Compound	Dipropylene glycol mono methyl ether acetate (DPGMEA)	*Data collection sheet*
Nº CAS 88917-22-0	**EU-Classification: -**	
1 ppm = 7.82 mg/m^3 (23 °C)	**CLP,** harmonised classification: none with respect to toxicity	
Organisation name	**AgBB**	**CARB**
Risk value name	NIK ('Lowest Concentration of Interest')	8-hr REL
Risk value (mg/m^3)	3.9 (read-across from DPGME)	0.08
Reference period	Chronic (general population)	Acute (8 h)
Year	2018	2010
Key study		Landry and Yano, 1984
Study type		Inhalation study with 0, 15, 50, 200 ppm DPM
Species		Rats, rabbits
Duration of exposure in key study		6 h/d, 5 d/week, 13 weeks
Critical effect		Kidney weight
Critical dose value		NOAEC: 15 ppm
Adjusted critical dose		15 ppm x 6 h/8 h x 5 d/7 d = 8 ppm
Single assessment factors		UF_S $10^{0.5}$ x UF_A 2 x $10^{0.5}$ x UF_H 10 x $10^{0.5}$ = 600
Other effects		
Remarks	The EU-LCI value of 3100 µg/m^3 for DPGME was adopted. The EU-LCI value for DPGME is an "ascribed EU-LCI-value". The NIK value for DPGMEA was calculated by molar adjustment.	Read-across was performed: The derivation is based on data from a subchronic inhalation study with dipropylene glycol methyl ether

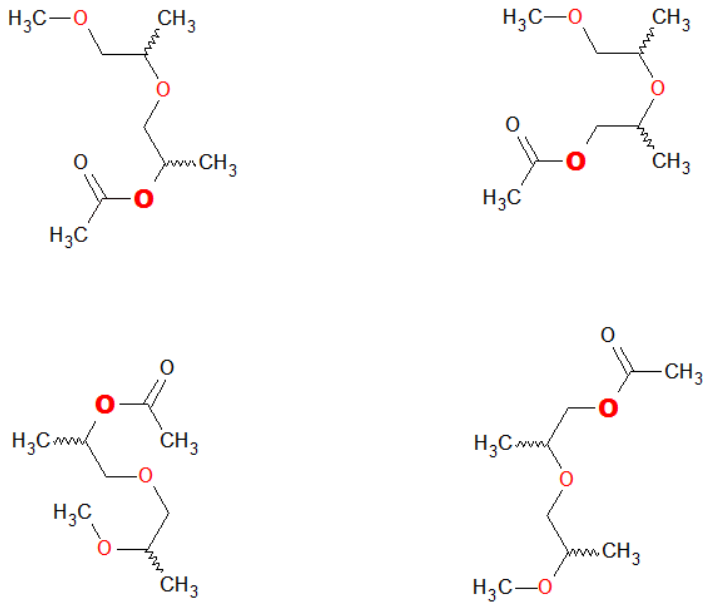
AgBB = Ausschuss zur gesundheitlichen Bewertung von Bauprodukten
UF_L Used LOAEL; UF_H Intraspecies variability; UF_A interspecies variability; UF_S Used subchronic study UF_D data deficiencies.

Compound	**Dipropylene glycol mono methyl ether acetate (DPGMEA) C9H18O4**		***Factsheet***
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI value and status			
EU-LCI value	1	[µg/m^3]	950
EU-LCI status	2	Draft/Final	Final
EU-LCI year of issue	3	Year when EU-LCI value has been issued	2019
General information			
CLP-Index No.	4	INDEX	-
EC-No.	5	EINECS	406-880-6
CAS-No.	6	Chemical Abstract Service number	88917-22-0 (mixture of isomers)
Harmonised CLP classification	7	Human health risk related classification	-
Molar mass and conversion factor	8	[g/mol] and [ppm – mg/m^3]	190.3 1 ppm = 7.83 mg/m^3
Key data / database			
Key study, authors, year	9	Critical study with lowest relevant effect level	
Read across compound	10	Where applicable	Propylene glycol methyl ether acetate (PGMEA)
Species	11	Rat, human, etc.	
Route / type of study	12	Inhalation, oral feed, etc.	
Study length	13	Days, subchronic, chronic, etc.	
Exposure duration	14	h/d, d/w	
Critical endpoint	15	Effect (s), site of	
Point of departure (POD)	16	LOAEC, NOAEC, BMD, etc.	
POD value	17	[mg/m^3] or ppm or [mg/kg$_{BW}$×d]	POD/TAF from the fact sheet for PGMEA: 0.643 mg/m^3
Assessment factors (AF)	18		
Adjustment for exposure duration	19	Study exposure h/d, d/w	-
Study length	20	sa→sc→c	-
Route-to-route extrapolation factor	21	-	-
Dose-response	22a	Reliability of dose-response, LOAEL to NOAEL	-
	22b	Severity of effect (R8 6d)	-
Interspecies differences	23a	Allometric Metabolic rate (R8-3)	-
	23b	Kinetic + dynamic	-
Intraspecies differences	24	Kinetic + dynamic general population	-
AF (sensitive population)	25		-
Other adjustment factors Quality of database	26		-
Result			
Summary of assessment factors	27	Total Assessment Factor	

POD/TAF	28	Calculated value [µg/m³ and ppb]	643 µg/m³ and 119 ppb
Molar adjustment factor	29		0.694 (= 132.16 / 190.3)
Rounded value	30	[µg/m³]	950
Additional comments	31		
Rationale section	32		

Data compilation and evaluation for dipropylene glycol monomethyl ether acetate is based on a project funded by the German Environment Agency (Voss, 2020).

Dipropylene glycol monomethyl ether acetate (DPGMEA) is a mixture of four isomers (each of these isomers are themselves racemates of the RR and RS isomers): (2-(2-methoxy-1-methyl)ethoxy)-1-methylethyl acetate; (2-(2-methoxy-2-methyl)ethoxy)-1-methylethyl acetate; (2-(2-methoxy-2-methyl)ethoxy)-2-methylethyl acetate; and (2-(2-methoxy-1-methyl)ethoxy)-2-methylethyl acetate:



Two of these isomers (those on the right in the figure above) are derivatives of the beta-isomer form, i.e. of a primary alcohol. After hydrolysis, this alcohol may be directly oxidised to the corresponding alkoxy propionic acid. However, it is reported that theses isomers are usually present in the racemic mixture at concentrations below 5 % (CARB, 2010).

<u>Rationale for read-across</u>

There are limited data for DPGMEA. Inhalation studies with repeated exposure to DPGMEA are not available. Additional data are available from studies with structurally related propylene glycol ethers and ether acetate.

In a subacute inhalation study with propylene glycol mono methyl ether acetate (PGMEA), a degeneration with metaplasia of the olfactory nasal epithelium was observed in rats at 3000 ppm (NOAEC 1000 ppm) and in mice at all exposure concentrations (LOAEC: 300 ppm, no NOAEC) (Miller et al., 1984).

Similar lesions in the olfactory nasal epithelium of rats and mice have been described in a number of subacute or subchronic inhalation studies in which the animals had been exposed to other aliphatic esters of alkanoic acids: methyl acetate, ethyl acetate, n-butyl acetate, vinyl acetate, n-amyl acetate, n-butyl propanoate, or methyl methacrylate. The concentrations at which such effects were observed were in the range of 350 – 2500 ppm, similar to that of PGMEA. The epithelial lesions are attributed to the formation

of acetic, propanoic or methacrylic acid, leading to cytotoxicity when the specific intracellular buffer capacity of the cells is exceeded and exhausted (Hardisty et al., 1999).

Studies on the toxic effects and the toxicokinetic of PGMEA and the non-esterified PGME (propylene glycol monomethyl ether) clearly indicated that both are essentially toxicologically equivalent, with the exception of nasal irritation, which was observed in inhalation studies of PGMEA but not PGME despite the high absorption of both chemicals by this tissue (Domoradzki et al., 2003).

Similar conclusions can be drawn in the case of DPGMEA and DPGME (dipropylene glycol mono methyl ether). Studies of DPGMEA indicate a low systemic toxicity, similar to that of the non-esterified DPGME. The similarity in the systemic effects of these two compounds is corroborated by toxicokinetic data showing that DPGMEA is rapidly hydrolysed *in vivo* with the formation of DPGME (and acetate)[1].

For DPGME, subchronic toxicity studies of rats and rabbits provided a NOAEC of 200 ppm, for the highest concentrations tested (ECHA Dissemination, 2019e). DPGMEA was not genotoxic *in vitro*, and no genotoxicity was observed in structurally related glycol ethers (PGME) or ether acetates (DEGMEA, diethylene glycol mono ethyl ether acetate) *in vivo* (ECHA Dissemination, 2019e; OECD SIDS, 2003a). Carcinogenicity data are not available for DPGME(A), but in a two-year carcinogenicity study of rats PGME was not found to be carcinogenic (OECD SIDS, 2003b).

No fertility study is available for DPGMEA. The no-observed-effect-level (NOEL) for fertility and reproductive effects of PGME in a two-generation inhalation reproduction study was 1000 ppm (3710 mg/m^3). Mild parental toxicity was noted at this concentration (ECHA Dissemination, 2019c). Developmental toxicity studies have been conducted with both DPGMEA and DPGME. No developmental toxicity was observed with DPGMEA up to the highest oral dose of 1000 mg/(kg bw x d) in rats (ECHA Dissemination, 2019) and up to the highest inhalation concentration of 300 ppm DPGME in rats and rabbits (Breslin, 1990; OECD SIDS, 2003b).

Overall, the data for DPGMEA and DPGME as well as for other propylene glycol ethers indicate a low systemic toxicity. At the same time, data for PGMEA show that this acetate ester ¬– which is structurally similar to other aliphatic esters – produces local irritation effects in the olfactory nasal epithelium of rodents which are not observed at similar concentrations of the non-esterified glycol ether.

Thus, to conclude, data for DPGME and other propylene glycol ethers do not provide a suitable basis for the derivation of an EU-LCI value for DPGMEA. Instead, a read-across using data from the structurally-related PGMEA will be carried out to derive an EU-LCI value for DPGMEA.

The subacute inhalation toxicity study of PGMEA in rats and mice (Miller et al., 1984) is considered a suitable key study to derive an EU-LCI value (via read-across) for DPGMEA. This leads to a rounded EU-LCI value for DPGMEA of 950 µg/m^3.

<u>Alternative EU-LCI derivations</u>

A developmental toxicity study with oral exposure of rats to DPGMEA indicated a NOAEL of 1000 mg/(kg bw x d) for maternal and developmental toxicity. Toxicokinetic data *in vivo* indicate a rapid and nearly complete absorption of DPGMEA after oral administration. No substance-specific data are available regarding absorption after inhalation; however, glycol ethers in general are known to be well absorbed by inhalation (ECETOC, 2005; OECD SIDS, 2003b). Therefore, similar oral and inhalation absorption may be assumed when performing a route-to-route extrapolation.

[1] In the case of ethyl acetate, calculations indicate that no change of blood pH or systemic acidosis is to be expected from the small amounts of acetic acid which formed via enzymatic hydrolysis of the ester at airborne concentrations of 400 ppm during an 8-hr work shift (Ad-hoc AG, 2014). Moreover, the amount of acetate produced via hydrolysis of the ester is very small compared to the daily uptake and the internal metabolic production of acetic acid (Voss, 2018). These considerations also apply in the case of DPGMEA.

Considering the maternal toxicity, the study length (GD 6-21) can be regarded as a "subacute" duration. Using the following standard assessment factors (EC, 2013; ECHA, 2012):

- Route-to-route extrapolation (rats): 1.15 m^3(kg bw x d)
- Adjusted study length factor (subacute exposure study): 6
- Allometric scaling: already included in route-to-route extrapolation
- Interspecies extrapolation: 2.5
- Intraspecies extrapolation (interindividual variability, general population): 10

a total assessment factor of 172.5 m^3/(kg bw x d) was obtained. This leads to a concentration of 1000 mg/(kg bw x d): 172.5 m^3/(kg bw x d) = 5.797 mg/m^3 (0.74 ppm). This value is about 6 times higher than that derived (from read-across) on the basis of local effects in the respiratory tract after inhalation exposure. The proposed EU-LCI value of 950 µg/m^3 will therefore also offer protection against the systemic effects of DPGMEA.

A comparison may also be performed with the derivation of a value for DPGMEA based on a read-across using data from inhalation studies of DPGME. In two subchronic studies of rats and rabbits, no adverse effects were observed up to the highest concentration of 200 ppm (ECHA Dissemination, 2019e). Using the following standard assessment factors:

- Adjustment for continuous exposure (6 h/d, 5 d/week): 5.6
- Adjusted study length factor (subchronic exposure study): 2
- Interspecies extrapolation:
  allometry: 1 (inhalation exposure, local effect)
  remaining differences: 2.5
- Intraspecies extrapolation (interindividual variability, general population): 10

a total assessment factor of 280 was obtained. This leads to a concentration of 200 ppm : 280 = 0.714 ppm.

Performing a molar adjustment with 1 ppm DPGMEA = 7.82 mg/m^3 would lead to a value of 5583 µg/m^3. This value is also about 6 times higher than the proposed EU-LCI value based on the local effects of the acetate ester of propylene glycol as derived above.

The derivation of the EU-LCI value should therefore be based on the local effects observed in an inhalation study of PGMEA, using read-across. This derived EU-LCI value will protect against the systemic effects of DPGMEA.

An EU LCI value for DPGMEA of 950 µg/m^3 is proposed.

DPGMEA is reported to have a mild odour. However, data on odour thresholds are not available.

References

Ad-hoc AG (2014) Richtwerte für Ethylacetat in der Innenraumluft. Bundesgesundheitsblatt 57:1442-1450

AgBB (2018) Anforderungen an die Innenraumluftqualität in Gebäuden: Gesundheitlichen Bewertung der Emissionen von flüchtigen organischen Verbindungen (VVOC, VOC und SVOC) aus Bauprodukten. Ausschuss zur gesundheitlichen Bewertung von Bauprodukten. https://www.umweltbundesamt.de/themen/gesundheit/kommissionen-arbeitsgruppen/ausschuss-zur-gesundheitlichen-bewertung-von#textpart-1 (last accessed on 10.02.2021)

Breslin, W. et al (1990) Development toxicity of inhaled dipropylene glycol monomethyl ether (DPGME) in rabbits and rats. Toxicologist 10:39

Domoradzki JY, Brzak KA, Thornton CM (2003) Hydrolysis Kinetics of Propylene Glycol Monomethyl Ether Acetate in Rats in Vivo and in Rat and Human Tissues in Vitro. Toxicological Sciences 75:31-39

CARB (2010) Draft Interim REL March 2010. Dipropylene Glycol Methyl Ether Acetate (CAS 88917-22-0). California Air Resources Board (CARB)

EC, European Commission (2013) Harmonisation framework for health based evaluation of indoor emissions from construction products in the European Union using the EU-LCI concept. Report No 29. EUR 26168 EN. Joint Research Centre, Institute for Health and Consumer Protection, Chemical Assessment and Testing Unit. http://publications.jrc.ec.europa.eu/repository/handle/JRC83683 (last accessed on 10.02.2021)

ECETOC (2005) The Toxicology of Glycol Ethers and its Relevance to Man (Fourth Edition). Volume I. European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC). Brussels, Belgium. http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-095-Vol-I.pdf (last accessed on 10.02.2021)

ECHA Dissemination (2019) A mixture of RR and RS isomers of: (2-(2-methoxy-1-methyl)ethoxy)-1-methylethyl acetate; (2-(2-methoxy-2-methyl)ethoxy)-1-methylethyl acetate; (2-(2-methoxy-2-methyl)ethoxy)-2-methylethyl acetate; (2-(2-methoxy-1-methyl)ethoxy)-2-methylethyl acetate. In: European Chemicals Agency (ECHA), Annankatu 18, P.O. Box 400, FI-00121 Helsinki, Finland. https://echa.europa.eu/registration-dossier/-/registered-dossier/15979 (last accessed on 10.02.2021)

ECHA Dissemination (2019c) [2-(2-methoxymethylethoxy)methylethoxy]propanol (Tripropylene glycol monomethyl ether, TPGME). In: European Chemicals Agency (ECHA), Annankatu 18, P.O. Box 400, FI-00121 Helsinki, Finland. https://echa.europa.eu/registration-dossier/-/registered-dossier/13199 (last accessed on 10.02.2021)

ECHA Dissemination (2019e) (2-methoxymethylethoxy)propanol (Dipropylene glycol monomethyl ether, DPGME). In: European Chemicals Agency (ECHA), Annankatu 18, P.O. Box 400, FI-00121 Helsinki, Finland. https://echa.europa.eu/registration-dossier/-/registered-dossier/14751 (last accessed on 10.02.2021)

ECHA (2011) Decision on a compliance check of a registration pursuant to Article 41(3) of regulation (EC) No 1907/2006. Decision number CCH-D-0000001716-72-04/F. European Chemicals Agency (ECHA), Annankatu 18, P.O. Box 400, FI-00121 Helsinki, Finland.

Hardisty JF, Garman RH, Harkema JR, Lomax LG, Morgan KT (1999) Histopathology of nasal olfactory mucosa from selected inhalation toxicity studies conducted with volatile chemicals. Toxicol Pathol 27:618-627

Miller RR, Hermann EA, Young JT, Calhoun LL, Kastl PE (1984) Propylene glycol monomethyl ether acetate (PGMEA) metabolism, disposition, and short-term vapor inhalation toxicity studies. Toxicol Appl Pharmacol 75:521-530

OECD SIDS (2003a) SIDS Initial Assessment Report for SIAM 17: Propylene Glycol Ethers. UNEP Publications. . https://hpvchemicals.oecd.org/ui/handler.axd?id=fdbb6972-3dd4-4046-ba21-eeb6e28c05fb (last accessed on 10.02.2021)

OECD SIDS (2003b) SIDS Initial Assessment Report for SIAM 17: Dipropylene Glycol Methyl Ether. UNEP Publications. https://hpvchemicals.oecd.org/ui/handler.axd?id=fdbb6972-3dd4-4046-ba21-eeb6e28c05fb (last accessed on 10.02.2021)

Landry, TD and Yano, BL (1984) Dipropylene glycol monomethyl ether: A 13 week inhalation toxicity study in rats and rabbits. Fundam. Appl. Toxicol. 4, 612-617. Cited in CARB (2010) and OECD SIDS 2003b

Voss, J.-U. (2018) Toxicological evaluation of indoor air pollutants, subproject 1: Toxicological evaluation of acetic acid and C1-C9-alkanoic acids as basis for the derivation of indoor air guide values. Umweltbundesamt. Berlin, Germany.

Voss, J.-U. (2020) Toxicological basic data for the derivation of EU-LCI values for five substances from building products. UBA Texte 16/2020. https://www.umweltbundesamt.de/publikationen/toxicological-basic-data-for-the-derivation-of-eu-1 (last accessed on 10.02.2021)