



## CHEMICAL UPDATE WORKSHEET

<b>Chemical Name:</b>	<b>1,2,4-Trimethylbenzene</b>
<b>CAS #:</b>	<b>95-63-6</b>
<b>Revised By:</b>	RRD Toxicology Unit
<b>Revision Date:</b>	August 19, 2015

### (A) Chemical-Physical Properties

	Part 201 Value	Updated Value	Reference Source	Comments
<b>Molecular Weight (g/mol)</b>	120.2	120.20	EPI	EXP
<b>Physical State at ambient temp</b>	Liquid	Liquid	MDEQ	
<b>Melting Point (°C)</b>	---	-43.80	EPI	EXP
<b>Boiling Point (°C)</b>	168.89	169.30	EPI	EXP
<b>Solubility (ug/L)</b>	55890	57000	EPI	EXP
<b>Vapor Pressure (mmHg at 25°C)</b>	2.13	2.10E+00	EPI	EXP
<b>HLC (atm-m<sup>3</sup>/mol at 25°C)</b>	5.87E-3	6.16E-03	EPI	EXP
<b>Log Kow (log P; octanol-water)</b>	3.67	3.63	EPI	EXP
<b>Koc (organic carbon; L/Kg)</b>	965	614.3	EPI	EST
<b>Ionizing Koc (L/kg)</b>		NR	NA	NA
<b>Diffusivity in Air (Di; cm<sup>2</sup>/s)</b>	0.08	6.07E-02	W9	EST
<b>Diffusivity in Water (Dw; cm<sup>2</sup>/s)</b>	8.0E-6	7.92E-06	W9	EST
<b>Soil Water Partition Coefficient (Kd; inorganics)</b>	NR	NR	NA	NA

	Part 201 Value	Updated Value	Reference Source	Comments
Flash Point (°C)	112 F	44	CRC	EXP
Lower Explosivity Level (LEL; unit less)	0.009	0.009	CRC	EXP
Critical Temperature (K)		649.17	EPA2004	EXP
Enthalpy of Vaporization (cal/mol)		9.37E+03	EPA2004	EXP
Density (g/mL, g/cm <sup>3</sup> )		0.8758	CRC	EXP
EMSOFT Flux Residential 2 m (mg/day/cm <sup>2</sup> )	1.82E-06	2.63E-05	EMSOFT	EST
EMSOFT Flux Residential 5 m (mg/day/cm <sup>2</sup> )	1.82E-06	5.81E-05	EMSOFT	EST
EMSOFT Flux Nonresidential 2 m (mg/day/cm <sup>2</sup> )	2.18E-06	4.12E-05	EMSOFT	EST
EMSOFT Flux Nonresidential 5 m (mg/day/cm <sup>2</sup> )	2.18E-06	8.78E-05	EMSOFT	EST

**(B) Toxicity Values/Benchmarks**

	Part 201 Value	Updated Value	Source/Reference/Date	Comments/Notes/Issues
Reference Dose (RfD) (mg/kg/day)	0.14	2.0E-2	IRIS, 2013	
RfD details	<p>RfD derived using 1,3,5-TMB toxicity data, based on similarities in excretion of metabolites in rats and quantitative structure activity relationship analysis predictions. Subchronic (90-day) oral gavage study with Sprague-Dawley rats on 1,3,5-TMB (IITRI, 1995). Adjusted NOAEL for dose administered 5/7 days/week = 143 mg/kg; UF = 1000; 100 for intra and interspecies extrapolation and 10 for subchronic to chronic extrapolation.</p>	<p><b>Tier 1 source:</b>  <b>IRIS:</b>  <b>Basis:</b> Route-to-route extrapolation of the point of departure based on the neurotoxic effects (i.e., decreased pain sensitivity) observed by Korsak and Rydzynski (1996) following inhalation exposure to 1,2,4-TMB as presented in the IRIS Toxicological Review of Trimethylbenzene (August 2013 Revised External Review Draft). EPA expects to receive final peer review report from the Science Advisory Board in 2015.</p> <p><b>Tier 1 Source:</b>  <b>IRIS:</b> No IRIS file for 1,2,4-TMB is available at this time. Rather, the Toxicological Review of Trimethylbenzenes (August 2013 Revised External Review Draft) reports an RfD value of 2E-2 mg/kg/d for 1,2,4-TMB based on the route-to-route extrapolation from a 1,2,4-TMB inhalation exposure study.</p> <p><b>Critical Study:</b> Korsak, Z. and K. Rydzynski. (1996) Neurotoxic effects of acute and subchronic inhalation exposure to Trimethylbenzene isomers (pseudocumene, mesitylene, hemimellitene) in rats. Int. J. Occup. Med. Environ. Health. 9:341–349.</p> <p><b>Methods:</b> The available data supports route-to-route extrapolation of 1,2,4-TMB inhalation data to an oral exposure. Sufficient evidence exists that demonstrates similar qualitative profiles of metabolism and patterns of parent compound distribution across exposure routes. Further, no evidence exists that would suggest toxicity profiles would differ to a substantial degree between oral and inhalation exposures. The Hissink et al. (2007) PBPK model for 1,2,4-TMB, assuming continuous oral ingestion and 100% absorption of the ingested 1,2,4-TMB by constant infusion of the oral dose into the liver, was used by EPA to develop the human equivalent dose (HED) point of departure (POD) for the RfD derivation.</p> <p><b>Critical effect:</b> Altered CNS function, measured as decreased pain sensitivity in rats.</p> <p><b>End point or Point of Departure (POD):</b> <math>POD_{HED} = 6.3 \text{ mg/kg/d}</math>.</p> <p><b>Uncertainty Factors:</b> UF = 300 (10 for intraspecies variability and 3 each for interspecies extrapolation, subchronic-to-chronic, and database deficiencies).</p>		Complete



	Part 201 Value	Updated Value	Source/Reference/Date	Comments/Notes/Issues
		<p><b>Source and date:</b> IRIS Toxicological Review of Trimethylbenzene (August 2013, Revised External Review Draft).</p> <p><b>Tier 2 Sources:</b>  <b>PPRTV (6/11/2007):</b> Per PPRTV, the database for 1,2,4-trimethylbenzene is inadequate to derive a provisional RfD.</p> <p><b>MRL:</b> No MRL record for 1,2,4-TMB is available at this time.</p> <p><b>Tier 3 Source:</b>  <b>MDEQ/RRD (02/11/1998):</b> RfD = 1.4E-1 mg/kg/d.                      Per DEQ-CCD, RfD derived using 1,3,5-TMB toxicity data, based on similarities in excretion of metabolites in rats and quantitative structure activity relationship analysis predictions. Subchronic (90-day) oral gavage study with Sprague-Dawley rats on 1,3,5-TMB (IITRI, 1995). Adjusted NOAEL for dose administered 5/7 days/week = 143 mg/kg; UF = 1,000; 100 for intra and interspecies extrapolation and 10 for subchronic to chronic extrapolation. Previous RfD basis was oral rat LD<sub>50</sub> of 4,200 mg/kg for 98% 1,2,4-TMB; oral LD<sub>50</sub> adjusted to 4,120 mg/kg for 100% 1,2,4-TMB. (United States Testing Co., 1994-Unpublished study).</p>		
<b>Oral Cancer Slope Factor (CSF) (mg/kg-day)<sup>-1</sup></b>	NA	NA	MDEQ, 2015	
<b>CSF details</b>	NA	<p><b>Tier 1 Source:</b>  <b>IRIS:</b> No IRIS file is available at this time. Per the August 2013 revised external review draft of the IRIS Toxicological Review of Trimethylbenzenes, the database for 1,2,4-TMB provides “inadequate information to assess carcinogenic potential”. This characterization is based on the limited and equivocal genotoxicity findings, and the lack of data indicating carcinogenicity in experimental animal species via any route of exposure. Information available on which to base a quantitative cancer assessment is lacking, and thus, no cancer risk estimates for either oral or inhalation exposures are derived.</p> <p><b>Tier 2 Sources:</b></p>		Complete



	Part 201 Value	Updated Value	Source/Reference/Date	Comments/Notes/Issues
		<p><b>PPRTV (06/11/2007):</b> Per PPRTV, collectively, the available carcinogenicity and genotoxicity data do not adequately assess the carcinogenic potential of 1,2,4-trimethylbenzene in humans or animals. Under the current U.S. EPA (2005) cancer guidelines, the human and animal data are inadequate for a determination of the human carcinogenic potential of 1,2,4-trimethylbenzene. There are no appropriate human or animal data from which to derive an oral slope factor for 1,2,4-trimethylbenzene.</p> <p><b>MRL:</b> NA; MRLs are for non-cancer effects only.</p> <p><b>Tier 3 Source:</b></p> <p><b>MDEQ:</b> Per DEQ-CCD, no oral slope factor value is available for 1,2,4-TMB at this time.</p>		
<b>Reference Concentration (RfC) or Initial Threshold Screening Level (ITSL) (<math>\mu\text{g}/\text{m}^3</math>)</b>	1.23E+3	7.0E+0	PPRTV, 2007	
<b>RfC/ITSL details</b>	<p>This ITSL is based on occupational exposures causing eyes, nose and throat irritation. Because 1,2,4-trimethyl benzene is one of three isomers having the same ITSL, the screening level of 1230 <math>\mu\text{g}/\text{m}^3</math> is for a combined ambient impact of all trimethyl benzene</p>	<p><b>Tier 2 source:</b></p> <p><b>PPRTV:</b></p> <p><b>Basis:</b> PPRTV (06/11/2007) chronic p-RfC = 7.0E-3 <math>\text{mg}/\text{m}^3</math> (= 7E+0 <math>\mu\text{g}/\text{m}^3</math>).</p> <p><b>Tier 1 Source:</b></p> <p><b>IRIS:</b> No IRIS file is available at this time. Per EPA Toxicological Review of Trimethylbenzene (August 2013 Revised External Review Draft), RfC = 5E-2 <math>\text{mg}/\text{m}^3</math> (5E+1 <math>\mu\text{g}/\text{m}^3</math>) derived as follows:</p> <p><b>Critical Study:</b> Korsak, Z. and K. Rydzynski. (1996) Neurotoxic effects of acute and subchronic inhalation exposure to Trimethylbenzene isomers (pseudocumene, mesitylene, hemimellitene) in rats. Int. J. Occup. Med. Environ. Health. 9:341–349.</p> <p><b>Method(s):</b> Rats were exposed to 0, 123, 492, or 1,230 <math>\text{mg}/\text{m}^3</math> 1,2,4-TMB for 6 hours/day, 5 days/week, for 3 months. Neurobehavioral effects were assessed using performance testing.</p> <p><b>Critical effect:</b> Decreased pain sensitivity in male rats (neurotoxicity)</p>		Complete



	Part 201 Value	Updated Value	Source/Reference/Date	Comments/Notes/Issues
	isomers.	<p><b>End point or Point of Departure (POD):</b> A deterministic rat PBPK model was used to convert non-continuous external inhalation concentrations (in mg/m<sup>3</sup>) of 1,2,4-TMB to the internal blood dose metric of average weekly venous blood concentration (in mg/L) of 1,2,4-TMB. Internal doses were modeled using BMDS. The resulting POD was adjusted for the non-continuous exposures in this study, POD<sub>ADJ</sub> = 0.086 mg/L, and then converted to human equivalent concentrations using a human PBPK model, POD<sub>HEC</sub> = 15.8 mg/m<sup>3</sup>.</p> <p><b>Uncertainty Factors:</b> UF = 300 (10 for intraspecies variability and 3 each for use of a subchronic study, interspecies extrapolation, and database deficiencies).</p> <p><b>Tier 2 Sources:</b>  <b>PPRTV (06/11/2007):</b> chronic p-RfC = 7E-3 mg/m<sup>3</sup> (= 7E+0 µg/m<sup>3</sup>)  <b>Critical Study:</b> Korsak, Z., J. Stetkiewicz, W Majcherek, I. Stetkiewicz, J. Jajte and K. Rydzyński. (2000) Sub-chronic inhalation toxicity of 1,2,4-trimethylbenzene (pseudocumene) in rats. Int. J. Occup. Med. Environ. Health. 13(2):155-164.  <b>Methods:</b> Outbred Imp:WIST rats (10/sex/group; 20/sex/group at the highest exposure concentration) were exposed to 0, 123, 492 or 1,230 mg/m<sup>3</sup> of 1,2,4-trimethylbenzene vapors for 6 hours/day, 5 days/week for 3 months.  <b>Critical effect:</b> Decreased clotting time in female rats.  <b>End point or Point of Departure (POD):</b> A NOAEL of 123 mg/m<sup>3</sup> was identified and adjusted for non-continuous exposure, NOAEL<sub>ADJ</sub> = 21.8 mg/m<sup>3</sup>. A human equivalent concentration was calculated from the adjusted value, NOAEL<sub>HEC</sub> = 21.8 mg/m<sup>3</sup>.  <b>Uncertainty Factors:</b> UF = 3,000 (10 each for intraspecies variability, use of a subchronic study, and database insufficiencies, and 3 for interspecies extrapolation)  <b>Source and date:</b> PPRTV, 6/11/2007</p> <p><b>MRL:</b> No MRL record is available at this time.</p> <p><b>Tier 3 Source:</b>  <b>MDEQ:</b> Per DEQ-CCD (1/26/2010), AQD established 2 ITSLs: 1,200 µg/m<sup>3</sup> (8 hr. AT) and 50 µg/m<sup>3</sup> (annual AT). These are applied to all 3 TMB isomers in combination. The acute value is protective of irritancy and other potential effects, based on human</p>		

	Part 201 Value	Updated Value	Source/Reference/Date	Comments/Notes/Issues
		experimental studies and occupational experience. The annual value is partially consistent with the PPRTVs (chronic) of 5 µg/m <sup>3</sup> (1,2,3-TMB) and 7 µg/m <sup>3</sup> (1,2,4-TMB) which were based on rat studies and CNS effects. For the PPRTVs, EPA employed database UF of 10 which was not employed in the derivation of the chronic ITSL. The PPRTVs apply only to each specific isomer, and no PPRTV is available for 1,3,5-TMB; the AQD justified grouping the 3 isomers together. AQD does not routinely apply database UF =10 in their own risk assessments.		
<b>Inhalation Unit Risk Factor (IURF) ((µg/m<sup>3</sup>)<sup>-1</sup>)</b>	NA	NA	MDEQ, 2015	
<b>IURF details</b>	NA	<p><b>Tier 1 Source:</b>  <b>IRIS:</b> No IRIS file is available at this time. Per the August 2013 revised external review draft of the IRIS Toxicological Review of Trimethylbenzenes, the database for 1,2,4-TMB provides “inadequate information to assess carcinogenic potential”. This characterization is based on the limited and equivocal genotoxicity findings, and the lack of data indicating carcinogenicity in experimental animal species via any route of exposure. Information available on which to base a quantitative cancer assessment is lacking, and thus, no cancer risk estimates for either oral or inhalation exposures are derived.</p> <p><b>Tier 2 Sources:</b>  <b>PPRTV (06/11/2007):</b> Per PPRTV, collectively, the available carcinogenicity and genotoxicity data do not adequately assess the carcinogenic potential of 1,2,4-trimethylbenzene in humans or animals. Under the current U.S. EPA (2005) cancer guidelines, the human and animal data are inadequate for a determination of the human carcinogenic potential of 1,2,4-trimethylbenzene. There are no appropriate human or animal data from which to derive an inhalation unit risk for 1,2,4-trimethylbenzene.</p> <p><b>MRL:</b> NA; MRLs are for non-cancer effects only.</p> <p><b>Tier 3 Source:</b>  <b>MDEQ:</b> Per DEQ-CCD, no inhalation unit risk factor value is available for 1,2,4-TMB at</p>		Complete



	Part 201 Value	Updated Value	Source/Reference/ Date	Comments/Notes/ Issues
		this time.		
Mutagenic Mode of Action (MMAA)? (Y/N)	--	NO	USEPA, 2014	
MMAA Details	--	Not listed as a carcinogen with mutagenic MOA in the USEPA OSWER List.		
Developmental or Reproductive Effector? (Y/N)	No	No, the RfD or RfC/ITSL is not based on a reproductive-developmental effect.	MDEQ, 2015	
Developmental or Reproductive Toxicity Details	NA	NA		
State Drinking Water Standard (SDWS) (ug/L)	--	--	SDWA, 1976	
SDWS details	NA	MI Safe Drinking Water Act (SDWA) 1976 PA 399		
Secondary Maximum Contaminant Level (SMCL) (ug/L)	NO	NO	SDWA, 1976 and USEPA SMCL List	
SMCL details	NA	MI Safe Drinking Water Act (SDWA) 1976 PA 399 and USEPA SMCL List		
Is there an aesthetic value for drinking water? (Y/N)	NO	63	MDEQ, 2015/Pirnie, 1998	
Aesthetic value (ug/L)	--	Determination of Threshold Odor Concentrations for Four Chemicals in Water. Prepared for MDEQ. November, 1998.		
Aesthetic Value details	NA	NA		
Phytotoxicity Value? (Y/N)	NO	Not evaluated.	NA	
Phytotoxicity details	NA	NA	NA	

	<b>Part 201 Value</b>	<b>Updated Value</b>	<b>Source/Reference/ Date</b>	<b>Comments/Notes/ Issues</b>
<b>Others</b>				

**(C) Chemical-specific Exposure Factors**

	Part 201 Value	Update	Source/Reference/ Dates	Comments/Notes/ Issues
Gastrointestinal absorption efficiency value (ABS <sub>gi</sub> )	---	1.0	MDEQ, 2015/USEPA RAGS-E	
ABS <sub>gi</sub> details		RAGS E (EPA, 2004) Default Value		
Skin absorption efficiency value (AE <sub>d</sub> )	---	0.1	MDEQ, 2015	
AE <sub>d</sub> details				
Ingestion Absorption Efficiency (AE <sub>i</sub> )		1.0	MDEQ, 2015	
AE <sub>i</sub> Details				
Relative Source Contribution for Water (RSC <sub>w</sub> )		0.2	MDEQ, 2015	
Relative Source Contribution for Soil (RSC <sub>s</sub> )		1.0	MDEQ, 2015	
Relative Source Contribution for Air (RSC <sub>A</sub> )		1.0	MDEQ, 2015	
Others		--		



**(D) Rule 57 Water Quality Values and GSI Criteria**

<b>Current GSI value (µg/L)</b>	17
<b>Updated GSI value (µg/L)</b>	17
<b>Rule 57 Drinking Water Value (µg/L)</b>	190

	<b>Rule 57 Value (µg/L)</b>	<b>Verification Date</b>
<b>Human Non-cancer Values- Drinking water source (HNV-drink)</b>	190	1/2001
<b>Human Non-Cancer Values- Non-drinking water sources (HNV-Non-drink)</b>	330	1/2001
<b>Wildlife Value (WV)</b>	NA	NA
<b>Human Cancer Values for Drinking Water Source (HCV-drink)</b>	NA	NA
<b>Human Cancer values for non-drinking water source (HCV-Non-drink)</b>	NA	NA
<b>Final Chronic Value (FCV)</b>	17	2/2001
<b>Aquatic maximum value (AMV)</b>	150	2/2001
<b>Final Acute Value (FAV)</b>	310	2/2001

Sources:

1. MDEQ Surface Water Assessment Section Rule 57 [website](#)
2. MDEQ Rule 57 [table](#)

**(E) Analytical Information**

	<b>Value</b>	<b>Source</b>
<b>Target Detection Limit – Soil (<math>\mu\text{g}/\text{kg}</math>)</b>	100	MDEQ, 2015
<b>Target Detection Limit – Water (<math>\mu\text{g}/\text{L}</math>)</b>	1	MDEQ, 2015
<b>Target Detection Limit – Air (ppbv)</b>	4.40E+01	MDEQ, 2015
<b>Target Detection Limit – Soil Gas (ppbv)</b>	1.50E+03	MDEQ, 2015

**CHEMICAL UPDATE WORKSHEET ABBREVIATIONS:**

CAS # - Chemical Abstract Service Number.

**Section (A) Chemical-Physical Properties****Reference Source(s):**

CRC	Chemical Rubber Company Handbook of Chemistry and Physics, 95th edition, 2014-2015
EMSOFT	USEPA Exposure Model for Soil-Organic Fate and Transport (EMSOFT) (EPA, 2002)
EPA2001	USEPA (2001) Fact Sheet, Correcting the Henry's Law Constant for Soil Temperature. Office of Solid Waste and Emergency Response, Washington, D.C.
EPA4	USEPA (2004) User's Guide for Evaluating Subsurface Vapor Intrusion into Buildings. February 22, 2004.
EPI	USEPA's Estimation Programs Interface SUITE 4.1, Copyright 2000-2012
HSDB	Hazardous Substances Data Bank
MDEQ	Michigan Department of Environmental Quality
NPG	National Institute for Occupational Safety and Health Pocket Guide to Chemical Hazards
PC	National Center for Biotechnology Information's PubChem database
PP	Syracuse Research Corporation's PhysProp database
SCDM	USEPA's Superfund Chemical Data Matrix
SSG	USEPA's Soil Screening Guidance: Technical Background Document, Second Edition, 1996
USEPA/EPA	United States environmental protection agency's Risk Assessment Guidance for Superfund Volume I: Human Health Evaluation Manual (Part E, Supplemental Guidance for Dermal Risk Assessment). July, 2004.

W9 USEPA's User Guide for Water9 Software, Version 2.0.0, 2001

**Basis/Comments:**

EST	estimated
EXP	experimental
EXT	extrapolated
NA	not available or not applicable
NR	not relevant

**Section (B) Toxicity Values/Benchmarks****Sources/References:**

ATSDR	Agency for Toxic Substances and Disease Registry
CALEPA	California Environmental Protection Agency
CAL DTSC	California Department of Toxic Substances Control
CAL OEHHA	CAEPA Office of Environmental Health Hazard Assessment
CCD	MDEQ Chemical Criteria Database
ECHA	European Chemicals Agency (REACH)
OECD HPV	Organization for Economic Cooperation and Development HPV Database
HEAST	USEPA's Health Effects Assessment Summary Tables
IRIS	USEPA's Integrated Risk Information System
MADEP	Massachusetts Department of Environmental Protection
MDEQ/DEQ	Michigan Department of Environmental Quality
DEQ-CCD/AQD	MDEQ Air Quality Division
DEQ-CCD/RRD	MDEQ Remediation and Redevelopment Division
DEQ-CCD/WRD	MDEQ Water Resources Division
MNDOH	Minnesota Department of Health
NJDEP	New Jersey Department of Environmental Protection

NYDEC	New York State Department of Environmental Conservation
OPP/OPPT	USEPA's Office of Pesticide Programs
PPRTV	USEPA's Provisional Peer Reviewed Toxicity Values
RIVM	The Netherlands National Institute of Public Health and the Environment
TCEQ	Texas Commission on Environmental Quality
USEPA	United States Environmental Protection Agency
USEPA OSWER	USEPA Office of Solid Waste and Emergency Response
USEPA MCL	USEPA Maximum Contaminant Level
WHO	World Health Organization
WHO IPCS	International Programme on Chemical Safety (IPCS/INCHEM)
WHO IARC	International Agency for Research on Cancers
NA	Not Available.
NR	Not Relevant.

**Toxicity terms:**

BMC	Benchmark concentration
BMCL	Lower bound confidence limit on the BMC
BMD	benchmark dose
BMDL	Lower bound confidence limit on the BMD
CSF	Cancer slope Factor
CNS	Central nervous system
IURF or IUR	Inhalation unit risk factor
LOAEL	Lowest observed adverse effect level
LOEL	Lowest observed effect level
MRL	Minimal risk level (ATSDR)
NOAEL	No observed adverse effect level
NOEL	No observed effect level
RfC	Reference concentration

RfD	Reference dose
p-RfD	Provisional RfD
aRfD	Acute RfD
UF	Uncertainty factor
WOE	Weight of evidence

**Section (C) Chemical-specific Absorption Factors**

MDEQ	Michigan Department of Environmental Quality
USEPA RAGS-E	United States Environmental Protection Agency's Risk Assessment Guidance for Superfund Volume I: Human Health Evaluation Manual (Part E, Supplemental Guidance for Dermal Risk Assessment). July, 2004.

**Section (D) Rule 57 Water Quality Values and GSI Criteria**

GSI	Groundwater-surface water interface
NA	A value is not available or not applicable.
ID	Insufficient data to derive value
NLS	No literature search has been conducted