Compound	TOLUENE	*Data collection sheet (1/3)*
N°CAS 108-88-3 1 ppm (in air, 25 °C) = 3.76 mg/m³	**CLP**: Flam. Liq. 2, Asp. Tox. 1, Skin. Irrit. 2, STOT SE 3, Rep. 2, STOT RE 2	

Organization Name	**OMS**	**US EPA IRIS**	**Santé Canada**	**RIVM**	**OEHHA**	**ATSDR**
Risk Value Name	Guide Value	RfC	CJA	TCA	REL	MRL
Risk Value (mg/m³)	**0.26**	**5**	**3.75**	**0.4**	**0.3**	**0.3**
Risk Value (ppm)	0.07	1.3	1	0.1	0.07	0.08
Reference period	Chronic	Chronic	Chronic	Chronic	Chronic	Chronic
Year	2005	2005	1992	2001	2003	2000
Key Study	Foo et al., 1990, Chronic neurobehavioural effects of toluene	Abbate *et al.*, 1993, Boey *et al.*, 1997, Cavalleri *et al.*, 2000, Eller *et al.*, 1999, Foo *et al.*, 1990, Murata *et al.*, 1993, Nakatsuka *et al.*, 1992, Neubert *et al.*, 2001, Vrca *et al.*, 1995, Zavalic *et al.*, 1998a	Andersen *et al.*, 1983, Human response to controlled levels of toluene in 6-h exposures	Foo *et al.*, 1990, Chronic neurobehavioural effects of toluene	Hillefors-Berglund *et al.*, 1995 supported by Foo *et al.*, 1990, Orbaek et Nise 1989 (human)	Zavalic *et al.*, 1998, Assessment of colour vision impairment in male workers exposed to toluene generally above occupational exposure limits
Study type	Neurobehavioural tests: measuring manual dexterity (grooved peg board), visual scanning (trail making, visual reproduction, Benton visual retention, and digit symbol), and verbal memory (digit span)	See below	Human response to controlled levels of toluene in six-hour exposures	Neurobehavioural tests: measuring manual dexterity (grooved peg board), visual scanning (trail making, visual reproduction, Benton visual retention, and digit symbol), and verbal memory (digit span)	Subchronic inhalation study	Colour vision was evaluated by Lanthony-D-15 desaturated test

Species	Human (30 female workers)	Human (occupationally-exposed workers)	Human	Human	Rat	Human (45 male workers occupationally exposed to toluene, employed in a printing press)
Duration of exposure in key study	Average of 5.7 years	See below	6-h exposures to clean air and to 10, 40 or 100 ppm of toluene	Average of 5.7 years	6 h/d, 5 d/w, 4 weeks, followed by 29-40 days recovery	Average of 16.8 years (mean value of [toluene] in ambient air = 119.96 ppm)
Critical effect	Decrease in performance at neuropsychological tests	Neurological effects (impaired color vision, impaired hearing, reduced performance in neuropsychological tests, sensations of concentration difficulties, headaches, dizziness)	Decrease in neuroligal function as measured by various tests, increased neurological symptoms and respiratory irritation	Decrease performance in neuropsychological tests	Neurological effects (decrease the weight of the subcortical limbic area of the brain and alteration of dopamine receptors)	Neurological effects (dysfunctions of color vision)
Critical dose value		Average NOAEC = 128 mg/m^3 (34 ppm)	NOAEC 150 mg/m^3 (40 ppm)		NOAEC 150 mg/m^3 (40 ppm)	
	LOAEC 332 mg/m^3 (88 ppm)			LOAEC 332 mg/m^3 (88 ppm)	LOAEC 306.4 mg/m^3 (80 ppm)	LOAEC 134 mg/m^3 (35 ppm)
Adjusted critical dose	Temporal	Temporal	Temporal	Temporal	Temporal	Temporal
	80 mg/m^3 (21 ppm)= 332 mg/m^3 x 8h/24h x 5j/7j	46 mg/m^3 (12 ppm) = 128 mg/m^3 x10m^3/20m^3 x 5j/7j	38 mg/m^3 (10 ppm)= 150 mg/m^3 x 6h/24h	119 mg/m^3 (30 ppm)= 332 mg/m^3 x 10m^3/20m^3 x 5j/7j	26.8 mg/m^3 (7 ppm)= 150 mg/m^3 x 6h/24h x 5j/7j	32 mg/m^3 (8.3 ppm)= 134 mg/m^3 x 5j/7j x 8h/24h

Single assessment factors (see table R.8.6)	UF_L 10 x UF_H 10 x UF(for potential effects on the developing CNS) 3 = 300	UF_H 10	UF_H 10	UF_L 10 x UF_H 10 x UF_D (on neurotoxicity and respiratory irritation on animal) 3 = 300	UF_S 10 x UF_H 10 = 100	UF_L 10 x UF_H 10 = 100
Other effects						
Confidence		High		High		
UF_L used LOAEL; UF_H intraspecies variability; UF_A interspecies variability; UF_S Used subchronic study; UF_D data deficiencies						

Compound	**TOLUENE**			***Data collection sheet (2/3)***		
N°CAS 108-88-3						
1 ppm (in air, 25 °C) = 3.76 mg/m³						
Organization Name	**Afsset**	**German IAQ**	**Austrian IAQ**	**EU-RAR- based***	**EU-RAR-based***	**ECHA Registered Substances**
Risk Value Name	VTR	IAG (I)	IAG	DNEL consumer	DNEL consumer	DNEL
Risk Value (mg/m³)	**3**	**0.3**	**0.075**	**1.40**	**2.5**	**56**
Risk Value (ppm)	0.8	0.07	0.02	0.37	0.66	14.75
Reference period	Chronic	Chronic	Chronic	Chronic	Chronic	Chronic
Year	2010	1996	2006	2011	2011	2011
Key Study	Zavalic *et al.,* 1998	Echeverria et al. 1989 supported by various studies, including long term occupational exposure	Campagna et al. 2001	Thiel and Chahoud In RAR, 2003	Pryor et al. in RAR, 2003	
Study type	Colour vision was evaluated by Lanthony-D-15 desaturated test	Cognitive tests	Colour Confusion Index, Lanthony D-15 desaturated panel,	Developmental toxicity	Multisensory conditioned avoidance response test	

Species	Human (45 male workers occupationally exposed to toluene, employed in a printing press)	Human volunteers	72 human workers, occupationally exposed		Male fisher rats	
Duration of exposure in key study	Average of 16.8 years (mean value of [toluene] in ambient air = 119.96 ppm)	3 days, 7 hours, 281 and 562 mg Toluene/m^{-3}			14 weeks treatment	
Critical effect	Neurological effects (disorders of color vision)	CNS effects	CNS-effects: color vision loss	Effects on fertility and reproduction (dev.): reduced foetal weights and birth weights in the offspring of exposed mothers. Long-lasting developmental neurotoxicity, manifest as impaired learning ability.	Hearing loss	No information about DNEL derivation
Critical dose value	NOAEC 123 $mg.m^{-3}$ *(32 ppm)*			NOAEC 2250 mg/m^3	NOAEC 2660 mg/m^3	Long term inhalation DNEL (systemic effects) for the general population derived from industry
		LOAEL: 281 mg/m^3 (73 ppm)	LOAEL 35 mg/m^3 (9 ppm)			
Adjusted critical dose	Temporal	Chronic	Chronic	Chronic	Subchronic	No information about DNEL derivation
	29 mg/m^3 (7.5 ppm)= 123 mg/m^3 x 5j/7j x 8h/24h		35 mg/m^3 / 4.2 = 8 mg/m^3	401.8 mg/m^3 = 2250 mg/m^3x 5j/7j x 6h/24h		

Single assessment factors (see table R.8.6)	UF_H 10	Toxicokin: 5x Intrasp. 10x UF (sens) 2x 10x = 1000	UF LOAEL-NOAEL 10x UF Intrasp. 10 =100	UF 2x Intersp. 2.5x4 Intrasp. 10x UF (sens) 2x =600	Intersp. 2.5x4 Intrasp. 10x Exp.dur:3x UF (sens) 2x =600	Total AF: 1.7
Other effects						
Confidence						
UF_L used LOAEL; UF_H intraspecies variability; UF_A interspecies variability; UF_S Used subchronic study; UF_D data deficiencies						

*DNELs derived based on key studies selected for risk characteriszation in the EU RAR (risk characterization in the RAR is based on the margin of safety MOS concept for defined consumer scenarios (e.g. spray painting).

Compound	**TOLUENE**	***Data collection sheet (3/3)***

STUDIES supporting the US EPA RfC

Study number and reference	**Number of workers and duration of exposure (average years ± SD)**	**NOAEL (ppm)**	**LOAEL (ppm)**	**Effect/test**	**Response level at the LOAEL (statistically significant response compared to controls)[a]**	**Noted potential limitations**
1. Abbate et al., 1993	Reference (n=40), exposed (n=40) (12-14 years; no SD reported)	None	97	Brainstem response auditory-evoked potential	28% increase of the latency shift for wave-I during passage from 11 to 90 repetitions.	

2. Boey et al., 1997	Reference (n = 29) exposed (n = 29) (4.9 ± 3.5 years; range of 1-13 years)	None	91	Neuropsychological examination; digit span, visual reproduction, Benton visual retention test, trail making test, symbol digit modality test, grooved pegboard test, and finger tapping tests	Increased time to complete the grooved pegboard test 7% and 6% for dominant and non-dominant hands respectively, increase in time to complete trail-making test parts A&B, 31% & 28%, respectively; 15% decrease in backward digit span test; 12% and 10% decrease in symbol digit modality test for written and oral sections, respectively.	Control workers were exposed to 12 ppm toluene
3. Cavalleri et al., 2000	Reference (n=16), exposed (n=33) (9.75 years; no SD reported)	None	42	Color vision impairment (Lanthony D-15)	29% increase in CCI and 49% increase in total confusion index (TOCI) (reported as mean of both eyes).	Exposure measured from urinary excretion of toluene: on the basis of previous data, air concentrations estimated to be 42 ppm.
4. Eller et al., 1999	Reference (n=19), low exposure (n=30), high exposure (n=49) low exposure (1-12 years; no SD reported) high exposure (>12 years)	20	>100	Neuropsychological examination (Cognitive Function Scanner); verbal and nonverbal learning and memory, visuomotor function, computerized neurological examination (CATSYS, TREMOR, and SWAY), subjective assessment	13% increase in performance time on Bourdon Wiersma Test but no increase in the number of missed or incorrect detections; 33% of exposed population reported concentration difficulties.	The high exposure classification was based on historical exposures which may have exceeded 100 ppm for up to 27 years.

5. Foo et al., 1990	Reference (n=30), exposed (n=30) (5.7 ± 3.2 years)	None	88	Neurobehavioral tests: Benton visual retention test, visual reproduction, trail making, grooved pegboard, digit span, digit symbol, finger tapping, and simple reaction time	Increased time to complete the trail-making test parts A&B, 51% & 63%, respectively; 25% decrease in digit symbol test performance; 16% decrease in total digit span test scores (both forward and backward).	Control workers were exposed to 13 ppm toluene for 2.5 ± 3.2 years. The education level was lower in the exposed group. As a result, data from the neurobehavioral tests were adjusted for years of education using a generalized linear model.
6. Murata et al., 1993	Reference (n=10), exposed (n=10) (11 years; range of 1-36 years; no SD reported)	None	83	Electrophysiological analysis of maximal motor and sensory nerve conduction velocity (MCV & SCV)	9% reduction in the MCV in the forearm and 6% reduction in the SCV in the palm.	Exposed workers were matched for age but not alcohol consumption.
7. Nakatsuka et al., 1992	Reference (n=120), exposed (n=174)	44-48	None	Color vision impairment (Lanthony's new color test and Ishihara's color vision test)	No measured effect on color vision.	In lieu of determining exposure duration, groups were age-matched to control for effects of aging on color vision.
8. Neubert et al., 2001	Ref-ex (n=109), ref-int (n=48), exp gp I (n=316), exp gp II (n=535), exp gp III (n=308), exp gp IV (n=65)	39 (exp gp 1)	81 (ex gp IV)	Psychophysiological and psychomotor testing: verbal memory span, visuomotor performance, immediate visual memory, self-rating of feeling, biosensory vigilance, critical flicker fusion frequency test, personality dispositions	5% reduction in ascending flicker fusion frequency.	Exposure was identified as chronic but the duration was not reported.

9. Vrca et al., 1995	Reference (n=59), exposed (n=49) (21.4 ± 7.4 years)	None	40-60	Visual evoked potentials	The amplitudes of visual evoked brain potentials were 24, 43, and 55% higher for N75, P100, and N145, respectively.	Exposure levels were estimated based on urinary levels of metabolites and toluene levels in blood.
10. Zavalic et al., 1998a	Reference (n=90), low exposure (n=46), high exposure (n=37) low exposure (16.21 ± 6.1 years) high exposure (18.34 ± 6.03 years)	32	132	Color vision impairment (Lanthony D-15)	10-14% increase in CCI (both eyes).	The results from this investigation were reported in several publications (Zavalic et al., 1998a,b,c); some reporting discrepancies exist regarding the number of workers in the exposed and control groups and the statistical analyses.

Compound	TOLUENE		*Factsheet*
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI Value and Status			
EU-LCI value	1	Mass/volume [µg/m^3]	2900
EU-LCI status	2	Draft / Final	Final
EU-LCI year of issue	3	Year when the EU-LCI value has been issued	29 August 2012
General Information			
CLP-INDEX-Nr.	4	INDEX	R2B
EC-Nr.	5	EINECS – ELINCS - NLP	203-625-9
CAS-Nr.	6	Chemical Abstracts Service number	108-88-3
Harmonised CLP classification	7	Human Health Risk related classification	Flam. Liq. 2, Asp. Tox. 1, Skin. Irrit. 2, STOT SE 3, Rep. 2, STOT RE 2
Molar mass	8	[g/mol]	92.14
Key Data / Database			
Key study, Author(s), Year	9	Critical study with lowest relevant effect level	Zavalic et al., 1998
Read across compound	10	Where applicable	
Species	11	Rat,… human	Human
Route/type of study	12	Inhalation, oral feed,…	Inhalation, occupational
Study length	13	Days, subchronic, chronic	17 years
Exposure duration	14	Hrs/day, days/week	
Critical endpoint	15	Effect(s), site of	Neurological effects (color vision impairment)
Point of departure (POD)	16	LOAEC*L, NOAEC*L, NOEC*L, Benchmark dose,….	LOAEC
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	4.2
AF Study Length	20	sa→ sc→ c *(R8-5)*	
Route-to-route extrapolation factor	21		
AF Dose-response	22 a	Reliability of dose-response, LOAEL → NOAEL	2
	22 b	Severity of effect *(R 8-6d)*	
Interspecies differences	23 a	Allometric Metabolic rate *(R8-3)*	
	23 b	Kinetic + dynamic	
Intraspecies differences	24	Kinetic + dynamic Worker - General population	5
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)	42
POD/TAF	28	Calculated value (µg/m³ and ppb)	……2928.57 µg/m³ ….. 772.58 ppb
Molar adjustment factor	29	Used in read-across	
Rounded value	30	[µg/m³]	2900
Additional Comments	31		
Rationale Section	32		

Rationale for critical effects

Neurological effects have been demonstrated in rodents and in humans exposed by the respiratory route during chronic exposure. Toluene like many other organic solvents can impair color vision, even at concentrations below 50 ppm. Reprotoxic and developmental effects have also been shown, particularly in animals; however, the neurological effects were reported at lower concentrations than those for effects on fertility or development.

WHO, RIVM, ATSDR, US-EPA, Anses, German IAQ, Austria IAQ, based their values on human studies showing neurologic effects (could be neurobehavioural, vision impairment …).

Rationale for key study

The reference value is based on the Zavalic´et al. (1998) study. In this study, color vision was examined in two groups of workers occupationally exposed to toluene and in a control group. The autors referenced standard methods for measuring both ambient air concentrations and individual blood toluene levels. Significantly higher values of color confusion index and alcohol intake-adjusted color confusion index in exposed groups in comparison to the non-exposed group were reported. The color confusion index scores were adjusted for alcohol consumption. A LOAEC of 134 mg/m^3 (35 ppm) could be derived from this study.

ATSDR (2000) and Anses (2010) also based their toxicological reference value on this study. US-EPA (2005) considered several human studies as key studies, including the Zavalic´et al. (1998). An average NOAEC from these studies was used.

The study from Zavalic´was selected as the key study as it is an epidemiological study on workers exposed for many years and a dose-response relationship for neurological effects was observed in this study.

Rationale for starting point

In the study of Zavalic´ et al. (1998), two groups of exposed workers to toluene and a control group have been evaluated:

- the first exposed group, Group E1, comprised 41 workers (toluene exposure ranged from 11.3 to 49.3 ppm; median 32.0)
- the second exposed group, Group E2, comprised 32 workers (toluene exposure ranged from 66.00 to 250.00 ppm; median 132.00).
- the non-exposed group, Group NE, comprised 83 subjects.

Each group was divided into two subgroups; alcohol consumers and non-consumers. Color vision loss was expressed as a color confusion index (CCI) and as an age and alcohol intake-adjusted colour confusion index (AACCI).

The AACCI value was significantly higher in Group E2 compared to Group NE (t-test, $P < 0.0001$) and Group E1 (t-test; $P < 0.05$), and in Group E1 compared to Group NE (t-test; $P < 0.05$). Difference was not established in CCI value between groups E1 and NE. No statistically significant correlation was established between AACCI and any marker of toluene exposure in Group E1, or in the subgroups of alcohol consumers and non-consumers. Significant correlation was established between the AACCI value and toluene in air, between AACCI and orthocresol in urine and between AACCI and hippuric acid in urine in this Group.

The authors concluded that age and alcohol intake play a role in color vision impairment. Alcohol intake play a role as an additive cofactor with toluene.

Based on the evidence that the AACCI value was significantly higher in Group E1 (median toluene exposure 32.0 ppm) compared to Group NE, 32 ppm could be considered as a LOAEC.

Rationale for Uncertainty factors

- AF Dose response: An assessment factor of 2 is applied to account for extrapolating from a LOAEC to a NOAEC. This low factor is justified by the fact that numerous human studies have identified NOAELs in the range of 25-50 ppm toluene for individual neurological effects and also by the fact that US-EPA considered 34 ppm as a NOAEC (US-EPA, 2005).
- Adjusted study length factor: an assessment factor to account for extrapolating from less than chronic results was not necessary. Most of the studies used in the analysis were of chronic duration.
- Adjusted exposure duration factor: The LOAEL (average) of 32 ppm (123 mg/m^3) was adjusted from an occupational exposure scenario to continuous exposure conditions as follows:

NOAEL (adj) = NOAEL (average) x 8 hours /24 hours x 5 days/7 days = 123 mg/m^3 x $10m^3/20m^3$ x 5 days/7 days = 30 mg/m^3

- Interspecies differences: an assessment factor to account for laboratory animal-to-human interspecies differences was not necessary because the point of departure is based on human exposure data.
- Intraspecies differences: a 5-fold assessment factor for was used to account for potentially susceptible human subpopulations and life stages. Differences in human susceptibility may

also be due to life stage (e.g., childhood or advanced age), differences among the adult population, genetic polymorphisms, decreased renal clearance in disease states, and unknown pharmacodynamic variations in response to toluene exposure.

References

Echeverria D, Fine L, Langolf G, Schork A, Sampaio C. Acute neurobehavioural effects of toluene. Br J Ind Med. 1989 Jul;46(7):483-95.

Foo SC, Jeyaratnam J, Koh D. (1990) Chronic neurobehavioural effects of toluene. British Journal if Industrial Medicine. 1990 Jul;47(7):480-4.

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