

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): bis(2-methoxyethyl) ether (Diglyme)

EC Number(s): 203-924-4

CAS Number(s): 111-96-6

Submitted by: Environment Agency Austria on behalf of the Austrian Competent Authority (Austrian Federal Ministry of Agriculture, Forestry, Environment and Water Management)

In cooperation with: Belgian Competent Authority (Belgian Federal Public Service (FPS) Health, Food Chain Safety and Environment, Risk Management Service)

and Polish Competent Authority (Bureau for Chemical Substances)

PUBLIC VERSION: *This version does not include the confidential annex referred to in Parts I and II.*

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ABBREVIATIONS

AFSSET	French Agency for Environmental and Occupational Health Safety, now “ANSES”, Agence nationale de sécurité sanitaire
BCF	Bioconcentration factor
1BG2ME	Butylene glycol monomethylether
BUA	Beratergremium für umweltrelevante Altstoffe
CAS	Chemical Abstracts Service
CICAD	Concise International Chemical Assessment Documents
CLP	Classification, Labelling and Packaging
CMR	Carcinogenic, Mutagenic and toxic to Reproduction
CSR	Chemical Safety Report
DEGBE	Diethylene glycol monobutyl ether
DEGDBE	Butyl diglyme
DEGDME	Diethylene glycol dimethyl ether (Diglyme)
DEGEE	Diethylene glycol monoethyl ether
DEGME	Diethylene glycol monomethyl ether
DGCCRF	Direction Générale de la Concurrence, de la Consommation, et de la Répression des Fraudes
DNEL	Derived No Effect Level
DPGME	Dipropylene glycol monomethyl ether
EC	European Community
EC ₅₀	Effective Concentration 50%
ECHA	European Chemicals Agency
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals

EEC	European Economic Community
EGBE	Ethylene glycol monobutyl ether
EGDEE	Ethylene glycol diethyl ether
EGDME	Ethylene glycol dimethyl ether
EGE	ethylene glycol ethers
EGEE	Ethylene glycol monoethyl ether
EGME	Ethylene glycol monomethyl ether
EGPE	Propylene Glycol Monopropyl Ether
EGPhE	Ethylene glycol phenyl ether
ERC	Environmental release category
ESIS	European chemical Substances Information System
ETUC	European Trade Union Confederation
HPV	High Production Volume
HSDB	Hazardous Substances Data Bank
ICCA	International Council of Chemical Associations
IKSR	Internationale Kommission zum Schutz des Rheins (International Commission for the Protection of the Rhine)
INERIS	Institut National de l'Environnement industriel et des risques (French National Institute for Industrial Environment and Risks)
INRS	Institut National de Recherche et de Sécurité (French National Institute for Research and Safety)
IOEL	Indicative occupational exposure limit
LOAEL	Lowest Observed Adverse Effect Level
MAA	Methoxyacetic acid
NACE	European Classification of Economic Activities
NOAEC	No Observed Adverse Effect Concentration

NOAEL	No Observed Adverse Effect Level
OECD	Organisation for Economic Co-operation and Development
OSPA	Oxygenated Solvents Producers Association
PBT	Persistent, Bioaccumulative and Toxic
2PG1BE	2-Propylene glycol 1-butyl ether
2PG1EE	Propylene glycol monoethyl ether
PGME	Propylene glycol monomethyl ether
PROC	Process category
REACH	Registration, Evaluation, Authorisation and Restriction of Chemical substances
RIWA	Association of River Water Supply Companies
SIN	Substitute it now
SPIN	Substances in Preparations in the Nordic countries
SRC	Syracuse Research Corporation
SU	Sector of end use
SVHC	Substance of Very High Concern
TEGDME	Triethylene glycol dimethyl ether
TGD	Technical guidance document
TPGME	Tripropylene glycol monomethyl ether
TWA	Time Weighted Average
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): bis(2-methoxyethyl)ether (Diglyme, DEGDME)

EC Number(s): 203-924-4

CAS number(s): 111-96-6

- 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.

Summary of how the substance(s) meet(s) the CMR (Cat 1 or 2) criteria:

Bis(2-methoxyethyl)ether (diglyme) is listed as entry 603-139-00-0 in Annex VI, part 3, Table 3.1 (the list of harmonised classification and labelling of hazardous substances) of Regulation (EC) No 1272/2008¹ as Repr. 1B, H360FD (May damage fertility. May damage the unborn child.) This corresponds to a classification as toxic to reproduction Repr. Cat. 2; R60-61 (“May impair fertility; 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(s) 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 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

PART I

JUSTIFICATION

PUBLIC VERSION

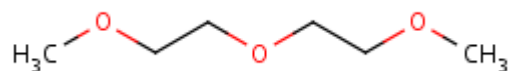
1 IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES

1.1 Name and other identifiers of the substance

Table 1: Substance identity

EC number:	203-924-4
EC name:	Bis(2-methoxyethyl)ether
CAS number (in the EC inventory):	111-96-6
CAS number:	111-96-6
CAS name:	Ethane, 1,1'-oxybis[2-methoxy-
IUPAC name:	1-methoxy-2-(2-methoxyethoxy)ethane
Index number in Annex VI of the CLP Regulation	603-139-00-0
Molecular formula:	C ₆ H ₁₄ O ₃
Molecular weight range:	134.17g/mol
Synonyms:	<p>Diglyme</p> <p>DEGDME</p> <p>Diethylglycoldimethylether</p> <p>Dimethyldiglycol</p> <p>2-(2-Methoxyethoxy)-1-methoxyethane</p> <p>2,5,8-Trioxanonane</p> <p>Di(2-Methoxyethyl) ether</p> <p>Dimethyl carbitol</p> <p>Ether, bis(2-methoxyethyl)</p> <p>1,1'-Oxybis[2-methoxyethane]</p> <p>Methyldiglyme</p> <p>(CAS registry numbers still in use: 70-992-86-8, 54631-70-8, 142939-39-7 although deleted in CAS registry)</p>

Structural formula:



1.2 Composition of the substance

Name: bis(2-methoxyethyl)ether

Description: -

Degree of purity: > 80% (m/m)

Table 2: Constituents

Constituents	Typical concentration	Concentration range	Remarks
bis(2-methoxyethyl)ether EC-No 203-924-4	> 80% m/m		

Table 3: Impurities

Impurities	Typical concentration	Concentration range	Remarks
<i>See confidential Annex</i>			

Purity according to website information from Clariant GmbH²: ≥99%.

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

²[http://www.clariant.de/C12575E4001FB2B8/vwLookupDownloads/2000_SpecialSolvents_Newsroom_Brochures_GlymesBrochure.pdf/\\$FILE/2000_SpecialSolvents_Newsroom_Brochures_GlymesBrochure.pdf](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 101.3 kPa	<i>Clear liquid with a pleasant odor</i>	<i>from registration*</i>
Melting/freezing point	<i>-68°C</i>	<i>from registration</i>
Boiling point	<i>162°C at 1013 hPa</i>	<i>from registration</i>
Vapour pressure	<i>0.6 hPa at 20°C *</i>	<i>from registration</i>
Water solubility	<i>Miscible at each ratio pH=7 at 20°C 940 g/l at 20°C</i>	<i>from registration</i>
Partition coefficient n-octanol/water (log P _{ow})	<i>-0.36 at 25°C</i>	<i>Funasaki, 1984</i>
Flashpoint	<i>59°C at 102.1 kPa</i>	<i>from registration</i>
Auto Flammability at 1013hPa	<i>190°C</i>	<i>from registration</i>
Reactivity	<i>Oxidizes readily in air to form unstable peroxides that may explode spontaneously.</i>	<i>Chemical Book³</i>
Density	<i>0.943 – 0.945g/cm³ at 20°C</i>	<i>from registration</i>

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

Conversion factors (20°C, 1014hPa) (Ectoc, 2005): 1mg/m³ = 0.179ppm

1ppm = 5.579mg/m³

³ http://www.chemicalbook.com/Search_EN.aspx?keyword=111-96-6

2 HARMONISED CLASSIFICATION AND LABELLING

Bis(2-methoxyethyl)ether is covered by index number 603-139-00-0 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)		
603-139-00-0	bis(2-methoxyethyl) ether	203-924-4	111-96-6	Flam. Liq. 3 Repr. 1B	H226 H360-FD	GHS02 GHS08 Dgr	H226 H360FD	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
603-139-00-0	bis(2-methoxyethyl) ether	203-924-4	111-96-6	R10 R19 Repr. Cat. 2; R60-61	T R: 60-61-10-19 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

Bis(2-methoxyethyl)ether (diglyme) is listed as entry 603-139-00-0 in Annex VI, part 3, Table 3.1 (list of harmonised classification and labelling of hazardous substances) of Regulation (EC) No 1272/20084 as Repr. 1B, H360FD (May damage fertility. May damage the unborn child.) . This corresponds to a classification as toxic to reproduction Repr. Cat. 2; R60-61 (“May impair fertility; 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(s) 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.

4 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

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

Diglyme was identified as EU HPV Chemical under Regulation 793/93⁵. The IUCLID Chemical Data set (2000) indicated an import/production of 10.000-50.000 tonnes. Diglyme has however not been listed in a priority list.

The IUCLID dataset (Feb 2000) displays the list of companies producing or importing diglyme at that time (see Table 7).

Table 7: List of producers/importers according to ESIS⁶.

Country	Company
NL	Chemimpo BV
DE	Clariant GmbH
IT	Eigenmann & Veronelli S.P.A.
DE	Hoechst AG
UK	ICI Chemicals & Polymers limited
FR	Sylachim Divison Sochibo

In 1990 about 400t diglyme were manufactured in Germany, of which 200t were exported (BUA, 1991). According to the Oxygenated Solvent Producer Association (OSPA) there is currently only one glyme producer in Europe.

The terms E-series and P-series are often used to refer to ethylene glycol ethers and propylene glycol ethers, respectively. E-series members generally are more toxic, diglyme is one of them.

⁵ Council Regulation (EEC) No 793/93 on the evaluation and control of the risks of existing substances

⁶ <http://tcsweb3.jrc.it/esis/>

According to INERIS, 2007, glymes of the E-Series (monoglyme, diglyme, triglyme) are produced by Clariant GmbH.

Diglyme is listed as HPV chemical in the US EPA HPV Challenge Program, produced or imported in the United States in quantities of 450tonnes or more per year (450- 4500t in 2005⁷). Diglyme is registered as a high-production volume chemical by the OECD⁸ meaning that its production volume in at least one OECD member state is 1000tonnes/year. The International Council of Chemical Associations (ICCA) put diglyme on its HPV Working List (2000) as the chemical is listed in several regions as HPV (EU, US and Japan)⁹.

For further details on volumes from registration see confidential Annex III, Chapter 2.

1.2 Uses of the Substance

1.2.1 Overview

Diglyme is commercially available as it can be found in product catalogues on the websites of chemical suppliers and manufacturers.

According to producer information diglyme is used primarily as a solvent in a wide variety of applications (reaction solvent for Grignard-reactions, reduction-reactions, alkylation-reaction, organo-metallic reactions) because of its dipolar aprotic properties and its chemical stability. It further has application as entrainer for azeotropic distillations and in reactions involving alkali metals such as lithium, sodium and potassium and can dissolve Na/K alloy. Other possible applications include use as active pharmaceutical ingredient, as additive for diesel fuels¹⁰, for photolithography and for the manufacture of semiconductor chips. Diglyme is also used as solvent for battery electrolytes. Further uses in sealants and adhesives, automotive care products and paints and coatings are indicated (U.S. EPA, 2003; WHO, 2002; Clariant¹¹).

The use of diglyme (process categories) according to information from the registration dossiers is given in the confidential Annex III, Chapter 3.

⁷ <http://www.epa.gov/oppt/champ/pubs/hazchar/Diglyme.111966.Web.SupportDocs.031808.pdf>

⁸ OECD existing chemicals database : <http://webnet.oecd.org/hpv/UI/Result.aspx?Q=9da503d3-da90-4d76-9ee9-7ef2d617f43e>

⁹ ICCA HPV WORKING LIST http://www.icca-chem.org/ICCADocs/2000_07_01_ICCA_HP_V_Working_List.pdf

¹⁰ Oxygenated additives like diglyme lower emission profile for all hydrocarbons (<http://www.mtsu.edu/urc/images/PosterLukeBolin.pdf>)

¹¹ <http://www.clariant.de/C12576720021BF8F/vwWebPagesByID/BC1DA8FD9146F6C2C125770C0032E76F>

France:

The AFSSET report (AFSSET, 2008) refers to different investigations carried out on glycol ethers. Diglyme 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 INRS¹² (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) in human medical drugs was nearly phased out in 2008 (AFSSET, 2008). SICOS (Syndicat de l'Industrie Chimique Organique de Synthèse et de la Biochimie) mentioned the presence of Diglyme in paints (INERIS, 2007).

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. New glycol ethers emerged: 2PG1EE, 2PG1BE, DEGEE, EGDME, DEGDME, TPGME and 1BG3ME (AFSSET, 2008).

Austria:

In 2010 an inquiry was carried out by the Austrian Central Labour Inspectorate among 102 Austrian companies from the industrial sector chemistry/paint and varnish production on the use of seven glycolethers (Repr. 1B), diglyme being one of them. In total 15 % of all answers were positive, indicating that one or more of the glycolethers were still in use. Diglyme was used by one manufacturer as "Helper"-solvent to produce binding agents. In the finished binding agents the content of the substance was reported to be less than 0.5 %. The overall results of the inquiry show that the use of the seven glycolethers at Austrian workplaces in the examined branch declined during the last years.

1.2.2 Use of diglyme 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 considered as Repr. 1B (see Table 8). Amongst those 3 formulations contain diglyme (DEGDME) (AFSSET, 2008).

¹² INRS: Institut National de Recherche et de Sécurité

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

Nordic countries:

The SPIN database¹³ was searched for information on diglyme in products on the national markets of Norway, Sweden, Finland and Denmark (see Table 9). In Norway, Sweden and Denmark diglyme is on the market although in low volumes. The latest registration from Finland was in 2004.

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

Country	2006		2007	
	number of preparations	tonnage	number of preparations	tonnage
Norway	Conf*		Conf	
Sweden	5	<100kg	5	<100kg
Denmark	4	0.3t	4	<100kg

Country	2008		2009	
	number of preparations	tonnage	number of preparations	tonnage
Norway	Conf		Conf	
Sweden	4	<100kg	4	<100kg
Denmark	Conf		Conf	

¹³Substances in Preparations in the Nordic countries <http://195.215.251.229/DotNetNuke/default.aspx>

* "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 Norwegian Competent Authority there have been 7t of diglyme on the Norwegian market in 2009. The bulk of the volume was for professional use and it was used for "purification and solvent in production of magnetic polystyrene beads." Very limited amount of the professional use was sold in small quantities for laboratory use (personal communication, 2011)

According to SPIN diglyme was registered in Sweden (2006 and 2007) for the Industrial use "Manufacture of rubber and plastic products" with low amounts (Table 10). In Finland it was registered before 2005 for "Manufacture of other transport equipment n.e.c" and "Manufacture of fabricated metal products" with no further information due to confidentiality.

Table 10: Industrial uses according to the SPIN database (2000-2007).

Country	Year	NACE Code*	Industrial Use	# Preparations	Amount
S	2007	25	Manufacture of rubber and plastic products	3	<100kg
S	2006	25	Manufacture of rubber and plastic products	3	<100kg
FIN	2004	35	Manufacture of other transport equipment n.e.c.		
FIN	2003	35	Manufacture of other transport equipment n.e.c.		
FIN	2002	28	Manufacture of fabricated metal products, except machinery and equipment		
FIN	2002	35	Manufacture of other transport equipment n.e.c.		
FIN	2001	28	Manufacture of fabricated metal products, except machinery and equipment		
FIN	2001	35	Manufacture of other transport equipment n.e.c.		
FIN	2000	28	Manufacture of fabricated metal products, except machinery and equipment	1	
FIN	2000	35	Manufacture of other transport equipment n.e.c.	2	

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.

Additionally, the SPIN database was searched for other use categories in the Nordic countries. The technical function of the preparations containing diglyme is described by a UC62 code (Use Code 62). Only Finland is listed (Table 11). 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 11: Use categories (UC62) according to the SPIN database.

Country	Year	Code	Use Category	# Prep	Amount
FIN	2004	55	Others (not described elsewhere)		<100kg
FIN	2003	55	Others (not described elsewhere)		<100kg

FIN	2002	09	Cleaning/washing agents		<100kg
FIN	2002	55	Others (not described elsewhere)		<100kg

1.2.3 Diglyme as Impurity

According to the Glycol Ether Charta by OSPA¹⁴ 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 diglyme).

1.2.4 Use restrictions

Diglyme is listed in Annex XVII, Group 30, of the REACH regulation¹⁵ 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”. This restriction was introduced in 2003 (Directive 2003/36/EC amending, for the 25th time, Council Directive 76/769/EEC).

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 676, diglyme must not be a part of the composition of cosmetic products.

Due to its boiling point of 162 °C at 1013hPa (ECETOC, 1995) diglyme falls under the definition as VOC according to Directive 2004/42/EC¹⁶ 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 diglyme is on the European Market in relatively high tonnages. It is manufactured at one site in Europe and is mainly used as solvent for a variety of applications.

¹⁴ <http://www.glycol-ethers.eu/press-room/position-papers>

¹⁵ 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

¹⁶ 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

Two exemplary uses of diglyme are the production of magnetic polystyrene beads and the manufacture of rubber and plastic products. 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 diglyme (Table 12). 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 be considered as an indicative screening tool. No information for exposure of workers is given.

Table 12: Exposure potential based on data in Nordic product registers¹⁷.

Country	Latest year	Use Index					Range of use
		Surface water	Air	Soil	Waste water	Human consumers	
DK	2008	-	-	-	-	-	Very narrow range of applications
NO	2008	x	x	x	xx	xx	Very narrow range of applications
SE	2008	-	x	-	xx	x	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.

1.3.2 Human exposure

1.3.2.1 Workplace exposure

Occupational exposure to diglyme may occur through inhalation and through dermal contact with this compound at workplaces where diglyme is produced or used (SRC in HSDB¹⁸). Dermal absorption of glycol ether liquids or vapours is very high. With a permeability constant of 1×10^{-3} cm/h and a lag time of approximately half an hour diglyme is among the glycol ethers with the

¹⁷ 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).

¹⁸ <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB>

highest percutaneous absorption rate. Significant permeation of protective gloves of different materials by EGEs is reported in literature. Gloves made of nitrile and butyl rubber or neoprene provide the best protection. (Larese Filon et al, 1999; WHO, 2002).

According to OSPA production and use takes place in closed systems with tight monitoring. Contact is assumed to occur mainly during cleaning and maintenance operations (WHO, 2002). No measured data are available on diglyme exposure concentrations at the workplace.

Exposure limits for diglyme are established in several European countries (Table 13) but no EU-wide indicative occupational exposure limit (IOEL) has been established.

Table 13: National exposure limit values for diglyme.

Country	Limit value (8h)	Short term limit value	Reference
Austria	27mg/m ³ (5ppm) *	108mg/m ³ (20ppm) *	BGBL II 253/2001 ¹⁹
Denmark	27mg/m ³ (5ppm)	54mg/m ³ (10ppm)	²⁰
Germany	28mg/m ³ (5ppm) *	224mg/m ³ (40ppm) *	TRGS 900 ²¹
Switzerland	27mg/m ³ (5ppm)	216mg/m ³ (40ppm)	²⁰

* with notation on the possibility of significant uptake through the skin.

France:

In total, 5 558 measurements of professional exposure to glycol ethers were done between 2000 and 2006. 1874 of them were representatives of professional inhalation exposure, and therefore comparable to OEL (AFSSET report 2008). For diglyme 6 measurements were done in this period. As no further figures for professional exposure to DEGDME are reported in the AFSSET report, we can assume that the 6 measurements were not conclusive of an inhalation exposure.

WHO, 2002 presented a rough approximation of diglyme exposure concentration at the workplace by using data on other glycol ethers produced in the same way, with comparable use pattern and similar volatilization behaviour (based on data by ECETOC 1995). Assuming that exposure concentrations for diglyme are the same as for other EGEs, the TWA may be up to 36mg/m³ (6.5ppm) for exposure in the production process, up to 3mg/m³ (0,5ppm) in the semiconductor industry, and up to 31mg/m³ (5.6ppm) in painting operations.

Exposure estimations in the Chemical Safety Report of the registration dossier are based on model calculations and are in the same order of magnitude as the estimations in WHO, 2002 (see confidential Annex III, Chapter 5).

¹⁹ Grenzwerteverordnung BGBL II 253/2001

²⁰ http://www.dguv.de/ifa/de/gestis/limit_values/index.jsp

²¹ http://www.baua.de/de/Themen-von-A-Z/Gefahrstoffe/TRGS/pdf/TRGS-900.pdf;jsessionid=AE8925DD0A464F6A31321CC6AC390471?_blob=publicationFile&v=7

1.3.2.2 Consumer exposure

It is noted that according to U.S. EPA consumers may be exposed through use of adhesives and sealants, automotive care products, paints and coatings. In general consumer exposure to articles containing adhesives, paints, coatings etc. is theoretically still possible in the EU, as those articles are not restricted. Although that exposure is probably significantly lower than the exposure due to use of the mixtures themselves, which is restricted in the EU for consumers (see 1.2.4).

Literature further indicates that the general population may be exposed to diglyme via inhalation of vehicle exhaust and ingestion of contaminated drinking water (SRC in HSDB; IKS, 2010a). The existing restriction does not necessarily limit effectively the overall releases to the environment.

1.3.3 Environmental Exposure

1.3.3.1 General Aspects

As a result of its highly hydrophilic character (miscible with water, low $\log K_{OW}$) and its low tendency to volatilize from aqueous solutions (low Henry's law constant) or to adsorb onto inorganic and organic soil constituents, it is expected that the main target compartment of the chemical is the hydrosphere (WHO, 2002). Consequently diglyme may reach groundwater. The possibility that the chemical will subsequently enter wells and drinking water cannot be excluded but is only likely if groundwater originates out of surface water. Data on the concentration of diglyme in drinking water are not available (WHO, 2002; BUA, 2006).

Diglyme is considered to be moderately persistent in the environment thus a potential exposure of the general population from environmental release can be assumed. The $\log K_{OW}$ of -0.36 indicates a negligible potential for bioaccumulation.

An estimated BCF of 3 suggests that the potential for bioconcentration in aquatic organisms is low. Hydrolysis is not expected to be an important environmental fate process since this compound lacks functional groups that hydrolyze under environmental conditions.

In an electrolytic respirometer test the biodegradation of diglyme in industrial waste, in the presence of other organics, appeared to be more efficient (80% after 32 days) than that observed for the pure compound (lag phase of 7 days, 33% after 25 days). High salt concentrations in the wastewater result in a decrease in biodegradation indicated by a significant increase in the lag phase (Roy et al., 1994).

If released to air, the vapour pressure indicates that diglyme will exist solely as a vapour in the atmosphere. Vapour-phase diglyme will be degraded in the atmosphere by reaction with photochemically-produced hydroxyl radicals; the half-life for this reaction in air is estimated to be 22 hours (SRC in HSDB). Due to the miscibility of diglyme with water it is further expected to be deposited easily with rain or other wet deposition. Therefore the long-distance transport of diglyme in ambient air is assumed to be negligible (WHO, 2002).

Direct photolysis of diglyme is assumed to be of minor importance due to diglyme's weak absorption at wavelengths above 230nm (WHO, 2002).

1.3.3.2 Exposure data

The release from the production of diglyme at a German manufacturer for the year 1990 is estimated as follows: <2.5g/tonne released into air, about 133-188g/tonne released into water, and <7.5g/tonne released with solid wastes. Data on the degree of recycling of diglyme from its application as a solvent or as an inert reaction medium in industrial processes are not available (WHO, 2002). Due to its use patterns as solvent it can be assumed that the whole amount of produced/used diglyme will end up in waste water, air or solid waste to be treated (BUA, 2006).

Confidential data from the CSR are given in Annex III, Chapter 5.2.

Netherlands:

Several industrially used organic solvents like diglyme are regularly detected in the river Rhine by RIWA (Association of River Water Supply Companies). For diglyme, RIWA reported a peak exposure of 3.79µg/l for 2008 and 5.3µg/l for 2009 (see Table 14) and a mean exposure of 0.727µg/l for 2008 and 0.635µg/l for 2009 in the Netherlands.

Table 14: Diglyme concentrations (monthly mean) in the River Rhine near Lobith (NL) (2008, 2009).

Diglyme (in µg/l)	Jan.	Feb.	March	April	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.	mean	max
2008	0.305	0.466	<	<	1.36	1.17	1.6		1.7	1.47	0.501	0.267	0.727	3.76
2009	<	<	<	<	<	2.08	<	1.31	<	<	<	<	0.635	5.3

Germany:

For the river Rhine in Germany peak exposure for diglyme is documented in the "Warning and Alarm Plan Rhine" (IKSR, 2009 and IKSR, 2010). Table 15 gives an overview of warnings in cases of water pollution incidents with diglyme.

Table 15: Peak concentration of Diglyme in the river Rhine for 2008 and 2009 (IKSR, 2009 and IKSR, 2010).

Location	Date	Peak concentration (µg/l)
Bad Honnef	09.02.2009	4.7

Bad Honnef	17.10.2008	4
Düsseldorf Flehe Stürzelberg	29.8.2008	3.5
Bad Honnef	02.08.2008	6.4
Bad Honnef	13.05.2008	6

A qualitative assessment of contaminations in the river Rhine by the International Commission for the Protection of the Rhine (IKSR, 2010a) shows for diglyme, which was marked as “relevant for drinking water”, two point emission pathways into the surface water of the river:

- Discharge from urban wastewater treatment plants
- Industry

Wastewater treatment plants

In the influent of a sewage treatment plant near Paris EGEE, EGDME, EGDEE, PGME, EGPE, DEGDME (diglyme), EGBE, DPGME, DEGME, DEGEE, TEGDME, DEGBE, EGPhE were detected in concentrations between 0.009 and 0.716 mg/l from end 1999 to mid 2000. At the outflow of the wastewater treatment plant diglyme was below the detection threshold (<1µg/l or <10µg/l) (AFFSET, 2008; INERIS, 2001).

Groundwater

Groundwater analyses carried out in the proximity of waste water treatment have also shown the presence of derivatives of diethylene glycol and triethylene glycol at concentrations lower than 1 mg/l. Diglyme was measured but not detected above the limit of quantification (AFFSET, 2008; INERIS, 2001).

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 (Ketttenis, 2005). According to the Association of Oxygenated Solvent Producers (OSPA) no substitutes for present industrial uses of diglyme 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 market of these glycol ethers to industrial applications for which a substitute solution does not yet exist.

One company provides the information that for Grignard reaction diglyme can be substituted by butyl diglyme (CAS No 112-73-2, EC No 204-001-9)²². **Butyl diglyme** (DEGDDBE or Bis-(2-butoxyethyl)-ether) is not listed in part 3 of Annex VI of Regulation (EC) No 1272/2008. The substance may cause explosive peroxides and it may cause skin and eye irritation and irritation of the respiratory tract. No data on the reproductive toxicity of dibutyl glyme are available. According to Directive 2004/42/EC butyl diglyme (boiling point 256°C) is no VOC.

3 RISK-RELATED INFORMATION

No risk assessment has been carried out for diglyme according to Regulation EEC/793/93. 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 (absorption, metabolism, distribution and elimination) and effects on reproduction and development see Annex I.

3.2 Risk characterisation

3.2.1 Environment

Release of diglyme into the environment is expected from its use as a solvent, reaction medium and separating agent in industrial processes unless these uses are operated under strictly controlled conditions. The main target compartment of diglyme is the hydrosphere. The chemical is inherently biodegradable with rather long log phase and significant adsorption to activated sludge. Bioaccumulation is of minor importance (WHO, 2002).

The 48h EC₅₀ value for daphnia is 943mg/l and the 72h EC₅₀ value for algae is ≥10000mg/litre. The dissemination database (according Regulation (EC) No.1907/2006 article 119) also gives the results of a long-term toxicity test (Daphnia magna reproduction test, acc. OECD Guideline 211) with a NOEC=320mg/l (resulting PNECaqua=6.4mg/l). No long-term toxicity fish test is available, due to waiving.

Monitoring data from the 1980's gave diglyme concentrations of 0.005mg/l (WHO, 2002). Data from the river Rhine in Germany 2008 show peak exposure up to 0.006mg/l. The available short-term toxicity data (EC₅₀=943mg/l) and the long-term toxicity data (NOEC=320mg/l) do not indicate a significant risk associated with exposure of aquatic organism to diglyme.

²² <http://www.clariant.de/C12576720021BF8F/vwWebPagesByID/BC1DA8FD9146F6C2C125770C0032E76F>

The exposure values used in the registration documents (CSR) are based on model calculations. Based on these data the risk ratios are significantly below 1, therefore no significant risk can be expected.

From the use pattern and environmental fate properties of diglyme, significant exposure of terrestrial organisms is not expected (WHO, 2002).

3.2.2 Man via the Environment

According to U.S. EPA, 2008 there is potential for exposure to the general population from environmental releases. Literature data also indicate that the general population may be exposed to diglyme via inhalation of vehicle exhaust and ingestion of contaminated drinking water (HSDB).

No actual data for air concentrations and drinking water are available. Monitoring data from surface water (river Rhine 2008) show peak exposure up to 0.006mg/l. When drinking water originates from contaminated surface water similar exposure levels can be expected in the drinking water as diglyme does not adsorb onto inorganic and organic soil constituents.

According to registration data the risk arising from exposure of man via the environment is very low (RCR well below 1).

3.2.3 Human health

3.2.3.1 Data from literature

WHO, 2002 published a guidance value (according to EHC 170, 1994) for the uptake of diglyme via inhalation of **0.1ppm (0.6mg/m³)** which is derived based on a LOAEL of 25ppm (140mg/m³) from a developmental toxicity study in rats (DuPont, 1988a) (applying the following safety factors: 2 for extrapolation to a NOAEL, 10 for intraspecies variations and 10 for interspecies variations). For the oral route, a guidance value of **0.25mg/kg bw/day** has been obtained based on a NOAEL of 25mg/kg bw/day from a developmental toxicity study with rabbits (NTP, 1987) (applying safety factors of 10 for intraspecies variations and 10 for interspecies variations). Dermal exposure has not been investigated.

3.2.3.2 Information from the registration

The information on the registered substance diglyme according to Regulation (EC) No.1907/2006 article 119²³ (dissemination website) is shown in Table 16. For more detailed (confidential) information see Annex III, Chapter 4.

²³ <http://apps.echa.europa.eu/registered/registered-sub.aspx>

Table 16: DNEL values according to the registration.

	DNEL _{Dermal}	DNEL _{Inhalation}	DNEL _{Oral}
Workers	2.08mg/kg bw/day	26.8 mg/m ³	-
General population	1.04mg/kg bw/day	6.7 mg/m ³	1.04mg/kg bw/day

3.2.3.3 Derivation of DNELs for developmental toxicity

The REACH guidance document on information requirements and chemical safety assessment, Chapter R.8 gives detailed information for the derivation of DNELs. Calculations according to this guidance result in different No Effect Levels than presented by industry especially due to the different application of assessment factors. An overview on the DNEL-values calculated by the submitters of the current Annex XV dossier is presented in Table 17. The detailed calculations are presented in Annex II.

Table 17: DNEL values calculated.

	DNEL _{Dermal}	DNEL _{Inhalation}
Workers	0.8mg/kg bw/day	11.6 mg/m ³ (2.1ppm)
General population	0.4mg/kg bw/day	2.8 mg/m ³ (0.5ppm)

3.2.3.4 Conclusion on DNELs

An overview of the presently derived DNELs, DNELs from the registration and guidance values published in WHO (2002) as well as exposure estimates from the WHO (2002) and the registration dossier are presented in Table 18. Currently no information on consumer exposure is available.

For workers a DNEL_{dermal}= 0.8mg/kg bw/day and a DNEL_{inhal}=11.6mg/m³(2.1ppm) were calculated. National occupational exposure limits (27mg/m³ or 28mg/m³) exceed the DNEL_{inhal} derived in the present document. The DNEL presented within industry's registration (DNEL_{inhal}=26.8 mg/m³ (4.8ppm)) is similar to the OEL.

WHO, 2002 assumed exposure concentrations for diglyme to be between 3mg/m³ (0.5ppm) and 36mg/m³ (6.5ppm) (see 1.3.2). The highest concentration exceeds the derived DNELs for workers by a factor of 3 indicating that there is a concern for workers.

Table 18: Comparison of no effect levels with available exposure estimations.

Long-term, systemic	DNELs from the present document	DNELs from the registration	Guidance values (WHO, 2002)	Exposure estimates (WHO, 2002)	Exposure (registration dossier)

Worker dermal	0.8mg/kg bw/day	2.08mg/kg bw/day	-	-	*
Worker inhalation	11.6mg/m ³ (2.1ppm)	26.8mg/m ³ (4.8ppm)	0.6mg/m ³ (0.1ppm)	36mg/m ³ (6.5ppm) (production) 3mg/m ³ (0.5ppm) (semiconductor industry) 31mg/m ³ (5.6ppm) (painting op.)	*
Worker oral	-	-	0.25mg/kg bw/day	-	-
General Population dermal	0.4mg/kg bw/day	1.04mg/kg bw/day	-	-	-
General Population inhalation	2.8mg/m ³ (0.5ppm)	6.7mg/m ³ (1.2ppm)	0.6mg/m ³ (0.1ppm)	-	-
General Population oral		1.04mg/kg bw/day	0.25mg/kg bw/day	-	-

* see confidential Annex III, Chapter 5

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PUBLIC VERSION

ANNEX I

SUPPLEMENTARY INFORMATION ON TOXICOKINETICS, TOXICITY FOR REPRODUCTION AND NON-CLASSIFICATION FOR THE ENVIRONMENT

1 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

Diglyme is readily absorbed by oral, dermal and inhalation route of exposure (low molecular weight, excellent solvating properties, logPow, see section 1.3 physico-chemical properties). Diglyme is rapidly and completely absorbed from the gastrointestinal tract (US EPA, 2003). Dermal absorption of glycol ether liquids or vapours is very high. With a permeability constant of 1×10^{-3} cm/h and a lag time of approximately half an hour diglyme is among the glycol ethers with the highest percutaneous absorption rates (Larese Filon et al, 1999; WHO, 2002).

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 metabolic pathway is shown in figure 1. The main metabolite is 2-methoxyethoxyacetic acid. The reproductive toxicity of diglyme is attributed to the minor metabolite 2-methoxyacetic acid, which is generated from 2-methoxyethanol. The metabolite 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).

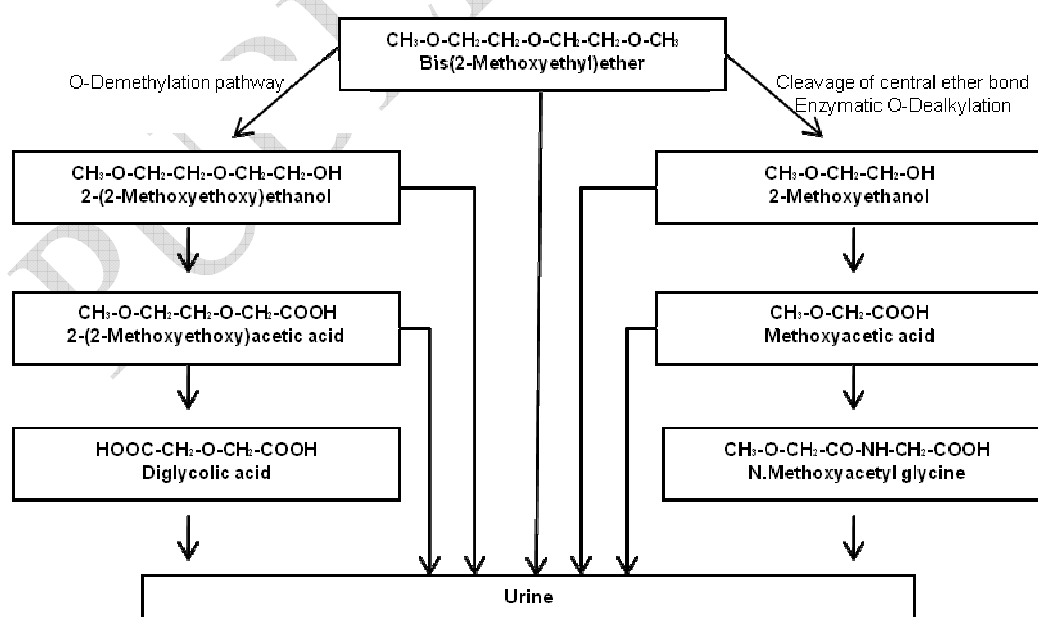


Figure 1: Metabolism and disposition of diglyme (WHO, 2002; Sullivan, 2001).

Diglyme is a developmental toxicant in rats and mice but at higher doses, compared to other glycol ethers. This may be explained by the low levels of the metabolites 2-methoxyethanol (EGME) and methoxyacetic acid (MAA) formed (ECETOC, 2005).

2 TOXICITY FOR REPRODUCTION

2.1.1.1 Effects on fertility

The reproductive organs of male animals are a specific target for diglyme. Several well conducted studies are available and summarized in Table 19.

From these studies the NOAEL for effects on the testis/spermatocytes is 30ppm (167mg/m³).

2.1.1.2 Developmental toxicity

Diglyme is a developmental toxicant by the inhalatory and the oral route in rat, mice and rabbits. An overview of relevant studies is given in Table 20 (key study) and Table 21.

Oral exposure of New Zealand White rabbits to diglyme at 25mg/kg bw/day produced no adverse maternal or developmental effects. Doses of 50 and 100mg/kg bw/day were associated with adverse developmental effects but did not produce distinctive evidence of maternal toxicity. At 175mg/kg bw/day developmental effects were accompanied by increased maternal toxicity. The principal manifestations of developmental toxicity were increased resorptions and higher incidence of major malformations among surviving foetuses with a NOAEL_{fetal} of 25mg/kg bw/day (NTP, 1987). In 1992 Schwetz et al. published the NTP data with a diverging interpretation of the results showing a dose related developmental toxicity with a NOAEL_{maternal} of 25mg/kg bw/day and a NOAEL_{fetal} of 50mg/kg bw/day.

3 ENVIRONMENT

Diglyme is not classified as hazardous to the environment. The EU-Working Group has decided that there are insufficient data in order to classify (SUMMARY RECORD Commission Working Group on the Classification and Labelling of Dangerous Substances, 1999, ECBI/60/99 Rev. 4).

The available registration data support the non-classification for environmental effects.

Table 19: Fertility, study overview.

Species	Route of exposure	Dose/ Concentration	Observations, effects	NOAEL	Reference
rat (CrI:CD) male 20 animals/group	Inhalation 6h/day 5days/week for 2 weeks 84 days post exposure	0, 110, 370, 1100ppm	370ppm (2065mg/m³) and 1100ppm: absolute weight of testis, epididymides. Seminal vesicles and prostate ↓ 1100ppm (6138mg/m³): relative weight of testes ↓, testicular atrophy (all spermatogenic stages affected) Effects were reversible within 84 days (but not at 1100ppm).		DuPont (1988b), Valentine et al., (1999)
rat (CrI:CD) male 20 animals/group	Inhalation 6h/day 5days/week for 2 weeks 14 days post exposure	0, 3, 10, 30, 100ppm	Some effects (degenerative germ cells in epididymal tubules, spermatoc granuloma in the epididymis, prostatitis) occurred at concentrations below 100ppm, most lesions were minimal to mild. It is not clear whether the different lesions observed occurred in the same or different animals. 100ppm (558mg/m³): mean body weight ↓, mild testicular atrophy	30ppm (167mg/m ³)	DuPont (1989)
rat (CD) male 10 animals/group	Inhalation 7h/day 5days	0, 250, 1000ppm	Dominant lethal test (males were mated at weekly intervals for 10 weeks with untreated females, females killed 17days after mating) 1000ppm (5580mg/m³): reduced body weight in male rats; pregnancy frequency in mated female rats was only about 10% in week 5 to 7 after exposure, preimplantation		McGregor et al. (1981, 1983)

			losses Recovery in exposed males was completed in week 10.		
mice (B6C3F1)	Inhalation 7h/day 4 days	0, 250, 1000ppm	Sperm isolation on day 35 after exposure Mice of both exposure groups showed a reduction in body weight gain. 4 mice of 1000ppm exposure group died on exposure day 4. 1000ppm: morphologically altered sperm (32%; control 5%) (all categories of abnormalities involved but most frequent were amorphous heads)		McGregor et al. (1981, 1983)
rats (Sprague-Dawley) male 5 animals per group	Oral 20 days	684mg/kg bw 8week recovery	Primary and secondary spermatocyte degeneration, spermatidic giant cells, reduced testis to body weight ratio from day 12 till end of study, testicular LDH-X activity by day 18 ↓		Cheever et al. (1985, 1989)

↓ decreased compared with controls

↑ increased compared with controls

Table 20: Developmental toxicity, key study, overview (according to WHO, 2002).

Species	Route of exposure	Dose/ Concentration	Observations, effects	Maternal NOAEL	Fetal NOAEL/ LOAEL	Reference
Rabbits (New Zealand) Female 15-25 animals/group	Gavage in distilled water Days 6-19	0, 25, 50, 100, 175mg/kg bw	<p>50 mg/kg body weight: dams: weight gain ↓ (due to decrease in gravid uterine weight), adversely affected implants per litter ↑ (21.4%, controls 7.9%)</p> <p>100 mg/kg body weight: gravid uterine weight ↓, prenatal mortality (mainly from resorptions) ↑, malformations ↑ (mainly abnormal development of the kidneys and axial skeleton and clubbing of the limbs)</p> <p>175 mg/kg body weight: dams: faecal output ↓, mortality ↑ (15%, controls 4%) Evidence of maternal toxicity was observed only at 175mg/kg/day.</p> <p><i>New evaluation of NTP (1987) performed by Schwetz et al.(1992)</i></p>	NOAEL 100mg/kg bw	NOAEL 25mg/kg bw	NTP (1987) cited in WHO, 2002
				NOAEL 25mg/kg bw	NOAEL 50mg/kg bw	Schwetz et al. (1992)

↓ decreased compared with controls

↑ increased compared with controls

Table 21: Developmental toxicity, additional studies, overview (according to WHO, 2002).

Species	Route of exposure	Dose/ Concentration	Observations, effects	Maternal NOAEL	Fetal NOAEL/L OAEL	Reference
Rats (CD), female 25-26 animals/group	Inhalation 6h/day days 7-16	0,25, 100, 400ppm (0, 140, 558, 2232mg/m ³)	<p>25 ppm (140 mg/m³): fetal weights ↓, variations (delayed ossification, rudimentary ribs) (mean percentage of fetuses per litter with variations): 44.5% versus controls 32.1%</p> <p>100 ppm (558 mg/m³): dams: relative liver weight ↑, fetus: structural malformations, mainly skeletal (abnormally formed tails, distended lateral brain ventricles, axial skeletal malformations, appendicular malformations [bent limbs], 6.2% compared with 1.7% in controls); fetal weight ↓; variations (mean percentage of fetuses per litter with variations): 74.5% versus controls 32.1%</p> <p>400 ppm (2232 mg/m³): dams: food consumption ↓, body weight gain ↓; resorptions 100%</p>	NOAEL 25ppm (140mg/m ³)	LOAEL 25ppm (140mg/m ³)	DuPont (1988a) cited in WHO, 2002 Driscoll et al. (1998)
mice CD-1 20–24 animals/group	gavage in distilled water, days 6–15	0, 62.5, 125, 250, 500 mg/kg bw	<p>125 mg/kg body weight: fetal weights ↓</p> <p>250 mg/kg body weight: dams: weight gain ↓ (due to decrease in gravid uterine weight); late fetal deaths ↑, malformations ↑ (mainly neural tube, limbs and digits, craniofacial structures, abdominal wall, cardiovascular system, urogenital organs, axial and appendicular skeleton)</p>	NOAEL 500 mg/kg bw	NOAEL 62.5 mg/kg bw	NTP (1985), Price et al. (1987)

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			500 mg/kg body weight: dams: weight gain (due to decrease in gravid uterine weight) ↓; resorptions ↑			
mice CD-1 not given	gavage in distilled water, single application on day 11	0, 537 mg/kg bw	only examination for gross external malformations and fetal body weight 537 mg/kg body weight: malformations ↑ (paws, digits)			Hardin et al. (1986, 1987)
mice CD-1 49 animals/group	gavage in distilled water, days 6–13	0, 3000 mg/kg bw	reproductive screening according to Chernoff and Kavlock, no systematic examination for malformations 3000 mg/kg body weight: dams: mortality ↑ (20/49); no viable litters (0/27)			Schuler et al. (1984), Plasterer et al. (1985), Hardin et al. (1987)

↓ decreased compared with controls

↑ increased compared with controls

PUBLIC VERSION

ANNEX II

CALCULATION OF DERIVED NO EFFECT LEVELS (DNELs) FOR WORKERS AND THE GENERAL POPULATION

Developmental toxicity was identified as the most critical effect. The lowest NOAEL of 25mg/kg bw was derived from an oral study in rabbits (NTP, 1987). Derivations have been carried out according to the REACH guidance document on information requirements and chemical safety assessment, Chapter R.8.

Diglyme is readily absorbed by all routes of exposure (see Annex I). Therefore, 100% absorption has been assumed for oral, dermal and inhalation exposure. Dermal and inhalation exposure have been identified as the most relevant routes of exposure for workers and the general population.

From the rat inhalation study (DuPont, 1988a) a LOAEL of 25ppm (=140mg/kg bw/day) has been derived (WHO, 2002). In the absence of a no effect level for fetal effects in this study and the high absorption via oral, dermal and inhalation routes of exposure it has been decided to use the NOAEL from the oral study (NTP, 1987) as starting point for the derivation of DNELs for all exposure routes.

➤ Dermal exposure - Workers

$$\text{NOAEL}_{\text{oral}} = \text{NOAEL}_{\text{dermal}} = 25\text{mg/kg bw}$$

Following the REACH guidance (Chapter R.8) an assessment factor of 5²⁴ was used for the intraspecies variability among workers. For interspecies differences between rabbits and humans an assessment factor of 6 (2.4 for allometric scaling, 2.5 for remaining differences) was applied.

$\text{Worker DNEL}_{\text{long-term, dermal, systemic}} = \frac{25\text{mg/kg bw}}{(5 * 2.4 * 2.5)} = 0.8\text{mg/kg bw}$
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²⁴ The default AF of 5 for the working population was used following the REACH guidance recommendations. It should be noted that other frameworks use a factor of 10 and make no difference between general and working population.

➤ **Dermal exposure - General Population**

$$\text{NOAEL}_{\text{oral}} = \text{NOAEL}_{\text{dermal}} = 25\text{mg/kg bw}$$

For the general population intraspecies variability an assessment factor of 10 was applied, for interspecies differences between rabbits and humans an assessment factor of 6 (2.4 for allometric scaling, 2.5 for remaining differences) was applied.

$\text{General Population DNEL}_{\text{long-term, dermal, systemic}} = \frac{25\text{mg/kg bw}}{(10 * 2.4 * 2.5)} = 0.4\text{mg/kg bw}$

➤ **Inhalation exposure - Workers**

Following the REACH guidance (Chapter R.8) a corrected $\text{NOAEC}_{\text{inhal}}$, adapted to working conditions, has been calculated using the following formula:

$$\text{corrected inhalatory NOAEC} = \text{oral NOAEL} * \frac{1}{\text{sRV}_{\text{rabbit}}} * \frac{\text{ABS oral-rat}}{\text{ABS inh-human}} * \frac{\text{sRV}_{\text{human}}}{\text{wRV}}$$

sRV...standard Respiratory Volume

ABS...Absorption

wRV...worker Respiratory Volume

In the REACH guidance (chapter R.8), following values are given:

$$\text{sRV}_{\text{human}} (8\text{h}) = 6.7 \text{ m}^3$$

$$\text{wRV} = 10 \text{ m}^3/\text{worker} \text{ (for 8h exposure, light activity)}$$

According to the TGD (2003) an inhalation volume of 750ml/min has been used for the rabbit (3kg) resulting in a $\text{sRV}_{\text{rabbit}}$ of 250ml/min/kg.

For an exposure of 8h per day the following can be assumed:

$$\text{sRV}_{\text{rabbit}}(8\text{h}) = 0.00025\text{m}^3/\text{min}/\text{kg} * 60\text{min} * 8\text{h} = 0,12\text{m}^3/\text{kg}$$

$\text{corrected inhalatory NOAEC} = 25\text{mg/kg bw} * \frac{1}{0.12\text{m}^3/\text{kg}} * \frac{100\%}{100\%} * \frac{6.7\text{m}^3}{10\text{m}^3} = 139,6\text{mg/m}^3$
--

For worker intraspecies variability an assessment factor of 5²⁴ was applied. For the interspecies differences the assessment factor of 2.5 (remaining differences) was applied, the allometric scaling has already been considered in the derivation of the corrected inhal. NOAEC.

$$\text{Worker DNEL}_{\text{long-term, inhal, systemic}} = \frac{139.6\text{mg/kg bw}}{(5 * 2.5)} = \mathbf{11.6\text{mg/m}^3 (2.1\text{ppm})}$$

It should be noted that the derived DNELs are calculated for light work load and 8h exposure per day.

➤ **Inhalation exposure - General Population**

For the general population a corrected NOAEC_{inhal} has been derived from the NOAEL_{oral} according to the following formula:

$$\text{corrected inhalatory NOAEC} = \text{oral NOAEL} * \frac{1}{\text{sRV}_{\text{rabbit}}} * \frac{\text{ABS oral-rat}}{\text{ABS inh-human}}$$

According to the TGD (2003) an inhalation volume of 750ml/min has been used for the rabbit (3kg) resulting in a sRV_{rabbit} of 250ml/min/kg.

For an exposure of 24h per day the following can be assumed:

$$\text{sRV}_{\text{rabbit}}(24\text{h}) = 0.00025\text{m}^3/\text{min}/\text{kg} * 60\text{min} * 24\text{h} = 0.36\text{m}^3/\text{kg}/\text{day}$$

$$\text{corrected inhalatory NOAEC} = 25\text{mg/kg bw} * \frac{1}{0.36\text{m}^3/\text{kg}/\text{day}} * \frac{100\%}{100\%} = 69.4\text{mg/m}^3$$

For the general population intraspecies variability an assessment factor of 10 was applied. For interspecies differences the assessment factor of 2.5, the allometric scaling has already been considered in the derivation of the corrected inhal. NOAEC.

$$\text{General Population DNEL}_{\text{long-term, inhal, systemic}} = \frac{69.4\text{mg/kg bw}}{(10 * 2.5)} = \mathbf{2.8\text{mg/m}^3 (0.5\text{ppm})}$$

ANNEX III

Non-disclosure of confidential data.

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