Compound	Isopropylbenzene (cumene)	*Data collection sheet*
N°CAS 98-82-8 1 ppm=5.0 mg/m³	CLP (human health only): Asp. Tox. 1 (H302), STOT SE 3 (H335)	

Organisation Name	**ACGIH**	**DFG**	**REACH Registrants**	**Umweltbundesamt (D)**
Risk Value Name	TWA	MAK	DNEL	GV II (RW II)
Risk Value (mg/m³)	250	50	16.6	1.3
Risk Value (ppm)	50	10	3.32	0.26
Reference period	chronic (worker)	chronic (worker)	chronic (general population)	chronic (general population)
Year	1997	2013	2015 (last modification)	2012
Key Study	Sandmeyer EE (1981) Aromatic Hydrocarbons. In: Patty's Industrial Hygiene and Toxicology, Vol. IIB, 3rd Ed., GD Clayton, Ed., John Wiley and Sons, New York pp. 3256, 3308 – 3310; Werner HW, Dunn RC, von Oettingen WF (1944): The acute effects of cumene vapors in mice. J Ind Hyg Toxicol 26, 264 – 268	NTP (2009) Toxicology and carcinogenesis studies of cumene (CAS No. 98–82–8) in F344/N rats and B6C3F1 mice (inhalation studies)	NTP (2009) Toxicology and carcinogenesis studies of cumene (CAS No. 98–82–8) in F344/N rats and B6C3F1 mice (inhalation studies)	NTP (2009) Toxicology and carcinogenesis studies of cumene (CAS No. 98–82–8) in F344/N rats and B6C3F1 mice (inhalation studies)
Study type	acute or subchronic inhalation study	chronic	subchronic	chronic
Species	rats and mice	rat	rat	rat
Duration of exposure in key study	acute or subchronic (5 months)	6 h/d on 5 d/w over 105 w	6 h/d on 5 d/w over 14 w	6 h/d on 5 d/w over 105 w
Critical effect	CNS depression, narcosis	carcinogenicity	systemic toxicity (haematology, clinical chemistry and organ weights)	respiratory toxicity (hyperplasia, adenoma of nasal epithelia)
Critical dose value	500 ppm	BMD_{05} of 117 ppm	NOAEC of 125 ppm	$BMCL_{10}$ of 370 mg/m³
Adjusted critical dose	chronic	chronic	chronic	
Single assessment factors (see table R.8.6)	10	10 (for differences in the sensitivity rat → human)	overall assessment factor of 2	time scaling: 5.6 interspecies factor: 1 (kinetic) and 2.5 (dynamic); intraspecies factor: 10; sensitive population factor: 2
Other effects				
Confidence				

UFL used LOAEL; UFH intraspecies variability; UFA interspecies variability; UFS used subchronic study; UFD data deficiencies

Organisation Name	SCOEL	US EPA IRIS	US EPA	EU-RAR
Risk Value Name	TWA	RfC	AEGL-1	
Risk Value (mg/m³)	100	0.4	250	
Risk Value (ppm)	20	0.08	50	
Reference period	chronic (worker)	chronic (general population)	general population (1-8 h exposure)	
Year	1993	1997	2007	2001
Key Study	Bushy Run Research Center (1989): Cumene (isopropylbenzene) fourteen-week vapour inhalation study in rats with neurotoxicity evaluation. Project report 52-628	Cushman JR, Norris JC, Dodd JC et al. (1995): Subchronic inhalation toxicity assessment of cumene in Fisher 344 rats. J Am Coll Toxicol 14:129–147	Dow Chemical Company (1948): Toxicology and hygiene - isopropylbenzene.	Cushman JR, Norris JC, Dodd JC et al. (1995): Subchronic inhalation toxicity assessment of cumene in Fisher 344 rats. J Am Coll Toxicol 14:129–147
Study type	subchronic	subchronic	health surveillance	subchronic
Species	rat	rat	human	rat
Duration of exposure in key study	90 days (not further specified)	6 h/d on 5 d/w for 13 w	up to 2 years	6 h/d on 5 d/w for 13 w
Critical effect	CNS depression	increased kidney weights in female rats and adrenal weights in male and female rats	eye and respiratory tract irritation	changes in several hematol. and clinical chem. parameters, increased kidney weights in female rats and adrenal weights in male and female rats
Critical dose value	NOAEC of 100 ppm	NOAEC of 435 mg/m³	300 – 400 ppm	NOAEC 100ppm LOAEC 500ppm
Adjusted critical dose	chronic	chronic		
Single assessment factors (see table R.8.6)	5 (absence of human data)	1000	2 (for obtaining a concentration that would cause effects within the scope of AEGL-1 (i.e. mild eye and respiratory tract irritation)) and 3 (as uncertainty factor intraspecies variability)	
Other effects				
UFL used LOAEL; UFH intraspecies variability; UFA interspecies variability; UFS used subchronic study; UFD data deficiencies				

Compound	**Isopropylbenzene (cumene)**		***Factsheet***
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI value and status			
EU-LCI value	1	Mass/volume [µg/m^3]	1700
EU-LCI status	2	Draft/final	Final
EU-LCI year of issue	3	Year when the EU-LCI value was issued	2017
General information			
CLP Index No	4	INDEX	601-024-00-X
EC No	5	EINECS – ELINCS - NLP	202-704-5
CAS No	6	Chemical Abstracts Service number	98-82-8
Harmonised CLP classification	7	Human health risk-related classification	Asp. Tox. 1 (H304) STOT SE 3 (H335)
Molar mass and conversion factor	8	[g/mol] and [ppm – mg/m^3]	120.19 1 ppm = 4.94 mg/m^3
Key data / database			
Key study, author(s), year	9	Critical study with lowest relevant effect level	NTP (2009)
Read-across compound	10	Where applicable	
Species	11	Rat etc. / human	Rodent Male and female F344/N rats
Route/type of study	12	Inhalation, oral feed, etc.	Inhalation
Study length	13	Days, subchronic, chronic	Chronic 105 weeks
Exposure duration	14	Hours/day, days/week	6 hrs/day, 5 days/week
Critical endpoint	15	Effect(s), site of	Respiratory toxicity (hyperplasia in the olfactory epithelium)
Point of departure (POD)	16	LOAEC*L, NOAEC*L, NOEC*L, benchmark dose, etc.	$BMC_{10}L_{95}$
POD value	17	[mg/m^3] or [ppm] or [mg/kg$_{BW}$×d]	48 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	1
	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)	140
POD/TAF	28	Calculated value (µg/m³ and ppb)	…. 1693µg/m³ …. 340 ppb
Molar adjustment factor	29	Used in read-across	
Rounded value	30	[µg/m³]	1700
Additional comments	31		
Rationale section	32		

Data compilation for isopropylbenzene is based on a project funded by the German Environment Agency (Wibbertmann et al., 2017).

Isopropylbenzene (cumene) is a colourless liquid with low water solubility. The substance is used as an intermediate for the production of phenol and acetone, and in smaller amounts as a solvent or additive in aviation fuels.

In studies with volunteers, isopropylbenzene was rapidly absorbed after inhalation exposure, distributed in the body and rapidly excreted primarily in the urine. The major metabolite was 2-phenyl-2-propanol (Seńczuk & Litewka, 1976). The results of experimental animal studies also show that isopropylbenzene is rapidly absorbed, after oral administration or inhalation, distributed in the body and excreted via urine. From experiments with rats it appears that isopropylbenzene undergoes enterohepatic circulation and that saturation of specific degradation pathways occurs after intake of high doses (Chen et al., 2011). More than 15 partly unidentified metabolites were identified including α-methyl styrene.

In a chronic inhalation study, groups of 50 male and 50 female rats were exposed to cumene vapour at concentrations of 0, 250, 500, or 1 000 ppm, 6 hours per day, 5 days per week for 105 weeks. Survival of all exposed groups of rats was similar to that of the chamber controls. Mean body weights in 1 000 ppm females were slightly less than those of the chamber controls during the second year of the study but were similar to the chamber controls at the end of the study. Incidences of adenoma of the respiratory epithelium in the nose occurred with a positive trend in males and were significantly increased in all exposed groups of males and in 250 ppm females. Incidences of hyperplasia of basal cells in the olfactory epithelium in the nose of all exposed groups and hyperplasia of the respiratory epithelium in the nose of all exposed groups of males and 1 000 ppm females were significantly increased. The incidence of renal tubule adenoma in all exposed groups of males, renal tubule carcinoma in 500 and 1 000 ppm males, and renal tubule adenoma or carcinoma (combined) in all exposed groups of males was increased; the difference from chamber controls for the combined incidence was significant, at 500 ppm. The incidence of hyperplasia of the renal tubule and transitional epithelium of the renal pelvis in 500 and 1 000 ppm males and mineralisation of the renal papilla in all exposed groups of males was significantly greater than that of the chamber controls. The incidence of interstitial (including bilateral) cell adenoma of the testis was significantly increased in 1 000 ppm male rats and there was a positive trend in the incidences across all groups (NTP, 2009). As the critical endpoint was local damage of the respiratory epithelium in the nose, and as, in all, there is no evidence for genotoxic potential of cumene, a threshold can be assumed.

In a parallel study, groups of 50 male and 50 female mice were exposed to cumene vapour at concentrations of 0, 125 (female mice only), 250, 500, or 1 000 (male mice only) ppm, 6 hours per day, 5 days per week for 105 weeks. An exposure concentration-related decrease in survival occurred in male mice, and the survival of 1 000 ppm males was significantly less than that of the chamber controls. Mean body weights in 1 000 ppm males were generally less than those of the chamber controls after week 8 of the study, and those of 500 ppm females were less from week 28 until week 76 of the study. The incidence of alveolar/bronchiolar adenoma, alveolar/bronchiolar carcinoma, and alveolar/bronchiolar adenoma or carcinoma (combined) in all exposed groups of mice occurred with positive trends and was significantly greater than those in the chamber controls. The incidence of alveolar epithelial bronchiole metaplasia and bronchiole hyperplasia was significantly increased in all exposed groups of mice. p53 and Kras mutations were found in 52 % and 87 % of lung neoplasms in exposed mice, compared to 0 % and 14 % in the chamber controls, respectively. In female mice, the incidence of hepatocellular adenoma and hepatocellular adenoma or carcinoma (combined) occurred with positive trends and was significantly increased in the 500 ppm group. In male mice, there were significant

increases in the incidence of eosinophilic foci of the liver. The incidence of haemangiosarcomas in the spleen and of follicular cell adenoma in the thyroid gland was significantly increased in 1 000 ppm male mice. In the nose, the incidence of olfactory epithelium atrophy, basal cell hyperplasia of the olfactory epithelium, atypical hyperplasia of the olfactory epithelium, hyperplasia of olfactory epithelium glands, and suppurative inflammation was generally significantly increased in 500 and 1 000 ppm males and 500 ppm females. The incidence of squamous metaplasia of the respiratory epithelium was significantly increased in 500 ppm females. The incidence of basal cell hyperplasia was also significantly increased in 250 ppm females (NTP, 2009).

Cumene is classified as possibly carcinogenic for humans (group 2B) by the IARC. In mutagenicity/genotoxicity assays, both in vitro and in vivo, cumene was negative. Dose-related increases in DNA damage were observed in male rat liver cells and female mouse lung cells, but not in other tissues. Therefore, the mode of action of cumene appears to be primarily non-genotoxic. The observed difference between rats and mice in lung carcinogenicity may be explained by differences in the local metabolism, as there are more Clara cells in mice than in rats, which contain the ring-oxidising cytochromes P-450 CYP2F and CYP2E1. As in humans there are even less Clara cells than in rats, very low susceptibility of humans may be reasonably anticipated. The renal effects of cumene in male rats (tubular adenomas/ carcinomas) may reasonably be related to the specific α2μ-globulin-nephropathy, which is not relevant to humans. Damage to rat nasal tissue was not observed in subchronic studies at any concentration tested. In total, the existence of a threshold for the experimentally observed carcinogenic effects of cumene is very likely (NTP, 2009, 2012, 2013).

POD

The LCI derivation is based on a $BMC_{10}L_{95}$ of 48 ppm (237 μg/m^3), which was calculated considering hyperplasia of the olfactory epithelium (basal cells) (at 250ppm) in female rats as the critical endpoint (NTP, 2009). Based on the recommendations in EFSA guidelines (EFSA, 2009), and considering the design of the data (quantal data), the calculation of BMC_{10}/$BMC_{10}L_{95}$ was performed by the EU-LCI Group itself using BMDS software developed by the US EPA (Anses, France, data not published). BMC_{10}/$BMC_{10}L_{95}$ were calculated with the log-logistic model, with the assumption that the graph cuts both coordinates at zero (restriction).

Assessment factors

Factors further applied to the POD were: for exposure duration 24/6×7/5=5.6, for interspecies differences a default factor of 2.5, and for intraspecies difference a default factor of 10. Overall, the TAF is 5.6×2.5×10=140.

EU LCI

The calculated EU-LCI value is POD/TAF = 48 ppm/140=0.34 ppm (1693 μg/m^3 at 23 °C). After rounding, the EU-LCI-value is 1700 μg/m^3.

Cumene has a sharp, penetrating, gasoline-like odour, with an absolute odour threshold of 0.0084 ppm (Nagata, 2003).

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