Compound	PROPYLENE GLYCOL	*Data collection sheet*
N°CAS 57–55–6 1 ppm=3.131 µg/m^3 at 23 °C	**EU- Classification:** - **CLP:** -	
Organisation name	**REACH registrants**	**AIHA** **(American Industrial Hygiene Association)**
Risk value name	DNEL worker/consumer	WEEL
Risk value (µg/m^3)	10000	10000
Risk value (ppb)	3194	3194
Reference period		
Year	2014	2004
Key study	Adopted WEEL	Suber et al. 1989
Study type	See AIHA	subchronic, inhalation
Species	See AIHA	rat
Duration of exposure in key study	See AIHA	90 days, 6hrs/d, 5d/week
Critical effect	See AIHA	LOAEC 160 mg/m^3 eye irritation NOAEC 160 mg/m^3 nasal irritation
Critical dose value	See AIHA	160 mg/m^3
Adjusted critical dose	See AIHA	10 mg/m^3
Single assessment factors (see table R.8.6)	TAF 15 (3 for dose-response, 5 for intraspecies difference).	not indicated
Other effects		

Compound	**PROPYLENE GLYCOL**		***Factsheet***
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI value and status			
EU-LCI value	1	Mass/volume [µg/m^3]	2100
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	-
EC No	5	EINECS – ELINCS - NLP	200-338-0
CAS No	6	Chemical Abstracts Service number	57-55-6
Harmonised CLP classification	7	Human health risk-related classification	-
Molar mass and conversion factor	8	[g/mol] and [ppm – mg/m^3]	76.09 1 ppm = 3.11 mg/m^3
Key data / database			
Key study, author(s), year	9	Critical study with lowest relevant effect level	Suber et al. 1989
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	90 days
Exposure duration	14	Hours/day, days/week	6h/day, 5 days/week
Critical endpoint	15	Effect(s), site of	Local ocular and respiratory tract irritation
Point of departure (POD)	16	LOAEC*L, NOAEC*L, NOEC*L, benchmark dose, etc.	LOAEC
POD value	17	[mg/m^3] or [ppm] or [mg/kg$_{BW}$×d]	160 mg/m^3
Assessment factors (AF)	**18**		
Adjustment for exposure duration	19	Study exposure hours/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	3
	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)	75
POD/TAF	28	Calculated value (µg/m³ and ppb)	2133 µg/m³ and 681 ppb
Molar adjustment factor	29	Used in read-across	
Rounded value	30	[µg/m³]	2100
Additional comments	31		
Rationale section	32		

Inhalation exposure to propylene glycol (PG) may result in local ocular and respiratory tract irritation in experimental animals and human volunteers.

Acute exposure of human volunteers for 1 minute to PG atmospheres of 176-851 mg/m³ resulted in sore dry eyes, throat dryness, irritative cough and a mild decrease in tear film stability (Wieslander et al., 2001). In a subchronic (90-day) repeated exposure study with rats, a LOAEC of 160 mg/m³ was identified based on a slightly increased incidence in nasal haemorrhaging (in the absence of a histopathological correlate at this dose level) and ocular discharge (Suber et al., 1989).

The LOAEL of 160 mg/m³ from the subchronic study is the most relevant dose descriptor for the derivation of a limit value for local effects, and the weight of evidence from the human volunteer study substantiates its reliability.

Assessment factors

Adjustment for exposure duration: 1 (local effect, and completely reversible at weekends)
Exposure duration factor (subchronic/chronic): 1
LOAEL→NOAEL: 3 (slight effect without histopathological correlate)
Allometry: 1 (inhalation exposure, local effect)
Remaining differences interspecies toxicodynamics factor (rat-to-human): 2.5
Intraspecies factor (general population): 10
Quality of database factor: 1 (weight of evidence of animal and human data)

The TAF is 75. The calculated EU-LCI value for propylene glycol is POD/TAF = 160 mg/m³/75=2133 µg/m³ (681 ppb). After rounding, the EU-LCI-value is 2100 µg/m³.

Extrapolation of a vapour threshold based on data for the aerosol bears a significant uncertainty.

Appendix / Background

Propylene glycol is a naturally occurring chemical in foods. The FDA and the Joint FAO/WHO Expert Committee on Food Additives (JEFCA) consider PG to be generally recognised as safe (GRAS) and approved as a food additive for all food categories up to 2 %.

The WHO Joint Expert Committee on Food Additives (JECFA) has established an ADI of 0-25 mg/kg/day (FAO/WHO Expert Committee, 1974).

The FDA Center for Drug Evaluation and Research (FDA CDER, 1996, www.fda.gov) has included PG on the revised'Inactive Ingredients for Currently Marketed Drug Products' list for use in 'inhalation solution' and 'metered nasal spray', where the specific potency and formulation range for PG remains unspecified at this time. The vapour pressure of PG is 0.2 hPa at 25 °C, resulting in a calculated saturated vapour concentration of 0.63 mg/l (= 630 mg/m³).

Acute toxicity

Propylene glycol is not acutely toxic via the oral or dermal route of exposure.

In an acute inhalation assay, rats were nose-only exposed for 4 hours to single atmospheres of 14.4, 30.5, and 44.9 mg/L of fully respirable PG. Treatment-related clinical signs included slight localised bleeding around the eyes and nose at day 7. On study days 1–3 post-exposure, there were 5-10 % decreases in body weight, which were fully reversible by study day 7 (Werley et al., 2011).

In another acute inhalation assay, rats were exposed nose-only for 4 hours/day for seven consecutive days. Groups of 5 animals/sex/concentration were exposed to either 20.8 or 41.0 mg/L fully respirable PG aerosol. There were no treatment-related clinical observations. Since no treatment-related effects were observed, the NOEL was > 41 mg/L (Werley et al., 2011).

In an acute assay with beagle dogs, 2 male and 2 female animals were exposed via face mask to an ascending dose phase and a 7-day repeated dose phase. PG aerosols were fully respirable and the concentrations and exposure times were 1.5-30 mg/l for 8-60 minutes in the ascending phase and 5 mg/l for 60 minutes in the 7-day repeated dose phase.

In the ascending dose phase, dogs were generally intolerant (e.g. showing restlessness) of high exposure concentrations (15 and 30 mg/L). There was an inverse relationship between the tolerable exposure concentration and the time of exposure.

In the 7-day repeated dose study, 5 mg/L for up to 60 minutes duration was well tolerated (Werley et al., 2011). PG is essentially non-irritating to the skin, mildly irritating to the eyes and not sensitising. In addition, the substance is not mutagenic.

Repeated dose toxicity — oral

Chronic oral exposure of rats did not result in adverse effects at and up to dose levels of 1.7 and 2.1 g/kg bw/day in feed for male and female animals, respectively (OECD limit dose 1 g/kg bw/day) for exposure periods up to 2 years (Gaunt et al., 1972).

In a chronic study of dogs, groups of 5 male and 5 female animals were fed diets containing PG dose levels of 5 and 2 g/kg bw/day for 104 weeks. Slight, reversible haematotoxicity was observed in the high dose group, characterised by slight decrease in haemoglobin, haematocrit, total erythrocyte count and reticulocytes (NOAEL 2 g/kg bw/day) (Weil et al., 1971).

Cats appear to be more sensitive to PG haematotoxicity. Male animals were subchronically exposed via the diet to dose levels of 443 and 4239 mg/kg bw/day for 94 days and 80, 675 and 1763 mg/kg bw/day for 69 days.

A species-specific and dose-dependent increase in Heinz bodies was reported. The NOAEL was identified as 443 mg/kg bw/day based on a secondary increase in haemosiderin deposits in liver and spleen. Heinz bodies represent membranous protein aggregations, which in certain cases represent the most sensitive endpoint of haematotoxicity; however, they are generally not considered to be adverse (Toxicology Research Laboratory 1979).

In a further cat study, induction of Heinz bodies was noted, albeit at higher dose levels of 2400 mg/kg bw/day or higher when gavaged for 17 weeks (Weiss et al., 1990).

Repeated dose toxicity — inhalation

In a subchronic inhalation study, rats were exposed to PG aerosol at dose levels of 0, 0.16, 1, and 2.2 mg/l for 6h/day, 5 days/week for 90 days.

Reversible, treatment-related nasal haemorrhaging was observed in 1, 64, 74 and 75 % of males and in 1, 14, 71 and 71 % of females in the control, low-, medium-, and high-exposure group, respectively. Similar trends were observed for ocular discharge (5, 16, and 40 % in males, and 8, 14, 28, and 35 % in females).

Microscopic examination of the nasal cavity showed a thickening of the respiratory epithelium (an increased number of goblet cells or an increase in the mucin content of goblet cells) in the medium and high dose groups only. In the absence of a histopathological correlate in the low-dose group, 160 mg/m^3 is considered to be an acceptable LOAEL for local effects for the risk assessment.

The increased number of goblet cells and/or increased mucin content appear to be an adaptive response. Minimal local irritation and histopathological changes in the nasal cavity are well known unspecific observations which are commonly observed with high aerosol concentrations. Indeed this dosimetry and interpretation is fully supported by the proceedings of an international expert workshop of the European Society of Toxicology (Kaufmann et al., 2009). Accordingly, such lesions might be assessed as 'non-adverse'.

The observed nasal haemorrhage might be explained by pigment/porphyrin staining following an increase in lacrimal secretion caused by the mildly irritating or drying effect of propylene glycol aerosol on mucous membranes (Suber et al., 1989).

In a more recent subacute (28 day) study, PG aerosols were generated in a novel capillary aerosol generator resulting in highly respirable particles. The aerosols were nose-only exposed to rats and via a face mask with an oropharyngeal tube to dogs (Werley S.W. et al., 2011).

In the rat study, 31 animals/sex/group were exposed to concentrations of 30 mg/l respirable PG for up to 120 minutes/day in order to obtain deposited lung doses of 7.2, 21.6, 72 and 216 mg/kg/day.

The only biologically relevant findings included clinical signs of ocular and nasal irritation indicated by minor bleeding around the eyes and nose, and minimal laryngeal squamous metaplasia in the 72 and 216 mg/kg/day dose groups (NOEL approx. 20 mg/kg bw). This finding is commonly observed in inhalation studies in rats, and is likely related to the unique sensitivity of the tissue but also to the circuitous airflow pathway through the larynx, which increases particle deposition.

In the dog study, 4 animals/sex/group were exposed to aerosol concentrations of 5 mg/l for 3-31 minutes and 37 to 49 minutes in the high-dose group in order to obtain deposited lung doses of 3, 6, 18 and 60 mg/kg bw/day.

No local effects of statistical significance were identified. Treatment-related decreases in haemoglobin, red blood cells and haematocrit were observed in the two highest exposure groups, equivalent to approximately 18 and 60 mg/kg/day (NOEL 6 mg/kg bw/day). In male dogs from the high dose group, similar small (albeit non-statistically significant) decreases were observed in these haematological markers as well.

This study in rats and dogs substantiates the effects observed in other studies (local ocular and respiratory irritation in rats, mild haematotoxicity in dogs). However, its value in identifying a dose descriptor for deriving an emission threshold is limited, since daily exposure times were varied in order to obtain targeted deposited lung doses.

No toxicity to reproduction was identified in a continuous breeding study with mice (NOAEL 10.1 g/kg bw/day; NTP 1985) or in a prenatal developmental toxicity study in mice (NOAEL 10.4 g/kg bw/day; Bushy Run Center 1993).

Systemically available propylene glycol is converted to lactate involving alcohol dehydrogenase. Lactate is efficiently excreted or detoxified via gluconeogenesis (NTP 2004).

Human evidence

In a human volunteer study, 27 individuals were exposed to PG atmospheres of 176-851 mg/m^3 in an aircraft simulator for 1 minute. Sensations of sore and dry eyes, throat dryness and irritative cough were reported. In addition, a decrease in tear film stability was found (Wieslander et al., 2001).

Due to significant co-exposures, paint emission studies and studies with theatrical smokes were not taken into account since no reliable dose descriptors can be derived (Wieslander & Norbäck, 2010; Ernstgard et al., 2007; NIOSH, 1992; Moline et al., 2000).

Alternative derivation of an EU-LCI for systemic effects

Propylene glycol has a low potential to cause systemic effects following acute or repeated inhalation. The biological relevance of haematological changes in cats and dogs at high dose levels is unclear. However, an alternative derivation of an EU-LCI for systemic effects is presented for plausibility:

NOAEL: 443 mg/kg bw from a subchronic cat study
EU-LCI: Route-to-route extrapolation:
NOAEC = NOAEL x 1/sRVcat x ABSoral/ABSinhal
= 443 mg/kg bw x 1/0.2 x 1 = 2215 mg/m^3
Exposure duration factor (subchronic/chronic): 2
Allometry (cat/human): 1 (reflected in route-to-route extrapolation)
Remaining differences interspecies toxicodynamics factor (rat-to-human): 2.5
Intraspecies factor (general population): 10
Quality of database factor: 1
EU-LCI = 2215 mg/m^3 /(2 × 2.5 × 10) = 44.3 mg/m^3 = 44 000 µg/m^3
Respiratory volume for cats 0.2 l/min/kg bw

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