

Adopted as Rule: November 2023

## Toxicological Summary for: 1,2,4-Trimethylbenzene; 1,3,5-Trimethylbenzene; and 1,2,3-Trimethylbenzene

CAS: 95-63-6; 108-67-8; 526-73-8

1,2,4-Trimethylbenzene Synonyms: 1,2,4-TMB; pseudocumene; asymmetrical trimethylbenzene

1,3,5-Trimethylbenzene Synonyms: 1,3,5-TMB; mesitylene; symmetrical trimethylbenzene

1,2,3-Trimethylbenzene Synonyms: 1,2,3-TMB; hemimellitene; hemellitol; pseudocumol

The trimethylbenzene (TMB) isomers, 1,2,4-TMB, 1,2,3-TMB, and 1,3,5-TMB, have similar chemical structures and properties. Toxicological studies in laboratory animals demonstrate similar health effects at similar dose levels and durations (USEPA 2016). Based on these similarities, the Minnesota Department of Health (MDH) used the information provided in the 2016 USEPA IRIS review to derive HBVs for the short-term, subchronic, and chronic durations that are applicable for all three isomers.

**Acute Non-Cancer Health Risk Limit (nHRL<sub>Acute</sub>) = Not Derived (Insufficient Data)**

**Short-term Non-Cancer Health Risk Limit (nHRL<sub>Short-term</sub>) = 30 µg/L**

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

$$= \frac{(0.042 \text{ mg/kg-d}) \times (0.2)^* \times (1000 \text{ µg/mg})}{(0.290 \text{ L/kg-d})^{**}}$$

$$= 28.9 \text{ rounded to } \mathbf{30 \text{ µg/L}}$$

\*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 = 4.2/100 = 0.042 mg/kg-d (Wistar rat)
Source of toxicity value:	Determined by MDH in 2018
Point of Departure (POD):	22.0 mg/m <sup>3</sup> (MDH calculated continuous inhalation exposure based on Gralewicz et al 1997 for NOAEL of 123 mg/m <sup>3</sup> identified in USEPA, 2016)
Dose Adjustment Factor (DAF):	0.19 mg/kg-d per mg/m <sup>3</sup> (ratio of subchronic oral POD <sub>HED</sub> (3.5 mg/kg-d) to inhalation POD <sub>HEC</sub> (18.15 mg/m <sup>3</sup> ) from (USEPA, 2016). Chemical-Specific PBPK model-based route-to-route extrapolation.)

Human Equivalent Dose (HED):  $POD \times DAF = 22.0 \text{ mg/m}^3 \times 0.19 \text{ mg/kg-d per mg/m}^3 = 4.2 \text{ mg/kg-d}$

Total uncertainty factor (UF): 100

Uncertainty factor allocation: 3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 3 for database uncertainty (lack of a multi-generation developmental/reproductive study and lack of a neurodevelopmental study)

Critical effect(s): Central nervous system changes (increased open field grooming), decreased pain sensitivity (lowered step down latency and paw lick latency)

Co-critical effect(s): Central nervous system changes (impaired learning of passive avoidance and deleterious effects on locomotor activity), decreased pain sensitivity (paw lick latency)

Additivity endpoint(s): Nervous system

**Subchronic Non-Cancer Health Risk Limit ( $nHRL_{\text{Subchronic}}$ ) =  $nHRL_{\text{Short-term}}$  = 30  $\mu\text{g/L}$**

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

$$= \frac{(0.035 \text{ mg/kg-d}) \times (0.2)^* \times (1000 \text{ } \mu\text{g/mg})}{(0.074 \text{ L/kg-d})^{**}}$$

$$= 94.5 \text{ rounded to } 90 \text{ } \mu\text{g/L}$$

\*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:  $HED/\text{Total UF} = 3.5/100 = 0.035 \text{ mg/kg-d}$  (Wistar rat)

Source of toxicity value: USEPA, 2016

Point of Departure (POD):  $POD_{\text{ADJ}}$  (0.099 mg/L) weekly average blood concentration resulting from an inhalation  $POD_{\text{HEC}}$  of  $18.15 \text{ mg/m}^3$  (dose metric from Korsak and Rydzynski, 1996 calculated by EPA, Table 2-5, USEPA, 2016)

Dose Adjustment Factor (DAF): Chemical-Specific PBPK model as calculated by USEPA, 2016 (USEPA, 2016)

Human Equivalent Dose (HED): 3.5 mg/kg-d (PBPK basis as calculated by USEPA, 2016 (page 2-34))

Total uncertainty factor (UF): 100

Uncertainty factor allocation: 3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 3 for database

uncertainty (lack of a multi-generation developmental/reproductive study and lack of a neurodevelopmental study)

Critical effect(s): Decreased pain sensitivity (paw lick latency)

Co-critical effect(s): Central nervous system changes (impaired learning of passive avoidance and deleterious effects on locomotor activity), decreased pain sensitivity (paw lick latency)

Additivity endpoint(s): Nervous system

**The Subchronic nHRL must be protective of short-term exposures that occur within the subchronic period and therefore, the Subchronic nHRL is set equal to the Short-term nHRL of 30 µg/L. Additivity endpoints: Nervous system**

**Chronic Non-Cancer Health Risk Limit (nHRL<sub>Chronic</sub>) = (nHRL<sub>Short-term</sub>) = 30 µg/L**

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

$$= \frac{(0.012 \text{ mg/kg-d}) \times (0.2)^* \times (1000 \text{ µg/mg})}{(0.045 \text{ L/kg-d})^{**}}$$

$$= 53.3 \text{ rounded to } 50 \text{ µg/L}$$

\*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 = 3.5/300 = 0.012 mg/kg-d (Wistar rat)

Source of toxicity value: USEPA, 2016

Point of Departure (POD): POD<sub>ADJ</sub> (0.099 mg/L) weekly average blood concentration resulting from an inhalation POD<sub>HEC</sub> of 18.15 mg/m<sup>3</sup> (dose metric from Korsak and Rydzynski, 1996 calculated by EPA, Table 2-5, USEPA, 2016) (subchronic exposure)

Dose Adjustment Factor (DAF): Chemical-Specific PBPK model as calculated by USEPA, 2016 (USEPA, 2016)

Human Equivalent Dose (HED): 3.5 mg/kg-d (PBPK basis as calculated by USEPA, 2016 (page 2-34))

Total uncertainty factor (UF): 300

Uncertainty factor allocation: 3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, 3 for database uncertainty (lack of a multi-generation developmental/reproductive study and lack of a neurodevelopmental study), and 3 for subchronic

to chronic extrapolation (use of subchronic study and slight potential for an increased severity of effects with increasing duration)

Critical effect(s): Decreased pain sensitivity (paw lick latency)

Co-critical effect(s): Central nervous system changes (impaired learning of passive avoidance and deleterious effects on locomotor activity), decreased pain sensitivity (paw lick latency)

Additivity endpoint(s): Nervous 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 30 µg/L. Additivity endpoints: Nervous system**

#### **Cancer Health Risk Limit (cHRL) = 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:**

Short-term, subchronic, and chronic duration health-based values (HBV) of 100 µg/L were derived for 1,3,5-TMB in 2008 and promulgated as health-risk limits (HRL) in 2009. Short-term, subchronic, and chronic duration risk assessment advice (RAA) of 100 µg/L was derived for 1,2,4-TMB in 2010, and was based on the MDH guidance values for 1,3,5-TMB. The derived guidance values for 1,3,5-TMB and 1,2,4-TMB were re-evaluated in 2018. The re-evaluation included one additional TMB isomer, 1,2,3-TMB. All three isomers were evaluated together for the purposes of updating and deriving guidance values. As a result of the 2018 re-evaluation, short-term, subchronic, and chronic HBVs of 30 µg/L were derived for all three TMB isomers (1,2,3-; 1,2,4-; and 1,3,5-). The values are lower than previous MDH guidance as a result of 1) incorporation of more recent toxicological information, 2) route-to-route extrapolation using US EPA PBPK results, and 3) rounding to one significant digit. In 2020 MDH incorporated updated intake rates (US EPA 2019). Using the updated intake rates did not result in changes to the 2018 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	Yes	Yes	Yes
Effects observed?	_1	_2	Yes <sup>3</sup>	Yes <sup>4</sup>	Yes <sup>5</sup>

**Comments on extent of testing or effects:**

<sup>1</sup>Endocrine activity of the trimethylbenzene isomers has not been tested. There is some evidence that other alkylbenzenes may modulate endocrine function and signaling. Alkylbenzene alterations of hormone concentrations may be tied to alterations in fetal growth and the development of inflammatory responses.

<sup>2</sup>Immunotoxicity was not directly tested with trimethylbenzene isomers. Studies examining nonimmune endpoints reported increases in immune and inflammatory cells and alveolar macrophages in lung lavage fluid. The increased macrophages could potentially indicate immune suppression activity at high doses in laboratory animals.

<sup>3</sup>Limited information is available on the developmental effects of the trimethylbenzene isomers. Decreased fetal body weight in decreased maternal body weight was observed in laboratory animals at doses over 3000 times higher than the reference dose for the short-term duration. The lack of a multigenerational study is addressed with a database uncertainty factor for all three durations.

<sup>4</sup> Limited information is available on the reproductive effects of the trimethylbenzene isomers. Decreased maternal body weight in addition to decreased fetal body weight was observed in laboratory animals at doses over 3000 times higher than the reference dose for the short-term duration. The lack of a multi-generational study is addressed with a database uncertainty factor for all three durations.

<sup>5</sup>The reference doses for the short-term, subchronic, and chronic durations are based on neurotoxicity endpoints (central nervous system disturbances and decreased pain sensitivity) observed in inhalation studies. Co-critical effects are also based on the same nervous system effects at doses up to the non-PBPK adjusted dose associated with the reference dose.

**Resources Consulted During Review:**

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