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 (ATSDR, 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” (USEPA, 2003).

**Acute Non-Cancer Health Based Value (nHBVAcute) = 700 μg/L**

\[
(\text{Reference Dose, mg/kg-d}) \times (\text{Relative Source Contribution}) \times (\text{Conversion Factor})
\]

\[
(\text{Acute Intake Rate, L/kg-d})
\]

\[
= (1.0 \, \text{mg/kg-d}) \times (0.2)^* \times (1000 \, \mu\text{g/mg})
\]

\[
(0.285 \, \text{L/kg-d})^**
\]

\[
= 702 \text{ rounded to } 700 \, \mu\text{g/L}
\]

**Short-term Non-Cancer Health Based Value (nHBV\textsubscript{short-term}) = 300 \mu g/L**

\[
\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}
\text{ (Short-term Intake Rate, L/kg-d)}
\]

\[
= (0.38 \text{ mg/kg-d}) \times (0.2) \times (1000 \mu g/mg)
\text{(0.285 L/kg-d)}^{**}
\]

\[
= 267 \text{ rounded to } 300 \mu g/L
\]

\**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81

Reference Dose/Concentration: HED/Total UF = 115/300 = 0.38 mg/kg-d (F344/N Rat)
Source of toxicity value: Determined by MDH in 2019
Point of Departure (POD): 500 mg/kg-d (NOAEL; NTP, 1986 (14 day study))
Dose Adjustment Factor (DAF): 0.23, Body weight scaling, default (MDH, 2017) (USEPA, 2011)
Human Equivalent Dose (HED): POD x DAF = 500 mg/kg-d x 0.23 = 115 mg/kg-d
Total uncertainty factor (UF): 300
Uncertainty factor allocation: 3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 10 for database uncertainty (lack of multigenerational reproductive study as well as adequate ototoxicity and neurotoxicity studies. Neurotoxicity was identified as a sensitive endpoint from inhalation studies.)
Critical effect(s): Decreased body weight gain
Co-critical effect(s): Altered visual evoked potentials, decreased fetal body weight, increased fetal malformations
Additivity endpoint(s): Developmental, Nervous System

**Subchronic Non-Cancer Health Based Value (nHBV\textsubscript{subchronic}) = 300 \mu g/L**

\[
\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}
\text{ (Subchronic Intake Rate, L/kg-d)}
\]

\[
= (0.12 \text{ mg/kg-d}) \times (0.2) \times (1000 \mu g/mg)
\text{(0.070 L/kg-d)}^{**}
\]

\[
= 343 \text{ rounded to } 300 \mu g/L
\]

**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81

Reference Dose/Concentration: HED/Total UF = 34.5/300 = 0.12 mg/kg-d (SD Rat)
Source of toxicity value: Determined by MDH in 2019
Point of Departure (POD): 150 mg/kg-d (NOAEL; Condie, 1988)
Dose Adjustment Factor (DAF): 0.23, Body weight scaling, default (MDH, 2017) (USEPA, 2011)

Human Equivalent Dose (HED): POD x DAF = 150 mg/kg-d x 0.23 = 34.5 mg/kg-d

Total uncertainty factor (UF): 300

Uncertainty factor allocation: 3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 10 for database uncertainty (lack of multigenerational reproductive study as well as adequate ototoxicity and neurotoxicity studies. Neurotoxicity was identified as a sensitive endpoint from inhalation studies.)

Critical effect(s): Increased kidney weights, minimal chronic nephropathy

Co-critical effect(s): Altered visual evoked potentials, decreased fetal body weight, decreased adult body weight gain, increased fetal malformations, hyperactivity

Additivity endpoint(s): Developmental, Nervous system, Renal (kidney) system

Chronic Non-Cancer Health Based Value (nHBVChronic) = nHBVSubchronic = 300 µg/L

\[
\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)} = (0.16 \text{ mg/kg-d}) \times (0.2)^* \times (1000 \mu g/mg) \\
= 0.044 \text{ L/kg-d}^{**}
\]

= 727 rounded to 700 µg/L


**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81

Reference Dose/Concentration: HED/Total UF = 48.3/300 = 0.16 mg/kg-d (F344/N rat)

Source of toxicity value: Determined by MDH in 2019

Point of Departure (POD): 179 mg/kg-d (NOAEL; NTP, 1986 (2 year study))

Dose Adjustment Factor (DAF): 0.27, Body weight scaling, default (MDH, 2017) (USEPA, 2011)

Human Equivalent Dose (HED): POD x DAF = 179 mg/kg-d x 0.27 = 48.3 mg/kg-d

Total uncertainty factor (UF): 300

Uncertainty factor allocation: 3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 10 for database uncertainty (lack of multigenerational reproductive study as well as adequate ototoxicity and neurotoxicity studies. Neurotoxicity was identified as a sensitive endpoint from inhalation studies.)

Critical effect(s): Decreased body weight gain
Co-critical effect(s): Altered evoked visual potentials, decreased body weight gain, hyperactivity, minimal chronic nephropathy and increased kidney weights

Additivity endpoint(s): Nervous system, Renal (kidney) system

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

Cancer Health Based Value (cHBV) = Not Applicable

Cancer classification: Not Classified
Slope factor (SF): Not Applicable
Source of cancer slope factor (SF): Not Applicable
Tumor site(s): Not Applicable

Volatile: Yes (high)

Summary of Guidance Value History:
A non-cancer Health Risk Limit (HRL) of 10,000 µg/L was promulgated in 1993/1994. Acute, short-term, subchronic, and chronic health-based values (HBV) of 800, 300, 300, and 300 µg/L, respectively, were derived in 2010 and were promulgated as HRLs in 2011. In 2019, MDH re-evaluated the non-cancer HRLs, resulting in a lower acute duration value of 700 µg/L and no changes to the values for short-term, subchronic, and chronic durations. The changes to existing guidance were due to 1) using MDH’s most recent risk assessment methodology and 2) rounding to one significant digit.

Summary of toxicity testing for health effects identified in the Health Standards Statute (144.0751):
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. MDH has considered the following information in developing health protective guidance.

<table>
<thead>
<tr>
<th>Tested for specific effect?</th>
<th>Endocrine</th>
<th>Immunotoxicity</th>
<th>Development</th>
<th>Reproductive</th>
<th>Neurotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effects observed?</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Comments on extent of testing or effects:
1Decreased thymus and spleen weights have been reported in laboratory animals at doses over 1,000 times higher than the current short-term reference dose.
2Developmental effects are included as co-critical effects for the short-term, subchronic, and chronic durations. Increased fetal malformations, mostly cleft palate malformations, were observed in
laboratory animals in the absence of maternal toxicity at doses less than one fold higher than doses that caused increased kidney weights and mild nephropathy and decrease body weight gain in short-term, subchronic, and chronic duration studies.

 Decreased uterine weight and increased resorptions have been reported in laboratory animals at doses approximately 700 times higher than the current short-term reference dose. Other studies in laboratory animals at similar doses reported no adverse reproductive effects.

The acute reference dose is based on neurotoxicity in male rats with observed effects of altered visual evoked potentials. Transient hyperactivity was observed in laboratory animals at doses at or less than one fold difference than doses observed to cause increased kidney weights and mild nephropathy in laboratory animals. Nervous system effects of altered visual evoked potentials and transient hyperactivity were listed as co-critical effects for the short-term, subchronic, and chronic durations. The nervous system was identified as a sensitive endpoint following inhalation exposure.

Resources Consulted During Review:


National Toxicology Program. (1986). *NTP Toxicology and Carcinogenesis Studies of Xylenes (Mixed) (60% m-Xylene, 14% p-Xylene, 9% o-Xylene, and 17% Ethylbenzene) (CAS No. 1330-20-7) in F344/N Rats and B6C3F1 Mice (Gavage Studies).* (0888-8051). Retrieved from https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr327.pdf


