Development Support Document
Original: February 13, 2009
Revised Odor: March 21, 2014
Revised Odor: September 14, 2015

Xylenes

CAS Registry Numbers:

Xylene mixture: 1330-20-7

m-Xylene: 108-38-3

o-Xylene: 95-47-6

p-Xylene: 106-42-3

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TEXAS COMMISSION ON ENVIRONMENTAL QUALITY

Revision History

Original Development Support Document (DSD) posted as final on February 13, 2009.

Revised DSD March 21, 2014: the odor-based value was updated based on a geometric mean of approved odor values (TCEQ 2012).

Revised DSD September 14, 2015: the odor-based value was withdrawn because xylene does not have a pungent, disagreeable odor (TCEQ 2015).

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Chapter 1 Summary Tables

Table 1 provides a summary of health- and welfare-based values from an acute and chronic toxicity evaluation of xylene (m-xylene, o-xylene, p-xylene, and mixed isomers). Table 2 provides summary information on xylene's physical/chemical data.

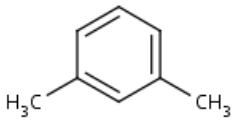
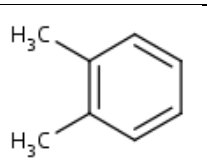
Table 1 Health- and Welfare-Based Values for Xylene, All Isomers

Short-Term Values	**Concentration**	**Notes**
$^{acute}ESL$ [1 h] (HQ = 0.3)	2,200 µg/m^3 (510 ppb) **Short-Term ESL for Air Permit Reviews**	**Critical Effect(s):** Mild respiratory effects and subjective symptoms of neurotoxicity in human volunteers
Acute ReV (HQ = 1.0)	7,400 µg/m^3 (1,700 ppb) *	**Critical Effect(s):** Same as above
$^{acute}ESL_{odor}$	---	Sweet odor (revised based on TCEQ 2015)
$^{acute}ESL_{veg}$	---	No data found
Long-Term Values	**Concentration**	**Notes**
$^{chronic}ESL_{nonlinear(nc)}$ (HQ = 0.3)	180 µg/m^3 (42 ppb) **Long-Term ESL for Air Permit Reviews**	**Critical Effect(s):** Mild respiratory and subjective neurological effects in factory workers
Chronic ReV (HQ = 1.0)	610 µg/m^3 (140 ppb) *	**Critical Effect(s):** Same as above
$^{chronic}ESL_{linear(c)}$ $^{chronic}ESL_{nonlinear(c)}$	---	Inadequate data
$^{chronic}ESL_{veg}$	---	No data found

* Values that may be used for evaluation of ambient air monitoring data

Abbreviations used: **HQ**, hazard quotient; **ppb**, parts per billion; **µg/m^3**, micrograms per cubic meter; **h**, hour; **ESL**, Effects Screening Levels; **ReV**, Reference Value; **^{acute}ESL**, acute health-based ESL; **$^{acute}ESL_{odor}$**, acute odor-based ESL; **$^{acute}ESL_{veg}$**, acute vegetation-based ESL; **$^{chronic}ESL_{nonlinear(nc)}$**, chronic health-based ESL for nonlinear dose-response noncancer effects; **$^{chronic}ESL_{linear(c)}$**, chronic health-based ESL for linear dose-response cancer effect; **$^{chronic}ESL_{nonlinear(c)}$**, chronic health-based ESL for nonlinear dose-response cancer effect; and **$^{chronic}ESL_{veg}$**, chronic vegetation-based ESL

Table 2 Chemical and Physical Data

Parameter	m-xylene	o-xylene	p-xylene	Reference
Molecular Formula	C_8H_{10}	C_8H_{10}	C_8H_{10}	HSDB (2002)
Chemical Structure				ChemIDplus
Molecular Weight	106.17	106.16	106.16	HSDB (2002)
Physical State	liquid	liquid	liquid	HSDB (2002)
Color	colorless	colorless	colorless	HSDB (2002)
Odor	sweet odor	sweet odor	sweet odor	HSDB (2002)
CAS Registry Number	108-38-3	95-47-6	106-42-3	HSDB (2002)
Synonyms	m-dimethylbenzene; dimethylbenzene, 1,3-; m-xylol	o-dimethylbenzene; dimethylbenzene, 1,2-; o-xylol	p-dimethylbenzene; dimethylbenzene, 1,4-; p-xylol	HSDB (2002)
Water Solubility	162 mg/L @ 25°C	178 mg/L @ 25°C	198 mg/L @ 25°C	HSDB (2002)
Log K_{ow}	3.20	3.12	3.15	HSDB (2002)
Vapor Pressure	8.29 mm Hg @ 25°C	6.61 mm Hg @ 25°C	8.84 mm Hg @ 25°C	HSDB (2002)
Relative Vapor Density	3.7	3.7	3.7	HSDB (2002)
Density	0.8684 @ 20°C	0.8801 @ 20°C	0.8610 @ 20°C	HSDB (2002)
Melting Point	-47.4°C	-25°C	13.2°C	HSDB (2002)
Boiling Point	139.3°C	144.4°C	138.3°C	HSDB (2002)
Conversion Factors @ 25°C	1 ppb = 4.34 μg/m^3 1 μg/m^3 = 0.23 ppb	1 ppb = 4.34 μg/m^3 1 μg/m^3 = 0.23 ppb	1 ppb = 4.34 μg/m^3 1 μg/m^3 = 0.23 ppb	Toxicology Division

Chapter 2 Major Uses or Sources

Xylene exists in ambient air as a mixture of meta (m-), ortho (o-), and para (p-) isomers. Xylenes are primarily manufactured in the petroleum refining industry. Xylene mixtures are used in the production of individual xylene isomers, with p-xylene accounting for the largest percentage of isomer production. The p-xylene isomer is produced in high quantities because of its use in the production of polyester fibers. Xylene isomers are used as intermediate feedstocks in the production of resins, which are used to produce molded plastic, films, and beverage bottles. Mixtures of xylene isomers are used as solvent for paints and coatings, and are added to gasoline to increase its octane rating. Xylene emission sources include petroleum refineries and fuel terminals, chemical and polyester manufacturing industries, as well as the production and use of paints, dyes, and lacquers.

Chapter 3 Acute Evaluation

3.1 Health-Based Acute ReV and ESL

3.1.1 Physical/Chemical Properties and Key Studies

Isomers of xylene have similar physical and chemical properties and produce similar toxicological effects. No single isomer exhibits a greater potency. Therefore, this toxicity assessment considers xylenes as a chemical category, and the term xylene or xylenes is used interchangeably. Xylene is a colorless liquid having a sweet hydrocarbon odor. In addition, xylenes have a low water solubility and an octanol-water partition (K_{ow}) value suggesting an affinity for lipid rich tissues such as adipose, liver, and brain tissue. The main chemical and physical properties for xylene are summarized in Table 2.

This acute evaluation is based, in part, on the recent ATSDR (2007) toxicological profile for xylenes. Numerous toxicity studies have been conducted in laboratory animals and human volunteers inhaling xylene after acute duration exposures (<14 days). Since human data are the preferred source from which to base a toxicity assessment, several well conducted human inhalation studies were considered in identifying a point of departure (POD). Neurological and respiratory effects were identified as critical endpoints. These co-critical effects have been observed in humans after xylene inhalation exposures ranging between 50 ppm (Ernstgard et al. 2002) and 690 ppm (Carpenter et al. 1975).

The acute duration human inhalation study conducted by Ernstgard et al. (2002) was selected as the key study for the assessment. Fifty six healthy human volunteers (28 per sex) were exposed to either 50 ppm m-xylene, clean air (controls), or 150 ppm 2-propanol for 2 hours (h) in an inhalation chamber. The 50 ppm m-xylene exposure group revealed mild respiratory effects that included increased discomfort in the throat and airways of females and breathing difficulty in both sexes. In addition, the 50 ppm m-xylene exposure group reported subjective symptoms of neurotoxicity, including fatigue, headache, dizziness, and a feeling of intoxication. All of the

reported respiratory effects and subjective symptoms were considered minimal. This study was chosen as the key study over other acute studies that identified a lowest-observed-adverse-effect-level (LOAEL), because it was recently published, it was chosen by ATSDR (2007) as its key study for developing an acute minimal risk level (MRL), and it identified 50 ppm as the lowest LOAEL. The following three supporting studies in human volunteers inhaling xylene that demonstrated similar critical effects at concentrations above 50 ppm were also considered:

- Eye, nose, and throat irritation were evaluted among 50 healthy human subjects exposed by inhalation to mixed xylenes at concentrations of 0 (clean air), 100, 200, or 400 ppm for 30 minutes (Hastings et al. 1984, as cited by Cal EPA 1999). Eye irritation was reported at the 200 and 400 ppm exposure groups. Since incidence of eye irritation was similar to the controls (56% for controls versus 60% at 100 ppm), the 100 ppm exposure concentration was considered the no-observed-adverse-effect-level (NOAEL).
- Carpenter et al. (1975) as cited by Cal EPA (1999), concluded that an exposure of 100 ppm xylene would not be objectionable to most people. Six human volunteers were exposed by inhalation to 110, 230, 460, and 690 ppm mixed xylenes for a single 15-minute period. Eye irritation was reported at the 230, 460, and 690 ppm exposure groups. The 690 ppm group also reported dizzines/light-headedness. Except for one individual who experienced mild throat discomfort at 110 ppm, but not at 230 ppm, no adverse effects were reported at the 110 ppm group.
- Riihimaki et al. (1980) reported neurological effects in human volunteers exposed by inhalation to concentrations that ranged between 100 and 400 ppm m-xylene. Neurological effects included increased reaction times and impaired body balance.

A number of studies examined potential reproductive/development effects of airborne mixed xylenes or individual xylene isomers in animals, but adverse effects were reported at exposure concentrations greater than those at which neurological effects were reported (USEPA 2003).

3.1.2 Mode of Action (MOA) and Dose Metric

Xylene is readily absorbed by the respiratory tract. Studies in humans indicate that lung absorption is greater than 50% following inhalation exposure to xylene. Approximately 90% of xylene's absorbed dose is metabolized in the liver, primarily to isomers of methylhippuric acid and rapidly excreted in the urine. Unmetablolized xylene is quickly eliminated in exhaled air. It has been estimated that human excretion of xylene by exhaled air and urine is rapid with an elimination half-life of 0.5 to 1 h within the first hours (Riihimaki et al. 1980).

Higher concentrations of xylene can be found in tissues with high lipid content (e.g., adipose, liver, brain). Although xylene tends not to accumulate in the body, xylene can be retained briefly in fat tissue due to its lipophilicity. As a result, xylene elimination may be slower in individuals having a higher percentage of body fat.

Inhalation is the primary route of xylene exposure, and respiratory effects (e.g., breathing

difficulty, discomfort in throat), and neurological effects (e.g., dizziness, headache) are sensitive endpoints. Breathing difficulty and throat discomfort are considered threshold effects (i.e., nonlinear MOA) and should not vary over time (i.e., the effects are concentration dependent, not duration dependent).

Although the mechanism underlying xylene's neurological effects is not fully understood, it may be related to the distribution and accumulation of the parent compound in the neuronal membranes (rather than its metabolites). Therefore, exposure concentration of the parent compound is considered the appropriate dose metric for xylene exposure for producing both respiratory and neurological effects.

3.1.3 Critical Effects, POD for the Key Study, and Dosimetric Adjustments

Neurological and respiratory effects were identified as critical endpoints. Ernstgard et al. (2002) was conservatively chosen the key acute study. After selecting the LOAEL of 50 ppm as the Human Equivalent Concentration Point of Departure (POD_{HEC}), consideration was given to adjust the LOAEL from a 2 h to a 1 h exposure duration following guidance in Section 3.2.2 from *Guidelines to Develop Effects Screening Levels, Reference Values, and Unit Risk Factors* (hereafter referred to as ESL Guidelines) (TCEQ 2006). However, since exposure concentration and not duration seems to play the dominant role in xylene's respiratory effects and neurological changes, no adjustment was deemed necessary. Therefore, the POD for a 1 h exposure was assumed to be 50 ppm.

3.1.4 Adjustments of the POD_{HEC}

Since the mild respiratory effects and neurological changes in humans produced by xylene are considered to have a threshold (i.e., a nonlinear MOA), uncertainty factors (UFs) were applied to the POD_{HEC}. An UF of 10 for intraspecies variability (UF_H) was used to account for sensitive subpopulations, an UF of 3 for using a minimal LOAEL (UF_L) considering that the respiratory and neurological effects were considered to be minimal, magnitude of the effects was small, and a database UF of 1 (UF_D) since xylene's acute toxicological database is extensive. The total UFs applied were 30. The acute ReV was calculated as follows:

$$\text{Acute ReV} = POD_{HEC} / (UF_H \times UF_L \times UF_D)$$
$$= 50 \text{ ppm} / (10 \times 3 \times 1)$$
$$= 1.7 \text{ ppm}$$
$$= 1{,}700 \text{ ppb}$$

3.1.5 Health-Based Acute ReV and ^{acute}ESL

The acute ReV value was rounded to two significant figures at the end of all calculations. The rounded acute ReV was then used to calculate the ^{acute}ESL. Rounding to two significant figures, the 1 h acute ReV is 7,400 µg/m^3 (1,700 ppb). At the target hazard quotient of 0.3, the ^{acute}ESL is 2,200 µg/m^3 (510 ppb) (Table 3). As previously discussed in Section 3.1.1, xylene toxicity is

similar among its isomers. Furthermore, 2 of the supporting studies (Hastings et al. 1984 and Carpenter et al. 1975) reported a NOAEL and LOAEL for mixed xylenes at higher concentrations than the reported LOAEL for m-xylene from the key study (Ernstgard et al. 2002). Therefore, the derived acute ReV and ^{acute}ESL, which are based on m-xylene, are expected to be protective for mixed and individual isomers of xylene as well.

Table 3 Derivation of the Acute ReV and ^{acute}ESL

Parameter	**Study**
Study	Ernstgard et al. (2002)
Study population	28 male and 28 female human volunteers
Study quality	High
Exposure Methods	2 h at inhalation exposure of 0 and 50 ppm
LOAEL	50 ppm
NOAEL	Not Applicable (NA)
Critical Effects	Mild respiratory and subjective neurological effects
POD_{HEC}	50 ppm (LOAEL)
Exposure Duration	2 h
Extrapolation to 1 h exposure	Concentration dependent; no adjustment needed
Extrapolated 1 h concentration (POD_{ADJ})	50 ppm
Total Uncertainty Factors (UFs)	30
Interspecies UF	NA
Intraspecies UF	10
LOAEL UF	3
Incomplete Database UF	1
Database Quality	High
Acute ReV [1 h] (HQ = 1)	**7,400 µg/m^3 (1,700 ppb)**
^{acute}ESL [1 h] (HQ = 0.3)	**2,200 µg/m^3 (510 ppb)**

3.2 Welfare-Based Acute ESLs

3.2.1 Odor Perception (Revised September 2015)

Although xylene isomers have similar physical and chemical properties and produce similar toxicological effects, individual isomers have odor thresholds that cover a wide range of values. In general, xylene isomers have a sweet aromatic hydrocarbon odor, and odor detection concentrations range from 0.012 to 20 ppm, and odor recognition concentrations range from 0.23 to 40 ppm. Since xylene isomers does not have a pungent or disagreeable odor, an $^{acute}ESL_{odor}$ was not developed (TCEQ 2015).

3.2.2 Vegetation Effects

No acute vegetative studies have been identified for xylene.

3.3 Short-Term ESL and Values for Air Monitoring Evaluation

The acute evaluation resulted in the derivation of the following acute values:

- acute ReV = 7,400 µg/m^3 (1,700 ppb),
- ^{acute}ESL = 2,200 µg/m^3 (510 ppb)

The short-term ESL for reviewing air permit applications is the health-based ^{acute}ESL of 2,200 µg/m^3 (510 ppb) (Table 1). Similarly, for the evaluation of ambient air monitoring data, the acute ReV of 7,400 µg/m^3 (1,700 ppb) may be used (Table 1). The ^{acute}ESL (HQ = 0.3) is not used to evaluate ambient air monitoring data.

Chapter 4 Chronic Evaluation

4.1 Noncarcinogenic Potential

4.1.1 Physical/Chemical Properties and Key Studies

Refer to Section 3.1.1 for a discussion of physical/chemical properties.

The toxicological database for chronic exposure to xylene is limited in humans, but is more extensive in animals. However, neurological effects have been identified as sensitive endpoints after repeated inhalation exposures to xylene in both animals and humans.

This chronic evaluation is based, in part, on the recent ATSDR (2007) Toxicological Profile for xylenes.

Since human data are a preferred source from which to base a toxicity assessment, a well-conducted human inhalation study was selected to identify a POD. The occupational study by Uchida et al. (1993) was chosen as the key study, with a reported LOAEL of 14 ppm as a

geometric mean of exposure concentrations. This study was also chosen by Cal EPA (1999) for developing its chronic inhalation Reference Exposure Level (REL), and was selected by ATSDR (2007) for developing its chronic MRL. One-hundred seventy-five factory workers were exposed to mixed xylenes at an estimated concentration of 14 ppm over a 7+ year period and evaluated for subjective symptoms in a questionnaire, and also examined for objective parameters (hematology, serum chemistry, and urinalysis). This study meets the cut-off point for chronic human exposure (i.e., 10% of a 70 year lifespan). A control population of 241 factory workers was also included in the study. Subjective symptoms of neurotoxicity (i.e., anxiety, forgetfulness, floating sensation), respiratory effects (i.e., nasal irritation and sore throat), and eye irritation were reported for workers exposed to 14 ppm mixed xylenes. Interestingly, the observed critical effects (respiratory and neurological effects) in this study are similar to those noted in the acute human inhalation exposure study conducted by Ernstgard et al. (2002).

Two supporting subchronic inhalation studies in animals that reported neurobehavioral effects were also considered. These studies identified a NOAEL of 50 ppm and a LOAEL of 100 ppm for neurobehavioral changes:

- Korsak et al. (1994) conducted a subchronic inhalation study in male rats exposed to xylene vapor and reported neurological effects (impaired rotarod performance) at a concentration of 100 ppm m-xylene over a 6 h/day, 5 day/week, and 3-month period. The study identified 50 ppm as the NOAEL. Although USEPA chose Korsak et al. (1994) as its key study (IRIS 2003), the human occupational study reported by Uchida et al. (1993) was chosen for this evaluation.

- Gralewicz et al. (1995) observed altered radial maze performance in male rats exposed to 100 ppm m-xylene over a 6 h/day, 5 day/week, and 3-month period.

4.1.2 MOA and Dose Metric

As previously stated, xylene is rapidly absorbed from the respiratory tract and is quickly eliminated in exhaled air and urine. Inhalation is the primary route for xylene exposure, and respiratory and neurological effects are the most sensitive endpoints. Although the MOA whereby xylene produces neurological effects is unknown, it is probably related to the parent compound. Considering that mild respiratory effects in humans are considered to have a threshold (i.e., a nonlinear MOA), xylene's MOA is considered to be dependent on concentration and not duration dependent. Therefore, concentration of the parent compound is considered the appropriate dose metric regarding chronic xylene exposure for producing mild respiratory effects and subjective neurological changes.

4.1.3 Critical Effects and Dosimetric Adjustment to POD_{HEC}

The LOAEL of 14 ppm based on mild subjective symptoms (i.e., eye and nasal irritation) and neurological effects (i.e., anxiety, forgetfulness, floating sensation) was chosen as the

Occupational Point of Departure (POD_{OC}). Since xylene is quickly absorbed and rapidly excreted (i.e., rapid detoxification), exposure duration is deemed negligible. Therefore, continuous exposure duration adjustment for the general population is not necessary. Furthermore, the chronic MRL from the toxicological profile for xylenes (ATSDR 2007) was similarly not adjusted for continuous exposure. Therefore, the $POD_{OC} = POD_{HEC}$, and the POD_{HEC} = 14 ppm.

4.1.4 Adjustments of the POD_{HEC}

Since the respiratory and neurological effects in humans produced by xylene are considered to have a threshold (i.e., a nonlinear MOA), UFs were applied to the POD_{HEC}. An UF_H of 10 was used to account for sensitive subpopulations. An UF_L of 3 was chosen considering that the LOAEL was minimal and that the magnitude of the effects was small. An UF_D of 3 was chosen since the database lacks supportive chronic neurotoxicity studies of xylene. Total UFs applied were 100. The chronic ReV was calculated as follows:

$$\text{chronic ReV} = POD_{HEC} / (UF_H \times UF_L \times UF_D)$$
$$= 14 \text{ ppm} / (10 \times 3 \times 3)$$
$$= 0.14 \text{ ppm}$$
$$= 140 \text{ ppb}$$

4.1.5 Health-Based Chronic ReV and $^{chronic}ESL_{nonlinear(nc)}$

The chronic ReV value was rounded to two significant figures at the end of all calculations. The rounded chronic ReV is 140 ppb (610 µg/m^3). The rounded chronic ReV was then used to calculate the $^{chronic}ESL_{nonlinear(nc)}$. At the target hazard quotient of 0.3, the $^{chronic}ESL_{nonlinear(nc)}$ is 42 ppb (180 µg/m^3) (Table 4). As previously discussed in Section 3.1.1, xylene toxicity is similar among its isomers. Therefore, the chronic ReV and $^{chronic}ESL_{nonlinear(nc)}$, which are based on mixed isomers of xylene, are expected to be protective for individual isomers of xylene as well.

Table 4 Derivation of the Chronic ReV and $^{chronic}ESL_{nonlinear(nc)}$

Parameter	**Study**
Study	Occupational exposure of workers inhaling mixed xylene isomers (Uchida et al. 1993)
Study population	175 factory workers occupationally exposed to mixed isomers, and a control population of 241 workers
Study quality	Moderate
Exposure Method	Average 7+ years of inhalation exposure at 14 ppm
Critical Effects	Mild respiratory and subjective neurological effects
POD_{OC}	14 ppm geometric mean of exposure concentrations (LOAEL)
Exposure Duration	8 h/day, 5 days/week, for average of 7+ years
Extrapolation to continuous exposure (POD_{ADJ})	Concentration dependent, no adjustment needed
POD_{HEC} Dosimetry adjustment from occupational to general human population	Concentration dependent, no adjustment needed POD_{HEC} = 14 ppm
Total UFs	100
Interspecies UF	NA
Intraspecies UF	10
LOAEL UF	3
Subchronic to chronic UF	NA
Incomplete Database UF	3
Database Quality	Medium to High
Chronic ReV (HQ = 1)	**610 µg/m3 (140 ppb)**
$^{chronic}ESL_{nonlinear(nc)}$ (HQ = 0.3)	**180 µg/m3 (42 ppb)**

4.2 Carcinogenic Potential

Data are inadequate for an assessment of human carcinogenic potential via the inhalation pathway for xylene. The United States Environmental Protection Agency (USEPA 2003) classifies xylene as not classifiable as to human carcinogenicity. The International Agency for Research on Cancer (IARC 1999), and the American Conference of Governmental Industrial Hygienists (ACGIH 2007) determined that xylene is not classifiable as a human carcinogen.

In addition, xylenes were found to be nonmutagenic in bacterial test systems with *S. typhimurium*

(Bos et al. 1981; Florin et al. 1980; NTP 1986) and *E. coli* (McCarroll et al. 1981) or in cultured mouse lymphoma cells (Litton Bionetics 1978) as cited in USEPA (2003). No increase in the frequency of sister chromatid exchanges was observed in peripheral lymphocytes in individuals exposed to xylenes in an occupational setting (Haglund et al. 1980; Pap and Varga 1987) or an experimental setting (Richer et al. 1993) as cited in USEPA (2003).

4.3 Welfare-Based Chronic ESL

No chronic vegetation-based studies have been identified for any isomer of xylene.

4.4 Long-Term ESL and Values for Air Monitoring Evaluation

The chronic evaluation resulted in the derivation of the following chronic values:

- Chronic ReV = 610 µg/m^3 (140 ppb)
- $^{chronic}ESL_{nonlinear(nc)}$ = 180 µg/m^3 (42 ppb)

The long-term ESL for air permit evaluations is the $^{chronic}ESL_{nonlinear(nc)}$ of 180 µg/m^3 (42 ppb) (Table 1). For evaluation of monitoring data, the chronic ReV of 610 µg/m^3 (140 ppb) is used (Table 1). The $^{chronic}ESL_{nonlinear(nc)}$ (HQ = 0.3) is not used to evaluate ambient air monitoring data.

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