Adopted as Rule: March 21, 2011

Toxicological Summary for: Ethylbenzene

CAS**: 100-41-4**

Synonyms: Ethylbenzol, EB, phenylethane**Acute Non-Cancer Health Risk Limit (nHRL) = Not Derived (Insufficient Data)**

Short-term Non-Cancer Health Risk Limit (nHRL) = 50 µg/L

(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)
(Short-term Intake Rate, L/kg-d)

= (0.075 mg/kg-d) x (0.2) x (1000 µg/mg)
(0.289 L/kg-d)

= 51.9 rounded to **50 µg/L**

Reference Dose/Concentration:	0.075 mg/kg-d (laboratory animal)
Source of toxicity value:	MDH 2010
Point of Departure (POD):	75 mg/kg-d (NOAEL based on Mellert et al, 2007
Human Equivalent Dose (MDH, 2011):	Insufficient data for calculation
Total uncertainty factor:	1000
Uncertainty factor allocation:	10 for interspecies extrapolation, 10 for intraspecies variability, 10 for database deficiencies (to address concerns regarding lack of oral studies of developmental and reproductive toxicity, lack of toxicity data in more than 1 species, as well as limited evidence of toxicity that may be relevant to the oral route of exposure).
Critical effect(s):	Changes in liver and kidney weights (with histological changes; and blood chemistry changes at higher doses)
Co-critical effect(s):	None
Additivity endpoint(s):	Hepatic (liver) system, Renal (kidney) system
Secondary effect(s):	None

Subchronic Non-Cancer Health Risk Limit (nHRL) = $nHRL_{Short\text{-}term}$ = 50 µg/L

(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)
(Subchronic Intake Rate, L/kg-d)

= (0.048 mg/kg-d) x (0.2) x (1000 µg/mg)
(0.077 L/kg-d)

= 124 rounded to 100 µg/L

Reference Dose/Concentration:	0.048 mg/kg-d (laboratory animal)

Source of toxicity value:	MDH 2010
Point of Departure (POD):	48 mg/kg-d ($BMDL_{10}$, EPA 2009 based on Mellert et al, 2007)
Human Equivalent Dose (MDH, 2011):	Insufficient data for calculation
Total uncertainty factor:	1000
Uncertainty factor allocation:	10 for interspecies extrapolation, 10 for intraspecies variability, 10 for database deficiencies (to address concerns regarding lack of oral studies of developmental and reproductive toxicity, lack of toxicity data in more than 1 species, as well as limited evidence of ototoxicity that may be relevant to the oral route of exposure).
Critical effect(s):	Changes in liver (with histological changes; and blood chemistry changes at higher doses)
Co-critical effect(s):	None
Additivity endpoint(s):	Hepatic (liver) system
Secondary effect(s):	Renal (kidney) system

The Subchronic nHRL must be protective of the short-term exposure that occur within the subchronic period and therefore, the Subchronic nHRL is set equal to the Short-term nHRL of 50 µg/L. Additivity Endpoints: Liver System and Kidney System

Chronic Non-Cancer Health Risk Limit (nHRL) = 50 µg/L

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

$$= \frac{\text{(0.016 mg/kg-d) x (0.2) x (1000 µg/mg)}}{\text{(0.043L/kg-d)}}$$

= 74.4 rounded to 70 µg/L

Reference Dose/Concentration:	0.016 mg/kg-d (laboratory animal)
Source of toxicity value:	MDH 2010
Point of Departure (POD):	48 mg/kg-d ($BMDL_{10}$, EPA 2009 based on Mellert et al, 2007)
Human Equivalent Dose (MDH, 2011):	Insufficient data for calculation
Total uncertainty factor:	3000
Uncertainty factor allocation:	10 for interspecies extrapolation, 10 for intraspecies variability, 3 for subchronic-to-chronic extrapolation (database does not contain a chronic study and the liver effects were observed at a lower dose in the 90-day study than in the 28-day study (Mellert et al, 2007), and 10 for database deficiencies (to address concerns regarding lack of oral studies of developmental and reproductive toxicity, lack of toxicity data in more than 1 species, as well as limited evidence of ototoxicity that may be relevant to the oral route of exposure).
Critical effect(s):	Changes in liver and kidney weights (with histological changes; and blood chemistry changes at higher doses)
Co-critical effect(s):	None
Additivity endpoint(s):	Hepatic (liver) system

Secondary effect(s): Renal (kidney) 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 50 µg/L. Additivity Endpoints: Liver System and Kidney System

Cancer Health Based Value (cHRL) = Not Applicable

Cancer classification: D; not classifiable as to human carcinogenicity (EPA IRIS, 1991).
Slope factor: None
Source of slope factor: None
Tumor site(s): None

Volatile: Yes (highly)

Summary of Guidance Value History:
The short-term, subchronic and chronic HRLs (50 µg/L) are lower than the 1993/94 HRL value (700 µg/L) as the result of: 1) more recent toxicity studies; 2) use of MDH's most recent risk assessment methodology; and 3) rounding to one significant figure. In 2015 a re-evaluation of the lack of an oral slope factor was requested by MDH. There was no new information available to support derivation of a cancer water guidance value.

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	Yes	Yes	Yes
Effects observed?	- [1]	- [2]	Yes[3]	No	Yes[4]

Comments on extent of testing or effects:

[1] No oral endocrine studies available. There is an available reproduction study that reported that acute oral exposure to 500 or 1,000 mg/kg ethylbenzene decreases peripheral hormone levels and may block or delay the estrus cycle in female rats during the diestrus stage.

[2] No oral immunotoxicity studies were found. Observations reported in a 90-day rat study include a significant decrease in absolute and relative thymus in females treated with ≥250 mg/kg/day for 13 weeks, but no histopathological findings were observed.

[3] There are no oral developmental studies. There are several inhalation developmental studies. Results of studies in rats indicate that ethylbenzene produces reduced fetal weight, skeletal anomalies, and

anomalies and delayed development of urogenital tract; skeletal and urogenital anomalies were observed in the presence of maternal toxicity.

[4] Significant ototoxic effects were observed in male rats administered 900 mg/kg/day (the only dose tested) by gavage for 2 weeks. The authors reported an almost complete loss of the three rows of OHCs in the organ of Corti 10 days after the last exposure to ethylbenzene.

In male and female rats exposed to 75–750 mg/kg/day ethylbenzene by gavage for 13 weeks, no neurological effects were observed, based on negative results of motor activity tests and a functional observational battery (FOB). Note: female rats did show increased motor activity at the highest dose tested.

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EPA Toxicity and Exposure Assessment for Children's Health (TEACH) http://www.epa.gov/teach/

EPA Voluntary Children's Chemical Evaluation Program (VCCEP) http://www.epa.gov/oppt/vccep/pubs/chemmain.htm

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