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-dimethoxyethane (EGDME)

EC Number(s): 203-794-9

CAS Number(s): 110-71-4

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

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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
DEGBE	Diethylene glycol monobutyl ether
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
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
EGEE	Ethylene glycol monoethyl ether
EGME	Ethylene glycol monomethyl ether
EGPE	Propylene Glycol Monopropyl Ether

EGPhE	Ethylene glycol phenyl ether
ERC	Environmental release category
HPV	High Production Volume
HSDB	Hazardous Substances Data Bank
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)
IUR	Inventory Update Reporting
LOAEL	Lowest Observed Adverse Effect Level
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
SIN	Substitute it now
SPIN	Substances in Preparations in the Nordic countries
STEL	Short Term Exposure Limit
SVHC	Substance of Very High Concern

TEGDME	Triethylene glycol dimethyl ether
TLV	Threshold Limit Value
US EPA	U.S. Environmental Protection Agency
VOC	Volatile organic compounds
vPvB	Very Persistent and very Bioaccumulative

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-dimethoxyethane (Ethylene glycol dimethyl ether, EGDME)

EC Number(s): 203-794-9

CAS number(s): 110-71-4

- 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 1A or 1B) criteria:

1, 2-dimethoxyethane (EGDME) is listed as entry 603-031-00-3 in Annex VI, part 3, Table 3.1 (the list of harmonised classification and labelling of hazardous substances) of Regulation (EC) No 1272/2008[1] as Repr. 1B, H360FD ("May damage fertility. May damage the unborn child") This corresponds to a classification as toxic for reproduction Repr. Cat. 2; R60 R61 ("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 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

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:	203-794-9
EC name:	1,2-dimethoxyethane
CAS number (in the EC inventory):	110-71-4
CAS number:	110-71-4
Deleted CAS number:	173201-80-4
CAS name:	Ethane, 1,2-dimethoxy-
IUPAC name:	1,2-dimethoxyethane
Index number in Annex VI of the CLP Regulation	603-031-00-3
Molecular formula:	$C_4H_{10}O_2$
Molecular weight range:	90.121 g/mol
Synonyms:	EGDME; Ethylene glycol dimethyl ether; 1,2-Dimethoxyethane; 1,2-Ethanediol, dimethyl ether; 2,5-Dioxahexane; DME; DME (glycol ether); Dimethyl Cellosolve; Ethylene dimethyl ether; Glycol dimethyl ether; Glyme; Hisolve MMM; Monoethylene glycol dimethyl ether;

	Monoglyme; NSC 60542; α,β-Dimethoxyethane.

Structural formula:

1.2 Composition of the substance

Name: 1, 2- dimethoxyethane

Description: -

Degree of purity: *see confidential Annex*

Table 2: Constituents

Constituents	Typical concentration	Concentration range	Remarks
1,2-dimethoxyethane EC-No 203-794-9	*See confidential Annex*		

Table 3: Impurities

Impurities	Typical concentration	Concentration range	Remarks
See confidential Annex			

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

1.3 Physico-chemical properties

Table 4: Overview of physico-chemical properties

Property	Value	Remarks
Physical state at 20°C and 1013 hPa	colourless liquid with ethereal odor	*from registration**
Melting/freezing point at 1013 hPa	-58°C	*from registration*
Boiling point at 1013 hPa	82-84,8 °C	*from registration*
Relative density	0.87 g/cm³at 20°C	*from registration**
Vapour pressure	66 hPa at 20°C	*from registration*
Surface tenstion	70.7 mN/m (23°C, 1g/L)	*from registration**
Water solubility	1000g/L at 25°C	*from registration**
Partition coefficient n-octanol/water (log P_{OW}) at 25°C	-0,21	*from registration*
Flashpoint	-0.3°C at 1013 hPa	*from registration*
Flammability at -0.3°C (flash point)	Lower explosion limit: 1.6% (v/v), Upper explostion limit:10.4% (v/v), No pyrophoricity. No flammability on contact with water.	*from registration*
Autoflammability	205°C at 1008hPa	
Reactivity	Highly flammable. Slightly soluble in water.	*Chemical Book*[2]

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

Conversion factors (25°C, 1013hPa) (Ecetoc, 1995): 1mg/m³ = 0.267ppm

1ppm = 3.74mg/m³

[2] http://www.chemicalbook.com/Search_EN.aspx?keyword=110-71-4

2 HARMONISED CLASSIFICATION AND LABELLING

EGDME is covered by index number 603-031-00-3 in Annex VI, part 3 of Reg. (EC) No 1272/2008 as follows:

Table 5: Harmonised Classification and Labelling of EGDME 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)		
603-031-00-3	1,2-dimethoxyethane, ethylene glycol dimethyl ether, EGDME	203-794-9	110-71-4	Flam. Liq. 2 Repr. 1B Actute Tox. 4 *	H225 H360FD H332	GHS02 GHS08 GHS07 Dgr	H225 H360FD H332	EUH019		

Table 6: Harmonised Classification and Labelling of EGDME 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	Concentra-tion Limits	Notes
603-031-00-3	1,2-dimethoxyethane, ethylene glycol dimethyl ether, EGDME	203-794-9	110-71-4	F;R11 R19 Repr.Cat.2; R60 Repr.Cat. 2; R61 Xn;R20.	F;T R:60-61-11-19-20 S:53-45		E

Besides, all the registrants have also self-classified EGDME as Skin Irrit. 2 (H315: Causes skin irritation) in their hazard statement.

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

EGDME is listed as entry 603-031-00-3 in Annex VI, part 3, Table 3.1 (the list of harmonised classification and labelling of hazardous substances) of Regulation (EC) No 1272/2008[3] as Repr. 1B, H360FD ("May damage fertility. May damage the unborn child") This corresponds to a classification as toxic for reproduction Repr. Cat. 2; R60 R61 ("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 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.

3 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

EGDME is registered as a high-production volume chemical by the OECD[4] meaning that its production volume in at least one OECD member state is 1000tonnes/year.

EGDME is listed as a HPV chemical in the US EPA HPV Challenge Program, produced or imported in the United States in quantities of 450tonnes or more per year (1 million to 10 million pounds in 2005[5]).

EGDME is not listed in the Annex I of the regulation (EC) 689/2008[6]. EGDME was identified as an EU LPV Chemical under Regulation 793/93[7].

According to current information from the registered dossiers, manufacture accounts for the main part, import being of less importance. There is no current information about export of EGDME.

The order of magnitude of the total volume in 2010 is within the range 100 t to 1000 t. It is noticed that the volume is relatively decreased with a slight decrease for some companies over the last 3 years (for further details see confidential Annex II, Chapter 2).

In 2002, more than 1000 t were manufactured in France (Inserm 2006, data provided by industries of OSPA).

The terms E-series and P-series [8]are often used to refer to ethylene glycol ethers and propylene glycol ethers, respectively. E-series members generally are more toxic, EGDME is one of them. According to INERIS (2007), glymes of the E-Series (EGDME, Diglyme, Triglyme) are produced by Clariant GmbH.

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[4] The 2007 OECD List of high production volume chemicals: http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=ENV/JM/MONO(2009)40&docLanguage=En

[5] http://www.epa.gov/hpvis/rbp/EGDME.110714.Web.RBP.31308.pdf

[6] Export and Import of Dangerous Chemicals (Regulation (EC) 689/2008).

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

[8] http://www.glycol-ethers.eu/what-are-glycol-ethers

1.2 Uses of the Substance

1.2.1 Overview

The use of EGDME as substance or in mixture is restricted to industrial and professional users.

According to the Clariant website EGDME is mainly used as an inert special solvent for grignard-, reduction- and alkylation-reactions. It is also useful as an inert solvent for organo metallic reactions in general, e.g reactions involving alkali metals such as lithium, sodium and potassium, Pd catalyzed couplings (Suzuki reaction), …

EGDME has a high solubility for Na/K alloy. Potassium is slightly soluble. It is also used as solvent a for electrolytes of lithium batteries and as a process solvent for the recycling of Li-batteries (Ferro 1993, EPA 2008).

EGDME is used in a process for the surface treatment of aluminium in order to ensure surfaces are less reactive[9].

It is a preferred solvent in the production of Lithium batteries because of its low viscosity and cation solvating property. Likewise as an industrial reaction solvent, it facilitates certain reactions including use as a solvent to facilitate formation of alkali metal-hydrocarbon adducts and it is used in the Reformatsky reaction with methyl gamma-bromocrotonate (HSDB[10]).

According to U.S. EPA (2011b) EGDME is also used as cleaning solvent and within solder fluxes within the microelectronics industry. It has one confirmed use in a consumer product, as an electrolyte solvent (1-5%) in sealed lithium ion batteries.

In the printing industry, EGDME is also used as a constituent within flexo gravure water-solvent based inks, lithographic plate developers and glass cleaning solvents (Communication from BAUA).

The use of EGDME (process categories) according to information from the dissemination website is given in Table 7 and in Table 8.

[9] http://www.clariant.de/C12576720021BF8F/vwWebPagesByID/DC511A8F2C8F16DDC125770C002E285A

[10]Hazardous Substance Data Bank (http://toxnet.nlm.nih.gov/cgi-bin/sis/search/f?./temp/~K9Mf1W:1)

Table 7: Uses by workers in industrial settings

Identified Use (IU) name	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

Table 8: Uses by professional workers

Identified Use (IU) name	**Substance supplied to that use**	**Use descriptors**
Uses of laboratory reagents in analyses or QC e.g. as processing aid or in reactive processings	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-

indoor		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 8a: Wide dispersive indoor use of processing aids in open systems **Sector of end use (SU):** SU 24: Scientific research and development SU 20: Health services SU 9: Manufacture of fine chemicals

France:

The AFSSET report (AFSSET, 2008) refers to different investigations carried out on glycol ethers. DGCCRF (Direction Générale de la Concurrence, de la Consommation, et de la Répression des Fraudes) have carried out investigations on paints, varnishes and wide-spread drugstore-products. None of 7 glycol ethers classified toxic for reproduction (EGEE/A, EGME/A, EGDME, DEGDME and TEGDME) have been detected (Communication DGCCRF 2007 from AFSSET). EGDME has not been detected in solvents (Triolet, 2005) nor in garages, cleaning, hairdressing and general mechanics, (investigation carried out in 123 small and medium-sized enterprises Beaujean et al., 2005)

The use of glymes (EGDME, DEGDME and TEGDME) in human medical drugs was nearly phased out in 2008 (AFSSET, 2008).

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.

Germany[11]:

EGDME is used as a solvent or processing aid in the manufacture or formulation of industrial chemicals. The large majority of the EGDME sold by the producer is used as a site limited processing aid for industrial chemical manufacture. The remaining volume is used in quantities of <10 – 1000 kg/site over 100-1000 additional sites.

[11] Letter from German producer to EPA (2008)

Used as solvent for industrial chemical manufacturing, EGDME is limited to less than 5 sites (< 200 t/year, no offsite distribution). Used as processing aid for Fluoropolymer Etchant formulation, EGDME is limited to less than 10 sites. Fluoropolymer Etchant products are used to make fluoropolymers bondable to a wide variety of articles, i.e., Teflon.

1.2.2 Use of EGDME 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 2 formulations contain EGDME (AFSSET, 2008).

According to Pharmaceutical companies 0.170t of EGDME were used in 2007 as raw material in chemicals synthesis of compounds. Only 2 preparations have been registered in the SEPIA database between 2000 and 2006 (AFSSET report 2008).

Nordic countries:

The SPIN database[12] (Substances in Preparations in the Nordic countries) was searched for information on EGDME in products on the national markets of Norway, Sweden, Finland and Denmark. From Norway, Sweden and Finland no public information about tonnages is available due to confidentiality[13].

In Finland EGDME was registered (2007-2009) for the Industrial use “Manufacture of other transport equipment”.

In Denmark the following table (Table 9) indicates the volumes available on the market.

Table 9: EGDME in preparation in Denmark according to SPIN database (2007-2009)

Years	# Preparations	Tonnages
2007	6	41.3 t
2008	5	41.1 t
2009	6	58.2 t

The tonnage information are always “netto” ton = tons imported + tons produced – tons exported.

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

[13] 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 SPIN EGDME was registered in Finland (2007-2009) for the Industrial use "Manufacture of other transport equipment (n.e.c)" with no further information due to confidentiality (Table 10).

Table 10: Industrial uses in Finland according to the SPIN database (2007-2009)

Year	NACE Code*	Industrial Use	# Preparations	Amount
2007	35	Manufacture of other transport equipment n.e.c.		
2008	C30	Manufacture of other transport equipment		
2009	C30	Manufacture of other transport equipment		

* The NACE code indicates the branches of industry where the products are used.

Additionally, the technical function of the preparations containing EGDME is described by a UC62 code (Use Code 62). Only Finland is listed (Table 11).

Table 11: Use categories (UC62) according to the SPIN database

Country	Year	Code	Use Category	# Prep	Amount
FIN	2007	36	Odour agents		
FIN	2008	36	Odour agents		
FIN	2009	36	Odour agents		

1.2.3 EGDME as Impurity

According to the Glycol Ether Charter by OSPA[14] 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 EGDME.

1.2.4 Use restrictions

EGDME is covered by entry 30 of Annex XVII of REACH regulation: "Substances which appear in Annex VI of Regulation (EC) No 1272/2008 classified as toxic to reproduction category 1A or 1B (Table 3.1) or toxic to reproduction category 1 or 2 (Table 3.2)".

It shall therefore not be placed on the market, or used for supply to the general public as a substance or constituent of substances or in mixtures above the generic concentration limit specified for

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

classification purposes. The packaging of such substances and mixtures must be marked legibly and indelibly as follows: “Restricted to professional users”.

According to the Cosmetics Directive 76/768/EEC (amended by Directive 2005/80/EC), Annex II, n° 1142, EGDME must not be a part of the composition of cosmetic products.

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.

Due to its boiling point of 82.5°C at 1013hPa, EGDME falls under the definition as VOC according to Directive 2004/42/EC[15] on the limitation of emissions of volatile organic compounds regarding the use of organic solvents in certain paints and varnishes and vehicle refinishing products.

Additionaly, since 2003, 7 glycol ethers (including EGDME) are banned in veterinary drugs in France (AFSSET, 2008).

In France, the decree of October 28, 2004 establishes the prohibition of placing on the market and use limitations for EGDME and TEGDME, and preparations containing 0.5% or more.
However, this order of usage restriction does not apply, among others to:
• derivatives of mineral oil intended for use as fuel in combustion plants moving or stationary;
• fuels sold in closed systems;
• artists' paints.

Conclusion on manufacture, import, export and uses:

According to current information EGDME is on the European Market. It is mainly used as solvent for a variety of applications. Due to existing restrictions the use of the substance as such or in mixtures by consumers is not expected. However, a few measurements in Germany[16] indicate indoor emission above the maximum concentration level:

- 12/500 measurements are above the detection limit. The maximum concentration level amounts 13µg/m³ and the 95.percentile 0.5µg/m³,

- 8/23 measurements are above the detection limit. The maximum concentration level amounts 5µg/m³ and the 95.percentile 4.6µg/m³,

meaning that consumer exposure should not be excluded.

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[15] 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

[16] Communication from BAUA. Data available in:

1) “Bereitstellung einer Datenbak zum Vorkommen von fl[uchtigen organischen Verbindungen in der Raumluft”, Hofmann H, Plieninger, P, Ed. Unweltbundesamt, Wabolu-Hefte http://www.umweltdaten.de/publikationen/fpdf-l/3637.pdf

2) “Berliner Studie zu umweltbezogenen Erkrankungen“ Ed. Robert koch Institute http://www.apug.de/archiv/pdf/Berichtsband_Berliner-Studies.pdf

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 EGDME (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 can 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 registers[17]

Country	Latest year	Use Index					Range of use
		Surface water	Air	Soil	Waste water	Human consumers	
DK	2009	-	x	x	xx	x	narrow range of applications
NO	2009						
SE	2009						

(-)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

Exposure is limited by process controls and protective equipment. There is no occupational level set by EPA Ferro 1993). Ferro Corporation, in their publications, recommended a Threshold Limit Value (TLV) for glycol ethers of 5 ppm (Time Weighted Average) with a Short Term Exposure Limit (STEL) of 25 ppm. The 15-minute STEL should not be achieved more than 4 times in 8 hours (Ferro 2001). Based on the 2006 Inventory Update Reporting (IUR) reporting, the maximum total number of potentially exposed industrial workers to EGDME during manufacturing and industrial processing and use is less than 100 (U.S. EPA 2011_a).

Only Latvia reported having an OEL = 10mg/m³ (8 hour limit value) (European Agency for Safety and Health at Work 2008)

[17] Note: Registered Use Categories do not include all potential uses of the chemical and possibility for direct exposure can therefore not be excluded.

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 EGDME 29 measurements were done in this period. As no further figures for professional exposure to EGDME are reported in the AFSSET report, we can assume that the 29 measurements were not conclusive of an inhalation exposure.

Exposure estimations in the registration dossiers are based on model calculations (see confidential Annex III, Chapter 5).

1.3.2.2 Consumer exposure

In Germany, two investigations have indicated indoor emissions/household dusts as potential sources of EGDME exposures. For 500 measurements done, 12 were above the detection limit (13µg/m³ equivalent to 0.035 ppm) and for 23 measurements carried out, 8 were above the detection limit (5µg/m³ equivalent to 0.013 ppm). Even if the measured values were very low, consumers are exposed to EGDME via indoor emissions (personal communication BAUA)

For women at child-bearing age, Ferro recommended a TLV of 1 ppm with a STEL of 5 ppm (Ferro 2001).

It is noted that according to U.S. EPA consumers may be exposed through use of sealed lithium batteries (Ferro Corporation 2001).

1.3.3 Environmental Exposure

1.3.3.1 General Aspects

Theoretical Distribution (Fugacity) of EGDME in the environment was estimated using the Mackay Level III model with measured values for physical and fate constants were available and standard defaults in EPIWIN v 3.05. The results for distribution using a model calculated Ko/c (adsorption coefficient based on organic carbon content) of 0.253 are:

- Air 0.91 %
- Water 61 %
- Soil 38 %
- Sediment 0.1 %

The EQC Level III model suggests it will distribute primarily to water (US EPA 2001). Environmental fate information for EGDME indicates that it is highly soluble in water (10^6mg/L).

EGDME is resistant to hydrolysis and biodegradation by acclimated bacteria. Using a high concentration of acclimated bacteria, initially obtained from a petroleum refinery wastewater treatment plant, Babeu (1987) and Kawai (1995) were unable to detect significant biodegradation of EGDME. This result is supported by three earlier publications that reported EGDME was recalcitrant to biodegradation, has questionable biodegradation, or is not

assimilated as a substrate by bacteria. Biodegradation is judged to be slow (log Kow -0.21). Bioaccumulation potential is ranked low (B1) based on its estimated BCF of 3.

Environmental degradation to carbon dioxide will likely occur by a combination of slow biodegradation and reaction with atmospheric hydroxyl radicals after volatilization.

EGDME will mainly exist in the vapour phase in the atmosphere because of its high vapour pressure (48 mmHg at 20°C). In the atmosphere, EGDME has an estimated half-life of 25 hours due to photooxidation with hydroxyl radicals. Volatization of EGDME may be possible from dry soil surfaces, based on its vapour pressure, but will be low from moist soil and water surface based on an estimated Henry's Law constant (10^{-6} atm-cu m/mole) (Ferro corporation 2001, US EPA 2008).

1.3.3.2 Exposure data

France

Wastewater treatment plants

In the influent of a sewage treatment plant near Paris EGEE, EGDME (EGDME), EGDEE, PGME, EGPE, DEGDME, 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 (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 concentration lower than 1 mg/l (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 (Kettenis, 2005). According to registrants no substitutes for present industrial uses of EGDME are available (communication, May 2010).

In 1996, the producers have signed a voluntary agreement on the commercialization of Glycol Ethers. This Charter forbids, under penalty of non-delivery, all uses of glycol ethers classified as reprotoxic in any product sold to the public and strictly limits the use of glycol ethers classified toxic for reproduction category 2 to industrial applications, for which no substitute has been found so far. OSPA states that customers must ensure that Occupational Exposures/Emissions are within the legal constraints.

3 RISK-RELATED INFORMATION

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

The 48h EC_{50} value for daphnia is > 4000 mg/L (based on immobility). A read-across from supporting substance (Triethyleneglycoldimethylether, CASNo.: 112-49-2, structural analogue or surrogate) indicates a 96h LC50 for zebrafish > 5000 mg/L with a NOEC (96h) ≥ 5000 mg/L (as no mortality or other visible abnormalities were determined at the test fish during the test period of 96 hours). Another read-across (Diethylenglykoldimethylether, structural analogue or surrogate) 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 (dissemination website).

EPA assumes there is potential for exposure to aquatic organisms from environmental releases. The concern for potential environmental risk is low because although EGDME is considered moderately persistent in the environment, it has a low acute aquatic toxicity hazard (Ferro Corporation 2001).

3.2.2 Man via the Environment

According to U.S. EPA (2011a) there is potential for exposure to the general population from environmental releases. It is believed that disposal of the lithium batteries containing EGDME could present the potential for release of these chemicals to environmental media and subsequent exposure to humans and ecological receptors.

According to registration data the risk arising from exposure of man via the environment is very low due to the low bioaccumulation factors.

3.2.3 Human health

3.2.3.1 Data from literature

A repeated-dose toxicity (2-methoxyethanol surrogate chemical, drinking water) established a **LOAEL = 750 ppm** (approximately 70 mg/kg-bw/day) in rats, based on testicular degeneration in males and decreased thymus weight in both sexes (NTP Technical Report TOX 26, 1993).

A developmental study (Sprague-Dawley rat, oral gavage) published a **LOAEL (developmental toxicity) =30 mg/kg bw/day** based on increased stillborn, fetal edema, increased gestation length) and **NOAEL (maternal toxicity) = 60 mg/kg bw/day** (Leonhardt *et al.* 1991).

3.2.3.2 Information from the registration

The information on the registered substance EGDME according to Regulation (EC) No.1907/2006 article 119[18] (dissemination website) is shown in Table 16. For more detailed (confidential) information see Annex II, Chapter 4 (Table 13).

Table 13: DNEL values according to the registration

	$DNEL_{Dermal}$	$DNEL_{Inhalation}$	$DNEL_{Oral}$
Workers	1.1mg/kg bw/day	3.1 mg/m^3	-
General population	0.23mg/kg bw/day	1.5 mg/m^3	0.23mg/kg bw/day

[18] http://apps.echa.europa.eu/registered/registered-sub.aspx

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ANNEX I

TOXICOKINETICS, TOXICITY FOR REPRODUCTION AND NON-CLASSIFICATION FOR THE ENVIRONMENT

1 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

It has been demonstrated that most of the toxic effects of the monoalkyl glycol ethers arise as a result of the metabolic conversion of the glycol ether into a substituted acetic acid derivative. The metabolic pathway is shown in Figure 1. The competing reaction, demethylation of 2-Methoxyethanol to ethylene glycol is comparatively slow as it is accomplished by the mixed-function oxidase system. The pharmacokinetics of these transformations have been determined in the rat and the approximate ratio of production for 2methoxyacetic acid:ethylene is 5:1. The relative first-order rate constants have been determined to be 31 L/h/kg liver for conversion of 2-Methoxyethanol to 2-methoxyacetic acid and 5.6 L/h/kg liver for conversion of 2-Methoxyethanol to ethylene glycol (Hay *et al.* 2000).

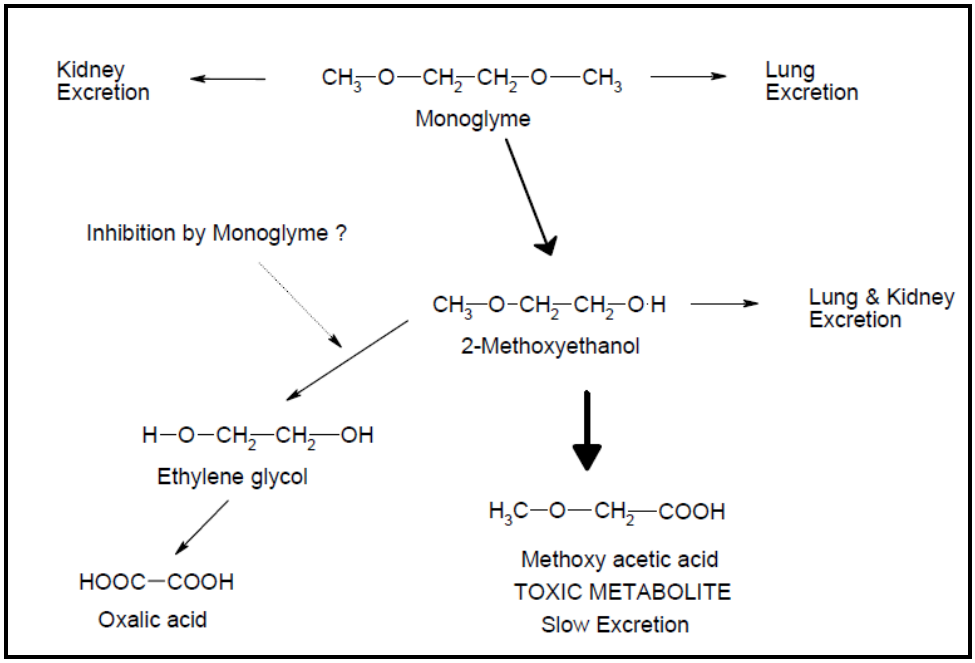

Figure 1: Metabolism and disposition of EGDME (US EPA 2001)

The main metabolite is 2-methoxyethoxyacetic acid.

Larson et al. (1999) confirmed the high percutaneous absorption of EGDME: 3.4 mg/cm²/h. It is the fastest solvent (followed by DEGDME, EGMEE and PGMME with values between 0.470 and 0.952 mg/cm²/h).

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).

2 TOXICITY FOR REPRODUCTION

It has been demonstrated that most of the toxic effects of the monoalkyl glycol ethers arise as a result of the metabolic conversion of the glycol ether into a substituted acetic acid derivative (Klassen 2001).

The reproductive toxicity of EGDME is attributed to the metabolite 2-methoxyacetic acid, which is generated from 2-methoxyethanol (EGME). The metabolite 2-methoxyacetic acid has shown evidence of accumulation in animals and humans (Ferro Corporation 2001).

Information about the metabolic pathways and nearly identical developmental effects at similar dose levels indicates that the repeated-dose, reproductive, and developmental toxicity of EGDME can be ascertained from the results of studies on EGME. The similarity in effects and dose levels for the perinatal toxicity in rats (Leonhardt *et al*. 1991) argue that EGME is an excellent surrogate for repeated dose toxic effects of EGDME.

2.1.1.1 Effects on fertility

The reproductive toxicity of EGDME is allocated to EGME. NTP Technical Report TOX-26 carried out investigations on rats and mice. Table 14 summed up the fertility toxicity in mice and in rat exposed to 2-Methoxyethanol.

In rat

Oral exposure for 2 weeks at **200 mg/kg bw/day** indicates no adverse effects on testis degeneration. Degeneration was clearly present in the testis of male rats in all but the lowest dose group.

In oral exposure for 13 weeks, degeneration was noticed **> 750 ppm**. Histopathologic changes in the testes consisted of a minimal to marked degeneration of germinal epithelium in the seminiferous tubules.

In mice

Oral exposure for 2 weeks carried out indicates **$NOEL_{male}$= 200 mg/kg bw/day** based on reduction of relative testis weight.

Oral exposure for 13 weeks indicates **NOAEL** <2000 ppm induced by reduction of testes in the 3 highest-dose groups.

2.1.1.2 Developmental toxicity

Table 15 indicates findings of the exposure to EGDME by inhalation in rabbits and rats.

Inhalation exposure of rats to EGDME produced no adverse maternal effects at any dose level. Body weight gain, food consumption and the organ weights were within the control range. No macroscopic changes occurred at any dose level.

Above **10 ppm (0.037 mg/L air)** developmental effects were recorded.

Conclusion:

Regarding fertility, the literature on 2-methoxyethanol and the metabolic data indicating that EGDME's oxidative metabolism to 2-methoxyacetic acid indicates a clear and significant reproductive hazard from overexposure to EGDME.

Regarding development, EGDME indicates that it has the potential to be teratogenic and fetotoxic. The studies show a dose-response relationship and indicate the potency range for EGDME as a developmental toxin.

An overview of different studies from dissemination site is presented in Table 16.

3 ENVIRONMENT

EGDME is not classified as hazardous to the environment.

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

Table 14 Oral exposure toxicity, 2-Metoxyethanol (NTP Technical Report TOX-26)

Species	Route of exposure	Dose/ Concentration	Observations, effects	NO(A)EL
			1st study	
5/sex/species OECD guideline 407	Drinking water *Ad libitum* for 2 weeks	0, 200, 400, 600,1000, or 1200 mg/kg bw	**Rats**: Absolute and relative thymus weights decreased in a dose-related fashion for males and females as did absolute and relative testis weights for males. In addition to chemical-related gross lesions, the testis and epididymis from all dosed and control rats were examined microscopically. Degeneration was clearly present in the testis of male rats in all but the lowest dose group (200mg/kgbw/d) : moderate to marked loss of germinal epithelium and the presence of multinucleated Spermatid giant cells and cell debris in the lumen of seminiferous tubules. In male rats in the three highest dose groups, the lumen of the epididymis contained necrotic cells and cell debris and only a few spermatozoa. **Mice :** For male mice, absolute and relative testis and thymus weights decreased in a dose-related fashion, and for female mice in the two highest dose groups (1000 and 1200 mg/kg), absolute and relative thymus weights were lower than those of the control group.	**Rats**: **NOAEL:** 200 mg/kg bw/day based on testes degeneration **Mice :** **$NOEL_{male}$:** 200 mg/kg bw/day based on reduction of relative testis weight **$NOEL_{female}$**:600 mg/kg bw/day based on reduced relative thymus weight
			2nd study	
10/sex/species OECD guideline 408	Drinking water *Ad libitum* for 13 weeks	**rats** : 0, 750, 1500, 3000, 4500, or 6000 ppm **mice**: 0, 2000, 4000, 6000, 8000, or 10,000 ppm.	**Rats:** Dose-related decreases were noted for the absolute and relative testis weights of male rats. Degeneration was present at all dose levels but was only minimal in 7 of 10 rats in the 750 ppm group. Histopathologic changes in the testes consisted of a minimal to marked degeneration of germinal epithelium in the seminiferous tubules. in more severely affected rats, the atrophic seminiferous tubules contained only Sertoli cells and a few spermatogonia.	**Rats:** **NOAEL**:< 750 ppm based on testicular degeneration in males and decreased thymus weight in males and females

			Also, spermatozoal measurements were significantly decreased for males in the two highest dose groups (1500 or 3000 ppm). For females, there was evidence to suggest that animals in the 1500 and 3000 ppm groups differed from the control animals in the relative frequency of time spent in estrous stages. **Mice :** Dose-related decreases were noted for the absolute and relative testis weights of male mice and the absolute and relative thymus weights of male and female mice. In male mice, degeneration of the testis was characterized microscopically by a dose related. Sperm morphology evaluations showed significant decreases in epididymal and cauda epididymal weights and in testicular weight. The values for sperm motility were significantly less than controls and spermatid measurements were significantly lower than controls. For females, all dose groups differed significantly from controls in the relative frequency of time spent in estrous stages.	**Mice:** **NOAEL:**<2000 ppm based on reduced sperm motility and concentration in males and histopathologacal changes in the spleen and adrenal gland incl. increases hematopoesis in female mice

Table 15: Developmental toxicity, key studies, overview of exposure to EGDME (according to dissemination site)

Species	Route of exposure	Dose/ Concentration	Observations, effects	Maternal NOAEL	Fetal NOAEL/LOAEL	Reference
Rabbits (SPF Wiga) Pregnant Female	Inhalation : Vapour (whole body) 6h/day	0, 5ppm (0.019 mg/L), 16ppm (0.06 mg/L), 50ppm (0.187	**Maternal observations**: All animals survived, no serious clinical signs were noted at any dose level. (only one abortion in the 16 ppm dose group). During the first week of treatment the body weight of the animals of the 50 ppm dose group was decreased. Within the second week of treatment this effect	NOAEC: **0.06 mg/L air (16 ppm)**	NOEC : **0.06 mg/L air (16 ppm)**	Key study (1988)

15 animals/group OECD 414	Daily Days 6-18 Recovery period: 10 days	mg/L)	disappeared. There were no effects upon the mean daily food consumption observed at the 5 ppm dose level. The food consumption of the animals of the 50 ppm and 16 ppm dose level was slightly decreased during the exposure period. **Litter examinations:** There was no effect on foetal development and body weight observed at any dose level. The vitality of the litters within the first 24 hours after Caesarean section at 50 ppm exposure was considerably decreased. In the 50 ppm dose group 10 foetuses had an abnormal orientation of one or both fore-paws. Two foetuses showed skull malformations. Irregularity of the skull ossification 8 foetuses of the high dose group. 2 foetuses of the high dose group had red-bordered spots on the skin (mandible, neck and below the eyes).	Based on slightly decreased food consumption	Based on decreased vitality within the first 24 hours at 0.187mg/L	
Rats (APF71) Pregnant Female 20 animals/group OECD 414	Inhalation: Vapour (whole body) Days 7-16 Recovery period: 10 days	10 ppm (0.037 mg/L), 32 ppm (0.12 mg/L) , 100 ppm (0.374 mg/L)	**Maternal observations:** All animals survived. No clinical signs were noted at any dose level. **Litter examinations:** There was a slight decrease of fetal weight observed in middle dose group and the body weight of the fetuses of the highest dose group was considerably decreased. The fetuses of the high dose group showed a retarded development. Resorptions as well as dead fetuses were found in this dose group. The number of resorptions at the high dose level was increased compared to the others. The number of viable fetuses was considerably decreased in the highest dose group. In this group 11 fetuses had malformations of the extremities and scapula (crooked, shortened). One fetus group had a shortened tail and 4 fetuses showed subcutaneous oedema. The ossification of the fetuses of the two higher dose groups was considerably retarded. In these dose groups fragmented thoracic and lumbar vertebrae	NOEC **0.374 mg/L air (100 ppm)** No effects	NOEC **0.037 mg/L air (10 ppm)** based on retarded development and increased incidence of malformations at 0.12 mg/L	Supporting study (1986)

			were observed. The number of fetuses showing malformations of ribs was significantly increased at exposure to 32 ppm and 100 ppm of the test substance. Blood in the pericardium and enlarged ureter were observed in fetuses of the 32 ppm and 100 ppm dose group.			

Table 16: Repeated-dose, studies overview of exposure to EGDME (according to the dissemination site)

Species	**Route of exposure**	**Dose/ Concentration**	**Observations, effects**	**NO(A)EC**	**Reference**
rat (Hoechst) 10animals/sex/ groug OECD 412	Inhalation 6h/day 5days/week for 2 weeks Recovery period: 36 days	10 ppm (0.037 mg/L) 50 ppm (0.187 mg/L) 250 ppm (0.935 mg/L)	All animals survived and no clinical signs were noted at any dose level. No neurological or ophthalmological effects or changes in mucosa were noted. Body weight gain of all animals was not affected. There were no effects upon the mean daily food consumption observed at all dose levels. There were no haematological changes noted at any dose level. All determined clinical parameters were within the control range. Relative organ weights were within the control range. **250 ppm:** The reduction of cell layers of seminiferous epithelium in male rats was observed at dose group. This effect was reversible.	**NOEC** **50 ppm** (0.187 mg/L). Based on the observed slight changes in the seminiferous epithelium in male rats at the 250 ppm dose group.	Key study 1986
rat (Hoechst) male/pregnant female	Inhalation 6h/day	0, 100, 500ppm	**100 ppm:** All animals survived and no clinical signs were noted. Body weight gain of the rats was unaffected. There were no effects upon the mean daily food consumption. There were no changes in haematology noted. The microsopic examination of the testes and epidymis showed	**NOAEC** < 100 ppm Based on the observed oligospermia in rats and the retardation of foetal development and	Supporting study (1985)

5animals/group OECD 412	5days/week For 2 weeks Recovery period: 3 days		oligospermia. A retardation of foetal development was observed. **500 ppm** : No deaths or clinical signs occurred in the rats. The body weight of the male rats of the 500 ppm dose group was unaffected; the body weight of three female rats was decreased. Food consumption of all females was decreased. the leucocyte count was decreased in all animals. No macroscopic changes occurred in all rats. Severe lesions of the seminiferous epithelium. An increase of resorptions occurred.	resorption of embryos in rats.	
Rabbit (SPF Wiga) Male/Female 6animals/group OECD 412	Inhalation 6h/day 5 days/ week For 2 weeks Recovery period: 36 days	0, 10, 50, 250ppm	All other animals survived and no clinical signs were noted at any dose level. No neurological or ophthalmological effects or changes in mucosa were noted. Body weight gain of all animals was not affected within the first 15 days of the study. With one exception there were no effects upon the mean daily food consumption observed at all dose levels. **250 ppm:** During the 36 days recovery period the body weight gain of the male animals was considerably decreased, the body weight gain of the females of this dose group was slightly decreased. The food consumption of the animals was decreased during the exposure period. No macroscopic/microscopic changes occurred at any dose level with the exception of changes of the seminiferous epithelium in male rabbits of the 250 ppm dose group which caused aspermia. This effect was irreversible within the recovery period of 36 days	**NOEC** 10 ppm Based on the decreased reticulocyte count in female rabbits exposed to 50 ppm and the observed changes in the seminiferous epithelium in male rabbits at 250 ppm	Supporting study (1985)