Compound	**1,2-Propylene glycol n-butyl ether**		***Data collection sheet (1/1)***
N°CAS: **5131-66-8 (α isomer)** **29387-86-8 (mixture)** **15821-83-7 (β isomer)** **63716-40-5 (-)** **1 ppm ~ 5.44 mg/m³**	**CLP : Skin irrit. 2 (H315), Eye irrit. 2 (H319)**		
Organisation name	**AgBB**	**REACH Registrants**	**Denmark**
Risk value name	NIK (=LCI)	DNEL (General population, systemic, long-term, inhalation)	OEL (8h TWA)
Risk value (ppm)	0.3	7.9	100
Risk value (mg/m³)	1.6	43	544
Reference period	Chronic	Chronic	Chronic
Year	2018	2018	N/A
Key study	Pozzani & Carpenter, 1965 (extracted from REACH registration dossier)	Grandjean et al., 1992	N/A
Study type	Subacute inhalation study	Subchronic oral drinking water study	N/A
Species	Rats	Rats	N/A
Duration of exposure	31 days	90 days	N/A
Critical effect	No adverse effects observed	Increased liver and kidney weights	N/A
Critical dose value	DNEL: 30 ppm (based on the NOAEC of 600 ppm)	NOAEL: 350 mg/kg bw	N/A
Adjusted critical dose	N/A	$NOAEC_{adj}$: 350/1.15 = 304 mg/m³	N/A
Single assessment factors	100 (use of DNEL)	UF_H 5 x UF_S 1.4 = 7	N/A
Other effects	N/A	Slight changes on haematology	N/A
UF_H Intraspecies variability; UF_S Used subchronic study			

Compound	**1,2-Propylene glycol n-butyl ether (PGBE)**		***Factsheet***
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI value and status			
EU-LCI value	1	Mass/volume [µg/m^3]	650
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	603-052-008 (α isomer)
EC-No.	5	EINECS – ELINCS - NLP	225-878-4 (α isomer) 605-138-0 (β isomer) 249-598-7 (mixture)
CAS-No.	6	Chemical Abstracts Service number	5131-66-8 (α isomer) 15821-83-7 (β isomer) 29387-86-8 (mixture) 63716-40-5
Harmonised CLP classification	7	Human Health Risk related classification	Skin irrit. 2 (H315) Eye irrit. 2 (H319)
Molar mass and conversion factor	8	[g/mol] and [ppm – mg/m^3]	132.20 1 ppm = 5.44 mg/m^3
Key data / database			
Key study, author(s), year	9	Critical study with lowest relevant effect level	Klonne et al., 1989
Read across compound	10	Where applicable	
Species	11	Rat, human, etc.	Rats
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, 5 days/week for 11 days
Critical endpoint	15	Effect(s), site of	Eye lesions
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]	300 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)*	6
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)	2520
POD/TAF	28	Calculated value (µg/m³ and ppb)	647.62 µg/m³ and 119 ppb
Molar adjustment factor	29	Used in read-across	
Rounded value	30	[µg/m³]	650
Additional comments	31		
Rationale section	32		

Data compilation and evaluation for 1,2-propylene glycol n-butyl ether (PGBE; also known as butoxypropan-1-ol) is based on a project funded by the European Commission and prepared by Ramboll Environment & Health GmbH (formerly BiPRO GmbH).

Some organisations or national agencies have published comprehensive assessments on PGBE as part of the assessment reports on glycol ethers and propylene glycol ethers (ECETOC, 2005; INERIS, 2015; OECD, 2003). Literature searches using PubMed, TOXNET and Google Scholar have been conducted to identify any relevant literature on PGBE that is not addressed in the aforementioned data sources. In addition, there is a REACH registration dossier available for PGBE (the α-isomer form) (ECHA, 2018a). The compiled data were taken together for the derivation of the EU-LCI value for PGBE.

Commercial PGBE (CAS No 29387-86-89) is produced primarily as a mixture of the α-isomer (also known as 1-butoxypropan-2-ol, CAS No 5131-66-8) and the β-isomer (also known as 2-butoxypropan-1-ol, CAS No 15821-83-7). The α-isomer consists of the ether linkage on the terminal hydroxyl group of propylene glycol, whereas the β-isomer has the ether linkage on the secondary hydroxyl group with the primary hydroxyl group unsubstituted. During the synthesis of the propylene glycol ethers (PGEs) including PGBE using propylene oxide and alcohol, the α-isomer is the more thermodynamically favoured isomer compared to its β counterpart. Commercial PGBE is composed predominantly (>95%) of the α-isomer and less than 5% of the β-isomer. The two isomers have not been produced as pure isomeric chemicals (CIR, 2017; Cragg, 2012; HERA, 2005; OECD, 2003).

The two isomers have different toxicity profiles, with the β-isomer being more toxic than the α-isomer. The difference in toxicity lies with the fact that the α-isomer cannot be metabolised to an alkoxypropionic acid as the free hydroxyl group is a secondary rather than primary alcohol, whereas the β-isomer can be metabolised to an alkoxypropionic acid, which can then trigger developmental effects. However, as mentioned above, commercial PGBE is composed mainly of the α-isomer. It has also been reported that exposure to propylene glycol ether composed of 17% β-isomer showed no developmental toxicity effects (Cragg, 2012). The toxicity of β-isomer is therefore not expected to be observed from exposure to commercial PGBE.

Rationale for critical effects/POD

There were no suitable animal or human data on PGBE available in peer-reviewed publications for the EU-LCI derivation of PGBE. On the other hand, the REACH registration dossier on PGBE (α-isomer form) and the OECD assessment report on PGEs contain detailed descriptions and results of several repeated inhalation animal studies (ECHA, 2018a; OECD, 2003). These served as the primary data source for identifying the key study for the EU-LCI derivation of PGBE.

The derivation of the EU-LCI for PGBE is based on ocular effects observed from the key subacute inhalation study by Klonne et al. (1989), which is described in both the REACH registration dossier for PGBE and the OECD assessment report of PGEs. In this study, male and female Fischer 344 (F344) and Sprague-Dawley (SD) rats (n= 10/sex/dose) were exposed (whole body) to 0, 10, 100, 300 or 600 ppm (equivalent to 0,

54.4, 544, 1632 or 3264 mg/m^3) of PGBE vapours for 11 days (6 hours/day, 5 days/week for a total of 9 exposures) followed by a 4-week recovery period. Increased liver weights without accompanying histopathology (at 600 ppm) were found in male and female F344 rats, whereas no exposure-related effects on organ weights occurred in the SD rats. Mild eye lesions were observed in both F344 and SD rats. Histopathological examination showed one female SD rat exposed to 600 ppm with minimal suppurative keratitis and another female SD rat exposed to 600 ppm with mild corneal fibrosis. In F344 rats, fibroblastic proliferation occurred with an increased incidence and severity in rats exposed to 300 or 600 ppm (the REACH registration dossier or OECD assessment report contained no further details). Suppurative keratitis was also observed in the group exposed to 600 ppm (4 out of 20 rats of both sexes) at the end of the exposure, but was transient as it was no longer observed after the 4-week recovery period. Corneal degeneration was observed in some F344 rats exposed to 600 ppm that persisted by the end of the 4-week recovery period (8 of 40; primarily females). Corneal degeneration was also observed in only one control rat (ECHA, 2018a; Klonne et al., 1989; OECD, 2003).

The selection of eye lesions is considered the most critical effect compared to the other repeated inhalation studies as described in the REACH registration dossier and/or OECD assessment report.

In a subchronic repeated inhalation study by Pozzani and Carpenter (1965), male and female rats were exposed (whole body) to 0 or 600 ppm (3264 mg/m^3) of PGBE vapours for 7 hours/day, 5 days/week for 31 days. The only apparent PGBE-induced effect was an increase in the female liver weights but without accompanying histopathology. In another subacute inhalation study by Corley et al. (1989), male and female F344 rats were exposed nose-only to 0, 50, 200 or 700 ppm (equivalent to 0, 272, 1088 or 3808 mg/m^3) of PGBE for 2 weeks (6 hours/day; 5 days/week for a total of 9 exposures). Similar to the two above-mentioned studies, increased liver weights were also observed in females as well as males. No histopathological findings in the liver were observed to reflect the increased liver weights. However, corneal inflammation and mineralisation were also observed and confirmed via histopathology in the left eye of one male rat exposed to 700 ppm PGBE (equivalent to 3808 mg/m^3). A subchronic 13-week oral study by Grandjean et al. (1992) also reported increased liver weights in male rats exposed to 1000 mg/kg/day as well as increased kidney weights in females exposed to the same high dose. However, no corresponding histopathology was found for either effects. Finally, a 13-week dermal study by Jonker & Lina showed that topical application of doses up to 880 mg/kg bw/day PGBE triggered no systemic toxicity in rats.

Overall, increased liver weights have been observed in most repeated exposure studies but without any histopathological findings in the liver. There also appears to be a sex-specific difference in this effect, although the evidence for this is equivocal. On the other hand, in the Klonne et al. (1989) study, mild eye lesions with confirmed histopathology were observed in both F344 and SD rats exposed to 600 ppm of PGBE vapours, and corneal degeneration persisted in 8 out of 40 rats exposed to 600 ppm PGBE (both strains) some 4 weeks after exposure had ceased. The Corley et al. (1989) study also observed corneal inflammation and mineralisation in one male rat exposed to 700 ppm PGBE vapours. PGBE is also classified as an Eye Irritant Cat. 2 (H319) under the Classification, Labelling and Packaging (CLP) Regulation. Considering the weight of evidence and severity of the effects, eye lesions are considered more critical than increased liver weights without histopathological findings. The point of departure for the critical effect of eye lesions is therefore the LOAEC of 300 ppm (the next lower concentration after 600 ppm tested in the Klonne et al. (1989) study), at which fibroblastic proliferation of the eye in exposed F344 rats was observed (no further data provided on the incidence and severity). The tested concentration of 100 ppm in the Klonne et al. (1989) study was not selected as the NOAEC for the EU-LCI derivation of PGBE due to the lack of eye assessment data at this concentration in the registration dossier or in the OECD assessment report of PGEs.

Assessment factors

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

- Exposure duration: 5.6
- Study length: 6
- Dose-response: 3

- Interspecies difference: 2.5
- Intraspecies difference: 10

The total assessment factor is 2520.

This resulted in a calculated value of 647.62 µg/m^3 (119 ppb) and a derived EU-LCI for PGBE of 650 µg/m^3. This EU-LCI value (650 µg/m^3 or ~119 ppb) is above the reported odour threshold level of 191 µg/m^3 (32.4 ppb) (SEPA, 2010). Odour perception may therefore occur at this EU-LCI value.

References

CIR, 2017. The Cosmetic Ingredient Review (CIR): Amended safety sssessment of butyl polyoxyalkylene ethers as used in cosmetics.

Corley RA, Philips JE, Johnson KA and Verschuuren HG, 1989. Propylene glycol n-butyl ether: two-week vapour inhalation study with Fischer 344 rats. Unpublished report. Dow Chemical, Midland, Michigan, USA.

Cragg ST, 2012. Glycol Ethers: Ethers of Propylene, Butylene Glycols, and Other Glycol Derivatives. In E. Bingham & B. Cohrssen (Eds.), Patty's Toxicology (pp. 789-877): John Wiley & Sons, Inc.

ECETOC, 2005. The toxicology of glycol ethers and its relevance to man. Technical Report 95. (fourth edition).

ECHA 2018a. 1-butoxypropan-2-ol. Retrieved from https://echa.europa.eu/fr/registration-dossier/-/registered-dossier/14287 (last retrieved on 3.12.2019).

Grandjean M, Szabo JR and Verschuuren HG, 1992. Propylene glycol n-butyl ether: 13-week drinking water study in Fischer 344 rats. Internal Dow Report.

HERA, 2005. Human & Environmental Risk Assessment (HERA) on ingredients of household cleaning products. Propylene Glycol n-Butyl Ether (CAS No 5131-66-8; 29387-86-8)

INERIS, 2015. Données technico-économiques sur les substances chimiques en France : DRC-15-136881-10158A. 40.

Jonker D and Lina BAR, 1988. Subchronic (13-week) dermal toxicity study with propylene glycol n-butyl ether in rats. TNO Study No. V 87.464/270613. April 1988. Unpublished report.

Klonne DR, Kintigh WJ, Gorham WF, Dodd DE and Frank FR, 1989. Propasol Solvent B: Nine-day vapor inhalation study on rats. Unpublished report of Union Carbide Corporation, Bushy Run Research Center Project, report 51-5.

OECD, 2003. Propylene Glycol Ethers.

Pozzani UC and Carpenter CP, 1965. Repeated inhalation of n-butoxypropanol (mixed isomers) by rats. Unpublished report of Union Carbide Corporation, Mellon Institute, report 28-11.

SEPA 2010. Odour guidance 2010. Retrieved from https://www.sepa.org.uk/media/154129/odour_guidance.pdf (last retrieved on 3.12.2019).