Health Based Guidance for Water
Health Risk Assessment Unit, Environmental Health Division
651-201-4899

Adopted as Rule: November 2023

Toxicological Summary for: Ethylbenzene

CAS**: 100-41-4**
Synonyms: Phenylethane, ethylbenzol, EB, 1-Ethylbenzene

Acute Non-Cancer Health Risk Limit ($nHRL_{Acute}$) = Not Derived (Insufficient Data)

Short-term Non-Cancer Health Risk Limit ($nHRL_{Short\text{-}term}$) = 40 µg/L

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

$$= \frac{\text{(0.06 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.290 L/kg-d)}^{**}}$$

= 41 rounded to **40 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5

Reference Dose/Concentration:	HED/Total UF = 18/300 = 0.06 mg/kg-d (Wistar rat)
Source of toxicity value:	Determined by MDH in 2018
Point of Departure (POD):	75 mg/kg-d (administered dose NOAEL, Mellert 2007)
Dose Adjustment Factor (DAF):	0.24, Body weight scaling, default (USEPA 2011) (MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 75 mg/kg-d x 0.24 = 18 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 studies via oral exposure including a lack of developmental and reproductive studies and toxicity data in multiple species)
Critical effect(s):	Changes in liver and kidney weight in males with corresponding histological changes; and blood chemistry changes at higher doses
Co-critical effect(s):	None
Additivity endpoint(s):	Hepatic (liver) system, Renal (kidney) system

Subchronic Non-Cancer Health Risk Limit ($nHRL_{Subchronic}$) = $nHRL_{Short\text{-}term}$ = 40 µg/L

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

$$= \frac{\text{(0.036 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.074 L/kg-d)}^{**}}$$

= 97 rounded to 100 µg/L

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5

Reference Dose/Concentration:	HED/Total UF = 10.68/300 = 0.036 mg/kg-d (Wistar rat)
Source of toxicity value:	ATSDR 2010
Point of Departure (POD):	6.61 µmol/L (Liver serum concentration $BMDL_{10}$, ATSDR 2010 analysis of Mellert 2007)
Dose Adjustment Factor (DAF):	Chemical-Specific PBPK model (ATSDR 2010)
Human Equivalent Dose (HED):	10.68 mg/kg-d HED from PBPK modelling conducted by ATSDR 2010
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 studies via oral exposure including a lack of developmental and reproductive studies and toxicity data in multiple species)
Critical effect(s):	Centrilobular hepatocyte hypertrophy
Co-critical effect(s):	None
Additivity endpoint(s):	Hepatic (liver) system

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 40 µg/L. Additivity endpoints: Hepatic (liver) system, Renal (kidney) system

Chronic Non-Cancer Health Risk Limit ($nHRL_{Chronic}$) = $nHRL_{Short\text{-}term}$ = 40 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Chronic Intake Rate, L/kg-d)}}$$

$$= \frac{\text{(0.011 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.045 L/kg-d)}^{**}}$$

= 48 rounded to 50 µg/L

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5

Reference Dose/Concentration:	HED/Total UF = 10.68/1000 = 0.011 mg/kg-d (Wistar rat)
Source of toxicity value:	ATSDR 2010
Point of Departure (POD):	6.61 µmol/L ($BMDL_{10}$ based on concentration of ethylbenzene in the liver, ATSDR 2010 analysis of Mellert 2007) (subchronic exposure)
Dose Adjustment Factor (DAF):	Chemical-Specific PBPK model (ATSDR 2010)
Human Equivalent Dose (HED):	10.68 mg/kg-d HED from PBPK modelling conducted by ATSDR 2010
Total uncertainty factor (UF):	1000
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, 10 for database uncertainty (lack of studies via oral exposure including a lack of developmental and reproductive studies and toxicity data in multiple species), and 3 for extrapolation to a chronic duration from a subchronic duration study
Critical effect(s):	Centrilobular hepatocyte hypertrophy
Co-critical effect(s):	None
Additivity endpoint(s):	Hepatic (liver) system

The Chronic nHRL must be protective of the short-term and subchronic exposures that occur within the chronic period and therefore, the Chronic nHRL is set equal to the Short-term nHRL of 40 µg/L. Additivity endpoints: Hepatic (liver) system, Renal (kidney) system

Cancer Health Risk Limit (cHRL) = Not Applicable

Cancer classification:	2B - possibly carcinogenic to humans (IARC 2000); D - not classifiable as to human carcinogenicity (USEPA 1991)
Slope factor (SF):	Not Applicable
Source of cancer slope factor (SF):	Not Applicable
Tumor site(s):	liver and kidney

Volatile: Yes (high)

Summary of Guidance Value History:

A noncancer chronic Health Risk Limit (HRL) of 700 µg/L was promulgated in 1993. In 2011, MDH derived short-term, subchronic, and chronic HRLs of 50 µg/L. In 2015, MDH evaluated the potential of incorporating an oral slope factor into the assessment. There was no new

information to support derivation of a cancer water guidance value. In 2018, MDH re-evaluated the existing HRLs, resulting in slightly lower Health Based Values (HBV). The 2018 HBVs are lower than the previous HRLs as a result of 1) use of MDH's most recent risk assessment methodology and 2) rounding to one significant digit. In 2020 MDH incorporated updated intake rates (US EPA 2019). Use of the updated intake rates did not result in any changes to the guidance values. In November 2023, the guidance values were adopted into Minnesota Rules, 4717.7860, as Health Risk Limits (HRLs).

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.

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested for specific effect?	No	No	No	Yes	Yes
Effects observed?	-[1]	-[2]	-[3]	Yes[4]	Yes[5]

Comments on extent of testing or effects:

[1] Endocrine activity of ethylbenzene has not been tested. However, an acute oral study noted decreases in peripheral hormone levels and possible effects on the estrus cycle in rats at doses 2000 or more times higher than the short-term reference dose. Rats and mice exposed to ethylbenzene in an inhalation exposure study showed an increased incidence of follicular cell hyperplasia in the thyroid gland and hyperplasia in the pituitary gland over the two-year study period.

[2] Immunotoxicity of ethylbenzene has only been studied by inhalation in laboratory animals. Some studies noted changes in immune cell numbers and increased spleen weights, but these results were not consistently seen across all studies. One general toxicity oral study noted decreased thymus weights in rats exposed at doses over 900 times higher than the short-term reference dose.

[3] Developmental effects have not been studied in laboratory animals exposed through the oral route. Effects observed in rat inhalation exposure studies include reduced fetal weight and skeletal and urogenital anomalies observed in the presence of maternal toxicity.

[4] Very limited information is available on reproductive effects following oral exposures. Decreases in hormone levels affecting the estrus cycle and uterine effects were indicated in a single acute reproductive study in laboratory animals with oral exposure at doses 2000 or more times higher than the short-term reference dose. Adverse reproductive effects were not observed in laboratory animals studies with inhalation exposure.

[5] Significant ototoxic effects have been reported, including loss of the outer hair cells in a part of the ear. This effect was observed in male rats at a single oral dose over 3000 times higher than the short-term reference dose. Ototoxicity has also been seen following inhalation exposure to ethylbenzene.

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