Compound	Trimethylbenzenes		Data collection sheet
N°CAS 25551-13-7, 95-63-6, 108-67-8, 526-73-8	**CLP:** Flam. Liq. 3, Acute Tox. 4, Skin Irrit. 2, Eye Irrit. 2, Asp. Tox. 1,		
	Alkylbenzenes	Trimethylbenzenes	1,2,4-Trimethylbenzene
Organization Name	**RIVM**	**Ontario Ministry of Environment**	**ECHA: Registered substances**
Risk Value Name	TCA	AAQC	DNEL
Risk Value (µg/m³)	**870**	**220**	**29400**
Risk Value (ppb)			
Reference period	Chronic	Chronic	Chronic
Year	2007	2007	2013
Key Study	Based on Isopropylbenzene EU (2001) Risk Assessement Report – Cumene. European Chemicals Bureau, Existing Substances.	Korsak and Rydzynski, 1996; Gralewicz and Wiaderna, 2001; Wiaderna *et al.*, 2002	Clark DG, et al. 1989
Study type	chronic	Subchronic inhalation	Chronic inhalation
Species	Rats	Rats	Rats
Duration of exposure in key study	6h/day, 5 days/week chronic	6h/day, 5 days/week	6h/day, 5 days/week, 1 year
Critical effect	Neurotoxicity	Neurotoxicity	Irritation (respiratory tract)
Critical dose value			Long term inhalation DNEL for consumers (systemic effects) derived by industry (ECHA-website: registered substances), no transparent information about derivation of DNEL
	NOAEL 490 mg/m³	NOAEL 123 mg/m³	NOAEC 1800 mg/m³
Adjusted critical dose	5.6	5.6	
Single assessment factors (see table R.8.6)	UF_H 10 x UF_A 10 = 100	UFs 3 x UF_H 3 x UF_A 10 = 100	1.7 (Overall assessment factor)
Other effects			
UFL used LOAEL; UFH intraspecies variability; UFA interspecies variability; UFS Used subchronic study; UFD data deficiencies			

Compound	TRIMETHYLBENZENES		*Factsheet*
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI Value and Status			
EU-LCI value	1	Mass/volume [µg/m^3]	450
EU-LCI status	2	Draft / Final	Final
EU-LCI year of issue	3	Year when the EU-LCI value has been issued	2012
General Information			
CLP-INDEX-Nr.	4	INDEX	601-025-00-5 601-043-00-3 601-025-00-5
EC-Nr.	5	EINECS – ELINCS - NLP	247-099-9 202-436-9 203-604-4 208-394-8
CAS-Nr.	6	Chemical Abstracts Service number	25551-13-7 95-63-6 108-67-8 526-73-8
Harmonised CLP classification	7	Human Health Risk related classification	Not harmonised
Molar mass	8	[g/mol]	120.19
Key Data / Database			
Key study, Author(s), Year	9	Critical study with lowest relevant effect level	Korsak and Rydzynski, 1996, 1997, 2000a, 2000b
Read across compound	10	Where applicable	
Species	11	Rat,… human	Rat
Route/type of study	12	Inhalation, oral feed, …	Inhalation
Study length	13	Days, subchronic, chronic	Subchronic
Exposure duration	14	Hrs/day, days/week	6h/24h / 5d/7d
Critical endpoint	15	Effect(s), site of	Neurotoxicity and local effects on lungs
Point of departure (POD)	16	LOAEC*L, NOAEC*L, NOEC*L, Benchmark dose, ….	NOAEC
POD Value	17	[mg/m^3] or [ppm]	123 mg/m^3
Assessment Factors (AF)	**18**		
Adjustment for exposure duration	19	Study exposure hrs/day, days/week	5.6
AF Study Length	20	sa→ sc→ c *(R8-5)*	2
Route-to-route extrapolation factor	21		
AF Dose-response	22 a	Reliability of dose-response, LOAEL → NOAEL	
	22 b	Severity of effect *(R 8-6d)*	
Interspecies differences	23 a	Allometric Metabolic rate *(R8-3)*	
	23 b	Kinetic + dynamic	2.5

Intraspecies differences	24	Kinetic + dynamic Worker - General population	10
AF (sensitive population)	25	Children or other sensitive groups	
Other adjustment factors Quality of whole database	26	Completeness and consistency Reliability of alternative data *(R8-6 d,e)*	
Result			
Summary of assessment factors	27	Total Assessment Factor (TAF)	280
POD/TAF	28	Calculated value (µg/m³ and ppb)	……439.29 µg/m³ ….. 88.84 ppb
Molar adjustment factor	29	Used in read-across	
Rounded value	30	[µg/m³]	450
Additional Comments	31		
Rationale Section	32		

Trimethylbenzene (CAS 25551-13-7) has three isomers:
1,3,5-trimethylbenzene (synonym: mesitylene; CAS 108-67-8)
1,2,4-trimethylbenzene (synonym: pseudocumene; CAS 95-63-6)
1,2,3-trimethylbenzene (synonym: hemimellitene; CAS 526-73-8)

None of the agencies WHO, EPA, ATDSR, EU RAR, INDEX) provide a human health risk assessment for TMB exposure in indoor environments, but the Ontario Ministry of Environment [2007] and RIVM [Dusseldorp et al. 2007] reviewed the compound and derived a 24-hour Ambient Air Quality Criterion (AAQC) of 220 µg/m³ for trimethylbenzenes and a chronic air limit value (TCA) of 870 µg/m³ respectively. An industry sponsored study [Firt 2007] derived an RfD of 3 mg/m³ using standard USEPA methods.

POD

The LCI derivation is based mainly on the key studies by Korsak et al. [1996, 2000a, b] and Wiaderma et al. [2002], In accordance with Ontarion Ministry of Environment [2007] CNS effects were chosen as the critical effect observed in 5 subchronic inhalation studies on rats. In subchronic inhalation studies of 1,2,3 and 1,2,4-trimethylbenzene [Korsak et al., 2000a and 2000b; Korsak and Rydzynski, 1996] rats were exposed to 123 mg/m³, 492 mg/m³ and 1230 mg/m³, 6 h/day, 5 days/week for 3 months. The same neurotoxic effects were observed as in the subacute studies. A NOAEC of 123 mg/m³ and a LOAEC of 492 mg/m³ was identified for TMB which includes also local effects in the lung and is below the exposure concentration (1476 mg/m³) at which reprotoxic effects were observed [Sallenfait et al. 2005]. A comparison of the available toxicity data for 1,2,4-TMB and 1,3,5-TMB suggests similar toxicity.

Assessment factors

Standard default assessment factors for adjustment for exposure duration (note 19), study length (note 22), interspecies AF (note 23b) and intraspecies AF (note 24) were applied.

No additional factor for combined effects was introduced, because according to Clark et al. (1989), the NOAEL for a mixture of high aromatic naphtha was without systemic toxicity with a NOAEC of 1800 mg/m³ in a 12 month rat study.

References

Trimethylbenzenes: 1,2,3-Trimethylbenzene, 1,2,4-Trimethylbenzene, 1,3,5-Trimethylbenzene. Standards, Development Branch, Ontario Ministry of the Environment.
http://www.ene.gov.on.ca/envision/env_reg/er/documents/2007/PA05E0031-f.pdf

Dusseldorp A., M. van Bruggen, J. Douwes, P.J.C.M. Janssen, G. Kelfkens. Health-based guideline values for the indoor environment. RIVM report 609021044/2007. RIVM, Bilthoven, the Netherlands. 2007

Korsak, Z. and Rydzynski, K. 1996. Neurotoxic effects of acute and subchronic inhalation exposure to trimethylbenzene isomers (pseudocumene, mesitylene, hemimellitene) in rats. J Occup Med Env Health 9(4):341-349

Korsak, Z., Stetkiewicz, J., Majcherek, W., Stetkiewicz, I., Jajte, J. and Rydzynski, K. 2000a. Sub-chronic inhalation toxicity of 1,2,4-trimethylbenzene (pseudocumene) in rats. Int J Occup Med Environ Health 13(2):155-164.

Korsak, Z., Stetkiewics, J., Majcherek, W., Stetkiewicz, I., Jajte, J. and Rydzynski, K. 2000b. Sub-chronic inhalation toxicity of 1,2,3-trimethylbenzene (hemimellitene) in rats. Int J Occup Med Environ Health 13(3):223-232.

Wiaderna, D., Gralewicz, S., and Tomas, T. 2002. Assessment of long-term neurotoxic effects of exposure to mesitylene (1,3,5-trimethylbenzene) based on the analysis of selected behavioural responses. J Occup Med Env Health 15(4):385-391.

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Clark DG, Butterworth ST, Martin JG, Roderick HR, Bird MG. Inhalation toxicity of high flash aromatic naphtha. Toxicol Ind Health. 1989 May;5(3):415-28.
TMB is listed by ECHA: http://apps.echa.europa.eu/registered/registered-sub.aspx#search