

Adopted as Rule: November 2023

Toxicological Summary for: Toluene

CAS: 108-88-3

Synonyms: methyl-Benzene, methylbenzol, monomethyl benzene, phenylmethane, Tol, Toluol, tolu-sol

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

Short-term Non-Cancer Health Risk Limit (nHRL_{Short-term}) = 70 µg/L

$$\begin{aligned} & \frac{(\text{Reference Dose, mg/kg-d}) \times (\text{Relative Source Contribution}) \times (\text{Conversion Factor})}{(\text{Short-term Intake Rate, L/kg-d})} \\ &= \frac{(0.10 \text{ mg/kg-d}) \times (0.2)^* \times (1000 \text{ µg/mg})}{(0.290 \text{ L/kg-d})^{**}} \\ &= 68.9 \text{ rounded to } \mathbf{70 \text{ µg/L}} \end{aligned}$$

*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 = 3.08/30 = 0.10 mg/kg-d (CD-1 mice)
Source of toxicity value:	Determined by MDH in 2019
Point of Departure (POD):	22 mg/kg-d (NOAEL; Hsieh, 1989)
Dose Adjustment Factor (DAF):	0.14, Body weight scaling, default (USEPA, 2011b) (MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 22 mg/kg-d x 0.14 = 3.08 mg/kg-d
Total uncertainty factor (UF):	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics) and 10 for intraspecies variability
Critical effect(s):	Immunosuppression
Co-critical effect(s):	behavior changes due to nervous system effects, neurotransmitter level changes in the brain, changes in immune response
Additivity endpoint(s):	Immune system, Nervous system

Subchronic Non-Cancer Health Risk Limit (nHRL_{Subchronic}) = nHRL_{Short-term} = 70 µg/L

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

$$= \frac{(0.18 \text{ mg/kg-d}) \times (0.2)^* \times (1000 \text{ } \mu\text{g/mg})}{(0.074 \text{ L/kg-d})^{**}}$$

$$= 486 \text{ rounded to } 500 \text{ } \mu\text{g/L}$$

*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 = 54.7/300 = 0.18 mg/kg-d (F344 rats)
Source of toxicity value:	Determined by MDH in 2019
Point of Departure (POD):	238 mg/kg-d (BMDL ₁₀ ; USEPA, 2005 using NTP, 1990)
Dose Adjustment Factor (DAF):	0.23, Body weight scaling, default (USEPA, 2011b) (MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 238 mg/kg-d x 0.23 = 54.7 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 (concerns regarding lack of evaluation of immunological and neurotoxicity endpoints. Alterations in immune response and in behavior were reported in shorter-term studies at doses lower than the subchronic and chronic PODs.)
Critical effect(s):	Increased liver and kidney weights (with histological changes in higher doses)
Co-critical effect(s):	Increased liver weight, behavior changes due to nervous system effects, neurotransmitter level changes in the brain, changes in immune response and immunosuppression
Additivity endpoint(s):	Hepatic (liver) system, Immune system, Nervous system, Renal (kidney) 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 70 µg/L. Additivity endpoints: Immune system, Nervous system.

Chronic Non-Cancer Health Risk Limit (nHRL_{Chronic}) = nHRL_{Short-term} = 70 µg/L

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

$$= \frac{(0.055 \text{ mg/kg-d}) \times (0.2)^* \times (1000 \text{ } \mu\text{g/mg})}{(0.045 \text{ L/kg-d})^{**}}$$

$$= 244 \text{ rounded to } 200 \text{ } \mu\text{g/L}$$

*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: $\text{HED/Total UF} = 54.7/1000 = 0.055 \text{ mg/kg-d}$ (F344 Rat)
Source of toxicity value: Determined by MDH in 2019
Point of Departure (POD): 238 mg/kg-d (BMDL; NTP, 1990; subchronic exposure)
Dose Adjustment Factor (DAF): 0.23, Body weight scaling, default (USEPA, 2011b)(MDH, 2017)
Human Equivalent Dose (HED): $\text{POD} \times \text{DAF} = 238 \text{ mg/kg-d} \times 0.23 = 54.7 \text{ mg/kg-d}$
Total uncertainty factor (UF): 1000
Uncertainty factor allocation: 3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, 10 for database uncertainty (For concerns regarding lack of evaluation of immunological and neurotoxicity endpoints. Alterations in immune response and in behavior were reported in shorter-term studies at doses lower than the subchronic and chronic PODs), and 3 for subchronic to chronic extrapolation
Critical effect(s): Increased liver and kidney weights (with histological changes in higher doses)
Co-critical effect(s): Increased liver weight, behavior changes due to nervous system effects, neurotransmitter level changes in the brain, changes in immune response and immunosuppression
Additivity endpoint(s): Hepatic (liver) system, Immune system, Nervous system, Renal (kidney) system

The Chronic nHRL must be protective of the short-term exposures that occur within the chronic period and therefore, the Chronic nHRL is set equal to the Short-term nHRL of 70 µg/L. Additivity endpoints: Immune system, Nervous system.

Cancer Health Risk Limit (cHRL) = Not Applicable

Cancer classification: Inadequate information to assess the carcinogenic potential in humans (USEPA, 2005)
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 1000 µg/L was promulgated in 1993/1994. Short-term, subchronic, and chronic health-based values (HBV) of 200 µg/L were derived in 2009 and were promulgated as HRLs in 2011. In 2019, MDH re-evaluated the non-cancer HRLs, resulting in lower

water guidance values of 70 µg/L for the short-term, subchronic, and chronic durations. The changes to existing guidance were the result of 1) using MDH’s most recent risk assessment methodology and 2) rounding to one significant digit. In 2020 MDH updated intake rates (US EPA 2019). Use of the updated intake rates did not result in changes to the 2019 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	Yes	Yes	No	Yes
Effects observed?	- ¹	Yes ²	Yes ³	- ⁴	Yes ⁵

Comments on extent of testing or effects:

¹Endocrine activity of toluene has not been studied. However, increased adrenocorticotrophic hormone (ACTH) was observed at the highest dose tested in a short-term drinking water study in mice. The biological significance of this limited data is uncertain.

²The short-term reference dose is based on immunosuppression (decreased lymphocyte culture responses and decreased antibody PFC responses) in male mice. The immunological effect of decreased IL-2 production was seen at similar doses in other studies, and was included as co-critical effect for the subchronic and chronic durations. In a single dose study, additional immunological effects were seen at doses approximately 800 times higher than the short-term RfD. A database uncertainty factor was added to the subchronic and chronic RfDs to account for a lack of immunological studies at longer durations.

³Neurodevelopmental behavioral effects as well as other developmental effects (fetal body weight and organ weight decreases, kidney pelvis dilation) have been seen at doses 1,000 (fetal body weight and organ weight decreases) and up to 3,000 (kidney pelvis dilation) times higher than the short-term RfD.

⁴Oral exposure multigenerational or reproductive studies have not been conducted. No functional reproductive effects were observed in single dose developmental studies at doses up to 3,000 times the short-term RfD. Increased testicular weights were observed at high doses in a systemic subchronic study, but reproductive performance was not evaluated.

⁵Several short-term and subchronic studies have reported changes in brain neurotransmitter levels, histological changes in the brain, and mild behavioral changes in rodents. Changes in neurotransmitter levels as well as mild behavior changes were observed at similar doses to the critical effects dose ranges, and were included as co-critical effects for the short-term, subchronic, and chronic durations. A database uncertainty factor was added to the subchronic and chronic RfDs to account for a lack of neurological studies at longer durations.

Resources Consulted During Review:

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