Compound	**Glutaraldehyde**	***Data collection sheet (1/3)***
N°CAS 111-30-8 **1 ppm = 4.12 mg/m³**	**CLP: Acute tox. 3, Skin corr. 1B, Skin sens. 1A, Acute tox. 2, STOT SE 3, Resp. sens. 1**	

Organisation name	**ACGIH**	**AgBB**	**ANSES**	**ATSDR**	**DFG**
Risk value name	TLV-Ceiling	NIK (=LCI)	CLI (=LCI)	MRL (draft)	MAK
Risk value	0.2 mg/m³	2 µg/m³	0.08 µg/m³	0.1 µg/m³	0.21 mg/m³
Risk value	0.05 ppm	0.0005 ppm	0.02 ppb	0.03 ppb	0.05 ppm
Reference period	Chronic (workers)	Chronic	Chronic	Chronic	Chronic (workers)
Year	1976, updated in 2015	2018	2004	2015	2002 (Supplement 2006)
Key study	Nörback, 1988 Pisaniello et al., 1997	NIK derivation based on the review performed by the Committee on Hazardous Substances (AGS)	NTP 1999	NTP, 1993 Gross et al., 1994	Cain et al., 2007 Waters et al., 2003
Study type	Human health surveillance		Continuous inhalation exposure	Subchronic inhalation exposure	Human health surveillance
Species	Human		Male and female F344 rats and B6C3F1 mice (50/sex/group)	Male and female F344 rats and B6C3F1 mice	Human
Duration of exposure in key study	Acute (15 minutes)		6h/d, 5d/w for 104 w	6 h/d, 5 d/w for 13 w	Acute (3 to 15 minutes)
Critical effect	Nose, throat, eye, and skin irritation; skin sensitisation and contact dermatitis; headaches		Respiratory epithelium squamous metaplasia	Inflammation of the anterior nasal passage in mice	Sensory/irritative irritation; respiratory symptoms
Critical dose value		200 µg/m³			

	LOAEL: ≤0.1 ppm		LOAEL: 0.0625 ppm	LOAEL: 0.0625 ppm	LOAEL: 0.1 ppm
Adjusted critical dose			BMC_{05}: 20.5 ppb	$BMCL_{10HEC}$: 0.00008 ppm	
			BMC_{HEC} = 0.62 ppb = 20.5 ppb x 6/24 x 5/7 x 0.17 (RGDR)		
Single assessment factors		100	UF_S 1 x UF_A 3 x UF_H 10 = 30	UF_H 3	
Other effects/comments	A TLV-ceiling value of 0.05 ppm was first adopted in 1976 based on the three occupational studies that reported irritation, headaches and other symptoms with airborne glutaraldehyde concentrations at or below 0.1 ppm. As there is no clear dose-response relationship data available for humans, the current weight of evidence supports the TLV-ceiling value of 0.05 ppm.		The current CLI value was determined based on the derivation of the OEHHA's REL value.	The intermediate-duration inhalation MRL (0.00003 ppm) is considered protective of longer-term exposure to glutaraldehyde because available animal data provide a less conservative MRL for chronic-duration inhalation exposure (0.00007 ppm).	Sensory irritation is not to be expected until glutaraldehyde concentrations above 0.1 ppm. Since these studies with test persons were based merely on short-term exposures of up to fifteen minutes, the provisional MAK value of 0.05 ppm has been retained. *See data collection sheet 3/3 for more information.*
UF_H Intraspecies variability; UF_A Interspecies variability; UF_S Used subchronic study; UF_D Data deficiencies					

Compound	Glutaraldehyde	*Data collection sheet (2/3)*
N°CAS 111-30-8 **1 ppm = 4.12 mg/m³**	**CLP: Acute tox. 3, Skin corr. 1B, Skin sens. 1A, Acute tox. 2, STOT SE 3, Resp. sens. 1**	

Organisation name	**NIOSH**	**OEHHA**	**OSHA (California, USA)**	**DECOS**	**Sweden**
Risk value name	REL-Ceiling	REL	PEL-Ceiling	OEL-TWA	OEL-Ceiling
Risk value	0.8 mg/m³	0.08 µg/m³	0.2 mg/m³	0.08 mg/m³	0.8 mg/m³
Risk value	0.2 ppm	0.02 ppb	0.05 ppm	0.02 ppm	0.2 ppm
Reference period	Chronic (worker)	Chronic	Chronic (worker)	Chronic (worker)	Chronic (worker)
Year	1991	2000	2006	2005	1997
Key study	No information available	NTP, 1999	Tkaczuk et al., 1993 Nörback, 1988 Pisaniello et al., 1997	NTP, 1999	NTP, 1993
Study type		Continuous inhalation exposure	Human health surveillance	Continuous inhalation exposure	Subchronic inhalation exposure
Species		Male and female F344 rats and B6C3F1 mice (50/sex/group)	Human	Male and female F344 rats and B6C3F1 mice (50/sex/group)	Male and female F344 rats and B6C3F1 mice
Duration of exposure in key study		6h/d, 5d/w for 104 w	Acute (e.g. 15 minutes)	6h/d, 5d/w for 104 w	6 h/d, 5 d/w for 13 w
Critical effect	Eye, nose, and throat irritation	Respiratory epithelium squamous metaplasia	Occupational asthma and skin sensitisation responses such as contact dermatitis	Respiratory epithelium squamous metaplasia in female mice	Inflammation of the anterior nasal passage in mice
Critical dose value				NOAEL: 0.0625 ppm	
		LOAEL: 0.0625 ppm	LOAEL: ≤0.1 ppm		LOAEL: <0.2 ppm
Adjusted critical dose		BMC_{05}: 20.5 ppb			

Single assessment factors		UF_S 1 x UF_A 3 x UF_H 10 = 30		UF_H 3	
Other effects/comments	In 1989, OSHA, along with NIOSH, proposed a ceiling limit of 0.2 ppm based on ACGIH's recommendation in 1986 (NIOSH, 2011).		The derivation of the Californian OSHA PEL was based on the documentation for the ACGIH's TLV established in 1997 (OSHA, 2012).	Because mice are obligatory nose breathers, the committee is of the opinion that mice are more sensitive for nasal effects than humans. Since squamous metaplasia occurs at the nasal surface, the committee does not compensate for differences between species.	"There are very few data which can be used as a scientific basis for an occupational exposure limit for glutaraldehyde. The critical effect, based on these data, is irritation of the skin, the eyes and the mucous membranes. The LOEL for irritative effects is below 0.2 ppm."
UF_H Intraspecies variability; UF_A Interspecies variability; UF_S Used subchronic study; UF_D Data deficiencies					

Compound	**Glutaraldehyde**		***Factsheet***
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI value and status			
EU-LCI value	1	Mass/volume [µg/m^3]	1
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	605-022-00-X
EC-No.	5	EINECS – ELINCS - NLP	203-856-5
CAS-No.	6	Chemical Abstracts Service number	111-30-8
Harmonised CLP classification	7	Human Health Risk related classification	Acute tox. 3, Skin corr. 1B, Skin sens. 1A, Acute tox. 2, STOT SE 3, Resp. sens. 1
Molar mass and conversion factor	8	[g/mol] and [ppm – mg/m^3]	100.13 1 ppm = 4.12 mg/m^3
Key data / database			
Key study, author(s), year	9	Critical study with lowest relevant effect level	NTP, 1999
Read-across compound	10	Where applicable	
Species	11	Rat, human, etc.	Mice
Route/type of study	12	Inhalation, oral feed, etc.	Inhalation
Study length	13	Days, subchronic, chronic	Chronic
Exposure duration	14	Hrs/day, days/week	6h/d, 5d/w for 104 w
Critical endpoint	15	Effect(s), site of	Respiratory epithelium squamous metaplasia in females
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]	0.0421 ppm
Assessment factors (AF)	**18**		
Adjustment for exposure duration	19	Study exposure hrs/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)	1.24 µg/m³ and 0.3 ppb
Molar adjustment factor	29	Used in read-across	
Rounded value	30	[µg/m³]	1
Additional comments	31		
Rationale section	32		

Data compilation and evaluation for glutaraldehyde is based on a project funded by the European Commission and prepared by Ramboll Environment & Health GmbH (formerly BiPRO GmbH).

Several organisations or national agencies have published comprehensive assessments on glutaraldehyde. These were considered for the EU-LCI derivation (Beije & Lundberg, 1997; DECOS, 2005; OECD, 2005; ACGIH, 2015; ATSDR, 2015a).

Rationale for key study/POD

As there is no human data on chronic exposure to glutaraldehyde, the EU-LCI for glutaraldehyde is derived from the chronic two-year inhalation glutaraldehyde study in rats and mice from the National Toxicology Program within the U.S. Department of Health and Human Services (NTP, 1999). This study was used as the key study by a number of national authorities (e.g. Germany, France, Netherlands, USA) to derive inhalation limit values and is considered to be representative for chronic human exposure.

F344/N rats (both sexes) were exposed to 0, 250, 500 or 750 ppb glutaraldehyde vapour for 6 hours/day, 5 days/week for 104 weeks. Glutaraldehyde-exposed male rats at all doses and female rats starting at ≥ 500 ppb exhibited reduced body weights compared to controls, and there was decreased survival observed in female rats exposed to ≥ 500 ppm. There was also a dose-dependent increase in non-neoplastic nasal lesions, including hyperplasia and inflammation of the squamous and respiratory epithelia as well as squamous metaplasia of the respiratory epithelium (NTP, 1999).

B6C3F1 mice (both sexes) were also exposed to 0, 62.5, 125 or 250 ppb glutaraldehyde vapour for 6 hours/day, 5 days/week for 104 weeks. Female mice exposed to 250 ppb glutaraldehyde had lower average body weight compared to controls throughout the study. Similar to effects observed in rats, non-neoplastic nasal lesions were also reported in mice. Glutaraldehyde-exposed female mice at all doses showed increased incidences of hyaline degeneration of the respiratory epithelium. Squamous metaplasia of the respiratory epithelium was significantly higher in female and male mice exposed to ≥ 125 ppb and 250 ppb glutaraldehyde respectively (NTP, 1999).

Among the observed effects in this study, squamous metaplasia in the respiratory epithelium in female mice served as the critical endpoint for the EU-LCI derivation. The incidence of this effect at the different concentrations is shown below:

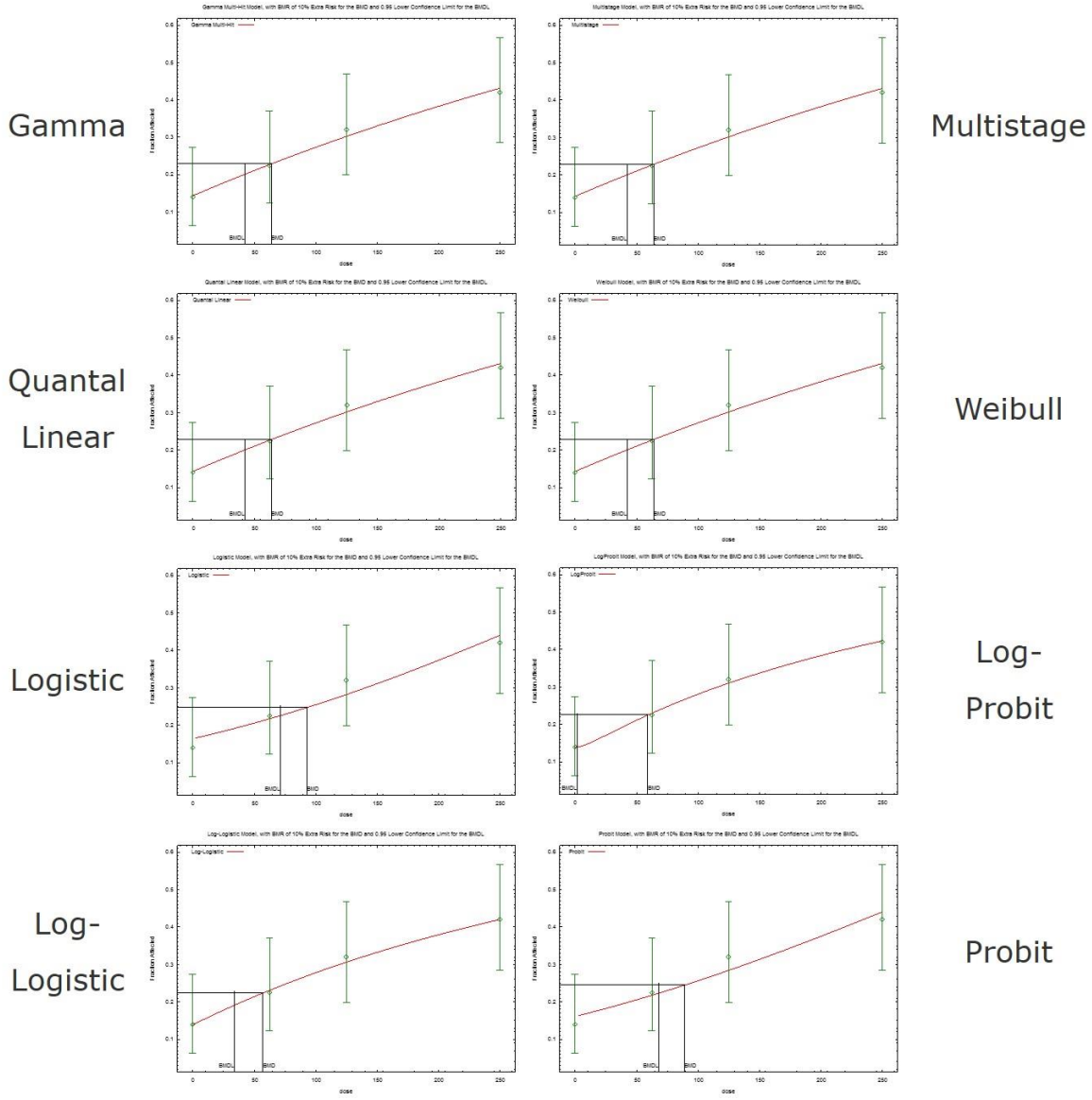
Concentration [ppb]	No. of affected mice	No. of examined mice
0	7	50
62.5	11	49
125	16*	50
250	21*	50

* statistically significant ($p < 0.05$) compared to control (0 ppb)

As there is a clear linear dose-response relationship with this endpoint, a benchmark concentration (BMC) approach was taken. Taking into consideration the European Food Safety Authority (EFSA) guidance

document on benchmark dose/concentration (EFSA Scientific Committee et al., 2017) and the nature of the study design (i.e. quantal data), the BMCL was calculated using the Benchmark Dose Software (BMDS) developed by the U.S. Environmental Protection Agency. The benchmark response was set at 10% (extra risk) and the confidence level at 95%. The model with the highest p-value and lowest Akaike information criterion (AIC) was selected to determine the $BMCL_{10}$. Based on the modelling data (see table and figure below), the gamma, multistage, quantal-linear and Weibull models provided the same highest p-value (0.947) and lowest AIC (227.51). The BMC_{10} of 42.13 ppb was set as POD.

Model	p-value	AIC	BMC [ppb]	BMCL [ppb]
Gamma	**0.947**	**227.51**	**64.16**	**42.13**
Multistage	**0.947**	**227.51**	**64.16**	**42.13**
Quantal-linear	**0.947**	**227.51**	**64.16**	**42.13**
Weibull	**0.947**	**227.51**	**64.16**	**42.13**
Logistic	0.718	228.07	93.04	71.51
Log-probit	0.858	229.43	59.15	1.44
Log-logistic	0.821	229.45	57.18	34.18
Probit	0.750	227.97	89.12	67.98



Assessment factors

Standard default assessment factors were applied to adjust for exposure duration, interspecies and intraspecies differences. The assessment factors include:

- Exposure duration: 5.6
- Interspecies difference: 2.5
- Intraspecies difference: 10

The total assessment factor is 140.

This resulted in a calculated EU-LCI value of 1.24 µg/m^3 and a derived EU-LCI for glutaraldehyde of 1 µg/m^3. The EU-LCI value (1 µg/m^3 or ~0.24 ppb) is slightly below the lowest reported odour threshold of 0.3 ppb (Cain et al., 2007).

Appendix: Glutaraldehyde as a respiratory sensitiser

Glutaraldehyde is classified as a Category 1 respiratory sensitiser (Resp. Sens. 1) under the Classification, Labelling and Packaging (CLP) Regulation. In addition to the CLP, glutaraldehyde has been classified or identified as a respiratory sensitiser by several national authorities (e.g. from the Netherlands, Germany, United Kingdom, etc.) and organisations (e.g. American Conference of Governmental Industrial Hygienists (ACGIH)). This classification is primarily based on human studies of occupational asthma and/or rhinitis in workers exposed to glutaraldehyde mainly in the healthcare industry and experimental animal evidence of glutaraldehyde-mediated Th-2 cytokine profile that is associated with respiratory sensitisation and slightly elevated IgE levels after glutaraldehyde exposure.

Several human studies found glutaraldehyde to be a respiratory sensitiser via workplace challenge or laboratory provocation tests. Observed effects from these studies include altered FEV_1, peak expiratory flow, non-specific bronchial responsiveness, nasal airway resistance as well as late and dual asthmatic reactions in several but not all patients or workers. Many of the positive responses occurred in patients/workers with asthmatic history, making it challenging to associate glutaraldehyde with occupational asthma. Glutaraldehyde was measured in a limited number of studies, with reported average workplace glutaraldehyde levels of around 0.21 mg/m^3 (range of 0.06-0.82 mg/m^3) and challenge levels ranging between 0.065-0.40 mg/m^3. The studies failed to establish a dose-response relationship, and there are no long-term human longitudinal studies on glutaraldehyde-induced respiratory sensitisation (ACGIH, 2015; ATSDR, 2015a; DECOS, 2005).

Some animal studies also reported slightly elevated IgE levels and selective Th2-type cytokine secretion patterns in mice. However, there were also other animal studies with no indication of respiratory sensitisation after glutaraldehyde exposure. For example, in a guinea pig sensitisation study, there were no changes in the respiratory rate (ACGIH, 2015; ATSDR, 2015a; DECOS, 2005).

The overall data on glutaraldehyde exposure leading to respiratory sensitisation is not conclusive. There is also a lack of understanding of the immunological mode of action of glutaraldehyde leading to respiratory sensitisation and concerns that some of the reported symptoms might result from respiratory irritation rather than sensitisation (ATSDR, 2015a; DECOS, 2005; OECD, 2005). The uncertainty of the existing evidence on respiratory sensitisation is one of the arguments for national authorities setting their occupational exposure limit values as ceiling values (range of 0.2-0.8 mg/m^3).

The EU-LCI value for glutaraldehyde of 1 µg/m^3 is derived from the critical effect of respiratory epithelium squamous metaplasia based on a two-year inhalation mice study and should be health-protective from a lifelong exposure of the general population to glutaraldehyde. However, because of the potential of glutaraldehyde as a respiratory sensitiser, exposure of the general population to glutaraldehyde should be minimised and kept as low as possible.

References

ACGIH, 2015. American Conference of Governmental Industrial Hygienists. Glutaraldehyde. Documentation of the Threshold Limit Values and Biological Exposure, 13 pages.

ATSDR, 2015a. Draft Toxicological Profile for Glutaraldehyde. Available from https://www.atsdr.cdc.gov/toxprofiles/tp208-p.pdf (last retrieved on 4.12.2019).

Beije B and Lundberg P, 1997. Nordic Council of Ministries. DECOS and NEG Basis for an Occupational Standard. Glutaraldehyde. Available from http://www.inchem.org/documents/kemi/kemi/ah1997_20.pdf (last retrieved on 4.12.2019).

Cain WS, Schmidt R and Jalowayski AA, 2007. Odor and chemosthesis from exposures to glutaraldehyde vapor. Int Arch Occup Environ Health 80, 721-731.

DECOS, 2005. Dutch Expert Committee on Occupational Standards. Glutaraldehyde: Health-based recommended occupational exposure limit. 140 pp. Available from https://www.healthcouncil.nl/documents/advisory-reports/2005/05/12/glutaraldehyde (last retrieved on 4.12.2019).

EFSA Scientific Committee, Hardy A, Benford D, Halldorsson T, Jeger MJ, Knutsen KH, et al., 2017. Update: use of the benchmark dose approach in risk assessment. EFSA Journal 15, e04658.

NTP, 1999. NTP Toxicology and Carcinogenesis Studies of Glutaraldehyde (CAS NO. 111-30-8) in F344/N Rats and B6C3F1 Mice (Inhalation Studies). Natl Toxicol Program Tech Rep Ser 490, 1-234.

OECD, 2005. Glutaraldehyde CAS No: 111-30-8.