Substance Name: 1,2-bis(2-methoxyethoxy)ethane (Triglyme)

EC Number: 203-977-3

CAS Number: 112-49-2

SUPPORT DOCUMENT FOR IDENTIFICATION OF

1,2-BIS(2-METHOXYETHOXY)ETHANE (TRIGLYME)

AS A SUBSTANCE OF VERY HIGH CONCERN BECAUSE OF ITS CMR PROPERTIES

CONTENTS

TABLES AND FIGURES

Tables

ABBREVIATIONS

AFSSET French Agency for Environmental and Occupational Health Safety, now "ANSES", Agence nationale de sécurité sanitaire

CAS Chemical Abstracts Service

CLP Classification, Labelling and Packaging

CMR Carcinogenic, Mutagenic and toxic to Reproduction

CSR Chemical Safety Report

DEGDME Diethylene glycol dimethyl ether (Diglyme)

DGCCRF Direction Générale de la Concurrence, de la Consommation, et de la Répression des Fraudes

DNEL Derived No Effect Level

EC European Community

ECETOC European Centre for Ecotoxicology and Toxicology of Chemicals

EEC European Economic Community

EGDME Ethylene glycol dimethyl ether

EGEE Ethylene glycol monoethyl ether

EGME Ethylene glycol monomethyl ether

ERC Environmental release category

EU European Union

INRS Institut National de Recherche et de Sécurité (French National Institute for Research and Safety)

NACE European Classification of Economic Activities

NOAEC No Observed Adverse Effect Concentration

NOAEL No Observed Adverse Effect Level

OSPA Oxygenated Solvents Producers Association

PBT Persistent, Bioaccumulative and Toxic

PROC Process category

REACH Registration, Evaluation, Authorisation and Restriction of Chemical substances

SPIN Substances in Preparations in the Nordic countries

SU Sector of end use

SVHC Substance of Very High Concern

TEGDME Triethylene glycol dimethyl ether

US EPA U.S. Environmental Protection Agency

VOC Volatile organic compounds

vPvB Very Persistent and very Bioaccumulative

WHO World Health Organization

Substance Name: 1,2-bis(2-methoxyethoxy)ethane (Triglyme, TEGDME)

EC Number: 203-977-3

CAS number: 112-49-2

The substance is identified as a substance meeting the criteria of Article 57 (c) of Regulation (EC) 1907/2006 (REACH) owing to its classification as toxic for reproduction 1B[1].

Summary of how the substance meets the criteria as category 1B reproductive toxicant.

1,2-bis(2-methoxyethoxy)ethane (Triglyme) is listed as entry 603-176-00-2 in Annex VI, part 3, Table 3.1 (the list of harmonised classification and labelling of hazardous substances) of Regulation (EC) No 1272/2008[2] as Repr. 1B, H360D ("May damage the unborn child"). This corresponds to a classification as toxic for reproduction Repr. Cat. 2[3]; R61 ("May cause harm to the unborn child") in Annex VI, part 3, Table 3.2 of Regulation (EC) No. 1272/2008 (list of harmonised classification and labelling of hazardous substances from Annex I to Directive 67/548/EEC).

Therefore, this classification of the substance in Regulation (EC) No 1272/2008 shows that the substance meets the criteria for classification as toxic for reproduction in accordance with Article 57 (c) of REACH.

Registration dossiers submitted for the substance? Yes

1 Classification in accordance with Regulation (EC) No 1272/2008 Annex VI, part 3, Table 3.1 List of harmonised classification and labelling of hazardous substances.

2 Regulation (Ec) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006.

3 Classification in accordance with Regulation (EC) No 1272/2008, Annex VI, part 3, Table 3.2 List of harmonised classification and labelling of hazardous substances (from Annex I to Council Directive 67/548/EEC).

JUSTIFICATION

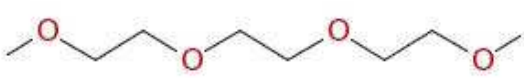
1 Identity of the substance and physical and chemical properties

1.1 Name and other identifiers of the substance

Table 1: Substance identity

EC number:	203-977-3
EC name:	1,2-bis(2-methoxyethoxy)ethane
CAS number (in the EC inventory):	112-49-2
CAS number:	112-49-2, 70992-85-7 (deleted CAS registry)
CAS name:	2,5,8,11-tetraoxadodecane
IUPAC name:	2,5,8,11-tetraoxadodecane
Index number in Annex VI of the CLP Regulation	603-176-00-2
Molecular formula:	$C_8H_{18}O_4$
Molecular weight range:	178.23 g/mol
Synonyms:	Triglyme TEGDME Triethylene glycol dimethyl ether Ansul Ether 161 DMTG Ethane, 1,2-bis(2-methoxyethoxy)- Glyme 4 Hisolve MTM Methyltriglyme NSC 66400

Structural formula:



1.2 Composition of the substance

Name: 1,2-bis(2-methoxyethoxy)ethane

Description: -

Degree of purity: *see confidential Annex II*

Table 2: Constituents

Constituents	Typical concentration	Concentration range	Remarks
1,2-bis(2-methoxyethoxy)ethane EC-No 203-977-3	*See confidential Annex*		

Table 3: Impurities

Impurities	Typical concentration	Concentration range	Remarks
See confidential Annex			

Purity according to website information from Clariant GmbH[4]: ≥99%.

Additional confidential information from registrations is included in Annex II, Chapter 1.

[4] http://www.clariant.de/C12575E4001FB2B8/vwLookupDownloads/2000_SpecialSolvents_Newsroom_Brochures_GlymesBrochure.pdf/$FILE/2000_SpecialSolvents_Newsroom_Brochures_GlymesBrochure.pdf

1.3 Physico-chemical properties

Table 4: Overview of physico-chemical properties

Property	Value	Remarks
Physical state at 20°C and 1013 hPa	clear colourless liquid with ethereal odor	*from registration**
Melting/freezing point	-45 °C at 1013 hPa	*from registration*
Boiling point	216°C at 1013 hPa	*from registration*
Relative density	0.987 g/cm³ at 20°C	*from registration*
Vapour pressure	2.7 Pa at 20°C	*from registration*
Surface tension	31.4 mN/m at 23°C	*from registration*
Water solubility	> 1000 g/L at 20°C	*from registration*
Partition coefficient n-octanol/water (log POW)	-0,52 at 23°C	*from registration*
Flashpoint at 1013 hPa	106 °C	*from registration*
Auto Flammability at 1013 hPa	190 °C	*from registration*
Flammability	Lower explosion limit: 0.7%(v/v) No pyrophoricity No flammability on contact with water	*from registration*

*From dissemination database according to Regulation (EC) No.1907/2006, article 119

Conversion factors (20°C, 1014hPa) (ECETOC, 1995): 1ppm = 7.3mg/m³
1mg/m³=0.14ppm

2 HARMONISED classification and labelling

1,2-bis(2-methoxyethoxy)ethane (Triglyme) is covered by index number 603-176-00-2 in Annex VI, part 3 of Reg. (EC) No 1272/2008 (CLP regulation) as follows:

Table 5: Classification according to part 3 of Annex VI, Table 3.1 (list of harmonised classification and labelling of hazardous substances) of Regulation (EC) No 1272/2008:

Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Spec. Conc. Limits, M-factors	Notes
				Hazard Class and Category Code(s)	Hazard statement code(s)	Pictogram, Signal Word Code(s)	Hazard statement code(s)	Suppl. Hazard statement code(s)		
603-176-00-2	1,2-bis(2-methoxyethoxy)ethane; TEGDME; triethylene glycol dimethyl ether; triglyme	203-977-3	112-49-2	Repr. 1B	H360-Df	GHS08 Dgr	H360Df	EUH019		

Table 6: Classification according to part 3 of Annex VI, Table 3.2 (list of harmonized classification and labelling of hazardous substances from Annex I of Council Directive 67/548/EEC) of Regulation (EC) No 1272/2008:

Index No	International Chemical Identification	EC No	CAS No	Classification	Labelling	Concentration Limits	Notes
603-176-00-2	1,2-bis(2-methoxyethoxy)ethane; TEGDME; triethylene glycol dimethyl ether; triglyme	203-977-3	112-49-2	R19 Repr. Cat. 2; R61 Repr. Cat. 3; R62	T R: 61-19-62 S: 53-45		

3 Environmental fate properties

Not relevant

4 Human health hazard assessment

See section 2 Harmonised Classification and Labelling and Supplementary Information in Annex I.

5 Environmental hazard assessment

Not relevant

6 Conclusions on the SVHC Properties

6.1 PBT, vPvB assessment

Not relevant

6.2 CMR assessment

1,2-bis(2-methoxyethoxy)ethane (Triglyme) is listed as entry 603-176-00-2 in Annex VI, part 3, Table 3.1 (list of harmonised classification and labelling of hazardous substances) of Regulation (EC) No 1272/2008[5] as Repr. 1B, H360D ("May damage the unborn child"). This corresponds to a classification as toxic to reproduction Repr. Cat. 2[6]; R61 ("May cause harm to the unborn child") in Annex VI, part 3, Table 3.2 of Regulation (EC) No. 1272/2008 (list of harmonised classification and labelling of hazardous substances from Annex I to Directive 67/548/EEC).

Therefore, this classification of the substance in Regulation (EC) No 1272/2008 shows that the substance meets the criteria for classification as toxic for reproduction in accordance with Article 57 (c) of REACH.

6.3 Substances of equivalent level of concern assessment

Not relevant.

[5] Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006

[6] Classification in accordance with Regulation (EC) No 1272/2008, Annex VI, part 3, Table 3.2 List of harmonised classification and labelling of hazardous substances (from Annex I to Council Directive 67/548/EEC).

7 References

Dissemination website, dissemination database according to Regulation (EC) No.1907/2006, article 119 http://apps.echa.europa.eu/registered/registered-sub.aspx

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ANNEX I SUPPLEMENTARY INFORMATION ON TOXICOKINETICS, AND TOXICITY FOR REPRODUCTION

1 Toxicokinetics (absorption, metabolism, distribution and elimination)

Due to the high structural similarity of triglyme and diglyme (difference: one ethyl group; but same functional groups) and hence the strong likelihood that both compounds will be metabolised by the same enzymes/metabolic path, a read across from the metabolism data generated with diglyme is used to clarify the toxicokinetic behaviour of triglyme in the registration dossier (dissemination website).

Due to the high structural similarity of triglyme and diglyme, a similar skin penetration behaviour is expected. Since the molecular weight of triglyme (178.23 g/mol) is higher than that of diglyme (134.18 g/mol), the substance is expected to be absorbed by the skin in a smaller amount than diglyme (dissemination website).

Glycol ethers in general are readily distributed throughout the body and eliminated through the urine. No substantial accumulation of the parent compound has been observed (ECETOC, 2005).

The reproductive toxicity of diglyme is attributed to its minor metabolite 2-methoxyacetic acid, which is generated from 2-methoxyethanol. 2-methoxyacetic acid has shown evidence of accumulation in animals and humans. In humans its half-life was calculated as 77.1h (ECETOC, 1995, WHO, 2002). 2-methoxyacetic acid is also considered to be responsible for the reproductive toxicity of triglyme. A formation of a smaller amount of 2-methoxyacetic acid is however expected to occur in the case of triglyme (in comparison with diglyme).

2 Toxicity for reproduction

2.1 Effects on fertility

The reproductive organs of male animals are a specific target for triglyme. The key study is summarized in Table 16 (Hofmann *al*., 1992). The NOAEL of this study for effects on the testis/spermatocytes is 250 mg/kg bw/day.

2.2 Developmental toxicity

Triglyme is toxic for development by the oral route in mice and rabbits. An overview of relevant studies is given in Table 16.

Oral exposure of New Zealand White rabbits to triglyme at 75mg/kg bw/day produced no adverse maternal or developmental effects. At 125 mg/kg bw/day an increased embryo toxicity was observed. Doses of 175 and 250mg/kg bw/day were associated with adverse developmental effects and evidence of maternal toxicity. The principal manifestations of developmental toxicity were increased external and visceral malformations at 175 and 250 mg/kg bw/d. The $NOAEL_{maternal}$ is set to 125 mg/kg bw/d and the $NOAEL_{foetal}$ is set to 75 mg/kg bw/d (George *et al*., 1990).

Table 16: Studies* considered for the classification of triglyme as toxic for reproduction

	Species (Strain)	Route	Animals per dose level	Time	Exposure conc. or dose	Response	Reference
Repeated dose toxicity study	Wistar rats	Oral (gavage)	5M, 5F	28d	62.5 mg/kg/d 250 mg/kg/d 1000 mg/kg/d	No effects ↓*thymus weight* ↓testis size, Oligo- and aspermia	Hofmann *al*., 1992
Reproduction and Develop-mental studies	Mice	Oral (gavage)	20F	g.d. 11	713 mg/kg bw	No effects.	Hardin and Eisenmann, 1987
	Mice	Oral (gavage)	50F	g.d. 7-14	3500 mg/kg bw	Maternal death (2/50); 100% resorption	Schuler *et al*., 1984
	Mice	Oral (gavage)	29-30 f	g.d. 6-15	250 mg/kg bw 500 mg/kg bw 1000 mg/kg bw	No effects. ↑maternal liver weight, ↓foetal bw ↑maternal liver weight, ↓foetal bw. Malformations.	George *et al*., 1987
	Rabbit	Oral (gavage)	27-32 f	g.d. 6-19	75 mg/kg bw 125 mg/kg bw 175 mg/kg bw 250 mg/kg bw	No effects. ↑increased embryo toxicity ↓maternal bw, ↑external and visceral malformations ↓maternal bw, ↑external and visceral malformations	George *et al*., 1990
	Mice	Oral (drinking water)	20M, 20F	Ad libitum, Continuous breeding protocol with cross-over mating	0 mg/kg bw/d 440 mg/kg bw/d 880 mg/kg bw/d 1750 mg/kg bw/d	No effects. No effects. ↓ pup bw ↓ pup bw, live pups/litter and litters/pair	Morrissey *et al*., 1989

*compiled from the ECETOC Technical Report No.64, 1995. The key studies in the registration dossier are highlighted in gray (dissemination website).