Annex XV dossier

PROPOSAL FOR IDENTIFICATION OF A SUBSTANCE AS A CMR CAT 1 OR 2, PBT, vPvB OR A SUBSTANCE OF AN EQUIVALENT LEVEL OF CONCERN

Substance Name(s): 2-Methoxyethanol (ethylene glycol monomethyl ether; EGME)

EC Number(s): 203-713-7

CAS Number(s): 109-86-4

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 the Belgian Federal Public Service (FPS) Health, Food Chain Safety and Environment, Risk Management Service

and the Polish Bureau for Chemical Substances and Preparations

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TABLES

LIST OF ABBREVIATIONS

AFSSET	**French Agency for Environmental and Occupational Health Safety, now "ANSES", Agence nationale de sécurité sanitaire**
BLV	**Biological Limit Value**
CICAD	**Concise International Chemical Assessment Document**
CMR	**Carcinogenic, Mutagenic or toxic to Reproduction**
DEGDME	**Diethylene glycol dimethylether**
DEGME	**Diethylene glycol methylether**
EASE	**Estimation and Assessment of Substance Exposure**
EEP	**Ethyl-3-ethoxypropion**
EGBE	**2-Butoxyethanol**
EGBEA	**2-Butoxyethyl acetate**
EGDME	**Ethylene glycol dimethylether**
EGEE	**2-Ethoxyethanol**
EGEEA	**2-Ethoxyethanol acetate**
EGME	**2-Methoxyethanol**
EGMEA	**2-Methoxyethanol acetate**
EGPE	**Ethylene glycol monopropyl ether**
EGPEA	**Ethylene glycol monopropyl ether acetate**
EU RAR	**European Union Risk Assessment Report**
INERIS	Institut National de l'Environnement industriel et des RISques
INRS	Institut National de Recherche et de Sécurité
IOELV	Indicative Occupational Exposure Limit Value
IUCLID	**International Uniform Chemical Information Database**
LOD	**Limit of Detection**
OEL	**Occupational Exposure Limit**
OSPA	**Oxygenated Solvents Producers Association**
MAA	2-Methoxyacetic acid

MALD	2-Methoxy-acetaldehyde
MOS	**Margin of Safety**
PGME	**1-Methoxy-2-propanol**
PGMEA	**1-Methoxy-2-propyl acetate**
PBT	**Persistent, Bioaccumulative and Toxic**
RAPEX	EU rapid alert system for dangerous consumer products
SCOEL	**Scientific Committee on Occupational Exposure Limits**
SME	**Small and medium enterprises**
SPIN	**Substances in Preparations in the Nordic countries**
STEL	**Short Term Exposure Level**
TEGDME	**Triethylene glycol dimethylether**
TEGME	**Triethylene glycol methylether**
TRGS	**Technische Regeln für Gefahrstoffe; Technical rules for Hazardous substances**
TWA	**Time Weighted Average**
vPvB	**Very Persistent and very Bioaccumulative**

PROPOSAL FOR IDENTIFICATION OF A SUBSTANCE AS A CMR CAT 1 OR 2, PBT, VPVB OR A SUBSTANCE OF AN EQUIVALENT LEVEL OF CONCERN

Substance Name(s): 2-Methoxyethanol (ethylene glycol monomethyl ether; EGME)

EC Number(s): 203-713-7

CAS number(s): 109-86-4

- The substance is proposed to be identified as 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 meets the CMR (Cat 1 or 2), PBT or vPvB criteria, or is considered to be a) substance giving rise to an equivalent level of concern

2-Methoxyethanol (EGME) is listed as entry 603-011-00-4 in Annex VI, part 3, Table 3.2 (the list of harmonised classification and labelling of hazardous substances from Annex I to Directive 67/548/EEC) of Regulation (EC) No 1272/2008 as toxic to reproduction, category 2[1].

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 number(s) of the substance or of substances containing a given constituent/impurity or leading to the same transformation or degradation products:

-

[1] This corresponds to a classification as toxic for reproduction (1B) in Annex VI, part 3, Table 3.1 of Regulation (EC) No. 1272/2008 (list of harmonised classification and labelling of hazardous substances)

PART I

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:	203-713-7
EC name:	2-methoxyethanol
CAS number (in the EC inventory):	109-86-4
CAS number:	109-86-4
CAS name:	Ethanol, 2-methoxy-
IUPAC name:	2-methoxyethanol
Index number in Annex VI of the CLP Regulation	603-011-00-4
Molecular formula:	C3H8O2
Molecular weight range:	76.09 g/mol
Synonyms:	ethylene glycol monomethyl ether; EGME

Structural formula:

1.2 Composition of the substance

Name: 2-methoxyethanol

Description:

Degree of purity: >99 % w/w (according to IUCLID)[2]

[2] http://ecb.jrc.ec.europa.eu/IUCLID-DataSheets/109864.pdf

Table 2: Constituents

Constituents	Typical concentration	Concentration range	Remarks
2-methoxyethanol	>99 % w/w		

Table 3: Impurities

Impurities	Typical concentration	Concentration range	Remarks
unknown impurities	<1 % w/w		

1.3 Physico-chemical properties

Table 4: Overview of physicochemical properties, from IUCLID, amended

Property	Value	References
Physical state at 20°C and 101.3 kPa	Colourless, viscous liquid	
Melting/freezing point	-85 °C	Hoechst AG, 17.12.1992
Boiling point	123.5 – 125.5 °C at 1013 hPa	BASF AG, 6.4.1994
Vapour pressure	10 hPa at 20°C	Hoechst AG, 28.2.1996
Water solubility	completely miscible, pH = 7 and 20°C	BASF AG,18.3.1994 WHO, 2009
Partition coefficient n-octanol/water (log value)	Log Pow = 0.77 Calculated -0.85	BASF AG, 9.1.1989 (unpublished)
Dissociation constant	-	
Density	0.964 - 0.966 g/m^3 at 20°C	BASF AG, 6.4.1994

2 HARMONISED CLASSIFICATION AND LABELLING

2-Methoxyethanol is classified and labelled according to Annex VI of Reg. (EC) No 1272/2008, Annex VI, Table 3.1. as follows:

Index Number: 603-011-00-4

Hazard Class and Category Codes

Flam. Liq. 3

Repr. 1B

Acute Tox. 4 *[3]

Acute Tox. 4 *

Acute Tox. 4 *

Hazard statement Codes

H226

H360FD

H332

H312

H302

Pictogram Signal Word Code(s)

GHS02

GHS08

GHS07

Dgr

Specific Conc. Limits; M-factors; Notes: none

[3] Minimum classification for a category is indicated by the reference * in the column 'Classification' in Table 3.1.

For certain hazard classes, including acute toxicity and STOT repeated exposure; the classification according to the criteria in Directive 67/548/EEC does not correspond directly to the classification in a hazard class and category under this Regulation. In these cases the classification in this Annex shall be considered as a minimum classification. This classification shall be applied if none of the following conditions are fulfilled:

— the manufacturer or importer has access to data or other information as specified in Part 1 of Annex I that lead to classification in a more severe category compared to the minimum classification. Classification in the more severe category must then be applied;

— the minimum classification can be further refined based on the translation table in Annex VII when the physical state of the substance used in the acute inhalation toxicity test is known to the manufacturer or importer. The classification as obtained from Annex VII shall then substitute the minimum classification indicated in this Annex if it differs from it.

Classification and Labelling of EGME according to Reg. (EC) No 1272/2008, Annex VI, Table 3.2:

Index Number: 603-011-00-4

Classification

R10

Repr. Cat. 2; R60-61

Xn; R20/21/22

Labelling

T

R: 60-61-10-20/21/22

S: 53-45

3 ENVIRONMENTAL FATE PROPERTIES

Not relevant for this type of dossier.

4 HUMAN HEALTH HAZARD ASSESSMENT

See section 2 on Harmonised Classification and Labelling.

5 ENVIRONMENTAL HAZARD ASSESSMENT

Not relevant for this type of dossier.

6 CONCLUSIONS ON THE SVHC PROPERTIES

6.1 CMR assessment

2-Methoxyethanol (EGME) is listed as entry 603-011-00-4 in Annex VI, part 3, Table 3.2 (the list of harmonised classification and labelling of hazardous substances from Annex I to Directive 67/548/EEC) of Regulation (EC) No 1272/2008 as toxic to reproduction, category 2. This corresponds to a classification as toxic for reproduction (1B) in Annex VI, part 3, Table 3.1 of Regulation (EC) No. 1272/2008 (list of harmonised classification and labelling of hazardous substances).

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.

PART II

INFORMATION ON USE, EXPOSURE, ALTERNATIVES AND RISKS

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

1 INFORMATION ON EXPOSURE

1.1 Information on volumes

2-Methoxyethanol has not been reported to occur as a natural product (USEPA, 1986; IPCS, 1990). The substance is produced commercially by the reaction of ethylene oxide with anhydrous methanol. There are no known reactions that would lead to the in situ production of 2-methoxyethanol or other glycol ethers in the atmosphere (Rogozen et al., 1987).

The substance has been reported to be a high production volume chemical (HPVC) under the ESR program[4] and to find a wide application as a solvent, chemical intermediate and solvent coupler of mixtures and water-based formulations. Use has declined, however, in recent years as a result of its classification and consequent replacement by other substances in some countries. The compound is produced by two European companies. In total, 260 EU pre-registrations have been submitted to ECHA. Registrations are expected in the > 1ktpa tonnage band (information from industry) (OSPA, 2010).

According to a report by AFSSET (2008) the European production of glycol ethers in general had slightly increased between 2000 and 2006, whereas the partition between E- (based on ethylene oxide) series and P-series (based on propylene oxide) glycols had changed. In 2006, SICOS (French Association of the Organic Chemistry and Biochemistry Industries) posted an annual European production of about 650 000 tons (40% E-series, 60% P-series). In 2000, the annual European production was stated with about 500 000 tons (60% E-series, 40% P-series) (Ministère de la santé, internet consultation, 2007). In the E-series, the glycol ethers EGMEA and EGEEA are no more produced in Europe, while EGME and EGEE are still produced, but only in small amounts (**2005: 3000 tons EGME**, 500 tons EGEE).

[4] Council Regulation (EEC) No 793/93 of 23 March 1993 on the evaluation and control of the risks of existing substances

1.1.1 Information from Product Register Data (SPIN database)

The SPIN database (Substances in Preparations in the Nordic countries) was searched for information on 2-methoxyethanol in products on the national markets of Norway, Sweden, Finland and Denmark. The information provided concerns the years 2005 - 2008. (Table 5):

Table 5: 2-methoxyethanol in products according to SPIN for 2005 – 2008

Country	2005		2006	
	number of preparations	tonnage	number of preparations	tonnage
Norway	5	3698	7	4794.8
Sweden	17	1	17	0
Finland	13	0.5	12	0.5
Denmark	12	0.4	13	0.4
Total:		3699.9 tons		4795.7 tons

Country	2007		2008	
	number of preparations	tonnage	number of preparations	tonnage
Norway	5	4357.9	5	3896.8
Sweden	15	0	17	0
Finland	13	0.5	12	0.5
Denmark	14	0.4	13	0.4
Total:		4358.8 tons		3897.7 tons

It is important to mention how the data are recorded in SPIN: The total amount of a substance included in the SPIN database is the added quantity of the substance in all products without the amount of substances exported. Therefore, if a substance is registered first as the imported raw material and then again as part of the final preparation the quantity will be counted twice. Substances which are imported and then used for the formulation of chemical products, which is very often the case in the Nordic countries, will thus be accounted for with up to double the actual amount. Therefore, the tonnages in Table 5 might be considered as overestimations.

Small volumes of 2-methoxyethanol (≤ 0.5 tons) were notified in Denmark and Finland, the volumes remained constant between 2005 and 2008. Between 2006 and 2008 Sweden showed quantities of “0.0 tons”, which means that the notified volumes were smaller than 0.1 ton. In contrast to all other Nordic countries, Norway showed notably high quantities ranging from 3698 to 4794.8 tons.

1.1.2 Information on 2-methoxyethanol quantities from pre-registration data

An excerpt from pre-registration shows that 172 companies pre-registered 2-methoxyethanol 260 times. In order to obtain an estimation of 2-methoxyethanol quantities in the next years, pre-registration data were analyzed. The results of the pre-registered tonnages and companies are summarized in Table 6.

Table 6: Information on 2-methoxyethanol tonnages according to pre-registration data

No. of companies	172
No. of companies pre-registrations	260
min* t/a acc. no. of pre-registrations	13787 t/a
max t/a acc. no. of pre-registrations	47870 t/a

According to the tonnage band 1-10 t/a, the minimum (min) would be 1 to/a and the maximum (max) would be 10 t/a

For pre-registration each company had to indicate the tonnage band (1-10 t/a, 10-100 t/a, 100-1000 t/a, and 1000+ t/a) of the actual amount of produced and / or imported 2-methoxyethanol. For the estimation of annual tonnages each tonnage band (minimum and maximum amount) is multiplied with the number of pre-registrations and then summed up to give the total amount of imported and / or produced tonnage of 2-methoxyethanol per year.

This estimate results in a minimum of **13787 t/a** and a maximum of **47870 t/a** of 2-methoxyethanol imported and/or produced in Europe. **It is noted that these estimates based on pre-registration data are not entirely reliable and represent only very rough estimates.**

1.1.3 Information from other Member States

Poland

According to data collected by the Polish Bureau for Chemical Substances and Preparations three companies place on the market 340 kg of mixtures containing 2-methoxyethanol. These data include the years 2009 and 2010. One company is manufacturer of mixtures containing EGME.

France (AFSSET report, 2008)

In France, there is only one producer of glycol ethers, and no production of 2-methoxyethanol is reported. In France, a few uses of 2-methoxyethanol are reported in the AFSSET report (2008), however, no indication are given on the volumes. Only global amounts are given. There is only a small proportion of glycol ethers amongst the solvents used in France (4% of total amount, approx. 22 000 t). There is only a small proportion of use of glycol ethers regarded as toxic to reproduction (cat.2) – approx. 130 t/a (0,4% of all glycol ethers) and these glycol ethers are solely used in professional context, predominantly EGEE. The volumes of EGME are therefore expected to be

low, and solely for professional use. The total amount of glycol ethers used on the French market has remained stable over the last 10 years, but an inversion between the proportions of the P - and the E-series glycol ethers (diminution of E-series) took place.

Conclusion:

In total 260 EU pre-registrations were received. The estimate of the pre-registration data indicates a total EU volume in the range of **13787 t/a** to **47870 t/a**. Industry stated that registrations are expected in the > 1ktpa tonnage band. The future trend on EU volumes is difficult to predict. No clear trend can be observed when analyzing the total volume of 2-methoxyethanol according to the SPIN database (Norway, Sweden, Finland and Denmark). Over the period of 2005 – 2008 only Norway notified high quantities of 2-methoxyethanol, which were varying between min. 3698 (2005) and max. 4795 (2006) tons. According to the AFSSET report (2008), 3000 tons of 2-methoxyethanol were produced in Europe in 2005. In France, there is only one producer of glycol ethers, and no production of 2-methoxyethanol is reported. No volume related to the use of 2-methoxyethanol in France is reported. Only a small proportion of glycol ethers regarded as toxic to reproduction (cat.2), approx. 130 t/a (0,4% of all glycol ethers) are used in France, solely in professional context. More reliable data on production/import are expected to become available after the first registration deadline (December 1st, 2010). Such information may be taken into account during the consultation phase.

1.2 Information on uses

2-Methoxyethanol found a wide application as a solvent, chemical intermediate and solvent coupler of mixtures and water-based formulations. Use has declined, however, in recent years as a result of its classification and consequent replacement by other substances in some countries. For cosmetics the use of EGME is forbidden.

According to recent information provided by the member companies of the Oxygenated Solvent Producers Association, EGME is now mainly used as a chemical intermediate or as additive for fuels (OSPA, 2010). In addition, it can also be used as industrial processing aid in different areas (e.g. in the manufacture of medical devices) (OSPA, 2010). Based on the OSPA Charter on Glycolethers, inappropriate end-use applications are not supported by member companies. All downstream users are further required to make an annual declaration on their safe use and handling measures (OSPA, 2010). In 2001, OSPA (AFSSET, 2008) stated that the remaining uses from glycol ethers toxic to reproduction (cat 2.) are notably related to lack of alternative technology (e.g. solvents for extraction in the pharmaceutical industry or solvents for chemical syntheses). They are also used for certain production steps of surface coating in aeronautics.

Uses according to the SPIN database

The SPIN database was searched for industrial uses of 2-methoxyethanol in Norway, Sweden, Finland and Denmark. The industrial uses are presented in Table 7.

Table 7. Industrial Uses according to the SPIN database

Country	Year	Code	Industrial Use	# Prep**	Tons*
S	2008	G45	Wholesale and retail trade and repair of motor vehicles and motorcycles	3	0.0
FIN	2008	C20	Manufacture of chemicals and chemical products		
FIN	2008	C21	Manufacture of basic pharmaceutical products and pharmaceutical preparations		
FIN	2008	C22	Manufacture of rubber and plastic products		
FIN	2008	C30	Manufacture of other transport equipment		
FIN	2008	F43	Specialised construction activities		
FIN	2008	S96	Other personal service activities		
N	2007	24	Manufacture of chemicals and chemical products	5	4357.9
FIN	2007	24	Manufacture of chemicals and chemical products		
FIN	2007	25	Manufacture of rubber and plastic products		
FIN	2007	35	Manufacture of other transport equipment n.e.c.		
FIN	2007	93	Other service activities		
N	2006	24	Manufacture of chemicals and chemical products	6	4794.8
FIN	2006	24	Manufacture of chemicals and chemical products		
FIN	2006	25	Manufacture of rubber and plastic products		
FIN	2006	35	Manufacture of other transport equipment n.e.c.		
FIN	2006	93	Other service activities		
N	2005	24	Manufacture of chemicals and chemical products	5	3698.6
FIN	2005	24	Manufacture of chemicals and chemical products		
FIN	2005	35	Manufacture of other transport equipment n.e.c.		
FIN	2005	93	Other service activities		

*The information "0.0 tons" means that the volume is less than 100 kg in Sweden in that particular branch of industry. The tonnage information is always "net" tons = tons imported + tons produced – tons exported.
**The reason for the lack of information on the number of preparations and tons particularly for Finland is that data are kept confidential if the substance is a component in less than 4 preparations.

The industrial use categories with the highest volumes are given as "Manufacture of chemicals and chemical products" (Table 7, Norway, 6 preparations, 2006, 4794.8 tons).

Additionally, the SPIN database was searched for use categories of 2-methoxyethanol in Norway, Sweden, Finland and Denmark. The use categories are presented in Table 8.

Table 8. Use categories (UC62) according to the SPIN database

Country	Year	Code	Use Category	# Prep**	Tons*
FIN	2008	34	Laboratory chemicals	6	0.4
S	2008	35	Lubricants and additives	9	0.0*
FIN	2008	10	Colouring agents		
FIN	2008	28	Fuel additives		
FIN	2008	33	Intermediates		
FIN	2008	42	Photochemicals		
FIN	2008	48	Solvents		
FIN	2008	59	Paints, laquers and varnishes		
FIN	2007	34	Laboratory chemicals	6	0.5
S	2007	35	Lubricants and additives	7	0.0
FIN	2007	10	Colouring agents		
FIN	2007	28	Fuel additives		
FIN	2007	33	Intermediates		
FIN	2007	42	Photochemicals		
FIN	2007	43	Process regulators		
FIN	2007	48	Solvents		
FIN	2007	55	Others		
FIN	2007	59	Paints, laquers and varnishes		
FIN	2006	34	Laboratory chemicals	5	0.4
S	2006	35	Lubricants and additives	8	0.0
FIN	2006	42	Photochemicals		
FIN	2006	43	Process regulators		
FIN	2006	48	Solvents		
FIN	2006	55	Others		
FIN	2006	59	Paints, laquers and varnishes		
FIN	2005	34	Laboratory chemicals	5	0.4

S	2005	35	Lubricants and additives	8	0.0
FIN	2005	41	Pharmaceuticals		
FIN	2005	42	Photochemicals		
FIN	2005	43	Process regulators		
FIN	2005	48	Solvents		
FIN	2005	55	Others		
FIN	2005	59	Paints, laquers and varnishes		

*The information "0.0 tons" means that the volume is less than 100 kg in Sweden in that particular branch of industry. The tonnage information is always "net" tons = tons imported + tons produced – tons exported.
**The reason for the lack of information on the number of preparations and tons particularly for Finland is that data are kept confidential if the substance is a component in less than 4 preparations.

In 2008, the following use categories (UC62) for 2-methoxyethanol have been notified in the SPIN database: Laboratory chemicals, Lubricants and additives, Colouring agents, Fuel additives, Intermediates Photochemicals, Solvents, Paints, lacquers and varnishes.

France (AFSSET, 2008)

The very low use of Glycol ethers considered as toxic to reproduction (cat. 2) in France is supported by all the available investigations from 2000 to 2006. Only a few uses are reported for EGME in France (9 preparations are indicated in SEPIA[5] between 2000 and 2006), among others in the aeronautic sector.

The AFSSET report (AFSSET, 2008) refers to following investigations carried out on glycol ethers: An investigation on use in garages, cleaning, hairdressing and general mechanics, carried out in 123 SMEs, has not shown any use of EGME (Beaujean et al., 2005). A study on solvents carried out in 2004 by the INRS has not identified EGME either (Triolet, 2005). The most recent 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, have not shown any glycol ethers classified as toxic to reproduction, including EGME (Communication DGCCRF 2007 from AFSSET).

Concerning mixtures, glycol ethers classified as toxic to reproduction are practically not found in marketed mixtures (see Table 9). In total, out of the 13 000 formulations notified in the SEPIA database between 2000 and 2006, only 142 formulations (1% of all) contain glycol ethers considered as toxic to reproduction (cat 2). Amongst those 142 formulations, 82 contain impurities of 1PG2ME or 1PG2MEA of which 78 have a concentration lower than 0.5% and 2 a concentration between 0.5 and 3%. Thus, there are around 60 formulations with considerable content of glycol ethers toxic to reproduction listed in the SEPIA database of the INRS and amongst them, 9 formulations which contain 2-methoxyethanol.

[5] The SEPIA database of the INRS relates to the chemical preparations placed on the French market. The registration in this confidential database is mandatory for the preparations very toxic, toxic, corrosive or for the biocides.

Table 9. Number of occurrence of glycol ether mixtures registered in SEPIA between 2000 and 2006

Product category	total registered formulations	total number of formulations containing glycol ethers	total number of formulations containing glycol ethers classified as "Repr. cat 2"
paints, varnishes, inks for printing and associated products	1790	809	76
diverse	1709	159	25
biocides	4220	363	23
construction material	212	13	3
products for caoutchouc (rubber) and plastics	237	14	2
products for household and industrial cleaning	2129	360	2
products for metallurgic and mechanic use	1121	234	2
prod. for industrial textiles and dyeing	86	31	1
glues and associated products	325	21	1
not specified	-	-	7

Number of occurrence of glycol ethers classified as toxic for reproduction (Cat 2) in mixtures registered in SEPIA between 2000 and 2006. A mixture can be counted several times if several uses are reported or if it contains several glycol ethers classified as Reprotox Cat.2.

Germany

According to the German exposure database MEGA[6] following substance relevant exposure scenarios have been identified (observation period: 2000 – 2009): wood processing, electro-techniques, metal processing, production and processing of plastics, offices, painting, coating, printing applications.

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 glycol ethers, EGME being one of them. In total 15 % of all answers were positive, indicating that one or more of the glycol ethers were still in use. The results of the inquiry show that the use of the seven glycol ethers classified as toxic to reproduction at Austrian workplaces in the examined branch is generally declining, but still occurs for specific applications. Random checks in the Austrian Safety Datasheet database of the Environment agency Austria (EAA) show that, e.g., 2-Methoxyethanol still occurs (e.g., Glycol Cleaning Solvent 100%).

Poland

According to data from an industry survey, collected by the Bureau for Chemical Substances and Preparations in Poland for the observation period 2005 – 2010, EGME is used in following

[6] Exposure database MEGA "Measurement data relating to workplace exposure to hazardous substances" - MEGA is a compilation of data gathered through atmospheric measurements and material analyses. (http://www.dguv.de/ifa/en/gestis/mega/index.jsp)

chemical product categories: polymer preparations and compounds, intermediates, printing toners and inks. The process categories mentioned by industry are: use in closed, continuous process with occasional controlled exposure.

Use restrictions

EGME is listed in Annex XVII, Group 30, of the REACH regulation[7] and thus shall not be placed on the market, or used for supply to the general public. Suppliers shall ensure before the placing on the market that the packaging of such substances and mixtures is marked visibly, legibly and indelibly as follows: “Restricted to professional users”.

According to the Cosmetics Directive 76/768/EEC[8], Annex II, No. 665, 2-methoxyethanol must not form part of the composition of cosmetic products.

Due to its boiling point of 124 °C at 1013hPa EGME falls under the definition as VOC according to Directive 2004/42/EC[9] on the limitation of emissions of volatile organic compounds due to the use of organic solvents in certain paints and varnishes.

Conclusion on uses

Very recent information from member companies of OSPA (Oxygenated Solvent Producers Association) indicates that EGME is now mainly used as a chemical intermediate or as additive for fuels (OSPA, 2010). It can also be used as industrial processing aid in different areas (e.g. in the manufacture of medical devices).

The SPIN database indentified the industrial use categories with the highest volumes as “Manufacture of chemicals and chemical products” (Norway, 6 preparations, 2006 4794.8 tons). In 2008, the following use categories (UC62) for 2-methoxyethanol have been notified to the SPIN database: Laboratory chemicals, lubricants and additives, colouring agents, fuel additives, intermediates, photochemicals, solvents paints, lacquers and varnishes.

In France, only a few uses are reported for EGME (9 preparations are indicated in SEPIA[10] between 2000 and 2006), among others in the aeronautic sector.

[7] 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

[8] Council Directive 76/768/EEC of 27 July 1976 on the approximation of the laws of the Member States relating to cosmetic products

[9] 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

At present, there are not sufficient data available which allow to identify all remaining specific uses. It is expected that the information will be available following the first registration deadline, 1st December 2010.

1.3 Information on exposure – Environmental and human health monitoring data

The main focus within this part of the dossier is to present collected information on environmental and workplace monitoring data. These data are compared with the Concise International Chemical Assessment (CICAD) Document 67 (further mentioned as WHO, 2009) on 2-methoxyethanol. The document was prepared as part of the Priority Substances Program under the *Canadian Environmental Protection Act, 1999* (CEPA) (Environment Canada & Health Canada, 2002). The objective of assessments on priority substances under CEPA is to assess potential effects of indirect exposure in the general environment on human health as well as environmental effects. The human health aspect for workers is not specifically addressed.

1.3.1 SPIN Exposure Toolbox

The Nordic SPIN database has been extended with a new feature, called SPIN Exposure Toolbox. The new tool is called Use Index. The tool makes it possible to search for a general indicative exposure of human beings and environment from different chemical uses. It is based on the extensive information stored in the Nordic product registers. The spin exposure toolbox uses confidential data which cannot be published on the SPIN web site, but available information can be used to get more information on the substance. Use Index can be considered as an indicative screening tool.

The potential exposure of surface water, air, soil, waste water and human consumers in Norway, Sweden and Denmark for 2-methoxyethanol is presented in Table 10.

Table 10: Exposure potential for primary recipients based on data in Nordic product registers (Use Index)

Country	Latest year	Surface water	Air	Soil	Waste water	Human consumer
DK	2008	-[1]	x[2]	x	x	x
NO	2008	-	-	-	xx[3]	x
SE	2008	x	x	xxx[4]	x	xx

[1]The substance is not registered in the country, or the registered use does not indicate direct exposure (Note that registered Use Categories do not include all potential uses of the chemical and possibility for direct exposure can therefore not be excluded); [2]One or several uses indicate a potential exposure; [3]One or several uses indicate a probable exposure; [4]One or several uses indicate a very probable exposure

Summary

[10] The SEPIA database of the INRS relates to the chemical preparations placed on the french market. The registration in this confidential database is mandatory for the preparations very toxic, toxic, corrosive or for the biocides.

In all three countries included in the Use Index (Denmark, Norway and Sweden) one or several uses of products containing 2-methoxyethanol indicate a potential/probable exposure of human consumers and wastewater. In Sweden, the use of 2-methoxyethanol indicates a very probable exposure of soil.

1.3.2 Environmental monitoring data

Very few data on levels of 2-methoxyethanol in the environment have been identified (USEPA, 1986; IPCS, 1990; AFSSET, 2008). In Canada, no data were identified on the concentration of 2-methoxyethanol in ambient air, surface water or soil, although one study was conducted to determine concentrations of 2-methoxyethanol in multiple Canadian media to which humans are exposed, including drinking-water and indoor and outdoor air (WHO, 2009).

1.3.2.1 Measured concentrations of 2-methoxyethanol in the influent and effluent of wastewater treatment plants (WWTPs), groundwater, indoor air, outdoor, personal air, drinking water, and consumer products

Influent and effluent of wastewater treatment plants

France

In the influent of a sewage treatment plant near Paris EGEE, EGDME, DEGDME (and EGDEE, PGME, EGPE, EGBE, DPGME, DEGME, DEGEE, TEGDME, DEGBE, EGPhE were detected in concentrations between 0.009 and 0.716 mg/l (AFSSET report, 2008). At the outflow of the wastewater treatment plant, there were generally no derivatives of ethylene glycol and propylene glycol, though there could be found derivatives of diethylene glycol, triethylene glycol and dipropylene glycol at concentrations lower than 1 mg/l (INERIS, 2001). EGME was not detected in influent and effluent of this STP, contrary to the other glycol ethers mentioned above.

Groundwater

France

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 (INERIS, 2001).

Indoor air samples of housing

France

During the campaign Habit'Air Nord-Pas-de-Calais, which was carried out between February and August 2005, 8 glycol ethers have been investigated (3 in the first phase, and 8 in a second phase). In the first phase, passive sampling was performed over a week in 60 main residences, which were recruited on voluntary basis. The median of the total of the measured glycol ethers was less than 2 µg/m³. The maxima were between 4 µg/m³ (EGEE) and 20 µg/m³ (PGME). No positive finding could be obtained for EGME in indoor air of housing (AFSSET, 2008).

Table 11. Concentration of EGME (µg/m³) in 60 residences in the North of Pas-de-Calais (Feb. to August 2005)

Glycol ether	Limit of detection	Frequency of detection	Median	Maximum
EGME	0,03	0	-	-

Germany

In a study conducted in Germany, indoor air samples were collected following the sealing of wooden parquet flooring in a school room with a product containing 2-methoxyethanol. The concentrations of 2-methoxyethanol in samples collected 10, 18, 25, 35, 52 and 90 days after sealing were 220, 150, 180, 160, 59 and 26 µg/m3, respectively (Schriever & Marutzky, 1990).

According to the German exposure database MEGA[11] following substance relevant exposure scenarios have been identified for the period from 2000 to 2009: wood processing, electro-techniques, metal processing, production and processing of plastics, offices, painting, coating, printing applications.

Italy

In northern Italy, six indoor air samples were collected from homes in 1983–1984 and analyzed for several organic pollutants by gas chromatography coupled with mass spectrometric detection. The concentration of 2-methoxyethanol in one of the samples was 70 µg/m^3; in the remaining five samples, however, the concentration was below the limit of detection (not specified). (De Bortoli et al., 1986).

EGME in Consumer Products

France

According to the AFSSET report (AFSSET, 2008) 32 household products of 7 categories have been analyzed for glycol ethers emissions under realistic condition (experimental house) or in emission test-chambers. Sampling was performed during 30 min. Emission of EGME was found from a carpet stain (27µg/m^3) and a ground cloth (49 µg/m^3). Maximum results were obtained during the first 30 minutes after the application of the product.

Table 12: Emissions of EGME from household products (CSTB, 2006)

Tested product	Exposure concentrations (µg/m^3) after			
	0-30 min	30-60 min	60-90 min	90-120 min
Carpet stain	27.1	13.2	11.7	6.1
Ground cloth	49.2	6.4	3.2	2.6

11 Exposure database MEGA "Measurement data relating to workplace exposure to hazardous substances" - MEGA is a compilation of data gathered through atmospheric measurements and material analyses. Institute for Occupational Safety and Health of the German Social Accident Insurance, Sankt Augustin/Germany (http://www.dguv.de/ifa/en/gestis/mega/index.jsp)

EU

RAPEX[12] is the EU rapid alert system for all dangerous consumer products, with the exception of food, pharmaceutical and medical devices. One RAPEX notification for EGME in consumer products in 2005 was notified in the database. The consumer product is a construction product containing 2-methoxyethanol at a concentration of 39.8% 2-methoxyethanol.

EGME in drinking-water, indoor and outdoor air Canada (WHO, 2009)

Thirty-five inhabitants from the Greater Toronto area in Ontario, six inhabitants from Queens Subdivision in Nova Scotia and nine from Edmonton, Alberta, were randomly selected. For each of the 50 participants samples of drinking-water and indoor, outdoor and personal air were collected over a 24-h period.

The concentration of 2-methoxyethanol was below the method detection limit (0.6 µg/l) in all samples of drinking-water.

Samples of foods and beverages were not analyzed for the determination of 2-methoxyethanol. The concentration of 2-methoxyethanol was below the method detection limit (0.6 µg/l) in all samples of drinking-water. Similarly, it was not detected (<5 µg/m3) in any sample of indoor, outdoor or personal air (Conor Pacific Environmental Technologies Inc., 1998).

Environmental concentrations of EGME were estimated by ChemCAN version 4 modelling (DMER & AEL, 1996). This is a Level III fugacity-based regional model developed to estimate the environmental fate of chemicals in Canada. Environmental concentrations of EGME in southern Ontario predicted by ChemCAN modelling are as follows:
0.146 ng/m ng/g dry in air;
4.8×10^{-5}µg/l in water;
9.4×10^{-4} ng/g dry weight in soil;
and 2.34×10^{-5} ng/g dry weight in sediments.

1.3.3 Human Exposure

This chapter is based on the information given in the Concise International Chemical Assessment Document 67 (WHO, 2009). While consumer exposure to EGME has decreased because of the ban of 2-methoxyethanol for consumer products, following its classification and labelling as toxic to reproduction category 2, there is still relevant workers exposure. Workplace monitoring data are included in this dossier from some European Member States.

In addition an estimation on consumer exposure was made. It was shown that the limit value of 0.5% which should not be exceeded in consumer products was not sufficient to protect consumers when applying paint and window cleaning. Comparing the EGME concentration (1.72 mg/m^3 and 34.48 mg/m^3) in air from two scenarios (cleaning, painting) with the $DNEL_{long\text{-}term\ inhalation}$values derived herein, consumers and professional users are at risk even if the concentration of EGME is only 0.5 % in window-cleaning agents or paints.

[12] http://ec.europa.eu/consumers/dyna/rapex/create_rapex_search.cfm

1.3.3.1 General information

2-Methoxyethanol is a colourless, volatile liquid, with high water solubility. EGME is readily adsorbed following oral, inhalation or dermal exposure and distributed extensively through the body, including the developing foetus. A major route of exposure can be the absorption through skin, particularly for the occupational setting.

EGME is metabolised via alcohol and aldehyde dehydrogenase to MALD, then MAA. MAA is the principal metabolite found in the urine of rat, mouse and humans exposed to EGME by ingestion or inhalation (WHO, 2009). The toxic metabolite MAA is excreted more slowly in humans than in pregnant rats and pregnant monkeys. The level of MAA metabolite in urine can be used as a specific and suitable indicator of overall exposure (e.g. Veulemans et al., 1987).

Monitoring data for the general population to 2-methoxyethanol are limited. Although relevant data are limited, exposure of the general population through environmental media is expected to be low, as a result of reported classification and declining use of the compound in recent years as it is replaced with less hazardous compounds (WHO, 2009).

EGME is listed in Directive 2009/161/EU establishing a third list of indicative occupational exposure limit values in implementation of Council Directive 98/24/EC with an Indicative Occupational Exposure Limit Values (IOELV) of 1 ppm (8 hours, skin notation).

1.3.4 Workplace monitoring data

Epidemiological data are limited but are suggestive of effects on the haematological system and on reproduction in men and women employed in occupations involving exposure to 2-methoxyethanol. A clear association between effects on the blood and exposure to 2-methoxyethanol has been reported in a study on a group of workers. Effects on red blood cell counts in a worker population not exposed to other alkoxy alcohols or chemicals known to affect the bone marrow have been reported at levels of exposure at which effects on spermatogenesis were not observed. The studies contain reliable exposure data on both airborne levels and workplace urinary MAA (as a measure of actual uptake), which can be used as a basis for characterizing the risk from exposure to airborne 2-methoxyethanol (WHO, 2009).

Austrian workplaces monitoring data

Older Austrian workplace monitoring data exist on 2-methoxyethanol, which show exceedance of OEL values in few individual cases (for "solder-stop varnish" in the PC board production). In the meantime the substance has been substituted from the varnish (company´s information).

Table 13. Austrian workplace monitoring data

Substance	CAS no.	Location	personal exposure (pe) or stationary analyses (sa)	AT-Limit value (e.g. MAK)	Date	Max.	Data obtained from
EGME	109-86-4	work area = casting implements	pe	16 mg/m^3	1996/97	23 mg/m^3	Labour Inspectorate
		work area = varnish reservoir	sa	16 mg/m^3	1996/97	34 mg/m^3	Labour Inspectorate

German workplace monitoring data (Exposure Database MEGA)

Within the period 2000 - 2009 290 EGME measurements in 484 workplaces were performed in Germany by the Institute for Occupational Safety and Health of the German Social Accident Insurance (IFA).

Following substance relevant exposure scenarios have been identified for the period from 2000 to 2009: wood processing, electro-techniques, metal processing, production and processing of plastics, offices, painting, coating, printing applications although actual concentrations are well below the LOD.

Data were derived from the Exposure Database MEGA (Measurement data relating to workplace exposure to hazardous substances). 99.2% of the data from personal sampling measurements in 83 workplaces were below the detection limit of 4.2 mg/m^3; measurements from stationary sampling procedures were in 99.7% of the cases below the detection limit of 2.2 mg/m^3.

Table 14: EGME Exposure data from MEGA

Glycol ether	CAS-No.	No. of measurements	personal exposure (pe) or stationary analyses (sa)	No. of workplaces	LOD Limit of detection (mg/m^3)	No. meas. below LOD (%)
EGME	110-80-5	128	pe	83	4.2	127 (99.2)
EGME	110-80-5	356	sa	233	2.2	355 (99.7)

France

Information on French monitoring according to the AFSSET report 2008 are presented in the following Tables (Table 15, 16 and 17).

Between 2000 and 2006 the concentration of EGME from exposure measurements revealed no exceedence of the limit value (Table 15). In contrast, between 1987 and 1998 the concentration of EGME exceeded the limit value (Table 16). Table 15 and 16 cover professional exposure to EGME.

Table 15. Exposure Measurements conducted between 2000 and 2006

				Exposure concentration (mg/m³)			
Glycol ether	CAS-No.	Limit value	No. of measurements	mean	median	95-percentil	maximum
EGME	109-86-4	16 mg/m³	9	0,29	0,15	0,50	0,50

Extracted information from the COLCHIC database from INRS; results from exposure measurements (exposure is representative for inhalation, comparable with limit value for France (8h)); conducted between 2000 and 2006; individual investigation, measurement period between 60 and 480 minutes)

Table 16. Exposure Measurements conducted between 1987 and 1998

			Exposure concentration (mg/m³)			
Glycol ether	CAS-No.	No. of measurements	mean	median	95-percentil	maximum
EGME	109-86-4	67	30,7	4,6	65	701

Measurement period between 60 and 480 minutes (extracted information from the COLCHIC database from INRS, 1999)

Table 17. Results of the exposure measurements for EGME

industrial branch	personal exposure (pe) or stationary analyses (sa)	Date	No. measured values	No. of positive findings [%] *	Min. (mg/m^3)	Max. (mg/m^3)	Median (mg/m^3) minimum approach	Mean (mg/m^3) minimum approach	Ref.
chemical industry	pe (60 to 480 minutes of sampling)	2000-2006		3 results	0.5	0.5	-	0.5	AFSSET report, 2008 (COLCHIC database, INRS, 2000-2006)
rubber and plastic	pe (60 to 480 minutes of sampling)	2000-2006		5 results	0.1	0.2	-	0.1	AFSSET report, 2008 (COLCHIC database, INRS, 2000-2006)
building of transport materials (code NAF 35)	pe (60 to 480 minutes of sampling)	2000-2006		1 result	-	-	-	0.5	AFSSET report, 2008 (COLCHIC database, INRS, 2000-2006)

Exposure is representative for inhalation at the workplace, comparable with limit values (Occupational exposure limit value for France (8 hours): 16 mg/m^3)Main industrial branches between 2000 and 2006 are indicated (individual investigation, measurement period between 60 and 480 minutes, results in mg/m^3)

French exposure data based on the metabolite MAA

MAA is a metabolite of EGME, as well as of EGDME, DEGME, DEGDME, TEGME and TEGDME (e.g. Inserm, 1999). MAA is excreted in the urine in free and conjugated form. The free form has a half life of 71 h and represents 85.5% of the absorbed dosage in the case of EGME (Groeseneken et al., 1989).

Between 1988 and 1993, INRS carried out a campaign of biomonitoring in different workplaces, on 944 employees in 55 companies, grouped as 63 worksituations (Vincent, 1966). Three sectors have had detectable levels of MAA (> 2 mg/l urine or ~ 2 mg/g creatinine)

- producers of printed circuit boards (mean 39,2 mg/g creatinin, range btw. 2 and 121,4 mg/g creatinine)
- paint-industry (mean: 2,3 mg/g, max: 3,6 mg/g)
- wood industry (mean: 2,3 mg/g, max: 15 mg/g)

According to the authors, the presence of MAA is linked to the use of EGME, in particular for photosensitive varnishes as used in the production of printed circuit boards and in the fabrication of paints and varnishes as mordants and coating for furniture. It has been proposed as bio-indicator for the exposure to EGME (BEI[13]) by Taiwanese authors (Shih et al., 1999) for a level of 40 mg/g creatinine corresponding to an atmospheric exposure of 16 mg/m³ EGME (corresponding to TLV) for 8h, 5 days a week.

Shih et al., 2003

Haematological effects were examined in 29 (25 males and 5 females) exposed workers and 90 non-exposed workers during 8-hours full shift personal exposure to 2-methoxyethanol. Impregnation workers were exposed to EGME in the coating department of a copper clad laminate manufacturing plant. The regular operations included mixing, implantation, drying, cutting, lamination, trimming, and inspection. The volatile chemicals used were acetone and EGME (coating glue: 30% acetone and 70% EGME). MAA has been shown to be a suitable biomarker for the EGME exposure via all routs, because non-exposed people have no background levels of MAA. Urinary 2-methoxyacetic acid (MAA) was repeatedly measured in 3 surveys within 6 months.

The first exposure survey was carried out in February 1997. Mean EGME air concentration was evaluated by measuring personal weekly means of 5 days, 8 hr full shift air concentrations. For the 2nd and 3rd survey 8 hr personal samples were collected for one day. For all 3 surveys spot urine samples were taken from exposed and comparison group after they had finished their shift on Friday. The following haematological parameters were examined: haemoglobin, packed cell volume, red and white blood cells, neutrophils, lymphocytes, platelets, mean corpuscular volume and haemoglobin.

The first exposure survey revealed a personal 5-day mean concentration of **35.7 ppm** (**113 mg/m^3**; range 0.75 – 320 ppm, n=29, SD 77.9) and a urinary MAA concentration of 57.7 mg/g creatinine (range 24.3 – 139 mg/g creatinine, n=29, SD 31.8). The comparison group (heat press workers) were exposed to EGME at a concentration of 0.19 ppm and a urinary MAA concentration of 1.02 mg/g creatinine (n=32, range ND – 4.22 mg/g creatinine, SD 1.25). The first follow up study revealed a personal 8 hr EGME concentration of **2.65 ppm** (**8.4 mg/m^3**) and a post shift urinary MAA concentration of 24.6 mg/g creatinine. The second follow up study revealed a personal 8 hr

[13] biologic exposition indicator

EGME concentration of **0.55 ppm** (**1.7 mg/m^3**) and a post shift urinary MAA concentration of 13.5 mg/g creatinine.

The first exposure survey revealed that haemoglobin, packed cell volume and red blood cell count were significantly lower in male (not in female) exposed workers than in male comparison workers. Female workers (n=5) stayed mainly in the location of product compiling, which was far from the emission with much lower exposure. Red blood cell count was significantly and negatively associated with airborne 2-ME concentration. Haemoglobin, packed cell volume, and red blood cell count were found to return to normal values in both the first (2.5 months later) and second (6 months later) follow up study. A significant increasing trend was noted for heamoglobin, packed cell volume, and red blood count.

SCOEL, 2006

According to Recommendation from the SCOEL (SCOEL, 2006) on Occupational Exposure Limits for 2 Methoxyethanol (ME) and 2 Methoxyethyl Acetate (MEA) the reported average exposure levels are in the range <0.1 to 23 mg/m3 (<0.3 to 7.4 ppm) for 2ME, and from <0.1 to 143 mg/m^3 (<0.2 to 29 ppm) for 2MEA. Exposure has been reported from semiconductor and circuit board manufacture, printing, painting (especially automobile and ship painting), furniture finishing, paint production and automobile repair.

Conclusion

Very few monitoring data from Austrian workplaces have obtained exceedence of Austrian limit values. Results from exposure measurements from the COLCHIC database from INRS conducted between 2000 and 2006 indicate EGME median/mean concentrations of 0.15 / 0.29 mg/m^3 (AFSSET report, 2008). Some measurements have been conducted (2000 – 2006) in the chemical industry, rubber and plastic sector, and the building of transport materials. SCOEL (SCOEL, 2006) reported average exposure levels in the range of <0.1 to 23 mg/m^3 (<0.3 to 7.4 ppm) for 2-methoxyethanol. In a copper clad laminate manufacturing plant 8 hr personal EGME concentrations of 8.4 and 1.7 mg/m^3 were obtained.

2 CURRENT KNOWLEDGE ON ALTERNATIVES

According to the German Technical Rules for Hazardous Substances TRGS 609 (TRGS 609, 1992)[14] the use of alternative substances as a solvent in lacquer and plastic industry has to be investigated in detail for each application. Therefore it is not possible to list alternative substances for all applications in general. 1-methoxy-2-propanol (PGME), 1-methoxy-2-propyl acetate (PGMEA), 2-butoxyethanol (EGBE), 2-butoxyethyl acetate (EGBEA), and ethyl-3-ethoxypropionate (EEP) were mentioned as possible substitutes for methoxyethanol, ethoxyethanol and their acetates. According to TRGS 609 these substances may be used as alternatives regarding their toxicological properties. None of them are classified as CMR, with PGME, PGMEA, EGBE and EGBEA included in Annex VI of the CLP Regulation and EEP with no harmonised classification (see Table 18). Information on alternative substances for other applications was not available in this paper.

According to US Occupational Safety and Health Administration (OSHA, 1993) the most common substitutes for 2-methoxyethanol, 2-ethoxyethanol and their acetates are PGME, EGBE, ethylene glycol monopropyl ether (EGPE) and their acetates (PGMEA, EGBEA, EGPEA). These chemicals account for almost 90 percent of reported substitutions.

According to OSHA (2003) use of 2-methoxyethanol, 2-ethoxyethanol and their acetates has largely been replaced by less-toxic substitutes, primarily by ethylene glycol butyl ethers from the E-series (The E-series, the ethylene glycol ethers, consist mainly of ethylene glycol methyl, ethyl and butyl ethers), P-series glycol ethers (propylene glycol ethers), and ethyl-3-ethoxypropionate.

Table 18: List of harmonised classification and labelling of alternative substances.

Abbreviation	Chemical Name(s)	CAS-Number	EC-Number	Classification**		Labelling	
				Hazard Class and Category Code(s)	Hazard Statement Code(s)	Pictogram Signal Word Code(s)	Hazard Statement Code(s)
PGME	propylene glycol methyl ether; 1-methoxy-2-propanol	107-98-2	203-539-1	Flam. Liq. 3 STOT SE 3	H226 H336	GHS02 GHS07 Wng	H226 H336

[14] TRGS 609 (1992). Technical Rules for Hazardous Substances. *Federal Institute for Occupational Safety and Health.* In German: Technische Regeln für Gefahrstoffe, Ersatzstoffe, Ersatzverfahren und Verwendungsbeschränkungen für Methyl- und Ethylglykol sowie deren Acetate

PGMEA	Propylene glycol methyl ether acetate; 2-methoxy-1-methylethyl acetate; 1-methoxy-2-propyl acetate	108-65-6	203-603-9	Flam. Liq. 3	H226	GHS02 Wng	H226
EGBE	Ethylene glycol butyl ether; 2-butoxyethanol; butyl cellosolve	111-76-2	203-905-0	Acute Tox. 4 * Acute Tox. 4 * Acute Tox. 4 * Eye Irrit. 2 Skin Irrit. 2	H332 H312 H302 H319 H315	GHS07 Wng	H332 H312 H302 H319 H315
EGBEA	Ethylene glycol butyl ether acetate; 2-butoxyethyl acetate; butyl glycol acetate	112-07-2	203-933-3	Acute Tox. 4 * Acute Tox. 4 *	H332 H312	GHS07 Wng	H332 H312
EGPE	Ethylene glycol propyl ether; Ethylene glycol monopropyl ether; 2-(propyloxy)ethanol	2807-30-9	220-548-6	Acute Tox. 4 * Eye Irrit. 2	H312 H319	GHS07 Wng	H312 H319
EGPEA	Ethylene glycol propyl ether acetate; Ethylene glycol monopropyl ether acetate; 2-propoxyethyl acetate; 2-(propyloxy)ethanol acetate	20706-25-6	-	Not classified acc. to CLP Reg			
EEP	Ethyl-3-ethoxypropionate	763-69-9	212-112-9	Not classified acc. to CLP Reg			

** Classification and labelling of PGME, PGMEA, EGBE, EGBEA and EGPE according to CLP Reg 2008

2.1.1 Volumes of alternative substances

Table 19: Production volumes of alternative substances and the number of production sites within the EU

Alternative substance	Production volume in the EU (tonnes/year)	Year	Number of production sites in the EU	Reference
PGME	188 000	2001-2003	5*	EU RAR PGME[15]
PGMEA	78 000	2001-2003	3*	EU RAR PGMEA[16]
EGBE	155 000	2001-2003	5*	EU RAR EGBE[17]
EGBEA	12800	2001-2003	3*	EU RAR EGBEA[18]
EGPE	n.a.**		5	ESIS[19]
EGPEA	n.a.			
EEP	n.a.			

* Production sites exceeding 1000 tonnes/year, **not available

[15] EU RAR PGME 2006: European Union Risk assessment report 1-methoxypropan-2-ol (PGME) Part I – environment; EUR 22474 EN, 2006

EU RAR PGME 2008: European Union Risk assessment report 1-methoxypropan-2-ol (PGME), Final Human Health draft, TRD_AXVREP_RAR_HH_France_PGME.rtf, October 2008

[16] EU RAR PGMEA 2006: European Union Risk assessment report 2-methoxy-1-methylethyl acetate (PGMEA) Part I - environment; EUR 22484 EN, 2006

EU RAR PGMEA 2008 : European Union Risk assessment report 1-methoxypropan-2-ol acetate, Final Human Health draft, TRD_AXVREP_RAR_HH_France_PGMEA.rtf, October 2008

[17] EU RAR EGBE: European Union Risk assessment report 2-butoxyethanol (EGBE) Part I – environment; EUR 22501 EN, 2006; and Part II Human health, final approved version, R408_0808_HH_CLEAN, August 2008

[18] EU RAR EGBEA: European Union Risk assessment report 2-butoxyethyl acetate (EGBEA) Part I – environment; EUR 22475 EN, 2006; and Part II Human Health, final approved version, R409_0808_HH_CLEAN.DOC, August 2008

[19] http://ecb.jrc.ec.europa.eu/esis/

2.1.2 Risk related information on alternative substances

Information on risks arising from the alternative substances mentioned above was extracted mainly from risk assessments performed according to Reg (EEC) 793/93. In the framework of these assessments the following alternative conclusions may be drawn:

Conclusion (i): There is need for further information and/or testing.

Conclusion (ii): There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Conclusion (iii): There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

2.1.2.1 1-Methoxy-2-propanol (PGME)

Environment (according to EU RAR PGME, 2006)

Conclusion (ii) is applied to all levels of the life cycle of PGME: production, formulation,

processing and private use.

Human Health (according to EU RAR PGME, 2008)

Workers

Conclusion (iii) applies to formulation and industrial spraying (coating/painting) for systemic and local toxicity after repeated dermal exposure, to industrial spraying, cleaning (spraying and wiping) and printing (silk screening and flexography) for systemic toxicity after repeated inhalation exposure and to cleaning spraying and wiping (coating/painting) for eye and respiratory tract irritation. For combined exposure, conclusion (iii) applies for formulation, for coating-painting scenarios (industrial spraying), for cleaning (spraying, wiping), for printing (silk screening, flexography).

Conclusion (ii) is reached for the other toxicological endpoints and the other scenarios.

Consumers

Conclusion (iii) applies to eye and respiratory tract irritation for house cleaners scenarios.

Conclusion (ii) is reached for the other toxicological endpoints and the other scenarios

Humans exposed via the environment

Conclusion (ii) applies.

2.1.2.2 2-Methoxy-1-methylethyl acetate (PGMEA)

Environment (according to EU RAR PGMEA 2006)

Conclusion (ii) is applied to all levels of the life cycle of PGMEA: production, formulation, processing and private use.

Human Health (according to EU RAR PGMEA 2008)

Workers

Conclusion (iii) applies for local effects (chronic irritation of the respiratory tract) due to repeated exposure for coating and painting scenario: industrial (spraying and other works) and decorative and for systemic toxicity due to repeated dermal exposure for formulation and industrial spraying scenarios.

Conclusion (ii) applies for the other toxicological endpoints and the other scenarios.

Consumers

Conclusion (iii) applies for eye and respiratory tract irritation for house cleaners scenarios and for repeated dose toxicity (local effects) for aqueous paints and floor varnishes and for house cleaners scenarios.

Conclusion (ii) applies for the other toxicological endpoints and the other scenarios.

Humans exposed via the environment

Conclusion (ii) applies.

2.1.2.3 2-Butoxyethanol (EGBE, according to EU RAR EGBE)

Environment

Conclusion (ii) is applies to all levels of the life cycle of EGBE: production, formulation,

processing and private use.

Human Health

Workers and Consumers

Conclusion (ii) applies to all scenarios and all toxicological end-points

Humans exposed via the environment

Conclusion (ii) applies.

2.1.2.4 2-Butoxyethyl acetate (EGBEA, according to EU RAR EGBEA)

Environment

Conclusion (ii) is applied to all levels of the life cycle of EGBEA: production, formulation,processing and private use.

Human Health

Workers and Consumers

Conclusion (ii) applies for all end points and for all scenarios

Humans exposed via the environment

Conclusion (ii) applies.

2.1.2.5 2-(Propyloxy)ethanol (EGPE)

No risk assessment following Regulation (EEC) No 793/93 on the evaluation and control of the risks of existing substances has been performed for EGPE.

Human Health (hazard assessment according to OECD SIDS) 20

EGPE (assessed in a group of four mono ethylene glycol ethers) possesses properties indicating a hazard for human health (reversible eye and skin irritation, reversible CNS depression). Hemolysis and associated organ toxicity are noted in rats, mice and rabbits exposed to EGPE. Humans are many-fold less sensitive to these effects and associated organ toxicity.

An increase in the number of fetuses with skeletal variations was noted in offspring of rats exposed to maternally toxic concentrations of EGPE by inhalation (≥ 200 ppm or 966 mg/m3); the derived NOAEL for developmental toxicity was 100 ppm, i.e. 450 mg/m3.

Environment (hazard assessment according to OECD SIDS)

EGPE shows a low hazard profile.

2.1.2.6 2-(Propyloxy)ethanol acetate (EGPEA)

There was no risk assessment performed pursuant Reg. (EEC) No 793/93 and there is no OECD, SIDS publication available. Kasavage and Katz reported developmental effects by EGPEA in rats (Kasavage and Katz, 1984).

2.1.2.7 Ethyl-3-ethoxypropionate (EEP)

There was no risk assessment performed pursuant Reg. (EEC) No 793/93 and there is no OECD, SIDS publication available. According to Boggs, 1989 EEP is a less toxic substitute for ethylene-glycol-ether solvents in positive photoresists.

[20] OECD SIDS, UNEP PUBLICATIONS, Initial Assessment Report for SIAM 19 Monoethylene glycol ethers; http://www.inchem.org/documents/sids/sids/MonoethyleneGlycolEthers.pdf

3 RISK-RELATED INFORMATION

It is noted that no risk assessment has been carried out for EGME at European level. A comprehensive risk assessment is outside the scope of this dossier. The following information is based on available data collected by the submitting Member States and a rough assessment by experts. It can be expected that more detailed information on risks will become available from chemical safety reports submitted to ECHA by the first registration deadline of 30th November 2010.

3.1 Environmental Effects Assessment

Data on the effects of EGME on aquatic organisms are limited. The most sensitive organism was reported to be the flagellate protozoan, *Chilomonas paramecium*. No data were identified on the effects of 2-methoxyethanol on terrestrial wildlife (WHO, 2009)

According to ECBI/20/97-Add.10 2-methoxyethanol is ready biodegradable (73-94% biodegradation after 14 days, MITI I Test). The fish LC_{50} (96h) is 16000 mg/L (Johnson, 1980). The value is supported by numerous other tests showing EC_{50} >1000 mg/L (ECBI/20/97-Add.10). The test DIN 38412 Teil 11 (Daphnia 48h) showed an EC_{50} value (24h) for Daphnia > 10000 mg/L. Test on algae revealed a LOEC (8 days) of > 10000 mg/L (Zellvermehrungshemmtest, BASF AG).

According to the summary record (ECBI/48/97 – Rev.1) the Commission Working Group on the Classification and Labelling of Dangerous Substances (Environmental Effects) agreed that the substance should not be classified as dangerous to the environment.

3.2 Human health Effects Assessment (summarized from WHO, 2009)

3.2.1 Toxikokinetics (adsorption, distribution, and elimination)

EGME is readily adsorbed following oral, inhalation or dermal exposure and distributed extensively through the body, including the developing foetus. A major route of exposure can be the absorption through skin, particularly for the occupational setting. EGME is metabolised via alcohol and aldehyde dehydrogenase to MALD, then MAA. MAA is the principal metabolite found in the urine of rat, mouse and humans exposed to EGME by ingestion or inhalation (WHO, 2009). The toxic metabolite MAA is excreted more slowly in humans than in pregnant rats and pregnant monkeys. The level of MAA metabolite in urine can be used as a specific and suitable indicator of overall exposure (e.g. Veulemans et al., 1987).

3.2.2 Acute Toxicity

EGME is of low to moderate acute toxicity in laboratory animals following oral, inhalation or dermal exposure with oral median lethal doses (LC_{50}s) generally in the range of 1000 mg/kg body weight or more (e.g. ECETOC, 1995).

3.2.3 Irritation

2-methoxyethanol has a low potential to cause skin and eye irritation (e.g. Devillers & Chessel, 1995).

3.2.4 Corrosivity

EGME is not a corrosive substance.

3.2.5 Sensitisation

EGME has not been shown to be a skin sensitizer in the guinea pig by the maximized Magnusson and Kligman method (Zissu, 1995).

3.2.6 Repeated dose toxicity

The thymus, testes and blood were the primary targets of 2-methoxyethanol-induced toxicity in rats exposed subchronically by gavage or in drinking-water. Atrophy or decreased weight of the thymus and testes and alterations in haematological parameters (including mean haemoglobin concentration, packed cell volume, and red and white blood cell counts) were observed in rats administered oral doses of 285 mg/kg body weight per day (the lowest dose tested) or more for 6 weeks (USEPA, 1992). Testicular degeneration and decreased thymus weights, along with effects on the blood (including anaemia and reduced white blood cell and platelet counts), were also reported in F344/N rats exposed to 2-methoxyethanol in drinking-water for 13 weeks at concentrations equivalent to doses of 71 mg/kg body weight per day or more (NTP, 1993), which therefore constitutes a lowest-observed-adverse-effect level (LOAEL) for the oral route. A no-observed-adverse-effect level (NOAEL) was not identified in these studies.

Effects on red blood cell counts in a worker population not exposed to other alkoxy alcohols or chemicals known to affect the bone marrow have been reported at levels of exposure at which effects on spermatogenesis were not observed (WHO, 2009).

3.2.7 Mutagenicity

2-methoxyerhanol does not induce gene mutations in *in vitro* investigations; there is some indication that EGME induces clastogenic damage (WHO, 2009).

Consistent results in several cell lines support that the initial metabolite MALD is genotoxic. *In vivo* results of EGME show that EGME is not genotoxic in somatic cells. Results from male germ cell are inconclusive.

3.2.8 Carcinogenicity

No studies on the effects of chronic exposure to EGME have been identified.

3.2.9 Toxic for Reproduction and Development

3.2.9.1 Effects on fertility

In the large number of relevant studies identified, 2-methoxyethanol was consistently toxic to the male reproductive system in multiple species (mice, rats, guinea-pigs, rabbits and dogs) exposed by all routes of administration (subcutaneous, dermal, oral or inhalation). Effects on reproductive ability as well as reproductive organs have been observed, often at the lowest dose or concentration tested. Single or repeated oral administration of 2-methoxyethanol induced adverse effects on the testes (including weight and histopathological changes or biochemical indicators of testicular damage, such as urinary creatine) and/or various sperm parameters in every identified study in which these end-points were examined.

3.2.9.2 Developmental toxicity

2-Methoxyethanol and its principal metabolite, MAA, have consistently induced developmental toxicity in numerous oral studies in several species of laboratory animals (although data are

insufficient to evaluate variations in sensitivity across species), generally at doses or concentrations lower than those that are maternally toxic, and often at the lowest exposure level tested.

In 2009, WHO summarized the developmental toxicity in a concise report (WHO, 2009). In inhalation studies in rats, developmental effects, including increased resorptions, decreased pup or fetal weights, and increased incidences of skeletal variations and malformations, were observed following repeated maternal exposure (on days 6–17, 6–15 or 7–15 of pregnancy) to 2-methoxyethanol concentrations of 160 mg/m^3 and above (Doe et al., 1983; Hanley et al., 1984a,b; Nelson et al., 1984a), whereas visceral malformations, such as heart defects, were noted at 320 mg/m^3 (Nelson et al., 1984a). No developmental effects were observed at 9 or 32 mg/m^3 (Hanley et al., 1984a,b). No overt maternal toxicity was evident in one study at 640 mg/m^3 (Nelson et al., 1984a). Doe et al. (1983) reported maternal toxicity at 320 mg/m^3, whereas Hanley et al. (1984a,b) described 160 mg/m^3 as slightly toxic to the dams. Dose-related, slight decreases in red blood cell count, blood haemoglobin concentration and packed cell volume were also observed in dams at exposure concentrations of 9 mg/m^3, the lowest exposure studied (Hanley et al., 1984a,b). Neurochemical changes and behavioural effects were observed in offspring of rats exposed to 79 mg/m^3 (Nelson et al., 1984b). In rabbits, an increased incidence of malformations and skeletal variations, as well as of resorptions and decreased fetal weight, was observed at 160 mg/m^3. At 32 mg/m^3, there was a statistically significant increase in the delay of ossification of sternebrae, whereas for the centra, there was statistically significant less delayed ossification than in controls. For the other three ossification centrae, there were no differences. The investigators concluded that this represents the normal variation in the species and is not a sign of fetotoxicity or teratogenicity at this dose level. In mice, unilateral hypoplasia of testis (at 160 mg/m^3) but no teratogenic effects were observed (highest exposure studied, 160 mg/m^3). The **NOAEC** for developmental effects in all three species was 10 ppm (**32 mg/m^3**). The WHO (WHO, 2009) concluded that the most informative study on developmental toxicity in experimental animal studies by inhalation (Hanley et al., 1984 a,b) derives **32 mg/m^3** as the **NOAEC** (although slight effects on the blood were seen at the lowest levels).

Conclusion of the Commission Working group on Classification and Labelling of Dangerous Substances, 1992

On the 55th Meeting (4-5 May 1992) the Commission Working Group on the Classification and Labelling of Dangerous Substances agreed with the unanimous opinion of Specialized Experts to classify the substance 2-methoxyethanol based on developmental and fertility data from inhalation and oral studies as Repr. Cat. 2; R60-61. Exposure of male rats to 300 ppm vapour has been shown to result in infertility due to testicular atrophy which is, at least partially reversible. A **no effect level** for fetotoxicity and teratogenicity of **10 ppm** (**32 mg/m^3**) has been demonstrated in inhalation studies in the rat, mouse and rabbit (Document XI/261/89).

ECETOC, 2005

The NOAEC value has been disputed by ECETOC (ECETOC, 2005) which takes into account a delay of ossification in the 10 ppm group and thus defines a **NOAEC** of **3 ppm** (rabbit). INRS (France) reports also a NOAEC of 3 ppm (Demeter, 2008).

3.2.10 Other effects

Haematological effects (WHO, 2008)

Haematological effects have been observed after a single high dose of 2-methoxyethanol and after repeated administration by inhalation, ingestion or dermal application. In a developmental toxicity study in rats, dose-related, slight decreases in blood haemoglobin and packed cell volume were observed in dams at an exposure concentration of **9 mg/m^3**, the lowest exposure studied (Hanley et al., 1984 a,b).

A clear-cut haematotoxic effect was observed in workers at a time-weighted exposure to an average 2-methoxyethanol concentration of 113 mg/m^3, with recovery towards normal at an exposure level of 8.4 mg/m^3 and full recovery at 1.7 mg/m^3.

Effects on red blood cell counts in a worker population not exposed to other alkoxy alcohols or chemicals known to affect the bone marrow have been reported at levels of exposure at which effects on spermatogenesis were not observed.

Immuntoxicity (WHO, 2008)

Exposure to 2-methoxyethanol significantly altered immune function in rats exposed orally or dermally. Although fewer studies are available, mice appear to be much less sensitive than rats to the immunotoxicity of 2-methoxyethanol. Immunosuppression was observed in several studies in male and/or female rats (several strains) repeatedly administered oral doses of 50 mg 2-methoxyethanol/kg body weight per day or more over periods of 2–21 days, based on alterations in lymphoproliferative response of splenic lymphocytes to various mitogens, antibody plaque-forming cell response to antigens and other immune function parameters (Exon et al., 1991; Smialowicz et al., 1991a,b, 1992a,b, 1993; Riddle et al., 1992, 1996; Williams et al., 1995). In addition, thymus weights were decreased in most studies (at doses as low as 25 mg/kg body weight per day); occasionally, reductions in spleen weights or cellularity were also observed. In mice, however, there was no consistent evidence of immunosuppression at repeated doses of up to 1000 mg 2-methoxyethanol/kg body weight per day or 1920 mg methoxyacetic acid (MAA)/kg body weight per day, although decreased thymus weights were observed, and there was evidence of enhancement or modulation of immune system response in some studies (House et al., 1985; Kayama et al., 1991; Riddle et al., 1992, 1996; Smialowicz et al., 1992b, 1994). The results of studies in rats in which enzyme inhibitors were administered indicated that the parent compound was not in itself immunotoxic, but that both the aldehyde and acid metabolites (MALD: 2-methoxy-acetaldehyde and MAA: methoxyacetic acid) suppressed immune system function (Smialowicz et al., 1991a,b, 1993).

Neurotoxicity (WHO, 2008)

Although the database is limited to two studies in rats and a single study in mice, 2-methoxyethanol appears to induce neurological effects following acute or short-term inhalation exposure, including inhibition of conditioned avoidance response, increased barbiturate-induced sleeping time or partial hindlimb paralysis, at concentrations of 395 mg/m^3 or greater and altered enzyme activities in the brain at 160 mg/m^3 or more (Goldberg et al., 1962; Savolainen, 1980). Repeated exposure of pregnant rats to 79 mg/m^3 induced effects on avoidance conditioning and neurochemical changes in the offspring (Nelson et al., 1984b).

3.3. Risk Characterisation

For the summaries on effects assessments it is referred to chapters 4, 5 and 7 of this SVHC dossier for the exposure assessment please see part 1.3 of this section.

3.3.1. Environment

According to WHO, 2009 the concentrations of 2-methoxyethanol in air, water and soil in Canada are unlikely to cause adverse effects on populations of wildlife, soil and aquatic organisms.

Terrestrial wildlife: The estimated exposure value (0.146 ng/m^3) was compared with the critical toxicity value (3.2×10^7 ng/m^3, Hanley et al., 1984 a,b). To the critical toxicity value (CTV) an uncertainty factor of 10 was applied to account for the extrapolation from laboratory to field conditions and inter/intra species variation. The **estimated no-effect value** (PNEC) is **3.2×10^6 ng/m^3** (= 3.2 mg/m3).

Risk quotient: 0.146 ng/m^3/3.2×10^6 ng/m^3 = 4.6×10^{-8}

Maximum reported concentrations of EGME in indoor air was reported from a study conducted in Germany (220 µg/m^3; Schriever & Marutzky, 1990), which is well below the estimated no-effect value.

Soil organism: The estimated exposure value (9.4×10^{-4} ng/g dry weight) was compared with the hazardous concentration 5% of benthic organism HC_5 (estimated 1800 ng EGME/g, Van Leeuwen et al., 1992). To the HC_5 an uncertainty factor of 100 was applied to account for the extrapolation from benthic to soil organisms. The estimated **no-effect value** (PNEC) is **18 ng/g** for soil organism.

Risk quotient: 9.4 × 10-4 ng/g / 18 ng/g = 5.2×10^{-5}

Aquatic organisms: The estimated exposure value (4.8×10^{-5} ng/g dry weight) was compared with the 2-day toxicity threshold for *Chilomonas paramecium* (2200 µg/L), based on inhibition of cell multiplication. To the CTV an uncertainty factor of 10 was applied to account for the extrapolation from laboratory to field conditions and inter/intra species variation. The estimated **no-effect value** (PNEC) is 18 ng/g for soil organism.

Risk quotient: 4.8×10^{-5} µg/L/220 µg/L = 2.2×10^{-7}

3.3.2. Human Health

Derivation of DNELs for developmental toxicity and haematological effects

For long-term systemic toxicity the developmental and haematological effects were identified as most critical.

Workers

For developmental effects the lowest NOAEC = 9.3 mg/m^3 (3 ppm) could be derived from an inhalation study in rabbits (Hanley et al., 1984b). According to the REACH guidance (Chapter R.8) this NOAEC has to be corrected for exposure duration:

$_{corr}$NOAEC = $_{inhal}$NOAEC ***** 6h/day / 8h/day ***** 6.7 m^3 (8h) / 10 m^3 (8h)

$_{corr}$NOAEC = 9.3 mg/m^3 ***** 6h/day / 8h/day ***** 6.7 m^3 (8h) / 10 m^3 (8h)

$_{corr}$NOAEC = 4.7 mg/m^3

For haematological effects a NOAEC of 1.7 mg/m^3 (0.55 ppm) could be derived from a study in humans (Shih et al., 2003). No correction factor for exposure duration is needed, as the value is derived from workers exposed at a typical workplace situation (8 hour shift).

$DNEL_{long\text{-}term,\ inhalation,\ systemic}$

- developmental effects:

The corrected NOAEC of 4.7 mg/m^3 is used as starting point. For worker intraspecies variability an assessment factor of 5[21] is applied, for interspecies differences the assessment factor of 6 (rabbit to human) is applied.

$$\text{Worker DNEL}_{long\text{-}term,\ inhalation,\ systemic} = \frac{4.7\ mg/m^3}{5 * 6} = 0.16\ mg/m^3$$

- haematological effects:

The NOAEC of 1.7 mg/m^3 is used as starting point. The only assessment factor is needed for variability among workers = 5.

$$\text{Worker DNEL}_{long\text{-}term,\ inhalation,\ systemic} = \frac{1.7\ mg/m^3}{5} = 0.34\ mg/m^3$$

It should be noted that the derived DNELs are calculated for light work load.

[21] 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.

General population

To correct for exposure duration for the general population the NOAECs have to be adapted to a 24 hour exposure (according to REACH guidance Chapter R.8).

For developmental toxicity the NOAEC of 9.3 mg/m^3 (3 ppm) from an inhalation study in rabbits (Hanley et al., 1984a,b) was applied:

$_{corr}NOAEC = {}_{inhal}NOAEC_{rabbit}$ ***** 6h/day / 24h/day

$_{corr}NOAEC$ = 9.3 mg/m^3 ***** 6h/day / 24h/day

$_{corr}NOAEC$ = 2.3 mg/m^3

For haematological effects the NOAEC of 1.7 mg/m^3 from the study in human workers (Shih et al., 2003) was identified:

$_{Corr}NOAEC = {}_{inhal}NOAEC_{human}$ ***** 8h/day / 24h/day

$_{Corr}NOAEC$ = 1.7 mg/m^3 ***** 8h/day / 24h/day

$_{Corr}NOAEC$ = 0.57 mg/m^3

DNEL $_{long\text{-}term\ for\ inhalation\ route,\ systemic}$

- developmental effects:

The corrected NOAEC of 2.3 mg/m^3 is used as starting point. An assessment factor for interindividual variation of 10 and a factor for interspecies differences of 6 (rabbit to human) have to be applied.

$$\text{General population DNEL}_{\text{long-term, inhalation, systemic}} = \frac{2.3\ \text{mg/m}^3}{10 * 6} = 0.04\ \text{mg/m}^3$$

- haematological effects:

The corrected NOAEC of 0.57 mg/m^3 is used as starting point. The only assessment factor needed is 10 for interinidivdual variability within the general population.

$$\text{General population DNEL}_{\text{long-term, inhalation, systemic}} = \frac{0.57\ \text{mg/m}^3}{10} = 0.057\ \text{mg/m}^3$$

Justification for the applied assessment factors

Correction for Duration

The results of the developmental study and the study in human workers were adapted to the appropriate duration using the formulas recommended in guidance R.8.

For the worker DNEL the rabbit data, which were generated in experiments using daily exposure durations of 6 hours, were transformed to the duration of a working day (i.e. 8 hours). The data generated in humans did not have to be adapted, as they were derived from workers exposed at a typical workplace situation (8 hour shift).

For the general population DNEL the results had to be adapted to an exposure duration of 24 hours.

Interspecies Correction

An interspecies factor of 6 is applied to extrapolate from animals (rabbit) to humans. No inter-species factor is necessary for the NOAEL of 1.7 mg/m^3 from the study in humans.

Intraspecies Correction

Human studies cover at least some of the human inter-individual variability. The REACH guidance Chapter R.8 recommends assessment factors between 2 to 5[22] and 2 to 10 for workers and general population, respectively when using human data. With only 25 males and 5 females participating in the study on workers occupationally exposed to EGME human variability is insufficiently covered. No deviation from the default values of 5 and 10 is therefore introduced.

Nature and severity of effect

The effects seen at 10 ppm can be regarded as slightly adverse, as they are presumed to be of reversible nature. The use of 3 ppm as NOAEC is therefore considered conservative, to address the steep exposure effect relationship. No extra assessment factor for the severity and nature of the effect was applied.

Conclusion on DNELs

The results of long term toxicity tests on EGME indicate that developmental and haematological effects are the most critical effects.

From an inhalation study in rabbits (Hanley et al., 1984b) the lowest NOAEC of 9.3 mg/m^3 (3 ppm) for developmental toxicity could be derived. This is based on delayed sternebral ossification observed at the next higher concentration (31.1 mg/m^3 or 10 ppm). At 155.5 mg/m^3 (50 ppm) significant multiple organ system teratogenic effects were observed, indicating a very steep dose effect relationship. ECETOC (ECETOC, 2005) and INRS (Demeter, 2008) used 3 ppm as NOAEC based on delayed ossification in the 10 ppm group.

For the present dossier the NOAEC of 9.3 mg/m^3 (3 ppm) for developmental effects was used as starting point for the derivation of long-term DNELs for the inhalation route:

0.16 mg/m^3 (0.05 ppm) for **workers** performing light work and **0.04 mg/m^3** (0.013 ppm) for the **general population.**

[22] 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.

DNELs were also derived for haematological effects observed in workers (Shih et al. 2003). However, the derived values were higher than for developmental effects and therefore not used as the leading DNELs.

The DNELs in the present dossier are lower, but in the same range as other critical exposure levels. The biggest distance is found in relation to the IOELV.

Most organisations that evaluated the toxicity of 2-methoxyethanol relied on either developmental toxicity or haematological effects to derive critical exposure levels. When using the developmental effects as basis for the critical exposure values, some organisations used 10 ppm (e.g. WHO) others 3 ppm (e.g. ECETOC, INRS) as starting point. The following paragraphs give an overview on the different exposure levels derived.

Following the recommendation of the Scientific Committee on Occupational Exposure Limits for 2-methoxyethanol (SCOEL, 2006) SCOEL recommends a health based **OEL of 1 ppm** (3.11 mg/m^3). This value is based on haematological effects observed in workers exposed to 4 ppm (Shih et al., 1999), while no effects were recorded at 2.3 ppm (Shih et al., 2003). The SCOEL group regarded this value to be protective also against reproductive effects. No irritation or other immediate effects occur near this value, hence no STEL value is deemed necessary.

EGME is listed in Directive 2009/161/EU establishing a third list of indicative occupational exposure limit values in implementation of Council Directive 98/24/EC with an **IOELV of 1 ppm** (8 hour TWA, skin notation) and a BLV of 8 mg MAA per gram creatinine, in urine samples at the end of work after at least two weeks at work. It is noted, that the IOELV (1 ppm equivalent to 3.11 mg/m^3) clearly exceeds the DNELs derived in the present dossier.

The WHO, 2009 (WHO, 2009) derived a tolerable concentration of **0.08 mg/m^3** (0.03 ppm) based on the NOAEC of 31.1 mg/m^3 (10ppm, Hanley et al., 1984b) for developmental effects. They applied the IPCS default uncertainty factors (IPCS, 1994) of 10 for interspecies and 10 for intraspecies extrapolation and corrected to continuous exposure (6/24 h). In addition, the WHO derived a tolerable concentration of **0.04 mg/m^3** based on the NOAEC of 1.7 mg/m^3 for haematological effects in workers, adjusting for continuous exposure and applying an uncertainty factor of 10 for interindividual variation.

Comparing monitoring data with tolerable threshold concentration

Very few monitoring data from Austrian workplaces have obtained exceedence of Austrian limit values, the IOELV and the herein derived DNELs. Results from exposure measurements from the COLCHIC database from INRS conducted between 2000 and 2006 indicate EGME median/mean concentrations of 0.15 / 0.29 mg/m^3 (AFSSET report, 2008). The EGME concentration of 0.29 mg/m^3 is lower than the IOELV, but higher than the DNEL$_{\text{long-term inhalation}}$ of 0.16 mg/m^3 derived herein for the worker population. Some measurements have been conducted (2000 – 2006) in the chemical industry, rubber and plastic sector, and the building of transport materials. The mean EGME concentrations are in the range of 0.1 and 0.5 mg/m^3. Again the mean values of 0.5 mg/m^3 is lower than the IOELV, but higher than the herein derived DNEL$_{\text{long-term inhalation}}$ for workers.

Consumers

For consumers and workers risk indices were calculated for consumers and workers exposed to reprotoxic glycol ethers (GE) in domestic and industrial activities (Cicolella, 2006). A risk index (RI) was calculated for two scenarios (maximal and minimal) using the following equation:

RI = DD (estimated daily dose)/ RfDD (reference dose for developmental effects).Very high figures in the range 1000–10000 have been found for popular consumer goods, such as water-based paints (0.9% EGME), window cleaner (4% EGME + 15% EGEE), and parquet floor varnish (32% EGEE).

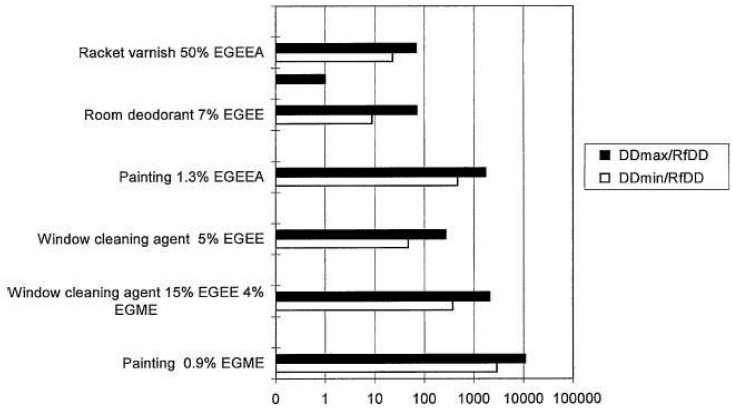

FIGURE 1. Developmental toxicity risk index for consumers adapted from Cicolella.[4]

Figure 1

It was obvious therefore that pregnant consumers or workers exposed in these conditions have long been at risk, even when using products with glycol ether respecting the EU 0.5% concentration limit in consumer products. French Higher Council of Public Health (CSHPF) issued a report on risk due to exposure to 0.5% in domestic products and concluded similarly that 0.5% level recommended by EU in domestic products was inadequate to protect consumers' health (Cicolella, 2006).

The WHO, 2009 concluded that available data are insufficient to conclude that margins are adequate between estimates of exposure from consumer products and levels that have been associated with haematological effects in workers and between these exposure levels and lowest effect levels identified in laboratory animal studies. These estimates are extreme worst case and have not been validated (WHO, 2009).

In the following section we have included an exposure estimation for theoretical consumer products containing 0.5% EGME.

Estimation of exposure resulting from the application of consumer products containing 0.5% EGME

Inhalation exposure

Reasonable worst-case assumption: Inhalation of saturated air:

The saturation concentration of 2-methoxyethanol in air is estimated from following equation (ideal gas law):

$W = (1000*P*V*M) / (R*T)$

where W is the concentration in air (mg/m^3)

P is the vapour pressure (1300 Pa at 25°C) (Riddick et. al, 1986)

V is the volume of air (1 m^3)

M is the molecular weight (76.1 g/mol)

R is the gas constant (8.314 J/mol/K)

T is the temperature (298 K ~ 25°C)

Tier 1: Using the values listed above, the saturation concentration of 2-methoxyethanol in air is calculated to be 39930 mg/m^3. Assuming that 2-methoxyethanol is saturated in air due to gaseous release as a conservative assumption, an inhalation rate of 1.25 m^3/h, an inhalation absorption of 100% and a duration of exposure of 8 hours, results in a systemic exposure level of 399302 mg 2-methoxyethanol/d. Considering a bodyweight of 60 kg (default, adult), results in 6655 mg/kg bw/d.

$$39930\ mg/m^3 \times 1.25\ m^3/h \times 8h/d \times 1 / 60\ kg = 6655\ mg/kg\ bw/d$$

Scenario: Application of 2-methoxyethanol for painting

According to Cicolella *et* al., 2006 EGME was used for painting in a concentration of 0.9%. In order to question if a risk for workers and consumers exists at a "theoretical" concentration of 0.5% EGME in paints was assumed.

1. **Inhalation exposure: Assumption of total release**

The calculation of the 2-methoxyethanol concentration in air is based on the following assumptions.

Applied amount of product: 400 g (estimate of the assessor)

Concentration of 2-methoxyethanol in product: 0.5% w/w

Room volume: 58 m^3 (default, ConsExpo 4.1)

Referring to the values given above, this results in a concentration of 34.48 mg/m^3 in air

$$400\ g \times 0.005 \times 1000\ (\text{conversion g to mg}) / 58\ m^3 = 34.48\ mg/m^3$$

Tier 1: Assuming the derived concentration of 2-methoxyethanol in air, an inhalation rate of 1.25 m^3/h, an inhalation absorption of 100% and a duration of 8h exposure, results in a systemic exposure level of 17.2 mg 2-methoxyethanol/d. Considering a bodyweight of 60 kg, results in 5.747 mg/kg bw/d.

$$1.72\ mg/m^3 \times 1.25\ m^3/h \times 8h/d \times 1\ /60\ kg = 5.747\ mg/kg\ bw/d$$

2. Dermal exposure: Exposure of both hands

Tier 1: Assuming one event per day of dermal exposure of both hands (840 cm^2, default, surface area of both hands of an adult), a thickness of 0.01 cm of film on skin (thin layer model), a concentration of 0.5 % w/w present in product (density: 1000 mg/cm^3; default, density of pure water) and a dermal absorption of 100%, results in a systemic exposure level of 42 mg/d via the dermal route. Considering a bodyweight of 60 kg, results in 0.700 mg/kg bw/d.

$$1 \times 840\ cm^2 \times 0.001\ cm \times 1000\ mg/cm^3 \times 0.005 \times 1\ /60\ kg = 0.700\ mg/kg\ bw/d$$

3. Combined exposure

Considering operators are exposed via the inhalation and the dermal route, combination of the first and the second scenario results in 6.447 mg/kg bw/d (5.747 + 0.700).

Scenario: Application of 2-methoxyethanol for window-cleaning

According to Cicolella *et* al., 2006 EGME was used for window cleaning at a concentration of 4% (in combination with EGGE 15%). In order to question if a risk for workers and consumers exists at a "theoretical" concentration of 0.5% EGME in window-cleaning agents was assumed.

1. Inhalation exposure: Assumption of total release

The calculation of the 2-methoxyethanol concentration in air is based on the following assumptions.

Applied amount of product: 20 g (estimate of the assessor)

Concentration of 2-methoxyethanol in product: 0.5% w/w

Room volume: 58 m^3 (default, ConsExpo 4.1; Cleaning and Washing→ All purpose cleaners→ liquid cleaner→ application)

Referring to the values given above, this results in a concentration of 1.72 mg/m^3 in air

$$20\ g \times 0.005 \times 1000\ (\text{conversion g to mg}) / 58\ m^3 = 1.72\ mg/m^3$$

Tier 1: Assuming the derived concentration of 2-methoxyethanol in air, an inhalation rate of 1.25 m^3/h, an inhalation absorption of 100% and a duration of 8h exposure, results in a systemic exposure level of 17.2 mg 2-methoxyethanol/d. Considering a bodyweight of 60 kg, results in 0.287 mg/kg bw/d.

$$1.72\ mg/m^3 \times 1.25\ m^3/h \times 8h/d \times 1\ /60\ kg = 0.287\ mg/kg\ bw/d$$

2. Dermal exposure: Exposure of both hands

Tier 1: Assuming one event per day of dermal exposure of both hands (840 cm^2, default surface area of both hands of an adult), a thickness of 0.01 cm of film on skin (thin layer model), a concentration of 0.5 % w/w present in product (density: 1000 mg/cm^3; default, density of pure water) and a dermal absorption of 100%, results in a systemic exposure level of 42 mg/d via the dermal route. Considering a bodyweight of 60 kg, results in 0.700 mg/kg bw/d.

$$1 \times 840\ cm^2 \times 0.001\ cm \times 1000\ mg/cm^3 \times 0.005 \times 1 / 60\ kg = 0.700\ mg/kg\ bw/d$$

3. Combined exposure

Considering operators are exposed via the inhalation and the dermal route, combination of the first and the second scenario result in 0.987 mg/kg bw/d (0.287 + 0.700).

Conclusion:

The exposure from two applications (cleaning, painting) for EGME have been calculated for following consumer products: window-cleaning agent and paint. A theoretical concentration of 0.5% EGME was assumed to evaluate a potential risk for consumers. Additionally, it is important to note, that the all used EGME from the product will enter the gas-phase, as the substance reveals a high volatility as demonstrated in the reasonable worst case scenario (saturated air) and the applied amounts are expected to release gaseous residues during drying (paints, detergents).

The calculated EGME concentration in air for both scenarios are: For window-cleaning a EGME concentration of 1.72 mg/m^3 and for painting: 34.48 mg/m^3 was calculated. Furthermore, it needs to be stressed that inhalation exposure via spraying of paints and window cleaner was not assessed for these activities (generation of inhalable aerosols). Considering also this source of exposure, the contribution would result in even higher EGME exposure levels. The dermal exposure would further contribute to total systemic exposure.

Comparing the EGME concentration (1.72 mg/m^3 and 34.48 mg/m^3) in air from these two scenarios (cleaning, painting) with the $DNEL_{long\text{-}term\ inhalation}$values from workers (0.16 mg/m^3) or with the $DNEL_{long\text{-}term\ inhalation}$values from the general population (0.04 mg/m^3), consumers and professional users are at risk even if the concentration of EGME is only 0.5 % in window-cleaning agents or paints.

Humans exposed via the environment (WHO, 2009)

Monitoring data for the general population to 2-methoxyethanol are limited. Although relevant data are limited, exposure of the general population through environmental media is expected to be low, as a result of reported classification and declining use of the compound in recent years as it is replaced with less hazardous compounds (WHO, 2009). Margins between worst-case estimates of exposure from environmental media and levels identified at which haematological parameters had returned to normal in exposed workers are considered adequate, as are those between exposure estimates and lowest effect levels for developmental toxicity obtained in toxicological investigations in laboratory animals.

The worst-case exposure level in air in Canada (5 μg/m3) is 13% of the tolerable concentration derived from the studies in Taiwan, China. An even greater margin (6%) exists between this upper exposure level in Canadian air and the tolerable concentration derived from the developmental toxicity in rats, mice or rabbits (Hanley et al., 1984a,b). With respect to ingestion, no epidemiological investigations of the effects of ingested 2-methoxyethanol in humans were identified. However, the margin between the intake (14 μg/kg body weight) equivalent to inhalation of 2-methoxyethanol at a concentration of 40 $\mu g/m^3$ (assuming a daily inhalation volume of 22 m3, a body weight of 64 kg (IPCS, 1994) and 100% absorption) and the worst-case exposure scenario for ingestion of 2-methoxyethanol in drinking-water (0.013 μg/kg body weight per day), assuming a

2-methoxyethanol concentration of 0.6 µg/l in drinking-water, daily water consumption of 1.4 litres and a body weight of 64 kg (IPCS, 1994), is about 3 orders of magnitude.

Overall conclusion to chapter 3

As noted above, the information presented in this chapter is based on available data collected by the submitting Member States and a rough assessment by experts. From this assessment it is confirmed that the workplace exposure of EGME represents a major area of concern. Even though the use and, consequently, exposure of EGME has significantly decreased during the last years (mainly due to substitution measures by industry), the available monitoring data at workplace show that measurable concentrations of EGME can still be found in certain areas of use. An indicative occupational exposure value (IOELV) has been set on the basis of Council Directive 98/24/EC. Some monitored exposure levels have been found above this value. In addition, a preliminary assessment of effects data indicate that the IOELV may not be sufficiently protective for all situations. These findings clearly support the need for additional risk management measures as are proposed in the present dossier, aiming at a progressive substitution of the substance by non-SVHC alternatives.

It should also be noted that a potential risk was identified for consumers´ use in paint and window cleaning agents. The calculation was based on a content of 0.5 % of EGME in the product, with 0.5% being the limit for consumer restrictions according to Annex XVII of the REACH Regulation.

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