Annex XV dossier

PROPOSAL FOR IDENTIFICATION OF A SUBSTANCE AS A CATEGORY 1A OR 1B CMR, PBT, vPvB OR A SUBSTANCE OF AN EQUIVALENT LEVEL OF CONCERN

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

EC Number(s): 203-977-3

CAS Number(s): 112-49-2

Submitted by: **Belgian Competent Authority (Belgian Federal Public Service (FPS) Health, Food Chain Safety and Environment, Risk Management Service)**

In cooperation with:

Polish Competent Authority (Bureau for Chemical Substances)

PUBLIC VERSION

CONTENTS

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

PROPOSAL FOR IDENTIFICATION OF A SUBSTANCE AS A CATEGORY 1A OR 1B CMR, PBT, vPvB OR A SUBSTANCE OF AN EQUIVALENT LEVEL OF CONCERN

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

EC Number(s): 203-977-3

CAS number(s): 112-49-2

- The substance is proposed to be 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(s) meet(s) the CMR (Cat 1A or 1B) criteria:

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).

PART I

JUSTIFICATION

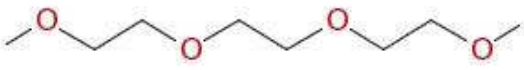
1 IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES

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 P_{OW})	*-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).

PART II

INFORMATION ON USE, EXPOSURE, ALTERNATIVES AND RISKS

1 INFORMATION ON MANUFACTURE, IMPORT/EXPORT AND USES – CONCLUSIONS ON EXPOSURE

1.1 Volumes for manufacture, import and export

According to the Oxygenated Solvent Producer Association (OSPA), the European production of Triglyme was more than 1000 tons in 2002 (INSERM, 2006).

According to current information (registration) the range of the overall volume (manufacture plus import) is currently below the level of 2002. For further details see confidential Annex II, Chapter 2.

1.2 Uses of the Substance

1.2.1 Overview

Triglyme is commercially available. A search of the internet revealed a large number of suppliers worldwide (www.chemicalbook.com, www.chemexper.com).

There is only limited information on the current use of the substance. The substance is registered for Industrial use as a solvent or as a process chemical (Dissemination website[7]).

The Clariant website (Clariant, 2011a) and product brochures give some details of its use as a solvent (Clariant, 2011b and 2011c).

Triglyme is used as an inert solvent for grignard-, reduction- and alkylation-reactions. Reactions involving alkali metals can be carried out in triglyme and alkali metal dispersions in triglyme are used for etching of Teflon and Fluoropolymers. Triglyme is also used as an inert solvent for reduction reactions using Sodium borohydride and used as a solvent to carry out methylation reactions using dimethyl carbonate (and other dialkyl carbonates) (Clariant, 2011a).

Triglyme is also used as part of absorbing liquids in the industrial cleaning of gases (gas scrubber) (Communication, May 2010).

[7] dissemination database according to Regulation (EC) No.1907/2006, article 119

Triglyme can also possibly be used as a catalyst for certain phase –transfer reactions (Clariant, 2010c). It is however not clear if triglyme is actually commercially used in this application, as the highest catalytic activity generally occurs with higher polyglycol dimethyl ethers than triglyme.

Glymes are also reported to be used in the formulation of electrolyte systems for lithium batteries (Clariant, 2010b). This use as an electrolyte solvent seems to be particularly true for the monoglyme. However, there is evidence from the published literature that triglyme could also be used for this purpose (Ryu et al., 2006; Choi et al., 2007; Kwon et al., 2010 amongst others).

Triglyme has been reported to be used in Brake fluids. The safety datasheets of different brake fluids give the following concentrations for triglyme: <0.5% (Prista®DOT-3), <1% (Hidrolik fren yagi DOT3), <2.5% (Eurol Remvloeistof DOT4), 1-10% (Voltronic super dot4 brake fluid) and 2.5-10%(w/w)(Eurol Remvloeistof DOT3).

The use of triglyme (process categories) according to information from the dissemination website (non-confidential information of the registration dossier(s)) is presented in Table 7.

Table 7: Uses by workers in industrial settings (dissemination website)

Identified Use	**Substance supplied to that use**	**Use descriptors**
Manufacture of the substance itself	as such (substance itself)	**Process category (PROC):** PROC 1: Use in closed process, no likelihood of exposure PROC 2: Use in closed, continuous process with occasional controlled exposure PROC 3: Use in closed batch process (synthesis or formulation) PROC 4: Use in batch and other process (synthesis) where opportunity for exposure arises PROC 8a: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities PROC 15: Use as laboratory reagent **Environmental release category (ERC):** ERC 1: Manufacture of substances **Sector of end use (SU):** SU 0: Other: SU3: Industrial uses: Uses of substances as such or in preparations at industrial sites
Industrial use as solvent or Process chemical and distribution of substance	as such (substance itself)	**Process category (PROC):** PROC 1: Use in closed process, no likelihood of exposure PROC 2: Use in closed, continuous process with occasional controlled exposure PROC 3: Use in closed batch process (synthesis or formulation) PROC 4: Use in batch and other process (synthesis) where opportunity for exposure arises

		PROC 8a: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities PROC 9: Transfer of substance or preparation into small containers (dedicated filling line, including weighing) PROC 15: Use as laboratory reagent **Environmental release category (ERC):** ERC 1: Manufacture of substances ERC 2: Formulation of preparations ERC 4: Industrial use of processing aids in processes and products, not becoming part of articles ERC 6a: Industrial use resulting in manufacture of another substance (use of intermediates) **Sector of end use (SU):** SU 8: Manufacture of bulk, large scale chemicals (including petroleum products) SU 9: Manufacture of fine chemicals SU 0: Other: SU3: Industrial uses: Uses of substances as such or in preparations at industrial sites

According to this information, triglyme is only registered for industrial use. No professional use is foreseen.

France:

The AFSSET report (AFSSET, 2008) refers to different investigations carried out on glycol ethers. Triglyme has not been found in:

- An investigation on use in garages, cleaning, hairdressing and general mechanics, carried out in 123 small and medium-sized enterprises (Beaujean et al., 2005)
- A study on solvents carried out in 2004 by the INRS[8] (Triolet, 2005),
- Investigations carried out by DGCCRF (Direction Générale de la Concurrence, de la Consommation, et de la Répression des Fraudes) in 2006 on paints, varnishes and wide-spread drugstore-products (Communication DGCCRF 2007 from AFSSET).

In France the use of glymes (EGDME, DEGDME and TEGDME (triglyme)) in human medical drugs was being phased out in 2008 (AFSSET, 2008).

[8] INRS: Institut National de Recherche et de Sécurité

In France the professional exposure to glycol ethers has changed. Between 1987 and 1998, glycol ethers were preferentially ethylene derivatives, whereas in the period 2000-2006, they were essentially derived from propylene (AFSSET, 2008).

According to OSPA, triglyme was not sold nor used in France in 2004[9].

1.2.2 Use of triglyme in mixtures and articles

France:

Glycol ethers classified as toxic to reproduction are practically not found in marketed mixtures. In total, out of the 13 000 formulations notified in the SEPIA database (INRS database, mixtures on the French market) between 2000 and 2006, only 142 formulations (1% of all) contain glycol ethers classified as Repr. 1B (see Table 8). Amongst those 1 formulation contains TEGDME (triglyme) (AFSSET, 2008).

Table 8: Number of occurrence of glycol ethers classified as Repr. 1B in formulations registered in SEPIA between 2000 and 2006.

Glycol ethers	Total number of formulations containing glycol ethers classified as "Repr. 1B"
1PG2ME	42
1PG2MEA	40
EGEE	24
EGEEA	21
EGME	9
DEGDME	3
EGDME	2
TEGDME	1
TOTAL	**142**

The AFSSET report (2008) further indicates a use of triglyme in cleaning products for cars [Communication Réseau de toxicovigilance, Septembre 2007].

Nordic countries:

The SPIN database[10] was searched for information on triglyme in products on the national markets of Norway, Sweden, Finland and Denmark (see Table 9). In Sweden, Finland and Denmark triglyme is on the market although in low volumes.

[9] http://www.glycol-ethers.eu/press-room/position-papers#glycol-ethers-charter

Table 9: Triglyme in products according to SPIN (2006–2009).

Country	2006		2007	
	number of preparations	tonnage	number of preparations	tonnage
Sweden	6	4	4	1.0
Finland	Conf*		Conf	
Denmark	4	3.8	4	3.8

Country	2008		2009	
	number of preparations	tonnage	number of preparations	tonnage
Sweden	3	1.0	4	1.0
Finland	-		Conf	
Denmark	4	0.6	Conf	

* "Conf" = Confidential: Total quantities and the total number of products have not been reported to SPIN if the substance is contained in less than 4 products and is registered by less than 3 companies.

According to the SPIN database triglyme was registered in Finland and Denmark in 2006 and 2007 for the Industrial use "Sale, maintenance and repair of motor vehicles and motorcycles; retail sale of automotive fuel" with relatively low amounts (Table 10). In 2008, it was registered in Denmark for "Wholesale and retail trade and repair of motor vehicles and motorcycles" in low amounts. In 2009, it was registered in Finland for "Wholesale trade, except of motor vehicles and motorcycles" and for "Warehousing and support activities for transportation" with no further information due to confidentiality.

Table 10: Industrial uses (NACE[11]**) according to the SPIN database (2006-2009).**

Country	Year	NACE Code*	Industrial Use	# Preparations	Amount (Tons)
FI	2009	G46	Wholesale trade, except of motor vehicles and motorcycles		
FI	2009	H52	Warehousing and support activities for transportation		
DK	2008	G45	Wholesale and retail trade and repair of motor vehicles and motorcycles	4	0.6
DK	2007	50	Sale, maintenance and repair of motor vehicles and motorcycles; retail sale of automotive fuel	4	3.8
FI	2007	50	Sale, maintenance and repair of motor vehicles and motorcycles; retail sale of automotive fuel		

[10]Substances in Preparations in the Nordic countries http://195.215.251.229/DotNetNuke/default.aspx

[11] NACE (Nomenclature générale des activités économiques dans les Communautés européennes)

DK	2006	50	Sale, maintenance and repair of motor vehicles and motorcycles; retail sale of automotive fuel	4	3.8
FI	2006	50	Sale, maintenance and repair of motor vehicles and motorcycles; retail sale of automotive fuel		

The tonnage information are always “netto” ton = tons imported + tons produced – tons exported.
* The NACE code indicates the branches of industry where the products are used.

In Table 11 "Industrial uses" national industry groups (based on NACE) from Denmark and Sweden are presented. They usually operate on a more detailed level than the 2 digit NACE code in Table 10. Therefore data that might be included in the overall presentation in the "Industrial use (NACE)" tab might be partly or totally suppressed in the "Industrial Use" tab due to confidentiality.

Table 11: Industrial Uses in DK and SE (using national codes) according to the SPIN database (2006-2008)

Country	**Year**	**Code**	**Use Category**	**# Prep**	**Tons***
DK	2008	G452010	Repair of motor vehicles	4	0.6
DK	2007	G0502010	General repair shops	4	3.8
DK	2006	G0502010	General repair shops	4	3.8
SE	2006	G50.3	Sales establishments for motor vehicles parts and accessories	3	1.0

Additionally, the SPIN database was searched for use categories in the Nordic countries. The technical function of the preparations containing triglyme is described by a UC62 code (Use Code 62). The use as “lubricants and additives” is registered in Sweden and another unspecified use is registered in Finland (Table 12). Information from other countries are not listed because the distribution to codes often results in a number of preparations below the limit of confidentiality, which means that code and volume cannot be presented.

Table 12: Use categories (UC62) according to the SPIN database.

Country	**Year**	**Code**	**Use Category**	**# Prep**	**Amount**
SE	2009	35	Lubricants and additives	3	1.0
FI	2009	55	Others (not described elsewhere)		
SE	2007	35	Lubricants and additives	3	1.0
FI	2007	55	Others (not described elsewhere)		
SE	2006	35	Lubricants and additives	4	2.0
FI	2006	55	Others (not described elsewhere)		

Furthermore, triglyme was also registered in Sweden in 2006 with the national use category S45120 “Brake grease” (3 preparations, 2.0 Tons) (Table 13).

Table 13: Use categories (National) according to the SPIN database.

Country	Year	Code	Use Category	# Prep	Amount
SE	2006	S45120	Brake grease	3	2.0

1.2.3 Triglyme as Impurity

According to the Glycol Ether Charter by OSPA[12] all producers confirm that the glycol ethers of the E-Series not classified toxic for reproduction do not contain as an impurity any of the glycol ethers classified toxic for reproduction (like triglyme).

1.2.4 Use restrictions

Triglyme is listed in Annex XVII, Group 30, of the REACH regulation[13] and shall not be placed on the market, or used for supply to the general public as substance, or constituent of substance or in mixtures above the generic concentration limit of 0.3%. Suppliers shall ensure before the placing on the market that the packaging of such substances and mixtures is marked visibly, legibly and indelibly as follows: “Restricted to professional users”.

According to Directive 2009/48/EC (Safety of toys) substances classified as CMR of category 1A, 1B or 2 shall not be used in toys or in components of toys.

According to the Cosmetics Directive 76/768/EEC (amended by Directive 2004/93/EC), Annex II, no 1147, triglyme must not be a part of the composition of cosmetic products.

Due to its boiling point of 216 °C at 1013hPa triglyme falls under the definition as VOC according to Directive 2004/42/EC[14] on the limitation of emissions of volatile organic compounds due to the use of organic solvents in certain paints and varnishes.

Conclusion on manufacture, import, export and uses:

According to current information triglyme is still on the European Market. The volumes seem to have declined from more than 1000 tons in 2002 to today. It is mainly used as solvent for a variety

[12] http://www.glycol-ethers.eu/press-room/position-papers

[13] Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC

[14] Directive 2004/42/EC of the European Parliament and of the Council of 21 April 2004 on the limitation of emissions of volatile organic compounds due to the use of organic solvents in certain paints and varnishes and vehicle refinishing products and amending Directive 1999/13/EC

of applications. Use in brake fluids has also been reported. Due to existing restrictions the use of the substance as such or in mixtures by consumers is not expected.

1.3 Exposure

1.3.1 SPIN exposure Toolbox

SPIN exposure Toolbox (called "Use index") makes it possible to search for general indicative exposure of the environment and human beings from the use of triglyme (Table 14). Use index is a method where confidential use information is converted into an exposure based index that can be made publicly available. It cannot be used to provide exact quantification on exposure but it can be considered as an indicative screening tool. No information for exposure of workers is given (under development).

Table 14: Exposure potential based on data in Nordic product registers[15].

Country	Latest year	Use Index					Range of use
		Surface water	Air	Soil	Waste water	Human consumers	
DK	2009	-	x	xxx	x	xx	Narrow range of applications
SE	2009	x	x	xx	x	xx	Very narrow range of applications

(-) The registered uses do not indicate direct exposure. (x) One or several uses indicate a potential exposure. (xx) One or several uses indicate a probable exposure. (xxx) One or several uses indicate a very probable exposure.

1.3.2 Human exposure

1.3.2.1 Workplace exposure

No measured data has been found on triglyme exposure concentrations at the workplace.

Exposure estimations in the Chemical Safety Report of the registration dossier are based on model calculations (see confidential Annex II, Chapter 4).

[15] Note: Registered Use Categories do not include all potential uses of the chemical and possibility for direct exposure can therefore not be excluded. Indirect exposure e.g. exposure of man via the environment or exposure to the environment through waste disposal is not included. Certain product types that may contribute to overall exposure are insufficiently represented in SPIN (articles such as toys, food packaging materials, cosmetic products, medicinal products).

Germany:

Brake fluids have been identified as an apparent use of triglyme. There is therefore potential for dermal exposure during maintenance and recycling work.

BAuA has performed field studies in car recycling (13 enterprises) and car repair shops (13).
It was found that during draining and dismantling operations dermal exposure occurs. Mostly hands are affected. Workers were found to be especially dermally exposed to liquids such as lubricating and engine oil, but also to used old grease (Auffarth *et al*., 1997; Auffarth *et al*., 2002).

1.3.2.2 Consumer exposure

No information could be found on consumer exposure in the EU.

The US EPA identified potential Consumer exposure in the US linked to some identified uses of triglyme (Federal Register/Vol.76, No. 133/Tuesday, July 12, 2011[16])(letter from industry to EPA, 15 June 2009):

- As process solvent for adhesives: it is possible that adhesives containing between 1 and 5% triglyme may be sold to consumers through distributors.
- As component of brake fluids: it is assumed that triglyme may be present in brake fluid accessible by consumers
- As component of paint/graffiti remover: it is assumed that triglyme may be present in paint/graffiti remover accessible by consumers.
- In paint production: it is possible that paint containing between 1 and 5% triglyme may be sold to consumers through distributors.

Due to the fact that triglyme is already restricted in the EU for consumer uses, triglyme is not expected as a component of paint/graffiti remover or paint for consumers.
The presence of triglyme in adhesives can however not be excluded (if used in articles). The presence of triglyme in brake fluid (professional use) can also be a potential source of consumer exposure.

1.3.3 Environmental exposure

Triglyme was measured monthly in 2008, 2009 and 2010 at four different locations (Lobith, Nieuwegein, Nieuwersluis and Andijk) of the river Rhine, in Germany and the Netherlands by RIWA (Association of River Water Supply Companies).

A guidance value (DMR[17] 2008) of 1µg/L has been allocated to triglyme.

This value was exceeded two times in 2008 (1.62 µg/L in Lobith and 1.2 µg/L in Nieuwersluis) (RIWA, 2008).

[16] http://www.gpo.gov/fdsys/pkg/FR-2011-07-12/pdf/2011-17084.pdf

[17] DMR= Donau-, Maas- en Rijnmemorandum 2008

In 2009, this value was exceeded once (1.5 µg/L in Lobith)

In 2010, triglyme was measured but not detected in the four stations (RIWA, 2010).

From these environmental exposure data, we can conclude that triglyme was detected in the river Rhine in 2008 and 2009, but not in 2010.

Furthermore, in 2009, 2 cases of water pollution incidents with triglyme were reported (the source of pollution was unknown):

- In Bad-Honnef: 4.1µg/L of triglyme (9/02/2009)
- In Kleve/Bimmen: 1.5 µg/L of triglyme (13/08/2009) (RIWA, 2009)

2 CURRENT KNOWLEDGE ON ALTERNATIVES

In general toxic ethylene glycol ethers, which are often used as solvents for special applications, can only be replaced easily with less toxic propylene glycol ethers which have similar physicochemical properties (Kettenis, 2005). A substitution of triglyme by propylene glycol ethers is also recommended by the website "www.substitution-cmr.fr"[18].

According to the Association of Oxygenated Solvent Producers (OSPA) no substitutes for present industrial uses of triglyme are available (communication, May 2010). OSPA further states that in general their members pay particular attention to promote alternatives to glycol ethers classified as "Toxic for reproduction". OSPA has therefore been recommending a policy to limit the marketing of these glycol ethers to industrial applications for which a substitute solution does not yet exist.

3 RISK-RELATED INFORMATION

A comprehensive risk assessment is outside the scope of this dossier. The following information is based on available literature data and information from the registration.

3.1 Human Health Effect Assessment

For information on toxicokinetics and effects on reproduction and development see Annex I.

[18]http://www.substitution-cmr.fr/index.php?id=112&tx_kleecmr_pi3%5buid%5d=34&tx_kleecmr_pi3%5bonglet%5d=1&cHash=a3ac8a2397

3.2 Risk characterisation

3.2.1 Human health

3.2.1.1 Data from literature

No guidance value has been found in the literature.

3.2.1.2 Information from the registration

The information on the registered substance triglyme according to Regulation (EC) No.1907/2006 article 119 (dissemination website) is shown in Table 15. For more detailed (confidential) information see Annex II, Chapter 3.

Table 15: DNEL values according to the registration.

	$DNEL_{Dermal}$	$DNEL_{Inhalation}$	$DNEL_{Oral}$
Workers	6.25 mg/kg bw/day	80.4 mg/m^3 (=11 ppm)	-
General population	3.13 mg/kg bw/day	19.9 mg/m^3(=2.7 ppm)	3.13 mg/kg bw/day

Further information on worker exposure is included in the confidential Annex.

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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	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

				cross-over mating			

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