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Chemical Name: 1,3,5 - Trimethylbenzene

CAS: 108-67-8

Synonyms: Mesitylene, Symmetrical Trimethylbenzene, sym-Trimethylbenzene

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

Short-term Non-Cancer Health Risk Limit (nHRL_{short-term}) = 100 ug/L

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

$$= \frac{(0.14 \text{ mg/kg/d}) \times (0.2) \times (1000 \text{ ug/mg})}{(0.289 \text{ L/kg-d})}$$

$$= 96.9 \text{ rounded to } \mathbf{100 \text{ ug/L}}$$

Toxicity value: 0.14 mg/kg-d (laboratory animal)
Source of toxicity value: MDH 2007
Point of Departure: 143 mg/kg-d (NOAEL, IIT Research Inst., 1995b)
Human Equivalent Dose Adjustment: None (inadequate information)
Total uncertainty factor: 1000
UF allocation: 10 interspecies, 10 intraspecies, 10 database gaps (absence of oral reproductive/developmental toxicity data as well as neurological and immunological studies (potential sensitive endpoints based on inhalation studies))
Critical effect(s): Decreased body weight, blood chemistry changes (including changes in cholesterol levels), increases in relative liver weight.
Co-critical effect(s): None identified
Additivity endpoint(s): Hepatic (liver) system
Secondary effect(s): None

Subchronic Non-Cancer Health Risk Limit (nHRL_{subchronic}) = nHRL_{short-term} = 100 ug/L

$$= \frac{(\text{Reference Dose, mg/kg/d}) \times (\text{Relative Source Contribution}) \times (\text{Conversion Factor})}{(\text{Subchronic intake rate, L/kg/d})}$$

$$= \frac{(0.14 \text{ mg/kg/d}) \times (0.2) \times (1000 \text{ ug/mg})}{(0.077 \text{ L/kg-d})}$$

$$= 364 \text{ rounded to } 400 \text{ ug/L}$$

Toxicity value: 0.14 mg/kg-d (laboratory animal)
Source of toxicity value: MDH 2007
Point of Departure: 143 mg/kg-d (NOAEL, IIT Research Inst., 1995b)
Human Equivalent Dose Adjustment: None (inadequate information)
Total uncertainty factor: 1000
UF allocation: 10 interspecies, 10 intraspecies, 10 database gaps (absence of oral reproductive/developmental toxicity data as well as neurological and immunological studies (potential sensitive endpoints based on inhalation studies))
Critical effect(s): Decreased body weight, blood chemistry changes (including changes in cholesterol levels), increases in relative liver and kidney weight, clinically observed wet/discolored inguinal fur.
Co-critical effect(s): None identified
Additivity endpoint(s): Hepatic (liver) system, renal (kidney) system
Secondary effect(s): None

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 100 ug/L. Additivity Endpoints: Hepatic (Liver) System.

Chronic Non-Cancer Health Risk Limit (nHRL_{chronic}) = nHRL_{short-term} = 100 ug/L

$$= \frac{(\text{Reference Dose, mg/kg/d}) \times (\text{Relative Source Contribution}) \times (\text{Conversion Factor})}{(\text{Chronic intake rate, L/kg/d})}$$

$$= \frac{(0.048 \text{ mg/kg/d}) \times (0.2) \times (1000 \text{ ug/mg})}{(0.043 \text{ L/kg-d})}$$

$$= 223 \text{ rounded to } 200 \text{ ug/L}$$

Toxicity value: 0.048 mg/kg-d (laboratory animal)
Source of toxicity value: MDH 2007
Point of Departure: 143 mg/kg-d (NOAEL, NCEA, IIT Research Inst., 1995)

Human Equivalent Dose Adjustment: None (inadequate information)
 Total uncertainty factor: 3000
 UF allocation: 10 interspecies, 10 intraspecies, 10 database gaps (absence of oral reproductive/developmental toxicity data as well as neurological and immunological studies (potential sensitive endpoints based on inhalation studies)). An oral chronic study for 1,3,5-TMB is not available, however, a 2 year oral carcinogenicity study has been conducted on 1,2,4-TMB. A slight decrease in survival was reported in this study at a time adjusted dose level (457 mg/kg-d) similar to the 1,3,5-TMB critical study LOAEL (429 mg/kg-d). Effects observed at 14, 30 and 90 days do not indicate that longer durations would result in a significantly lower point of departure, therefore an UF of 3 has been selected for extrapolation from subchronic to chronic duration.

Critical effect(s): Decreased body weight, blood chemistry changes (including changes in cholesterol levels), increases in relative liver and kidney weight, clinically observed wet/discolored inguinal fur.

Co-critical effect(s): None identified
 Additivity endpoint(s): Hepatic (liver) system, renal (kidney) system
 Secondary effect(s): None

The Chronic HRL 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 100 ug/L. Additivity Endpoints: Hepatic (Liver) System.

Cancer Health Risk Limit (cHRL) = Not Applicable

Volatile: Yes (highly volatile)

Summary of changes since 1993/1994 HRL promulgation:

No. 1993/94 cHRL or nHRL value had been derived. An HBV value of 300 ug/L (liver and kidney) was derived in 2002. The 2007 multiple duration (short-term, sub-chronic, chronic) nHRL values are 3-fold lower as the result of using more recent, higher intake rate data and rounding to one significant digit.

Summary of toxicity testing for health effects identified in the Health Standards Statute:

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested?	No	No	Yes	No	Yes
Effects?	--	Unclear ¹	Yes ²	--	Yes ³

Note: 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. Most chemicals have been subject to multiple studies in which researchers identify a dose where no effects were observed, and the lowest dose that caused one or more effects. A toxicity value based on the effect observed at the lowest dose across all available studies is considered protective of all other effects that occur at higher doses.

-- indicates that no specific tests for that effect were conducted, and that effect was not observed as a secondary effect in any other study used in the HRL evaluation.

Comments on extent of testing or effects:

¹ Not specifically tested. Increased white blood cell count with corresponding increases in neutrophil and lymphocytes were observed in one study but this observation was not observed in an additional study conducted by the same investigators. Limited data from inhalation studies suggests that the immune system may be a sensitive endpoint.

² Developmental toxicity was tested only in inhalation studies. Effects include decrease in maternal body weight gain and food consumption, and reduction in fetal body weight.

³ Neurotoxicity was tested only in inhalation studies. Effects include excitation followed by narcosis and ataxia.

References:

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Maltoni, C., Ciliberti A., Pinto, C., Soffritti M., Belpoggi F. , and Menarini L. 1997. Results of long-term experimental carcinogenicity studies of the effects of gasoline, correlated fuels, and major aromatics on rats. Ann. New York Acad. Sci. 837: 15-52 (Note: provides data on 1,2,4-trimethylbenzene)

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