Compound	1,2-Propylene glycol dimethyl ether (PGDME)	*Data collection sheet (1/1)*
N°CAS 7778-85-0 **1 ppm ~ 4.26mg/m³**	**Harmonised CLP classification:** No human health classification	
Organisation name	**AgBB**	**ANSES**
Risk value name	NIK (=LCI)	CLI (=LCI)
Risk value (µg/m³)	25	20
Risk value (ppb)	5.83	4.66
Reference period	Chronic	Chronic
Year	2018	2009
Key study	Ma-Hock et al., 2005 (read-across using 1-propylene glycol 2-methyl ether/1PG2ME)	Ma-Hock et al., 2005 (read-across using 1-propylene glycol 2-methyl ether/1PG2ME)
Study type	Subacute inhalation study	Subacute inhalation study
Species	Rats	Rats
Duration of exposure	6 h/d, 5 d/w for 4 weeks	6 h/d, 5 d/w for 4 weeks
Critical effect	Respiratory irritation	Respiratory irritation
Critical dose value	NOAEC	NOAEC
	110 ppm	110 ppm
Adjusted critical dose	NIK (1PG2ME) = 19 µg/m³	CLI (1PG2DME) = 20 µg/m³
	NIK derived from MAK value for 1PG2ME of 5 ppm divided by default factors of 100 x 10 (for Repr. 1B) = 5 ppb	
Single assessment factors	Molar adjustment factor = 104.149 / 90.122 = 1.15	N/A
Other effects	N/A	N/A

Compound	**1,2-Propylene glycol dimethyl ether (PGDME) C5H12O2**		***Factsheet***
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI value and status			
EU-LCI value	1	Mass/volume [µg/m^3]	500
EU-LCI status	2	Draft/Final	Final
EU-LCI year of issue	3	Year when the EU-LCI value has been issued	2019
General information			
CLP-INDEX-No.	4	INDEX	603-100-00-8
EC-No.	5	EINECS – ELINCS - NLP	404-630-0
CAS-No.	6	Chemical Abstracts Service number	7778-85-0
Harmonised CLP classification	7	Human health risk related classification	No human health classification
Molar mass and conversion factor	8	[g/mol] and [ppm – mg/m^3]	104.15 1 ppm = 4.26 mg/m^3
Key data / database			
Key study, author(s), year	9	Critical study with lowest relevant effect level	Waalkens-Berendsen, 1991
Read across compound	10	Where applicable	
Species	11	Rat, human, etc.	Rabbits
Route/type of study	12	Inhalation, oral feed, etc.	Oral
Study length	13	Days, subchronic, chronic	During organogenesis
Exposure duration	14	Hrs/day, days/week	GD 6- 18
Critical endpoint	15	Effect(s), site of	Developmental toxicity (foetal malformations)
Point of departure (POD)	16	LOAEC*L, NOAEC*L, NOEC*L, Benchmark dose, etc.	NOAEL
POD value	17	[mg/m^3] or [ppm] or [mg/kg$_{BW}$×d]	25 mg/kg$_{BW}$×d
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		0.285 (20/70)
Dose-response	22 a	Reliability of dose-response, LOAEL → NOAEL	1
	22 b	Severity of effect *(R 8-6d)*	3
Interspecies differences	23 a	Allometric Metabolic rate *(R8-3)*	2.4
	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)	0.285 x 180
POD/TAF	28	Calculated value (µg/m^3 and ppb)	486 µg/m^3 and 113 ppb
Molar adjustment factor	29	Used in read-across	
Rounded value	30	[µg/m^3]	500
Additional comments	31		
Rationale section	32		

Data compilation and evaluation for 1,2-propylene glycol dimethyl ether are based on a project funded by the European Commission and carried out by Ramboll Environment & Health GmbH.

Limited data on the toxicity of 1,2-propylene glycol dimethyl ether (PGDME) were identified. There were no assessment reports on PGDME in the public domain. Literature searches using PubMed, TOXNET and Google Scholar also revealed no relevant references on the toxicity of PGDME. A REACH registration dossier is also available for PGDME but it has very limited information as PGDME is registered under the old EU framework (67/548/EEC) for the notification of new substances (NONS) which was replaced by the REACH regulation.

Nevertheless, some toxicity data on PGDME were found in the US National Technical Reports Library, where a number of laboratory reports on studies such as the prenatal developmental toxicity study and the subacute repeated dose oral study have been archived. In addition, PGDME belongs to the family of (propylene) glycol ethers and understanding of the toxicity of PGDME can be extrapolated from existing information on other structurally similar glycol ethers. The data compiled and general understandings of glycol ethers were used to evaluate and derive an EU-LCI value for PGDME.

Rationale for critical effect/POD

The German Committee for Health-related Evaluation of Building Products (AgBB) and the French Agency for Food, Environmental and Occupational Health and Safety (ANSES) both derived their respective LCI values (NIK for AgBB and CLI for ANSES) for PGDME by taking the read-across approach using 1-propylene glycol 2-methyl ether (1PG2ME) (CAS No 1589-47-5).

Both AgBB and ANSES took the MAK value from Germany for 1PG2ME of 5 ppm (19 mg/m^3) as the basis for the derivation (MAK, 2018b). The MAK value for 1PG2ME was derived via a read-across approach using 1PG2ME acetate. The key study for the MAK value of 1PG2ME acetate is a 28-day inhalation study in Wistar rats with respiratory irritation as the critical effect and a NOAEC (point of departure) of 110 ppm (Ma-Hock et al., 2005). Applying a total adjustment factor of 18 (3 for interspecies difference and 6 for exposure duration) and taking the 'preferred value approach' resulted in a MAK value of 5 ppm (MAK, 2018a). AgBB applied the default assessment factors of 100 x 10 for reproductive/developmental effects along with a molar adjustment factor of 1.15 to yield a derived NIK value of 25 µg/m^3. ANSES took the same MAK value and assessment factor without applying a molar adjustment factor, which explains the discrepancy between the LCI values of the two authorities.

For the EU-LCI derivation of PGDME, the read-across approach using 1PG2ME was not applied for several reasons:

- There are differences in the biotransformation of 1PG2ME and PGDME such that the respiratory irritation observed from exposure to 1PG2ME would not be expected to occur with PGDME via the same mechanism. Inhalation of 1PG2ME acetate (or glycol ether acetates in general) would result in its rapid hydrolysis via carboxylesterases in the nasal mucosa to yield 1PG2ME and acetic acid (ECETOC, 2005; Stott & McKenna, 1985). Exposure to acetic acid via inhalation is known to trigger

respiratory irritation (Ernstgård et al., 2006; van Thriel et al., 2008). By contrast, the main metabolic pathway of PGDME is CYP450-mediated O-demethylation, yielding alcohols (ECETOC, 2005; Mangelsdorf et al., 2016). Given the difference in the initial biotransformation pathway between PGDME and 1PG2ME acetate, selecting respiratory irritative effects of 1PG2ME acetate might not be the most appropriate critical effect for deriving an EU-LCI value for PGDME.

- PGDME is a glycol ether with both alcohol groups etherified (also referred to as a glyme), and as mentioned earlier, the main metabolic pathway of such glycol ethers is believed to be O-demethylation. This reaction of PGDME would result in the formation of 1-methoxy-2-propanol (also known as propylene glycol monomethyl ether or PGME) or 1PG2ME and methanol. 1PG2ME is further metabolised via alcohol dehydrogenase (ADH) to yield 2-methoxypropionic acid (2-MPA), which is reported to be a developmental toxicant. PGME is further metabolised to yield conjugated forms (glucuronide or sulphate) of PGME and CO_2 via propylene glycol, which enters into the tricarboxylic acid (TCA) or Krebs cycle. It has been shown that PGME is not a reproductive or developmental toxicant (Carney et al., 1999; Doe et al., 1983; Hanley et al., 1984). Therefore, it can be assumed that not all absorbed PGDME will be metabolised to solely yield 1PG2ME, and this understanding of the metabolism of PGDME to metabolites other than 1PG2ME needs to be taken into account for the EU-LCI derivation.
- Developmental toxicity is considered to be a critical effect of PGDME given its expected conversion to 1PG2ME and subsequently to 2-MPA, the metabolite responsible for the developmental toxicity of 1PG2ME. There is a developmental toxicity study of PGDME (conducted in accordance to OECD Guideline 414; GLP-compliant) in rabbits available for evaluation (Waalkens-Berendsen, 1991). The study is considered reliable and suitable for the EU-LCI derivation of PGDME. Even though PGDME was administered orally in this study, there is sufficient understanding of the toxicokinetics of PGDME and glycol ethers such that a route-to-route extrapolation can be performed for the EU-LCI derivation.

Overall, given that reliable experimental data are available on repeated exposure to PGDME resulting in developmental toxicity and that there is an understanding of the metabolism of PGDME to yield PGME and/or 1PG2ME, the EU-LCI of PGDME was derived *de novo* instead of taking a read-across approach using 1PG2ME.

As there were no animal or human data on repeated inhalation exposure to PGDME, the derivation of the EU-LCI for PGDME is based on foetal malformations observed from a developmental toxicity oral study in rabbits (Waalkens-Berendsen, 1991). In this study, pregnant New Zealand White rabbits (20 animals/group) were exposed to 0, 25, 100 or 250 mg/kg bw/day of PGDME via gastric intubation daily from gestation day (GD) 6 to 18 and were sacrificed on GD 29. At 250 mg/kg bw/day, there were decreases in maternal body weight and food consumption during treatment. However, PGDME did not affect maternal performance and reproduction parameters, and there were no notable gross observations found in the pregnant rabbits of all groups. Regarding developmental toxicity, 250 mg/kg bw/day triggered increases in anomalies and variations in the viscera (e.g. spleen, urinary tract, gall bladder and circulatory system) as well as in the skeleton (e.g. sternum anomalies such as fused sternebrae and delayed skeletal ossification) of the foetuses. The skeletal effects were also observed to a lesser degree in the 100 mg/kg bw/day group and considered as marginally foetotoxic. Overall, the NOAEL of 25 mg/kg bw/day of PGDME was selected as the point of departure due to the critical effects of developmental toxicity.

In order to perform the route-to-route extrapolation of PGDME, understanding of the toxicokinetics of PGDME is needed. This information was drawn from a general understanding of glycol ethers. In general, glycol ethers are readily absorbed and widely distributed following oral or inhalation exposure. PGDME is expected to undergo CYP450-mediated O-demethylation to yield PGME and 1PG2ME. Toxicokinetic studies have shown that both of these metabolites are rapidly converted to other downstream metabolites (e.g. propylene glycol for PGME and 2-MPA for 1PG2ME) (Carney et al., 2003; ECETOC, 2005; Ferrala et al., 1994; Miller et al., 1983; Miller et al., 1986). CYP450 enzymes are expressed in both human nasal mucosa and the liver (Zhang et al., 2005).

With this considered, it is assumed that toxicokinetics following inhalation exposure to PGDME would be similar to that of oral exposure, therefore the route-to-route extrapolation from oral to inhalation exposure

was performed with the assumption that there would be 100% absorption of PGDME following oral or inhalation exposure (thus, an assessment factor of 1 for route-to-route extrapolation).

The NOAEL from the developmental toxicity oral study in rabbits was converted to the corresponding inhalation concentration in humans as shown below:

$NOAEC_{human}$: 25 mg/kg bw/day x 70 kg bw/person (assumed body weight) = 1750 mg/person/day
1750 mg/person-day ÷ 20 m^3/person-day (assumed inhalation volume) = 87.5 mg/m^3

Assessment factors (AF)

Standard default assessment factors were applied for interspecies as well as intraspecies differences. Because of the critical effect of foetal malformations, an AF of 3 was applied to account of the severity of effects (ECETOC, 2010).

- Severity of effect: 3
- Interspecies differences: 6 (2.4 for allometric scaling x 2.5 for kinetics + dynamics)
- Intraspecies differences: 10

The total assessment factor is 180.

This resulted in a calculated value of 486 µg/m^3 and a derived EU-LCI for PGDME of 500 µg/m^3.

No information on odour threshold of PGDME was available in the public domain.

Appendix: Comparative analysis of derived EU-LCI values between the Waalkens-Berendsen (1991) and Reijnders (1989) studies

Aside from the developmental effects of PGDME, a subacute oral toxicity study of PGDME performed in accordance with OECD Guideline 407 ("Repeated Dose 28-Day Oral Toxicity Study in Rodents" adopted in 1981) reported neurobehavioural effects (Reijnders, 1989). Male and female Sprague-Dawley rats (n= 5/sex/group) were exposed orally via gavage to 0, 100, 400, or 1000 mg/kg bw/day of PGDME (Proglyme MM) daily for 28 days.

No changes in mortality, body weight or food consumption were observed in either of the sexes. Furthermore, no significant changes in clinical biochemistry were indicated by the haematology results of the PGDME-treated group versus the control groups. The primary effect of PGDME observed in this study was reduced locomotor activity. Dose-related ataxia was noted in males and females exposed to 400 and 1000 mg/kg bw/day of PGDME.

There were statistically significant increases in relative liver and kidney weights (to body weight) observed in males receiving 400 and 1000 mg/kg bw/day of PGDME. An increase in relative liver weight was also observed in female rats exposed to 1000 mg/kg bw/day. The increase in liver weight may be associated with metabolic demand since there were no histopathological findings, whereas the relative kidney weight increase remains of questionable toxicological relevance for human health. Based on these results, the no-observed-adverse-effect-level (NOAEL) of this study was determined to be 100 mg/kg bw/day, which was selected as the POD for the EU-LCI derivation. This POD can be converted to the corresponding inhalation concentration in humans as shown below:

$NOAEC_{human}$: 100 mg/kg bw/day x 70 kg bw/person (assumed body weight) = 7000 mg/person/day
7000 mg/person-day ÷ 20 m^3/person-day (assumed inhalation volume) = 350 mg/m^3

Standard default assessment factors were applied for study length and interspecies and intraspecies differences.

- Study length: 6
- Interspecies differences: 10 (4 for allometric scaling x 2.5 for kinetics + dynamics)
- Intraspecies differences: 10

The total assessment factor is 600.

This resulted in a calculated value of 583 µg/m^3 and a derived EU-LCI for PGDME of 600 µg/m^3. The derived EU-LCI value of 500 µg/m^3 from the Waalkens-Berendsen (1991) study would protect against any reduced locomotor activity from PGDME.

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