Compound	Ethyl methyl ketone (2-butanone)	*Data collection sheet*
N°CAS 78-93-3	**CLP:** Eye Irrit. 2 (H319), STOT SE 3 (H336)	

Organisation name	**U.S. EPA**	**REACH registrants**	**OEHHA**	**NAC-AEGL**
Risk value name	RfC	DNEL	Acute REL	AEGL-1
Risk value (µg/m³)	5000	106000	13000	586000
Risk value (ppb)				
Reference period	chronic	chronic	acute (1 h)	acute (15 min – 8 h)
Year	2003	2011, update 2016	2008	2011
Key study	Schwetz, B.A.; Mast, T.J.; Weigel, R.J.; Dill, J.A.; Morrissey, R.E. (1991): Developmental toxicity of inhaled methyl ethyl ketone in Swiss mice. Fundam Appl Toxicol, 16, 742-748	not indicated	Nakaaki K (1974): An experimental study on the effect of exposure to organic solvent vapour in human subjects. J Sci Labour 50:89-96	Dick et al. 1992; Muttray et al. 2002; Seeber et al. 2002; Shibata et al. 2002
Study type	developmental toxicity	not indicated	acute study with exposure of human volunteers	acute study with exposure of human volunteers
Species	mouse	not indicated	human	human
Duration of exposure in key study	7 h/d, during days 6 – 15 of gestation		2 h	4 h
Critical effect	incidence of misaligned sternebrae	not indicated	subjective reports of eye, nose, and throat irritation, lacrimation and sneezing	subjective symptoms of irritation and annoyance
Critical dose value	LEC_{10} 5202 mg/m³	not indicated	LOAEC 270 ppm (802 mg/m³)	NOAEC 200 ppm (594 mg/m³)
Adjusted critical dose	LEC_{10} ($BMDL_{10}$) 1517 mg/m³ (continuous exposure); LEC_{10} (HEC) 1517 mg/m³		no adjustment required	no adjustment required
Single assessment factors (see table R.8.6)	UF_H 10 x UF_A 3 x UF_D 10 = 300	not indicated (total factor: 2)	UF_H 10 x UF_L 6 = 60	UF_H 1 = 1
Other effects				
Remarks	confidence: medium			

UFL used LOAEL; UFH intraspecies variability; UFA interspecies variability; UFS used subchronic study; UFD data deficiencies, AS allometric scaling

Compound	2-Butanone (ethyl methyl ketone)		Factsheet
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI value and status			
EU-LCI value	1	Mass/volume [µg/m^3]	20 000
EU-LCI status	2	Draft/final	Final
EU-LCI year of issue	3	Year when the EU-LCI value was issued	2016
General information			
CLP Index No	4	INDEX	606-002-00-3
EC No	5	EINECS — ELINCS — NLP	201-159-0
CAS No	6	Chemical Abstracts Service number	78-93-3
Harmonised CLP classification	7	Human health risk-related classification	Eye Irrit. 2, STOT SE 3
Molar mass and conversion factor	8	[g/mol] and [ppm — mg/m^3]	72.11 1ppm = 2.97 mg/m^3
Key data / database			
Key study, author(s), year	9	Critical study with lowest relevant effect level	Saillenfait et al. (2006)
Read-across compound	10	Where applicable	
Species	11	Rat etc. / human	Rat
Route/type of study	12	Inhalation, oral feed, etc.	Inhalation
Study length	13	Days, subchronic, chronic	GD 6-20
Exposure duration	14	Hours/day, days/week	6 h/d
Critical endpoint	15	Effect(s), site of	Maternal and foetal reduced weight
Point of departure (POD)	16	LOAEC*L, NOAEC*L, NOEC*L, benchmark dose, etc.	NOAEC
POD value	17	[mg/m^3] or [ppm] or [mg/kg$_{BW}$×d]	2000 ppm (5940 mg/m^3)
Assessment factors (AF)	**18**		
Adjustment for exposure duration	19	Study exposure hours/day, days/week	4
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)*	3

Result			
Summary of assessment factors	27	Total Assessment Factor (TAF)	300
POD/TAF	28	Calculated value (µg/m³ and ppb)	19800 µg/m³ and 6666.7 ppb
Molar adjustment factor	29	Used in read-across	
Rounded value	30	[µg/m³]	20 000
Additional comments	31		
Rationale section	32		

Data compilation and evaluation for ethyl methyl ketone is based on a project funded by the German Environment Agency (Voss JU, 2017, *in press*).

Ethyl methyl ketone (methyl ethyl ketone, MEK, 2-butanone) is a colourless, volatile liquid with an acetone-like minty odour. It occurs naturally at low concentrations in many plants and foodstuffs. In industry, large amounts are used as extraction solvent for grease and fats, in de-icing, adhesives and sealants and in polishes and waxes. MEK is detected at low concentrations (mostly < 10 µg/m^3) in indoor air in homes, nursery schools and offices. Traces (ca. 5 µg/L) have also been found in urine samples of non-occupationally exposed humans.

MEK is rapidly absorbed by inhalation (absorption rate ≥ 50 %). Distribution is rapid and into all organs. MEK is oxidised by P450 monoxygenases to 3-hydroxybutanone which is further metabolised. It is likely that most of the MEK is finally completely oxidised. Only small amounts of unchanged MEK are excreted by exhalation, and only small amounts (< 5 %) are excreted as metabolites in urine.

Rationale for critical effects

In a developmental study with mice, pregnant CD-1-mice (33/concentration) were exposed to 0, 400, 1000 or 3000 ppm MEK (0, 1188, 2970, 8910 mg/m^3, nominal concentrations) for 7 h/d on gestation day (GD) 6 – 15 (Schwetz et al., 1991). The liver weight of the dams was increased at the highest concentrations, without other signs of maternal toxicity. At the highest concentration, the body weight of male foetuses was significantly decreased (5 %), the effect was similar (4 %) but missed statistical significance in females. Additionally, there was a positive trend for an increased incidence of foetuses with misaligned sternebrae. The NOAEC in this study was 1010 ppm (2970 mg/m^3).

In a similar study with Sprague-Dawley rats (18-26/concentration) exposed 7 h/d on GD 6 – 15 to 0, 400, 1000, 3000 ppm MEK (0, 1188, 2970, 8910 mg/m^3), maternal toxicity (reduced weight gain) was observed at the highest concentration. Furthermore, there was an increased incidence of a skeletal variation (extralumbal rips) in foetuses at the highest concentrations. No teratogenic effects were observed (Deacon et al., 1981).

In a previous study with exposure of Sprague-Dawley rats (21-23/group) to 0, 1000 or 3000 ppm (0, 2970, 8610 mg/m^3), 7 h/d, GD 6 – 15, reduced ossification of sternebrae was observed in foetuses of dams exposed to 3000 ppm MEK (8610 mg/m^3). In this study, four rare malformations were also noted at the highest concentration (Schwetz et al., 1991). However, this effect was not confirmed in later studies of the same group in rats (Deacon et al., 1981) and mice (Schwetz et al., 1991).

In a further set of two developmental toxicity studies, Sprague-Dawley rats were exposed for 6 h/d on days 6 - 20 of gestation to 0, 1000, 2000, 4000, 6000 ppm (0, 2970, 5940, 11880, 17820 mg/m^3) (first experiment, 19-23 pregnant dams/concentration) or 0, 1000, 3000 ppm MEK vapour (0, 2970, 8910 mg/m^3) (second experiment, 15-19 pregnant dams/concentration). From 3000 ppm, maternal weight gain and food consumption were significantly lower compared to control. Foetal body weight also was lower at ≥ 3000 ppm. No exposure-related embryolethality was observed. No increases in skeletal or visceral variations or malformation were observed up to 3000 ppm; at 4000 and 6000 ppm, a total of four foetuses showed several malformations.

It should be noted that similar malformations (anal atresia, tail malformations) had already previously been observed in 2 foetuses in another study with rats and considered as rare (Schwetz et al., 1974). Skeletal variations (in total and incidence of supernumerary 14th rib) were non-significantly increased at 3000 ppm, and the

incidence of incomplete ossification of sternebrae was significantly increased at 4000 ppm (Saillenfait et al., 2006). The overall NOAEC from both experiments of this study is 2000 ppm (5940 mg/m^3).

Rationale for starting point (POD)

The NOAEC of 2000 ppm (5940 mg/m^3) from the developmental toxicity studies was taken as the POD for the derivation of EU-LCI.

Rationale for extrapolation factors

- Adjustment for exposure duration: 4 (24/6)
- Interspecies differences: 2.5
- Intraspecies differences: 10
- Uncertainty: 3 (no chronic toxicity/carcinogenicity study, no two-generation reproductive toxicity study).

Total extrapolation factor is 300, leading to a rounded value of 20000 µg/m^3. The derived value is higher than the reported absolute odour threshold of 0.44 ppm (1.3 mg/m^3) (Nagata, 2003). Thus, odour perception is likely at the proposed EU-LCI value.

References

Nagata Y. (2003): Measurement of odor threshold by triangle odor bag method. Odor Measurement Rev 118-127.

Saillenfait AM, Gallissot F, Sabate JP, et al. (2006) Developmental toxicity of combined ethylbenzene and methylethylke-tone administered by inhalation to rats. Food Chem Toxicol 44:1287-1298

Deacon MM, Pilny MD, John JA, et al. (1981) Embryo- and fetotoxicity of inhaled methyl ethyl ketone in rats. Toxicol Appl Pharmacol 59:620-622.

Schwetz BA, Leong BK, Gehring PJ (1974) Embryo- and fetotoxicity of inhaled carbon tetrachloride, 1.1-dichloroethane and methyl ethyl ketone in rats. Toxicol Appl Pharmacol 28:452-464.

Schwetz BA, Mast TJ, Weigel RJ, Dill JA, Morrissey RE (1991) Developmental toxicity of inhaled methyl ethyl ketone in Swiss mice. Fundam Appl Toxicol 16:742-748.

Voss JU (2017) Toxikologische Basisdaten und Textentwurf für die Ableitung von EU-LCI-Werten für Triethylamin (CAS Nr. 121-44-8), Tributylphosphat (CAS Nr. 126-73-8), Triethylphosphat (CAS Nr. 78-40-0), Methylmethacrylat (CAS Nr. 80-62-6) und Ethylmethylketon (CAS Nr. 78-93-3). UBA Texte, *in press*.