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Chemical Name: Xylenes

CAS: 1330-20-7

Synonyms: o-,m-,p-Xylene; m & p-xylene; m-,p-,o-Xylene; Dimethylbenzene; Dimethylbenzenes; Dimethylbenzene (mixed isomers); except p-xylene, mixed or all isomers; Socal aquatic solvent 3501; Total xylenes; Xylene; Xylene (o-,m-,p-); Xylene (o-, m-, p-isomers); xylenes; Xylenes ; Xylenes (o-, m-, p-isomers); Xylenes (mixed); Xylenes mixed isomers; Xylene (mixed); Xylene (mixed isomers); xylene, mixed or all isomers, except p-; Xylene mixture; Xylene mixture (m-xylene, o-xylene, p-xylene); Xylene mixture (60% m-xylene, 9% o-xylene, 14% p-xylene, 17% ethylbenzene); Xylene, (total); Xylol

Xylenes are a mixture of three isomers: meta-xylene (m-xylene), ortho-xylene (o-xylene), and para-xylene (p-xylene) with the meta-isomer usually being the dominant part of the mixture at 40-70%. The exact composition of the commercial xylene grade depends on the source but a typical mixture will also contain ethylbenzene at 6 - 20% in addition to the three isomers. The environmental fate (transport, partitioning, transformation, and degradation) is expected to be similar for each of the xylene isomers based on the similarities of their physical and chemical properties (Agency for Toxic Substances and Disease Registry 2007). The metabolism of each individual isomer is thought to be similar and the U.S. Environmental Protection Agency, 2003 IRIS Toxicological Review states that, "although differences in the toxicity of the xylene isomers have been detected, no consistent pattern following oral or inhalation exposure has been identified" (U.S. Environmental Protection Agency 2003).

Acute Non-Cancer Health Risk Limit ($nHRL_{acute}$) = 800 µg/L

$$= \frac{\text{(Reference Dose, mg/kg/d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Acute intake rate, L/kg/d)}}$$

$$= \frac{\text{(1.2 mg/kg/d) x (0.2) x (1000 µg/mg)}}{\text{(0.289L/kg-d)}}$$

= 830 rounded to **800 µg/L**

Reference Dose:	1.2 mg/kg-day (laboratory animal)
Source of toxicity value:	MDH 2010 (same as ATSDR Acute MRL 2007)
Point of Departure:	125 mg/kg-day (NOAEL- Dyer et al 1988, p-xylene isomer)
Human Equivalent Dose Adjustment:	NA
Total uncertainty factor:	100
UF allocation:	10 for interspecies variation; 10 for intraspecies variation
Critical effect(s):	Altered visually evoked potentials
Co-critical effect(s):	None
Additivity endpoint(s):	Nervous system

Secondary effect(s): None

Short-term Non-Cancer Health Risk Limit ($nHRL_{short\text{-}term}$) = 300 µg/L

$$= \frac{\text{(Reference Dose, mg/kg/d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Short-term intake rate, L/kg/d)}}$$

$$= \frac{\text{(0.50 mg/kg/d) x (0.2) x (1000 µg/mg)}}{\text{(0.289 L/kg-d)}}$$

= 346 rounded to **300 µg/L**

Reference Dose:	0.50 mg/kg-day (laboratory animal)
Source of toxicity value:	MDH 2010
Point of Departure:	500 mg/kg-day (NOAEL, NTP 1986; xylene mixture of 60.2% m-xylene, 9.1% o-xylene, 13.6% p-xylene, and 17% ethylbenzene)
Human Equivalent Dose Adjustment:	NA
Total uncertainty factor:	1000
UF allocation:	10 for interspecies variation; 10 for intraspecies variation; 10 for database deficiencies (The database lacked oral multi-generational reproductive as well as adequate ototoxicity and neurotoxicity studies. Inhalation studies have identified neurological effects as a sensitive endpoint.)
Critical effect(s):	Decreased body weight
Co-critical effect(s):	Altered visually evoked potentials, hearing loss as characterized by loss/damage to outer hair cells in cochlea
Additivity endpoint(s):	Nervous system
Secondary effect(s):	Shallow breathing, mortality, decreased thymus and spleen weight, decreased maternal uterine weight, overt maternal toxicity, increased resorptions, and fetal malformations (mainly cleft palate)

Subchronic Non-Cancer Health Risk Limit ($nHRL_{subchronic}$) = Short-term nHRL = 300 µg/L

$$= \frac{\text{(Reference Dose, mg/kg/d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Subchronic intake rate, L/kg/d)}}$$

$$= \frac{\text{(0.15 mg/kg/d) x (0.2) x (1000 µg/mg)}}{\text{(0.077 L/kg-d)}}$$

= 389 rounded to **400 µg/L**

Reference Dose: 0.15 mg/kg-day (laboratory animal)

Source of toxicity value:	MDH, 2010
Point of Departure:	150 mg/kg-day (NOAEL, Condie et al 1988; xylene mixture of 62.3% m- & p-xylene, 17.6% o-xylene, and 20% ethylbenzene)
Human Equivalent Dose Adjustment:	NA
Total uncertainty factor:	1000
UF allocation:	10 for interspecies variation; 10 for intraspecies variation; 10 for database deficiencies (The database lacked oral multi-generational reproductive as well as adequate ototoxicity and neurotoxicity studies. Inhalation studies have identified neurological effects as a sensitive endpoint.)
Critical effect(s):	Mild nephropathy in females and increased kidney weight in males
Co-critical effect(s):	Decreased body weight, altered visual evoked potential, hearing loss as characterized by loss/damage to outer hair cells in the cochlea
Additivity endpoint(s):	Renal (kidney) system*, Nervous system
Secondary effect(s):	Lethargy, shallow breathing, unsteadiness, tremors, paresis, decreased thymus and spleen weight, decreased body weight, fetal malformations (mainly cleft palate), decreased maternal uterine weight, increased resorptions

The Subchronic nHRL must be protective of the short-term exposures that occur within the subchronic period and therefore, the Subchronic nHRL is set equal to the Short-term nHRL of 300 µg/L. Additivity endpoints: Renal (kidney) system*, Nervous system

*The short-term and subchronic water concentrations were very similar (346 µg/L – short-term & 389 µg/L – subchronic) so renal effects were included as an additivity endpoint for the subchronic duration even though the subchronic HRL was set to the short-term value

Chronic Non-Cancer Health Risk Limit ($nHRLV_{chronic}$) = Short-term nHRL = 300 µg/L

$$= \frac{\text{(Reference Dose, mg/kg/d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Chronic intake rate, L/kg/d)}}$$

$$= \frac{\text{(0.18 mg/kg/d) x (0.2) x (1000 µg/mg)}}{\text{(0.043 L/kg-d)}}$$

= 837 rounded to **800 µg/L**

Reference Dose:	0.18 mg/kg-day (laboratory animal)
Source of toxicity value:	MDH 2010 (same as EPA IRIS 2003)
Point of Departure:	179 mg/kg-day(NOAEL, NTP 1986; xylene mixture of 60% m-xylene, 9.1% o-xylene, 13.6% p-xylene, and 17% ethylbenzene)
Human Equivalent Dose Adjustment:	NA
Total uncertainty factor:	1000
UF allocation:	10 for interspecies variation; 10 for intraspecies variation; 10 for

database deficiencies (The database lacked oral multi-generational reproductive as well as adequate ototoxicity and neurotoxicity studies. Inhalation studies have identified neurological effects as a sensitive endpoint.)

Critical effect(s): Decreased body weight
Co-critical effect(s): Altered visual evoked potential
Additivity endpoint(s): Renal (kidney) system*, Nervous system
Secondary effect(s): Hyperactivity, increased kidney weights, minimal nephropathy, hearing loss as characterized by loss/damage to outer hair cells in the cochlea

The Chronic nHRL must be protective of the short-term exposures that occur within the chronic periods and therefore, the Chronic nHRL is set equal to the Short-term nHRL of 300 µg/L. Additivity endpoints: Renal (kidney) system*, Nervous system

*Renal effects were listed as an additivity endpoint for the chronic duration because the chronic HRL must be protective of effects that occur during the subchronic duration. Even though the chronic duration HRL was set to the short-term value, renal effects were added as an additivity endpoint for the subchronic duration. The short-term and subchronic water concentrations were very similar (346 µg/L – short-term & 389 µg/L – subchronic) so renal effects were included as an additivity endpoint for the subchronic duration even though the subchronic HRL was also set to the short-term value.

Cancer Health Risk Limit (cHRL) = Not Applicable

Cancer classification: None
Slope factor: NA
Source of slope factor: NA
Tumor site(s): NA

Volatile: Yes (highly)

Summary of Guidance Value History:
The short-term, subchronic, and chronic 2011 HRLs are 33 times lower than the 1993/94 HRL (10,000 µg/L) as the result of: 1) a 4-fold fold lower, revised RfD, 2) utilizing more recent intake rates which incorporate higher intake rates during early life, and 3) rounding to one significant digit.

Summary of toxicity testing for health effects identified in the Health Standards Statute:

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested?	No	Yes	Yes	Yes	Yes
Effects?	--	Yes[1]	Yes[2]	Yes[3]	Yes[4]

Note: Even if testing for a specific health effect was not conducted for this chemical, information about that effect might be available from studies conducted for other purposes. Most chemicals have been subject to multiple studies in which researchers identify a dose where no effects were observed, and the lowest dose that caused one or more effects. A toxicity value based on the

effect observed at the lowest dose across all available studies is considered protective of all other effects that occur at higher doses.

Comments on extent of testing or effects:

[1] Decreased spleen and thymus and spleen weights were measured following oral exposure at a dose two times higher than the short-term critical study LOAEL (1000 mg/kg-day) and are identified as secondary effects for the short-term and subchronic durations.

[2] Developmental testing found effects of malformations including cleft palate, decreased fetal body weight and increased fetal death at doses two times higher than the LOAEL in the short-term critical study. Developmental effects were listed as a secondary effect for the short-term duration.

[3] Reproductive effects including increased resorptions and decreased uterine weight following oral exposure at doses two times higher than the short-term critical study LOAEL (1000 mg/kg-day) and eight times higher than the acute critical study LOAEL (250 mg/kg-day).

[4] Neurological effects of transient hyperactivity were seen at oral doses during the chronic duration that were three times higher than the critical acute LOAEL (250 mg/kg-day) which was based on altered evoked visual potentials. Transient signs of nervous system depression were observed in mice at oral doses that were six time higher than the acute LOAEL (250 mg/kg-day) and two times higher than the subchronic critical study LOAEL (750 mg/kg-day). Neurological effects were listed as critical, co-critical, and secondary effects. Neurotoxicity has been identified as the most sensitive endpoint following inhalation exposure.

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