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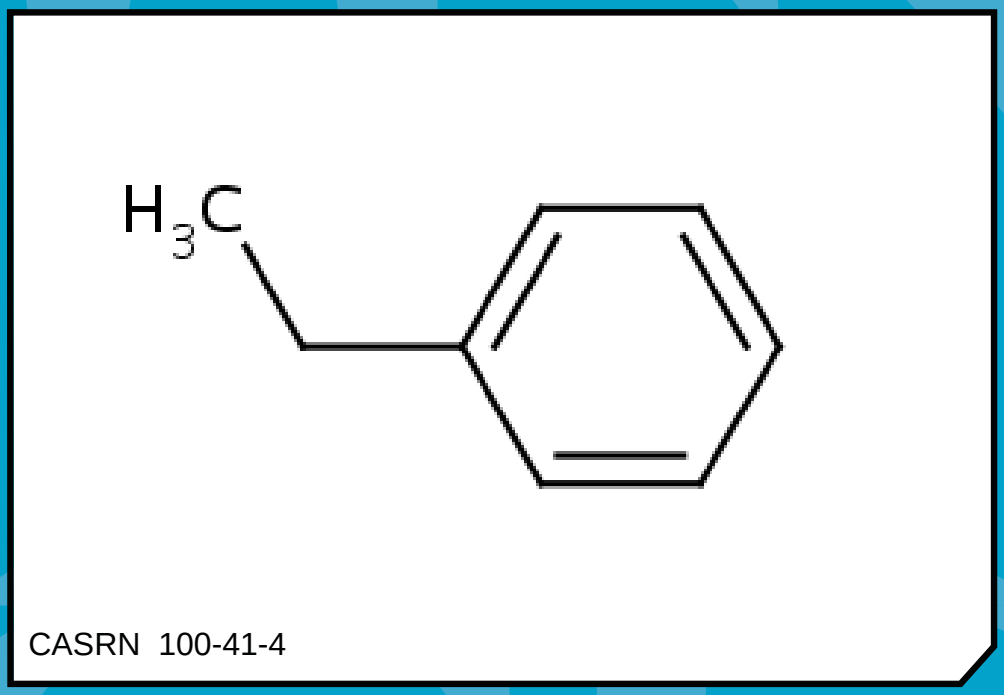
Inhalation Health Effect Reference Values for Ethylbenzene (CASRN 100-41-4)



National Center for Environmental Assessment
Office of Research and Development

U.S. Environmental Protection Agency
Research Triangle Park, NC

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Overview

The reader is strongly encouraged to read Section 1 of the following report for critical background information regarding the health effect reference values discussed in this summary: *Graphical Arrays of Chemical-Specific Health Effect Reference Values for Inhalation Exposures [Final Report]* (U.S. EPA, 2009). This report is available on-line at http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=211003.

In general, inhalation health effect reference values have been included which have been developed and formally reviewed by an authoritative governing body (government agency or professional association) for use in assessments of risk to support regulatory decision-making. This is a review of existing reference values, including the basis for each of the reference values as provided in the available technical support documents for those values, along with some basic contextual references; this is not a comprehensive review of the health effects literature for ethyl benzene.

General Properties

Ethylbenzene ($C_6H_5(C_2H_5)$); MW = 106.2) is flammable as a liquid or vapor, has very low solubility in water, and mixes well with most organic solvents (NLM, 1998). Ethylbenzene is also known as ethylbenzol, and phenylethane. Ethylbenzene has an aromatic odor similar to that of gasoline, with an odor threshold that varies between individuals, ranging from 2 to 200 ppm. Ethyl benzene becomes a vapor more slowly than the other BTEX solvents (Vapor Pressure = 9.6 mm Hg at 25 degrees Celsius), with a vapor which is denser than air (Vapor Density = 3.66; air = 1). Ethyl benzene tends to partition into organic solvents [Octanol/Water Partition Coefficient (log Kow) = 3.15] and fatty tissues once absorbed by the body. Commercial grade xylene contains between 6% to 15% ethylbenzene.

Production and Uses

Most ethyl benzene is used as a precursor in the production of styrene, but is also used as a solvent, feedstock for other chemical production, and as a component of gasoline. Xylene is one of the so-called BTEX aromatics (benzene, toluene, ethylbenzene, and xylene). Global production of ethylbenzene in 2010 was approximately 29.2 million metric tons (SRI, 2011).

Exposure Potential

The Toxic Release Inventory (TRI) for the 2010 reporting year (U.S. EPA, 2010) reported a total of 2,413,967 pounds of ethyl benzene were emitted to air from all industrial sources in the United States, with 1,382,187 pounds emitted from point sources (stacks, vents, ducts, or pipes) and 1,031,780 pounds coming from fugitive sources (equipment leaks, evaporative losses from surface impoundments and spills, and releases from building ventilation systems). Ambient air concentrations in the United States have been reported to range from 0.5 ppb (2.2 µg/m^3) in remote rural areas to greater than 150 ppb (> 650 µg/m^3) near industrial facilities and roadways (NLM, 1998).

Potential Health Effects

Acute exposures to ethyl benzene have been associated with various effects including eye and airway irritation, narcosis, and headache and sleepiness. Longer term and chronic exposures may lead to ototoxicity (effects on hearing), general developmental toxicity, cellular alterations and necrosis in the liver, testicular toxicity, and nephrotoxicity.

Cancer Potential

The U.S. EPA (1991) found that ethylbenzene was *"not classifiable as to human carcinogenicity"* based on a lack of animal bioassays and human studies; however, an update to the 1991 assessment is currently in preparation and there is a potential for that classification to change. The International Agency for Research on Cancer (IARC, 2000) assessed the cancer potential and found that *"Ethylbenzene is possibly carcinogenic to humans (Group 2B)."* The American Conference of Governmental Industrial Hygienists (ACGIH, 2007) found ethyl benzene to be classified as "*A3; Confirmed animal carcinogen with unknown relevance to humans.*"

Emergency Response Values

The Emergency Response reference values for ethylbenzene are limited to the Acute Exposure Guideline Levels (AEGLs); no Emergency Response and Planning Guideline (ERPG) values have been developed for ethylbenzene. The AEGL-1 value was based on upper respiratory irritation, and mild effects on the central nervous system (CNS); no duration scaling was performed due to the irritant effects that are not expected to change over the course of an exposure of up to 8 hours. Both the AEGL-2 and -3 used a physiologically-based pharmacokinetic (PBPK) model to extrapolate from observations in rats to humans, and to perform duration scaling. The assumption is that the CNS response observed following ethylbenzene exposure is directly related to the concentration of ethylbenzene reaching the brain, and that venous blood concentrations correlate with brain concentrations. For the AEGL-2, the venous blood concentration (Cv) of ethylbenzene following a 4-hour exposure to 2180 ppm would be expected to provide an internal dose measurement correlating with the minimum narcotic response. Similarly for the AEGL-3 derivation, a 6-hour exposure to 2000 ppm was established to provide an internal dose measurement correlating with the nonlethal response. The PBPK model was exercised to determine the internal dose (Cv) producing the respective effect in rats, then the human PBPK model was run for each defined AEGL time point to determine the equivalent exposure concentration producing the target Cv in humans. The total uncertainty factor (UF) applied in deriving values for all three AEGL levels was equal to 3: the AEGL-1 was based on human observations with an intraspecies UF of 3 deemed appropriate because direct acting irritant effects at the portal of entry are not expected to vary between individuals; for both the AEGL-2 and -3, the use of a PBPK model negated the need to apply an interspecies factor, and an intraspecies factor of 3 was applied due to the mode of action of ethylbenzene being similar to anesthetic chemicals, where a variation of 2-3 fold has been well documented (NRC, 2001). It should also be noted that the Interim Technical Support Document (TSD) for Ethylbenzene (NAC/AEGL, 2009) makes the following statement regarding the potential for additional effects from potentially repeated exposures in the data adequacy discussion for the AEGL-2: "It is acknowledged that the resulting AEGL 2 values may not be protective of ototoxicity which occurs after repeated exposures, however no data are available to assess this endpoint following a single exposure to ethylbenzene." It should also be noted that the AEGL-2 values are less than a factor of 2 lower than the AEGL-3 values, denoting a very thin margin

between the two; extra caution should be exercised if exposure concentrations begin to approach and have the potential to exceed AEGL-2 levels.

Occupational Exposure Limits (OELs)

The occupational values for ethylbenzene are all in strong concordance, with the time-weighted average (TWA) values from three organizations all being equal to one another, and the same being the case for the short-term exposure limits (STEL) values from two of those organizations. The TWA values include the recommended exposure level (REL) developed by the National Institute for Occupational Safety and Health (NIOSH); the permissible exposure limit (PEL) developed by the Occupational Safety and Health Administration (OSHA); and the Threshold Limit Value (TLV®) developed by the American Conference of Governmental Industrial Hygienists (ACGIH). The STEL values for ethylbenzene were developed by NIOSH and AGGIH. The most completely documented set of these occupational values are those developed by ACGIH, with those of NIOSH being the next most complete, but more publically available. There is only limited documentation on the basis for the OSHA PEL-TWA value. These traditional occupational reference values are only slightly higher in concentration than the AEGL-1 values, which anticipate that occupational exposures are generally to a healthy adult work force. The same study (Bardodej and Bardodejova, 1961) was used in the derivation of both the AEGL-1 and the ACGIH TLV-STEL, with no uncertainty factors (UFs) applied for the for the TLV-STEL and a UF of 3 applied for the AEGL-1 to account for inter-individual variability.

Special Use Occupational Values

In addition to the standard occupational values, specialty occupational reference values are also available in the form of the Spacecraft Maximum Acceptable Concentration (SMAC) values, which were developed for exposures ranging from 1 hour to 180 days. The documentation for the SMACs (NRC, 1996) is readily accessible from the National Academy of Science web site. The SMACs are somewhat lower than the traditional occupational values to account for the inability to escape exposure in the spacecraft environment.

General Public Values (Routine Non-emergency Exposures)

The reference values designed to protect the general public under normal exposure conditions (not for emergency response) include the Minimal Risk Levels (MRLs) developed by the Agency for Toxic Substances and Disease Registry (ATSDR) for acute (1-14 days), intermediate (15-365 days), and chronic (>1 year) durations; and the California Reference Exposure Levels (CA-REL) values developed by the Office of Environmental Health Hazard Assessment (OEHHA), and the U.S. EPA reference concentration (RfC) values, both of which are for chronic durations (>10% of lifespan, or >7 years). As shown in Table 1, the basis for each of these general public reference values varied somewhat, as did the UFs applied in their derivation.

All three ATSDR values were developed using a physiologically-based pharmacokinetic (PBPK) model to estimate the ethylbenzene blood level in laboratory animals for each inhalation concentration tested. Both the acute and intermediate MRL values were calculated using a single standard deviation of the lower confidence limit of the benchmark dose ($BMDL_{1\text{-}SD}$) for the ethylbenzene blood level causing effects to the auditory system (hearing). The BMDL blood level was converted to an exposure calculation and adjusted for continuous exposure to arrive at

the human equivalent concentration (HEC), to which uncertainty factors were applied, thereby deriving the final MRL value. The chronic MRL was calculated in a similar manner up to estimating the ethylbenzene blood level, but the data were not amenable to BMD analysis so the lowest observed adverse effect level (LOAEL) for progressive nephropathy (kidney failure) was used as the basis to which HEC adjustments and UFs were applied to deriving the final chronic MRL. A total UF of 30 was applied to the both the acute and intermediate MRLs (3 to account for extrapolating from animals to humans, and 10 for variability among the human population); an additional factor of 10 was applied to account for use of a LOAEL in the case of the chronic MRL.

Nephropathy and body weight reduction in rats, and abnormally rapid growth (hyperplasia) in the pituitary gland and effects on the liver in mice were the basis for the chronic CA-REL, with adjustments to move from repeated to continuous exposures and a total UF of 30 applied to derive the final value.

The chronic RfC was based on the no observed adverse effect level (NOAEL) for developmental toxicity in rats and rabbits, which was adjusted to account for repeated versus continuous exposure to arrive at the $NOAEL_{HEC}$. A total UF of 300 (3 for use of an animal study; 10 for variability among humans; and 10 for database uncertainty due to the lack of chronic studies or studies on multi-generational reproductive effects.

Summary

There is a high level of concordance among the occupational values for ethylbenzene, but less so for the chronic reference values for the general public. The point of departure for the chronic MRL and the chronic CA-REL were similar, but differences in adjusting from repeated to continuous exposure and in the application of UFs lead to a difference of almost an order of magnitude in final values. The final calculation of the chronic RfC (the oldest of these values) lies between the other two chronic values. Two notes of caution regarding the AEGL emergency response values should be heeded: (1) there is less than a two-fold difference between the AEGL-2 and -3 values; and (2) the AEGL TSD notes a potential for ototoxicity (effects on the auditory system) from repeated exposures near the AEGL-2 exposure concentration levels that are not addressed for the AEGL due to the assumption that such exposures will be extremely rare (i.e., “once-in-a-lifetime”).

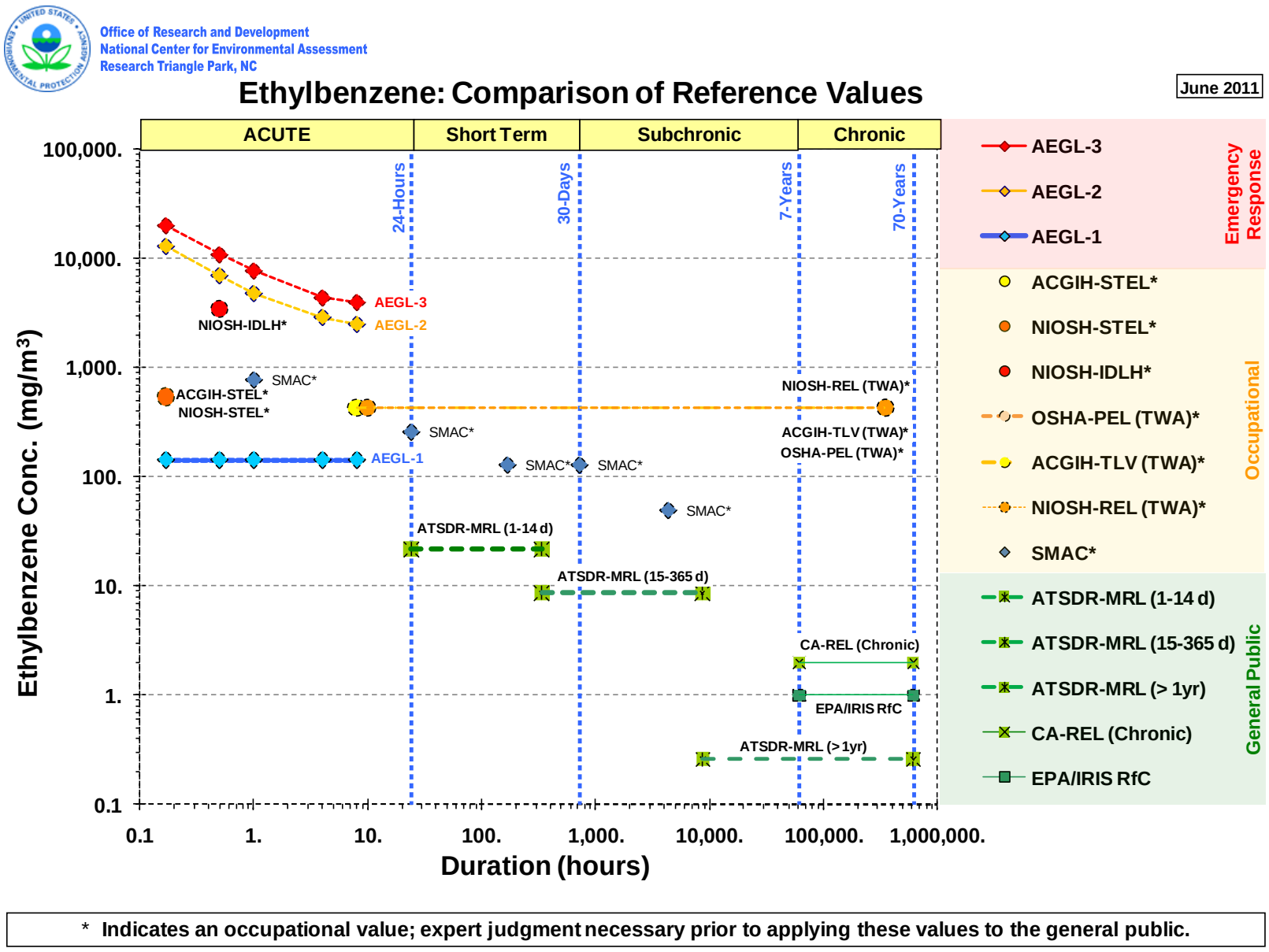

Figure 1. Inhalation health effect reference value array for ethylbenzene

Table 1. Details on derivation of the available health effect reference values for inhalation exposure to ethylbenzene

	Reference Value Name	Duration	Reference Value (mg/m^3)	Reference Value (ppm)	Health Effect	Point of Departure	Qualifier[1]	Principal Study	Uncertainty Factors[2]	Notes on Derivation	Review Status
Emergency Response	**AEGL-3**	10 minutes	20,400	4700	The internal dose producing a non-lethal condition in rats was determined, then an equivalent conc. was determined for humans via a PBPK model	2000 ppm (rats, 6 h/d, 5 d/wk, for 3 days)	No lethality	Andersson et al. (1981)	Total UF = 3 UF_A = 1 UF_H = 3	Application of PBPK model	Interim (NAC/AEGL, 2009)
		30 minutes	11,000	2600							
		1 hour	7800	1800							
		4 hours	4400	1000							
		8 hours	4000	910							
	AEGL-2	10 minutes	13,000	2900	Narcosis in rats	1500 ppm (4 hrs)	NOAEL	Molnar et al. (1986)	Total UF = 3 UF_A = 1 UF_H = 3		
		30 minutes	7000	1600							
		1 hour	4800	1100							
		4 hours	2900	660							
		8 hours	2500	580							
	AEGL-1	10 minutes	144	33	Irritation of the upper respiratory tract and eye, headache, sleepiness, and transient feelings of drunkeness	100 ppm (8 hrs in human volunteers) 180 ppm	NOAEL LOAEL	Bardodej and Bardodejova (1961)	Total UF = 3 UF_H = 3 UF_A = 1	No duration adjustment	
		30 minutes	144	33							
		1 hour	144	33							
		4 hours	144	33							
		8 hours	144	33							

[1] NOAEL – No observed adverse effect level; LOAEL – Lowest observed adverse effect level; HEC – Human equivalent concentration; BMCL – Benchmark concentration, lower confidence limit, with criteria in subscript (e.g., 1-SD = one standard deviation)

[2] 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

	Reference Value Name	Duration	Reference Value (mg/m^3)	Reference Value (ppm)	Health Effect	Point of Departure	Qualifier[1]	Principal Study	Uncertainty Factors[2]	Notes on Derivation	Review Status
Occupational	**NIOSH STEL**	< 10 minutes	435	125	Irritation and narcotic effects, with potential for chronic effects	Various	NR	NR	NA	WOE Approach	Final (NIOSH, 2007)
	NIOSH IDLH	30 minutes	3475	800	Protection from explosion; Acute inhalation toxicity data in humans and animals	Various	Effects levels	NIOSH (1994)		WOE Approach; 10% of the lower explosive limit of 0.8%	
	ACGIH TLV-STEL	< 15 minutes	545	125	Potential for eye and upper respiratory irritation; also protective for narcosis	125 ppm	LOAEL (Human)	Bardodej and Bardodejova (1961)	NR	WOE Approach	Final (ACGIH, 2006)
	ACGIH TLV-TWA	8 hour TWA	435	100		400 ppm	NOAEL (Rabbit and Monkey)	Wolf et al. (1956)			
	NIOSH REL (TWA)	10 hour TWA	435	100	Eye, skin and upper respiratory irritation	NR	NA	NR	NR	NR	Final (NIOSH, 2007)
	OSHA PEL (TWA)	8 hour TWA	435	100	Irritant, narcotic, and chronic effects	NR	NR	NR	NR	NR	Final Standard (OSHA, 2006)
	SMACs	1 hour	780	180	Eye and respiratory irritation, headache, sleepiness	180 ppm (8-hr)	LOAEL (Human, n = 11)	Bardodej and Bardodejova (1970)	Total UF = 1	No duration scaling.	Final (NRC, 1996)
		24 hour	260	60	Headache, sleepiness	180 ppm (8-hr)	LOAEL (Human, n = 11)		Total UF = 1	Duration adjusted using Haber's Rule	
		7 day	130	30	Eye and respiratory irritation, testicular toxicity	100 ppm (8-hr)	NOAEL (Human, n = 9)		Total UF = 1	Adjusted for small sample size (n/100 = 0.3)	
		30 day	130	30					Total UF = 1		

	Reference Value Name	Duration	Reference Value (mg/m^3)	Reference Value (ppm)	Health Effect	Point of Departure	Qualifier[1]	Principal Study	Uncertainty Factors[2]	Notes on Derivation	Review Status
		180 day	50	12	Testicular toxicity	400 ppm (7 h/d; 5 d/w; 186 d)	NOAEL (Rabbit, Monkey)	Wolf et al. (1956)	Total UF = 10 UF_A = 10	Duration adjusted using Haber's Rule	
General Public	**Acute ATSDR MRL**	1 -14 days	21.7	5.0	Compound Action Potential auditory shifts using an internal dose metric of time-averaged arterial blood conc.	81.1 µmol/L 154.26 ppm	$BMDL_{1\text{-}SD}$ HEC	Cappaert et al. (2000)	Total UF = 30 UF_A = 3 UF_H = 10	PBPK model used to estimate internal dose, BMD analysis results then converted to ppm for POD	Final (ATSDR, 2010)
	Intermediate ATSDR MRL	15-365 days	8.7	2.0	Auditory threshold shifts and outer hair cell loss	19.94 µmol/L 63.64 ppm	$BMDL_{1\text{-}SD}$ HEC	Gagnaire et al. (2007)	Total UF = 30 UF_A = 3 UF_H = 10		
	Chronic ATSDR MRL	Chronic (> 1 year)	0.26	0.06	Increased severity of chronic progressive nephropathy in female rats exposed to 75 ppm and higher	17.45 ppm 75 ppm	$LOAEL_{HEC}$ LOAEL	(NTP, 1999)	Total UF = 300 UF_A = 3 UF_H = 10 UF_L = 10	PBPK models used to estimate internal dose metrics and HECs were adjusted for intermittent exposure	
	Chronic CA-REL	Chronic	2.0	0.4	Nephrotoxicity, body weight reduction (rats) hyperplasia of the pituitary gland; liver cellular alterations and necrosis (mice)	13 ppm 75 ppm (6-h/d, 5 d/wk, 103 weeks)	$NOAEL_{ADJ}$ NOAEL	Chan et al. (1998) and (NTP, 1990)	Total UF = 30 UF_A = 3 UF_H = 10	Duration adjusted to account for 6 h/d and 5 d/wk exposures	Final (OEHHA, 2000)
	Chronic RfC (IRIS)	Chronic	1.0	0.2	Developmental toxicity in rats and rabbits	434 mg/m^3 (100 ppm) 4340 mg/m^3 (1000 ppm)	$NOAEL_{HEC}$ LOAEL	Andrew et al. (1981) and Hardin et al. (1981)	Total UF = 300 UF_A = 3 UF_H = 10 UF_{DB} = 10	Database UF due to absence of multi-generational reproductive and chronic studies	Final (U.S. EPA, 1991)

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