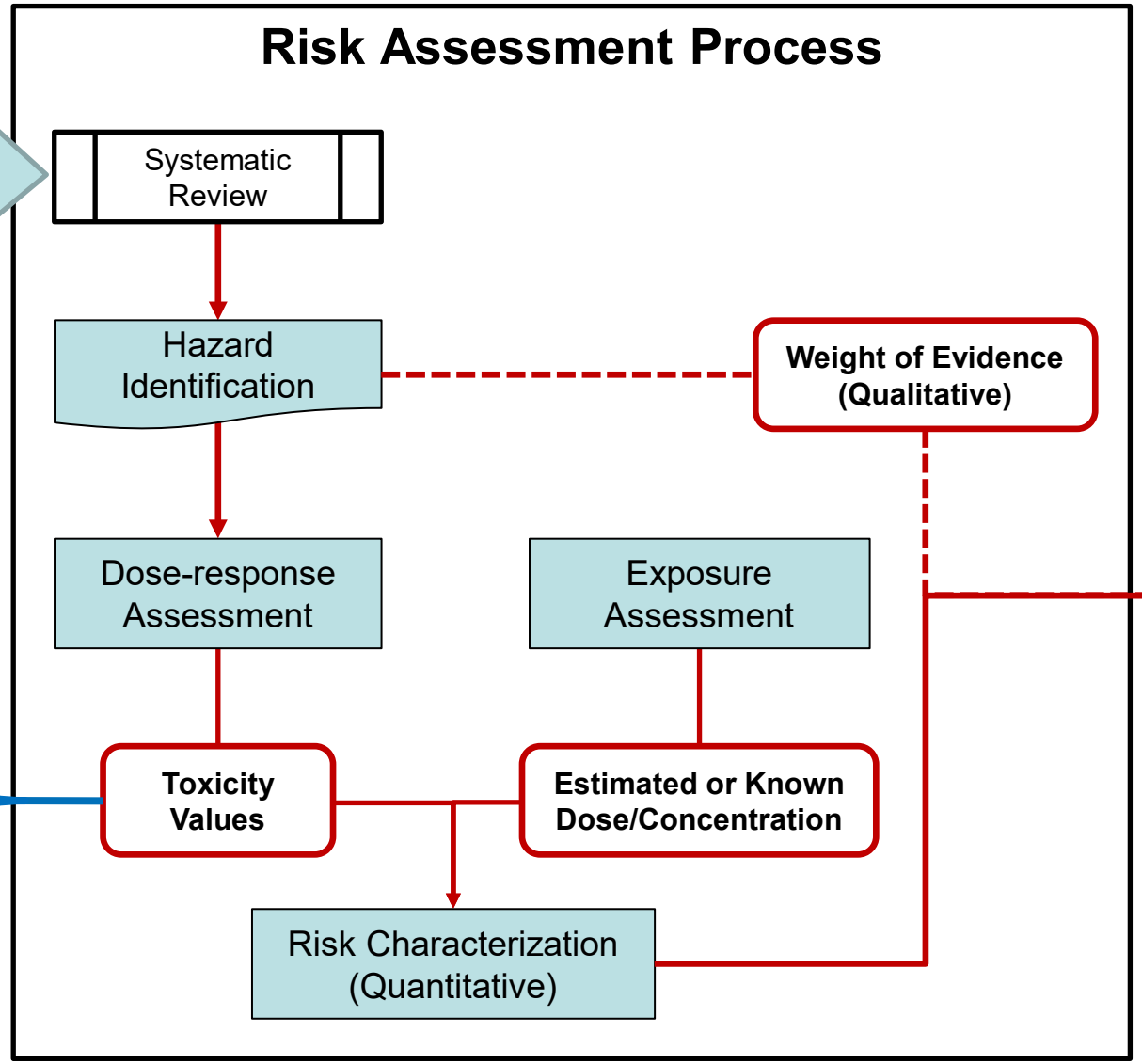
Risk Assessment Paradigm in Practice

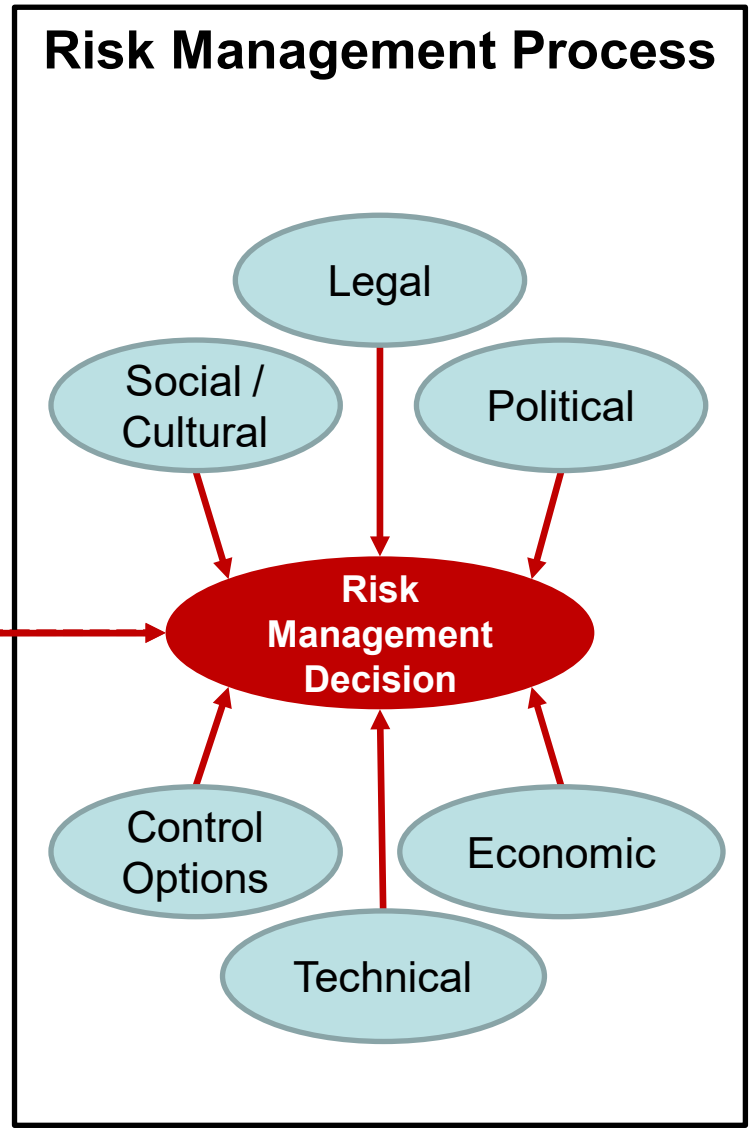
Research

- Epidemiology
- Clinical Studies
- Animal Studies
- *In vitro* & *Ex vivo*
- Modeling (*In Silico*)

Types of Toxicity Values

	Cancer	Noncancer
Oral / Dermal	Slope Factor	Reference Dose (RfD)
Inhalation	Unit Risk	Reference Concentration (RfC)





Toxicity Values

	Risk Estimates	Point Estimates
Oral	Slope Factor	Reference Dose (RfD)
Inhalation	Inhalation Unit Risk	Reference Conc. (RfC)

- **Point Estimates (Reference Values)** have most often been applied to noncancer endpoints
- **Risk Estimates** most often have been applied to cancer endpoints

Point Estimates

Recommended limits to exposure (often expressed as a dose or concentration) at or below which adverse human health are deemed “tolerable” or are not expected to occur.

Dose mg/kg-day

Milligram substance per kilogram body weight per day.

Concentration mg/L, mg/kg, or mg/m^3

Milligram substance per liter water, kilogram soil or food, or cubic meter air.

Practical Application

Air, water, soil, and food quality standards (and other exposure limits) to protect human health and the environment.

Quantitative Risk Estimates

Quantitative risk estimates are expressed as risk (proportion affected) per unit of dose for oral exposures or per concentration unit for inhalation exposures.

Slope Factor Risk/(mg/kg-day)

10^{-6} Risk per milligram substance per kilogram body weight per day.

Unit Risk Risk/(mg/m^3)

10^{-6} Risk per milligram substance per cubic meter air.

Practical Application

Air, water, soil, and food quality standards (and other exposure limits) to protect human health and the environment.

Entities that Develop Reference Values

Federal Agencies

ATSDR

OSHA

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

FDA

National Institute for Occupational Safety and Health NIOSH

State Agencies

Office of Environmental Health Hazard Assessment OEHHA State of California

TCEQ

Other Entities

ACGIH®

AIHA Protecting Worker Health

EPA United States Environmental Protection Agency

GUIDELINES AND STANDARDS

Reference Values: Levels of Enforceability

Regulatory Standards

- Relatively few
- Mandated by statute and legally enforceable
- Rigid development process
- Developed by government agencies as specified in statutes
- Intended to protect health and the environment, but balances other considerations

Advisory Guidelines

- Numerous
- Not legally enforceable
- Flexible development process
- Developed by many types of entities
- Intended to protect human health and the environment

National Exposure Standard Examples

Medium	Standard	Regulated Contaminants	Regulatory Authority
Air	National Ambient Air Quality Standards (**NAAQS**)	6 Criteria Pollutants in ambient air	EPA, as mandated by the Clean Air Act
	Permissible Exposure Limits (**PELs**)	~500 contaminants in workplace air	OSHA, as mandated by the Occupational Safety and Health Act
Water	Maximum Contaminant Levels (**MCLs**)	90 chemical, microbiological, radiological, and physical contaminants in drinking water	EPA, as mandated by the Safe Drinking Water Act
Food	Maximum Residue Limits (**MRLs**)	Hundreds of pesticide chemicals in food and feed commodities	EPA, as mandated by the Federal Food, Drug, and Cosmetics Act, as amended by the Food Quality Protection Act

Exposure Contexts

- General Public (Ambient)
- Occupational
- Emergency Response

Types of Health Effect Reference Values

Example

Type of Values	Example	Population	Exposure Type
Public Health	RfC	General Public	Continuous (24 h/d, 7 d/week, up to a lifetime)
Emergency Response	AEGLs	General Public & Workers	Catastrophic Release (10 m to 8 h)
Occupational	TLVs	Workers	Work day (8 h/d, 5 d/week, up to 40 years)

- RfC = Reference Concentration
- AEGL = Acute Exposure Guideline Level
- TLV = Threshold Limit Value

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GENERAL PUBLIC REFERENCE VALUES

General Public Values: Characteristics

- **Exposure Type:** Ambient
- **Duration:** Generally long-term
- **Medium:** Developed for air, water, and food
- **Enforceability:** Some are legally enforceable
- **Applicability:** Prevent harm from chemical exposures over the course of a lifetime; must protect sensitive subgroups
- **Adaptability:** Developed for protection of human health and the environment





Examples of General Public Guideline Values

Guideline	Organization and Context
RfD Oral/Dermal Reference Dose	EPA United States Environmental Protection Agency Integrated Risk information System (IRIS) values are: Developed to support hazard identification and dose-response assessment. Used to characterize public health risks of a given substance in a given situation. Used to form the basis for risk-based decision-making, regulatory activities, and other risk management decisions.
RfC Inhalation Reference Concentration	
OSF Oral/Dermal Slope Factor	
IUR Inhalation Unit Risk	
MRL Minimal Risk Level	ATSDR Recommended limits to support the identification of contaminants potentially harmful to human health at hazardous waste sites.

Examples of Standards for the General Population Context

Standards	Organization and Context
NAAQS National Ambient Air Quality Standards	Mandated by the CAA for criteria pollutants in air to protect the public from pollutants considered harmful to public health and the environment.
WQC Water Quality Criteria	Mandated by the CWA for over 150 pollutants in surface waters, EPA provides recommended concentrations that can be used by states and tribes to set legally enforceable water quality standards based on a specified use.

Example General Public Reference Values – Inhalation Exposures

Reference Value	Definition	Originating Organization	Level of Review
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)	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)	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)	Office of Environmental Health Hazard Assessment (OEHHA), State of California	External Peer 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)	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 continuous chronic exposure scenarios.** (WHO, 2000)	World Health Organization	Internal Peer Review

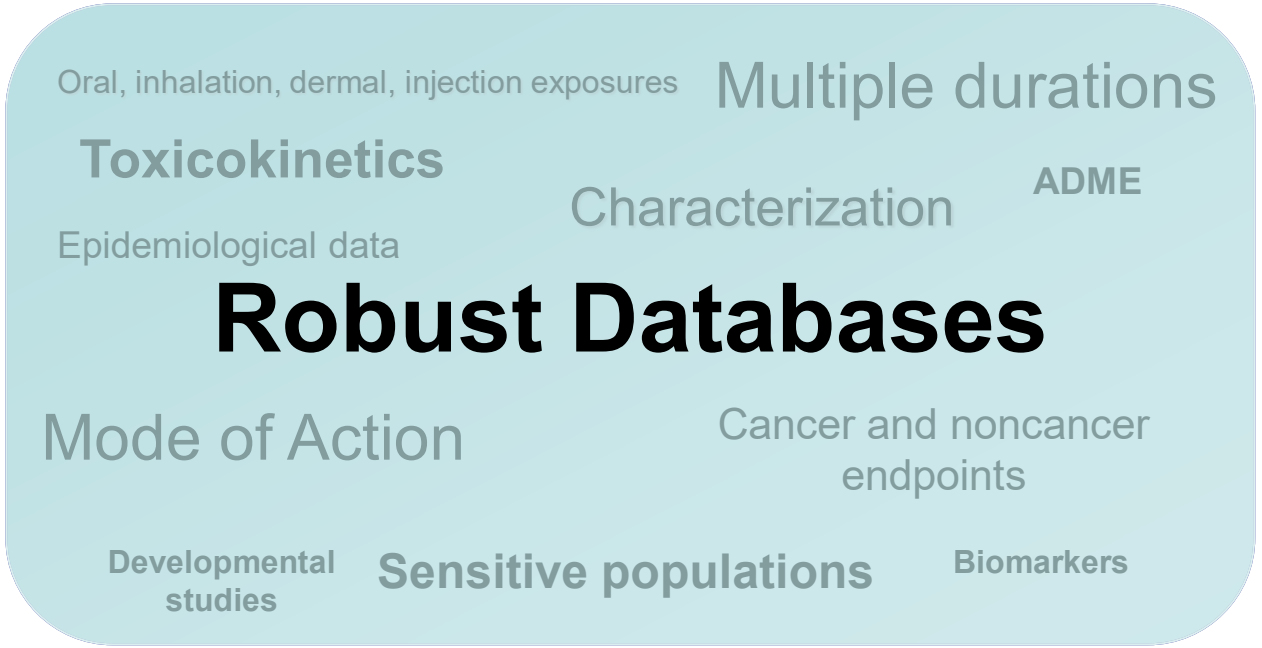
Also Used by States: NC Water Quality Standards Example

Toxicant	Aquatic Life (µg/L)[1]		Human Health (µg/L)[1,2]	
	Federal Guidelines (all waters)	NC Class C Waters[3]	Federal Guidelines (all waters)	NC Class WS-I Waters[4]
Aldrin	--	0.002	0.000050	0.00005
Arsenic	**150**	**50**	**0.018**	**10**
Chlordane	0.0043	0.004	0.00081	0.0008
DDT	0.001	0.001	0.00022	0.0002
Dieldrin	**0.056**	**0.002**	0.000052	0.00005
Endosulfan	0.056	0.05	62	--
Endrin	**0.036**	**0.002**	0.059	--
Heptachlor	0.0038	0.004	0.000079	0.00008
Lindane	--	0.01	0.98	--
Nickel	**52**	**88**	**610**	**25**
Toxaphene	0.0002	0.0002	0.00028	--

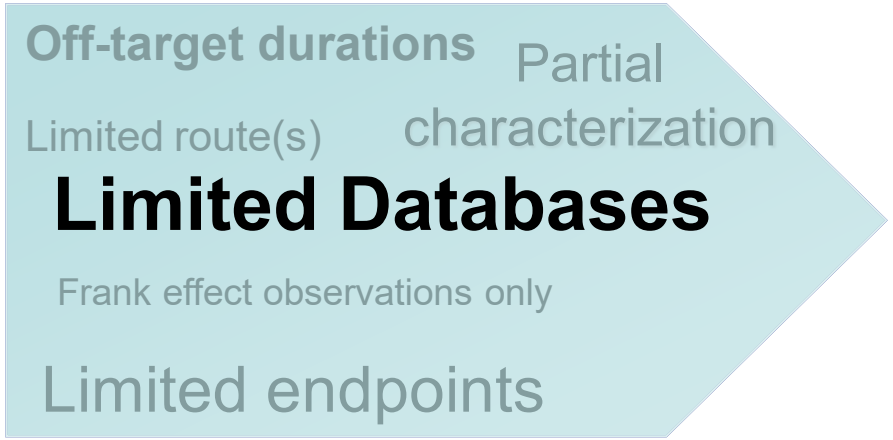
[1]All standards are chronic duration standards – those in bold are not adopted from EPA recommendations
[2]Human health standards based on a cancer risk of 10-6 for carcinogen and IRIS RfD for noncarcinogens from consumption of water and fish
[3]NC Class Waters: Freshwaters protected for secondary recreation, fishing, aquatic life including propagation and survival, and wildlife
[4]NC Class WS-I Waters: Freshwaters protected as water supplies which are essentially in natural and undeveloped watersheds

Sources: http://epa.gov/waterscience/standards/wqslibrary/nc/nc_4_denr.pdf and http://www.epa.gov/waterscience/criteria/wqctable/index.html#cmc

Confidence in the Data



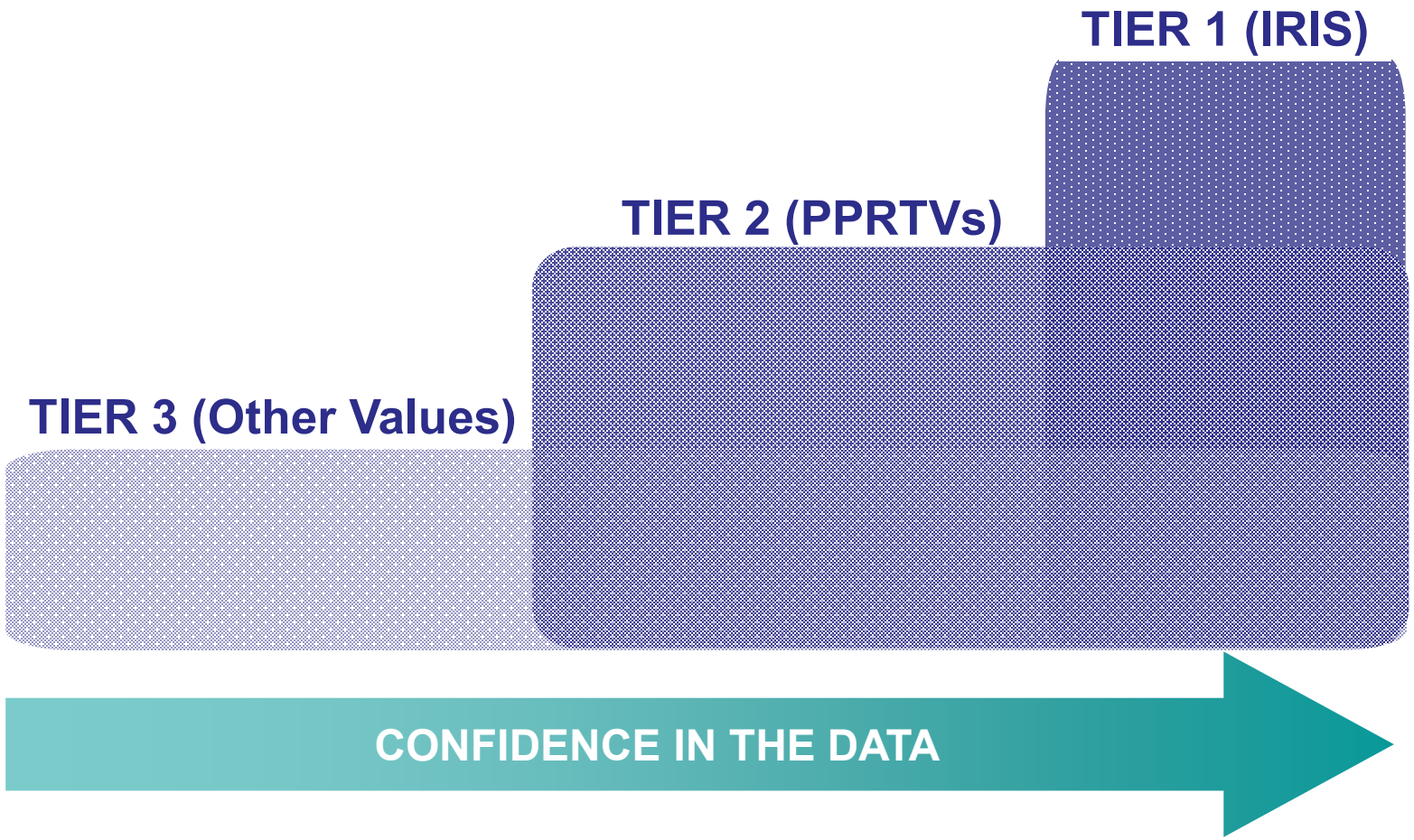
Top Tier Values



Lower Tier Values

Confidence in the Data: EPA's Tiered Approach

Hierarchy used by Superfund and RCRA Hazardous Waste Programs



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OCCUPATIONAL REFERENCE VALUES

Occupational Values: Characteristics

- **Exposure Type:** Healthy adult workers in occupational settings
- **Duration:** Acute to chronic. Generally include two types of values
  - Not to exceed – “ceiling” or Short-term Exposure Limit (STEL)
  - Time-weighted average (TWA)
- **Medium:** Generally concentrations in workplace air
- **Enforceability:** Some are legally enforceable
- **Applicability:** Inform risk management policies in the workplace
- **Adaptability:** Sometimes derived for special environments




Uses of Reference Values in Occupational Context

Guidelines and Standards	Organization and Context
PEL Permissible Exposure Level	Mandated to address hazardous substances or conditions in the workplace considering a continuous exposure during a normal 40-hour workweek.
REL Recommended Exposure Limit	Developed for hazardous substances or conditions in the workplace considering a continuous exposure during a normal 40-hour workweek.
IDLH Immediately Dangerous to Life or Health value	Developed only for the purpose of respirator selection under emergency conditions in the workplace.
TLV Threshold Limit Value	Developed to enable industrial hygienists to make decisions regarding safe values of exposure to chemical substances and physical agents found in the workplace.
CEGL Continuous Exposure Guidance Level	To protect workers on submarines from chemical exposures in an enclosed and isolated environment.

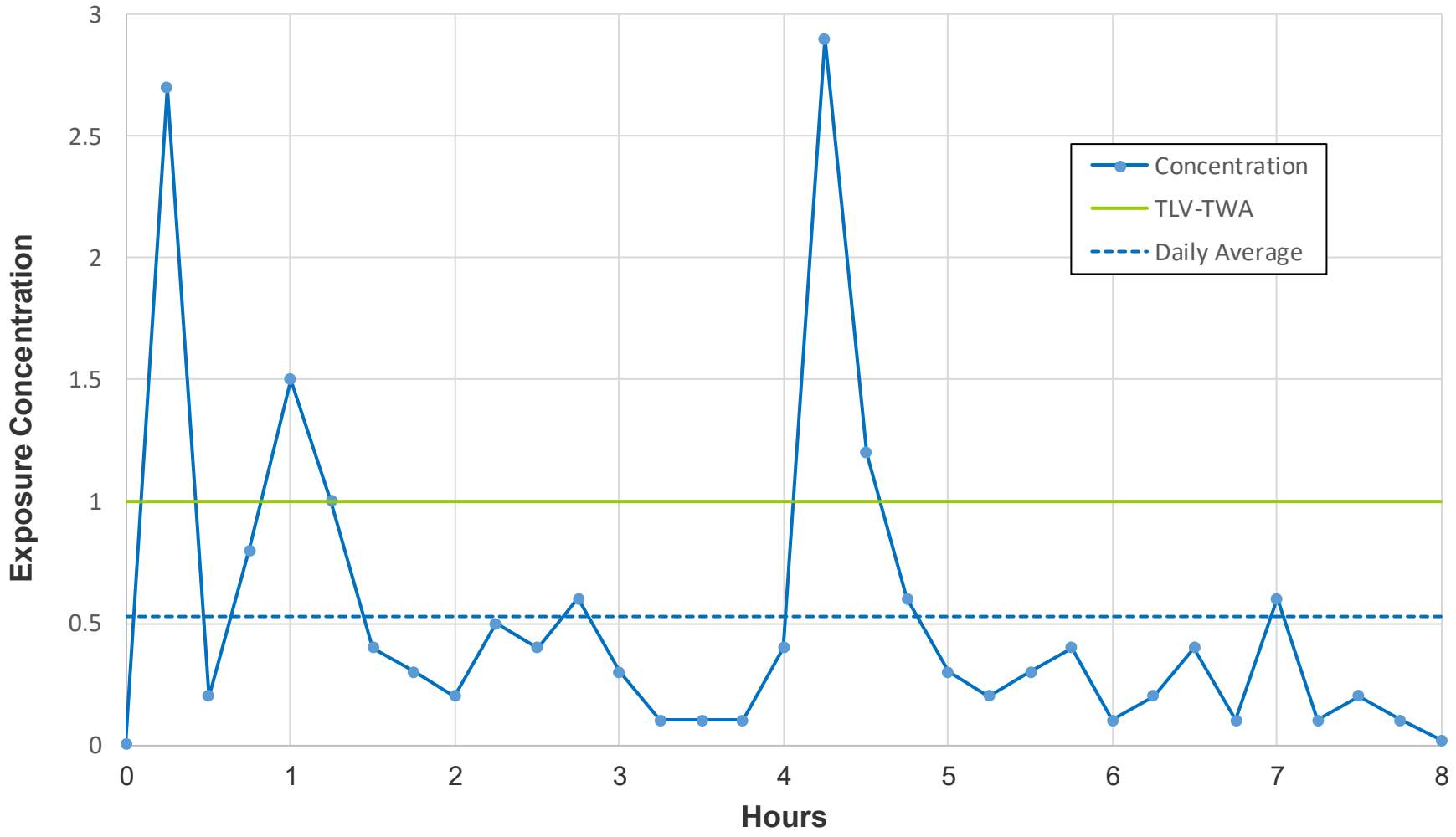
Occupational Reference Values

Reference Value	Definition	Originating Organization	Level of Review
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)	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)	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)	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)	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; CDC, 2004)	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)	ACGIH	Expert Panel Review
		NIOSH	Public Comment Period
		OSHA	Federal Register
Ceiling	"Level of exposure that should **not be exceeded at any time**." (NIOSH, 2006)	ACGIH	Expert Panel Review
		NIOSH	Public Comment Period
		OSHA	Federal Register

Occupational Reference Values

- **Protects workers**
  - Normal work-day and work-week for a typical career (e.g., 8 hours/day, 5 days/week, for 40 years).
- **Time-weighted average (TWA)** – normal average exposures over an extended period of time
- **Short-term exposure limits (STELs)** and/or **Ceiling values** are developed to protect from shorter-duration excursions to the average lost in a multi-hour average value.

Considering Duration – Occupational Values



Occupational Reference Values

- **Assumptions and Considerations:**
  - Population is healthy, working-age adults (e.g., 18-65 years old)
  - Less likely to include susceptible subpopulations.
  - May consider the technical feasibility and reliability of monitors
  - Potential trade-offs (work practices, length of time at a task, etc.) may be used to compensate for these monitoring and reporting considerations.

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EMERGENCY RESPONSE REFERENCE VALUES

Emergency Response Values: Characteristics

- **Exposure Type:** Workplace or general public
- **Duration:** Generally acute
- **Medium:** Generally concentrations in air (but not always)
- **Enforceability:** Not legally enforceable
- **Applicability:** Inform emergency response and public health planning
- **Adaptability:** Often specify levels of harm

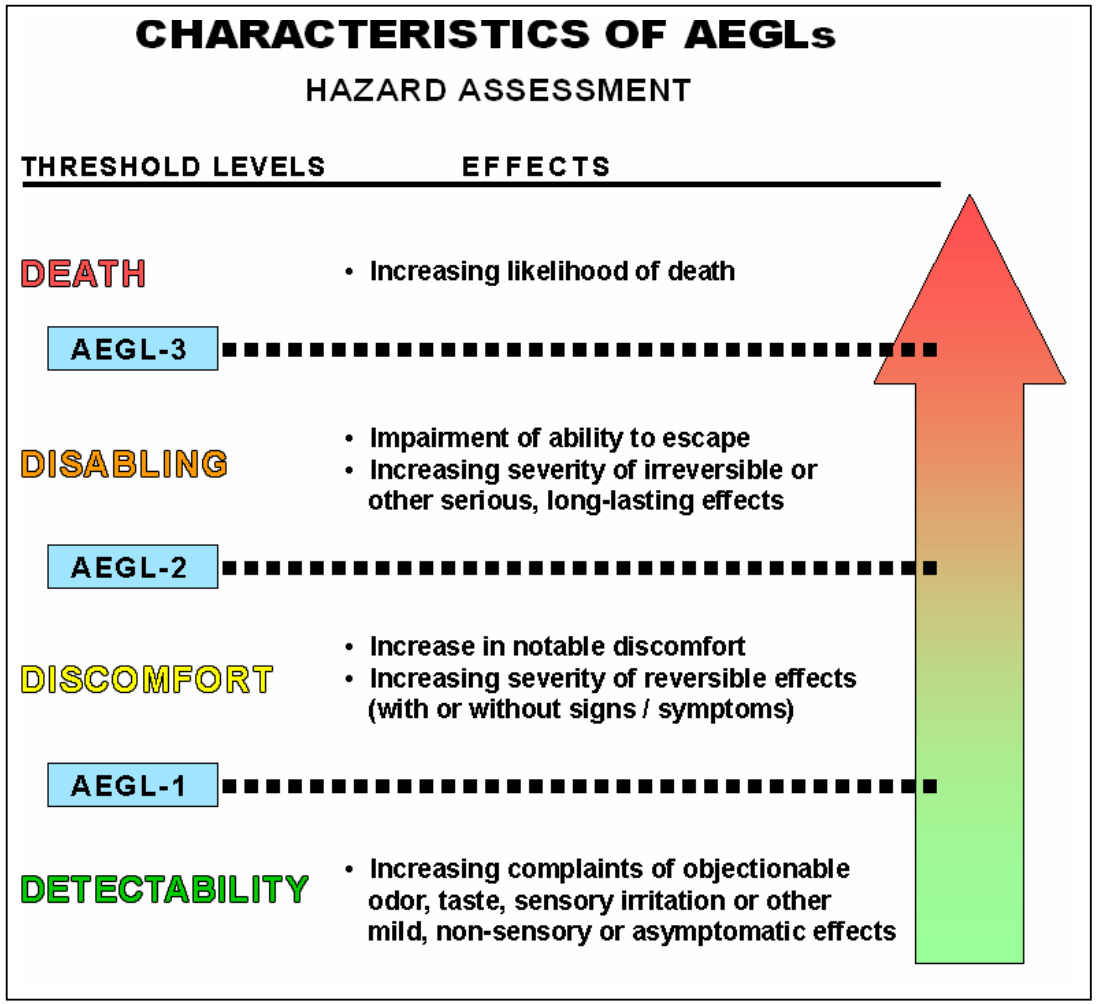




Emergency Response Reference Values

- **Design:**
  - Short duration exposure to high concentrations
  - Defines 3 or more levels of effects
    - Potential serious health effects
- **Assumptions and Limitations:**
  - Exposures to this level will be extremely rare (once-in-a-lifetime)
  - Does not indicate safety for repeated exposure
- **Uses:**
  - Determining a course of action in planning
  - Guides immediate reaction to a catastrophic release (i.e., evacuation or shelter-in-place)

AEGL Severity Categories



Courtesy of Ernest Falke, EPA

Acute Exposure Guideline Levels (AEGLs)

- Inhalation route only
- Acute durations – 10 minutes to 8 hours
- Three Severity Levels

Toluene AEGL Values

	10 minute	30 minute	1 hour	4 hour	8 hour
AEGL-1 (Non-disabling)	67 ppm	67 ppm	67 ppm	67 ppm	67 ppm
AEGL-2 (Disabling)	1400 ppm*	760 ppm	560 ppm	310 ppm	250 ppm
AEGL-3 (Lethal)	** 10,000 ppm	5200 ppm*	3700 ppm*	1800 ppm*	1400 ppm*

* Values ≥ 1400 ppm (10% of the Lower Explosive Limit of 14,000 ppm)

** Values ≥ 7000 ppm (50% of the LEL of 14,000 ppm)

Emergency Response Reference Values

Reference Value	Definition	Originating Organization	Level of Review
Emergency Response			
AEGL Acute Exposure Guideline Level	Three severity levels (10-min up to 8-hrs) (NRC, 2001) 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) 1 = Mild, transient effects; 2 = Irreversible effects or impairs ability to escape; 3 = Lethal	American Industrial Hygiene Association (AIHA)	Expert Panel Review

[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. These values are designed for coverage of the general public, including susceptible (e.g., children) but not hyper-susceptible individuals.

Uses of Reference Values in Emergency Context

Guidelines	Organization and Context
AEGL Acute Exposure Guideline Level	Developed to describe the risk to humans resulting from once-in-a-lifetime, or rare exposure to airborne chemicals. *Developed by committee managed by EPA
ERPG Emergency Response Planning Guideline	Used in community emergency planning to develop guidelines for responding to potential releases of airborne substances
PACs & TEELs Protection Action Criteria & Temporary Emergency Exposure Levels	PACs are the one-hour emergency response guidelines employed by the U.S. Department of Energy. DOE prefers to adopt AEGLs or ERPGs if available and develops TEELs (based on limited data) if no preferred value is available.
EEGL Emergency Exposure Guidance Level	Developed for military personnel operating under emergency conditions to prevent irreversible harm or serious impairment of judgment or performance.
EU-AETL European Union Acute Exposure Threshold Level	Used to support emergency-response and land-use planning following accidental chemical releases from industrial facilities.

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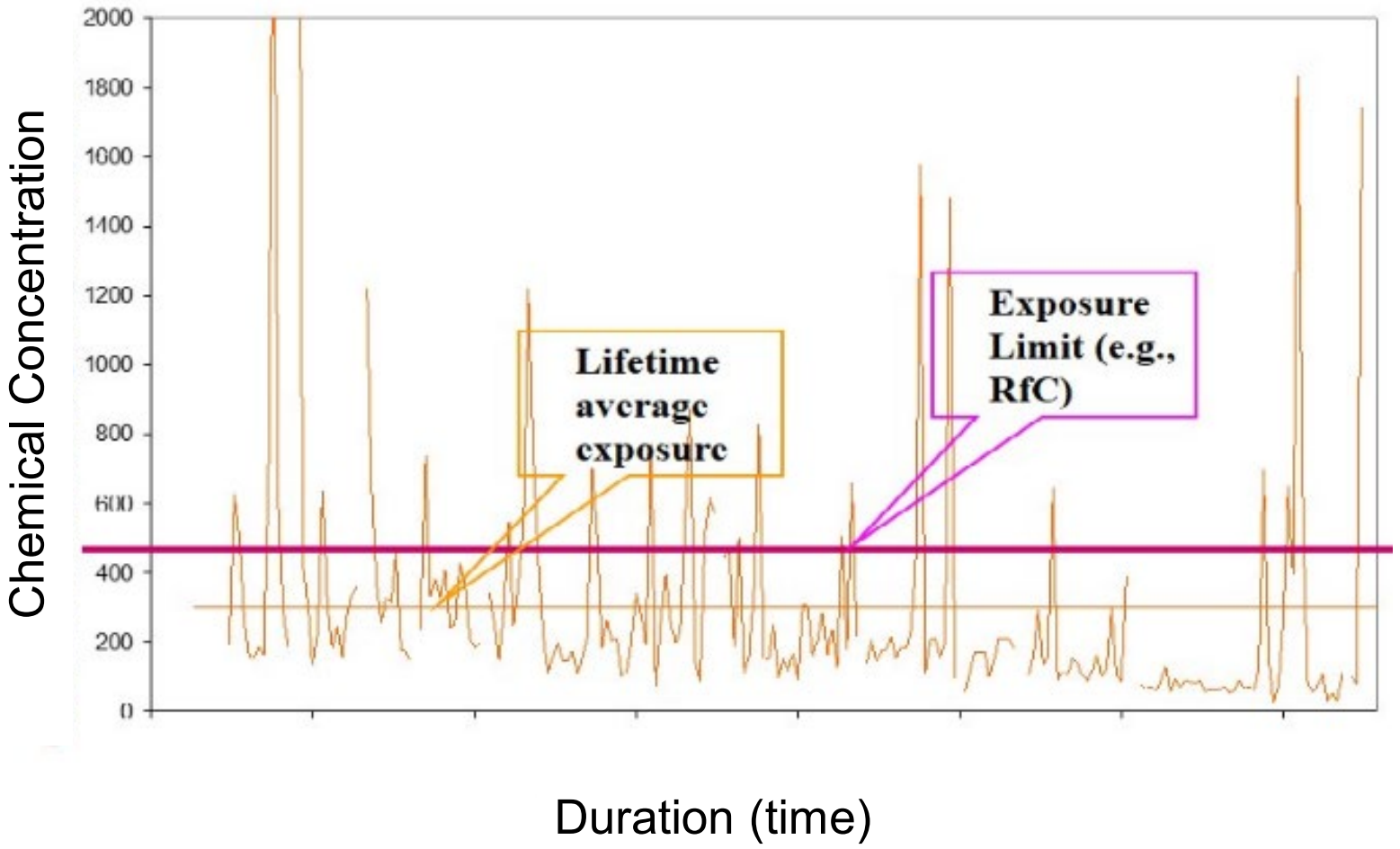
CONSIDERATION OF DURATION

Duration of Exposure

- Considerable variation in how organizations define the length of time associated with different exposure durations.
- EPA's Risk Assessment Forum (U.S. EPA, 2002) definitions:
  - **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).

U.S. EPA. A Review of the Reference Dose and Reference Concentration Processes. U.S. Environmental Protection Agency, Risk Assessment Forum, Washington, DC, EPA/630/P-02/002F, 2002. Available online - https://www.epa.gov/sites/default/files/2014-12/documents/rfd-final.pdf

Consideration of Duration in General Public Values



Duration Extrapolation (1)

- 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,
  - Acute reference value for one hour is needed
  - Study data comes from observations at 4 hours
  - Calculations are needed to estimate the concentration at the desired duration that would cause the same level of effect at the observed duration.

Duration Extrapolation (2)

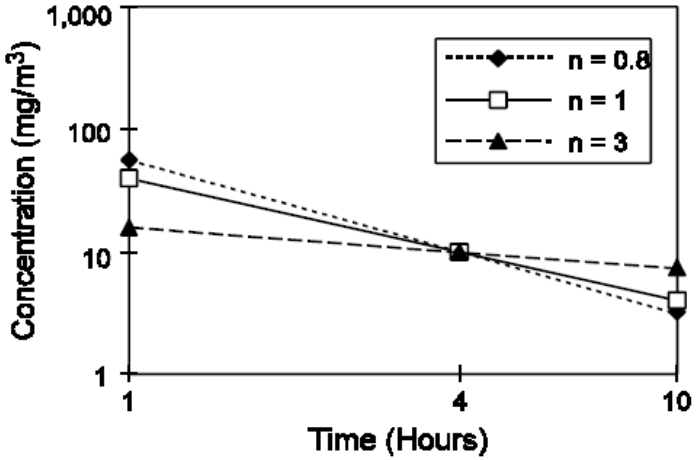
- Three basic approaches to duration extrapolation, from simple to more complex:
  1. Standard uncertainty factors when going from subchronic durations to chronic durations
  2. Concentration by time relationship ($C^n \times t$)
  3. Physiologically-based pharmacokinetic (PBPK) models to estimate the internal dose at the site in the body of toxic injury.

Duration Extrapolation in IRIS

- Typical assumption of Haber's relationship [C × t = k]
  - Example use of occupational study data [POD = 10 ppm]
    - Duration Adjusted from 5 d/week to 7 d/week
    - Physiological Adjustment:
      10 m^3 (occupational ventilation rate) to
      20 m^3 (normal daily ventilation rate)
    - POD_{ADJ} = 10 ppm × 10/20 × 5/7 = 3.6 ppm
- Adjustments based on years exposed:
  - Subchronic to Chronic Uncertainty Factor (3 or 10) when less than 20 years

Duration Extrapolation in AEGLs

- AEGLs – Usually apply C^n x t calculation (ten Berge variation on Haber's relationship)
  - Default: n = 3 for shorter durations
    n = 1 for longer durations
  - Better: n derived from lethality studies [in animals]
  - Best: n derived from endpoint-specific data (rarely available*)



* Can be calculated in BMDS ten Berge Model

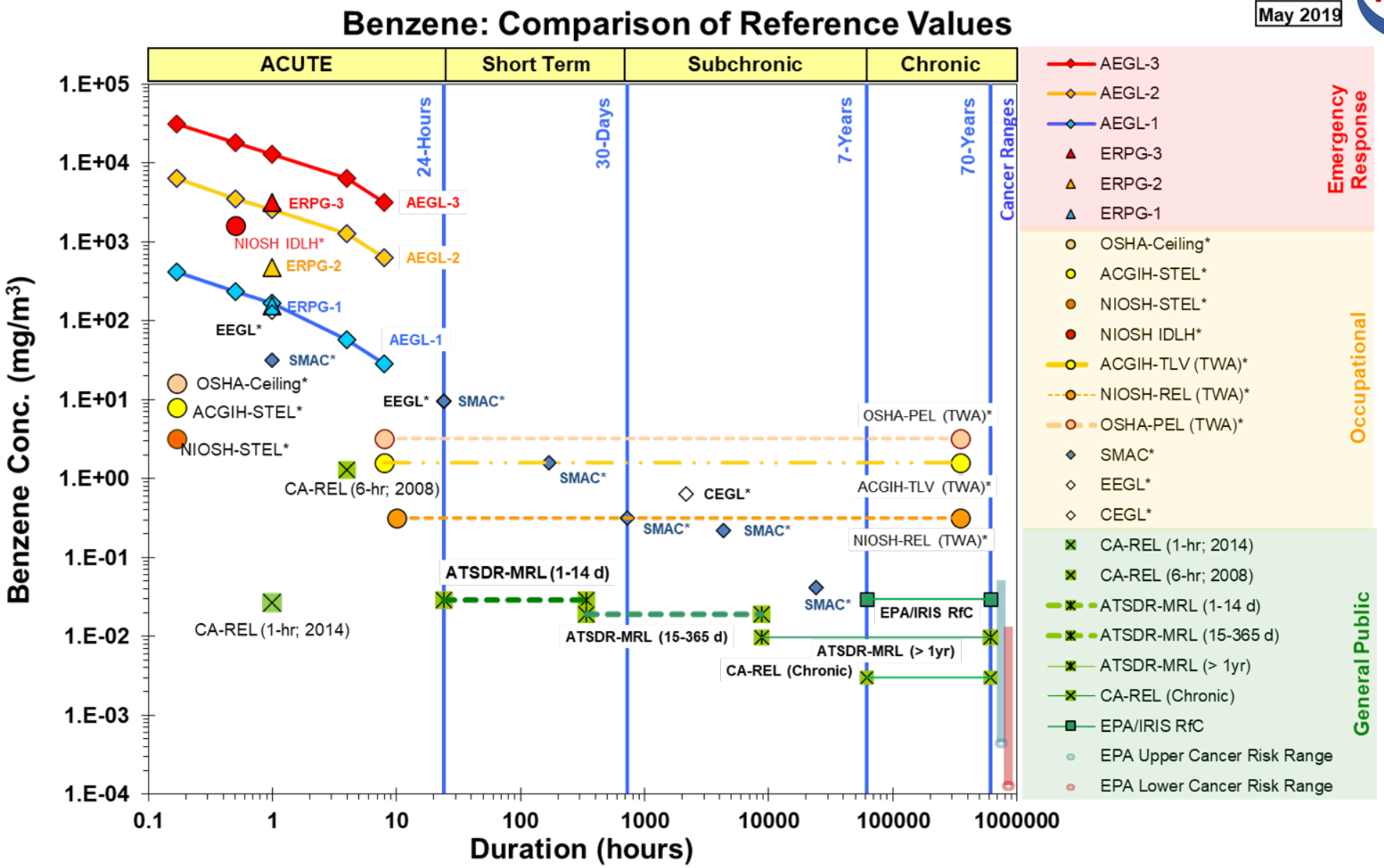
COMPARISONS ACROSS VALUES: REFERENCE VALUE ARRAYS

Reference Value Arrays

- **Reference Value Arrays** are graphical arrays that compare human health effect reference values across:
  - Multiple Agencies & Organizations
  - Durations of exposure
  - Populations of concern
  - Severity of effect
- A report on the purpose and development of reference value arrays is available from the U.S. EPA (2009).

U.S. EPA. Graphical Arrays of Chemical-Specific Health Effect Reference Values For Inhalation Exposures (2009 Final Report). U.S. Environmental Protection Agency, Washington, DC, EPA/600/R-09/061, 2009. https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=211003

Inhalation Reference Value Arrays



U.S. EPA. Mn and BTEX Reference Value Arrays (Final Reports). U.S. Environmental Protection Agency, Washington, DC, EPA/600/R-12/047F, 2013. https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=250571

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

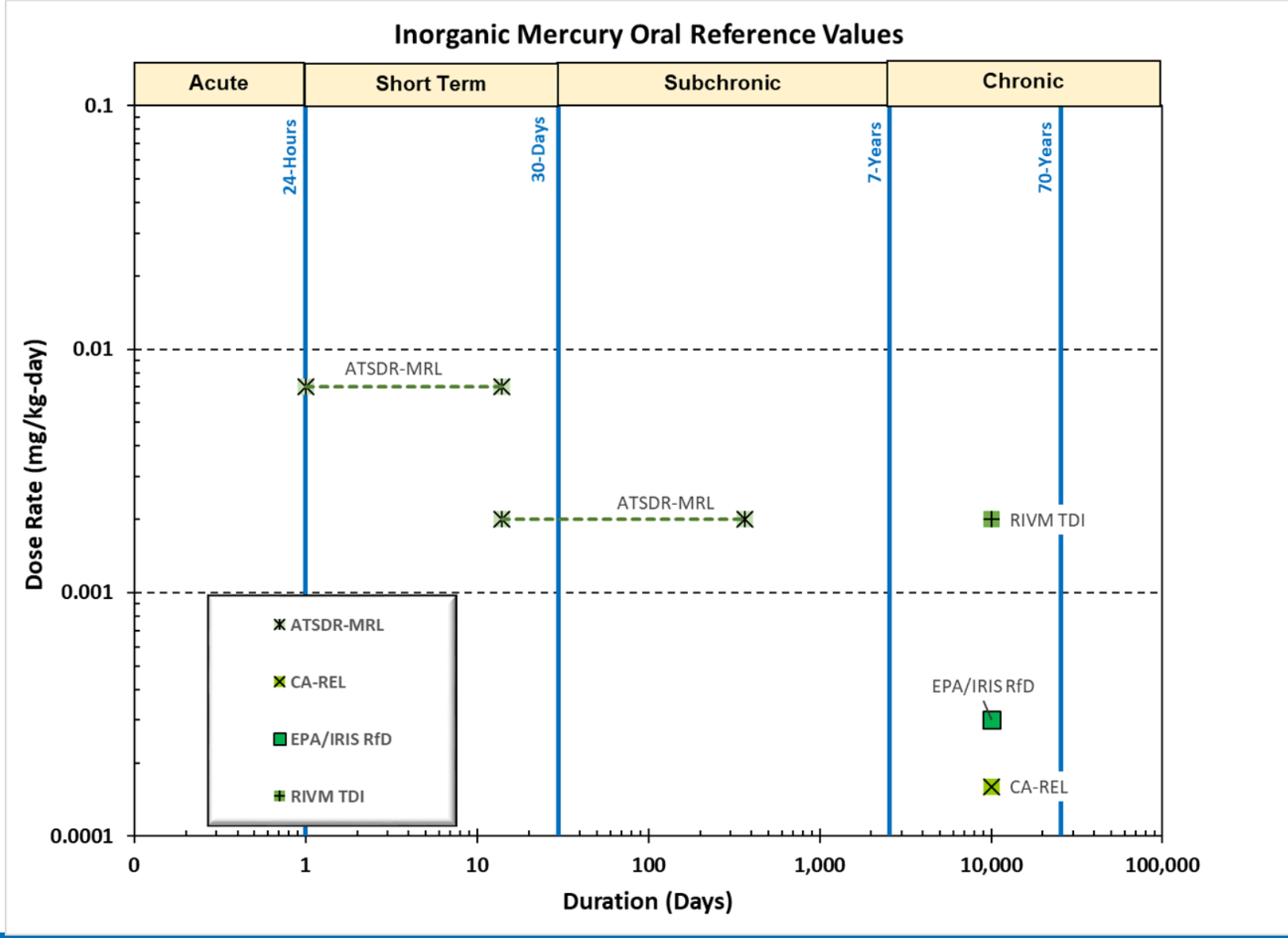
Table of Derivation Details for Benzene Inhalation Reference Values

	Reference Value Name	Duration	Reference Value (mg/m³)	Reference Value (ppm)	Health Effect	Point of Departure	Qualifier	Source	Uncertainty Factors	Notes on Derivation	Review Status
General Public	**Acute CA-REL (Severe Effects)**	6 hour	1.3	0.4	Decreased fetal body weights of pregnant female rats exposed 6-h/d, GD 6-15	40 ppm	NOAEL	(Coate et al., 1984)	Total UF = 100 UF_A = 10 UF_H = 10	No time extrapolation	Final (OEHHA, 2008a)
	Acute ATSDR MRL	1 -14 days	0.029	0.009	Immunological effects in exposed mice (6-h/d, 6 days)	10.2 ppm 2.55 ppm	LOAEL $LOAEL_{HEC}$	(Rozen et al., 1984)	Total UF = 300 UF_L = 10 UF_A = 3 UF_H = 10	Adjustment: (6-h/24-h)	Final (ATSDR, 2007)
	Intermediate ATSDR MRL	15 – 364 days	0.019	0.006	Immunological suppression effects in rats	10 ppm 1.8 ppm	LOAEL $LOAEL_{HEC}$	(Rosenthal and Snyder, 1987)	Total UF = 300 UF_L = 10 UF_A = 3 UF_H = 10	Duration adjusted: (6-h/24-h) × (5-d/7-d)	
	Chronic CA-REL	Chronic	0.06	0.02	Hematological effects for workers with an average exposure of 7.4 years (32% exposed for more than 10 years)	0.53 ppm 0.19 ppm	NOAEL $NOAEL_{HEC}$	(Tsai et al., 1983)	Total UF = 10 UF_H = 10	Adjustments: occupational breathing rate ($10m^3$ vs. $20m^3$) and 5 days per week.	Final (OEHHA, 2008a)
	Chronic ATSDR MRL	Chronic (> 1 year)	0.0096	0.003	B cell counts in workers of shoe manufacturing industries in Tianjin, China	0.10 ppm 0.03 ppm	$BMCL_{0.25sd}$ $BMCL_{ADJ}$	(Lan et al., 2004)	Total UF = 10 UF_H = 10	Duration adjusted: (8-h/24-h) × (6-d/7-d)	Final (ATSDR, 2007)
	Chronic RfC (IRIS)	Chronic	0.03	0.0094	Decreased lymphocyte count (Human occupational inhalation study, 8-hr TWA)	23 mg/m^3 8.2 mg/m^3	BMCL $BMCL_{HEC}$	(Rothman et al., 1996)	Total UF = 300 UF_A = 3 UF_S = 3 UF_H = 10 UF_{DB} = 3	Adjustments: occupational breathing rate ($10m^3$ vs. $20m^3$) and 5 days per week.	(U.S. EPA, 2002)

[1] UF_H – inter-human variability; UF_A – animal to human variability; UF_L – LOAEL to NOAEL adjustment; UF_S – subchronic to chronic adjustment; UF_{DB} – database uncertainty

Oral Reference Value Arrays

U.S. EPA. Systematic Review Protocol for the Inorganic Mercury Salts IRIS Assessment (Preliminary Assessment Materials). U.S. Environmental Protection Agency, Washington, DC, EPA/635/R-20/239, 2021. https://iris.epa.gov/document/&deid=349284



Summary

- **Guidelines and Standards**
  - Reference values are guidelines and can inform regulatory/risk management decisions
  - Standards are legally enforceable on their own
- **Exposure scenario** dictates applicability
  - Three major **categories** consider the populations being protected
    - General Public (Ambient)
    - Occupational
    - Emergency Response
- Developed by multiple entities as **tools** in **risk characterization** and **risk management**