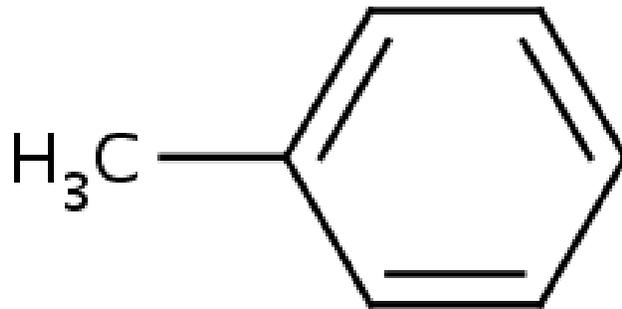


# Inhalation Health Effect Reference Values for Toluene (CASRN 108-88-3)



CASRN 108-88-3



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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 toluene.

### Background

Toluene (C<sub>6</sub>H<sub>5</sub>CH<sub>3</sub>; MW = 92.1) is a colorless, non-corrosive, flammable liquid with an aromatic odor similar to that of benzene. The odor threshold for toluene ranges between 2.5 and 8 ppm, and is irritating at 750 ppm (Henderson, 2001). Toluene has a density of 0.867 g/mL and vapor pressure of 28.4 mm Hg at 25 °C. The water solubility of toluene is 0.59 mg/mL at 25 °C with a water:octanol partition coefficient of Log K<sub>ow</sub> of 2.72 (U.S. EPA, 2005).

### Production and Uses

Toluene is one of the BTEX aromatics (benzene, toluene, ethylbenzene, and xylene). Global production of toluene in 2009 was nearly 18.4 million metric tons (SRI, 2011). Toluene is a leading petrochemical building block (used in the production of benzene, p-xylene, toluene diisocyanate [TDI], caprolactam, benzoic acid, and other compounds), and is also used as a solvent and an octane enhancer in gasoline.

### Exposure Potential

Inhalation is the primary route of exposure to toluene. Evaporation of gasoline and automobile exhaust are the largest sources of toluene in the environment, with industries using toluene as a solvent as the second largest emission source (U.S. EPA, 1991). Toluene is also found in indoor air due to use of common household products and as a component of cigarette smoke (ATSDR, 2000). The Toxic Release Inventory (TRI) for the 2010 reporting year (U.S. EPA, 2010) reported a total of 29,012,231 pounds of toluene were emitted to air from all industrial sources in the United States, with 16,960,245 pounds emitted from point sources (stacks, vents, ducts, or pipes) and 12,051,986 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 an median 0.66 ppb (2.5 µg/m<sup>3</sup>) in remote rural areas, with up to 5.5 ppm (20.7 mg/m<sup>3</sup>) near industrial facilities and 1.1 ppm (4.14 mg/m<sup>3</sup>) in urban areas with emissions dominated by traffic (NLM, 1998).



### *Potential Health Effects*

Toluene is a central nervous system (CNS) depressant, and a skin and mucous membrane irritant – severe dermatitis may result from its drying and defatting action. Other effects observed in humans after accidental or intentional inhalation (abuse situations) include renal (kidney) toxicity, cardiac arrhythmias, blood dyscrasias, enlargement of the liver, and developmental abnormalities ([Henderson, 2001](#)).

### *Cancer Potential*

EPA found that “*there is inadequate information to assess the carcinogenic potential*” for toluene ([U.S. EPA, 2005](#)). Likewise, IARC noted that there is “*inadequate evidence*” in humans for the carcinogenicity of toluene, that there is “*evidence suggesting lack of carcinogenicity*” of toluene in experimental animals, with an overall assessment that toluene is “*not classifiable as to its carcinogenicity to humans (Group 3)*” ([IARC, 1999](#)).

### **Emergency Response Values**

The emergency response values for toluene include interim Acute Exposure Guideline Level (AEGL) values and final Emergency Response Planning Guideline (ERPG) values 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 AEGL values are interim and were still in discussion at the 42<sup>nd</sup> meeting of the National Advisory Committee for AEGLs ([NAC/AEGL, 2007b](#)) where findings from a paper presented at the 2004 meeting of the Society of Toxicology ([Oshiro and Bushnell, 2004](#)) lead to the use of a 70-minute exposure to 2400 ppm (9050 mg/m<sup>3</sup> - identified as a NOAEL) in Long-Evans rats as the critical effect level; an internal dose (blood level) in the rat was calculated using a PBPK model and extrapolated to humans to derive the current AEGL-2 values. The Oshiro and Bushnell study has since been published in a more complete form ([Bushnell et al., 2007](#)) which indicates that exposures to the lowest concentration tested (1200 ppm, 4524 mg/m<sup>3</sup>) for a period of 34 minutes was a LOAEL, with a NOAEL at 1200 ppm observed for a 22 minute exposure. More recently, AIHA revisited the ERPG values for toluene in 2010 with no resulting change in values ([AIHA, 2010](#)). In comparing between the emergency response values, the ERPG values are approximately one-quarter of the exposure levels set for the comparable severity level AEGLs.

### **Occupational Exposure Limits**

ACGIH based the TLV-TWA value of 20 ppm on effects to the CNS (reaction times and changes in color vision) as observed in workers and potential increases in spontaneous abortions for exposed female workers. ACGIH did not find an adequate basis for development of a short-term exposure limit (STEL) or to indicate that toluene is a sensitizing agent. ACGIH noted that toluene was not assigned a “skin” notation based on study evidence showing slow absorption.

The OSHA Permissible Exposure Limit (PEL) for toluene ([OSHA, 2006c](#)) is 200 ppm on a TWA basis. In addition, exposures shall not exceed 300 ppm (ceiling) with the exception for a single time period up to 10 minutes for any 8-hour shift of not more than 500 ppm (peak). For the Construction Industry ([OSHA, 2006b](#)) the same 200 ppm PEL-TWA applies, as does for Maritime Industries ([OSHA, 2006a](#)). The basis for the OSHA PEL refers to the same NIOSH background document ([NIOSH, 1973](#)), which is the same document used for the NIOSH Recommended Exposure Level (REL). The NIOSH REL was established at 100 ppm based on effects of “...*changes in muscle coordination, reaction time, and production of mental confusion*”



*and irritation of mucous membranes...*” being observed at 200 ppm exposures to toluene, and a lack of those observed effects at 100 ppm. Toluene does not carry the “skin” designation from either NIOSH or OSHA, despite the observation that “*repeated or prolonged skin contact with liquid toluene has a defatting action, causing drying, fissuring, and dermatitis*” ([NIOSH, 1978](#)). NIOSH also developed an Immediately Dangerous to Life and Health (IDLH) value for toluene at 500 ppm based on observations of acute inhalation toxicity data in humans ([NIOSH, 1994](#)).

Discrepancies between the emergency response values (AEGLs and ERPGs) were discussed previously. The NIOSH IDLH value is lower than either the AEGL-3 or the ERPG-3 values – another apparent discrepancy. This discrepancy is due in large measure from use of debilitating yet non-fatal effects in humans (effects which may lead to an increase in accidental death) to derive the IDLH value ([NIOSH, 1994](#)) while animal lethality studies were used in the derivations of both the emergency response values (see Table 1).

#### *Special Use Occupational Values*

Specialty occupational values for exposures to toluene in submarines were developed by the National Research Council ([NRC, 2008a](#)) in the form of Emergency Exposure Guidance Levels (EEGLs) of 1 and 24 hour duration, and Continuous Exposure Guideline Levels (CEGLs) for durations of up to 90 days. NRC also developed spacecraft maximum acceptable limits (SMACs) for toluene ([NRC, 2008b](#)), with values derived for 1 and 24 hours, and 7, 30, 180 and 1000 days. The SMACs for 1 and 24 hours were set at 16 ppm (60 mg/m<sup>3</sup>) based on neurotoxicity (dizziness), and the 7 through 1000 day values were all set at 4 ppm (15 mg/m<sup>3</sup>) for auditory and visual toxicity effects with additional effects of a reduction in reproductive hormones associated with the 180 and 1000 day values.

The NRC derived SMACs using the same concentration level (40 ppm, 151 mg/m<sup>3</sup>) as the point-of-departure: as a NOAEL from the study of [Andersen et al. \(1983\)](#) for the short durations (1 and 24 hours); and as a LOAEL taken from a series of studies ([Vrca et al., 1997](#); [Vrca et al., 1996](#); [Vrca et al., 1995](#)) for the longer duration values (7 – 1000 days). The LOAEL was divided by a simple factor of 10 to account for use in lieu of a NOAEL, resulting in a final SMAC value of 4 ppm for the 7 through 1000 day duration values. The 40 ppm exposure concentration NOAEL for the shorter duration study (6-hours) was adjusted by a factor of 0.4 – the square root of 16 divided by 10 (16<sup>-2</sup>/10) due to the low number (16) of human study subjects to derive the final SMAC value of 16 ppm for 1 and 24 hours. Application of this factor is essentially equivalent to application of a UF of 2.5, and that is how it is represented in Table 1. Please refer to the technical support document ([NRC, 2008b](#)) for a more detailed discussion on these derivations.

#### **General Public Values (Routine Non-emergency Exposures)**

Values for the general public include California Reference Exposure Levels (CA-RELEs), developed by the Office of Environmental and Hazard Assessment – OEHHA) for both acute (1 hour) and chronic (lifetime) durations; Minimal Risk Levels (MRLs) developed by the Agency for Toxic Substances and Disease Registry (ATSDR) for chronic exposures (periods longer than 1 year) and for durations of 1-14 days; and a chronic Reference Concentration (RfC) developed by the U.S. Environmental Protection Agency (EPA) for the Integrated Risk Information System (IRIS) database.



The acute CA-REL and acute MRL were both derived from the NOAEL of 40 ppm (151 mg/m<sup>3</sup>) identified in the study by Andersen et al. (1983); however, the final values derived differ due to the varying definition of “acute” used by each organization, with a one-hour value derived for the acute CA-REL and a 24-hour value derived for the acute MRL.

For the chronic general public values, the point-of-departure on which each value was based on similar concentration levels and all were adjusted from intermittent to continuous exposure, but there are variations in endpoint, study selection, and application of uncertainty factors. The chronic CA-REL (OEHHA, 2000) is based on observations of changes in brain weight and dopamine receptor binding in a subchronic study in rats (Hillefors-Berglund et al., 1995), leading to application of an uncertainty factor of 10 for use of a subchronic study (UF<sub>S</sub>) and again for variation within the human population (UF<sub>H</sub>), but a factor of one applied for animal to human extrapolation (UF<sub>A</sub>). The chronic MRL (ATSDR, 2000) was based on a series of studies with a LOAEL for changes in color discrimination among exposed workers for multiple years (Zavalic et al., 1998b; Zavalic et al., 1998a); hence uncertainty factors of 10 each were applied for use of a LOAEL in lieu of a NOAEL (UF<sub>L</sub>) and for human variability (UF<sub>H</sub>).

A more comprehensive consideration of multiple neurological effects in occupational exposures was taken in developing the RfC for toluene (U.S. EPA, 2005), with identification of 34 ppm as the NOAEL in worker populations (Neubert et al., 2001b; Cavalleri et al., 2000; Eller et al., 1999; Zavalic et al., 1998a; Boey et al., 1997; Vrca et al., 1995; Abbate et al., 1993; Murata et al., 1993; Nakatsuka et al., 1992; Foo et al., 1990), which was adjusted to reflect the 5-day per week work schedule and with an assumption that workers breathe 10 m<sup>3</sup> during that duration versus a standard 20 m<sup>3</sup> breathed per day by the average person. The only uncertainty factor applied in deriving the RfC was a factor of 10 to account for human variability (UF<sub>H</sub>).

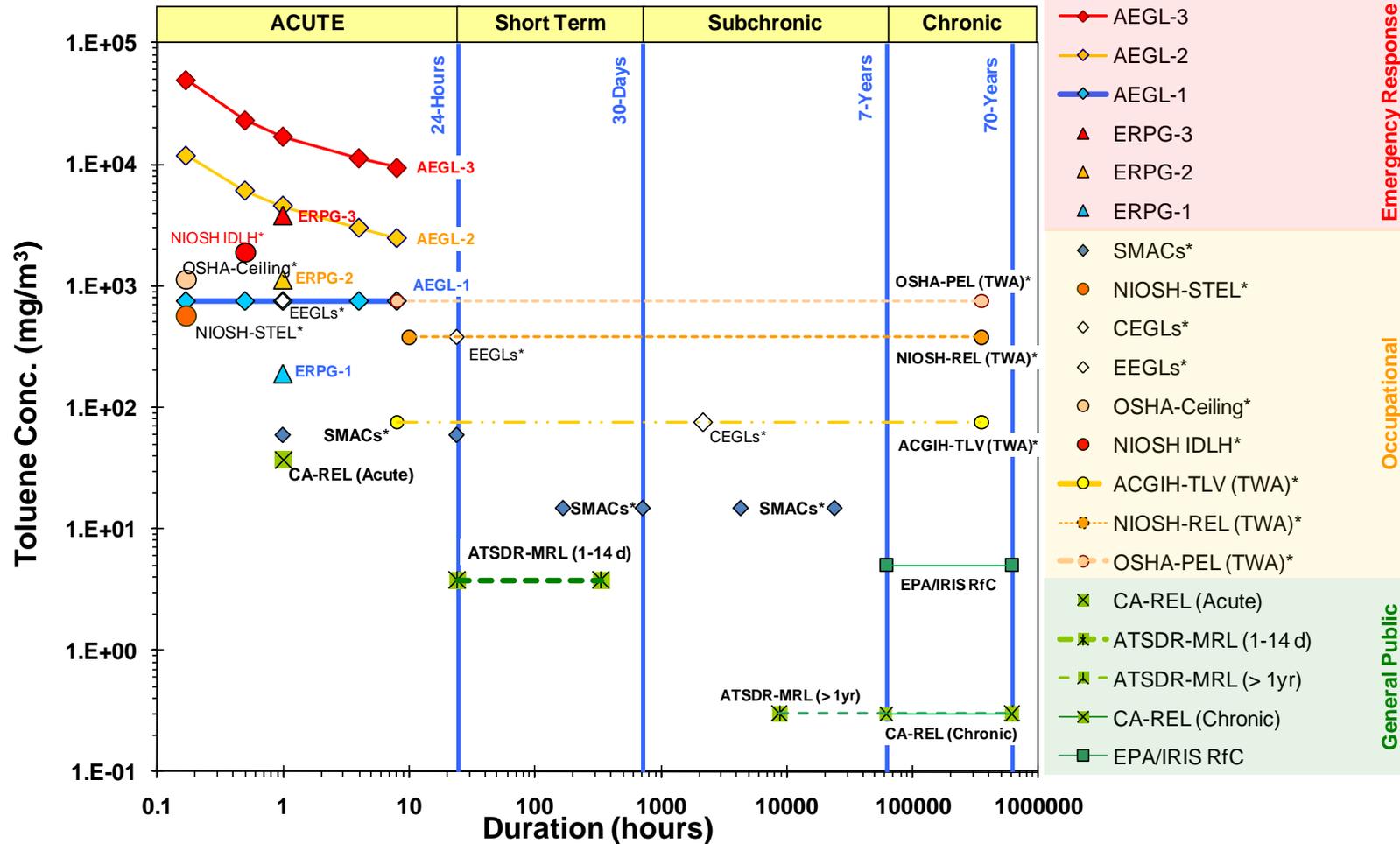
## **Summary**

In conclusion, the effects most noted in association with exposure to toluene across all durations are neurotoxic in nature (narcosis/intoxication, incoordination, headache, color vision, etc.). Short-duration exposures to elevated concentrations (e.g., > 100 ppm) have been associated with irritation of the eyes and upper respiratory system, with higher exposure concentrations showing effects on the kidney. Longer duration exposures may elicit a depression in reproductive hormone levels, depression in immunological response, and potential changes in brain weight and function.



## Toluene: Comparison of Reference Values

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

Figure 1. Inhalation health effect reference value array for toluene



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

	Reference Value Name	Duration	Reference Value		Health Effect	Point of Departure	Qualifier	Principal Study	Uncertainty Factors <sup>1</sup>	Notes on Derivation	Review Status
			(mg/m <sup>3</sup> )	(ppm)							
<b>Emergency Response</b>	<b>AEGL-3</b>	10 minutes	48,970	13,000	Threshold for lethality	6250 ppm (2 hours)	NOAEL	<a href="#">1982</a>	Total UF = 3 UF <sub>A</sub> = 1; UF <sub>H</sub> = 3	Duration extrapolation performed using a rat to human PBPK model	Interim ( <a href="#">NAC/AEGL, 2007a</a> )
		30 minutes	23,000	6100							
		1 hour	17,000	4500							
		4 hours	11,300	3000							
		8 hours	9040	2500							
	<b>AEGL-2</b>	10 minutes	11,680	3100	Threshold for narcosis in the rat	2400 ppm (70 mins)	NOAEL for ↓CNS in rats	<a href="#">Oshiro and Bushnell (2004)</a>	Total UF = 3 UF <sub>H</sub> = 3		
		30 minutes	6030	1600							
1 hour		4520	1200								
4 hours		2980	790								
<b>AEGL-1</b>	10 minutes	753	200	Effects ≤ notable discomfort in 17 clinical studies	200 ppm (various durations)	NOAEL	Various <sup>2</sup>	Total UF = 1	No duration extrapolation		
	30 minutes	753	200								
	1 hour	753	200								
	4 hours	753	200								
<b>ERPG-3</b>	1 hour	3750	1000	< 5% of the 1-hr LC <sub>50</sub> in rats	26,700 ppm (1 hour)	LC <sub>50</sub> in rats	<a href="#">Pryor et al. (1978)</a>	NA	NA	Final ( <a href="#">AIHA, 2010</a> )	
		1125	300								
		187.5	50								
<b>ERPG-2</b>	1 hour	300	100	Muscular weakness and incoordination in humans	300 ppm (8 hours)	Effect Level	<a href="#">vonOettingen et al. (1942)</a>				
		100	50								
<b>ERPG-1</b>	1 hour	50	10	Mild symptoms of fatigue, drowsiness, headache, dizziness, and intoxication in humans	100 ppm (various durations)	Effect Level	Various <sup>3</sup>				

<sup>1</sup> UF<sub>H</sub> – inter-human variability; UF<sub>A</sub> – animal to human variability; UF<sub>L</sub> – LOAEL to NOAEL adjustment; UF<sub>S</sub> – subchronic to chronic adjustment; UF<sub>DB</sub> – database uncertainty

<sup>2</sup> Including: Astrand et al. (1972); Gamberale and Hultengren (1972); Stewart et al. (1975); and Baelum et al. (1990)

<sup>3</sup> Including: [vonOettingen et al. \(1942\)](#); Andersen et al. (1983); and Gamberale and Hultengren (1972)



	Reference Value Name	Duration	Reference Value		Health Effect	Point of Departure	Qualifier	Principal Study	Uncertainty Factors <sup>1</sup>	Notes on Derivation	Review Status
			(mg/m <sup>3</sup> )	(ppm)							
<b>Occupational</b>	<b>OSHA Ceiling</b>	< 15 minutes	1125	300	Irritation - Eye, Nose, Throat, Skin; Moderate Narcosis	NR	NR	NR	NR	NR	Final ( <a href="#">NIOSH, 2007</a> )
	<b>OSHA Max. Peak</b>	<10 minutes	1880	500							
	<b>OSHA PEL (TWA)</b>	8 hour TWA	750	200							
	<b>NIOSH STEL</b>	< 15 minutes	750	200	Muscle coordination, reaction time, mental confusion, and irritation	200 ppm	LOAEL (Human)	( <a href="#">Carpenter et al., 1944</a> ; <a href="#">vonOettingen et al., 1942</a> )	NA	WOE Approach	Final ( <a href="#">NIOSH, 2007</a> )
	<b>NIOSH REL (TWA)</b>	10 hour TWA	375	100		100 ppm	NOAEL (Human)				
	<b>NIOSH IDLH</b>	30 minutes	1880	500	Acute inhalation toxicity data in humans	Various conc. and durations (<200-1400 ppm , 2-8 hrs)	Effects levels, worker studies	Various <sup>4</sup>	NA		
	<b>ACGIH TLV-TWA</b>	8 hour TWA	75	20	CNS effects; visual impairment; pregnancy loss	42 ppm (color vision)	LOAEL (Human)	Various <sup>5</sup>	NA	WOE Approach	Final ( <a href="#">ACGIH, 2007</a> )
	<b>EEGLs</b>	1 hour	750	200	Minimal CNS effects and irritation	200 ppm	LOAEL	Various <sup>6</sup>	None	WOE Approach	Final ( <a href="#">NRC, 2008a</a> )
		24 hour	375	100		100 ppm	NOAEL	Various <sup>7</sup>			
	<b>CEGL</b>	90 days	75	20	Cognition, vigilance, CNS	25 ppm	NOAEL	Various <sup>8</sup>			
<b>SMACs</b>	1 & 24 hours	60	16	Neurotoxicity (dizziness)	40 ppm (human, 6 h)	LOAEL	( <a href="#">Andersen et al., 1983</a> )	2.5 <sup>9</sup>	Adjusted for sample size	Final ( <a href="#">NRC, 2008b</a> )	
	7, 30, 180 & 1000 days	15	4	Auditory and visual effects; ↓reproductive hormone	40 ppm (human, 20.3 yrs avg. worker exposure)	LOAEL	Vrca et al. ( <a href="#">1997</a> ; <a href="#">1996</a> ; <a href="#">1995</a> );				UF <sub>LOAEL</sub> = 10

<sup>4</sup> ([Gamberale and Hultengren, 1972](#); [Wilson, 1943](#); [vonOettingen et al., 1942](#))

<sup>5</sup> ([Roberts et al., 2003](#); [Campagna et al., 2001](#); [Cavalleri et al., 2000](#); [Ng et al., 1992](#))

<sup>6</sup> ([Astrand et al., 1972](#); [Gamberale and Hultengren, 1972](#))

<sup>7</sup> ([Baelum et al., 1990](#); [Nielsen et al., 1985](#); [Andersen et al., 1983](#); [Stewart et al., 1975](#); [Ogata et al., 1970](#))

<sup>8</sup> ([Gericke et al., 2001](#); [Neubert et al., 2001a](#); [Neubert et al., 2001b](#))

<sup>9</sup> A factor [(16<sup>2</sup>)/10 = 0.4] was multiplied to the POD, which is effectively the same as division by an uncertainty factor of 2.5. Refer to the SMAC document ([NRC, 2008b](#)) for details regarding this adjustment.



	Reference Value Name	Duration	Reference Value		Health Effect	Point of Departure	Qualifier	Principal Study	Uncertainty Factors <sup>1</sup>	Notes on Derivation	Review Status
			(mg/m <sup>3</sup> )	(ppm)							
<b>General Public</b>	<b>Acute CA-REL (Severe Effects)</b>	6 hour	37	9.8	↓reaction time and headache, dizziness, intoxication, and slight eye and nose irritation	98 ppm,  40 ppm (human, 6 hours for 4 days)	NOAEL <sub>ADJ</sub>  NOAEL	<a href="#">Andersen et al. (1983)</a>	Total UF = 10 UF <sub>H</sub> = 10	Duration extrapolation via C <sup>n</sup> × t (n = 2) from 6 hrs to 1 hr	Final ( <a href="#">OEHHA, 2008</a> )
	<b>Acute ATSDR MRL</b>	1 -14 days	3.8	1.0	↑mucus flow, irritation of eyes and nose, headaches and dizziness	10 ppm  40 ppm (human, 6 hours for 4 days)	NOAEL <sub>HEC</sub>  NOAEL	<a href="#">Andersen et al. (1983)</a>	Total UF = 10 UF <sub>H</sub> = 10	HEC derived from 6 h/day to 24 h/day	Final ( <a href="#">ATSDR, 2000</a> )
	<b>Chronic CA-REL</b>	Chronic	0.3	0.07	↓brain weight, altered dopamine receptor binding	7 ppm  40 ppm (rat, 6 h/d, 5 d/wk)	NOAEL <sub>HEC</sub>  NOAEL	<a href="#">Hillefors-Berglund et al. (1995)</a>	Total UF = 100 UF <sub>S</sub> = 10 UF <sub>H</sub> = 10 UF <sub>A</sub> = 1	HEC derived from 6-h/d, 5-d/wk for 4 weeks	Final ( <a href="#">OEHHA, 2000</a> )
	<b>Chronic ATSDR MRL</b>	Chronic (> 1 year)	0.3	0.08	Color vision impairment in occupational exposures	8 ppm  35 ppm (human, 8 hr/d, 5 d/wk)	LOAEL <sub>HEC</sub>  LOAEL	Various <sup>10</sup>	Total UF = 100 UF <sub>L</sub> = 10 UF <sub>H</sub> = 10	HEC derived from 8 h/d and 5 d/wk for several years	Final ( <a href="#">ATSDR, 2000</a> )
	<b>Chronic RfC (IRIS)</b>	Chronic	5.0	1.3	Neurological effects in occupationally-exposed workers	46 mg/m <sup>3</sup>  128 mg/m <sup>3</sup> (human, 8 h/d, 5 d/wk)	NOAEL <sub>ADJ</sub>  NOAEL	Various <sup>11</sup>	Total UF = 10 UF <sub>H</sub> = 10	Adjustments: occupational breathing rate (10 m <sup>3</sup> vs. 20 m <sup>3</sup> ) and 5 days per week.	Final ( <a href="#">U.S. EPA, 2005</a> )

<sup>10</sup> ([Zavalic et al., 1998b](#); [Zavalic et al., 1998a](#))

<sup>11</sup> ([Neubert et al., 2001b](#); [Cavalleri et al., 2000](#); [Eller et al., 1999](#); [Zavalic et al., 1998a](#); [Boey et al., 1997](#); [Vrca et al., 1995](#); [Abbate et al., 1993](#); [Murata et al., 1993](#); [Nakatsuka et al., 1992](#); [Foo et al., 1990](#))



## Further Reading

U.S. EPA (U.S. Environmental Protection Agency). Toluene, Air Toxics Web Site.  
<http://www.epa.gov/ttn/atw/hlthef/toluene.html>

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