Compound	**Acetone**			***Data collection sheet (1/3)***
N°CAS 67-64-1 **1 ppm ~ 2.39 mg/m³**	**CLP: Eye irrit. 2 (H319), STOT SE 3 (H336)**			
Organisation name	**AgBB**	**DFG (DE)**	**BAuA (DE)**	**INRS (FR)**
Risk value name	NIK (=LCI)	MAK (OEL 8h)	AGW (OEL 8h)	VLEP
Risk value (mg/m³)	1.2	1200	1200	1210
Risk value (ppm)	0.5	500	500	500
Reference period	Chronic	Chronic	Chronic	Chronic
Year	2018	1993, 2013	2015	2012
Key study	NIK derivation based on the review performed by the Committee on Hazardous Substances (AGS)	Matsushita et al. 1969a	Matsushita et al. 1969a	Raleigh and McGee, 1972 Matsushita et al., 1969a, 1969b Seeber et al. 1992
Study type		Controlled inhalation chamber study	Controlled inhalation chamber study	Human inhalation studies
Species		Human (volunteers)	Human (volunteers)	Human (volunteers/workers)
Duration of exposure		6 h/day for 6 days	6 h/day for 6 days	(Sub)acute
Critical effect		Irritation of mucous membranes eyes, nose and throat CNS effects	Irritation of mucous membranes eyes, nose and throat CNS effects	Mild irritative and neurobehavioral effects

Critical dose value	1200 mg/m^3 (500 ppm)	LOEC: 500 ppm (1200 mg/m^3)	MAK: 1200 mg/m^3 (500 ppm)	LOEC: 1000 ppm (2420 mg/m^3)
Adjusted critical dose		"In view of the marked irritation and effects on ratings of well-being seen at an acetone concentration of 1000 ml/m^3 and the weak, reversible reactions seen at 500 ml/m^3 in some, but not all persons, a MAK value of 500 ml/m^3 (1200 mg/m^3) is considered to be appropriate."	In view of the marked irritation and effects on ratings of well-being seen at an acetone concentration of 1000 ml/m^3 and the weak, reversible reactions seen at 500 ml/m^3 in some, but not all persons, a MAK value of 500 ml/m^3 (1200 mg/m^3) is considered to be appropriate."	N/A
Single assessment factors	1000 (factor of 100 * an extra factor of 10 to account for developmental toxicity)	N/A	N/A	„In view of the mild nature of the symptoms, and because tolerance develops in workers, an uncertainty factor of 2 was considered adequate."
Other effects	N/A	N/A	N/A	N/A

Compound	Acetone				*Data collection sheet (2/3)*
N°CAS 67-64-1 **1 ppm ~ 2.39 mg/m³**	**CLP: Eye irrit. 2 (H319), STOT SE 3 (H336)**				
Organisation name	**AFS (SE)**	**RIVM (NL)**	**SCOEL (EU)**	**OSHA (EU)**	**ECHA registered substance**
Risk value name	NGV	OEL (TWA 8h)	OEL (TWA 8h)	OEL (TWA 8h)	DNEL(General population, long-term, inhalation, systemic)
Risk value (mg/m³)	600	1210	1210	1210	200
Risk value (ppm)	250	500	500	500	84
Reference period	Chronic	Chronic	Chronic	Chronic	Chronic
Year	1993	2004	1997	2000	2018
Key study	N/A	Raleigh and McGee, 1972 Matsushita et al., 1969a, 1969b Seeber et al. 1992	Raleigh and McGee, 1972 Matsushita et al., 1969a, 1969b Seeber et al. 1992	Raleigh and McGee, 1972 Matsushita et al., 1969a, 1969b Seeber et al. 1992	Raleigh and McGee, 1972 Matsushita et al., 1969a, 1969b Seeber et al. 1992
Study type	N/A	Human inhalation studies	Human inhalation studies	Human inhalation studies	Human inhalation studies
Species	N/A	Human (volunteers/workers)	Human (volunteers/workers)	Human (volunteers/workers)	Human (volunteers/workers)
Duration of exposure	N/A	(Sub)acute	(Sub)acute	(Sub)acute	(Sub)acute
Critical effect	N/A	Mild irritative and neurobehavioral effects	Mild irritative and neurobehavioral effects	Mild irritative and neurobehavioral effects	Mild irritative and neurobehavioral effects

Critical dose value	N/A	LOEC: 1000 ppm (2420 mg/m^3)	LOEC: 1000 ppm (2420 mg/m^3)	LOEC: 1000 ppm (2420 mg/m^3)	OEL: 1210 mg/m^3
Adjusted critical dose	N/A	N/A	N/A	N/A	1210 mg/m^3 * 0.33 (8 h /24 h to adjust for continuous exposure)
Single assessment factors	N/A	„In view of the mild nature of the symptoms, and because tolerance develops in workers, an uncertainty factor of 2 was considered adequate.“	„In view of the mild nature of the symptoms, and because tolerance develops in workers, an uncertainty factor of 2 was considered adequate.“	„In view of the mild nature of the symptoms, and because tolerance develops in workers, an uncertainty factor of 2 was considered adequate.“	UF_H 2
Other effects	N/A	N/A	N/A	N/A	N/A
UF_H Intraspecies variability					

Compound	**Acetone**			***Data collection sheet (3/3)***
N°CAS 67-64-1 **1 ppm ~ 2.39 mg/m³**	**CLP: Eye irrit. 2 (H319), STOT SE 3 (H336)**			
Organisation name	**ATSDR (US)**	**ACGIH (US)**	**NIOSH (US)**	**OSHA (US)**
Risk value name	MRL	TLV (8h TWA)	REL (10h TWA)	PEL (8h TWA)
Risk value (mg/m³)	31	594	590	2400
Risk value (ppm)	13	250	250	1000
Reference period	Chronic	Chronic	Chronic	Chronic
Year	1994	2015	1988	2009
Key study	Stewart et al., 1975	Matsushita et al., 1969a	Matsushita et al., 1969b supported by other human studies (Nelson et al., 1943; Parmengianni and Sissi, 1954; Vigiliani and Zurlo, 1955)	N/A
Study type	Controlled inhalation chamber study	Controlled inhalation chamber study	Human controlled inhalation and occupational studies	N/A
Species	Human (volunteers)	Human (volunteers)	Human (volunteers/workers)	N/A
Duration of exposure	3 or 7.5 h/day, 4 days/week for 1 (women) or 4 weeks (men)	6 h/day for 6 days	Various exposures	N/A
Critical effect	Neurological effects in men	Irritation of mucous membranes eyes, nose and throat	Narcosis, CNS depression	Slight eye, nose, and respiratory irritation

	(changes in the visual evoked response)	CNS effects	Eye, skin, nose and throat irritation	
Critical dose value	LOAEC: 1250 ppm (2987 mg/m^3)	LOEC: 250 ppm (594 mg/m^3)	LOAEC: 250 ppm (590 mg/m^3)	N/A
Adjusted critical dose	N/A	N/A	N/A	N/A
Single assessment factors	UF_H 10 x UF_L 10 = 100	"The TLV-TWA of 250 ppm…is recommended for occupational exposure to acetone in order to minimize the potential of upper respiratory tract and eye irritation as well as central nervous system impairment…The TLV recommendation for acetone has been developed to protect both workers who have developed sensory habituation due to repeated acetone exposure, and workers without habituation, occasionally exposed to acetone."	N/A	N/A
Other effects	Shortened menstrual cycle	N/A	N/A	N/A
UF_H Intraspecies variability; UF_L Used LOAEL				

Compound	**Acetone**		***Factsheet***
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI value and status			
EU-LCI value	1	Mass/volume [µg/m^3]	120000
EU-LCI status	2	Draft/final	Final
EU-LCI year of issue	3	Year when the EU-LCI value has been issued	2018
General information			
CLP-INDEX-No.	4	INDEX	none
EC-No.	5	EINECS – ELINCS - NLP	200-662-2
CAS-No.	6	Chemical Abstracts Service number	67-64-1
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]	58.08 1 ppm = 2.39 mg/m^3
Key data / database			
Key study, author(s), year	9	Critical study with lowest relevant effect level	Matsushita et al., 1969a
Read across compound	10	Where applicable	
Species	11	Rat, human, etc.	Human
Route/type of study	12	Inhalation, oral feed, etc.	Inhalation
Study length	13	Days, subchronic, chronic	Subacute
Exposure duration	14	Hrs/day, days/week	6 h/day for 6 days
Critical endpoint	15	Effect(s), site of	Sensory irritation
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]	250 ppm
Assessment factors (AF)	**18**		
Adjustment for exposure duration	19	Study exposure hrs/day, days/week	1
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	1
Intraspecies differences	24	Kinetic + dynamic Worker - general population	5
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)	5
POD/TAF	28	Calculated value (µg/m³ and ppb)	119500 µg/m³ and 50000 ppb
Molar adjustment factor	29	Used in read-across	
Rounded value	30	[µg/m³]	120000
Additional comments	31		
Study written in Japanese with English abstract and data presentation			
Rationale section	**32**		

Data compilation and evaluation for acetone are based on a project funded by the European Commission and carried out by Ramboll Environment & Health GmbH (formerly BiPRO GmbH).

The numerous comprehensive assessment reports on acetone published by various organisations or national agencies were evaluated for relevant data for the EU-LCI derivation of acetone (ACGIH, 2015; ATSDR, 1994, 2011; EPA, 2003; Health Canada, 2014; MAK, 1996, 2013; OECD, 1999; WHO, 1998). A targeted literature search using PubMed and Google Scholar was also conducted with the aim of identifying any relevant literature on the inhalation exposure of acetone that is not addressed in these data sources. The entire body of data was used for the evaluation and derivation of an EU-LCI value for acetone.

Rationale for key study/POD

No chronic toxicity studies are available of acetone in experimental animals. Repeated inhalation studies showed only mild neurobehavioural effects in rodents at concentrations starting at 6000 ppm (14340 mg/m³) (Bruckner & Peterson, 1981; Buron et al., 2009; Christoph et al., 2003; Goldberg et al., 1964). There is also an NTP developmental toxicity study in rats and mice that exhibited some developmental effects at 11000 and 6600 ppm (26290 and 15774 mg/m³), respectively. The NOAEC for developmental toxicity was set at 2200 ppm (5258 mg/m³, the second highest concentration tested) (NTP, 1988).

A number of occupational studies have reported effects of long-term exposure to acetone (Satoh et al., 1996; Vigliani and Zurlo, 1955), but they were not considered suitable for the EU-LCI derivation because

there was insufficient information on potential exposure to other solvents. Also, the Satoh et al. (1996) study only examined subjective symptoms reported by the workers via self-administered tests (i.e. no medical examinations or tests were conducted). Studies of single or acute exposure to acetone (less than 24 h) were also excluded from the evaluation. This resulted in two controlled inhalation chamber studies in humans being considered suitable for the EU-LCI derivation (Matsushita et al., 1969a; Stewart et al., 1975). Both studies reported some neurobehavioural and irritative effects upon exposure to acetone at much lower concentrations than those reported in animal studies.

A controlled inhalation chamber exposure study by Matsushita et al. (1969a) was performed on six adult male volunteers (average age 22; smoking status unclear) with exposures to 0, 250 or 500 ppm (0, 597, 1195 mg/m^3, respectively) acetone for 6 hours/day for 6 days. At 250 ppm, mild irritative effects were reported. At 500 ppm, irritation of the mucosal membrane and complaints of annoying odour were noted from most of the volunteers, along with some reports of eye, nose and throat irritation as well as complaints of weakness, headaches and heavy feeling in the head. Volunteers exposed to 500 ppm also showed haematological effects such as increased leukocyte and eosinophil counts and decreased neutrophil phagocytic activity (Matsushita et al., 1969a).

The other controlled inhalation chamber study by Stewart et al., (1975), as described in ATSDR (1994), Johanson (2012) and Health Canada (2014), investigated various health effects in healthy adult volunteers of both sexes exposed to progressively increasing concentrations of acetone vapours over 6 weeks in a controlled inhalation chamber. Four male subjects (age 22–27 years) were exposed for 3 or 7.5 h/day, 4 days/week to 0 ppm (week 1), 200 ppm (478 mg/m^3; week 2), 1000 ppm (2390 mg/m^3; week 3), 1250 ppm (2987 mg/^{3}; week 4), 0 ppm (week 5), and 750–1250 ppm (1792-2987 mg/m^3, fluctuating; average 1000 ppm i.e. 2390 mg/m^3; week 6) acetone vapours. The first day of each week was an additional control exposure to 0 ppm acetone. Examined health-related endpoints included clinical signs and symptoms, subjective responses, body temperature, blood pressure, complete blood count, clinical blood chemistry, urinary analyses and heart (heart rate, electrocardiography), lung (minute ventilation, expiratory flow rate, alveolar–capillary gas exchange, vital capacity) as well as neurophysiological and neurobehavioural tests. The only exposure-related effect observed was an increase in visual evoked response after 7.5 hours of exposure to 1250 ppm acetone in three of four subjects. Subjective symptoms, mainly of an irritative nature, were reported over the exposure weeks (Stewart et al., 1975). As only one concentration was tested, the LOAEC for this study was set at 1250 ppm (2987 mg/m^3) based on the increase in visual evoked response.

Of these two studies, the Matsushita et al. (1969a) study was selected as the key study for the following reasons:

- even though the Stewart et al. (1975) study had a longer exposure duration (6 weeks), exposure durations for both studies are subacute in nature;
- the volunteers in the Matsushita et al. (1969a) study were consistently exposed to the same concentration of acetone (i.e. 0, 250 or 500 ppm corresponding to approximately 0, 597, 1195 mg/m^3, respectively) over 6 days. The Stewart et al. (1975) study, however, progressively increased the acetone concentration over 6 weeks, starting with 0 ppm at week 1 and then going up to 1250 ppm (2987 mg/m^3) by week 6. Since effects (irritative, neurobehavioural and haematological) were reported and observed already at 500 ppm (1195 mg/m^3), the Matsushita et al. (1969) study is considered the more conservative of the two, and would also address the neurobehavioural effect of enhanced visual evoked response observed at 1250 ppm (2987 mg/m^3) in the Stewart et al. (1975) study.

With this considered, the NOAEC of the Matsushita et al. (1969a) study of 250 ppm (597 mg/m^3) for sensory irritative effects (eye, nose and throat) was selected as the point of departure (POD). The POD selection of 250 ppm as NOAEC is supported by other human exposure studies, in which no adverse effect levels have been reported at 250 ppm or higher (Ernstgard et al., 1999; OECD, 1999; Seeber et al., 1992).

It should be mentioned that the Matsushita et al. (1969a) study was used as a key study by several authorities and organisations (e.g. EU SCOEL, DFG, ACGIH) to derive the occupational limit value of 500 ppm (1195 mg/m^3) for acetone, also based on the reported irritative and neurobehavioural effects.

Assessment factors (AF)

At the POD of 250 ppm (597 mg/m^3), only slight irritative and neurobehavioural effects were observed. No AFs were applied for severity of effects (mild sensory irritation), study length or exposure duration, as these effects were reported to occur within minutes of exposure. No AFs were applied for interspecies extrapolation, as the key study is a human volunteer study. For intraspecies variability an AF of 5 was applied, since there are numerous human studies of inhalation exposure to acetone, including controlled chamber studies of healthy volunteers, occupational exposures, and accidental exposures, with the critical effect for the EU-LCI derivation of acetone of sensory irritation. Altogether, the total assessment factor was determined to be 5.

This resulted in a calculated value of 119500 µg/m^3 and a derived EU-LCI for acetone of 120000 µg/m^3 (50 ppm).

This EU-LCI value (120000 µg/m^3 or 50 ppm) is above the lowest odour threshold level of 13 ppm (ACGIH, 2015), but it is worth mentioning that acetone concentrations around 100 ppm in human studies do not exhibit health effects, and most people find an acetone concentration of 200 ppm in air to be acceptable (MAK, 1996, 2013).

Appendix: Endogenous production of acetone in humans

The derived EU-LCI value of acetone is based on inhalation exposure to acetone, but to assess human health risks it is important to also consider endogenous levels of acetone produced in humans due to the breakdown of acetyl-CoA during fatty acid metabolism and the citric acid cycle. Endogenous levels of acetone vary significantly among individuals, since numerous factors contribute to its endogenous production, such as health status, age, food consumption, etc.

Human plasma acetone concentrations under various scenarios (such as occupational exposure or disease) were estimated and provided in the OECD SIDS (1999) report on acetone. For healthy individuals and occupationally exposed workers, upper plasma acetone limits have been reported of 10 and 100 mg/L, respectively. Diseased individuals, such as those with diabetic ketoacidosis, have reported plasma acetone levels ranging from 100-700 mg/L with exposure classified as toxic from 200 mg/L.

Normal endogenous production of acetone results in concentrations of 1.3 mg/L (0.02 mM) in blood, 1.4 mg/L (0.02 mM) in urine and 1.7 mg/m^3 (0.7 ppm) in alveolar air (MAK, 2013). Several studies of biomonitoring or toxicokinetics of acetone indicated blood acetone background concentrations in healthy, non-occupationally exposed individuals in the range 0.84-13 mg/L, and plasma concentrations in the range 0.41-4.35 mg/L (Ernstgard et al., 1999; Gentry et al., 2003; Health Canada, 2014). The total turnover rate of acetone in healthy human subjects has been calculated at 0.10-0.25 mg/min (or 6-15 mg/h) (Johanson, 2012).

Toxicokinetic modelling and calculation using time-concentration data from 10 healthy male volunteers continuously exposed to 250 ppm acetone for 2 hours reported a steady-state blood acetone level of 59 mg/L (below the OECD-classified toxic level of 200 mg/L). At this concentration, no discomfort was mentioned by the volunteers (Ernstgard et al., 1999).

Putting this information in context, it is not expected that exposure of the general population (excluding diseased individuals) to the EU-LCI value for acetone of 120000 µg/m^3 (50 ppm) would result in the blood acetone concentration above 200 mg/L that is associated with toxicity.

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