Compound	Vinyl toluene (o-, m-, p-) and mix of o-, m-, and p-vinyl toluene	*Data collection sheet*
N°CAS 25013-15-4 (mixture of isomers)	**EU- Classification:** **CLP: no harmonised classification for mixture, 3- and 4-vinyl toluene** **2-vinyl toluene: Acute Tox 4 (H332), Aquatic Chronic 2 (H411)**	

Organisation name	**DFG**	**REACH registrants**
Risk value name	MAK	DNEL
Risk value (µg/m³)	98 mg/m^3 (20 ppm)	37 (7.5 ppm)
Reference period	Chronic (worker)	Chronic (worker)
Risk value (mg/m³) / Short term (15 min)	196 mg/m^3 (40 ppm)	-
Year	2016	2017
Key study	NTP (1990) NTP Technical Report on the Toxicology and Carcinogenesis of vinyl toluene (mixed isomers) (65%-71% meta-isomer and 32%-35% para-isomer) (CAS no. 25013-15-4) in F344/N rats and B6C3f1 mice (inhalation studies). U.S. Department of Health and Human Services PHS, National Institutes of Health	Not indicated
Study type	Inhalation	Not indicated
Species	Rat	Not indicated
Duration of exposure in key study	Chronic (2 years)	Not indicated
Critical effect	Irritation (respiratory tract)	Irritation (respiratory tract)
Critical dose value	NAEC: 162 mg/m^3 (33 ppm)	Not indicated
Adjusted critical dose	-	Not indicated
Single assessment factors (see table R.8.6)	UF_L 3 x UF_H 10 x UF_A 1 = 30	Not indicated (total factor: 4)
Other effects		
Remarks	Value derived using "preferred value approach", taking into account the assessment factors noted above	No DNELs derived in a further dossier (ECHA Dissemination, 2018)

UF_L Used LOAEL; UF_H Intraspecies variability; UF_A interspecies variability; UF_S Used subchronic study; UF_D data deficiencies

Compound	Vinyl toluene (o-, m-, p-) and mix of o-, m-, and p-vinyl toluene		Factsheet
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI value and status			
EU-LCI value	1	Mass/volume [µg/m^3]	1200
EU-LCI status	2	Draft/final	Final
EU-LCI year of issue	3	Year when the EU-LCI value was issued	2018
General information			
CLP Index No	4	INDEX	-
EC No	5	EINECS – ELINCS - NLP	246-562-2
CAS No	6	Chemical Abstracts Service number	25013-15-4 (mixture) 611-15-4 (2-vinyltoluene) 100-80-1 (3-vinyltoluene) 622-97-9 (4-vinyltoluene)
Harmonised CLP classification	7	Human health risk-related classification	none for mixture, 3- and 4-vinyl toluene; 2-vinyltoluene: Acute tox 4 (H332)
Molar mass and conversion factor	8	[g/mol] and [ppm – mg/m^3]	118.2 1 ppm = 4.87 mg/m^3
Key data / database			
Key study, author(s), year	9	Critical study with lowest relevant effect level	NTP (1990)
Read-across compound	10	Where applicable	
Species	11	Rat, human, etc.	Rat
Route/type of study	12	Inhalation, oral feed, etc.	Inhalation
Study length	13	Days, subchronic, chronic	Chronic (2 years)
Exposure duration	14	Hours/day, days/week	6 h/d, 5 d/week
Critical endpoint	15	Effect(s), site of	Lesions of nasal epithelia
Point of departure (POD)	16	LOAEC*L, NOAEC*L, NOEC*L, benchmark dose, etc.	LOAEC
POD value	17	[mg/m^3] or [ppm] or [mg/kg$_{BW}$×d]	490 mg/m^3 (100 ppm)
Assessment factors (AF)	18		
Adjustment for exposure duration	19	Study exposure hours/day, days/week	5.6
Study length	20	sa→ sc→ c *(R8-5)*	1
Route-to-route extrapolation factor	21		1
Dose-response	22 a	Reliability of dose-response, LOAEL → NOAEL	3
	22 b	Severity of effect *(R 8-6d)*	1
Interspecies differences	23 a	Allometric Metabolic rate *(R8-3)*	1
	23 b	Kinetic + dynamic	2.5
Intraspecies differences	24	Kinetic + dynamic Worker - general population	10

AF (sensitive population)	25	Children or other sensitive groups	1
Other adjustment factors Quality of whole database	26	Completeness and consistency Reliability of alternative data *(R8-6 d,e)*	1
Result			
Summary of assessment factors	27	Total Assessment Factor (TAF)	420
POD/TAF	28	Calculated value (µg/m³ and ppb)	1166 µg/m³ and 240 ppb
Molar adjustment factor	29	Used in read-across	
Rounded value	30	[µg/m³]	1200
Additional comments	31		
Rationale section	32		

Data compilation and evaluation for vinyl toluene (o-, m-, p-) and mix of o-, m-, and p-vinyl toluene are based on a project funded by the German Environment Agency (Voss, 2018).

Rationale for critical effects

In humans, vinyl toluene is irritating to the eyes and upper respiratory tract at concentrations ≥ 1960 mg/m³ (400 ppm). A strong odour is detectable at 980 mg/m³ (200 ppm), and a NOAEC for irritation at 245 – 490 mg/m³ (50 – 100 ppm) has been reported (DFG, 2017).

The critical effect of vinyl toluene inhalation is respiratory tract irritation. In a chronic inhalation study using F344 rats (50 M + 50 F/concentration) exposed to 0, 100 or 300 ppm (0, 490, 1460 mg/m³) of vinyl toluene (mixed isomers: 65-71% meta- and 32-35% para-isomer), increased incidences were observed of degenerative and non-neoplastic proliferative lesions of the nasal mucosa. The lesions included diffuse hyperplasia of the respiratory epithelium and focal erosion of the olfactory epithelium. Focal respiratory epithelial metaplasia of the olfactory epithelium was seen in some exposed males, and eosinophilic cytoplasm inclusions in the olfactory epithelium occurred at increased incidences in exposed female rats. The effects were observed at the lower exposure concentration tested (490 mg/m³, 100 ppm) (NTP, 1990).

As with rats, respiratory tract irritation similar to that in the nasal epithelia and, additionally, the lung were observed in mice but at much lower concentrations (LOAEC 49 mg/m³, 10 ppm). Metabolism studies provide strong evidence that mice are much more sensitive than rats or humans to the toxic effects of styrene and similar compounds (DFG, 1997). Data obtained in the exposure study using mice is not considered relevant for the quantitative risk evaluation for humans, therefore.

There was no evidence of carcinogenicity in rats or mice (NTP, 1990).

The NTP study described was conducted using a mixture of 65–71 % 3-vinyl toluene and 32–35 % 4-vinyl toluene. No data from repeated inhalation studies is available for 2-vinyl toluene, but the limited database from studies with other exposure paths does not indicate any gross differences in the toxicity of the three isomers.

Rationale for starting point

The derivation of the EU-LCI value is based on the observed lesions of the nasal epithelia in rats. Effects were observed at 490 mg/m³, the lowest concentration tested. This LOAEC serves as the starting point for the derivation of the LCI.

Rationale for assessment factors

- factor for adjustment for exposure duration: 5.6
- adjusted study length factor: 1 (chronic exposure)

- LOAEC → NAEC extrapolation: 3
- interspecies differences: 2.5 (According to ECA report No 29, no correction need to be made for differences in systemic metabolism when the POD is related to local effects. For remaining uncertainties, a value of 1 is used for remaining specific differences for effects on skin, eye and GI tract if the mode of action implies only a simple destruction of membranes, and a default value of 2.5 is used for effects on the skin, eye and GI tract if local metabolism or receptor-binding reactions are involved. Metabolism is known to be involved in the toxicity of vinyl toluenes and structurally related compounds. Metabolism data for styrene indicates that humans are not more – and perhaps less – sensitive than rats regarding effects on the nasal epithelia (DFG, 2017). No data for vinyl toluenes (methylstyrenes) are available, however, and therefore the extrapolation factor of 2.5 is retained.
- intraspecies differences: 10

The total assessment factor is 420, leading to a value of 490 000 µg/m^3 : 420 = 1200 µg/m^3.

The following EU-LCI is proposed for vinyl toluenes (mixture): 1200 µg/m^3.

The derived EU-LCI is below the concentration of 245 mg/m^3 (50 ppm) which was reported to be tolerated upon brief exposure in a study using volunteers (Wolf et al., 1956). No reliable odour threshold for vinyl toluene is available. For styrene, a wide range of odour thresholds in the range 0.012 - 263 mg/m^3 (0.0028 - 61 ppm) is reported (AIHA, 2013), and the odour of styrene and vinyl toluene are described similarly as strong and disagreeable (NTP, 1990). It is concluded that odour perception cannot be ruled out at the proposed EU-LCI.

References

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