Health-Based Guidance for Water
Health Risk Assessment Unit, Environmental Health Division
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Toxicological Summary for: *o*-Toluidine

CAS: 95-53-4
Synonyms: *ortho*-Toluidine; 2-Methylaniline; 2-Toluidine; 2-Methylbenzenamine; *o*-Tolylamine

Acute Non-Cancer Health-Based Value ($nHBV_{Acute}$) = Not Derived (Insufficient Data)

Short-term Non-Cancer Health-Based Value ($nHBV_{Short\text{-}term}$) = 10 µg/L

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

$$= \frac{\text{(0.021 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.290 L/kg-d)}^{**}}$$

= 14.5 rounded to **10 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 = 6.32/300 = 0.021 mg/kg-d (F344 rat)
Source of toxicity value:	Determined by MDH in 2026
Point of Departure (POD):	30.1 mg/kg-d (administered dose NOAEL, Haskell Laboratory 1994)
Dose Adjustment Factor (DAF):	Body weight scaling, default [US EPA 2011 and MDH 2017]
Human Equivalent Dose (HED):	POD x DAF = 30.1 mg/kg-d x 0.21 = 6.32 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 to account for the lack of adequate reproductive, developmental, and neurotoxicity studies
Critical effect(s):	Bladder epithelial cell proliferation
Co-critical effect(s):	Elevated liver enzymes and lipid peroxidation
Additivity endpoint(s):	Hepatic (liver) system, Renal (kidney) system

Subchronic Non-Cancer Health-Based Value ($nHBV_{Subchronic}$) = 10 µg/L

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

$$= \frac{\text{(0.021 mg/kg-d)}^{\#} \text{ x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.074 L/kg-d)}^{**}}$$

= 56.8 rounded to 60 µg/L

#The calculated subchronic RfD (0.035 mg/kg/day) based on methemoglobinemia is higher than the short-term RfD (0.021mg/kg-d), which is based on renal (kidney) system effects. The subchronic RfD must be protective of all types of adverse effects that could occur as a result of subchronic exposure, including short-term effects (MDH 2008, page 34). Therefore, the short-term RfD is used in place of the calculated subchronic RfD when deriving subchronic water guidance.
*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.

The Subchronic nHBV must be protective of shorter duration exposures that occur within the subchronic duration and therefore, the Subchronic nHBV is set equal to the Short-term nHBV of 10 µg/L. Additivity endpoints: Hematological (blood) system, Hepatic (liver) system, Renal (kidney) system

Chronic Non-Cancer Health-Based Value ($nHBV_{Chronic}$) = 10 µg/L

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

$$= \frac{\text{(0.020 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.045 L/kg-d)}^{**}}$$

= 88.9 rounded to 90 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.

The Chronic nHBV must be protective of shorter duration exposures that occur within the chronic period and therefore, the Chronic nHBV is set equal to the Short-term nHBV of 10 µg/L. Additivity endpoints: Hematological (blood) system, Hepatic (liver) system, Renal (kidney) system

Cancer Health-Based Value (cHBV) = 6 µg/L

$$\frac{\text{(Additional Lifetime Cancer Risk) x (Conversion Factor)}}{[(SF \times ADAF_{<2\ yr} \times IR_{<2yr} \times 2) + (SF \times ADAF_{2-<16\ yr} \times IR_{2-<16yr} \times 14) + (SF \times ADAF_{16+\ yr} \times IR_{16+yr} \times 54)] / 70}$$

$$= \frac{\text{(1E-5) x (1000 µg/mg)}}{[(0.016 \times 10^{*} \times 0.155\ \text{L/kg-d}^{**} \times 2) + (0.016 \times 3^{*} \times 0.040\ \text{L/kg-d}^{**} \times 14) + (0.016 \times 1^{*} \times 0.042\ \text{L/kg-d}^{**} \times 54)] / 70}$$

= 6.21 rounded to **6 µg/L**

*ADAF (Age-dependent adjustment factor) and Lifetime Adjustment Factor: MDH 2008, Section IV.E.2.
**Intake Rate: MDH 2008, Section IV.E.2. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Cancer classification: Known to be a human carcinogen (NTP 2021); Likely to Be Carcinogenic to Humans (EPA 2005)

Slope factor (SF):	1.6×10^{-2} $(mg/kg\text{-}d)^{-1}$ (subcutaneous fibroma and fibrosarcoma in male CD rats, Weisburger 1978)
Source of cancer slope factor (SF):	EPA 2012
Tumor site(s):	Bladder, Blood vessels, Bone, Liver, Skin and connective tissue, Spleen

Volatile: Yes (low)

Summary of Guidance Value History:
o-Toluidine has not previously been evaluated by MDH.

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	No
Effects observed?	-[1]	-[2]	-[3]	Yes[4]	-[5]

[1] No endocrine studies were identified for *o*-toluidine oral exposure in experimental animals. One rat study administering *o*-toluidine via injection for 7 days reported significant decreases in testosterone formation.

[2] No immunotoxicity studies were identified for *o*-toluidine.

[3] Though *o*-toluidine has not been tested for developmental toxicity in oral animal studies, another chemical in the same class has been shown to produce developmental effects with oral exposure. Dermal *o*-toluidine exposure to rats has been reported to induce delays in body weight gain, increased weight of kidney, ovary, and heart, and decreased weight of lung, spleen, and liver in offspring. The lack of developmental oral studies is, in part, the basis of a database uncertainty factor of 10, which was added to the *o*-toluidine reference dose.

[4] Information on reproductive effects of oral exposure to *o*-toluidine is limited to changes in weight of reproductive organs in male rats. Increased relative testis weight was reported in subchronic and chronic durations at *o*-toluidine doses 2500 times higher than the short-term reference dose. Increased relative epididymis weight was reported in a chronic study at an *o*-toluidine dose 2900 times higher than the chronic reference dose. *o*-Toluidine exposure through skin resulted in reproductive effects in rats, including changes in ovarian cycle, ovarian structure, changes in sperm production, and changes in ability to reproduce in females. The lack of adequate oral reproductive studies is, in part, the basis of a database uncertainty factor of 10, which was added to the *o*-toluidine reference dose.

[5] No oral neurotoxicity studies in experimental animals were identified for *o*-toluidine. Inhaled *o*-toluidine in male rats induced tremors and muscle spasms in one study. Occupational exposure in humans (dermal

and/or inhalation) has been associated with central nervous system depression in humans, including dizziness, headache, and confusion.

Resources Consulted During Review:

Australian Government National Industrial Chemicals Notification and Assessment Scheme (NICNAS). *Benzenamine, 2-methyl-: Human health tier II assessment CAS Number: 95-53-4*. Retrieved August 2025 from https://cdnservices.industrialchemicals.gov.au/statements/IMAP_1158%20-%20IMAP%20Assessment%20-%2018%20September%202014.pdf

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