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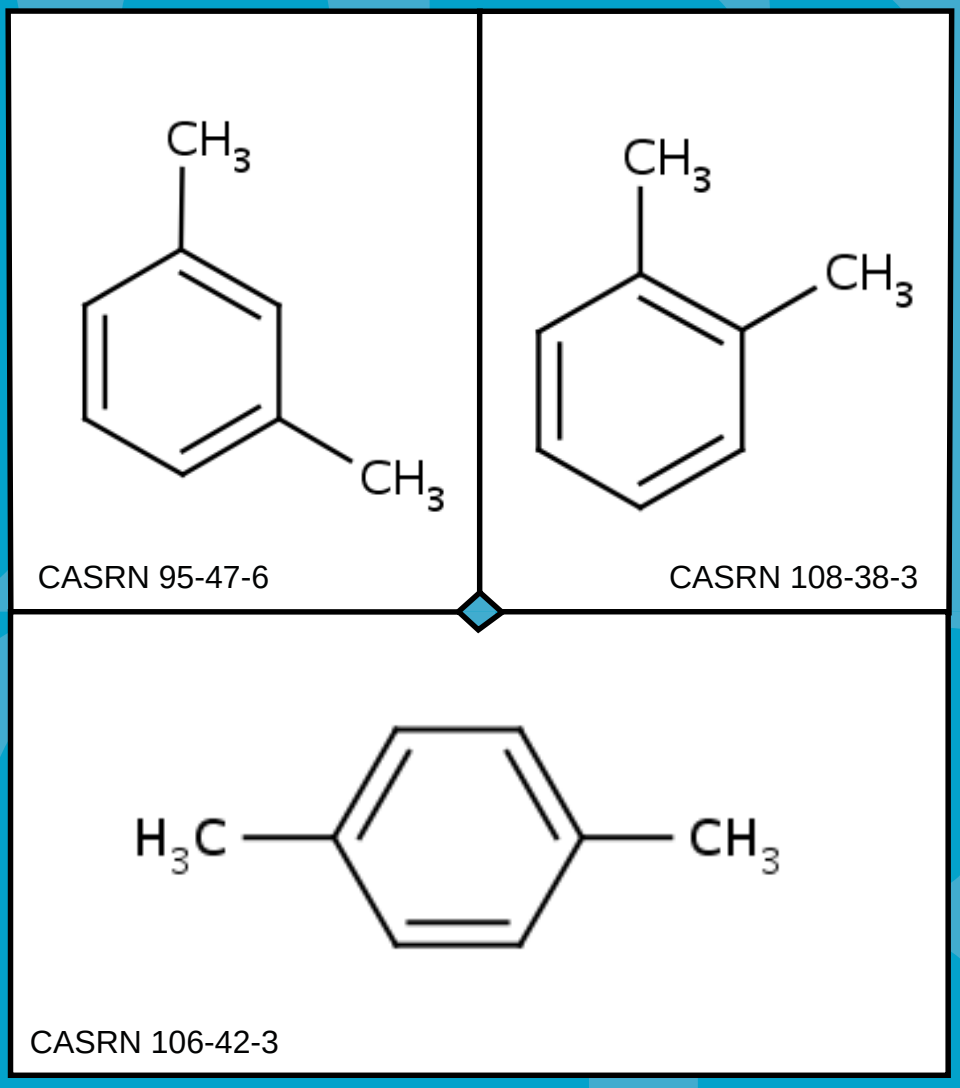
Inhalation Health Effect Reference Values for Xylene – All Isomers

(CASRNs Mixed Isomers – 1330-20-7; m-Xylene – 95-47-6; o-Xylene – 108-38-3; p-Xylene – 106-42-3)



National Center for Environmental Assessment
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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 xylene.

Background

Xylene ($C_6H_4(CH_3)_2$; MW = 106.17) can occur as one of three isomers: *ortho* – 1,2-dimethylbenzene or *o*-xylene; *meta* – 1,3-dimethylbenzene or *m*-xylene; and *para* – 1,4-dimethylbenzene or *p*-xylene. Synonyms for mixed xylenes include dimethylbenzene, methyltoluene, and xylol. Commercial grade xylene is most often a mixture of isomers, which is predominantly *m*-xylene (up to 60%) with approximately equal levels of *o*- and *p*-xylene (~20% each); technical grade xylene also contains ethylbenzene between 6% and 15%. Xylene is a colorless, non-corrosive, flammable liquid with an aromatic odor similar to that of benzene (Henderson, 2001). The odor threshold for xylene ranges from 0.09 to 0.4 ppm, and is noticeably irritating for very short durations at 750 ppm.

Production and Uses

Xylene is one of the BTEX aromatics (benzene, toluene, ethylbenzene, and xylene). Global production of xylene in 2010 was nearly 44 million metric tons (SRI, 2011). Mixed xylene is used as a solvent for cleaning and in paints and coatings, and is blended into gasoline. Specific isomers are used as a feedstock in chemical manufacturing with a diverse array of final products associated with each isomer.

Exposure Potential

Xylene is typically detected in ambient air, and can also be found in groundwater and food (ATSDR, 2007). Ambient air concentrations in the United States have been reported to average 0.18 ppb (0.78 µg/m^3) in remote rural areas and up to 99 ppb (430 µg/m^3) near industrial facilities and roadways (NLM, 1998). The Toxic Release Inventory (TRI) for the 2010 reporting year (U.S. EPA, 2010) reported a total of 12,871,595 pounds of xylene were emitted to air from all industrial sources in the United States, with 8,344,898 pounds emitted from point sources (stacks, vents, ducts, or pipes) and 4,526,697 pounds coming from fugitive sources (equipment leaks, evaporative losses from surface impoundments and spills, and releases from building ventilation systems).

Xylene can be absorbed into the human body via inhalation, ingestion, or dermal. There are more similarities between the isomers than differences on key issues, including: toxic potency; physical characteristics; toxicokinetics (how it behaves once absorbed); and toxicodynamics (how the body handles it). Each of the reference values discussed in this summary handles the individual isomers and any mixture of isomers as the same compound.

Potential Health Effects

Acute inhalation exposure to mixed xylenes in humans has been associated with shortness of breath, and irritation of the nose and throat; gastrointestinal effects (e.g., nausea, vomiting, and gastric discomfort); mild transient eye irritation; and neurological effects (e.g., impaired short-term memory, impaired reaction time, decreases in numerical ability, and alterations in equilibrium and body balance) (ATSDR, 2007). Exposure to a mixture of toluene and xylenes resulted in more than additive respiratory and neurological toxicity in humans and animals. Acute animal studies have also reported cardiovascular, liver, and kidney effects from inhalation exposure to mixed xylenes in addition to the effects previously noted.

Chronic inhalation exposures to xylenes in worker cohorts have primarily shown neurological effects such as headache, dizziness, fatigue, tremors, incoordination, anxiety, impaired short-term memory, and inability to concentrate (ATSDR, 2007). Other effects reported from chronic exposure include labored breathing, impaired pulmonary function, increased heart palpitation, severe chest pain, abnormal EKG, and possible effects on the kidneys. Mixed xylenes have not been extensively tested for chronic effects, although animal studies show effects on the liver and CNS from inhalation and oral exposures and effects on the kidneys from oral exposure to mixed xylenes.

Cancer Potential

The U.S. EPA (2003) found that *"data are inadequate for an assessment of the carcinogenic potential of xylenes"* Similarly, IARC (1999) assessed the cancer potential and found that *"Xylenes are not classifiable as to their carcinogenicity to humans (Group 3)."* Therefore, no reference values for cancer (e.g., cancer slope factors) are available for xylene.

Emergency Response Values

The emergency response reference values for xylene are limited to the Acute Exposure Guideline Levels (AEGLs); no Emergency Response and Planning Guideline (ERPG) values have been developed for xylene. Interim AEGL values for xylene were developed for all three severity levels (1 = mild, transient effects; 2 = irreversible effects or impeding ability to escape; and 3 = threshold for life threatening effects). The Protective Action Criteria developed by the U.S. Department of Energy adopts the AEGL (or ERPG) values when available for the three severity levels defined by the AEGLs. A Temporary Emergency Exposure Level (TEEL) value of 400 mg/m^3 for a zero (0) severity level was included in the Revision 26 listing (DOE, 2010), which is defined as *"the threshold concentration below which most people will experience no adverse health effects"*; however, DOE dropped the TEEL-0 level from their tables for all chemicals in the Revision 27 listing (DOE, 2012), therefore TEEL-0 values are not included in the table or figure for this summary on xylenes.

Occupational Exposure Limits

The occupational values for xylene show a very high level of concordance. All of the values based on a time-weighted average (TWA) for daily exposures (up to 10 hours per day,

and 5 days a week) for a working career (up to 40 years) were set at 100 ppm, which include the OSHA PEL, NIOSH REL, and the ACGIH TLV®. Similarly, both of the short-term exposure limits (STELs) for exposures less than 15 minutes developed by NIOSH and ACGIH were established at 150 ppm. All of the occupational values for xylene were based on irritation and a concern for neurotoxicity in the form of narcosis. In addition to the TWA and STEL values, NIOSH has also developed an Immediately Dangerous to Life and Health (IDLH) value of 900 ppm for a 30 minute exposure.

Special Use Occupational Values

In addition to the standard occupational values, a set of special use occupational values are also available which have been developed by and/or reviewed by the National Research Council (NRC): Spacecraft Maximum Acceptable Concentrations (SMACs) for durations of 1 and 24 hours, and 7, 30, 180, and 1000 days; and values derived for submarine crews – the Emergency Exposure Guideline Levels (EEGLs) for 1 and 24 hours, and the Continuous Exposure Guideline Levels (CEGL) for 90 days. The EEGL values (150 ppm for 1-hour and 100 ppm for 24-hours) are fairly consistent with the AEGL-1 and traditional occupational TWA values. Largely due to the confined working environment with no opportunity to be removed from exposure, however, the CEGL value of 50 ppm is lower than the 100 ppm occupational TWA values. Similarly, all of the SMACs are lower than other occupational reference values for similar durations, including the EEGLs. The SMACs for durations of 7-days or longer were based on concerns for potential narcosis and neurotoxic effects, including hearing loss (ototoxicity) for the 180 and 1000 day values.

General Public Values (Routine Non-emergency Exposures)

Several reference values have been developed for exposures of the general public to xylene. The California Reference Exposure Levels (CA-RELs) were developed by the Office of Environmental Health Hazard Assessment (OEHHA, 2008, 2000) for both acute (1-hour, 22 mg/m^3 or 5 ppm) and chronic (0.7 mg/m^3 or 0.2 ppm) durations. Minimal Risk Levels (MRLs) were developed by the Agency for Toxic Substances and Disease Registry (ATSDR, 2007) for acute (1-14 days,), intermediate (15-365 days), and chronic (>1 year) durations. A Reference Concentration (RfC) value of 0.1 mg/m^3 (0.02 ppm) was developed by the U.S. Environmental Protection Agency (U.S. EPA, 2003) for the Integrated Risk Information System (IRIS).

Both of the acute values (CA-REL and MRL) use the exposure level of 50 ppm as the point-of-departure (POD). The 50 ppm POD for the acute 1-hour CA-REL was the result of an adjustment to the 100 ppm NOAEL for a 30-minute exposure observed in the study by Hastings et al. (1986) using a simple C × t relationship (e.g., Haber's rule), whereas the 50 ppm LOAEL for a 2-hour exposure in humans from the study by Ernstgard et al. (2002) was not duration-adjusted for the acute MRL. Regardless, these organizations arrive at very different final values based on differences in the application of uncertainty factors (UF); a Total UF of 10 was applied in deriving the CA-REL versus 30 applied in derivation of the acute MRL; details on the application of UFs are presented in Table 1.

The intermediate MRL was based on a study on neurotoxicity in rats (Korsak et al., 1994), which was also used in the derivation of the RfC; however, there was no duration adjustment in the derivation of the POD for the MRL (50 ppm), while in the derivation of the RfC the POD was adjusted to match a continuous exposure scenario. Other differences in the derivation of the RfC and intermediate MRL values from this study was in the application of

uncertainty factors (UFs): a total UF of 90 was applied in the derivation of the intermediate MRL, whereas the RfC was calculated with a total UF of 300.

Likewise, both the chronic CA-REL and chronic MRL were derived based on the same study (Uchida et al., 1993) with an observed lowest observed adverse effect level (LOAEL) of 14 ppm for a combination of irritation and neurological effects in workers. The POD for the CA-REL was based on duration adjustments and a total UF of 10, whereas the chronic MRL made no duration adjustments but applied a total UF of 300 which included a modifying factor of 3 for database uncertainty. As noted in Table 1, these differences in derivation lead to final reference values which diverged considerably from the use of the same observations.

Summary

In conclusion, the effects most noted in association with exposure to xylene across all durations are neurotoxic in nature (narcosis/intoxication, incoordination, headache, ototoxicity, etc.). Short-duration exposures to elevated concentrations (e.g., > 50 ppm) have been associated with irritation of the eyes and upper respiratory system. At higher exposure levels, changes in body weight, liver morphology, liver weight, and enzymatic functions have all been noted (U.S. EPA, 2003). In addition, gestational exposure of animals to xylenes has resulted in neurodevelopmental and other possible developmental effects, but only at levels above those at which neurobehavioral effects in adult rats were reported. Finally, no reproductive effects have been reported in a one-generation reproductive/developmental study of male and female rats exposed to 500 ppm xylenes or in male rats exposed to 1000 ppm (U.S. EPA, 2003).

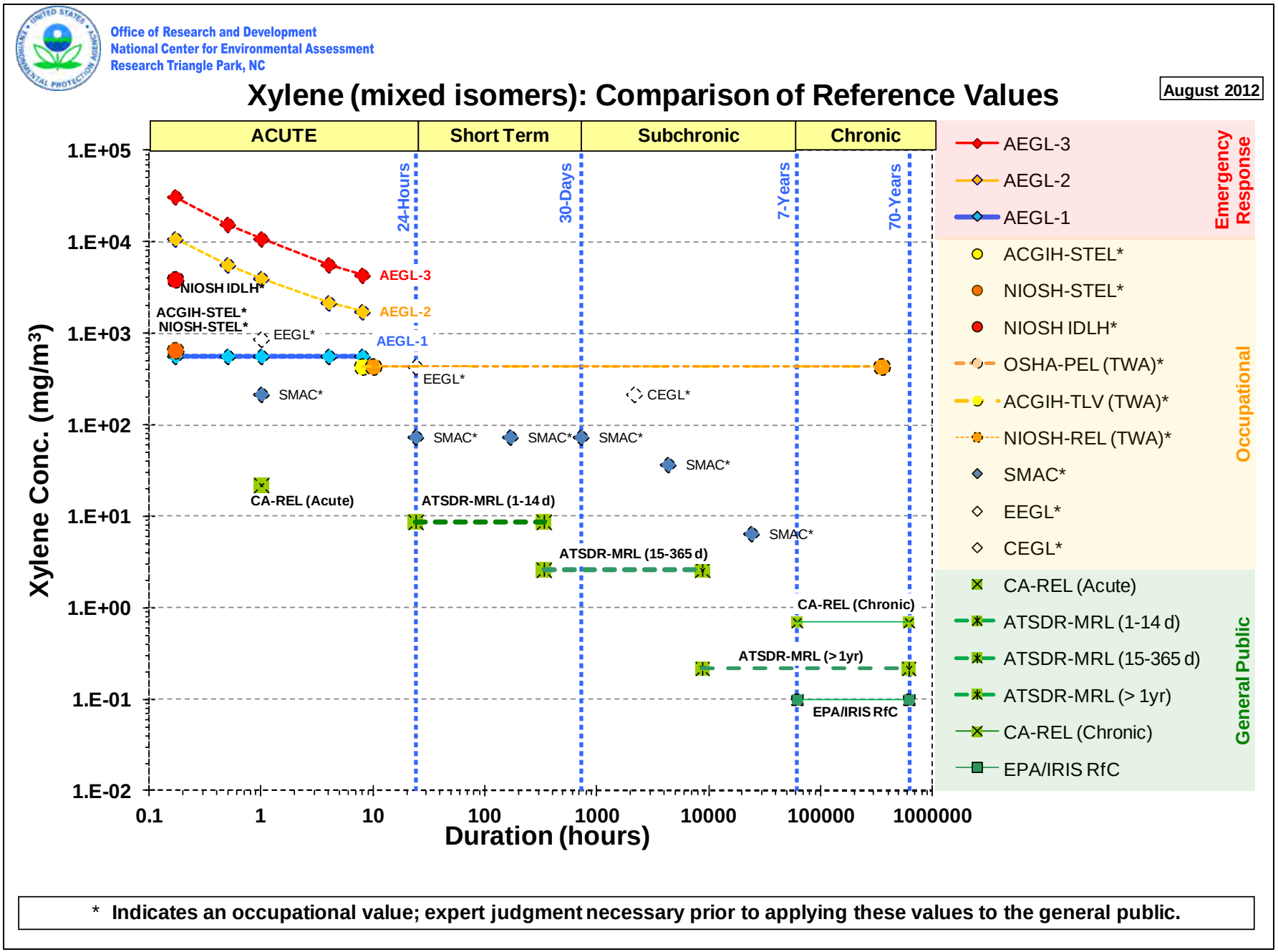

Figure 1. Inhalation health effect reference value array for xylene

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

	Reference Value Name	Duration	Reference Value (mg/m^3)	Reference Value (ppm)	Health Effect	Point of Departure	Qualifier	Principal Study	Uncertainty Factors[1]	Notes on Derivation	Review Status
Emergency Response	**AEGL-3**	10 minutes	>$LEL_{50\%}$	>$LEL_{50\%}$[2]	Rats exhibited prostration followed by full recovery	2800 ppm (4 hours, used in PBPK model)	NOAEL for Lethality	Carpenter et al. (1975)	Total UF = 3 UF_H = 3 UF_A = 1	A human PBPK model was run for each time period to determine the exposure producing the target internal dose	Final (NRC, 2010)
		30 minutes	16,000	3600							
		1 hour	11,000	2500							
		4 hours	5,600	1300							
		8 hours	4,300	1000							
	AEGL-2	10 minutes	11,000	2500	Rats exhibited poor coordination 2 h into a 4-h exposure	1300 ppm (2 hours, used in PBPK model)	LOAEL	Carpenter et al. (1975)	Total UF = 3 UF_H = 3 UF_A = 1		
		30 minutes	5,600	1300							
		1 hour	4,000	920							
		4 hours	2,200	500							
		8 hours	1,700	400							
	AEGL-1	10 minutes	560	130	Eye irritation in human volunteers exposed to mixed xylenes	400 ppm (30 minutes)	LOAEL	Hastings et al. (1986)	Total UF = 3 UF_H = 3 UF_A = 1	No duration scaling due to irritant effects	
		30 minutes	560	130							
		1 hour	560	130							
		4 hours	560	130							
		8 hours	560	130							

[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

[2] LEL = Lower Explosive Limit. The AEGL-3 for 10 minutes = 7,200 ppm, which is greater than 50% of the lower explosive limit for xylene.

	Reference Value Name	Duration	Reference Value (mg/m^3)	Reference Value (ppm)	Health Effect	Point of Departure	Qualifier	Principal Study	Uncertainty Factors[1]	Notes on Derivation	Review Status
Occupational	**OSHA PEL (TWA)**	8 hour TWA	435	100	Irritant, narcotic, and chronic effects	NR	NR	NR	NR	NR	Final (NIOSH, 2007)
	NIOSH STEL	< 10 minutes	655	150	Irritation and narcotic effects, with potential for chronic effects	Various	NA	NIOSH (1975)	NA	WOE Approach	Final (NIOSH, 2007)
	NIOSH REL (TWA)	10 hour TWA	435	100		Various	NA				
	NIOSH IDLH	30 minutes	3710	900	Acute inhalation toxicity data in animals	Various	Effects levels	Various[3]	NA		
	ACGIH TLV-STEL	< 15 minutes	651	150	Potential for eye and upper respiratory irritation; also protective for narcosis	200 ppm	LOAEL (Human)	Carpenter et al. (1975)	NA	WOE Approach	Final (ACGIH, 2007)
	ACGIH TLV-TWA	8 hour TWA	434	100		100 ppm	NOAEL (Human)	Nelson et al. (1943)			
	EEGLs	1 hour	870	200	Eye irritation	200 ppm	Various	Various[4]	None	WOE Approach	Final (NRC, 2008a)
		24 hour	435	100	Eye irritation (repeated)	100 ppm	NOAEL	Hake et al. (1981)			
	CEGL	90 days	217	50	Eye and throat irritation	50 ppm	NOAEL	Various[5]			
	SMACs	1 hour	217	50	Eye, nose, and throat irritation and headache	50 ppm (2 hours)	LOAEL	Ernstgard et al. (2002)	None	Not adjusted, concentration dependent	Final (NRC, 2008b)
		24 hour	74	17					Total UF = 3 UF_L = 3		
		7 day and 30 day	74	17	Neurotoxicity (motor function)	50 ppm (3 months)	NOAEL (rat)	Korsak et al. (1994)	Total UF = 3 UF_A = 3	No time adjustment	
		180 day	37	8.5	Ototoxicity	250 ppm 1000 ppm (Rat, 18 h/d, 61 days)	$LOAEL_{ADJ}$ LOAEL (rat)	Nylen and Hagman (1994)	Total UF = 30 UF_L = 10 UF_A = 3	Duration adjusted using C × t (Haber's)	
		1000 days	6.5	1.5		8.5 ppm	180 d SMAC			180 d SMAC adjusted to 1000 d	

[3] (DeCeaurriz et al., 1981; Harper et al., 1975; Cameron et al., 1942)
[4] (Hastings et al., 1986; Hake et al., 1981; Carpenter et al., 1975)
[5] (Ungvary, 1990; Carpenter et al., 1975; Jenkins et al., 1970)

	Reference Value Name	Duration	Reference Value (mg/m^3)	Reference Value (ppm)	Health Effect	Point of Departure	Qualifier	Principal Study	Uncertainty Factors[1]	Notes on Derivation	Review Status
General Public	**Acute CA-REL (Mild Effects)**	1 hour	22	5	Subjective reports of eye, nose, and throat irritation (50 healthy human volunteers)	50 ppm 100 ppm	$NOAEL_{ADJ}$ NOAEL (30-min)	Hastings et al. (1986)	Total UF = 10 UF_H = 10	Duration extrapolation via $C^n \times t$ (n = 1) from 30-min to 1 hr	Final (OEHHA, 2008)
	Acute ATSDR MRL	1 -14 days	8.7	2.0	Discomfort in the eyes and nose, detection of solvent smell, and feeling of intoxication	50 ppm (human volunteers, 2 hours)	LOAEL	Ernstgard et al. (2002)	Total UF = 30 UF_H = 10 UF_L = 3		Final (ATSDR, 2007)
	Intermediate ATSDR MRL	15-365 days	2.6	0.6	Dose-related increase in the failure rate of rats on the rotarod performance test	50 ppm	LOAEL	Korsak et al. (1994)	Total UF = 90 UF_A = 3 UF_H = 10 UF_L = 3		
	Chronic CA-REL	Chronic	0.7	0.2	Eye irritation, sore throat, floating sensation, and poor appetite (175 exposed and 241 control workers)	5.1 ppm 14.2 ppm (Human, 7-yr avg.)	$LOAEL_{ADJ}$ LOAEL	Uchida et al. (1993)	Total UF = 30 UF_L = 3 UF_H = 10	Adjustments: occupational breathing rate (10 m^3 vs. 20 m^3) and 5 days per week.	Final (OEHHA, 2000)
	Chronic ATSDR MRL	Chronic (> 1 year)	0.22	0.05	neurotoxicity (anxiety, forgetfulness, floating sensation), and nasal, throat and eye irritation	14 ppm (Human, 7-yr avg.)	LOAEL	Uchida et al. (1993)	Total UF = 300 UF_H = 10 UF_L = 10 MF[6] = 3	Not adjusted due to rapid clearance of xylene from the body	Final (ATSDR, 2007)
	Chronic RfC (IRIS)	Chronic	0.1	0.02	Impaired motor coordination (decreased rotarod performance) in a subchronic inhalation study in male rats	39 mg/m^3 217 mg/m^3 (50 ppm) 100 ppm	$LOAEL_{ADJ}$ LOAEL LOAEL	Korsak et al. (1994)	Total UF = 300 UF_A = 3 UF_H = 10 UF_L = 3 UF_{DB} = 3	NOAEL adjusted from 6 h/d and 5 d/wk to continuous exposure (24 h/d, 7 d/wk)	Final (U.S. EPA, 2003)

[6] A Modifying Factor was applied to account for the lack of supporting studies evaluating the chronic neurotoxicity of xylene.

Further Reading

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