Compound	Acetaldehyde		*Data collection sheet (1)*	
Nº CAS 75-07-0 1 ppm = 1.81 mg/m³ at 23 °C	**EU-Classification:** **CLP,** harmonised classification: Eye Irrit. 2, H319, STOT SE 3, H335, Muta. 2, H341, Carc. 1B, H350			
Organisation name	**EU LCI**	**OEHHA**	**US EPA**	**German AIR**
Risk value name	EU LCI	Inhalation REL	RfC	RW I
Risk value (µg/m³)	1200	140	9	100
Reference period	Chronic	Chronic	Chronic	Chronic
Year	2012	2008	1991	2013
Key study	Appelman et al., 1982	Appelman et al., 1982; 1986; supported by Saldiva et al., 1985; Woutersen et al., 1986, 1984; Woutersen and Feron, 1987	Appelman et al., 1986	Dorman et al., 2008
Study type	Subacute	Subacute	Subacute	Subchronic
Species	Rat	Rat	Wistar rat	F344 rats
Duration of exposure in key study	Inhalation exposure 6 h/d, 5 d/w, 4 w	Inhalation exposure 6 h/d, 5 d/w, 4 w	Inhalation exposure 6 h/d, 5 d/w, 4 w	Inhalation exposure 6 h/d, 5 d/w, 13 w
Critical effect	Nasal irritation	Respiratory system: degenerative, inflammatory and hyperplasic changes of the nasal mucosa in animals	Degeneration of olfactory epithelium	Degeneration of olfactory epithelium
Critical dose value	NOAEC: 275 mg/m³	NOAEC: 275 mg/m³	NOAEC: 275 mg/m³	LOAEC: 150 mg/m³
Adjusted critical dose	49 mg/m³	BMC_{05}: 178 mg/m³ HEC: 242 mg/m³ HEC adjusted: 43.2 mg/m³	Temporal + HC*: 8.7 mg/m³	48 mg/m³
Single assessment factors	UF_S 2 x UF_H 10 x UF_e 2	UF_A √10 x UF_S √10x UF_H (10 x √10) = 300	UF_S 10 x UF_A 10 x UF_H 10 = 1000	UF_L 10 x UF_H 10 x 2 UF_A 1 = 400
Other effects				
Remarks				RW (Indoor guide value) I set as 1/10 of RW II

AgBB = Ausschuss zur gesundheitlichen Bewertung von Bauprodukten

UF_L Used LOAEL; UF_H Intraspecies variability; UF_A interspecies variability; UF_S Used subchronic/subchronic study UF_D dose-response at low dose UF_e severity of effect.

*: The NOAEL(HEC) was calculated for a gas: respiratory effect in the extra thoracic region.
MVa = 0.23 m^3/day, MVh = 20 m^3/day, Sa(ET) = 11.6 sq. cm, Sh(ET) = 177 sq. cm.
RGDR(ET) = (MVa/Sa) / (MVh/Sh) = 0.18
NOAEL(HEC) = NOAEL(ADJ) x RGDR = 8.7 mg/m^3

Compound	Acetaldehyde	*Data collection sheet (2)*
Nº CAS 75-07-0 1 ppm = 1.81 mg/m³ at 23 °C	**EU-Classification:** **CLP,** harmonised classification: Eye Irrit. 2, H319, STOT SE 3, H335, Muta. 2, H341, Carc. 1B, H350	
Organisation name	**Health Canada**	**ANSES**
Risk value name	RIAQG	VGAI
Risk value (µg/m³)	280	160
Reference period	Chronic	1 a
Risk value (µg/m³) **Short term**	1420 (1 h)	3000 (1 h)
Year	2017	2014
Key study	Dorman et al. (2008)	Dorman et al. (2008)
Study type	Subchronic (90 d)	Subchronic (90 d)
Species	F344 rats	F344 rats
Duration of exposure in key study	Inhalation exposure 6 h/d, 5 d/w, 13 w	Inhalation exposure 6 h/d, 5 d/w, 13 w
Critical effect	Degeneration of olfactory epithelium	Degeneration of olfactory epithelium
Critical dose value	NOAEC: 89 mg/m³	NOAEC: 90 mg/m³
Adjusted critical dose	HEC: 120 mg/m³	HEC: 12 mg/m³ (adjustment to account for dosimetric differences between animal species and humans) No adjustment for continuous exposure (considering that the toxicity of sensory irritants such as acetaldehyde would be more dependent on concentration than on duration of exposure)
Single assessment factors	UF_H 10 x UF_A 2.5 x UF_S 2 x UF_D 3 = 75	UF_H 10 x UF_A 2.5 x UF_S 3 = 75
Other effects		
Remarks	Short-term value based on acute inhalation study in humans (Prieto et al., 2000)	Short-term value based on acute inhalation study in humans (Prieto et al., 2000)

AgBB = Ausschuss zur gesundheitlichen Bewertung von Bauprodukten
UF_L Used LOAEL; UF_H Intraspecies variability; UF_A interspecies variability; UF_S Used subchronic study UF_D dose-response at low dose.

Compound	**Acetaldehyde C2H4O**		***Factsheet***
Parameter	**Note**	Comments	Value / descriptor
EU-LCI value and status			
EU-LCI value	1	[µg/m^3]	300
EU-LCI status	2	Draft/Final	Final
EU-LCI year of issue	3	Year when EU-LCI value has been issued	2020
General information			
CLP-Index No.	4	INDEX	605-003-00-6
EC-No.	5	EINECS	200-836-8
CAS-No.	6	Chemical Abstract Service number	75-07-0
Harmonised CLP classification	7	Human health risk related classification	Eye Irrit 2, H319, Muta. 2, H341, Carc. 1B, H350, STOT SE 3, H335
Molar mass and conversion factor	8	[g/mol] and [ppm – mg/m^3]	44.05 (1 ppm = 1.81 mg/m^3)
Key data / database			
Key study, authors, year	9	Critical study with lowest relevant effect level	Dorman et al. (2008)
Read across compound	10	Where applicable	-
Species	11	Rat, human, etc.	Rat, F344 (12 male/dose)
Route / type of study	12	Inhalation, oral feed, etc.	Inhalation
Study length	13	Days, subchronic, chronic, etc.	3 months (subchronic)
Exposure duration	14	h/d, d/w	6 h/d, 5 d/week
Critical endpoint	15	Effect (s), site of	Lesions of nasal epithelia
Point of departure (POD)	16	LOAEC, NOAEC, BMD, etc.	NOAEC
POD value	17	[mg/m^3] or ppm or [mg/kg$_{BW}$×d]	90 mg/m^3
Assessment factors (AF)	18		
Adjustment for exposure duration	19	Study exposure h/d, d/w	5.6
Study length	20	sc→c	2
Route-to-route extrapolation factor	21	-	1
Dose-response	22a	Reliability of dose-response, LOAEL to NOAEL	1
	22b	Severity of effect (R8 6d)	1
Interspecies differences	23a	Allometric Metabolic rate (R8-3)	1
	23b	Kinetic + dynamic	2.5
Intraspecies differences	24	Kinetic + dynamic General population	10
AF (sensitive population)	25		1
Other adjustment factors Quality of database	26		1
Result			
Summary of assessment factors	27	Total Assessment Factor	280
POD/TAF	28	Calculated value [µg/m^3 and ppb]	321 µg/m^3 and 176.8 ppb
Molar adjustment factor	29		

Rounded value	30	[µg/m^3]	300
Additional comments	31		
Rationale section	32		

- **Rationale for critical effects**

Acetaldehyde is found ubiquitously in nature, including foodstuffs and in the human body, mainly as an intermediate in ethanol oxidation, but also from endogenous sources by regular intermediary metabolic reactions. The endogenous acetaldehyde concentration in whole blood is estimated as about 2.2 ± 1.1 µmol/l (96.9 ± 48.5 µg/l) (DFG, 2008). Acetaldehyde is excreted from the human body in small amounts with exhaled breath. A concentration of about 40 µg/m^3 (22 ppb) can be regarded as a mean physiological level of acetaldehyde (Lourenco and Turner, 2014).

Sensory irritation following acetaldehyde inhalation has been observed in controlled human studies. Eye irritation was reported after 15 min of exposure to ≥ 91 mg/m^3 acetaldehyde (Silverman et al., 1946). In a well-conducted controlled study with volunteers 50 ppm acetaldehyde (91 mg/m^3) caused no signs of sensory irritation and no increase in inflammation or in the concentration of inflammation indicators during or after a 4 h exposure (Muttray et al., 2009).

No human data relevant for the evaluation of repeated inhalation exposure effects of acetaldehyde is available. In animal inhalation studies, the upper respiratory tract, especially the nasal epithelia, is the target organ of the toxic and carcinogenic effects of acetaldehyde. Systemic (non-specific) effects (reduced body weight gain, loss of weight, mortality) were only observed after exposure to high concentrations of acetaldehyde which caused local tissue lesions in the respiratory tract.

In a subchronic inhalation toxicity study with rats a NOAEC of 90 mg/m^3 (50 ppm) was obtained for effects on the olfactory nasal epithelium which is the target tissue of the toxic effects of acetaldehyde upon inhalation. Acetaldehyde caused degeneration of the olfactory nasal epithelium at 270 mg/m^3 (150 ppm) (Dorman et al., 2008).

Chronic inhalation exposure to acetaldehyde at much higher concentrations (≥ 1350 mg/m^3) led to local cytotoxicity and to the development of tumours in the nasal epithelia of rats (and, with weaker evidence, in the respiratory epithelium of nose and larynx in hamsters). The olfactory nasal epithelium was more sensitive than the respiratory nasal epithelium. Chronic inhalation studies at lower exposure concentrations are not available.

- **Rationale for starting point**

The results of the subchronic inhalation toxicity study with rats (Dorman et al., 2008) are the most relevant for the derivation of an EU-LCI value for acetaldehyde. In this study a NOAEC of 90 mg/m^3 (50 ppm) was obtained for effects on the olfactory nasal epithelium. Acetaldehyde caused degeneration of the olfactory nasal epithelium at 270 mg/m^3 (LOAEC). The study was conducted in male animals. However, no relevant sex-specific differences are to be expected for the observed cytotoxic non-specific lesions and no additional factor is considered necessary to account for missing data for females.

The critical effect at the LOAEC was observed already after 4 exposures. The effect, if any, only very slightly increased in severity and incidence with further increasing exposure time. A similar time dependency was noted at 910 mg/m^3. A more pronounced increase in the severity of the lesions over time occurred at 2730 mg/m^3. Taking into account the observation that these lesions are not reversible after cessation of exposure (Woutersen and Feron, 1987) and that chronic inhalation of high, cytotoxic concentrations of acetaldehyde lead to the development of tumours in the nasal epithelia of rats, it is concluded that a time extrapolation factor of 3 is appropriate to avoid cytotoxic effects in the target tissue during chronic exposure.

In case of the structural analogue (but much more potent) formaldehyde, data from animal studies provide strong evidence that the local tissue damage in the epithelia of the respiratory tract depend on the concentration level during exposure and less on the total dose. A similar reaction to acetaldehyde can be assumed. However the data base for acetaldehyde is less extensive and does not allow firm conclusions. Therefore the experimental NOAEC is adjusted for continuous exposure.

The standard interspecies factor of 2.5 is retained in accordance with the ECA report (EC, 2013).

Acetaldehyde reacts directly with organic compounds without metabolic activation, hence enzyme polymorphism is not considered to play a significant role in this step. However the oxidation (and thus inactivation) of acetaldehyde is catalysed by enzymes, some of them expressing interindividual differences in activity. Especially, the aldehyde dehydrogenase ALDH2 is a polymorphic enzyme with a nearly inactive variant which is found in parts of the human population, especially in Asians. The role of this polymorphism is widely discussed within the scope of the carcinogenicity of ethanol and the role of its metabolite acetaldehyde (Mizumoto et al., 2017), but not well studied in case of acetaldehyde exposure itself. According to the PBPK model of Teeguarden et al. (2008), this polymorphism does not affect the local dose of acetaldehyde at the target tissue. On the other hand animal experiments with knockout mice deficient in ALDH2 (Oyama et al., 2007; Oyama et al., 2010) showed, especially at the higher concentration, more pronounced lesions in knockout than in wild-type mice in the nasal epithelium. The effects and the differences between wild-type and knockout-mice were less pronounced at the lower concentration. Overall the differences in these studies were within a range of 10.

In conclusion, the intraspecies factor of 10 is kept to allow for the interindividual variability within the human population.

- **Rationale for assessment factors**

The following factors are used:

► Adjustment for continuous exposure (6 h/d, 5 d/week): 5.6

► Adjusted study length factor (subchronic to chronic exposure): 2

► Interspecies extrapolation: 2.5

► Intraspecies extrapolation (interindividual variability, general population): 10

Total assessment factor: 280. This leads to a concentration of 90 mg/m^3 : 280 = 0.321 mg/m^3.

A EU-LCI value (rounded) for acetaldehyde of 300 µg/m^3 is proposed.

The German MAK commission calculated that under steady-state conditions the lowest mean endogenous aldehyde concentration of 2.2 ±1.1 µmol/l in equilibrium corresponds to an endogenous acetaldehyde formation of about 5.6 µmol acetaldehyde/min (0.25 mg/min). It was further estimated that the additional acetaldehyde dose from an inhalation concentration of 10 ppm (18 mg/m^3) would lead to an additional absorbed dose of acetaldehyde of 4.7 µmol/min (0.21 mg/min). This rate is within the range of the endogenously produced acetaldehyde of 0.25 mg/min (DFG, 2008). Extrapolating linearly to a continuous inhalation concentration of 300 µg/m^3 would lead to a rate of about 0.0035 mg/min. In conclusion, an acetaldehyde exposure at 300 µg/m^3, i.e. the concentration of the proposed EU-LCI, does not alter the systemic body burden of acetaldehyde and no systemic (or developmental) toxic effects are to be expected at this concentration of acetaldehyde.

Acetaldehyde is reported to have a fruity, but, especially at higher concentrations, pungent odour. An odour threshold of 2.7 µg/m^3 has been reported by Nagata (2003). Thus, odour perception is possible at the EU-LCI-value.

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