European Union Risk Assessment Report

1-METHOXYPROPAN-2-OL

(PGME)

CAS No: 107-98-2

EINECS No: 203-539-1

RISK ASSESSMENT

Final human health risk assessment

LEGAL NOTICE

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Final human health draft

October 2008

FRANCE

Rapporteur for the risk assessment of 1-methoxypropan-2-ol is the Ministry of Spatial Planning and the Environment as well as The Ministry of Employment and Social Affairs in co-operation with the Ministry of Public Health. Responsible for the risk assessment and subsequently for the contents of this report is the rapporteur.

The scientific work on this report has been prepared by the National Institute for Research and Security (INRS – occupational exposure, health effect section and occupational risk characterisation), the National Institute for Industrial Environment and Risks (INERIS – ecotoxicology sections) and Centre de toxicovigilance de Grenoble (consumers sections), by order of the rapporteur.

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Foreword

This Draft Risk assessment Report is carried out in accordance with Council Regulation (EEC) 793/93[1] on the evaluation and control of the risks of "existing" substances. "Existing" substances are chemical substances in use within the European Community before September 1981 and listed in the European Inventory of Existing Commercial Chemical Substances. Regulation 793/93 provides a systematic framework for the evaluation of the risks to human health and the environment of these substances if they are produced or imported into the Community in volumes above 10 tonnes per year.

There are four overall stages in the Regulation for reducing the risks: data collection, priority setting, risk assessment and risk reduction. Data provided by Industry are used by Member States and the Commission services to determine the priority of the substances which need to be assessed. For each substance on a priority list, a Member State volunteers to act as "Rapporteur", undertaking the in-depth Risk Assessment and recommending a strategy to limit the risks of exposure to the substance, if necessary.

The methods for carrying out an in-depth Risk Assessment at Community level are laid down in Commission Regulation (EC) 1488/94[2], which is supported by a technical guidance document[3]. Normally, the "Rapporteur" and individual companies producing, importing and/or using the chemicals work closely together to develop a draft Risk Assessment Report, which is then presented at a Meeting of Member State technical experts for endorsement. The Risk Assessment Report is then peer-reviewed by the Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE) which gives its opinion to the European Commission on the quality of the risk assessment.

This Draft Risk Assessment Report is currently under discussion in the Competent Group of Member State experts with the aim of reaching consensus. During the course of these discussions, the scientific interpretation of the underlying scientific information may change, more information may be included and even the conclusions reached in this draft may change. The Competent Group of Member State experts seek as wide a distribution of these drafts as possible, in order to assure as complete and accurate an information basis as possible. The information contained in this Draft Risk Assessment Report does not, therefore, necessarily provide a sufficient basis for decision making regarding the hazards, exposures or the risks associated with the priority substance.

This Draft Risk Assessment Report is the responsibility of the Member State rapporteur. In order to avoid possible misinterpretations or misuse of the findings in this draft, anyone wishing to cite or quote this report is advised to contact the Member State rapporteur beforehand.

[1] O.J. No L 084, 05/04/199 p.0001 – 0075

[2] O.J. No L 161, 29/06/1994 p. 0003 – 0011

[3] Technical Guidance Document, Part I – V, ISBN 92-827-801 [1234]

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0 OVERALL RESULTS OF THE RISK ASSESSMENT[4]

CAS Number: 107-98-2
EINECS Number: 203-539-1
IUPAC Name: 1-methoxypropan-2-ol

Environment

Human health

Human health (toxicity)

Workers

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

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 cleaining (spraying, wiping), for printing (silk screening, flexography).

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

4 Conclusion (i) There is a 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.

Consumers

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.

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) 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.

Human health (physico-chemical properties)

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.

CONTENTS

EUSES Calculations can be viewed as part of the report at the website of the European Chemicals Bureau: http://ecb.jrc.it

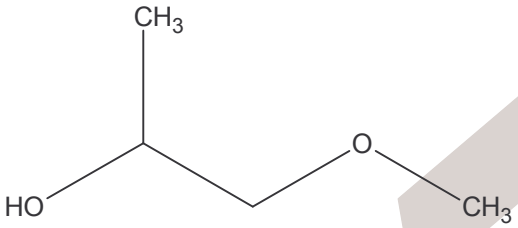
TABLES

1 GENERAL SUBSTANCE INFORMATION

1.1 IDENTIFICATION OF THE SUBSTANCE

CAS Number: 107-98-2
EINECS Number: 203-539-1
IUPAC Name: 1-methoxypropan-2-ol
Molecular formula: $C_4H_{10}O_2$

Structural formula:



Molecular weight: 90.1 g/mol
Synonyms: 1-methoxy-2-hydroxypropane; 1-methoxy-2-propanol; 1-methoxypropanol-2; 1-methoxypropane-2-ol; 2-methoxy-1-methylethanol; 2-propanol-1-methoxy; methoxy Propanol; methoxypropanol; monomethyl ether of propylene glycol; monopropylene glycol methyl ether; PGME; propylene glycol methyl ether; propylene glycol monomethyl ether; éther 1-méthylique d'alpha-propylèneglycol; éther monométhylique du propylène-glycol

In this assessment, the name PGME will be used for the substance, as this is the more common name.

1.2 PURITY/IMPURITIES, ADDITIVES

The commercially supplied product is usually a mixture of two isomers 1-methoxypropan-2-ol (PGME, alpha isomer) and 2-methoxypropan-1-ol (beta isomer, CAS n°1589-47-5).

PGME is the main compound, totalizing 99.5 % of the product with less than 0.5 % of 2-methoxypropan-1-ol, considered as an impurity.

No additive is contained in the marketed product.

1.3 PHYSICO-CHEMICAL PROPERTIES

At ambiant temperature and pressure, PGME is a colourless liquid with an ether-like odour.

1.3.1 Melting point

The melting point of PGME ranges from –100°C to –95°C (BASF, 2001 ; BP, 2000 ; DOW, 2001 ; LYONDELL, 1999). A producer used an ASTM D-97 method reporting a result of -96°C (SHELL, 2000). The test reports are not available.

In Ullmann's encyclopedia of industrial chemistry (1991), a value of -96°C for the melting point was reported.

A median value of –96°C has been calculated with the above data. This value will be used for the risk assessment.

1.3.2 Boiling point

The boiling point of PGME ranges from 117 to 122°C (BASF, 2001 ; BP, 2000 ; DOW, 2001 ; LYONDELL, 1999). A producer used an ASTM D-1078 method reporting values ranging from 117 to 125°C (SHELL, 2000). However, the test reports are not available.

In Ullmann's encyclopedia of industrial chemistry (1991), a value of 120.1°C for the boiling point was reported at 1013 hPa.

A median value of 120°C has been calculated using the above data. This value will be used for the risk assessment.

1.3.3 Relative density

The density of PGME ranges from 0.920 to 0.926 g/cm^3 at 20°C (BASF, 2001 ; BP, 2000; DOW, 2001). A producer used an ASTM D-4052 method reporting values ranging from 0.92 to 0.923 g/cm^3 (SHELL, 2000). At 25°C, a value of 0.92 g/cm^3 for the density of PGME was reported; (LYONDELL, 1999). However, the test reports are not available.

In Ullmann's encyclopedia of industrial chemistry (1991), a value of 0.923 for the density was reported at 20°C.

A median value of 0.921 g/cm^3 has been calculated using the above data. This value will be used for the risk assessment.

1.3.4 Vapour pressure

The vapour pressure of PGME ranges from 10 to 13.3 hPa at 20°C (BASF, 2001; BP, 2000; DOW, 2001; SHELL, 2000). At 25°C, a vapour pressure of 14.5 hPa is reported (LYONDELL, 1999). No test report is available.

A median value of 11.6 hPa at 20°C has been calculated using the above data. At 25°C, the value of 16.4 hPa has been calculated. This value will be used for the risk assessment.

1.3.5 Surface tension

A surface tension of 47.3 mN/m is reported by one producer. The concentration of the substance in water was 20 %. The surface tension was also measured at higher concentrations (BP, 1998) and si reported below:

Table 1.1: Surface tension at 20°C

Concentration (% product in water)	Surface tension (mN/m) at 20°C
20	47.3
40	40.6
60	35.8
80	32.7
100	29.6

Surface active properties can be assumed for glycol ethers. The values reported in the literature for PGME tend to indicate that this substance is a surface active reagent. Indeed, OECD guideline n°115 suggests that surface tension measurements should be performed using a concentration of 1 g/L for soluble substances.

The fact that glycol ethers show surface active properties could thus lead to the disturbance of analytical method employed to measure some physico-chemical characteristics of glycol ethers.

However, there is a difference between the surface activity of traditional surfactants and substances that can reduce the surface activity of solutions like PGME. What is observed with the glycol ethers during the surface tension measurements is the typical non ideal behaviour of a mixture of a water miscible solvent such as methanol and ethanol. The reason for the observed relationship between surface tension and concentration is the disruption of the hydrogen bonding of the water causing non-linear behaviour of the surface tension against the concentration. In this case the substance is not migrating to the surface; it is not acting in the traditional surface active manner. Therefore it would not affect the measurements of the physical chemical properties. One should also noticed that glycol ethers do not form micelles. They are fully miscible with water and form clear solutions.

Furthermore, considering the other properties of this substance (PGME is highly miscible in water, hydrosphere is the preferential target of PGME in the environment: >90), surface active properties of PGME will not be considered in this assessment. At worst, this could lead to an overestimation of the risks calculated for the aquatic compartment.

1.3.6 Water solubility

PGME is fully miscible with water (BASF, 2001; BP, 2000; DOW, 2001; LYONDELL, 1999; SHELL, 2000).

The value of 100 g/l for the solubility of PGMA was reported. According to the chemical structure, PGME should be more soluble. Staples and Davies used a solubility of 500 g/l in their report. Therefore this value of 500 g/l will be retained for the risk assessment.

1.3.7 Henry's law constant

Values of 0.002-0.087 Pa.m^3/mol were calculated at 25°C (BUA, 1995).

Staples and Davies (2002) calculated an Henry's law constant of 0.28 Pa.m^3/mol from aqueous solubility and vapour pressure using a solubility of 500,000 mg/l and a vapor pressure of 1573 Pa.

The Henry's law constant was also estimated using a structure activity relationship (HenryWin v3.10, US EPA and Syracuse Research Corporation, 2001). Calculated values ranged from 0.0018 Pa.m^3/mol (group method) to 0.0056 Pa.m^3/mol (bond method).

The Henry's law constant can be calculated using selected values of this report. The resulting value is 0.29 Pa.m^3/mol.

An average value of 0.12 Pa.m^3/mol has been calculated using the above data. This value will be used for the risk assessment.

1.3.8 Partition coefficient octanol water

A log P_{OW} value was determined by reverse-phase HPLC by Pearson (1986). The HPLC system used was a reverse-phase C_{18}-coated silica gel column with a mobile phase of 3 volumes methanol and 1 volume water (final pH 6.8). Samples of an approximate 1 mg/ml solution in the above mobile phase were injected and the emergence of the material observed using refractive index detection. From the retention time of the peak the log P_{OW} value was determined. Fourteen reference substances with log P_{OW} ranging from 0.94 to 5.88 were used to generate a linear relationship between the retention time and log P_{OW} and to determine log P_{OW} of PGME.

Pearson (1986) also calculated a log P_{OW} value from chemical structure using the fragment addition method of Hansch and Leo (1979).

The log n-octanol/water partition coefficient value of PGME was determined by both reverse-phase HPLC and the Fragment-addition method to be < 1.

Gonsior (1990) also estimated a log P_{OW} value using the Pomona-Med Chem Structural fragment method. A value of –0.43 was reported.

Using a QSAR (US EPA and Syracuse Research Corporation, 2001: KOWWIN v1.66), a log P_{OW} value of –0.49 was estimated. This value will be used for the risk assessment.

1.3.9 Other physical-chemical properties

1-methoxypropan-2-ol has a low odour threshold. An odour threshold (the level at which 50% of an odour panel can detect the odour) of 0.03 mg/m^3 has been determined in a panel with 6 volunteers (Danish EPA/ dk-Teknik 1992).

1.3.9.1 Flash point

The flash point of PGME ranges from 30°C to 35°C (BASF, 2001; BP, 2000; DOW, 2001; LYONDELL, 1999; SHELL, 2000). The test reports are not available.

In Ullmann's encyclopedia of industrial chemistry (1991), a value of 38°C for the flash point was reported.

A median value of 32°C has been calculated using the above data. This value will be used for the risk assessment.

1.3.9.2 Autoflammability

Decomposition of PGME starts at temperature ranging from 270°C to 290°C (BASF, 2001; BP, 2000; DOW, 2001; LYONDELL, 1999; SHELL, 2000). The test reports are not available.

A median value of 278°C has been calculated using the above data. This value will be used for the risk assessment.

1.3.9.3 Oxidising properties

There are some references which suggest that glycol ethers can be prone to the formation of peroxides on storage. However data from one of the producers, shown below, indicates that peroxide levels for PGME remain virtually unchanged, even during prolonged storage under adverse conditions, as shown in table 1.2.

Table 1.2: Peroxide levels in PGME during storage under adverse (daylight) and recommended (dark) conditions. No antioxidants used. Results in mmol active oxygen/litre

	In daylight	In the dark
Time 0	0.013	0.013
3 months	0.006	0.005
18 months	0.018	

The National Fire Protection Association's code for the reactivity of PGME is 0 indicating minimal hazard. In consequence, there is no requirement for classification R19.

1.3.10 Summary

Table 1.3: Summary of physico-chemical properties

Property	Value
Physical state	Liquid
Melting point	-96°C
Boiling point	120°C
Relative density	0.921 g/cm^3
Vapour pressure	16.4 hPa at 25°C
Water solubility	Fully miscible, 500 g/l
Partition coefficient n-octanol/water (log value)	-0.49
Flash point	32°C
Autoflammability	278°C
Henry's constant	0.12 Pa.m^3/mol

1.4 CLASSIFICATION

1.4.1 Current classification

PGME is classify for physico chemical properties only. No classification for health effects.

R10

S2-24

1.4.2 Proposed classification

Unchanged

R10 – R67

S2-24

2 GENERAL INFORMATION ON EXPOSURE

3 ENVIRONMENT

4 HUMAN HEALTH

4.1 HUMAN HEALTH (TOXICITY)

4.1.1 Exposure assessment

4.1.1.1 General discussion

Humans may be exposed to PGME at workplace, via consumer products and indirectly via the environment (i.e. ingestion of surface water). The highest potential exposure is likely to occur during occupational exposure.

Workers and consumers are primarily exposed via inhalation and dermal routes. PGME is readily absorbed through the skin including absorption from direct contact with liquid or aerosol form or contact with vapours. Because this compound has a relatively low vapour pressure (1.16 kPa at 20°C), dermal exposure from direct contact with the liquid may contribute significantly to overall exposure.

Exposure may occur during manufacture and use as intermediate in the chemical industry, and during formulation and use of products. PGME is a solvent used in many industrial activities or consumer applications. Over the past two decades, ethylene glycol methyl ether and ethylene glycol ethyl ether have progressively been replaced by propylene glycol derivatives. The main uses of PGME are in paints or surface coatings (solvent-based or water-based), followed by cleaners and printing inks. Other minor uses reported are solvent in the electronic industry, in cosmetics/personal care (capillary tinting, nail-varnish removers), leather finishing agents, adhesives, agricultural and oil field chemicals.

According to the SIDS initial assessment profile (2001), PGME is used in the manufacture of PGME acetate as well as in a wide variety of industrial and commercial products, including paints and varnishes (30% for surface coatings), printing inks (6%), cleaners (23%), adhesives and electronics (7%).

In the Swedish product register (KEMI, 2002), 906 products containing PGME (of which 250 were private household products) have been identified : 59 % are paints (or hardeners for paints), varnishes or adhesives, 9 % cleaning agents, 5 % dyestuffs and 5 % diluents.

In the Danish product register (Arbejdstilsynet, 2001), 3387 products containing PGME have been identified,. The most common uses were paints, lacquers and varnishes (74 %), solvents (4 %), cleaning/washing agents (5 %) and process regulators (4 %).

Other data extracted from the French product register SEPIA (INRS, 2003) showed that 243 products registered between 1997 and 2002 contained PGME. The main use category was: paints, varnishes and inks (45 %).

Dentan *et al*. (2000) analysed the chemicals registration database in Switzerland in order to identify users of PGME and potential exposure. In 1999, out of 150,000 products, 2,334 were found to contain PGME and most between 1% and 10% PGME. There was a great increase in the number of products declared between 1983 and 1991, which reflects the trend to replace certain ethylene glycol ethers by propylene glycol ethers. The most common uses were inks,

paints and varnishes (50 %), solvents, diluents and pickling solutions (13 %), cleaning agents (10 %), glues, mastics and jointings (5 %), auxiliary materials (5 %).

The distribution of concentration intervals in the main type of products is presented in the tables 4.1, 4.2 and 4.3.

Table 4.1: Concentration of PGME in the main use categories in the Danish product register (Arbejdstilsynet, 2001)

Content %	Cleaning agents	Solvents	Paints		Process regulators	
[0-2]	22	45	2071		44	
]2-20]	101	50	406		57	
]20-50]	28	28	31		22	
]50-100]	7	22	52		23	

Table 4.2: Concentration of PGME in the main use categories in the French product register SEPIA (INRS, 2003)

Concentration (%)	Paints, varnishes and inks	Metallurgical and mechanical sectors products	Cleaning products
[0-1]	15	1	-
]1-5]	34	3	10
]5-10]	17	1	1
]10-20]	25	2	4
]20-50]	7	2	2
]50-100]	5	1	2

Table 4.3: Concentration of PGME in the main use categories in the Swiss product register (2000)

Concentration (%)	Inks, varnishes and paints	Solvents, diluents, pickling solutions	Glue, mastics, jointing	Cleaning agents	Auxiliary materials
[0-1]	141	8	14	19	11
]1-10]	667	130	71	171	45
]10-30]	237	86	26	37	40
]30-50]	62	45	12	11	14
]50-100]	66	29	3	8	12

4.1.1.2 Occupational exposure

Definitions and sources

In this document, unless otherwise stated, the term exposure is used to denote external personal exposure as measured or otherwise, assessed without taking into account the attenuating effect of any personal protective equipment (PPE) which might have been worn. This definition permits the effects of controls other than PPE to be assessed and avoids the considerable uncertainty associated with attempting to precisely quantify the attenuation of exposure brought about by the proper use of PPE. Furthermore, inappropriate use of gloves may even increase dermal uptake.

The worst-case estimates generated in this exposure assessment are considered to be reasonable worst-case estimates, as they describe high-end or maximum exposures in feasible but not unrealistic situations. They are not intended to account for extreme or unusual use scenarios. The majority of exposures are expected to be well below these estimates.

Air sampling data are presented in this section from a number of sources and have been tabulated, where practicable. There is in general little or no information on the activities carried out while the sampling was running, the concentration of PGME in the products, the control measures, and other important matters, such as sampling strategy and measurement methods, mean and 90^{th} or 95^{th} percentile of results; this is most often a serious difficulty for interpreting the data correctly.

Measured exposure data are compared with that predicted from the EASE (Estimation and Assessment of Substance Exposure) model version 2. EASE is a general purpose predictive model for workplace exposure assessments. It is an electronic, knowledge based, expert system which is used where measured exposure data is limited or not available. The model is in widespread use across the European Union for the occupational exposure assessment of new and existing substances.

No measured dermal exposure data are available for PGME. A few results have been measured with relevant analogous substances. They will be considered together with modelling to predict occupational dermal exposure to PGME. Many of the references stress the importance of dermal exposure, particularly during use of products. All sections on dermal exposure deal with liquid exposure.

All models are based upon assumptions. Their outputs are at best approximate and may be wrong. EASE is only intended to give generalised exposure data; it predicts inhalation exposure as ranges for concentrations for continuous exposure at the process under consideration. Dermal exposure is provided by EASE as the quantity of a product adhering to the skin due to a task, it does not take into account evaporation of the product.

Since glycol ethers can be absorbed by all routes, biological monitoring represents the best approach for assessing total exposure. Determination of urinary excretion of PGME (Jones *et al*., 1997, Devanthéry *et al*., 2000) or its metabolite 1,2-propanediol (Laitinen *et al*., 1997) has been proposed to monitor exposure to PGME. However only one biomonitoring study is available (Laitinen *et al*., 1997). The excretion of 2-methoxypropanoic acid (metabolite of the reprotoxic impurity β-PGME) has also been monitored on some occasions.

In the present assessment inhalation exposures are expressed in mg/m^3 or ppm. All ppm have been converted to mg/m^3 using the following approximation:

$mg\ PGME/m^3 = ppm \times 90.1/24.05 = ppm \times 3.74$

Routes of exposure and relevant scenarios

The major occupational routes of exposure to PGME are inhalation and skin contact. Assuming proper hygiene measures are applied, oral exposure would normally not occur in the workplace.

Workers may be significantly exposed during the production of PGME, its processing as an intermediate or during the formulation and use of PGME containing products.

Occupational exposure assessment will be carried out through three main categories of scenarios:

(a) the manufacture of PGME and its use as an intermediate;

(b) the formulation of products containing PGME;

(c) the use of products containing PGME.

The third category will focus on particular sub-scenarios for exposure in the most frequent type of use, or particular pattern of use, when relevant.

Number of workers exposed

No data are available but due to the wide range of products containing PGME, it is assumed that a large number of workers in many professional sectors may be exposed daily or occasionally.

Occupational exposure limits (OELs)

OELs apply to workplace air concentrations of chemicals. They are normally intended to protect workers against short-term adverse effects (irritation, acute Central Nervous System (CNS) effects) or long-term effects (e.g. on liver, lungs, kidneys, or chronic CNS effects) after months or years of exposure. When applicable, a "short-term exposure limit" (STEL) may be proposed or imposed to protect against the former effects, and/or a "time-weighted average" (TWA) for the latter. The short term value ordinarily refers to a 15 minutes or so duration, the second to a shift (generally considered as an 8-hour shift).

Table 4.4 presents the OELs recommended for PGME in various countries. They are provided for information and are not an indication of the level of control of exposure achieved in practice in workplaces. For the β isomer, Germany recommends a MAK value of 2 ppm (7.5 mg/m^3).

Table 4.4: Occupational Exposure Limit values for PGME

Country	8-hr TWA		STEL, 15 min	
	mg/m^3	ppm	mg/m^3	ppm
EU[a,b]	375	100	568	150
Austria[b]	187	50		
Belgium	374	100	561	150
Denmark	185	50	-	-
Finland	370	100	560	150
France[b]	375	100	568	150
Germany	370	100	-	-
Ireland[b]	360	100	1,080	300
Italy	369	100	553	150
Netherlands	375	100	-	
Norway[b]	180	50	-	-
Spain[b]	374	100	748	200
Sweden[b]	190	50	300	75
Switzerland	360	100	720	200
UK[b]	375	100	748	200
USA (ACGIH)	369	100	553	150
USA (NIOSH)	370	100	553	150

a: Directive 2000/39/CE of 8 June 2000
b: with skin notation

4.1.1.2.1 Scenario 1 : Manufacture and use as intermediate

This scenario includes all activities concerning the production and use of PGME as intermediate, in particular for the production of its acetate (PGMA) in the chemical industry. Although the data mainly refer to the manufacture of PGME, exposure is expected to be similar during its use as intermediate. Both processes take place in closed systems under strict control. A few people are exposed during these activities. In the EU there are five sites producing PGME and three sites using PGME to produce PGMA (two sites produce both substances).

PGME is manufactured in a closed system, either continuously or on a campaign basis. Exposure during transfer to tankers or drums is generally minimized by the use of automated filling, where the operator is segregated from the area during transfer, and the use of local exhaust ventilation. Accidental exposure may occur when the process is breached or when

spills occur. Exposure may also occur during maintenance and cleaning activities ; however the purging of plant and equipment is generally standard practice (OSPA, 2003).

Inhalation exposure

Measured data

Airborne measurements were provided by EU manufacturers of PGME in the framework of this assessment:

- Producer 1: in 18 production and subsequent processing enterprises, analysis of 53 measurements (personal air sampling with exposure duration > 1 hour, which were calculated as shift averages) carried out during the period 1995-2000 leads to a 90th percentile of 1.05 mg/m^3 The highest results are obtained in the filling/storage area with a 90th percentile of 2.7 mg/m^3. Details are presented in table 4.5.
- Producer 2: personal air measurements were carried out in 2002 in two departments of the production plant. Shift TWA exposures were all < 1.57 mg/m3, the highest task level (5.54 mg/m3) was measured during connection/disconnection of filling hoses by the ship/jetty outside operator. Details are presented in table 4.6.
- Producer 3: 20 measurements made in the production plant in 2000 result in exposure ranging from < 0.03 mg/m3 to 2.54 mg/m3. No more details are available (probably personal exposure active carbon sampling tubes are used).
- Producer 4: exposure to PGME in a plant where conversion to the acetate takes place was measured in 2001 as 1.1 or 2.0 mg/m3(with a sampling time of 393 min, absorption on active carbon, probably personal exposure). No more details are available.

Table 4.5: Personal air measurements in Producer 1 enterprises (1995-2000)

Type of processing/workplace	No of results	No of enterprises	50 % value (mg/m^3)	90 % value (mg/m^3)	95 % value (mg/m^3)
All	53	18	0.41	1.05	4
Production (closed system)	8	1	0.42	0.52	
Subsequent users (closed system)	31	11	0.41	0.88	
Laboratory (with LEV)	5	4	-	-	-
Filling/storage (with LEV)	9	2	0.64	2.7	-

Table 4.6: Personal air measurements in Producer 2 plant (2002)

Job type	No of samples[1]	Shift level or task	Range[2] (mg/m^3)	Median (mg/m^3)	90 % percentile (mg/m^3)
Outside production operator	8 (1 <LOD)	Shift (TWA)	0.01-1.57	0.22	1.05
Road gantry operator	7 (5 <LOD)	Shift (TWA)	0.01-0.18[3]	0.01	0.09
Road gantry operator	7 (7 < LOD)	Task-Road tanker loading	0.02-2.4[3]	0.23	1.76
Ship/jetty outside operator	4	Shift (TWA)	0.4-0.92		
Ship/jetty outside operator	1	Task-connect loading hose,take jetty sample	5.54		
Ship/jetty maintenance operator	1	Task	0.628		
Preparation road/jetty outside operator	2	Shift	0.01-0.29		
Preparation road/jetty outside operator	2	Task-preparation of equipment for maintenance	0.22-0.65		

Note 1: LOD = lower limit of detection (5µg which equates to 0.21 for a 24 liter sample).

Note 2: for results < LOD, a value of 50 % of the LOD has been applied.

Note 3: three loading tasks ran over two shifts. Measurements were completed for the whole task and were therefore split between two operators, thus individual exposure approximates to 50% of the level recorded.

Modelled data

The EASE model used to predict exposure during production in closed system with full containment provides an exposure estimation of 0-0.1 ppm (0-0.37 mg/m^3). If the system is breached in some activities (like maintenance, sampling, cleaning, filling), concentrations could be in the range of 1-3 ppm (3.74 – 11.22 mg/m^3) (non dispersive use, low/moderate tendency to become airborne, presence of LEV).

Summary/statement of the exposure level

Limited monitoring data are available for production and use of PGME as intermediate. The results show very low workplace air levels. Due to automated processes for feeding reactors and for drum and tanker filling as well, typical inhalation exposure is likely to be < 1 mg/m^3 in most situations.

It is proposed to adopt the value of 2.7 mg/m^3 (highest 90th percentile of producer 1) as a reasonable worst-case TWA atmospheric concentration for these activities. Task exposure (short term exposure) may be twice this level.

Dermal exposure

Due to the enclosure of the process and control measures taken to minimize skin contact, for example, during transfer to tankers, dermal exposure at the plant is incidental and therefore likely to be low. The main source of potential exposure is during maintenance activities.

Incidental contact with the liquid seems appropriate for this scenario because exposure will be occasional (not daily) and intermittent contact would probably overestimate the exposure. The EASE model estimated a dermal exposure in the range of 0-0.1 mg/cm^2/day (non dispersive use with direct handling and incidental contact). Assuming exposed skin surface area is 420 cm^2 (palms of hands), maximum external dermal exposure would be 42 mg/day. This exposure will be mitigated by the use of suitable gloves.

4.1.1.2.2 Scenario 2: Formulation of products containing PGME

During the formulation of products containing PGME, workers may be exposed during pre-weighing before mixing, during transfer to the mixing tank, during mixing and during the filling of containers with products. The whole operation is generally carried out at room temperature. Because of the similarity of scenarios, it will be assumed that exposure during formulation is the same whatever the final use of products is.

Exposure strongly depends on the process, which may be enclosed or relatively open. When the transfer of PGME to the mixing vessel is carried out in a sealed system, potential exposure will be minimal, but when the operator adds the raw materials directly by drum to the mixing tank, exposure may be greater due to possible splashing and vapour and/or aerosol generation.

Exposure will also strongly depend on the quantities handled, the concentration in the products and the duration and frequency of exposure.

During preweighing and transfer to the mixing tank, workers are potentially exposed to pure PGME, they are exposed to a more dilute form during filling. However the frequency and duration of exposure may be greater. As operators may be involved in both mixing and filling, assessment of exposure is for the formulation process as a whole.

Quite a high number of workers are likely to be exposed during formulation of products. An enquiry was recently conducted by CEPE (European council of the paint, printing and artists' colours industry) on the industrial uses of 4 glycol ethers in paints or inks manufacturing industries, one of which is PGME: 108 answers were received from all over Europe, 76 users and 32 non-users. They comprise both multinationals and small or medium size enterprises from most of the EU countries. The number of workers exposed was indicated by 57 user

companies out of the 76, the answers were in the range of 1 to 250 and represent a total number of 1,935 workers (CEPE, 2002).

Information about exposure frequency and duration has also been recently collected in the CEPE enquiry (see table 4.7).

Table 4.7: Exposure frequency and duration in paints and inks manufacturing industries (CEPE, 2002)

	Exposure in days/year (53 answers)	Exposure in hours/day (50 answers)
Arithmetic mean	136	4.9
Median	150	6.0
Range	1-360	0.08-8

Inhalation exposure

Measured data

There are very few measured data published for assessment of exposure during formulation:

- Exposure of seventeen workers in a varnish production facility were examined. The workers (n=12) in the production area were found to be exposed to PGME at an average concentration of 7.0 ppm (26.3 mg/m^3); individual exposures ranged from < 0.1-24.1 ppm (< 0.4-90.4 mg/m^3). The exposure of the workers in the store (n=3) and in the laboratory (n=2) were too low to measure (Angerer *et al*., 1990).

- Between 1988 and 1993, INRS (Vincent *et al*., 1996) performed a large study of occupational exposure to glycols ethers by atmospheric and biological monitoring. During this study, personal exposure of 248 workers in 5 factories of the paint manufacturing industry were measured (328 air samples). The study was performed when the use of ethylene glycol ethers were still wide spread compared to propylene glycol ethers. PGME was not frequently detected and the majority of samples were under the limit of detection of 0.1 ppm (0.37 mg/m^3). The highest measured exposure was 0.3 ppm (1.12 mg/m^3).

In the inquiry of CEPE (2002), 23 facilities out of the 76 PGME users who answered the questionnaire said they performed workplace monitoring (49 replied negatively to the question while the others did not answer at all). Twenty three users indicated typical concentrations: 9 answers were < 1 mg/m^3, 5 in the range 1-10 mg/m^3 and 5 in the range 10-25 mg/m^3. In several instances, the companies specified total solvent concentration checking or too low concentration to measure.

Information from database

In the German MEGA database, 736 exposure measurements have been registered between 1996 and 2000, which were mainly obtained in the paint formulation industry. The results (measurement values with an exposure duration ≥ 1 hour and a sampling duration ≥1 hour converted to 8-hour weighted averages) are presented in table 4.8. The measurements were

mainly obtained during mixing and filling of PGME and during the cleaning of equipment or containers.

When possible, a distinction is made on the basis of whether or not control measures (LEV) were taken. In this regard, the results present an apparent paradox that the workplaces with LEV frequently do not exhibit lower exposures than those without LEV and the exposures may even be higher. Technical measures are mostly taken in place where the situation may result in a higher release of vapours, for instance when large quantities of substance are handled or when process occurs at high temperature. By contrast, the release is comparatively low during use of small quantities or processing at ambient temperature. In most cases, control measures create a situation where the exposure level in workplaces with large release approximately reaches the level of workplaces with only low releases but without control measures.

Table 4.8: Personal inhalation exposure (8- hr TWA) in the MEGA database, 1996-2000 (BGAA, 2001)

Paint production activity	No of results	No of companies	50% value (mg/m^3)	75 % value (mg/m^3)	90 % value (mg/m^3)	95 % value (mg/m^3)
Raw PGME handling, mixing and filling	507	103	a	13.00	37.30	63.00
- without LEV	180	58	a	16.00	37.00	60.00
- with LEV	321	86	5.50	13.00	37.80	71.60
Cleaning of containers	229	106	a	21.00	50.20	112.35
- without LEV	58	32	9.00	22.50	87.00	160.20
- with LEV	160	73	a	20.00	44.00	95.00

a : measurement value < analytical determination limit

Modelled data

Using the EASE model (non dispersive use, low/moderate tendency to become airborne), the exposure estimate would be in the range of 1-3 ppm (3.74-11.22mg/m^3) with LEV and 20-50 ppm (74.8 - 187 mg/m^3) in case of direct handling with dilution ventilation.

Summary/statement of the exposure level

Limited published data available for this particular scenario. Angerer obtained exposure of 90.4 mg/m^3 (highest value) and 26.3 mg/m^3 (median value). Recent data provided by industry indicate that exposure would not be higher than 25 mg/m^3 but very little information is available onthe context of these measurements.

Information presented in table 4.7 shows that frequency and duration of exposure may considerably vary. A continuous exposure for full shift (8 hours per day) will be assumed although the data suggests that this is unlikely to be a daily exposure.

Based on the highest 90^{th} percentile of the MEGA database values, the worst case inhalation exposure during formulation of products is assumed to be 87 mg/m^3. Typical exposure levels are probably much lower.

Dermal exposure

Measurements

As part of the "Riskofderm" project, a study was performed by the TNO (Riskofderm, 2002a; Gijsbers *et al*., 2004) to directly assess dermal exposure to products containing 2-(2-butoxyethoxy)ethanol (DEGBE), a chemical of the same family as PGME but much less volatile (vapour pressure 2.7 Pa at 20 °C compared to 11,600 Pa at 20 °C for PGME). Hand exposure was measured during loading (typically at the beginning of the formulation process, handled product is the substance, short task duration ranged between 1 and 15 minutes) and during filling (typically at the end of the formulation process, handled product is the formulation, task duration ranged between 22 and 125 minutes). The measurements were made using cotton sampling gloves which were worn over new protective gloves, where present. Exposure was mainly due to exposure on the hands. The most important source of variability was due to between-company variability, rather than to either between-worker or within-worker variability. Results (given in DEGBE and product) are presented in table 4.9.

Table 4.9: Results of measurements of potential hand exposure to DEGBE in loading mixers and filling containers with products containing DEGBE (after Riskofderm, 2002a and Gijsbers *et al.*, 2004)

Exposure to DEGBE or product	*N*	*Range (mg)*	*AM (mg)*	*GM (mg)*	*GSD (mg)*	*AM ($\mu g/cm^2/min$)*	*GM ($\mu g/cm^2/min$)*	*GSD ($\mu g/cm^2/min$)*
Loading (pure DEGBE)								
Hands DEGBE	28	0.28-28300.0	3313.6	218.9	19.9	727.4	52.9	17.2
Hands Product*	28	0.31-27745.1	3215.0	217.0	19.3	708.8	52.4	16.7
Filling (all data)								
Hands DEGBE	30	0.062 – 19000.0	1955.8	35.9	42.0	45.1	0.75	42.6
Hands Product*	30	4.1 – 18269.2	2726.6	555.4	9.4	58.5	11.5	9.6
Filling (only products < 10% DEGBE); data not published, but calculated from original data								
Hands Product*	21	4.1-11146	1216	249	8.5	15	4.1	7.6

N = number of measurements
AM = arithmetic average
GM = geometric average
GSD = geometric standard deviation)
*recalculated towards the full product by dividing the value measured for DEGBE by the fraction of DEGBE as analysed in the product

The 90th percentile from the measured data for loading was approximately 11,000 mg on 840 cm^2 (expressed as total product), approximately 11,100 mg on 840 cm^2 for filling (all products, including (almost pure) DEGBE) and approximately 3300 mg for filling of products containing less than 10% of DEGBE (not published data, derived from original data). This value would lead to a level of 330 mg for DEGBE if the percentage of DEGBE would be 10%. It appears that the situations with handling (almost) pure products lead to higher exposure levels. That can be caused by the fact that products with small percentages of DEGBE, such as paints can be packaged in cans by highly automated equipment, while (almost) pure DEGBE is often packaged in larger containers with more handling of the container by the workers.

Although assessed in a direct way and in actual working situations, these results should not be given excessive weight for the main following reasons:

- this is an isolated study, and it is known that there is an extreme variability in skin (and especially hand) exposure (Kromhout *et al*., 2004), depending of a number of most often qualitative factors that have been divided in six categories (Marquart *et al*., 2003);

- measurement durations are relatively short (range 1-139 min, arithmetic mean range 6-74 min, all tasks confounded; Gijsbers *et al*., 2004) compared to a shift, so the results may represent rather task-associated exposure measurements than shift exposure assessments.

- although from the same chemical family as PGME, DEGBE has very different physicochemical properties, among which volatility and the octanol/water partition coefficient (log values are -0.49 for PGME and 0.56 for DEGBE) may play a significant role.

Modelling

Considering the process and the tasks where exposure may occur, SIDS (1996) retained intermittent contact time of 20 % of the working day with a 1000 cm^2 skin area exposed (a hand and a forearm).

Taking into account the same assumption, the EASE model estimates a dermal exposure in the range of 0.1-1 mg/cm^2/day (non dispersive use with direct handling and intermittent contact). Assuming exposed skin surface area is 420 cm^2 (for consistency with other EU occupational risk assessments and default assumptions recommended in table 3 of Appendix I of the Technical Guidance), maximum external exposure would be:

- 42-420 mg/day for loading (pure substance)
- 21-210 mg/day for filling (assuming 50% PGME in the product)

Assessment

Dermal exposure can occur during part of the working day during loading of mixers (short periods, up to approximately 20 minutes, with an arithmetic mean of 6 min, according to Gijsbers *et al*., 2004, for DEGBE) and during packaging of products containing PGME (up to 120 minutes per day). Measured data for this scenario for PGME are not available. Data from DEGBE for similar processes may be relevant. The measured values, using cotton gloves as samplers, for DEGBE are generally high compared to the estimates by EASE. Geometric mean exposure levels to products, for situations where formulations were made, so excluding the filling of (almost pure) DEGBE, were in the order of 200-250 mg and the 90^{th} percentile was in the order of 3,300 mg for filling of products with less than 10% DEGBE and 11,000 mg for loading of DEGBE into mixers, both on $820cm^2$. (should read 840) The measured data for DEGBE may be an overestimate of potential dermal exposure for PGME for two reasons. Firstly, the measurement method may have led to overestimation of dermal exposure, because cotton gloves are considered to retain more liquid than the skin would do. Secondly, PGME is much more volatile than DEGBE and therefore, more of the substance may evaporate from the skin and not be available for uptake. The effect of both factors is difficult to estimate.

For the purpose of determining the evaporation time, the following equation can be used (TGD Appendix I.E):

$T(s)= (mRT/M\beta pA)K$

This equation leads for PGME to an estimate of evaporation time of 20 minutes, with the following input values: m = 10 000 mg, R = 8.134 $J.K^{-1}.mol^{-1}$, T = 305 Kelvin, K = 3.6 * 10^4, M = 90.1, β = 8.7 $m.h^{-1}$ (default), p = 1160 Pa, A = 820 cm^2)(should read 840). This indicates that in approximately 20 minutes all PGME would be evaporated from the skin. For comparison, the same calculation with DEGBE (vapour pressure = 2.7 Pa) leads to an evaporation time of more than 100 hours.

The estimate based on measured data is substantially higher than that based on EASE that is considered a weak model for dermal exposure. Although the measured data have a number of uncertainties, they should not be disregarded for risk characterisation.

Different evaluations may be made using data from the RiskofDerm study for DEGBE (Gijsbers *et al*., 2004), e.g. for loading:

0.709	x	1.00	x	840	x	6	=	3,570 mg
(mg/cm².min, A.M.)		(100% DEGBE)		(cm² for both hands)		(min, A.M.)		

using arithmetic mean (A.M.) data,
OR, using geometric mean data (and in this context the maximum duration reported for loading):

0.0524	x	1.00	x	840	x	15	=	660 mg
(mg/cm².min, G.M.)		(100% DEGBE)		(cm² for both hands)		(min)		

The first calculation probably gives an overestimate, since it uses arithmetic means (which gives a strong weight to high values), and the second an underestimate (the geometric mean giving a strong weight to low values). So an intermediate value should be given preference.
In the case of EGBE, a chemical with physico-chemical properties more similar to PGME than DEGBE, using data obtained from biomonitoring, it was estimated that the skin load might be around 500 mg/day; taking into account that "individual mean dermal exposure levels were on average within a 4-fold range" (Marquart *et al*., 2006), a reasonable worst case skin exposure was then re-evaluated as 2,000 mg/day, which is in-between the preceding evaluations but may still be slightly overestimated due to the greater volatility of PGME.

As it is difficult to characterize overestimation due to the greater volatility of PGME, it is proposed to use an exposure of 2000 mg/day for loading.

Similar evaluations may be made for filling (with an added multiplicative factor of 0.5 corresponding to an estimated concentration of 50%), which give 1000 mg/day.

If, on a worst case basis, a same worker is assumed to be in charge of both tasks, he then could be exposed to the sum of these assessments, i.e. 3,000 mg/day.

Dermal exposure may be lower if suitable gloves are worn.

4.1.1.2.3 Scenario 3: Use of products containing PGME

PGME is used in a wide variety of products. The following scenarios are considered as representative:

- use of paints and coatings

- use of printing inks

- use of cleaners.

Cleaning related to painting and printing activities are included in the first and second scenarios.

Measured exposure levels in general

From 1987 to 1998, the French COLCHIC database collected 10,593 personal sampling results of glycol ethers for 602 facilities (Vincent, 1999). PGME was found 2 638 times; the arithmetic atmospheric mean value of the 60 to 480 minutes samplings (880 results) was 33.4 mg/m^3 (median 6 mg/m^3; range 0.1-841 mg/m^3; 95th percentile 182.5 mg/m^3). Breakdown of exposure by industrial sectors is presented in table 4.10.

For the years 1999 to 2002, the COLCHIC database collected 323 personal atmospheric sampling results of PGME. The arithmetic mean value of 60 to 480 minutes samplings was found 24.8 mg/m^3 (median 2 mg/m^3, range 0.1-924 mg/m^3, 95th percentile 66 mg/m^3) (Vincent, 2003).

Table 4.10: Breakdown exposure by industrial sectors. Personal exposure results in the COLCHIC database, years 1987-1998 (Vincent, 1999).

INDUSTRIAL SECTOR	No of samplings	Median (mg/m^3)	A.Mean. (mg/m^3)	Range (mg/m^3)	95th percentile (mg/m^3)
Wood and wood articles carving	17	1.5	6.7	1.5-70	70
Printing industry	209	6	23.5	0.1-411	102
Chemical industry	33	4.5	4.4	0.2-26	23
Rubber and plastics	170	49.6	92.2	0.1-841	278
Ore and metal treatment	24	1	10.8	0.2-131	92
Metal finishing	132	4.8	7.4	0.5-39	28.1
Electrical engineering	14	4	3.9	0.1-7.5	7.5
Communication equipment	21	13.5	17.5	2-73	62
Medical, optical and precision instruments	18	2.7	3.3	0.2-9	9
Car industry	2	-	1.2	0.5-2	-
Furniture manufacture	33	3	4.7	0.5-22	18

- **Scenario 3-1 Painting/Surface coating**

PGME is used as a solvent in paints and surface coatings, particularly in water-based type. It is the main application of PGME and due to the high volume used, a large number of workers are potentially exposed.

The answers related to concentration of PGME in products, collected in the paint formulating industry by CEPE (2002) are presented in table 4.11. Taking into account this data together with the information collected in European products registers (tables 4.1, 4.2 and 4.3), a worst case representative PGME content of 30 % in industrial paints (solvent based) and 15 % in decorative paints (solvent based) will be assumed in this assessment. Therefore the conclusions in this section refer to solvent-based paints. Exposure from use of water-based paints (lower PGME content) would be much lower.

Table 4.11: Contents of PGME in paints (CEPE, 2002)

	Industrial paints		Decorative paints	
	Water-based	Solvent-based	Water-based	Solvent-based
Number of answers	16	48	4	14
Arithmetic mean	3 %	9.9 %	2.9 %	5.3 %
Median	2 %	6 %	-	2.5 %
Range*	0.6-10 %	0.1-60 %	0.4-5 %	0.2-30 %

* minimum values probably correspond to incorporation of PGME through additives

Coatings and paints are applied by spraying, rolling, brushing or dipping. Application techniques inventoried in the CEPE enquiry are presented in table 4.12 (CEPE, 2002):

Table 4.12: Relative frequencies of application techniques in painting/surface coating (CEPE, 2002)

Application technique	Number of mentions
Spray	46
Roll	31
Brush	30
Dipping	9

Inhalation exposure

Measured data

In the INRS study performed between 1988 and 1993 (Vincent *et al*., 1996), occupational exposure was measured for a battery of glycols ethers, including PGME. The results obtained for PGME during painting or coating activities are summarised in table 4.13.

Table 4.13: Personal inhalation exposure during painting (8 hr-TWA) (Vincent *et al.*, 1993)

Activity	No of sampling	Mean (mg/m^3)	Range (mg/m^3)
Furniture staining and varnishing	48	< 0.37	<0.37-6.73
Car repainting	38	1.49	<0.37-4.86
Coil coating	261	2.24	<0.37—82.28
Metal frame painting	50	0.37	<0.37-4.49
Printed circuit board manufacture	57	8.23	<0.37-50.86-
Plastic painting	79	0.75	<0.37-7.85

Information from database

Exposure measurements (sampling period 60-480 minutes) registered between 1987 and 1998 in the COLCHIC database were analysed by Vincent (1999). Results related to painting and coating are presented in table 4.14.

Table 4.14: Personal exposure in painting activities for measurements 60-480 minutes, years 1987-1998 (Vincent, 1999)

Type of work	No of samples	Mean (mg/m^3)	Range (mg/m^3)	Median (mg/m^3)	95th percentile (mg/m^3)
Pneumatic spraying of paint or varnish	73	6.3	0.5-92	2.8	23.9
Varnishing (curtain)	61	11.5	0.2-150	4	37
Brush or roll coating of paint or varnish	21	20.9	0.5-119	14	38

In the German MEGA database, 1397 exposure measurements have been registered between 1996 and 2000, which were obtained during application of paints or coatings. The results (measurement values with an exposure duration ≥ 1 hour and a sampling duration ≥ 1 hour converted to 8-hour weighted averages) are presented in table 4.15. When possible, a distinction is made on the basis of whether or not control measures (LEV) were taken (see comments in scenario 2).

Table 4.15: Personal exposure measurements in the MEGA database, 1996-2000 (BGAA, 2001)

Type of company/working area	No of results	No of companies	50% value (mg/m^3)	75 % value (mg/m^3)	90 % value (mg/m^3)	95 % value (mg/m^3)
Painting,brush and roller application, filling work	222	117	a	12.50	43.20	136.70
- without LEV	130	64	a	17.50	61.00	170.50
- with LEV	49	31	a	15.75	44.20	108.30
Spraying (compressed air, airless, airmix)	745	348	a	a	34.50	76.00
- without LEV	162	55	a	25.00	100.00	159.00
- with LEV	549	288	a	a	a	45.00
Surface coating, mechanical	237	94	a	19.75	39.00	50.00
- without LEV	61	28	a	19.25	30.00	40.70
- with LEV	166	64	a	19.00	37.80	50.00
Surface coating, general	193	104	a	16.00	49.10	75.05
- without LEV	72	42	a	19.00	30.40	67.00
- with LEV	112	61	a	13.00	47.60	72.20

a : measurement value < analytical determination limit

Modelled data

Exposure to vapours during the use of paints or surface coatings is estimated by EASE to be in the following range

- 140-200 ppm (524-748 mg/m^3) for widely dispersive use pattern, low/moderate tendency to become airborne, direct handling and dilution ventilation.

The model overestimates exposure levels, particularly because of non-consideration of the content of PGME in the mixtures. The estimates cannot be corrected for the partial vapour pressure because the composition of the formulations is not known. A simple approach based on a reduction of the exposure by a factor equivalent to the PGME concentration in the mixtures (up to 30 % for industrial paints and 15 % for decorative paints) would lead to exposure levels of 157-224 mg/m^3 for industrial paints and –79-112 mg/m^3 for decorative paints. However the validity of these estimates is rather questionable.

Summary/statement of the exposure level

Exposure to PGME during painting may be extremely variable, due to differences in frequency and duration of use, concentration of PGME in the paint, method of application and precautions taken during use. To some extent, this variation is reflected in the atmospheric monitoring data available for PGME during painting and surface treatment.

Based on the 90^{th} of the MEGA database values, we propose in a first approach the following worst case inhalation exposures:

- 100 mg/m^3 for spray application of paint
- 61 mg/m^3 for other application techniques.

Dermal exposure

Measurements

In a study performed by TNO (Riskofderm, 2002a and Gijsbers *et al*., 2004), a part of the Riskofderm project, potential hand exposure to an analogous but less volatile glycol ether DEGBE (2-(2-butoxyethoxy)ethanol) was measured during indoors application of paint by brushing over of periods of 57-149 minutes (arithmetic mean 74 min). The sampling was ended when the painters (who usually painted for most of the working day) took a break for coffee or lunch, resulting in the measurement durations mentioned. The measurements were made using cotton sampling gloves which were worn over new protective gloves, where present. The amount of used product was between 0.5 and 2.5 litre (AM 1.2 litre) and the paint contained between 0.4 and 3.2 % DEGBE (AM 2 %). The treated area during measurements was between 2 and 15 m^2 (AM 6.4 m^2). Exposure was mainly due to exposure on the hands. Results (given in DEGBE and product) are presented in table 4.16.

Table 4.16: Dermal exposure rates during brushing (Gijsbers *et al*., 2004)

Hands exposure	N	W	Range (mg)	AM (mg)	GM (mg)	GSD (mg)	AM[c] (µg/cm²/min)	GM[c] (µg/cm²/min)	GSD[c] (µg/cm²/min)
- DEGBE	36	18	0.19-33.0	6.5	2.8	4	0.091	0.045	3.6
- product	24[a]	13	11.3-733.3	170.5	98.4	3	2.8	1.7	2.9

N, number of measurements; W, number of workers involved

AM, arithmetic mean; GM, geometric mean; GSD, geometric standard deviation

Nota a : for 12 of the measurements, exposure to product could not be calculated due to contamination of samples by other sources of DEGBE.

Nota c : a surface area of 820 cm^2 was assumed for the hands exposure

The 90th percentile of the measured exposure levels was approximately 400 mg product (unpublished data, derived from original data).

No measurements for dermal exposure in spray painting of PGME or other direct analogues (e.g. other glycol ethers) are available. A number of dermal exposure data sets is available for other spray applications. Exposure to a non-volatile pigment was measured in car painting. Dermal exposure to the hands, expressed as total formulation, was between 2 and 211 mg (n = 30), with a median of 41 mg. Amount of product used was up to 1.5 kg in an average duration of 16 minutes (Riskofderm 2002b, Delgado *et al.,* 2004). Exposure to another non-volatile pigment was measured in marine anti-fouling painting. Dermal exposure to the hands, expressed as total formulation was between 286 and 27,000 mg (n = 24) for sampling periods of 1 to 3 hours. In this period 40 to 140 litres of paint were sprayed. Exposure was not only to workers actually doing spray painting, but also to auxiliary workers (so-called linesmen) assisting the spray painters. There was no difference in exposure between the two jobs. (Riskofderm 2002c, Hughson *et al.*, 2004). Spray application of a cleaning agent containing DEGBE was measured 12 times in the food industry. Duration of measurements ranged between 6 and 18 minutes. The in-use concentration of DEGBE was between 0.007 and 1.1%. The total amount of diluted product used was between 16.5 and 97.2 L. Dermal exposure to the hands, expressed as total formulation, was between 37 and 1974 mg (Riskofderm, 2003a). The 90th percentiles of these three data sets were respectively approximately 100, 13,600 and 1,000 mg per measurement period (unpublished data, derived from original data). Older data

are reported in the TGD, where for spray painting on large surface areas a reasonable worst case value of 10 000 mg product per day (on 840 cm^2) is given (Appendix I.E).

Modelling

For tasks as brushing and rolling, assuming direct handling and intermittent contact, the EASE model estimates a dermal exposure in the range of 1-5 mg of product/cm^2/day for wide dispersive use. For spraying, assuming an extensive contact leads to a dermal exposure range of 5-15 mg of product/cm^2/day. The estimation is made from a formulation containing up to 30 % of PGME (industrial paint) and a formulation containing up to 15 % of PGME (decorative paint) and an exposed skin surface area of 840 cm^2 (two hands). This leads to estimated external dermal exposures of :

- 252-1260 mg/day for industrial painting (excluding spray application)
- 1260-3780 mg/day for industrial spray painting
- 126 - 630 mg/day for decorative painting.

Assessment

Skin contact due to manual transfer of liquids, spray application and brushing, rolling and cleaning is to be expected. In several of the available references, the importance of skin exposure is stressed.

The preference should be given to measured data, although there are difficulties in interpreting the Riskofderm data. Compared to the estimates by EASE, they may be closer to reality.

In the TNO study, cotton sample gloves can retain more material than skin leads to overestimation of exposure. The size of this possible overestimation is difficult to estimate. It can be expected that this overestimation is smaller when more viscous paints are used than when less viscous pure product is used. The fact that workers (except for breaks) may almost continuously do the same tasks suggests that the task based exposures should be extrapolated to a full work shift. Whereas extrapolation is clearly not valid for high (product) exposures, due to saturation of the surface of the skin, this is not so much of a problem with lower task exposure levels. Given the fact that painters spend part of their working period in preparation, moving between rooms, cleaning up the material and other non-painting tasks, the exposure period for painting can be estimated to be up to 6 hours. Based on the estimated 90th percentile of the measured data (400 mg product in 2 hours), linear extrapolation to 6 hours of work and an assumed percentage of 30 % (industrial paint) or 15 % PGME (decorative paint), the exposure value to be used in risk characterisation is estimated as 400*3*0.3 = 360 mg or 400*3*0.15 = 180 mg PGME per day for brushing and rolling of industrial or decorative paints.

Using the RiskofDerm data (Gijsbers *et al*., 2004), hand exposure in brushing activities may be assessed (product, geometric mean, maximum time) as:

0.0017	x	0.30	x	840	x	140	=	60 mg/day
(mg/cm².min)		(30% PGME)		(cm², both hands)		(min/day)		

OR (arithmetic mean, mean time):

0.0028	x	0.30	x	840	x	74	=	52 mg/day
(mg/cm².min)		(30% PGME)		(cm², both hands)		(min/day)		

These evaluations are underestimates due to the fact that "if measurement times were up to 139 min, painters were painting during most of their working day" (Gijsbers *et al*., 2004). If

the time taken into account is re-evaluated in both calculations at 360 min (i.e. 6 hours) they become respectively 154 or 254 mg/day, which is consistent with what is proposed above.

The exposure levels from industrial spray application apparently depend on the scale of application, as well as on control measures in use. Without further information, it is assumed that large scale application with limited exposure control can be done with paints containing up to 30% PGME. The measured values over short periods cannot be extrapolated towards longer periods, because this would lead to oversaturation of the skin. Therefore, a reasonable worst case exposure level of 10,000 mg product per day is assumed, based on the levels mentioned in the TGD and the measurements by Hughson *et al.* (2004). This leads to an estimated exposure to PGME of 3,000 mg on 840 cm^2. Because PGME is much more volatile than the measured substances, this may be an overestimation. Also, if less large scale tasks are done, the exposure levels may be substantially lower. These uncertainties should be taken into account in the evaluation of the MOS.

Dermal exposure may be lower if suitable gloves are worn.

- **Scenario 3-2** : **Cleaning**

Exposure during cleaning is extremely variable, due to differences in frequency and duration of use, strength of solution used, method of application and precautions taken during use… Commercial products often need dilution before use. While the dilution procedure is usually of short duration, the potential exposure may be greater due to use of higher concentrations of PGME and the possibility of splashing. A number of different methods are used to apply the cleaning solution, for example, washing, wiping, mopping and spraying. The spraying method of application will potentially increase both dermal and inhalation exposure as the atmospheric concentration of PGME will be higher and dermal contact will be increased. The potential for exposure may also be increased where heat is applied during cleaning.

Taking into account the information collected in European products registers (table 4.1, 4.2 and 4.3), a maximum content of 50 % PGME in professional cleaners with dilution 1:1 and a task duration of 2 hours will be assumed in this assessment.

Inhalation exposure

Measured data

Anundi *et al.* (2000) estimated exposure levels to organic solvents for graffiti removers; PGME was identified among the various volatile organic chemicals the workers were exposed to. One of the products used was pure PGME. The 8-hr weighted average for the 22 personal samplings was 5.2 mg/m^3 (arithmetic mean) and the range 0.02-32.8 mg/m^3. The task was essentially cleaning trains in underground stations. Relatively high 15-minute exposure levels to PGME were measured: mean 40 mg/m^3 and range 0.2-216 mg/m^3 (31 samples). According to the authors, dermal exposure occurred frequently; few workers used gloves appropriate for skin protection. Increased urinary levels of the metabolite of 2-MPA (2-MethoxyPropionic Acid) of the reprotoxic impurity (β PGME) were measured compared to a control group.

Exposure of three workers cleaning vats in an ink factory was assessed by personal air monitoring and biological determination of PGME in the urine (Devanthéry *et al*., 2000). Shift-weighted atmospheric concentrations of PGME ranged between 20.2 and 40.2 ppm (75.8-151 mg/m^3, n=7) an correlated well with the urinary PGME after 5 hr of exposure.

Modelled data

Several parameters should be chosen to correspond to the real variability of conditions of use of cleaning products:

- wide dispersive use, low/moderate tendency to become airborne, direct handling would give 300-500 ppm (1122-1870 mg/m^3),

- wide dispersive use, low/moderate tendency to become airborne, direct handling and dilution ventilation, would give an estimation of 140-400 ppm (523-748 mg/m^3).

Assuming the exposure would occur 2 hours a day, this leads to exposure levels of 280-467 mg/m^3 or 131-187 mg/m^3.

The model overestimates exposure levels, particularly because of non-consideration of the content of PGME in the products. The estimates cannot be corrected for the partial vapour pressure because the composition of the formulations is not known. A simple approach based on a reduction of the exposure by a factor equivalent to the PGME concentration in the mixture (25 % if the estimation is made for a formulation containing up to 50 % of PGME with dilution 1:1) would lead to exposure levels of 70-117 mg/m^{3}or 32-47 mg/m^3. However the validity of these estimates is rather questionable.

Summary/statement of the exposure level

Very few measured exposure data are available and it is difficult to predict exposure because of the great variability of exposure conditions (in particular duration and content in the product). The highest exposure level measured by Devanthéry, 151 mg/m^3 is selected. This is also in line with the model calculation.

Dermal exposure

Measured data

A series of experiments was conducted in a room-size, controlled environment chamber to evaluate a user's inhalation and dermal exposure to constituents of a household spray cleaner dispensed from either a hand-trigger pump bottle or an aerosol can (Furtaw *et al*., 1997). Approximately 10 % of the amount of product used was transferred to the user's gloves (simulating dermal exposure), with the great majority found on the palms rather than the backs of the hands (88 % according to data presented). Using results presented, skin contamination can be evaluated (for both hands) at 0.22 mg/cm²/day for a 5 % solution. Note also that the right hand is roughly 4 times more contaminated than the left one (right-handed worker).

In a study performed by TNO (Riskofderm, 2003a), a part of the Riskofderm project, potential hand exposure to an analogous DEGBE (2-(2-butoxyethoxy)ethanol) was measured during spraying of a diluted cleaning agent (sampling-duration between 6 and 18 min) and during wiping (car washing, sampling duration between 5 and 12 min and cumulative duration of wiping per day 24-90 min). For spraying, the measurements were made using butylrubber protective (recommended by the employers) the in-use concentration was between 0.0007 and 1.1 % DEGBE. For wiping, hand exposure was evaluated by the hand wash method, the in-use concentration was between 0.04 and 0.82 %. Exposure was mainly due to exposure on the

hands. Results (given in product as well as recalculated to in-use solvent) are presented table 4.17. They show a substantially higher exposure rate during wiping activities.

Table 4.17: Dermal exposure rates during spray ing and wiping (Riskofderm, 2003a)

Hands exposure	Range (mg)	AM (mg)	GM (mg)	GSD (mg)	AM (µg/cm^2/min)*	GM (µg/cm^2/min)*
Spraying (n=12)						
- DEGBE	36-6302[a]	1000[a]	438[a]	3.73	0.15	0.04
- product	37-1974	719	522	2.72	68.4	48.1
Wiping (n=12)						
- DEGBE	1.8-29.8	10	6.8	2.50	1.8	1.1
- product	1508-4861	3161	2985	1.45	535	499

Nota a : these values are in µg

* Asurface area of 840 cm^2 was assumed for the hands

The 90th percentiles (expressed in mg of total product) for the sampling durations were 1,000 mg for spray application and 4,000 mg for car cleaning (unpublished data, derived from original data).

Modelled data

Dermal exposure is clearly predominant during cleaning activities. Intermittent contact seems appropriate for this scenario because the duration will generally be a part of the shift and continuous contact would probably overestimate the exposure.

Assuming wide dispersive use, direct handling and intermittent contact, the EASE model estimates a dermal exposure in the range of 1-5 mg of product/cm^2/day. The worst case estimation is made for a formulation containing up to 50 % of PGME with dilution 1:1 and a 420 cm^2 skin surface area exposed (one hand). This leads to an estimated external dermal exposure of 105-525 mg/day for cleaning.

Assessment

The results of the TNO study during spraying and wiping indicate relatively high potential for dermal exposure. However interpretation is difficult due to the relative small data set of measurements and the fact that during spraying the use of sample gloves may lead to different exposure levels than direct contact to the skin. Furthermore, PGME is much more volatile than DEGBE and this may lead to higher evaporation from the skin and lower effective exposure levels. Also, for tasks with cumulative exposure durations substantially longer than the sampling durations, extrapolation is difficult due to the effects of evaporation as well as the possibility of saturation of the skin with product, specifically for situations with direct contact and immersion, such as cleaning with a sponge or cloth. On the other hand, the kind of tasks performed with these products will often not be done for many hours per day.

Although the measured data are difficult to interpret, they provide more realistic exposure information than the EASE model, whose dermal exposure part is not based on real dermal exposure measurements.

A rough estimator of reasonable worst case dermal exposure (to the hands) is therefore assumed to be the 90th percentile of the exposure levels during the measurement period. This

appears to be reasonable, because the measurement periods were aimed at a covering one full "cycle" of the relevant activities and they were followed by periods without dermal exposure, when evaporation and other effects may lower the skin contamination levels before a new "cycle" will again contaminate the skin. Reasonable worst case exposure levels for hand exposure to diluted cleaning products containing up to 25 % of PGME are therefore expected to be:

- spray application: 250 mg/day;
- manual application including immersion of the hands into the solution: 1,000 mg/day.

The uncertainty in these values is rather large, because of the aspects mentioned earlier. This should be taken into account in the evaluation of the MOS. The estimate for manual application is substantially higher than that of EASE, while the estimate for spray application is similar to that of EASE. However, the measured data are preferred. Dermal exposure may be much lower if suitable gloves are worn.

Dermal exposure may be much lower if suitable gloves are worn.

- **Scenario 3-3** : **Printing**

PGME is used as a solvent in printing inks, particularly silk-screen inks used by professional trades. However there is a trend from solvent based inks to UV curing inks that contain no solvents.

Limited information have been collected in the enquiry recently performed in the ink formulating industry by CEPE (2002), only 11 answers were obtained in relation with the PGME content in printing inks. They indicated content from 0.1 % up to 20 % (0.4-7.5 % in water-borne inks and 0.1-20 % in solvent-borne inks). Other data recently provided by one of the main producer of screen printing in the EU indicate that typical percentages of glycol ethers range from 2 to 35 % in screen printing inks (BP, 2002a). Taking into account all this data, typical maximum contents of 35 % PGME in silk-screen inks and 20 % in others will be assumed in this assessment.

Inhalation exposure

Measured data

Urinary excretion of 1,2-propanediol was measured at the end of the work-week for 23 silkscreen printers (Laitinen *et al*., 1997). The mean concentration was 2.52 mmol per mole of creatinine (median 1.76, n=23). Workers were exposed to workplace atmosphere containing predominantly (90.2%) PGME (8 hr TWA mean 4.92 ppm (18.4 mg/m^3), median 2.31 ppm (8.6 mg/m^3), n=23). According to the authors, the high urinary 1,2 propanediol concentrations could be explained by the dermal exposure of workers in charge of washing the silk screens. In the same study, the authors also recorded mean urinary concentration of 2-MPA of 1.27 nmol/mol creatinine after shift which was linearly dependent on the personal airborne exposure to PGME.

Auffarth *et al*., 1998 measured personal exposure in the screen-printing activity; measurement time was at least 1 hr. For 4 samples (hand printing), PGME had a median of 8.0 mg/m^3 (range 5.7-32.2 mg/m^3). More samples (21) were available with a semi-automatic printing

process; medians and ranges were 16.3 (6.2-123.1) mg/m^3. With further automation (3/4), medians and ranges were 24.3 (3-175.8; 31 samples) mg/m^3; with complete automation, these results were: median 10.2 (4.1-21.5) mg/m^3.

Limited exposure measurements made in 2001 and provided by one of the main producer of screen printing inks in the EU have been presented by industry (BP, 2002a). Printers are exposed 1-8 hours per day but 2-3 hours is the typical length time when workers are exposed to solvents. Nearly all operations use LEV as well as general ventilation. PGME was detected in 13 samples amongst 161. The results are presented in table 4.18. The figures represent TWA over 2-3 hours.

Table 4.18: Personal air measurements during screen printing (BP, 2002a)

Activity	No of results	Mean (mg/m^3)	Maximum (mg/m^3)	5-95 % percentile (mg/m^3)
Print shop	101	2.7	14.7	0.1-7.5
Reclaim	26	5.3	28.5	0.2-27.8
Ink store	3	2.8	4.2	
Other	11	1.1	4.1	0.2-3.0

Information in database

Referring to the already cited French COLCHIC database (Vincent, 1999), 209 atmospheric personal samplings have been made between 1987 and 1998 in the printing industry, resulting in an arithmetic mean concentration of 23.5 mg/m^3 (range 0.1-411 mg/m^3; median 6 mg/m^3; 95th percentile 102 mg/m^3). Results for specified activity are presented in table 4.19.

Table 4.19: Personal exposure in printing activities made for measurements 60-480 minutes, years 1987-1998 (Vincent, 1999)

Activity	Nb of results	Mean (mg/m^3)	Range (mg/m^3)	Median (mg/m^3)	95th percentile (mg/m^3)
Screen printing	168	18.6	0.1.212	6.2	100
Screen washing	33	41	0.1-411	13	406
Offset printing	61	16.7	0.2.320	3	35
Cleaning	4	4.1	0.2-8	-	-
Flexography	212	94.2	0.2-841	148	304
Heliogravure	82	12.1	0.2.297	4	24.4

In the printing industry, the distribution of exposure levels to PGME has not significantly changed from 1987-92 to 1993-1998 but the mean exposure is significantly higher (p=0.039) : the arithmetic mean for personal samplings was 30.6 mg/m^3 (median 7 mg/m^3; 1-411 range

mg/m^3; 110 samples) for the first period, and 49.8 mg/m^3 (median 9.7 mg/m^3; range 0.1-843 mg/m^3; 79 samples) for the second (Vincent and Jeandel, 1999).

In the German MEGA database, 148 exposure measurements have been registered between 1996 and 2000, which were obtained during printing, mainly during screen printing and to some extent, during flexographic printing. The results (measurement values with an exposure duration ≥1 hour and a sampling duration ≥ 1 hour converted to 8-hour weighted averages) are presented in table 4.20. When possible, a distinction is made on the basis of whether or not control measures (LEV) were taken (see comments in scenario 2).

Table 4-20: Personal exposure mesurements in the MEGA database, 1996-2000 (BGAA, 2001)

Type of company/working area	No of results	No of companies	50% value (mg/m^3)	75 % value (mg/m^3)	90 % value (mg/m^3)	95 % value (mg/m^3)
Printing	148	57	a	15.00	32.00	59.00
- without LEV	68	32	a	15.00	32.40	50.00
- with LEV	77	34	a	15.00	25.60	68.20

Modelled data

Exposure to vapours during printing is estimated by EASE to be in the range of 20-50 ppm (74.8-187mg/m^3) for non dispersive use, low/moderate tendency to become airborne, direct handling with dilution ventilation.

The model overestimates exposure levels, particularly because of non-consideration of the content of PGME in the products. The estimates cannot be corrected for the partial vapour pressure because the composition of the formulations is not known. A simple approach based on a reduction of the exposure by a factor equivalent to the PGME concentration in the mixture (35 % for silk screen inks and 20 % for others) would lead to exposure levels of:

- 26 - 66 mg/m^3 for silk screening

- 15-37 mg/m^3 for general printing.

However the validity of these estimates is rather questionable.

Summary/statement of the exposure level

As can be seen from these relatively limited data and as was predictable in view of the variety in conditions of use and substance concentration in the product used, measured concentrations in air at the working place are highly variable depending the process and activities.

The highest exposure levels are likely to occur during screen printing and flexography. In COLCHIC; measured concentrations (95th percentiles) range from 100 to 400 mg/m^3. More recent results collected in the MEGA database are markedly lower (95th percentile range: 50-68 mg/m^3, 90th percentile range: 26-32 mg/m^3). A reasonable worst-case exposure of 100 mg/m^3 may be proposed for these activities.

Lower exposure levels are measured for other activities (offset, heliogravure). Mainly based on the COLCHIC data, a reasonable worst-case exposure of 35 mg/m^3 may be proposed for these activities.

¤- 100 mg/m^3 for silk screening and flexography

¤- 35 mg/m^3 for general printing.

Dermal exposure

Measurements

In a study performed in Finland by the Kuopio Regional Institute of Occupational Health (Riskofderm, 2003b), a part of the EU Riskofderm project, potential hands exposure to an other glycol ether EGBE (2 butoxyethanol, vapour pressure 0.1 kPa at 20°C) was measured during silk screening on 10 workers in three different enterprises. The measurements were made for 6 to 8 hours by giving protective gloves, which were collected after shift and analysed. Results (given in formulation) are presented in table 4.21. In the same study, measurements of actual hand exposure indicate that the use of gloves does lower hand exposure significantly. Hands seemed to be the most dominant potential dermal route exposure because EGBE could not be found on other body parts of printers.

Table 4.21: Potential dermal exposure measurements during silk screening (Riskofderm, 2003b)

	1st measurement day (µg/cm^2/h)	2nd measurement day (µg/cm^2/h)
No of samples	6	10
Average	5.328[a]	4.068[b]
90th %	15.684	12.937

a : 3 results were below the limit of detection
b : one result was below the limit of detection

The range of the measured exposure values for the formulation was <0.04-85 mg and the 90th percentile was 65 mg (unpublished data from the original data).

Modelling

Dermal exposure may occur during mixing, application and cleaning activities. Intermittent contact seems appropriate for this scenario (as for painting). Assuming non dispersive use, direct handling and intermittent contact, the EASE model estimates a dermal exposure in the range of 0.1-1 mg of product/cm^2/day. The estimation is made for a formulation containing up to 35 % (silk screen inks) or 20 % (others) of PGME and an exposed skin surface area of 840 cm^2 (two hands). This leads to an estimated external dermal exposure of:

- 29-294 mg/day for silk screening

- 17-168 mg/day for flexography and general printing.

Assessment

For general printing, no relevant exposure data are available. The EASE estimate therefore has to be used for risk characterisation. For silk screen printing, a set of 16 potential full shift hand exposure data is available with a 90th percentile of 65 mg of product. The "product" in

this case consisted of a printing ink with up to 10% of EGBE and a retarder (up to 100% EGBE) that was used by just two of the printers (as part of the total ink-system). Assuming that the concentration of PGME in screen printing inks can be up to 35 %, the reasonable worst case exposure level for PGME in this process would be approximately 23 mg/day. Because the measured values are based on more than 12 measurements and come from different workplaces, they can be considered sufficiently representative for use in risk characterisation.

In conclusion, the following range are proposed for dermal exposure during printing:

- 23mg/day for silk screening

- 168 mg/day for general printing.

Dermal exposure may be much lower if suitable gloves are worn.

- **Miscellaneous**

Hubner *et al.* (1992) studied occupational exposure to PGME used to check leaks in brakehoses manufacture. Mean atmospheric levels were 82.2 mg/m^3 in the production department (n = 5), 68.6 mg/m^3 in the leak testing facility (n = 7), and 11.3 mg/m^3 (n = 6) in the testing area. For the estimation of internal exposure, PGME was measured post-shift in both urine and blood. The average concentrations for PGME in urine and blood were respectively 4.6 mg/l and 13.5 mg/l for workers in the production section, and 4.2 mg/l and 11 mg/l for workers in the leak test area. The authors stress that measurement of external exposure is not sufficient to assess the risk, due to the high percutaneous penetration of PGME.

Kauppinen *et al.* (1997) constructed an international database of exposure measurements in the paper industry to be used in exposure assessment for epidemiology studies and hazard control. PGME was measured 32 times in the production department, and the TLV was exceeded 17% of the total 35 measurements. No more details are provided.

In 2000 and 2001, a study was performed in France to estimate the levels of exposure to glycol ethers in a sample population of 109 men employed by the Paris municipality by measuring the amount of alkoxycarboxylic acid metabolites in their urine. All men worked in maintenance, cleaning, transport, data processing and communication departments of the municipality, 54 were judged to be occupationally exposed to glycol ether-containing products. 2-MPA was the most frequently found metabolite and it was also the metabolite that presented the highest concentrations reaching 5.6 mmol/mol creatinine. The mean concentration was 1.12 mmol/mol creatinine (range : 0.29-4.52) after the first day and 1.22 mmol/mol creatinine (range : 0.28-5.58) after the 2nd day. The authors conclude that particular attention should be paid in the future to alkoxypropionic acids derived from minor isomers of propylene glycol ether derivatives.

4.1.1.2.4 Summary of occupational exposure

As pointed out in the report, dermal exposure may make a significant contribution to overall exposure and needs to be considered carefully. The estimates based on measured data from RISKOFDERM should be preferred to the EASE estimates as they represent real exposure situation and EASE is known to be a weak model for this purpose.

RISKOFDERM measured data are however overestimated, especially when measurements have been done with gloves and when they are based on the much less volatile DEGBE. The level of overestimation cannot be estimated but the uncertainty caused by the measurement method should be taken into account for risk characterisation in the evaluation of the MOS. This is particularly relevant for scenario 1 (formulation) and scenario 2 (painting).

Table 4.22: Summary of proposed reasonable worst case exposures

Scenario	8-hour TWA inhalation (mg/m^3)	External Dermal exposure (mg/day)
1 - Manufacture	2.7	42
2 - Formulation	87	2,000 (loading) 1,000 (filling)
3 - Use of products		
3.1 Coating/Painting*		
- industrial		
- Spraying	100	3,000
- Other works	61	360
- decorative	61	180
3.2 Cleaning		
- spraying	151	250
- wiping	151	1,000
3.3 Printing		
- silk screening	100	23
- flexography	100	168
- general printing	35	168

* The conclusions refer to solvent-based paints. Exposure from use of water-based paints (lower PGME content) would be much lower.

4.1.1.3 Consumer exposure

4.1.1.3.1 Exposure from uses

PGME is used in many consumer products at typical concentrations of about 0.5-20%. The identified consumer products are aqueous paints, floor varnishes, cleaning agents and detergents, and nail varnish remover.

In Europe, PGME is used as tension agent in aqueous paints and in floor varnishes at concentration ranging to 11 % (FIPEC, 2004). The concentration of PGME used in cleaning products is at maximum 20% (ADEPHY, 2001). The concentration of PGME used in nail varnish remover is about 20% (FIP, 2001).

With respect to the above mentioned indicated consumer uses of PGME and the availability of information especially about the concentration of PGME in the consumers products three exposure scenarios are considered: indoor air, aqueous paints and floor varnishes, house cleaners. The scenario about nail varnish remover is not relevant because levels of exposure from this scenario are negligible.

Scenario 1: Measurements in indoor air

Measurements of PGME concentration were performed in the indoor air of flats (Kirchner, 2002). Preliminary results indicate that the values ranged from 0.7 µg/m^3 to 32 µg/m^3 (mean value is 3 ± 5 µg/m^3) in bedroom. The values ranged from 0.7 µg/m^3 to 48 µg/m^3 (mean value is 4 ± 8 µg/m^3) in kitchen. Releases from building materials were also evaluated. Simulations were made by installing new carpets in reference rooms. After 24 hours, the concentration of PGME in air ranged from 0.4 to 1.2 µg/m^3. After 28 days, the concentration of PGME in air ranged from 1.5 to 1.8 µg/m^3.

As a worst case approach, the concentration in indoor air retained is **48 µg/m^3**.

Only exposure by inhalation is retained. For inhalation, based on a 20 m^3 respiratory volume a day for an adult weighing 60 kg and a 20 hours duration of exposure, the exposure will be:

$$\frac{20 \times 48 \times 20}{60 \times 24} = 13 \text{ µg/kg/d} = \textbf{0.01 mg/kg/d}$$

Scenario 2: Aqueous paints and floor varnishes

When PGME is used as an ingredient in aqueous paints and floor varnishes, the main exposure routes are by inhalation and by skin contact. The concentration of PGME in paints and floor varnishes is at maximum 11 %. No measured data was found about dermal and inhalation exposure of consumers by paints or floor varnishes during their use or after their application.

Also as worst case, we will take as values of consumers exposure that retained for the exposure of the workers in the scenario of painting by brush and roller application.

The external exposure will be **61 mg//m^3**

Assuming a respiratory volume a day of 20 m^3 and a bodyweight of 60 kg, the external inhalation exposure is:

61 x 20/60 = **20.3 mg/kg/d**

For dermal exposure, assuming direct handling and intermittent contact, the EASE model estimates a dermal exposure in the range of 1-5 mg of product/cm^2/day for wide dispersive use. The estimation is made from a formulation containing up to 11% of PGME and an exposed skin surface area of two hands of 840 cm^2.
This lead to estimated external dermal exposure of: 92.4-462 mg/day

Assuming a bodyweight of 60 kg, the external dermal exposure is: **1.5–7.7 mg/kg/d**

Scenario 3: House cleaners

When PGME is used as an ingredient in house cleaners the main exposure routes are by skin contact and by inhalation. The concentration of PGME in house cleaners is at maximum 20%. No data was found about dermal exposure and inhalation exposure of consumers using house cleaners during their use.

The consumer exposure to PGME is estimated with model of Technical Guidance Document. Two calculations of inhalation exposure and skin exposure where made, one with 2% and one with 20% PGME in house cleaners.

Inhalation exposure

In the Technical Guidance Document, data from AISE (2002) are provided for use of surface cleaners : the highest quantity of liquid surface cleaner used is 110 g/task when it is diluted in 5 L of wash water volume and the longest duration of exposure is 20 minutes.

Assuming 2% of PGME in house cleaners, 30% of house cleaners evaporate and a room volume of 20 m^3, the concentration in air is:

$$C_{inh} = \frac{110 \times 10^3 \times 0.02 \times 0.3}{20} = \mathbf{33\ mg/m^3}$$

For inhalation, based on a 20 m^3 respiratory volume a day for an adult weighing 60 kg and a 20 minutes (1/3 hour) duration of exposure, the exposure will be:

$$I_{inh} = \frac{33 \times 20 \times 1}{60 \times 24 \times 3} = \mathbf{0.15\ mg/kg/j}$$

Assuming 20% of PGME in house cleaners, 30% of house cleaners evaporate and a room volume of 20 m^3, the concentration in air is :

$$C_{inh} = \frac{110 \times 10^3 \times 0.2 \times 0.3}{20} = \mathbf{330\ mg/m^3}$$

For inhalation, based on a 20 m^3 respiratory volume a day for an adult weighing 60 kg and a 20 minutes (1/3 hour) duration of exposure, the exposure will be:

$$I_{inh} = \frac{330 \times 20 \times 1}{60 \times 24 \times 3} = \mathbf{1.5\ mg/kg/j}$$

Skin exposure

For dermal exposure, assuming direct handling and intermittent contact, the EASE model estimates a dermal exposure in the range of 1-5 mg of product/cm^2/day for wide dispersive use. Assuming 70% of house cleaners non evaporate, surface area of two hands of 840 cm^2 and 2% of PGME in house cleaners, estimated external dermal exposure is: 11.8-58.8 mg/day

Assuming a bodyweight of 60 kg, the external dermal exposure is: **0.2–1 mg/kg/d**

Assuming 20% of PGME in house cleaners, estimated external dermal exposure is: 117.6-588 mg/day

Assuming a bodyweight of 60 kg, the external dermal exposure is: **2–9.8 mg/kg/d**

4.1.1.3.2 Summary of consumer exposure

Table 4.23: Summary of proposed reasonable worst case exposures in the main scenarios

SCENARIO	INHALATION		SKIN	SUM OF EXPOSURES
	(MG/M^3)	(MG/KG/D)	(MG/KG/D)	(MG/KG/D)
1. INDOOR AIR	0.048	0.01		0.01
2. AQUEOUS PAINTS AND FLOOR VARNISHES	61	20.3	7.7	28
3. HOUSE CLEANERS	330	1.5	9.8	11.3

4.1.1.4 Humans exposed via the environment

The information relating to the estimation of the indirect exposure of humans via the environment are presented in table 4.24. The concentrations calculated in intake media (drinking water, fish, plant roots and leaves, milk, meat, air) and the subsequent estimation of human intakes via different routes are shown hereafter with the corresponding total daily intakes. Both local and regional levels are taken into consideration and the estimation of local environmental exposures has been performed for all scenarios listed in chapter 2.2. Concerning the production step, only the worst case has been reported. All calculations have been performed using EUSES 2 and default parameters of this software have been used excepted a value of 30% for dermal absorption and a value of 100% for inhalation exposure and a body weight of 60 kg.

Table 4.24: Concentrations for indirect exposure of humans via the environment and subsequent total daily intakes

	Conc. in drinking water (mg.L^{-1}) / Subsequent daily dose (mg.kg^{-1}.d^{-1})	Conc. in wet fish (mg.kg^{-1}) / Subsequent daily dose (mg.kg^{-1}.d^{-1})	Conc. in plant roots (mg.kg^{-1}) / Subsequent daily dose (mg.kg^{-1}.d^{-1})	Conc. in plant leaves (mg.kg^{-1}) / Subsequent daily dose (mg.kg^{-1}.d^{-1})	Conc. in milk (mg.kg^{-1} ww) / Subsequent daily dose (mg.kg^{-1}.d^{-1})	Conc. in meat (mg.kg^{-1} ww) / Subsequent daily dose (mg.kg^{-1}.d^{-1})	Conc. in air (mg.m^{-3}) / Subsequent daily dose (mg.kg^{-1}.d^{-1})	Total daily intake (mg.kg^{-1}.d^{-1})
Production (site-specific, worst case)	0.591 / 0.0197	0.29 / 5.56×10^{-4}	0.552 / 3.53×10^{-3}	13.2 / 0.264	8.03×10^{-3} / 7.51×10^{-5}	8.03×10^{-4} / 4.03×10^{-6}	0.716 / 0.239	0.526
Chemical industry: chemicals used in synthesis: Processing	0.066 / 2.20×10^{-3}	0.0932 / 1.79×10^{-4}	0.0443 / 2.83×10^{-4}	7.53×10^{-3} / 1.51×10^{-4}	3.32×10^{-5} / 3.11×10^{-7}	3.32×10^{-6} / 1.67×10^{-8}	3.99×10^{-4} / 1.33×10^{-4}	2.95×10^{-3}
Chemical industry: chemicals used in synthesis (Captive use): Processing	0.184 / 6.13×10^{-3}	0.26 / 4.98×10^{-4}	0.0328 / 2.1×10^{-4}	0.0257 / 5.15×10^{-4}	9.55×10^{-5} / 8.93×10^{-7}	9.55×10^{-6} / 4.79×10^{-8}	1.39×10^{-3} / 4.64×10^{-4}	7.82×10^{-3}
Paints and coating:								
- Water based: Formulation	0.05 / 1.67×10^{-3}	0.0706 / 1.35×10^{-4}	0.022 / 1.41×10^{-4}	0.311 / 6.23×10^{-3}	2.05×10^{-4} / 1.92×10^{-6}	2.05×10^{-5} / 1.03×10^{-7}	0.0169 / 5.64×10^{-3}	0.0138
Processing	0.188 / 6.28×10^{-3}	0.266 / 5.10×10^{-4}	0.0714 / 4.57×10^{-4}	1.2 / 0.0239	7.88×10^{-4} / 7.37×10^{-6}	7.88×10^{-5} / 3.95×10^{-7}	0.065 / 0.0217	0.0529
Private use	5.61×10^{-3} / 1.87×10^{-4}	6.46×10^{-3} / 1.24×10^{-5}	5.24×10^{-3} / 3.35×10^{-5}	4.87×10^{-3} / 9.74×10^{-5}	5.33×10^{-6} / 4.98×10^{-8}	5.33×10^{-7} / 2.67×10^{-9}	2.64×10^{-4} / 8.79×10^{-5}	4.18×10^{-4}
- Solvent based: Formulation	0.232 / 7.72×10^{-3}	0.327 / 6.27×10^{-4}	0.0889 / 5.69×10^{-4}	1.54 / 0.0307	1.01×10^{-3} / 9.42×10^{-6}	1.01×10^{-4} / 5.05×10^{-7}	0.0835 / 0.0278	0.0675
Processing	0.267 / 8.91×10^{-3}	0.266 / 5.10×10^{-4}	0.25 / 1.60×10^{-3}	6.71 / 0.134	4.07×10^{-3} / 3.81×10^{-5}	4.07×10^{-4} / 2.04×10^{-6}	0.364 / 0.121	0.267
Private use	5.61×10^{-3} / 1.87×10^{-4}	6.46×10^{-3} / 1.24×10^{-5}	5.24×10^{-3} / 3.35×10^{-5}	4.87×10^{-3} / 9.74×10^{-5}	5.33×10^{-6} / 4.98×10^{-8}	5.33×10^{-7} / 2.67×10^{-9}	2.64×10^{-4} / 8.79×10^{-5}	4.18×10^{-4}
Printing inks: Formulation	0.0672 / 2.24×10^{-3}	0.095 / 1.82×10^{-4}	0.0283 / 1.81×10^{-4}	0.428 / 8.55×10^{-3}	2.82×10^{-4} / 2.63×10^{-6}	2.82×10^{-5} / 1.41×10^{-7}	0.0232 / 7.75×10^{-3}	0.0189
Processing	0.0323 / 1.08×10^{-3}	0.0136 / 2.61×10^{-5}	0.0301 / 1.93×10^{-4}	0.539 / 0.0108	3.32×10^{-4} / 3.10×10^{-6}	3.32×10^{-5} / 1.67×10^{-7}	0.0293 / 9.77×10^{-3}	0.0218
Detergents, cleaners: Formulation	0.265 / 8.84×10^{-3}	0.374 / 7.18×10^{-4}	2.9×10^{-4} / 3.38×10^{-4}	0.269 / 5.37×10^{-3}	2.74×10^{-4} / 2.56×10^{-6}	2.74×10^{-5} / 1.38×10^{-7}	0.0146 / 4.86×10^{-3}	0.0201
Processing	0.0164 / 5.74×10^{-4}	0.0223 / 4.27×10^{-5}	0.0153 / 9.80×10^{-5}	4.92×10^{-3} / 9.84×10^{-5}	1.01×10^{-5} / 9.4×10^{-8}	1.01×10^{-6} / 5.04×10^{-9}	2.64×10^{-4} / 8.79×10^{-5}	8.74×10^{-4}
Leather finishing agent: Processing	1.9 / 0.0634	$2.69 / 5.15\times10^{-3}$	0.775 / 4.96×10^{-3}	9×10^{-3} / 1.8×10^{-4}	8.35×10^{-4} / 7.81×10^{-6}	8.35×10^{-5} / 4.19×10^{-7}	3.07×10^{-4} / 1.02×10^{-4}	0.0738
Electronic industry: Processing	0.0162 / 5.41×10^{-4}	0.0151 / 2.9×10^{-5}	0.0151 / 9.69×10^{-5}	5.91×10^{-3} / 1.18×10^{-4}	1.06×10^{-5} / 9.87×10^{-8}	1.06×10^{-6} / 5.3×10^{-9}	3.18×10^{-4} / 1.06×10^{-4}	8.91×10^{-4}
Agriculture: Processing	5.89×10^{-3} /	6.45×10^{-3} /	5.49×10^{-3} / 3.52×10^{-5}	0.0128 / 2.57×10^{-4}	1.01×10^{-5} / 9.48×10^{-8}	1.01×10^{-6} / 5.09×10^{-9}	6.96×10^{-4} / 2.32×10^{-4}	7.32×10^{-4}

	Conc. in drinking water (mg.L^{-1}) / Subsequent daily dose (mg.kg^{-1}.d^{-1})	Conc. in wet fish (mg.kg^{-1}) / Subsequent daily dose (mg.kg^{-1}.d^{-1})	Conc. in plant roots (mg.kg^{-1}) / Subsequent daily dose (mg.kg^{-1}.d^{-1})	Conc. in plant leaves (mg.kg^{-1}) / Subsequent daily dose (mg.kg^{-1}.d^{-1})	Conc. in milk (mg.kg^{-1} ww) / Subsequent daily dose (mg.kg^{-1}.d^{-1})	Conc. in meat (mg.kg^{-1} ww) / Subsequent daily dose (mg.kg^{-1}.d^{-1})	Conc. in air (mg.m^{-3}) / Subsequent daily dose (mg.kg^{-1}.d^{-1})	Total daily intake (mg.kg^{-1}.d^{-1})
	1.96×10^{-4}	1.24×10^{-5}						
Cosmetics/Personal care:								
Formulation	0.039 / 1.3×10^{-3}	0.0551 / 1.06×10^{-4}	0.0115 / 7.38×10^{-5}	0.0397 / 7.94×10^{-4}	4.04×10^{-5} / 3.78×10^{-7}	4.04×10^{-6} / 2.03×10^{-8}	2.16×10^{-3} / 7.19×10^{-4}	2.99×10^{-3}
Private Use	6.54×10^{-3} / 2.18×10^{-4}	9.24×10^{-3} / 1.77×10^{-5}	5.48×10^{-3} / 3.51×10^{-5}	4.87×10^{-3} / 9.74×10^{-5}	5.73×10^{-6} / 5.36×10^{-8}	5.73×10^{-7} / 2.88×10^{-9}	2.64×10^{-4} / 8.79×10^{-5}	4.56×10^{-4}
Regional	4.57×10^{-3} / 1.52×10^{-4}	6.45×10^{-3} / 1.24×10^{-5}	3.19×10^{-3} / 2.04×10^{-5}	4.86×10^{-3} / 9.72×10^{-5}	4.86×10^{-6} / 4.55×10^{-8}	4.86×10^{-7} / 2.44×10^{-9}	2.64×10^{-4} / 8.79×10^{-5}	3.7×10^{-4}

The highest indirect exposure is estimated for the production : 0.526 $mg.kg^{-1}.day^{-1}$. It can also be noted that the highest exposures are to be expected through intake of drinking water, fish and plants (leaves and roots). Moreover, based on the regional concentrations, the total daily intake for humans is 3.7×10^{-4} $mg.kg^{-1}.day^{-1}$. These two figures will be taken forward into the risk characterisation.

4.1.2 Effects assessment: Hazard identification and dose (concentration)-response (effect) assessment

This part of the report is based extensively on the OECD SIDS dossier dated 23-26 January 2001 (rapporteur: USA). The reporting of the studies and the conclusions are the same as those reached by OECD. Only a few details have been added in this report and some studies which were not included in the SIDS dossier. For this reasons, some studies in this report are not reported in details, but have been approved at OECD level.

4.1.2.1 Toxicokinetics, metabolism and distribution

4.1.2.1.1 Studies in animals

In vivo studies

Inhalation

Fischer 344 rats inhaled a single nose-only exposure of PGME (purity 98.6 % of α isomers and 1.4 % of β form) at doses of 300, 750, 1500 and 3000 ppm nose only (1.1, 2.8, 5.6 and 11.2 mg/l)- and 300 and 3000 ppm (1.1 and 11.2 mg/l) whole-body (Morgot and Nolan, 1987). A 10-day treatment schedule was also performed whole-body with the same doses than single whole-body exposure.

For nose-only exposures: Blood levels of PGME failed to reach a plateau during a single 6-hour exposure, indicating an absoption through respiration. The maximum blood Propylene Glycol (PG) concentrations resulting from the 750, 1500 and 3000 ppm exposures were 10.5, 20.7 and 16.4 μg/g respectively. Only a few of the blood sample collected from the 300 ppm group contained quantifiable amounts of PG. There were no differences in PGME kinetics for rats exposed once or for 10 days at the 300 ppm levels. At 3000 ppm rats exposed 10 times showed lower PGME blood levels than those exposed only one exposure. The clearance of PGME following a single exposure (nose only or whole body) is described as a pseudo-zero order process. Following ten 6-hour exposures, PGME at 3000 ppm was completely eliminated 24 hours after the last exposure. Repeated exposure to 3000 ppm increased liver weight and mixed function oxidase (MFO) activity. This enyzmatic induction may account for the rapid development of tolerance to repeated inhalation exposures to high concentrations of PGME. For the unique dose study, the average end-exposure level of blood PGME was higher in males than in females (about 40 %) and after 24 hours, blood PGME levels were 8 times greater in males than in females. PG blood levels (a metabolite of PGME) were 2-fold higher in males than in females throughout the 24-hour post exposure period.

Oral

Three F344 rats were dosed with 1 mmol/kg or 8.7 mmol/kg [^{14}C] PGME (corresponding to about 90 and 780 mg/kg) (Miller *et al*., 1983). Animals were kept 24 hours in a metabolism cage for expired air and excreta collection. Animals were sacrificed at the end of the 48-hour collection period.
For the 1 mmol/kg dose, 63 % of [^{14}C]PGME was eliminated as CO_2 within 48 hours, about 11 % in urine and about 0.9 % in faeces. 9 % of [^{14}C]PGME remained in the carcass. For the 8.7 mmol/kg dose, about 55 % of the dose was eliminated as CO2, 25 % in urine and 6.3 % remained in the carcass after 48 hours (see table 4.24 bis).

Table 4.24 bis: Percentage recovery values during a 48h period after dosing with PGME

	PGME dose (mmol/kg)	
	1	8.7
Urine	11.2	24.8
Faeces	0.9	0.7
Charcoal	3	6.9
CO2	63	56.5
Carcass	9.2	6.3
Skin	1.7	1.7
Wash	2.8	0.6
Total	91.8	98.4

According to these results a very high oral absorption is expected (almost 100 %).

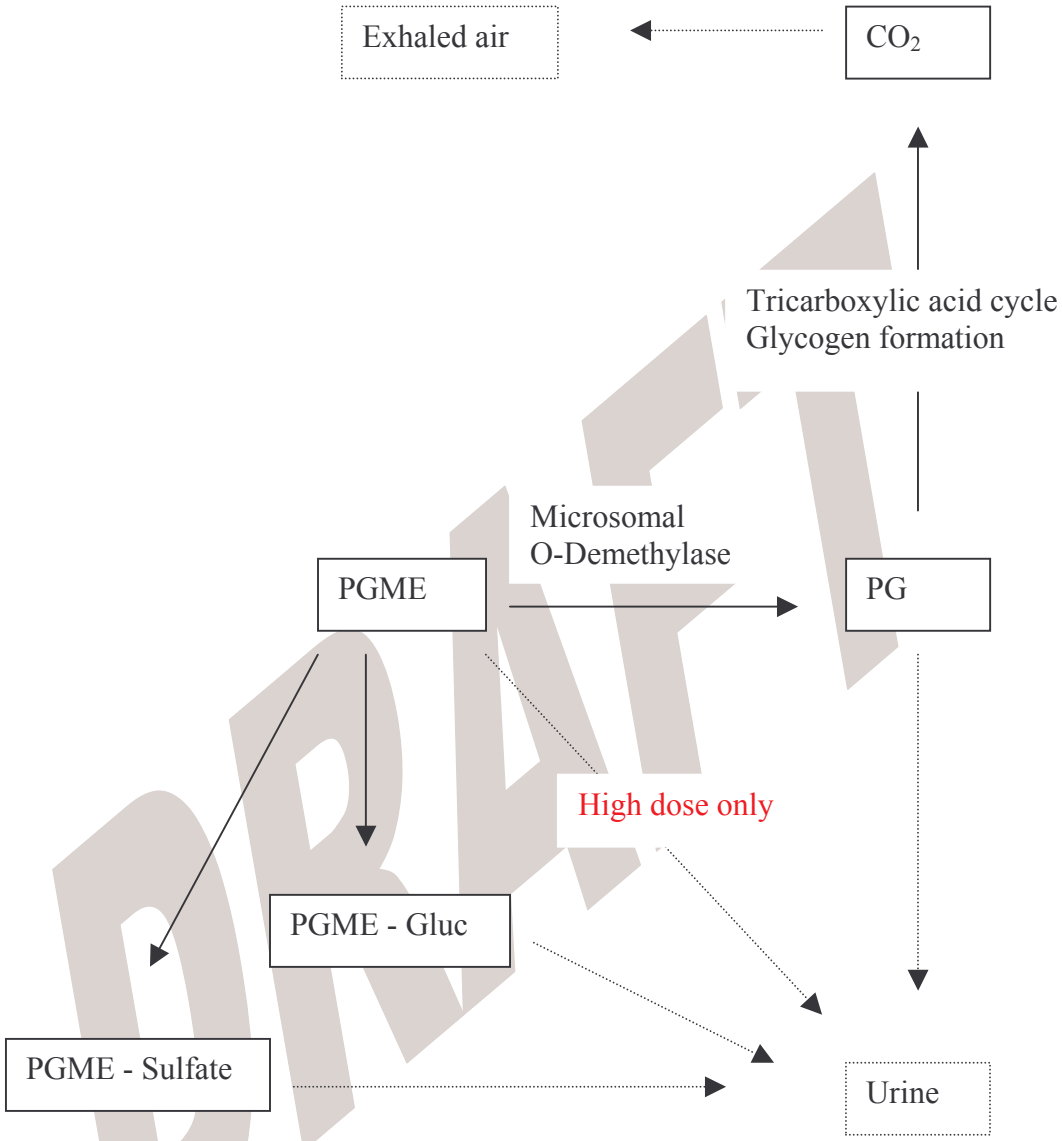
The mechanism of excretion seems to be saturated during the first 24 hours since the percentage excreted per hour remained relatively constant. The urinary excretion seems to be saturated since the amount excreted/hour during the 0-12 and 12-24 hr interval periods were relatively constant. The highest level of radioactivity was found in the liver when compared to blood levels (2.33 more than in blood). After liver, target organs were kidney, thymus and spleen. Very small amounts (less than 0.1 % of the dose) were recovered in testes, fat and general body tissues. In the urine, the quantities of metabolites found were summarized in the table 4.25.

Table 4.25: Percentages of PGME and metabolites found in urine

	8.7 mmol/kg		1 mmol/kg
Substances.	0-12 hr	12-24hr	0-12 hr
PGME – Sulfate	22 %	46 %	8 %
PGME – Glucuronide	46 %	46 %	43 %
PG	19 %	9 %	44 %
PGME	12 %		
Unidentified metabolite			4 %

According to the data available, the following metabolic scheme can be proposed for PMGE:

Figure 4.26: Metabolic pathway of PGME



PG: propylene glycol

PGME-gluc: glucuronide conjugate of PGME

In mice, PGME was readily absorbed and metabolized to propylene glycol following oral gavage with maximum concentrations of PGME and propylene glycol in plasma attained in 20 and 30 minutes following dosing, respectively (Ferrala *et al.*, 1994).

- dermal route

In recent experiment, the blood pharmacokinetics of PGMA (propylene glycol methyl ether acetate) and PGME in male rats was conducted following a single 6-hr dermal exposure at 100 or 1,000 (nominal) mg/kg (Sumner, 1999). Dermal application of PGMA at 130 mg/kg

and 935 mg/kg resulted in the average PGME AUC (Area Under the Curve) of 88 and 1,580 ug/mL, respectively. Similarly, PGME application gave the average PGME AUC of 1,663 and 15,051 ug/mL at the dose of 126 and 995 mg/kg, respectively. When AUCs were normalised to applied dose in terms of mmole basis, the mean combined PGME AUC after PGMA and PGME application were 0.0044 AUC/dose and 0.0141 AUC/dose, respectively. When AUC/dose of PGME is compared to that of PGMA, the ratio is 0.315, meaning that the efficiency of dermal absorption for PGMA is approximately 30% of that of PGME in rats. Dermal absorption rate for PGMA is assumed to be 1.17 mg/cm^2/hr, based on the conservative estimate, whereas 0.37 mg/cm2/hr is calculated when 0.315 for AUC ratio of PGME/PGMA in rats is applied.

Other routes

PGME was injected intravenously to rats at dose of 10 and 100 mg/kg (Domoradzki *et al*., 2001). Blood samples were collected up to 12 hours post exposure to determine kinetic parameters. PGMA was also tested with the same experimental procedures in order to determine kinetic differences between the two substances. Half lives of blood PGME were 10.36 and 38.62 min for the low and high dose respectively.

In vitro studies

In vitro studies were performed to evaluate glycol ethers as substrates for alcohol dehydrogenase (Calhoun and Miller, 1982). The following substances were tested: EGME (Ethylene Glycol Methyl Ether), EGEE (Ethylene Glycol Ethyl Ether), EGBE (Ethylene Glycol Butyl Ether), DEGME (DiEthylene Glycol Methyl Ether), DEGEE (Di Ethylene Glycol Ethyl Ether), DEGBE (Di Ethylene Glycol Butyl Ether), PGME (97.23 % pure – 2.73 % of β isomer) and DPGME.

According to this test, PGME is a very poor substrate for alcohol dehydrogenase. The majority of PGME (α isomer a secondary alcohol) undergoes an O-demethylation to form propylene glycol (Miller *et al.*, 1986).

An *in vitro* liver slice metabolism assay was used to investigate the formation of 2-methoxypropionic acid (2-MPA – a known reproductive toxican) from 6 propylene glycol ethers including PGME (purity > 98 %) (PGDME (Propylene glycol di methyl ether), DPGDME (Di Propylene glycol di methyl ether), PGMBE (propylene glycol methyl butyl ether), DPGMBE (di propylene glycol methyl butyl ether), TPGMBE (tri propylene glycol methyl butyl ether)). The test was performed with rat and rabbit liver (Pottenger *et al*., 1995).

The results showed that PGME led to the formation of much greater amounts of 2-MPA than any of the other glycol ethers investigated and that rat liver was 3 to 10 fold more effective to produce 2-MPA than rabbit liver.

In a similar experiment (Bartels *et al*., 2004) metabolism of PGME (isomers α and β), DPGME and TPGME was studied in rat, rabbit and human liver hepatocytes. An initial concentration of 4.8 mM of substrates was used. 2-MPA was found to be a significant metabolite of β PGME representing a total of 34 %, 5 % and 18 % of the PGME used for rat, rabbit and human hepatocytes respectively. 2-MPA was a minor metabolite of the commercial PGME (99.7 % of α isomer). In this series of experiments, lactic acid was also tested in the same experimental condition as glycol ethers to verify that methylation of lactic acid did not form 2-MPA formation *in vitro*. No MPA was formed from lactic acid.

4.1.2.1.2 Studies in humans

In vivo studies

Inhalation

Six volunteers (4 males and 2 females) were exposed to 100 ppm PGME (374 mg/m^3) vapour over 8 h including a 30 min break after 4 h exposure (Jones *et al*., 1997. Blood, breath and urine samples were taken before, during and up to 24 hours after exposure.

PGME was readily absorbed with rapid alveolar uptake and elimination. A steady state for PGME in alveolar air is reached within 1h. Lung clearance was biphasic with half lives of 4-15 min and 45-72 min respectively for each phase. A maximum of 103 µmol/l PGME was found in blood. The mean blood elimination half-life was 93 min. The mean level of free PGME in post exposure urine was 92 µmol/l. Urinary excretion of PGME was rapid with a mean half-life of 120 min. Only one volunteer was found to have a detectable urine level of PGME 16 hours after the exposure period and for him nothing were detected 2h later (18h post exposure).

Workers exposed to 20-40 ppm PGME (75 – 150 mg/m^3) for 5 hours had concentrations of 2-8 mg/L PGME in their urine, of which 40-60 % was in conjugated form (sulfate and glucuronide) (Devanthéry *et al.*, 2000).

Dermal

Six male volunteers were exposed during 12 separate sessions to PGME (Devanthéry *et al*., 2002). The exposures were conducted during 6 hours, including a 30-minute break in the middle. Each subject was exposed on 6 occasions at 15, 50 and 95 ppm (56, 187 and 355 mg/m^3) without respiratory protection of the total exposure to PGME vapour (inhalation and dermal) and 15, 50 and 95 ppm with a positive-pressure respirator for the evaluation of dermal only exposure. Samples of urine, blood and expired air were taken during and after exposure.

For "total exposure", the maximum urine PGME concentrations were found at the end of the exposure and were 2.5, 6.2 and 10.3 mg/l for 15, 50 and 95 ppm exposure respectively. For dermal only exposure, the values of the total PGME was below the detection limit (0.5 – 1 mg/l) whichever the exposure dose. Blood concentration of PGME reach a maximum at the end of the exposure time: 2.0, 4.9 and 11.8 mg/l for 15, 50 and 95 ppm exposure respectively. Free PGME in expired air reached 0.4, 1.4 and 2.9 ppm at the end of the 15, 50 and 95 ppm total exposure, respectively. No trace of PGME was seen after a skin only exposure whichever the dose tested. The mean value of urinary half-life of PGME was 3.5h and the mean half-life of free PGME in expired air was 10 min.
According to the authors, the dermal absorption of the PGME vapour probably provides potential contributions of approximately 4 % to 8 % to total body burden.

Dermal absorption of PGME in the vapor phase was investigated in male and female human volunteers (Jones, 1997). Each study involved two exposures of 100 ppm: in one a mask was worn which provided fresh air to exclude the inhalation route and leave only the dermal route available for absorption. In the other exposure volunteers were exposed by inhalation as well as dermal absorption. Volunteers were exposed for 4 hours and wore shorts and tee shirts during exposure. Blood, urine, and breath samples were taken before and after exposure.

Blood level measurements indicated that the mean dermal absorption contribution was 6.3% (range 2.0-10.3%). The estimated mean dermal absorption based on breath sample analysis was 5.6% (range 0.7-14.2%). Elimination half-life in the total absorption (dermal and inhalation) average 1.5 hours; by contrast, the mean apparent half-life for the dermal study was 2.7 hours. Urinary half life for the dermal-only study was nearly twice that for total exposure. It is possible that in the case of dermal absorption, absorption is delayed but there may be a reservoir effect giving an apparent delay in elimination.

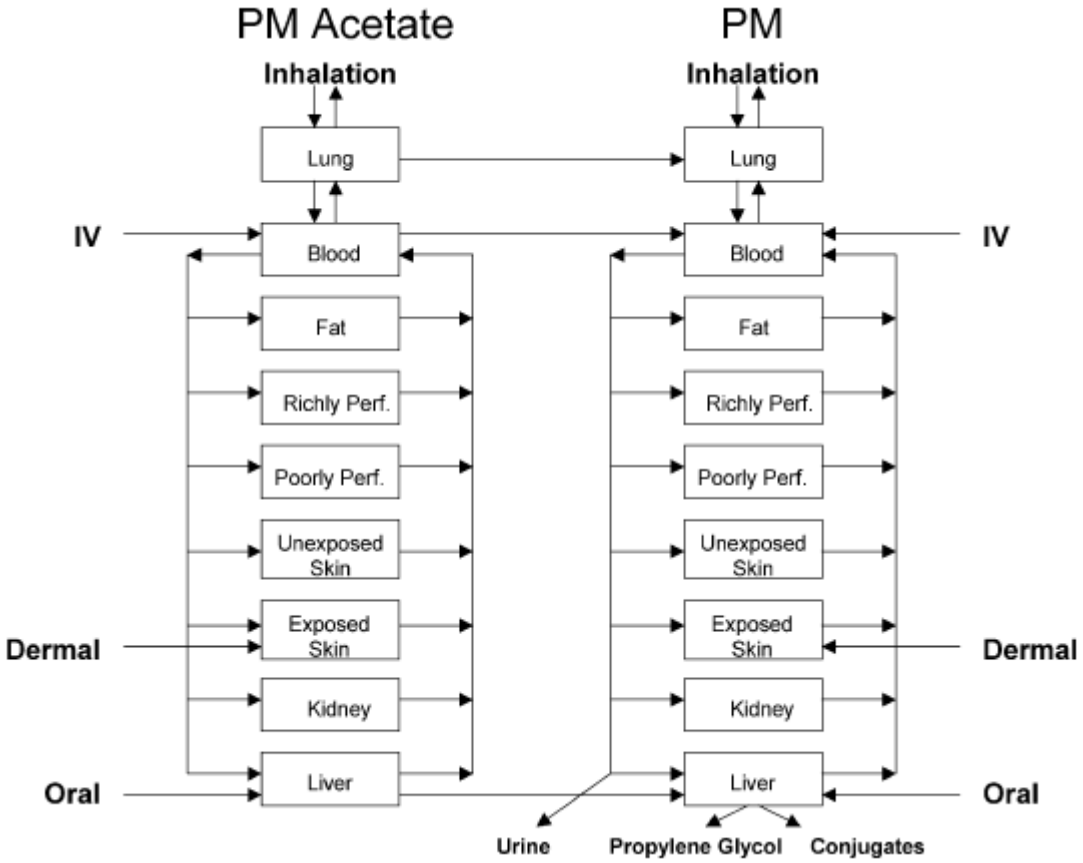
In vitro studies

In absorption tests with isolated human skin (abdominal epidermis), an absorption rate of 1.17 mg/cm2/hr was estimated for undiluted PGME (Dugard *et al.,* 1984).

4.1.2.1.3 PbPk model

A PbPk model on PGME and PGMA has been developed by Corley *et al*. (2005) based on available data on kinetic. This model take into account the kinetic of PGME and PGMA in rats, mice and human for inhalation, oral, dermal and I.V. administration.

The model is presented as following :



The parameters used were :

Physiological parameters used in the PBPK model for PM and its acetate in rats and humans

Parameter		Rat	Human
Physiology			
BW	Body weight (kg)[a]	0.23	70
QCC	Cardiac output (l/(h kg))[b]	20	15
QPC	Alveolar ventilation (l/(h kg))[b]	20	15
Tissue volumes (fraction of body weight)[c]			
VBC	Blood	0.059	0.059
VLC	Liver[d]	0.0253	0.0314
VKC	Kidneys	0.0063	0.0044
VluC	Lungs	0.0117	0.0115
VFC	Fat	0.07	0.231
VSKC	Skin	0.10	0.051
VRC	Richly perfused	0.0447	0.0466
VSC	Slowly perfused	0.91 − ∑(other tissues)	
Blood flows (fraction of cardiac output)[c]			
QLC	Liver	0.25	0.25
QKC	Kidney	0.25	0.25
QFC	Fat	0.05	0.05
QSKC	Skin	0.05	0.03
QRC	Richly perfused tissues	1.0 − ∑(other tissues)	
QSC	Poorly perfused tissues	0.19	0.19

[a] Study specific.
[b] Resting conditions scalable by $(BW)^{0.74}$. For the rat, alveolar ventilation estimated from data of Landry et al. (1983) for restrained animals in same laboratory as nose-only inhalation studies of Morgott and Nolan (1987).
[c] Corley et al. (1994, 1997); Brown et al. (1997).
[d] Study specific increases in repeated exposures.

The following partition coefficients were found :

Biochemical parameters used in the PBPK model for PM and its acetate in rats and humans

Parameter		PM acetate		PM	
		Rat	Human	Rat	Human
Absorption					
KPV	Skin permeability (cm/h), vapor[a]	–	1.4	–	1.4
KPL	Skin permeability (cm/h), liquid[b]	0.002	–	0.003	–
KAS	Oral (h^{-1})[c]	1.0	1.0	1.0	1.0
Distribution (partition coefficients)[d]					
PB	Blood:air	1251	609	4866	7107
PSAL	Saline:air	1284	1284	4555	4555
PSKA	Skin:air	1296	1296	2885	2885
PL	Liver:blood	1.50	1.50	0.94	0.94
PK	Kidney:blood	1.08	1.08	1.18	1.18
PLU	Lung:blood	1.84	1.84	1.88	1.88
PF	Fat:blood	1.33	1.33	1.15	1.15
PSK	Skin:blood	1.04	1.04	0.59	0.59
PR	Richly perf.:blood	1.42	1.42	1.37	1.37
PS	Poorly perf.:blood	1.33	1.33	1.16	1.16
Metabolism					
PM acetate → PM[e]					
KBC	First-order (h^{-1} kg^{-1}), blood	51.0	20.4	–	–
KLUC	First-order (h^{-1} kg^{-1}), lung	51.0	20.4	–	–
KLC	First-order (h^{-1} kg^{-1}), liver	68.8	55.9	–	–
PM → propylene glycol[f]					
Km1	Michaelis constant (mg/l)	–	–	45	45
Vmax1C	Maximum rate (mg/(h kg))	–	–	22	22
$Vmax1C_{Induced}$		–	–	44	–
PM → conjugates[g]					
Km2	Michaelis constant (mg/l)	–	–	80	80
Vmax2C	Maximum rate (mg/(h kg))	–	–	5	0.2
Elimination[h]					
CLUrC	Urinary clearance (l/(h kg))	–	–	0.0005	0.2

The model parameters were either estimated independently and held fixed (*fixed*), *measured* in independent experiments (*measured*), or estimated by fitting the model to the data (*fitted*) as described in the text with the sources for each estimation designated in footnotes to the table.

[a] *Fitted* to data of Brooke et al. (1998).

[b] *Fitted* to data of Sumner et al. (1999).

[c] First-order oral absorption *fixed* to value consistent with other solvents, amount absorbed (mg) = dose – dose × $e^{-(KAS \times T)}$.

[d] *Measured* in human blood, rat blood and rat tissues. Human tissue:blood partition coefficients assumed to be equal to rat (*fixed*).

[e] Hydrolysis of PM acetate in blood and liver *measured* by two-compartment model analysis of data from Domoradzki et al. (2001); constants for the lung *fixed* according to Stott and McKenna (1984). First-order metabolism constants scaled by $(BW)^{-0.3}$.

[f] Non-induced metabolism *fitted* to data of Morgott and Nolan (1987). Maximum metabolism rate constant scaled by $(BW)^{0.74}$. Induced metabolism (Vmax) and volume of liver (VLC) for repeated exposures to concentrations >3000 ppm *fixed* according to data of Corley et al. (1996). Reasonably foreseeable human exposures (ACGIH TLV and German MAK value is 100 ppm for PM) considered insufficient to induce metabolism as no induction observed in rats at 300 ppm.

[g] *Fitted* to data of Miller et al. (1984a, 1984b) for rats; scaled to humans with modifications by fitting to Devanthery et al. (2002). Maximum metabolism rate constant scaled by $(BW)^{0.74}$.

[h] *Fitted* to data of Miller et al. (1983) for rats; scaled to humans with modifications by fitting to Devanthery et al. (2002). First-order metabolism constants scaled by $(BW)^{-0.3}$.

According to this model, the author estimated that skin absorption of PGME vapor in humans contributed about 5 to 10 % to the total body burden of PGME following whole-body inhalation exposures.

The simulations of the peak concentrations Cmax and AUC for PGME in the blood of rats and humans exposed for 6h by whole body inhalation give the following figures:

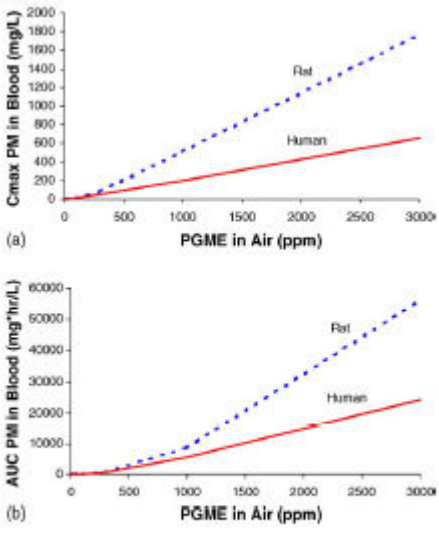


Fig. 16. Simulations of the (a) peak concentrations (Cmax) and (b) area under the curve (AUC) for PM in the blood of rats and humans exposed for 6 h by whole-body inhalation to various concentrations of PM.

According to these simulations it can be assumed that rats have higher Cmax and AUC than humans (about 2.5 fold more) and therefore that systemic effects of PGME would be expected to be less severe in humans than in rats at comparable inhalation exposures. To take this into account for the risk characterisation, a factor of 0.4 for kinetic parameters will be used in the interspecies safety factor.

The used of PbPk model has already been extensively discussed and justified in another RAR (EGBE). The same author has developed various PbPk models for a lots of glycol ethers. These models has given reliable extrapolating factors to allow accurate risk caracterisation for humans on the basis of animal data. In a general manner, for the models developed with a lot of data (i.e. EGBE) extrapolated factors were confirmed by experimental data.

It is considered that the PBPK model for PGME is sufficiently well developed to justify its used to derive animal to man toxicokinetic extrapolation factors for the inhalation route. According to this model a interspecies factor of 0.4 can be taken into account for extrapolation of values found in rats to values estimated in humans for exposure concentrations above 100 ppm and of 1 for exposure concentrations below 100 ppm since according to Corley *et al*., 2005, the rat and human blood levels of PGME are similar at exposure concentrations below 100 ppm .

4.1.2.1.4 Summary of toxicokinetics, metabolism and distribution

PGME is readily absorbed via oral and inhalation route. An absorption percentage of 100 % can be taken into account for these routes. Human data have shown that dermal absorption of vapour via the skin is limited. When exposed whole-body (normal clothing), PGME vapour provided contribution of approximately 4-8 % to the total body burden. An *in vitro* absorption rate of 1.17 mg/cm^2/h was estimated for pure PGME on human skin. If the dermal absorption of liquid PGME is compared to other glycol ether, the available data show that PGME is less absorbed than EGBE (it is estimated that PGME is twice less absorbed that EGBE).

According to this data, it is proposed to take into account a dermal absorption factor of 30 % for liquid PGME (as EGBE – see EGBE RAR) considering that this is a worst case value.

According to the PbPk model, vapour PGME absorbed through the skin in humans contributed to about 5 to 10 % to the total body burden of PGME. If adjustments needs to be make for the risk characterisation, the value of 10 % will be taken as a worst case value.

Also according to this model, maximum concentration of blood PGME are about 2.5 fold more higher in rats than in humans after a 6h inhalation exposure at the same exposure level, for exposure levels above 100 ppm. For exposure concentrations below 100 ppm, the rat and human blood levels of PGME are similar which leads to the use of a factor of 1 instead of 0.4 in this range of concentrations.Main target organs were liver, thymus and spleen (concentration > blood levels after oral dosing). Little amount of PGME or metabolites were found in fat or testes. According to the data available, PGME does not seem to accumulate in the body.

The main metabolic pathway of PGME is O-demethylation leading to PG formation. This mechanism is easily saturable. Other path are glucurono- and sulfo-conjugation. PG is excreted via urine or enter metabolic pathways to produce CO_2. At high dose, saturationof the metabolic pathways led to urinary elimination of PGME as such (see figure 4.23: metabolic pathway of PGME). PGME and metabolites are rapidly eliminated.

It appears that in rats, there is a sex difference in metabolism of PGME, females eliminating faster than males.

4.1.2.2 Acute toxicity

4.1.2.2.1 Studies in animals

Inhalation

Rat

Non-GLP acute inhalation studies conducted on rats indicated that rats survived single 7-hour exposures to 5,000 ppm (18.7 mg/l). At 10,000 ppm (37.4 mg/l), the time to reach an LC50 value was 5 to 6 hours, while at 15,000 ppm (56.1 mg/l), the time to reach an LC50 was 4 hours. Deaths resulting from single exposures appeared to be due to central nervous system depression (Rowe *et al*., 1954).

In a non GLP acute inhalation toxicity test performed on rats, a LCo of about 9800 ppm (36.4 mg/l) was found for a 6-hour treatment period (Smyth *et al*., 1962).

In a non GLP acute inhalation toxicity test performed on rats, a LCo of 1000 ppm (3.74 mg/l) was found for a 4-hour treatment period (Smyth *et al*., 1962).

In a non GLP acute inhalation toxicity test performed on rats, a LC50 of greater than 1600 ppm (6 mg/l) was found for a 4-hour treatment period (Gelbke, 1983).

In a non GLP acute inhalation toxicity test performed on rats, a LC50 of greater than 6400 ppm (24 mg/l) was found. Animals were exposed to concentration of 6800, 9700 and 14600 ppm (25.5, 36.4 and 54.6 mg/l) for periods of time varying between 1 and 8 hours (Gelbke, 1983).

In a GLP acute toxicity inhalation study, rats (Fischer 344) were exposed during 6 hours to two concentrations of PGME: 6038 and 7559 ppm (22.6 and 28.3 mg/l) (Cieszlak and Crissman, 1991). Animals were observed for two weeks after exposure. All rats survived exposure to 6038 or 7559 ppm; animals were laterally recumbent and generally unresponsive during exposure, but appeared normal by day two - three. Mean body weight for both sexes was decreased approximately 10% from pre-exposure levels, but exceeded pre-exposure levels within a week.

Mouse

In a GLP acute toxicity inhalation study, mice (B6C3F1) were exposed during 6 hours to two various concentrations of PGME (6038 - 7559 ppm (22.6 and 28.3 mg/l)) (Cieszlak and Crissman, 1991a). Animals were observed for two weeks after exposure. All mice were laterally recumbent during exposure to 6038 ppm, with 4/5 female mice dead or moribund on day 2. Male mice and surviving female mouse appeared normal on day 2. Male body weights were decreased 17% following exposure but recovered quickly. Only male mice were exposed to 7559 ppm; mice were laterally recumbent, motionless and unresponsive to noise for much of the exposure and upon removal from the chamber. By day 3, only 2/5 mice had survived. Survivors appeared normal but body weights decreased 12% from pre-exposure levels; body weights recovered within a week. In this study the LC50 is below 6038 ppm.

Rabbit

In a non GLP acute inhalation toxicity test performed on rabbits, a LCLo of 14600 ppm (54.6 mg/l) was found for a 7-hour treatment period (Rowe *et al*., 1954).

Guinea pig

Acute inhalation studies conducted on guinea pigs indicated that guinea pigs survived single 7-hour exposures to 5000 ppm (18.75 mg/l). At 14600 ppm (54.6 mg/l) the time to reach an LC50 was 10 hours (Rowe *et al*., 1954).

Dermal

Six doses from 5000 to 14000 mg/kg were applied for 24 h under occlusive dressing on the dorsal skin of rabbits (Rowe *et al*., 1954). Depression, incomplete anaesthesia, and slight skin irritation at application site were observed. The LD50 was estimated to be 13000 mg/kg.

In a non-GLP acute dermal toxicity test performed on rabbits, a LD50 of 14100 mg/kg was found (Smyth *et al*., 1962).

In a GLP study, the acute (24 h) percutaneous LD50 of the undiluted test material in rats was greater than 2000 mg/kg, no clinical signs, no deaths were observed at 2000 mg/kg (the maximum dose that could be applied) (SHELL, 1985).

Oral

Rat

Beta isomer was tested for acute oral toxicity (Smyth *et al*., 1941). A LD50 of 5710 mg/kg was found. The LD50 for the Alpha isomer is 7510 mg/kg. This test was not GLP.

In an non-GLP acute oral toxicity test a LD50 of 6100 mg/kg was calculated (Rowe *et al*., 1954). 170 rats dispatched in 9 dose groups were used.

In another non-GLP acute oral toxicity test performed with rats, a LD50 of 5200 mg/kg was calculated (Smyth *et al*., 1962).

In another non-GLP acute oral toxicity test performed with rats, a LD50 of about 5900 mg/kg was calculated (BASF, 1964).

In another non-GLP acute oral toxicity test performed with rats, a LD50 of greater than 5000 mg/kg was calculated (BASF, 1979).

In another non-GLP acute oral toxicity test performed with rats, a LD50 of 4016 mg/kg was calculated (SHELL, 1985).

Mouse

In another non-GLP acute oral toxicity test performed with mice, a LD50 of 10800 mg/kg was calculated (Stenger *et al*., 1972).

Rabbit

In another non-GLP acute oral toxicity test performed with rabbits, a LD50 of 5300 mg/kg was found (Stenger *et al*., 1972).

In another non-GLP acute oral toxicity test performed with rabbits, a single dose of 2 ml/kg (1840 mg/kg) was not lethal to any of four rabbits (BASF, 1965).

Dog

In another non-GLP acute oral toxicity test performed with dogs, a LD50 of 9000 mg/kg was calculated (Shideman and Puscita, 1951).

In another non-GLP acute oral toxicity test performed with dogs, a LD50 within 4600 - 5500 mg/kg was found (Stenger *et al*., 1972).

Cat

In another non-GLP acute oral toxicity test performed with cats, A single dose of 2 ml/kg (1840 mg/kg) was not lethal but led to some behaviour changes for 2 days. (BASF, 1965).

Other routes

Rat

PGME was administered to rats via intravenous route (Stenger *et al*., 1972). Rats were sacrificed after a 8-day observation period. Dyspnea, somnolence, ataxia, prostration, sleep, and muscle spasms were reported. LD50 was estimated to be 3900 mg/kg.

A LD50 of 3900 mg/kg was calculated in rats after i.p. administration of PGME (Stenger *et al.*, 1972).

A LD50 of 7200 mg/kg was calculated in rats after s.c. administration of PGME (Stenger *et al*., 1972).

Mouse

A LD50 of about 5900 mg/kg was found in mice after i.p. administration of PGME (BASF, 1964).

A LD50 of 4900 mg/kg was calculated in mice after i.v. administration of PGME (Stenger *et al*., 1972).

A LD50 of greater than 2000 mg/kg was found in mice after i.p. administration of PGME (BASF, 1979).

Rabbit

A LD50 of 1100 mg/kg was calculated in rabbits after iv administration of PGME (Stenger *et al.*, 1972).

A LD50 of 4600 mg/kg was calculated in rabbits after s.c. administration of PGME (Stenger *et al*., 1972).

Dog

A LD50 between 1800 - 2300 mg/kg was calculated in dogs after i.v. administration of PGME (Stenger *et al*., 1972). After injection, dogs experienced pain at the injection site, shallow breathing, decreased blood pressure, cardiac arrhythmia, and convulsions.

4.1.2.2.2 Studies in humans

Male human subjects were exposed to increasing concentrations of PGME from 50 to 1000 ppm (187 to 3740 mg/m^3) (2050 ppm (7700 mg/m^3) in one case) (Steward *et al*., 1970). Duration of exposure was up to 7 hr at concentrations up to 250 ppm (935 mg/m^3) and up to 2 hr at concentrations up to 2050 ppm. See the following table for experimental conditions.

Table 4.27: Experimental condition for human exposure in the Steward study

		Vapor concentration, ppm			
Experiment	No of subjects	Mean	SE	Range	Duration of exposure, hr
1	1	47.3	0.2	44.8-50.0	1
2	6	95	0.5	89.0-101.0	3.5
3	1	240.9	0.1	236.0-243.0	1
4	6	231.4	0.8	223.0-250.0	1.25
5	5	242.6	1.0	229.0-269.0	1.25
6	6	249	2.9	200.0-297.0	3.5
7	5	239	1.1	221.0-266.0	7
8	2	1056	4.3	0-2050.0	2

The substance become noticeable at 10 ppm (37 mg/m^3). Above 100 ppm (374 mg/m^3), the odor was transiently objectionable; eyes were slightly irritated after 1-2 hr exposure. At 300 ppm (1122 mg/m^3), there was mild eye and nasal irritation within 5 minutes which became intolerable after 1 hr. 750 ppm (2800 mg/m^3) was scored as very strongly irritating. At 1000 ppm, indications of CNS depression were recognized. Breath analysis data demonstrated that PGME was rapidly excreted via the lungs. The human volunteers all experienced rapid development of odor tolerance. Hence, unless prompt action is taken when objectionable odor is experienced, it cannot be relied upon to prevent exposures that may be hazardous. However, because the odor is readily detected and is objectionable, PGME vapours are considered to have adequate warning properties, if needed. Neurologic, clinical, chemical and general medical studies did not show any significant abnormalities. In this study, the NOAEL for CNS depression was 750 ppm. This value will be taken into account in the risk characterisation.

4.1.2.2.3 Summary of acute toxicity

See table 4.28:

Information available suggests that the acute toxicity of PGME is very low.

The oral LD_{50} value for PGME in experiments in rats ranges from 4016 to 7,510 mg/kg. Oral LD_{50} values from other animal experiments were 10,800 mg/kg for mice; 1,840 to 5,300 mg/kg for rabbits, and 4,600 to 9,000 mg/kg for dogs.

Similarly, LC_{50} values were > 6,000 to 15000 ppm (22,440 to 54,600 mg/m^3) for rats; < 6,038 to 7,559 ppm for mice (22,600 to 28.300 mg/m^3), and > 14600 ppm (54,600 mg/m^3) for guinea pigs.

When applied occluded to the skin of rabbits, the LD50 value was found to be in the range of 13-14 g/kg. The acute (24 hr) percutaneous LD50 of the undiluted test material in rats was greater than 2000 mg/kg (the maximum dose that could be applied).

CNS depression has been observed in both humans and animals as a lead, single exposure effect. The lowest value for CNS depression in animals was seen in a RDT inhalation toxicity (3000 ppm, derived from the 2 year studies) leading to a NOAEC of 1000 ppm. In humans, a NOAEL of 750 ppm was derived for CNS depression, this value will be taken into account for the risk characterisation of acute effects. A classification R67 is needed for this end-point.
By dermal route, no systemic effects were seen at doses of 1000 mg/kg in a 21 day study. Only local effects limited to slight inflammation were seen.

No other classification is needed for PGME for acute toxicity whichever the route of exposure.

Table 4.28: Summary of acute toxicity					
	Species	LD50 / LC50	Experimental conditions / Effects	Validity	Reference
Inhalation	F344 rat	> 7559 ppm (28.3 mg/l)	Lethargy, decrease in body weight. No death	+	Ciezlak and Crissman, 1991
	Rat	10000-15000 ppm (37.4 – 56.1 mg/l)	7hr treatment period: 5000 ppm no death 6hr treatment period: 10000 ppm LC50 4hr treatment period: 15000 ppm LC50	+/-	Rowe *et al*., 1954
	Rat		6hr treatment period LC_0 10000 ppm(36.4 mg/l) 4hr treatment period LC_0 1000 ppm (3.7 mg/l)	+/-	Smyth *et al*., 1962
	Rat	> 1600 ppm (6 mg/l) > 6400 ppm (24 mg/l)	4hr treatment period concentration 25.5, 36.4 and 54.6 mg/l for periods varying between 1 and 8 hrs	+	Gelbke, 1983
	Mouse B6C3F1	< 6083 ppm (22.6 mg/l)	6hr treatment period, 2 concentration tested (6038 and 7559 ppm). For the 6038 doses 4/5 death. CNS effects and reversible decrease of mean body weight	+	Ciezlak and Crissman, 1991
	Rabbit	LD50 14600 ppm (54.6 mg/l)	7hr treatment period	+/-	Rowe *et al*., 1954

	Guinea pig	LCLo 14600 ppm (54.6 mg/l)	10 hr treatment period 7hr treatment period with 18.75 mg/l: no effects	+/-	Rowe *et al*., 1954
Dermal	Rabbit	13000 mg/kg	6 doses: 5000 to 14000 mg/kg. 24 hr exposure period, occlusive. CNS symptoms and slight skin irritation.	+/-	Rowe *et al*., 1954
	Rabbit	14100 mg/kg	Only LD50 reported	+/-	Smyth *et al*., 1962
	Rabbit	> 2000 mg/kg	24 hr treatment period.	+	SHELL, 1985
Oral	Rat	6100 mg/kg	9 doses groups	+/-	Rowe *et al*., 1954
	Rat	7510 mg/kg	LD50: β isomer 5710 mg/kg	+/-	Smyth *et al*., 1941
	Rat	5200 mg/kg	Only LD50 reported	+/-	Smyth *et al*., 1962
	Rat	> 5000 mg/kg	Only LD50 reported	+	BASF, 1979
	Rat	5900 mg/kg	Only LD50 reported	+/-	BASF, 1964
	Rat	4016 mg/kg	CSN effects	+	SHELL, 1985
	Mouse	10800 mg/kg	Only LD50 reported	+/-	Stenger *et al*., 1972
	Rabbit	> 1840 mg/kg	Only LD50 reported	+/-	BASF, 1965
	Dog	9000 mg/kg	CNS and cardiac depressant	+/-	Shideman and Puscita, 1951
	Dog	4600-5500 mg/kg	Only LD50 reported	+/-	Stenger *et al*., 1972
	Cat	> 1840 mg/kg	Behavioural reversible changes	+/-	BASF, 1965

4.1.2.3 Irritation

4.1.2.3.1 Skin

Undiluted PGME (0.01 ml) was applied to the uncovered belly of rabbits for 24 h (Smyth *et al*., 1962). No appreciable irritation to the skin (primary skin irritation grade 2 = least visible capillary injection). Failed to cause more than a very mild irritation, and that after constant contact for several weeks.

In two GLP studies, PGME was found to be slightly irritating to rabbit skin (BASF, 1979; SHELL, 1985).

Summary skin irritation:

PGME was found to be slightly irritant in 3 studies performed on rabbits. No classification is needed for this end-point.

4.1.2.3.2 Eye irritation

Studies in animals

One drop of undiluted PGME was applied to the eyes of rabbits on each of 5 consecutive days (Rowe *et a*l., 1954). Only signs of slight irritation were observed.

In another rabbit study, irritation potential of 0.5 ml undiluted PGME is low; reported rating of 3 on a scale of 10 (Smyth *et al*., 1962).

PGME was found to be slightly irritant for rabbits eyes (BASF, 1979).

Studies in humans

In an inhalation experiment mild eye irritation has been reported at 100 ppm (375 mg/m^3) in experiment 2. In experiments 3-7, eight subjects were experiencing eye irritation and three had lacrimation after 15-30 minutes exposure at 250 ppm (937 mg/m^3), and 20 subjects had developed eye irritation and increased blinking after 45-60 minutes, doses of 750 ppm (2800 mg/m^3) were strongly irritating; and central nervous system depression was observed at 1,000 ppm (3740 mg/m^3) (see Steward *et al.*, 1970 in § 4.1.2.2.2).
In another inhalation experiment, testing was conducted on 12 healthy male volunteers using a repeated measures design. Each subject was exposed for 2.5 hours to each of three exposure conditions which were spaced 7 days apart. During all exposure sessions, 20 ppm diethylether was used as a masking agent to minimize any responses caused by PGME odor. Exposure to the test substance and the effect measurements were conducted in a double-blind fashion. Measurement of pre- and post-exposure eye redness, corneal thickness, tear film break-up time, conjuctival epithelial damage, blinking frequency, and subjective ratings were used to evaluate the possible irritating effects of PGME (Emmen *et al.*, 2003). There were no objective eye irritation effects at doses of 100 and 150 ppm. Subjective effects were reported at 150 ppm.

Summary eye irritation:

PGME was found to be slightly irritant in 3 studies performed on rabbits. In humans no sign of irritation were reported at doses up to 100 ppm. No classification is needed for this end-point.

4.1.2.3.3 Respiratory tract

See former § (Steward *et al*., 1970). In experiments 3-7, three subjects had throat irritation and one had nose irritation after 15-30 minutes exposure at 250 ppm, and 15 subjects complained of nose irritation and 2 of throat irritation after 45-60 minutes. In experiment 8, nose and throat irritation were severe at 500 ppm after 30 minutes of exposure, at 700 ppm rhinorrhea was observed, and at 2000 ppm the subject was unwilling to breathe through his nose because of the pain caused by the vapour and he complained of a very severe sore throat. This study is quite old and symptoms reported quite subjective. As only slight irritation was found in skin and eye animal irritation studies, it is likely than only slight respiratory tract irritation will occur after usual PGME exposure levels. Therefore, the classification criteria for respiratory tract irritation are not met (ie severe sign of irritation) and no classification is needed for this end-point.

4.1.2.3.4 Summary of irritation

In animal studies (rabbits), PGME was found to be slightly irritating to the skin and slightly irritating to the eye. PGME is not expected to be severely irritant for the respiratory tract. No classification is needed for irritation.

One study perfomed in human volunteers showed that PGME was moderately irritant at dose of 300 ppm for a short period of time. At 100 ppm no effects of irritation (objective) were seen. The value of 100 ppm will be taken into account in the risk characterisation for eye and upper respiratory tract irritation by inhalation.

4.1.2.4 Corrosivity

PGME is not a corrosive substance.

4.1.2.5 Sensitisation

4.1.2.5.1 Studies in animals

Skin

In a modified Maguire test, PGME was found to be not sensitizing (Carreon and Wall, 1984).

In a guinea-pig maximisation test of Magnusson and Kligman (GLP), none of the test animals showed positive responses at 24 or 48 hours after the removal of the challenge patches (SHELL, 1985).

Respiratory tract

No data. But due to SAR with other glycol ethers, PGME is not expected to be a respiratory tract sensitiser.

4.1.2.5.2 Studies in humans

No data

4.1.2.5.3 Summary of sensitisation

PGME was found to be non-sensitizing in guinea pigs. PGME is not expected to be a respiratory sensitiser. No classification is needed for these end-points.

4.1.2.6 Repeated dose toxicity

4.1.2.6.1 Studies in animals

Inhalation

Rat

In a 2-week study by inhalation (not GLP) rats were exposed to PGME 5h/day 5d/week at doses of 2500, 5000 and 10000 ppm (9.4 – 18.7 – 37.5 mg/l) (Goldberg *et al*., 1964). Animals in the 5000 and 10,000 ppm group displayed a transient nonspecific depression of behaviour for the first several exposures, followed by rapid development of tolerance. Decreased growth rate was seen at 10,000 ppm. In this study the NOAEC was 2500 ppm for behavioural effects (acute narcotic effects) and 5000 ppm for general RDT toxicity..

In a GLP two-week study by inhalation route, PGME was administered to Fischer 344 rats (9 exposures) at doses of 0, 300, 1000 and 3000 ppm (0 - 1.1 – 3.75 – 11.2 mg/l) (Miller *et al*., 1981). No deaths occurred during PGME exposure. Rats in the 3000 ppm groups appeared to be anaesthetised or sedated during exposure. There were no gross pathologic observations or histopathologic changes in the liver or kidneys in all groups. Liver weights of rats in the 3000 ppm group were higher than controls.,. The NOAEC in this study was 1000 ppm based on effects seen at 3000 ppm.

In a two-week study by inhalation (9 exposure in 11 days), Fischer 344 rats were exposed to an unique 3000 ppm (11.2 mg/l) concentration of PGME (Stott, 92). A control untreated group was also included. Exposure to 3000 ppm produced sedation in male and female rats during the first week of exposure. Resolution of sedation correlated with increases in relative liver weights. Increases in the rate of hepatocellular proliferation (mitotic response) was observed after the first week in male rats. No other histopathologic changes were noted in the livers of exposed rats. Relative kidney weights of both sexes were slightly, but statistically increased, following two weeks of exposure. Kidney weight changes in males was accompanied by the deposition of alpha 2µ-globulin characteristic of male rat specific “protein droplet nephropathy”.

In a GLP 13-week study by inhalation route (performed according to OECD guideline 413) Fischer 344 rats were exposed to PGME at doses of 300, 1000 and 3000 ppm (1.1 – 3.75 – 11.2 mg/l), 6h daily and 5 d/week (Landry *et al*., 1983). No treatment related effects were found in animals exposed to 300 or 1000 ppm. At 3000 ppm clinical observations indicated a transient central nervous system depression, relative liver weight increased slightly concomitant with non degenerative (adaptive) histological effects. Body weight gain was slightly decreased in females. For this study the NOAEC was 1000 ppm.

In a GLP study, Fischer 344 rats were exposed by inhalation to PGME during 13 weeks 6 hours daily and 5 days/week at doses of 0 – 300 and 3000 ppm (1.1 – 11.2 mg/l) (Cieszlak *et a*l., 1996). Exposure to 3000 ppm produced sedation in male and female rats during first week of exposure that was ameliorated by increased hepatic mixed function oxidase activity and hepatocellular proliferation which is a normal physiologic adaptation to increased metabolic demand. No sedation or adaptive hepatic effects were observed at 300 ppm. A male rat specific alpha 2µ-globulin nephropathy was observed at 3000 ppm and to a slight extent at 300 ppm. PGME produced effects at all doses in males leading to a LOAEC of 300 ppm. In females the NOAEC was 300 ppm.

In a 6 month study performed on rats by inhalation route, PGME was administered during 7h/day 5d/week (Rowe *et al*., 1954). A NOAEC greater than 1500 ppm was observed.

In a chronic GLP toxicity/carcinogenicity study (see section 4.1.2.8), animals were exposed 2 years at PGME concentrations of 0, 300, 1000 and 3000 ppm (0 - 1.1 – 3.75 – 11.2 mg/l) (Cieszlak *et al*., 1998a). PGME-induced sedation at 3000 ppm resolved in all animals during the second week of exposure in conjunction with the appearance of adaptive changes in the liver (MFO induction and hepatocellular proliferation-from previous work). MFO activities (PROD) subsequently dropped to near control values by week 52, coinciding with a return of sedation at 3000 ppm PGME. In male rats, the loss of metabolic adaptation was followed by a dose-related increase in eosinophilic foci of altered hepatocytes after two years of exposure to 1000 or 3000 ppm PGME. Kidney toxicity was observed in male rats only, which was confirmed immunohistochemically as an alpha 2µ-globin nephropathy. The 300 ppm exposure level was established as an NOAEL in rats based on liver effects.

Mouse

B6C3F1 mice were exposed to PGME by inhalation route at concentrations of 0, 300, 1000 and 3000 ppm (0 - 1.1 – 3.75 – 11.2 mg/l) 6h/day during 11 days (9 exposure) (Miller *et al*., 1981). This test was performed according GLP. No deaths occurred during PGME exposure. Mice in the 3000 ppm groups appeared to be anaesthetised or sedated during exposure. There were no gross pathologic observations or histopathologic changes in the liver or kidneys in all groups. All affected parameters (relative liver weight of female mice at 3000 ppm) recovered to normal levels after 6 weeks. In this study the NOAEC was 1000 ppm based on effects seen at 3000 ppm.

PGME was administered by inhalation during 2 weeks (9 exposures in 11 days) to B6C3F1 mice at doses of 0 and 3000 ppm (11.2 mg/l) 6 hours daily (Stott, 92). Exposure to 3000 ppm produced sedation in male and female mice during the first week of exposure. Resolution of sedation correlated with increases in relative liver weights. Increases in the rate of hepatocellular proliferation (mitotic response) was observed after the first week in both sexes,

and after the second week of exposures in females. No other histopathologic changes were noted in the livers of exposed mice.

In a GLP study, B6C3F1 mice were exposed by inhalation to PGME during 13 weeks 6 hours daily and 5 days/week (Cieszlak *et al*., 1996). Two groups were evaluated in this study: a first subgroup for standard subchronic toxicity assessment and dosed with 0, 300, 1000 or 3000 ppm (0 - 1.1 – 3.75 – 11.2 mg/l) and a second subgroup evaluated for enzyme induction and cellular proliferation (dose levels: 300 and 3000 ppm). Exposure to 3000 ppm produced sedation in male and female mice during the first three days of exposure. An accelerated atrophy of the X zone of the adrenal gland of female mice was observed at 3000 ppm and to a very slight degree at 1000 ppm. A slight numerical increase in renal and hepatic cellular proliferation, significantly increased hepatic enzyme induction was observed at 3000 ppm in both sexes; increased liver weight (females only) was also observed at 3000 ppm. No effects were observed at 300 ppm. The NOAEC in this study was 1000 ppm (whichever the subgroup). Atrophy of the X-zone of the adrenal gland was described as an age related event in mice and was considered to be a non-specific, non adverse effect.

In a chronic GLP toxicity/carcinogenicity study (see section 4.1.2.8), animals were exposed 2 years at PGME concentrations of 0, 300, 1000 and 3000 ppm (0 - 1.1 – 3.75 – 11.2 mg/l) (Cieszlak *et al*., 1998b). A transient sedation of mice inhaling 3000 ppm PGME during the first week of exposures was observed; however, this resolved during the second week concomitant with adaptive changes in the livers of these animals (previous study results). Mice exposed to 3000 ppm had increased mortality (males), decreased in-life body weights and body weight gains relative to controls, over much of the exposure period, as well as minimal increases in absolute and relative liver weights and hepatic MFO activity. No treatment-related histopatholgical changes accompanied these liver effects, nor were histopathological changes observed in any other tissues. These data, along with the occurrence of chronic, albeit small increases in hepatocellular proliferation in mice inhaling 3000 ppm suggested minimal regenerative response in the liver, likely related to shorted life span metabolically stressed hepatocytes. Minimal decreases in body weights (average 3%) were also observed, in both sexes exposed to 1000 ppm but less consistently than in the high exposure mice. A NOAEL of 1000 ppm was established based on an increased mortality in the high dose (3000 ppm) male group that may have been related to minimal liver toxicity. Effects seen on the body weight were not taken into account because they were minimal and not accompanied with other toxicological effects.

Rabbit

In a 3-6 months inhalation study performed on rabbits, PGME was administered at doses of 800, 1500, 3000 and 6000 ppm (3 – 5.6 – 11.2 – 22.3 mg/l) 7h/day, 5d/week (Rowe *et al*., 1954). Toxicological effects from repeated vapour exposures were Slightly increased liver weights in females and slight histological changes of liver and lungs at 1500, 3000 and 6000 ppm (no histological changes of the liver for the only animal of the 6000 ppm group. There were no observable treatment-related effects with repeated exposure to 800 ppm. In this study, the NOAEC was 800 ppm based on effects seen at 1500 ppm.

In a 13-week study by inhalation route, rabbits were exposed to PGME by inhalation route at doses of 0, 300, 1000 and 3000 ppm (0 - 1.1 – 3.75 – 11.2 mg/l), 6 hours daily and 5d/week (Landry *et al*., 1983). This test was performed according to OECD guideline 413 and was GLP. No treatment related effects were found in animals exposed to 300 or 1000 ppm. At

3000 ppm clinical observations indicated a transient central nervous depression and serum alkaline phosphatase was increased. The NOAEC was 1000 ppm based on effects seen at 3000 ppm.

Guinea pig

In a six-month study by inhalation, guinea-pigs were exposed 7 h/days, 5 d/week at PGME concentration of 0, 1500 and 3000 ppm (0 – 3.75 – 11.2 mg/l) (Rowe *et al*., 1954). No effects were seen at the highest dose tested.

Monkey

Monkey (strains unknown) were exposed during 6 months 7h daily and 5d/week to 0, 800, 1500 and 3000 ppm (0 - 3 – 5.6 – 11.2 mg/l) of PGME (Rowe, 1957). The NOAEC was reported to be 800 ppm with a LOAEC of 1500 ppm (no more details available for this study).

Summary inhalation route :

In the majority of the studies, transient CNS depression was seen at doses of 3000 ppm leading to a NOAEL of 1000 ppm for this effect (acute effect). In rats evidence of specific male nephropathy was noticed in almost all studies, this effect is not relevant for human and will therefore not be taken into account for the risk assessment. The main toxicological effects noticed in rats were liver effects: increases in liver and relative liver weight, induction of hepatic enzyme and cellular proliferation. Concerning this effect, a NOAEC of 300 ppm (1122 mg/m3) is derived from a well performed 2-year rat study.

Table 4.29: Summary inhalation route.

Study	Results	NOAEC	Validity	Reference
Rat				
Wistar 6h/d 10 days 0 – 200 – 600 ppm	Only testes effects checked. No effects	NA	2	Doe *et al*., 1983
Fischer 344 9 exposures 0 – 300 – 1000 – 3000 ppm	CNS depression at 3000 ppm. No irreversible effects on organs	1000 ppm 3740 mg/m^3	1	Miller *et al*., 1981
Fischer 344 9 exposures in 11 days 0 - 3000 ppm	Sedation in treated group. Increase in relative liver weight. Slight increases of kidneys weights. Specific nephropathy in male.	-	2	Stott, 1992

Study	Results	NOAEC	Validity	Reference
5h/d 5d/w 2 weeks 2500 – 5000 – 10000 ppm	Reversible CNS depression at 5000 and 10000 ppm. Decrease growth rate was seen at 10000 ppm.	2500 ppm 9350 mg/m^3	2	Goldberg *et al*., 1964
Fischer 344 6h/d 5d/w 13 weeks 0 – 300 – 3000 ppm	Sedation at 3000 ppm. Male specific nephropathy at all doses.	300 ppm 1122 mg/m^3	1	Cieszlak *et al*., 1996
Fischer 344 6h/d 5d/w 13 weeks 0 – 300 – 1000 – 3000 ppm	CNS depression at 3000 ppm. Slight increase in liver weight and slight decrease in female body weight gain.	1000ppm 3740 mg/m^3	1	Landry *et al*., 1983
7h/d 5d/w 6 months	-	> 1500 ppm 5600 mg/m^3	3	Rowe *et al*., 1954
2-year study 0 – 300 – 1000 – 3000 ppm	Effects on liver from 1000 ppm. Specific kidneys effects on male rats	300 ppm 1122 mg/m^3	1	Cieszlak *et al*., 1998
Mouse				
B6C3F1 9 exposures 0 – 300 – 1000 – 3000 ppm	CNS depression at 3000 ppm. No irreversible effects on organs.	1000 ppm 3740 mg/m^3	1	Miller *et al*., 1981
B6C3F1 9 exposures in 11 days 0 - 3000 ppm	CNS depression in the treated group. Increase in relative liver weight and hepatocellular proliferation.	< 3000 ppm < 11220 mg/m^3	2	Stott, 1992
B6C3F1 6h/d 5d/w 13 weeks 0 – 300 – 1000 – 3000 ppm	CNS depression at 3000 ppm. Renal and hepatic cellular proliferation ar 3000 ppm. Increase hepatic enzymatic induction at 3000 ppm. Increased in liver weight in females at 3000 ppm.	1000 ppm 3740 mg/m^3	1	Cieszlak *et al*., 1998
2-year study	Increased mortality in males at 3000 ppm	1000 ppm	1	Cieszlak *et al*.,

Study	Results	NOAEC	Validity	Reference
0 – 300 – 1000 – 3000 ppm	related to liver toxicity.	3740 mg/m^3		1998
Rabbit				
3 –6 month 800 – 1500 – 3000 – 6000 ppm	Slight increases of liver weight in females and slight histological changes of the liver and lungs at 1500 and 3000 ppm.	800 ppm 3000 mg/m^3	3	Rowe *et al*., 1954
6h/d 5d/w 13 weeks 0 – 300 – 1000 – 3000 ppm	CNS depression at 3000 ppm. Slight increases of alkaline phosphatase at 3000 ppm..	1000 ppm 3740 mg/m^3	1	Landry *et al*., 1983
Guinea pig				
7h/d 5d/w 6 months 0 – 1500 – 3000 ppm	No effects seen.	3000 ppmp < 11220 mg/m^3	3	Rowe *et al*., 1954
Monkey				
7h/d 5d/w 6 months 0 – 800 – 1500 – 3000 ppm	No details available	800 ppm 3000 mg/m^3	3	Rowe *et al*., 1957

Validity

1: valid without restriction

2: valid with restriction

3: not valid or not assessable

Dermal

In a 21 day dermal study, New Zealand White rabbits were applied daily a dose of 0 or 1000 mg/kg PGME (15 applications) (Calhoun and Johnson, 1984). Rabbits receiving 1000 mg/kg PGME showed no signs of systemic effects in various parameters including hematologic analysis and histopathology. The only treatment related effect was slight scaling and minimal inflammation with a protective thickening response of the skin. In this study the NOAEL was not determined due to the effect seen at the only dose tested.

In a 90 day dermal study, rabbits were administered PGME at doses of 0 to 10 ml/kg 5d/week (Rowe *et al*., 1954). Larger doses (7 to 10 ml/kg) produced narcosis which generally led to the death of the animal (8/9 deaths at 7 ml/kg, 11/11 deaths at 10 ml/kg). Repeated applications in doses of 1 to 5 ml/kg were generally without effect. Histologic examination of tissues of surviving animals were within normal limits. Slight narcosis at 3676 mg/kg (4 ml/kg) was

observed. In this study a NOAEL of 2 ml/kg bw was taken regarding the effects seen at 4 ml/kg bw.

Summary RDT dermal route:

Only two studies are available to assess effects of repeated exposure to PGME. The only systemic effect seen was narcosis from 3676 mg/kg and higher (moreover this effect can be considered as an acute effect). Slight inflammation was seen locally at doses < 1000 mg/kg. Based on the only reliable study a NOAEL of 1000 mg/kg will be taken into account for systemic effects by dermal route. The LOAEL for local effects is 1000 mg/kg.

Table 4.30: Summary of RDT dermal route

Study	Results	NOAEL	Validity	Reference
Rabbit				
5d/w 90 days 0 to 10 ml/kg	High doses (7 – 10 ml/kg) produced narcosis and mortality. Slight narcosis was seen from 4ml/kg.	2 ml/kg (about 1840 mg/kg)	3	Rowe *et al*., 1954
21 day (15 - application) 0 – 1000 mg/kg	No systemic effects at tested dose. Slight scaling and minimal inflammation was seen on the treated skin.	> 1000 mg/kg for systemic effects < 1000 mg/kg for local effects	2	Calhoun and Johnson, 1984

Validity

1: valid without restriction

2: valid with restriction

3: not valid or not assessable

Oral

Rat

In a 35 day study by oral route, rats were administered PGME by gavage at doses of 0, 91.9, 275.7, 919 and 2757 mg/kg (Rowe *et al*., 1954). No mortalities were found. At 2757 mg/kg, some animals initially lost body weight, but they recovered quickly. The final body weight was not significantly different from that of controls. 2757 mg/kg produced only minor effects on liver and kidney.

In a 13 weeks oral route study, CFE rats were exposed to PGME at concentrations of 459.5, 919, 1836 and 3672 mg/kg (Stenger *et al*., 1972). Mild to severe central nervous system depression was observed. This caused a growth depression due to reduced feed intake. Livers were enlarged, especially at doses > 919 mg/kg. Cell necrosis was observed, mainly in the peripheral portions of the lobules. There was minor kidney injury at higher doses. In this

study, no NOAEL could be identified because effects were seen at the lowest dose tested (459.5 mg/kg).

Rabbit

Three rabbits were dosed orally with 1840 mg/kg/d of PGME (BASF, 65). Only three animals were used for this study. One animal died after 9 applications. The treatment led to a slight decrease of erythrocytes and lymphocytes. PGME had no effect on the testes.

Dog

Male Dogs were feed orally with PGME at doses of 0.5; 1; 3 and 3 ml/kg/d (459.5; 919; 1836 and 3672 mg/kg) for a period of 14 weeks (5 treatments a week) (Stenger *et al*., 1972). Mild to severe central nervous system depression in a dose-related manner was observed. Male dogs developed numerous spermiophages in the epididymis. There were minor kidney changes at higher doses. In this study the NOAEL was found to be lower than 459.5 mg/kg based on effects seen at 459.5 mg/kg. As no data is available on purity, the relevance of spermiophages in the epididymis is unclear. As this effect was not seen in the well performed fertility studies and only in dogs in this study it can be consider to be not related to PGME.

Summary RDT oral route:

Only four studies were performed to assess the repeated dose toxicity properties of PGME by oral route. None was made according GLP and guidelines. Overall for oral route, a LOAEL of 460 mg/kg can be taken into account (from a rat and a dog study) based on slight CNS depression seen from this dose in rats and dogs (13-week study for rats and 14-week study for dogs) and a NOAEL of 919 mg/kg by oral route for systemic effects (hepatic effects).

Table 4.31: Summary RDT oral route

Study	Results	NOAEL	Validity	Reference
Rat				
CFE rats 13 week oral feed 460 – 919 – 1836 – 3672 mg/kg	CNS depression at all doses. Liver enlarged at doses > 919 mg/kg with cell necrosis. Kidneys effects at 3672 mg/kg	< 460 mg/kg	2	Stenger *et al*., 1972
35 days 0 – 92 – 276 – 919 – 2757 mg/kg	Reversible decrease in body weight gain at the high dose. At the higher dose, slight effects on the liver and kidneys were noted.	919 mg/kg	3	Rowe *et al*., 1954
Rabbit				
3 rabbits only one dose: 1840 mg/kr 9 treatments	Effects on erythrocytes and lymphocytes. One animal died.	< 1840 mg/kg	3	BASF, 1965
Dog				
5d/w 14 weeks 460 – 919 – 1836 – 3672 mg/kg oral feed	CNS depression. Kidney changes at highest dose.	< 460 mg/kg	2	Stenger *et al*., 1972

4.1.2.6.2 Studies in humans

No data.

4.1.2.6.3 Summary of repeated dose toxicity

There is no guideline study for oral or dermal repeated dose toxicity. There is no human data available.

Animals exposed to PGME via inhalation and oral route have developed central nervous systems effects (sedation).

Hepatic mixed function oxidase activity and hepatocellular proliferation were increased at high doses, sometimes accompanied with mild degenerative changes or necrosis (in rare cases).

Minimal nephropathy in male rats was sometimes described with specific alpha-2-µ-globulin deposition in the kidney. Therefore, these renal effects are not relevant to humans.

By dermal route, local effects were reported at doses of about 1 g/kg (the only dose tested): scaling, minimal inflammation, and skin thickening. No systemic effects were reported at this level of dose leading to a NOAEL of 1000 mg/kg. The LOAEL for local effects was 1000 mg/kg/d.

By inhalation, a NOAEC of 300 ppm for liver effects is derived from a well performed 2-year rat study (6 h exposure for 5 days a week). By dermal route, a NOAEL of 1000 mg/kg was found for systemic effects based on a 21-day study in rabbits. By oral route, a LOAEL of 460 mg/kg can be taken into account for CNS effects in rats and dogs (13-week study for rats and 14-week study for dogs) and a NOAEL of 919 mg/kg by oral route for systemic effects (hepatic effects).

4.1.2.7 Mutagenicity

4.1.2.7.1 Studies *in vitro*

PGME gave negative results in a series of AMES test (BASF, 1983 ; Dow Europe SA, 1983a).

Effects on lung (V79) cells of Chinese hamsters included cell growth inhibition, slight increase in Sister Chromatide Exchanges (SCEs), and dose dependent inhibition on intercellular communication (at non-cytotoxic levels) (Elias *et al.*, 1996). However, SCEs were only noted at very high concentrations, and the resulting dose response correlation was weak. As such, these data are not convincing of a true genotoxic effect.

PGME was not toxic to Chinese hamster ovary (CHO) cells at concentrations up to 5 mg/mL (Dow Europe SA, 1983b). However, survival was decreased to 50% at 10 mg/mL.
Treatment of cells with PGME resulted in a few marginal increases in gap and aberrations at some doses in the absence of S9, but none of these were statistically significant. In the presence of S9, frequencies of gaps and aberrations all decreased from the solvent control with PGME pre-treatment.

4.1.2.7.2 Studies *in vivo*

Concentrations up to 6,000 mg/kg administered to mice did not increase the frequency of micronuclei in polychromatic erythrocytes harvested from bone marrow (Elias *et al.*, 1996).

4.1.2.7.3 Summary of mutagenicity

PGME was not mutagenic in bacteria (*Salmonella typhimurium* TA 1535, TA 1537, TA 1538, TA 98, and TA 100), *in vitro* tests on mammalian cells, or in one *in vivo* test on mice. The data available would indicate the PGME is not genotoxic.

4.1.2.8 Carcinogenicity

4.1.2.8.1 Studies in animals

Inhalation

Rat

In a two-year inhalation study, Fischer 344 rats were exposed whole body 6h/day and 5d/week at PGME concentrations of 0, 300, 1000 and 3000 ppm (0 – 1.1 – 3.75 – 11.2 mg/l). This test was performed according to OECD guideline 453 and GLP (Cieszlak *et al*., 1998a). PGME-induced sedation at 3000 ppm resolved in all animals during the second week of exposure in conjunction with the appearance of adaptive changes in the liver (MFO induction and hepatocellular proliferation-from previous work). MFO activities (PROD) subsequently dropped to near control values by week 52, coinciding with a return of sedation at 3000 ppm PGME. In male rats, the loss of metabolic adaptation was followed by a dose-related increase in eosinophilic foci of altered hepatocytes after two years of exposure to 1000 or 3000 ppm PGME. Kidney toxicity was observed in male rats only, which was confirmed immunohistochemically as an alpha 2µ-globin nephropathy. No statistically-identified increases in tumors were observed in any tissue, however, a numerical increase in kidney tumors (3/50) were observed in male rats from the intermediate exposure level with 1/50 observed at 3000 ppm PGME. The lack of statistical significance or a dose-response relationship in renal tumors, in conjunction with the induction of the male rat-specific alpha 2µ-globulin nephropathy, render these minimal renal observations irrelevant for human risk assessment purposes.

Mouse

In a two-year inhalation study, B6C3F1 mice were exposed whole body 6h/day and 5d/week at PGME concentrations of 0, 300, 1000 and 3000 ppm (0 – 1.1 – 3.75 – 11.2 mg/l). This test was performed according to OECD guideline 453 and GLP (Cieszlak *et al*., 1998b).

A transient sedation of mice inhaling 3000 ppm PGME during the first week of exposures was observed; however, this resolved during the second week concomitant with adaptive changes in the livers of these animals (previous Cieszlak studies results in RDT section). Mice exposed to 3000 ppm had increased mortality (males), decreased in-life body weights and body weight gains relative to controls, over much of the exposure period, as well as minimal increases in absolute and relative liver weights and hepatic MFO activity. No treatment-related histopatholgical changes accompanied these liver effects, nor were histopathological changes observed in any other tissues. These data, along with the occurrence of chronic, albeit small increases in hepatocellular proliferation in mice inhaling 3000 ppm suggested minimal regenerative response in the liver, likely related to shorted life span metabolically stressed hepatocytes. Decreases in body weights were also observed, although less frequently, in both sexes exposed to 1000 ppm. No treatment-related increases in tumors were observed in any tissue of male or female mice.

4.1.2.8.2 Studies in humans

No data.

4.1.2.8.3 Summary of carcinogenicity

No human data available.

In a 2-year bioassay, no statistically significantly increases in tumors in any tissue (except kidney tumors in males) were observed in male and female rats exposed to PGME via inhalation (Cieszlak *et al.*, 1998a). The increase in kidney tumours was considered not relevant to humans since it is assumed to be due to a male rat specific mechanism.

There were no increases in tumors in any tissue in a 2-year study of male and female mice exposed to PGME via inhalation (Cieszlak *et al.*, 1998b).

PGME is not carcinogenic and that therefore, no Risk Assessment for this end-point is necessary.

4.1.2.9 Toxicity for reproduction

4.1.2.9.1 Effects on fertility

Studies in animals

Commercial PGME is a mixture of two isomers (α and β). The β-isomer is metabolized to 2-methoxypropionic acid, a stongly suspected animal teratogen (Hellwig *et al.*, 1994 - Merkle *et al*., 1987). Although commercially available PGME contains less than 0.5% of the β-isomer, the PGME tested in some animal studies described here was altered to contain approximately 2% of the β-isomer : Liberacki *et al*., 1997.

Rat

Male Wistar rats were exposed during 10 days to PGME concentrations of 200 or 600 ppm (750 or 2240 mg/m^3) by inhalation (Doe *et al*., 1983). After exposure animals were checked for testicular pathology and haematology. No effects were seen after 200 and 600 ppm exposures.

In a two generation study performed on SD rats by inhalation route (GLP and performed according to OECD GL 416), animals were exposed to PGME at doses of 0, 300, 1000 and 3000 ppm (0 – 1122 – 3740 – 11220 mg/m^3). Animals were exposed 6 hours a day. (Liberacki *et al*., 1997 - Carney *et al*., 1999). It should be noted that this test has been performed with a substance containing about 1.9 % 2-methoxy-1-propanol.

At 3000 ppm, toxicity in the P1 and P2 adults was marked, as evidenced by sedation during and after exposure for several weeks, and mean body weights which were as much as 21% lower than controls. This marked parental toxicity was accompanied by lengthened estrous cycles, decreased fertility, decreased ovary weights, reduced pup survival and litter size, slight delays in puberty onset, and histologic changes in the liver and thymus of the F1 and F2 offspring. At 3000 ppm, there was an increase in histologic ovarian atrophy in P1 and P2 females, and at 1000 ppm, there was a decrease in premating body weight in the P1 and P2 females. No treatment-related differences in sperm counts or motility were observed among the P1 or P2 males. The nature of the reproductive/neonatal effects and their close individual correlation with decreased paternal body weights suggest that these effects were secondary to general toxicity and/or nutritional stress.

The general toxicity was due to:

- The sedation observed at 3000 ppm and, according to the authors, its possible alteration of feeding patterns. In some publications, feed restrictions lead to lengthened estrous cycles when the body weight were decreased by 30 % or more (Chapin *et al*., 1993. Keenan *et al*., 1996). While in this study, mean female bw were decreased by as much as 21 % relative to controls, the lack of access to feed during for 6-7 hours/day during inhalation exposure was extended in the 3000 ppm by a further period of sedation. This probable alteration of feeding pattern may have been an exacerbating factor contributing to the reproductive effects seen in this study. This conclusion is based on a study showing that restrincting feed access for ≤ 8 hours/day inhibited estrous cyclicity, decreased ovarian weights and generally inhibited ovarian function (Parshad, 1990).

- The substantial decreases in body weights. Close examination of the P2 female body weights (individual) relative to ovarian histology and reproductive function further support an argument for nutritional stress and non-specific toxicity as the main cause of the observed ovarian and reproductive effects. The 3000 ppm F1b neonates, from which the P2 parents were selected, has significantly decreased body weights from birth and these remained decreased during the lactation period and P2 pre-breeding exposure. Among this group, the 15 high-exposure P2 females that were subsequently identified as having histologic ovarian atrophy had mean body weights below their dose group mean at the start of the 10 week pre-breeding period (test day –1) and at day 70 (last weight prior the breeding); significantly lower than those with normal ovaries. The mean day 70 body weight of the 3000 ppm P2 females which had histologic ovarian atrophy at termination was 20 % lower than controls and 11 % lower than the 3000 ppm P2 females without histologic ovarian atrophy (see table 4.32). There were 14 high-exposure females which failed to become pregnant, only one of which did not exhibit histologic ovarian atrophy at study end; thus, in the P2 females, there was a very high individual correlation between decreased pre-mating body weights, failure to become pregnant, and histologic ovarian atrophy at the study end.

Table 4.32: The relationship of mean body weight decrements and ovarian atrophy in P2 female rats exposed to 3000 ppm PGME in the pre-mating period.

	Day -1		Day 70	
	P1	P2	P1	P2
Control	145.2 g	142.5 g	314.4 g	314.8 g
300 ppm	144.6	143.6	320	308.9
1000 ppm	144.2	138	302.6	293.8
3000 ppm	144	112.2 (-21.2 %)	283.9 (-9.7 %)	265.9 (-15.5 %)
3000 ppm OA	na	107.7 (-24.4 %)	na	251.3 (-20.2 %)
3000 ppm NOA	na	117.6 (-17.6 %)	na	282.5 (-10.3 %)

OA = Ovarian Atrophy
NOA = No Ovarian Atrophy
na = not applicable

The somewhat lesser severity of exposure related ovarian atrophy among P1 females relative to the P2 females is also consistent with the more limited effects on oestrous cycle length and fertility parameters and less severe effects on body weights in the first generation. However, examination of this relationship between ovarian histology and other effects in the P1 females

is complicated by the older age at termination of the P 1 females vs. the P2 females. The Pl females were bred a second time following weaning of the F 1 a litters, as a result, they were older than the P2 females (8 months-of-age vs. 5.6 months) when they were necropsied.Due to the age factor, the Pl ovarian atrophy data includes a significant underlying incidence of age-related senescence, a normal and relatively young occurrence in the Sprague-Dawley rat, but one not yet present in the P2 females at necropsy. Senescence atrophy is indistinguishable from atrophy associated with the effects of daily direct or indirect exposure to 3000 ppm of PGME. Ovarian senescence in Sprague-Dawley rats commonly begins at 5-6 months-of-age (Everett, 1989); thus the high incidence of ovarian atrophy in P l controls was expected. Still, in the Pl generation, the stresses of 3000 ppm exposure were adequate to increase the incidence of histological moderate ovarian atrophy. These stresses were substantiated by the body weight decrement of approximately 10% noted for 3000 ppm PGME Pl females on day 70 (see table 4.32), however, in the Pl females, ovarian atrophy did not correlate with the premating body weight decrements on an individual basis as it did for the P2 females where the decrements were much larger. This may be due to the confounding effect that decreased caloric intake can, in some cases, delay reproductive senescence.

Based on the above discussion, we conclude that the ovarian effects, including atrophy, increased oestrous cycle length, decreased fertility, and decreased ovarian weight, observed among high-exposure Pl and P2 females were associated with non-specific toxicity and decreased body weights, magnified in the second generation by a severe starting decrement in body weight that persisted through the P2 pre-breeding period.

No such effects were observed at 1000 ppm, a concentration which caused less marked, but significant body weights effects without sedation.
In this study, a NOAEC of 300 ppm can be taken for general toxicity in adults and a NOAEC of 1000 ppm for specific reproductive toxicity on dams (effects on ovaries and estrous cycle). In pups, signs of toxicity were seen at 3000 ppm, leading to a NOAEC of 1000 ppm. This toxicity was observed concurrently with severe maternal toxicity and can be considered to be secondary to parental toxicity and/or nutritional stress in the offspring. Fertility effects were seen at the highest dose 3000 ppm (estimation from the authors of about 4000 mg/kg/d if oral route considered), and because this is a very high dose, there is no need for classification for this end point.

Mouse

In a two generation study performed on CD1 mice by oral route (in drinking water), PGME (purity not reported) was administered at doses of 0; 0.5; 1; 2.0 % (calculated consumption estimates of approximately 0.95, 1.9 and 3.3 g/kg/d). Premating periods for both males and females was 7 days (Chapin and Sloane, 1997).

There were no changes in body weight or food consumption in any of the first generation exposure groups except for a 4% reduction in pup weight at the highest dose tested. In the second generation exposure groups, reductions in male and female body weight were noted (14% reduction during nursing; 8% reduction in body weight in males during and after mating, and epididymus and prostate weights were 9 and 8% below controls in males, respectively). There was no evidence of reproductive toxicity; mating and fertility indices, and the number and viability of F1 and F2 offspring were not affected. F2 offspring from the 2% group displayed reduced pup weight at birth, which continued postnatally during nursing. At sacrifice, female body weights in the 2% group were lower than controls; absolute testis, and relative epididymis and prostate weights were also reduced. F1 female body-weight-

adjusted liver weights were increased. In this study the parental, the F1 and the F2 NOAELs were 1% (about 1900 mg/kg).

4.1.2.9.2 Developmental toxicity

Studies in animals

Rat

Female Wistar rats were exposed to PGME (purity not reported) by inhalation at concentration of 200 and 600 ppm (750 or 2240 mg/m^3) during pregnancy (GD6 to GD17) (Doe *et al*., 1983). No effects were seen in dams and in offspring at 200 and 600 ppm.

Fischer 344 rats were exposed by inhalation to PGME (purity 98.7 %, 1.32 % of 2-methoxy-1-propanol) during pregnancy (GD6-GD15) at doses of 0, 500, 1500 and 3000 ppm (1870 – 9350 and 11220 mg/m^3) (Hanley *et al*., 1984). This test was performed according to a method similar to OECD guideline 414.
For maternal general toxicity, mild transient CNS depression, decreased food consumption and body weight gain were observed in animals at 3000 ppm. For pregnancy/litter data, slight fetotoxicity (delayed sternebral ossification) was observed in rats exposed to 3000 ppm (see table 4.32 bis). No evidence of teratogenicity was seen at exposures up to 3000 ppm. In this study maternal and fetal NOAEC were 1500 ppm.

Table 4.32 bis: Incidence of delayed sternebral ossification in the Hanley study in rats

	Nb fetuses (nb litters) examined			
Dose (ppm)	0	500	1500	3000
delayed sternebral ossification	147 (26)	189 (27)	157 (25)	190 (27) *

* statistically significant from the control value ($\alpha = 0.05$)

CFE pregnant rats were dosed orally once a day with PGME (purity unknown) at doses of 0; 0.05; 0.1; 0.2; 0.4 and 0.8 ml/kg from GD1 to GD21 (Stenger *et al*., 1972). In this study, except for only one pup which had a delayed ossification of the skull, no effects were seen in dams or in pups. The NOAEL is therefore 0.8 ml/kg for maternal toxicity and fetal toxicity. In pups, delayed ossification was found when PGME was administered S.C.

Mouse

CFLP pregnant mice were dosed orally once a day with PGME (purity unknown) at doses of 0; 0.5; 1.2 ml/kg from GD1 to GD18 (Stenger *et al*., 1972). In this study no effects were seen in dams or in pups. The NOAEL is therefore 1.2 ml/kg for maternal toxicity and fetal toxicity. No maternal or fetotoxicity were observed when subcutaneous injections of PGME were administered at the same doses.

Rabbit

In a GLP test performed on New Zealand White Rabbits, pregnant females were administered PGME (purity 98.7 %, 1.32 % of 2-methoxy-1-propanol) by inhalation route at doses of 0, 500, 1500 and 3000 ppm from GD6 to GD18 (Hanley *et al*., 1984). For maternal toxicity, mild transient CNS depression, decreased food consumption were observed in animals at

3000 ppm. PGME was not teratogenic in rabbits at exposures up to 3000 ppm. In this study maternal NOAEC was 1500 ppm and fetal NOAEC 3000 ppm.

Gelbsilber pregnant rabbits were dosed orally once a day with PGME (purity unknown) at doses of 0; 0.25; 0.5; 1 ml/kg from GD1 to GD18 (Stenger *et al*., 1972). In this study no effects were seen in dams or in pups. The NOAEL is therefore 1 ml/kg for maternal toxicity and fetal toxicity. No maternal or fetotoxicity were observed when subcutaneous injections of PGME were administered at the same doses.

4.1.2.9.3 Summary of toxicity for reproduction

Fertility

Commercial PGME is a mixture of two isomers (α and β). The β-isomer is metabolized to 2-methoxypropionic acid, a stongly suspected animal teratogen (Hellwig *et al*., 1994 - Merkle *et al*., 1987). Although commercially available PGME contains less than 0.5% of the β-isomer, the PGME tested in some animal studies described here was altered to contain approximately 2% of the β-isomer : Liberacki *et al*., 1997,

NOAELs observed in a two-generation reproductive study on exposure to PGME via inhalation were 300 ppm (1122 mg/m^3) for adult rats and 1,000 ppm (3740 mg/m^3) for offspring (Liberacki *et al.*, 1997, Carney *et al,* 1999). Sedation and decreased body weight in adults was accompanied by lengthened estrous cycles, decreased fertility, decreased ovary weights and associated ovarian atrophy, reduced pup survival and litter size, slight delays in pubertal indices, and histological changes in the liver and thymus (in offspring) at the highest dose tested (3000 ppm). However, the nature of these effects and the close correlation with decreased maternal body weights suggest that these effects were secondary to general toxicity and/or nutritional stress. For oral exposures, a NOAEL of 1% in drinking water in a two-generation mice reproduction study was reported (Chapin and Sloane, 1997). Reduced pup weights, and in the second generation reduced adult body weights, and a decrease in epidydimal and prostate weights were observed at the highest dose tested (2% in drinking water). In another study (Doe *et al*., 1983), male rats exposed to 200 or 600 ppm PGME via inhalation (6 hours/day for 10 days) showed no effects on the testes.

Effects on fertility were seen at relatively high doses in the presence of slight systemic toxicity. In these study, the most relevant NOAEC was 1000 ppm seen in the 2-generation study based on effects seen on females at 3000 ppm.

Development

In all studies, maternal toxicity was found at high doses (mainly CNS depression and decrease food consumption with decrease body weight gain). In fetuses, slight effects were seen: delayed ossification in some studies (sternebral or skull) but always in presence of maternal toxicity. No teratogenic effects were observed at doses up to 3,000 ppm by inhalation route or 1 ml/kg by oral route.

In the 2-generation studies, foetotoxic effects were seen concurrently with maternal toxicity (3000 ppm by inhalation in rats (11220 mg/m^3) and 2% in drinking water in mice.)

This kind of effects (delayed ossification) are often reported concurrently with the maternal effects described in the available studies. Due to the low toxicity of PGME and that no

specific developmental effects were observed at relatively high dose without maternal toxicity, it is considered that developmental toxicity of PGME is of no concern.

4.1.3 Risk characterisation [5]

4.1.3.1 General aspects

The human population may be exposed to PGME at the workplace, both from use of consumer products and indirectly via the environment (see 4.1.1.1, 4.1.1.2 and 4.1.1.3)

For occupational exposure, the relevant routes of exposure are dermal and inhalation.

From the oral absorption studies it is concluded that oral absorption is complete. For risk characterisation 100 % oral absorption should be assumed. No quantitative data is available of absorption by inhalation route, but all studies showed that PGME is readily absorbed via inhalation route, an absorption percentage of 100 % will be taken into account. For dermal absorption, in the studies available and according to the PbPk modelling, whole body exposure to vapour PGME give a contribution of about 10 % maximum of the total body burden due to dermal absorption. For liquid PGME, absorption percentage has not been assessed. If compared to EGBE dermal absorption a maximum of 30 % can be expected for PGME. For risk characterisation 30 % dermal absorption should be assumed (worst-case estimate).

For interspecies extrapolation, PBPK models exist for the rat, mouse and human. These enable some kinetic extrapolations. The model available, (Corley *et al*., 2005) is considered complete and appropriate for potential use in the derivation of an interspecies extrapolation factor for all routes of exposure because it has been experimentally validated and covers relevant routes of exposure. Moreover this model has also been accepted for another glycol ether: EGBE.

According to this model a interspecies factor of 0.4 can be taken into account for extrapolation of values found in rats to values estimated in humans for exposure concentrations above 100 ppm and of 1 for exposure concentrations below 100 ppm since according to Corley *et al*., 2005 the rat and human blood levels of PGME are similar at exposure concentrations below 100 ppm .

Table 4.33: Absorption coefficients taken into account for the calculations of internal doses

	Oral	Inhalation	Dermal route	
% of absorption	100 %	100 %	PGME liquid	PGME vapour
			30 %	10 % of the internal dose

[5] Conclusion (i) There is a 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.

PGME has a very low acute toxicity by all routes of exposure. For CNS depression a NOAEL of 750 ppm (2,800 mg/m^3) was derived human exposure.

Only very slight signs of irritation were observed for skin, eyes or respiratory tract. In a human study, a NOAEL of 100 ppm is observed for eye and upper respiratory tract irritation.

PGME is not sensitising to animals, and there are no human data available.

Repeated dose toxicity of PGME was well studied in a 2 year toxicity study by inhalation. In this study, a NO(A)EC of 300 ppm (1,122 mg/m^3) was found based on hepatic effects seen at 1000 ppm. By dermal route, no systemic effects were seen at doses of 1000 mg/kg in a 21 day study. Only local effects limited to slight inflammation were seen. A LOAEL of 1,000 mg/kg is taken into account for Risk Characterisation for local repeated effects. By oral route studies performed on dogs and rats gives a LOAEL of 460 mg/kg based on CNS reversible effects seen at all tested doses. This effect can be considered as an acute effect due to narcotic properties of PGME. If risk characterisation is needed for oral route, the NOAEL of 919 mg/kg can be taken into account based on hepatic effects seen at higher doses in the Stenger studies.

PGME is not a mutagenic substance and no carcinogenicity is expected according to the data available.

Fertility effects of PGME were studied in a 2-generation study by inhalation in rats and in a continuous breeding study in mice. Effects on fertility were seen at relatively high doses in the presence of marked systemic toxicity. In these study, a NOAEC of 1000 ppm was seen in the 2-generation study based on effects seen on females at 3000 ppm.

Slight developmental effects of PGME was observed in pups of treated dams. These effects were seen at high doses and always in presence of maternal toxicity. Moreover this kind of effects (delayed ossification) are often reported concurrently with the maternal effects described in the available studies. Therefore no risk characterisation is needed for these effects.

Table 4.34: Summary of effects

Substance name	Inhalation (N(L)OAEL)	Dermal (N(L)OAEL)	Oral (N(L)OAEL)
Acute toxicity	< 6038 ppm (22.5 mg/l) (LD50) 750 ppm CNS depression in human	13g/kg (LD50: mortality) 1000 mg/kg	4016 mg/kg
Irritation / corrositivity	100 ppm for eye and upper respiratory tract irritation	NA	NA
Sensitization	NA	NA	NA
Repeated dose toxicity (local)	NA	< 1000 mg/kg	NA
Repeated dose toxicity (systemic)	1000 ppm (3740 mg/m^3) CNS depression 300 ppm (1122 mg/m^3) hepatic effects	> 1000 mg/kg	< 460 mg/kg (narcotic effects) 919 mg/kg (hepatic effects)
Mutagenicity	NA	NA	NA
Carcinogenicity	NA	NA	NA
Fertility impairment	1000 ppm (female) (3740 mg/m^3)	NA	NA
Developmental toxicity	NA	NA	NA

NA: not applicable

4.1.3.2 Workers

Table 4.35: Summary of proposed reasonable worst case exposures

Scenario	8-hour TWA inhalation (mg/m^3)	Dermal (mg/day)
1 - Manufacture	2.7	42
2 - Formulation	87	3,000 (loading and filling)
3 - Use of products		
3.1 Coating/Painting*		
- industrial		
- Spraying	100	3,000
- Other works	61	360
- decorative	61	180
3.2 Cleaning		
- Spraying	151	250
- Wiping	151	1000
3.3 Printing		
- silk screening	100	23
- flexography	100	168
general printing	35	168

* The conclusions refer to solvent-based paints. Exposure from use of water-based paints (lower PGME content) would be much lower.

4.1.3.2.1 Acute toxicity

The only effect taken into account for acute risk characterisation is CNS depression. For inhalation, a NOAEL of 750 ppm has been derived from human exposure. For dermal exposure a NOAEL of 1,000 mg/kg can be taken into account. This NOAEL(C) is compared with levels of exposure. The MOSs obtained are compared with minimal MOS calculated as follows:

Table 4.36: Assessment factors applied for the calculation of minimal MOS for acute toxicity (for inhalation and dermal route).

Interspecies differences	1 for inhalation route 2.4 x 2.5 = 6 for dermal route[1]
Intraspecies differences	5 (workers: homogen population)
Type of effect	1
Confidence of the database	1
Minimal MOS	5 for inhalation route 30 for dermal route

1 for dermal route, as a rabbit study is used as starting point, allometric scaling factor of 2.4 is applied, as recommended by the TGD.

Inhalation:

NOAEC of 2,800 mg/m^3 is compared with exposure estimates. The results are summarised in the table 4.37.

Based on the risk assessment for inhalation exposure, it is concluded that toxicity due to acute exposure are not expected.

Conclusion ii is reached for all occupational scenarios.

Dermal:

Dermal NOAEL is greater or equal to 1000 mg/kg for systemic effects, the only dose tested. When applied occluded to the skin of rabbits, the LD50 value was found to be in the range of 13-14 g/kg. This NOAEL of 1000 mg/kg is compared to exposure estimates. The results are summarised in the table 4.37.

Conclusion ii is reached for all occupational scenarios excepted for formulation and coating/painting - spraying, for which the MOS is 23. Otherwise, knowing that PGME has a very low acute toxicity by dermal route (LD50 value in the range of 13-14 g/kg), no risk is anticipated.

If the risk characterisation is conducted in using the dermal exposure estimation for the formulation scenario provided by NL (COM406_hh_NL6), a MOS of 23 would be obtained with a MOSref. But based on the high uncertainty regarding the hypothesis used in the exposure estimation and due to the very low acute toxicity by dermal route (LD50 value in the range of 13-14 g/kg), it is considered that a conclusion (ii) should be applied.

Table 4.37: Occupational risk assessment of PGME for acute toxicity.

Scenario		Risk assessment for inhalation exposure			Risk assessment for dermal exposure to liquid PGME		
		8-hour TWA inhalation (mg/m^3)	MOS	Conclusion	Estimated Skin exposure mg/day worst case (mg/kg bw/d	MOS	Conclusion
1 - Manufacture		2.7	1037	ii	42 (0.6)	1666	ii
2 - Formulation		87	32	ii	3,000 (43) ()	23	Iii - ii
3 - Use of products	3.1 Coating/Painting						
	Industrial						
	-spraying	100	28	ii	3000 (43)	23	iii - ii
	-other works	61	46	ii	360 (5.1)	196	ii
	- decorative	61	46	ii	180 (2.6)	385	ii
	3.2 Cleaning						
	- spraying	151	19	ii	250 (3.6)	278	ii
	-wiping	151	19	ii	1000 (14.3)	70	ii
	3.3 Printing						
	- Silk screening	100	28	ii	23 (0.32)	3125	ii

	- flexography	100	28	ii	168 (2.4)	416	ii
	general printing	35	80	ii	168 (2.4)	416	ii

Combined exposure:

For the combined exposure, the estimated internal doses are calculated from the biological exposure data. Inhalation exposure will give internal dose of:

X (value of the 8-hour TWA inhalation (mg/m^3)) x 10 m^3 (inhaled air during a workday) x 1 (100 % absorption by inhalation) / 70 (mean bw of a worker) = Y (inhalation internal dose).

So, the NOAEC of 2800 mg/m³ would lead to an internal doses of 400 mg/kg/day.

This internal dose should be compared with internal dose calculated. This NOAEC should be compared with internal doses calculated from exposures in each scenario (inhalation + dermal). The internal doses are calculated as follow:

This value does not take into account the possible dermal absorption of vapour during the 8hr TWA. It has been demonstrated that dermal absorption of vapour PGME could count for 10 % of the internal dose of PGME. To take into account this value, the value of internal dose due to dermal exposure to vapours (Z) should be added to the former value (Y). Z represents 10 % of the total internal dose and can be calculated as follow :

Z = 0.10/0.90 x Y = 0.11 Y

The total internal dose due to inhalation exposure (inhalation output + dermal vapour penetration output) is Y + Z = 1.11 Y

In this case, an internal dose of about 44 mg/kg (0.11 Y) can be calculated, to obtain a total internal dose of 444 mg/kg due to inhalation and dermal absorption of PGME.

For dermal exposure internal dose is calculated for a 70 kg bw worker with a percentage of absorption of 30 % (liquid PGME, worst case)

The minimal MOS chosen for the combined exposure will be the one taken for inhalation exposure: 5 as it is the MOS calculated for the inhalation NOAEC which is taken into account in the calculations.

Internal doses corresponding to each scenarios, MOS and conclusions are summarised in the table 4.38:

Table 4.38: Risk characterisation for combined exposure – acute toxicity

Scenario		Internal dose after inhalation exposure (mg/kg) Y + Z	Internal dose after dermal exposure to liquid PGME (mg/kg) 30 %	Total internal dose (inhalation + dermal combined exposure)	MOS[1]	Conclusion
1 - Manufacture		0.44	0.18	0.62	716	ii
2 - Formulation		13.8	12.9	26.7	16.6	ii
3 - Use of products	3.1 Coating/Painting					
	Industrial					
	-spraying	15.9	12.9	28.8	15.4	ii
	-other works	9.7	1.53	11.23	39.5	ii
	- decorative	9.7	0.78	10.48	42.4	ii
	3.2 Cleaning					
	spraying	24	1.08	25.08	17.7	
	wiping	24	4.29	28.29	15.7	ii
	3.3 Printing					
	- Silk screening	15.9	0.096	16	27.8	ii
	- flexography	15.9	0.72	16.6	26.7	ii
	general printing	5.6	0.72	6.3	70.5	ii

Based on the risk assessment for combined exposure, it is concluded that toxicity due to acute exposure is not expected.

Conclusion ii is reached for all occupational scenarios.

4.1.3.2.2 Irritation and corrosivity

Skin and eye irritation (liquid)

Given the effects observed in the skin and eye irritation studies it is concluded that PGME is of no concern for workers with regard to irritating effects (conclusion ii).

Eye and upper respiratory tract irritation (vapours):

A NOEC of 100 ppm (374 mg/m^3) is taken into account for this effect.

Since the NOEC for respiratory tract irritation is derived from humans, the only assessment factor needed is that to allow for possible intraspecies variation. This is particularly true since the effects are not only discomfort in nature. A factor of 3, and therefore minimal MOS of 3 is considered sufficient for this end point. The MOSs between the NOEC and the inhalation exposure levels and the conclusions of the risk assessment are mentioned in table 4.39:

Table 4.39: Risk characterization for eye and respiratory tract irritation

Scenario	8-hour TWA inhalation (mg/m^3)	MOS	Ccl
1 - Manufacture	2.7	139	ii
2 - Formulation	87	4	ii
3 - Use of products			
3.1 Coating/Painting			
- industrial			
- Spraying	100	4	ii
- Other works	61	6	ii
- decorative	61	6	ii
3.2 Cleaning spraying and wiping	151	2.5	iii
3.3 Printing			
- silk screening	100	4	ii
- flexography	100	4	ii
general printing	35	11	ii

For eye and respiratory tract irritation due to the exposure of PGME in vapour form, **conclusion iii** is reached for cleaning spraying and wiping. **Conclusion ii** is reached for all other scenarios.

4.1.3.2.3 Sensitisation

Given the effects observed in the dermal sensitisation studies it is concluded that PGME is of no concern for workers with regard to skin sensitisation (**conclusion ii**).

There are neither data from human experience nor other indications for respiratory sensitisation. (conclusion ii)

4.1.3.2.4 Repeated dose toxicity

Systemic effects:

Liver effects were seen in RDT studies. A NOAEC of 300 ppm (1122 mg/m^3) was derived from a 2-year chronic study in rats. For dermal systemic effects a NOAEL of 1000 mg/kg bw/d was derived from a dermal study. This value is supported by the NOAEL of the

90-day study (Rowe *et al*., 1954) where a NOAEL of 2 ml/kg bw (1838 mg/kg bw) was identified.

This NOAEC is compared with levels of exposure. The MOSs obtained are compared with minimal MOS calculated as follows:

Table 4.40: Assessment factors applied for the calculation of minimal MOS for repeated dose toxicity (for inhalation and dermal route).

Interspecies differences	Inhalation route: 2.5 (toxicodynamic factor) x 1 = 2.5 Dermal route: 2.5 x 2.4 = 6[1]
Intraspecies differences	5 (workers: homogen population)
Duration of exposure	2 [2] (dermal route)
Type of effect	1
Confidence of the database	1
Minimal MOS	12.5 for inhalation route 60 for dermal route

1: for dermal route, as a rabbit study is used as starting point, allometric scaling factor of 2.4 is applied, as preconised in the TGD.

2: a lower assessment factor of 2 was used instead of a factor of 6 (as recommended by the TGD) to extrapolate from 21-day to chronic study. No assessment factor was used to extrapolate from sub-acute to sub-chronic study since the NOAEL retained from 21-day study is lower than the NOAEL found in an old dermal 90-day study.

Inhalation:

NOAEC of 1122 mg/m^3 is compared with exposure estimates. The results are summarised in the following table:

Table 4.41: Occupational risk assessment of PGME for repeated dose toxicity: inhalation and dermal route.

Scenario	Risk assessment for inhalation exposure			Risk assessment for dermal exposure to liquid PGME		
	8-hour TWA inhalation (mg/m^3)	MOS	Conclusion	Estimated Skin exposure mg/day worst case (mg/kg bw/d)	MOS	Conclusion
1 - Manufacture	2.7	415	ii	42 (0.6)	1666	ii

2 - Formulation		87	13	ii	3000 (43)	23	iii
3 - Use of products	3.1 Coating/Painting						
	Industrial						
	-spraying	100	11	iii	3000 (43)	23	iii
	-other works	61	18	ii	360 (5.1)	196	ii
	- decorative	61	18	ii	180 (2.6)	385	ii
	3.2 Cleaning						
	spraying	151	7.4	iii	250 (3.6)	278	ii
	wiping	151	7.4	iii	1000 (14.3)	70	ii
	3.3 Printing						
	- Silk screening	100	11	iii	23 (0.32)	3125	ii
	- flexography	100	11	iii	168 (2.4)	416	ii
	general printing	35	32	ii	168 (2.4)	416	ii

Based on the risk assessment for inhalation exposure, it is concluded that toxicity due to repeated exposure can be excluded for the followingscenarios: manufacture, formulation, industrial (other works and decorative) and for printing (general printing) **conclusion ii**. For the other scenarios: industrial spraying, cleaning (spraying and wiping) and printing (silk screening and flexography), **conclusions (iii)** are drawn.

Dermal :

Dermal NOAEL is greater or equal to 1000 mg/kg for repeated toxicity (systemic). This NOAEL is compared to exposure estimates. The results are summarised in the table 4.41.

Conclusion ii is reached for most of the occupational scenarios for dermal exposure. For formulation and for industrial spraying (coating/painting) where a MOS of 23 is derived, a **conclusion (iii)** is drawn.

Combined exposure :

For the combined exposure, the estimated internal doses are calculated from the biological exposure data. Inhalation exposure will give internal dose of:

X (value of the 8-hour TWA inhalation (mg/m^3)) x 10 m^3 (inhaled air during a workday) x 1 (100 % absorption by inhalation) / 70 (mean bw of a worker) = Y (inhalation internal dose).

So, the NOAEC of 1122 mg/m³ would lead to an internal doses of 160 mg/kg.

This internal dose should be compared with internal dose calculated. This NOAEC should be compared with internal doses calculated from exposures in each scenario (inhalation + dermal). The internal doses are calculated as follow:

This value does not take into account the possible dermal absorption of vapour during the 8hr TWA. It has been demonstrated that dermal absorption of vapour PGME could count for 10 % of the internal dose of PGME. To take into account this value, the value of internal dose due to dermal exposure to vapours (Z) should by added to the former value (Y). Z represent 10 % of the total internal dose and can be calculated as follow :

Z = 0.10/0.90 x Y = 0.11 Y

The total internal dose due to inhalation exposure (inhalation output + dermal vapour penetration output) is Y + Z = 1.11 Y

In this case, an internal dose of about 17,6 mg/kg (0.11 Y) can be calculated, to obtain a total internal dose of 177.6 mg/kg due to inhalation and dermal absorption of PGME.

For dermal exposure internal dose is calculated for a 70 kg bw worker with a percentage of absorption of 30 % (liquid PGME, worst case)

The minimal MOS chosen for the combined exposure will be the one taken for inhalation exposure: 12.5 as it is the MOS calculated for the inhalation NOAEC which is taken into account in the calculations. Internal doses corresponding to each scenarios, MOS and conclusions are summarised in the table 4.42:

Table 4.42: Risk characterisation for combined exposure – repeated dose toxicity

Scenario		Internal dose after inhalation exposure (mg/kg) Y + Z	Internal dose after dermal exposure to liquid PGME (mg/kg)	Total internal dose (inhalation + dermal combined exposure)	MOS[1]	Conclusion
1 - Manufacture		0.44	0.18	0.62	286.5	ii
2 - Formulation		13.8	12.9	26.7	6.7	iii
3 - Use of products	3.1 Coating/Painting					
	Industrial					
	-spraying	15.9	12.9	28.8	6.2	iii
	-other works	9.7	1.53	11.23	15.8	ii
	- decorative	9.7	0.78	10.48	16.9	ii
	3.2 Cleaning					
	spraying	24	1.08	25.08	7.1	iii
	wiping	24	4.29	28.29	6.3	iii
	3.3 Printing					
	- Silk screening	15.9	0.096	16	11.1	iii
	- flexography	15.9	0.72	16.6	10.7	iii
	general printing	5.6	0.72	6.3	28.2	ii

Based on the risk assessment for combined exposure, it is concluded that toxicity due to repeated exposure can be excluded for the following scenarios: manufacture, coating and painting: other works, decorative and for general printing (conclusion (**ii**)). The other occupational scenarios present a risk, a conclusion (iii) is reached for combined exposure.

Local effects:

Slight local effects were seen in a 21-day study in rats at the maximum (and unique) tested dose: 1000 mg/kg bw/d. A LOAEL of 1000 mg/kg bw/d is therefore taken into account for risk characterisation.

This LOAEL is compared with levels of exposure. The MOSs obtained are compared with minimal MOS calculated as follows:

Table 4.42 bis: Assessment factors applied for the calculation of minimal MOS for repeated dose toxicity (for dermal route).

Interspecies differences	2.5 (toxicodynamic factor) *
Intraspecies differences	5 (workers: homogen population)
Type of effect	1
Extrapolation LOAEL to NOAEL	3
Confidence of the database	1
Minimal MOS	37.5

*(toxicokinetic factor not applied for local effects)

Table 4.42 ter : Risk characterisation for local effects

Scenario	Estimated Skin exposure mg/day worst case (mg/kg bw/d)	MOS	Conclusion
1 - Manufacture	42 (0.6)	1667	ii
2 - Formulation	3,000 (43)	23	iii
3 - Use of products			
3.1 Coating/Painting			
- industrial			
- Spraying	3000 (43)	23	iii
- Other works	360 (5.1)	196	ii
- decorative	180 (2.6)	384	ii
3.2 Cleaning			
spraying	250 (3.6)	278	ii
wiping	1000 (14.3)	70	ii
3.3 Printing			

- silk screening	23 (0.32)	3125	ii
- flexography	168 (2.4)	416	ii
general printing	168 (2.4)	416	ii

Conclusion **iii** is reached for formulation and industrial spraying (coating/painting), conclusion **ii** is reached for all other scenarios.

These MOS are calculated using worst case scenarios for dermal exposure and without use of PPE. It might be considered that using PPE conclusion ii could be reached instead for all scenarios.

4.1.3.2.5 Mutagenicity

Given the effects observed in the mutagenicity studies it is concluded that PGME is of no concern for workers with regard to mutagenicity (**conclusion ii**)

4.1.3.2.6 Carcinogenicity

Given the effects observed in the carcinogenicity study it is concluded that PGME is of no concern for workers with regard to carcinogenicity (**conclusion ii**)

4.1.3.2.7 Toxicity for reproduction

Effects on fertility:

Fertility effects were seen in female rats at doses of 3000 ppm in a 2-generation study leading to a NOAEC of 1000 ppm (3740 mg/m^3).
This NOAEC is compared with levels of exposure. The MOSs obtained are compared with minimal MOS calculated as follows:

Table 4.43: Assessment factors applied for the calculation of minimal MOS for reproductive (female fertility) toxicity (for inhalation and dermal route).

Interspecies differences	2.5 (toxicodynamic factor) x 1 (kinetic factor-PBPK) = 2.5 Dermal route: 4x2.5=10
Intraspecies differences	5 (workers, women only – homogeneous population)
Type of effect	1
Confidence of the database	1
Minimal MOS	12.5 for inhalation route 50 for dermal route

Inhalation:

NOAEC of 3740 mg/m^3 is compared with exposure estimates. The results are summarised in the following table:

Table 4.44: Occupational risk assessment of PGME for reproductive toxicity.

Scenario		Risk assessment for inhalation exposure			Risk assessment for dermal exposure to liquid PGME		
		8-hour TWA inhalation (mg/m^3)	MOS	Conclusion	Estimated Skin exposure mg/day worst case (mg/kg bw/d	MOS	Conclusion
1 - Manufacture		2.7	1385	ii	42 (0.6)	6025	ii
2 - Formulation		87	43	ii	3,000 (43)	84	ii
3 - Use of products	3.1 Coating/Painting						
	Industrial						
	-spraying	100	37	ii	3000 (43)	84	ii
	-other works	61	61	ii	360 (5.1)	708.8	ii

	- decorative	61	61	ii	180 (2.6)	1390	ii
	3.2 Cleaning						
	spraying	151	25	ii	250 (3.6)	1004	ii
	wiping	151	25	ii	1000 (14.3)	252.8	ii
	3.3 Printing						
	- Silk screening	100	37	ii	23 (0.32)	11297	ii
	- flexography	100	37	ii	168 (2.4)	1506	ii
	general printing	35	107	ii	168 (2.4)	1506	ii

Based on the risk assessment for inhalation exposure, it is concluded that toxicity to fertility is not expected.

Conclusion ii is reached for all occupational scenarios.

Dermal:

No dermal NOAEL is available for fertility assessment. A NOAEL can be extrapolated from inhalation NOAEC using the following parameters:

For MOS calculation: the rat inhalatory NOAEC of 3740 mg/m^3 has been converted into dermal NOAEL (in mg/kg bw/day) by using a 6 h respiratory volume of 0.29 m^3/kg bw (200 ml/min / 250g bw = 0.8 l/min/kg bw) for the rat and a correction for differences in absorption between rats and humans.

$$\text{corrected dermal N(L)OAEL} = \text{inhalatory N(L)OAEC} \times \text{sRV}_{\text{rat}} \times \frac{\text{ABS}_{\text{inh-rat}}}{\text{ABS}_{\text{derm-human}}}$$

sRV = standard respiratory volume

$\text{ABS}_{\text{inh-rat}} = 100\%$

$ABS_{derm - Human}$ = 30%

3740 * 0.29 * 100 / 30 = 3,615 mg/kg bw/day

The dermal NOAEL is converted to internal dose taking into account 30% absorption via skin and compared to the systemic dose per day via skin for each scenario.

The results are summarised in the table 4.44.

Based on the risk assessment for dermal exposure, it is concluded that reproductive toxicity (fertility) is not expected.

Conclusion ii is reached for all occupational scenarios.

Combined exposure:

For the combined exposure, the estimated internal doses are calculated from the biological exposure data. Inhalation exposure will give internal dose of:

X (value of the 8-hour TWA inhalation (mg/m^3)) x 10 m^3 (inhaled air during a workday) x 1 (100 % absorption by inhalation) / 70 kg (mean bw of a woman worker) = Y (inhalation internal dose).

So, the NOAEC of 3740 mg/m^3 would lead to an internal doses of 534 mg/kg.

This internal dose should be compared with internal dose calculated. This LOAEC should be compared with internal doses calculated from exposures in each scenario (inhalation + dermal). The internal doses are calculated as follow:

This value does not take into account the possible dermal absorption of vapour during the 8hr TWA. It has been demonstrated that dermal absorption of vapour PGME could count for 10 % of the internal dose of PGME. To take into account this value, the value of internal dose due to dermal exposure to vapours (Z) should by added to the former value (Y). Z represent 10 % of the total internal dose and can be calculated as follow :

Z = 0.10/0.90 x Y = 0.11 Y

The total internal dose due to inhalation exposure (inhalation output + dermal vapour penetration output) is Y + Z = 1.11 Y

In this case, an internal dose of about 58.7 mg/kg (0.11 Y) can be calculated, to obtain a total internal dose of 592.7 mg/kg due to inhalation and dermal absorption of PGME.

For dermal exposure internal dose is calculated for a 70 kg bw worker with a percentage of absorption of 30 % (liquid PGME, worst case).

The minimal MOS chosen for the combined exposure will be the one taken for inhalation exposure: 12.5 as it is the MOS calculated for the inhalation NOAEC which is taken into account in the calculations. Internal doses corresponding to each scenarios, MOS and conclusions are summarised in the table 4.45:

Table 4.45: Risk characterisation for combined exposure – Reproductive toxicity

Scenario		Internal dose after inhalation exposure (mg/kg) Y + Z	Internal dose after dermal exposure to liquid PGME (mg/kg) 30 %	Total internal dose (inhalation + dermal combined exposure)	MOS[1]	Conclusion
1 - Manufacture		0.44	0.18	0.62	956	ii
2 - Formulation		13.8	12.9	26.7	22.2	ii
3 - Use of products	3.1 Coating/Painting					
	Industrial					
	-spraying	15.9	12.9	28.8	20.6	ii
	-other works	9.7	1.53	11.23	52.8	ii
	- decorative	9.7	0.78	10.48	56.6	ii
	3.2 Cleaning					
	Spraying	24	1.08	25.08	23.6	ii
	wiping	24	4.29	28.29	20.9	ii
	3.3 Printing					
	- Silk screening	15.9	0.096	16	37	ii
	- flexography	15.9	0.72	16.6	35.7	ii
	general printing	5.6	0.72	6.3	94.1	ii

Based on the risk assessment for total exposure, it is concluded that fertility toxicity is not expected.

Conclusion ii is reached for all scenarios (**conclusion ii**).

Developmental toxicity:

PGME is not teratogenic. No effects were seen in foetuses without evident signs of maternal toxicity. It is concluded that that PGME is of no concern for workers with regard to developmental toxicity (conclusion ii).

4.1.3.2.8 Summary of risk characterisation for workers

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

For all other scenarios and end-points there is no concern (**Conclusion ii).**

4.1.3.3 Consumers

For risk characterisation, a value of 30% for dermal absorption and a value of 100% for inhalation exposure can be taken into account.

Table 4.46: Internal dose exposure depending on scenarios

SCENARIO	INHALATION		SKIN	SUM OF EXPOSURES
	(MG/M³)	(MG/KG/D)	(MG/KG/D)	(MG/KG/D)
1. INDOOR AIR	0.048	0.01		0.01
2. AQUEOUS PAINTS AND FLOOR VARNISHES	61	20.3	2.3	22.6
3. HOUSE CLEANERS	330	1.5	2.9	4.4

For repeated dose toxicity, and toxicity for reproduction, daily exposure level has to be averaged over a year. So the internal exposure dose used for risk characterisation is:

$$\frac{\text{internal dose} \times \text{number of events over a year}}{365}$$

Table 4.47: Internal/external dose exposure depending on scenarios average over a year

Scenario	Number of events	INHALATION		SKIN		SUM OF EXPOSURES
		MG/M³	(MG/KG/D)	(MG/KG/D) external	(MG/KG/D) internal	(MG/KG/D)
1. INDOOR AIR	Each day	0.048	0.01			0.01
2. AQUEOUS PAINTS AND FLOOR VARNISHES	10 events/year		0.6	0.2	0.06	0.7
3. HOUSE CLEANERS	94-250/year*		1.0	6.7	2.0	3.0

* Data from the Technical Guidance Document

4.1.3.3.1 Acute toxicity

The only effect taken into account for acute risk characterisation is CNS depression. For inhalation, a NOAEC of 750 ppm (2,800 mg/m^3) has been derived from human exposure. For dermal exposure a NOAEL of 1000 mg/kg can be taken into account.

These NOAEL are compared with levels of exposure. The MOSs obtained are compared with minimal MOS calculated as follows:

Table 4.48: Assessment factors applied for the calculation of minimal MOS for acute toxicity and for inhalation and dermal route.

Interspecies differences	1 for inhalation route 2.4 x 2.5 = 6 for dermal route[1]
Intraspecies differences	10
Type of effect	1
Confidence of the database	1
Minimal MOS	10 for inhalation route 60 for dermal route

1 for dermal route, as a rabbit study is used as starting point, allometric scaling factor of 2.4 is applied, as recommended by the TGD.

Inhalation:

NOAEC of 2800 mg/m^3 is compared with exposure. The results are summarised in the table 4.49.

Dermal:

Dermal NOAEL is greater or equal to 1,000 mg/kg for systemic effects, the only dose tested.. This NOAEL is compared to external exposure. Results are summarised in table 4.49.

Sum of exposures:

Assuming a daily inhalation volume for human of 20 m^3, a body weight of 60 kg and an absorption of PGME by inhalation of 100%, internal dose corresponding to the NOAEC of 2800 mg/m^3 is:

$$\frac{2800 \times 20}{60} = 933 \text{ mg/kg bw/d}$$

This internal dose corresponding to the NOAEC of 2800 mg/m^3 is compared to internal exposures. Results are summarised in table 4.49:

Table 4.49: MOS and conclusion for acute toxicity

SCENARIO	Inhalation		Dermal		Sum of exposures	
	MOS	Conclusion	MOS	Conclusion	MOS	Conclusion
2. AQUEOUS PAINTS AND FLOOR VARNISHES	46	ii	130	ii	41	ii
3. HOUSE CLEANERS	8.5	iii-ii	102	ii	212	ii

Conclusion iii would have been reached for house cleaners scenario by inhalation, but taken into account the worst case of exposure, conclusion ii is reached.
So, conclusion ii is reached for all consumers scenarios.

4.1.3.3.2 Irritation and corrosivity

Eye and respiratory tract irritation (vapours)

Scenarios of concern are those for which an inhalation exposure by vapours of PGME has been evaluated.

The NOAEC is 100 ppm (374 mg/m^3).
The minimal MOS is 3 (human data)

Table 4.50: MOS and conclusion for eye and respiratory tract irritation

SCENARIO	Inhalation (mg/m^3)	MOS	Conclusion
1. INDOOR AIR	0.048	7792	ii
2. AQUEOUS PAINTS AND FLOOR VARNISHES	61	6	ii
3. HOUSE CLEANERS	330	1.1	iii

For eye and respiratory tract irritation due to the exposure of PGME in vapour form, **conclusion iii** is reached for house cleaners scenarios, and **conclusion ii** is reached for indoor air and aqueous paints and floor varnishes scenarios.

4.1.3.3.3 Sensitisation

Given the results from sensitisation studies, it is concluded that PGME is of no concern for consumers with regard to sensitisation (conclusion ii)

4.1.3.3.4 Repeated dose toxicity

Systemic effects:
A NOAEC of 300 ppm (1122 mg/m^3) defined with an inhalation study (6h/day and 5 days a week) can be taken into account for liver effects. This NOAEC is compared with level of exposure for air indoor scenario. For aqueous paints and floor varnishes scenarios, an internal dose corresponding to this NOAEC has to be calculated and compared with the internal daily exposures.

The daily inhalation volume for human is 20 m^3, the mean body weight is 60 kg and the absorption of PGME by inhalation is 100%. So, the internal dose corresponding to the NOAEC of 1122 mg/m^3 is:

$$1122 \times 20 \times 6 \times 5 / 60 \times 24 \times 7 = 67 \text{ mg/kg bw/d}$$

The MOSs obtained are compared with minimal MOS calculated as follows:

Table 4.51: Assessment factors applied for the calculation of minimal MOS repeated dose toxicity.

Interspecies differences	Inhalation route: 2.5 (toxicodynamic factor) x1 = 2.5 Dermal route: 2.5 x 2.4 = 6[1]
Intraspecies differences	10
Duration of exposure	2*

Type of effect	1
Confidence of the database	1
Minimal MOS	25 for inhalation route 120 for dermal route

1 for dermal route, as a rabbit study is used as starting point, allometric scaling factor of 2.4 is applied, as recommended by the TGD.

*: a lower assessment factor of 2 was used instead of a factor of 6 (as preconised in the TGD) to extrapolate from 21-day to chronic study. No assessment factor was used to extrapolate from sub-acute to sub-chronic study since the NOAEL retained from 21-day study is lower than the NOAEL found in an old dermal 90-day study.

Inhalation:

Results are summarised in table 4.52.

Dermal:

Dermal NOAEL is greater or equal to 1000 mg/kg bw/d for repeated toxicity (systemic). This value is supported by the NOAEL of the 90-day study (Rowe, 1954) where a NOAEL of 2 ml/kg bw (1838 mg/kg bw) was identified.

This NOAEL is compared to external exposure. Results are summarised in table 4.52.

Sum of exposures:

The internal dose of 67 mg/kg bw/d, corresponding to the NOAEC of 1122 mg/m^3, is compared with internal exposures. Results are summarised in table 4.52:

Table 4.52: MOS and conclusion for repeated dose toxicity (systemic effects)

SCENARIO	Inhalation		Dermal		Sum of exposures	
	MOS	Conclusion	MOS	Conclusion	MOS	Conclusion
1. INDOOR AIR	6700	ii				
2. AQUEOUS PAINTS AND FLOOR VARNISHES	112	ii	5000	ii	96	ii
3. HOUSE CLEANERS	67	ii	149	ii	22	iii-ii

Conclusion iii would have been reached for house cleaners scenarios for sum of exposure but taken into account the worst case exposure, conclusion (ii) is reached. **Conclusion ii** is reached for all consumers scenarios.

Local effects:

Slight local effects were seen in a 21-day study in rats at the maximum (and unique) tested dose: 1000 mg/kg bw/d. A LOAEL of 1000 mg/kg bw/d is therefore taken into account for risk characterisation.

This LOAEL is compared with levels of exposure. The MOSs obtained are compared with minimal MOS calculated as follows:

Table 4.53: Assessment factors applied for the calculation of minimal MOS for repeated dose toxicity (for dermal route).

Interspecies differences	2.5 (toxicodynamic factor)*
Intraspecies differences	10
Type of effect	1
Extrapolation LOAEL to NOAEL	3
Confidence of the database	1
Minimal MOS	75

*(toxicokinetic factor not applied for local effects)

Table 4.54: MOS and conclusion for repeated dose toxicity (local effects)

SCENARIO	Dermal	
	MOS	Conclusion
2. AQUEOUS PAINTS AND FLOOR VARNISHES	5000	ii
3. HOUSE CLEANERS	149	ii

Conclusion ii is reached for all consumers scenarios.

4.1.3.3.5 Mutagenicity

Given the results from mutagenicity studies, it is concluded that PGME is of no concern for consumers with regard to mutagenicity (conclusion ii).

4.1.3.3.6 Carcinogenicity

Given the results from carcinogenicity studies, it is concluded that PGME is of no concern for consumers with regard to carcinogenicity (conclusion ii).

4.1.3.3.7 Toxicity for reproduction

Effects on fertility

A NOAEC of 1,000 ppm (3,740 mg/m^3) defined with an inhalation study (6h/day and 5 days a week) can be taken into account. This NOAEC is compared with level of exposure for air indoor scenario. For aqueous paints and floor varnishes scenarios, an internal dose corresponding to this NOAEC has to be calculated and compared with the internal daily exposures.

The daily inhalation volume for human is 20 m^3, the mean body weight is 60 kg and the absorption of PGME by inhalation is 100%. So the internal dose corresponding to the NOAEC of 3,740 mg/m^3 is:

3740 x 20 x 6 x 5 / 60 x 24 x 7 = 223 mg/kg/d

The MOSs obtained are compared with minimal MOS calculated as follows:

Table 4.55: Assessment factors applied for the calculation of minimal MOS fertility effects.

Interspecies differences	Inhalation route: 2.5 (toxicodynamic factor) x 1 = 2.5 Dermal route: 10
Intraspecies differences	10
Type of effect	1
Confidence of the database	1
Minimal MOS	25 for inhalation route 100 for dermal route

Inhalation:

Results are summarised in table 4.56.

Dermal:
No dermal NOAEL is available for fertility assessment. A NOAEL can be extrapolated from inhalation NOAEC using the following parameters:

For MOS calculation: the rat inhalatory NOAEC of 3740 mg/m^3 has been converted into dermal NOAEL (in mg/kg bw/day) by using a 6 h respiratory volume of 0.29 m^3/kg bw (200 ml/min / 250g bw = 0.8 l/min/kg bw) for the rat and a correction for differences in absorption between rats and humans.

$$\text{corrected dermal N(L)OAEL} = \text{inhalatory N(L)OAEC} \times \text{sRV}_{\text{rat}} \times \frac{\text{ABS}_{\text{inh-rat}}}{\text{ABS}_{\text{derm-human}}}$$

sRV = standard respiratory volume

$\text{ABS}_{\text{inh – rat}}$ = 100%

$\text{ABS}_{\text{derm – Human}}$ = 30%

3740 * 0.29 * 100 / 30 = 3,615 mg/kg bw/day

The dermal NOAEL is converted to internal dose taking into account 30% absorption via skin and compared to the systemic dose per day via skin for each scenario.

Results are summarised in 4.56.

Sum of exposures:

The internal dose of 223 mg/kg/d, corresponding to the NOAEC of 3,740 mg/ m^3, is compared with exposures estimates. Results are summarised in table 4.56:

Table 4.56: MOS and conclusion for fertility effects

SCENARIO	Inhalation		Dermal		Sum of exposures	
	MOS	Conclusion	MOS	Conclusion	MOS	Conclusion
1. INDOOR AIR	77917	ii				
2. AQUEOUS PAINTS AND FLOOR VARNISHES	372	ii	60250	ii	319	ii
3. HOUSE CLEANERS	223	ii	1807	ii	74	ii

Conclusion ii is reached for all consumers scenarios.

Developmental toxicity:

Given the results from developmental effects studies, it is concluded that PGME is of no concern for consumers with regard to developmental effects (conclusion ii).

4.1.3.3.8 Summary of risk characterisation for consumers

Conclusion iii is reached for eye and respiratory tract irritation for house cleaners scenario..
Conclusion ii is reached for all other consumers scenarios concerning all other toxicological end-points.

4.1.3.4 Humans exposed via the environment

The key health effects are repeated dose toxicity and reproductive toxicity (fertility effects) and their risk characterisation is reported below. The other endpoints such as mutagenicity or carcinogenicity are not characterised since there are no concern for these effects. Comparison of the total internal dose of 67 $mg.kg^{-1}$ (corresponding to the NOAEC of 300 ppm for repeated dose toxicity via inhalation and calculated assuming respiratory volume of 20 m^3 a day and a mean human bw of 60 kg) with the highest estimated exposure at regional (3.7×10^{-4} $mg.kg^{-1}.day^{-1}$) and local (0.526 $mg.kg^{-1}.day^{-1}$) levels leads to margins of safety of, respectively, 1.81×10^{6} and 127 which do not lead to concern (calculated minimal MOS for consumers for repeated dose toxicity is 25). For fertility effects, a NOAEC of 1,000 ppm (3,740 mg/m^3) defined with an inhalation study (6h/day and 5 days a week) would lead to margins of safety of, respectively, 6×10^{6} and 423 which do not lead to a concern (calculated minimal MOS for consumers for reproductive toxicity is 25)

Summary of risk characterisation for exposure via the environment

Conclusion

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

This conclusion applies for all endpoints in relation to local and regional exposure.

4.2 HUMAN HEALTH (PHYSICO-CHEMICAL PROPERTIES)

PGME has no explosive or oxidising properties but it is flammable (flash point is 32°C). Vapours can form flammable and explosive mixtures with air within the range of 1.7 to 11.5 % volume. Information on flammability and safety measures should be given on the label and the safety data sheet. There is at present no need for further information or risk reduction measures beyond those which are being applied already.

It is also noted that oxidation by air may involve peroxidation of the substance, which may increase explosive properties. A general warning to this effect is recommended. Use of antioxidants reduces the potential to peroxidation.

Conclusion ii.

5 RESULTS [6]

5.1 INTRODUCTION

5.2 ENVIRONMENT

5.3 HUMAN HEALTH

5.3.1 Human health (toxicity)

PGME has a very low acute toxicity by all routes of exposure. Only very slight signs of irritation were observed for skin, eyes or respiratory tract. PGME is not sensitising to animals, and there are no human data available.

Repeated dose toxicity show few hepatic effects after inhalation exposure and by oral route CNS reversible effects were seen at all tested doses. PGME is not a mutagenic substance and no carcinogenicity is expected according to the data available. Effects on fertility were seen at relatively high doses in the presence of marked systemic toxicity. Slight developmental effects of PGME was observed in pups of treated dams. These effects were seen at high doses and always in presence of maternal toxicity.

5.3.1.1 Workers

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

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 cleaining (spraying, wiping), for printing (silk screening, flexography).

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.

[6] Conclusion (i) There is a 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.

Conclusion ii is reached for all other scenarios**.**

5.3.1.2 Consumers

Conclusion iii is reached for eye and respiratory tract irritation for house cleaners scenario..
Conclusion ii is reached for all other consumers scenarios concerning all other toxicological end-points.

5.3.1.3 Humans exposed via the environment

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.

This conclusion applies for all endpoints in relation to local and regional exposure.

5.3.2 Human health (risks from physico-chemical properties)

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.

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ABBREVIATIONS

[update the list to correspond to the substance RAR]

2-MPA	2 Methoxy Propionic Acid
ADI	Acceptable Daily Intake
AF	Assessment Factor
ASTM	American Society for Testing and Materials
ATP	Adaptation to Technical Progress
AUC	Area Under The Curve
B	Bioaccumulation
BBA	Biologische Bundesanstalt für Land- und Forstwirtschaft
BCF	Bioconcentration Factor
BMC	Benchmark Concentration
BMD	Benchmark Dose
BMF	Biomagnification Factor
bw	body weight / *Bw*, *b.w.*
C	Corrosive (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
CA	Chromosome Aberration
CA	Competent Authority
CAS	Chemical Abstract Services
CEC	Commission of the European Communities
CEN	European Standards Organisation / European Committee for Normalisation
CEPE	European Council of the Paint, printing and Artists's coulours industry
CHO	Chinese Hamster Ovary
CMR	Carcinogenic, Mutagenic and toxic to Reproduction
CNS	Central Nervous System
COD	Chemical Oxygen Demand
CSTEE	Scientific Committee for Toxicity, Ecotoxicity and the Environment (DG SANCO)
CT_{50}	Clearance Time, elimination or depuration expressed as half-life
d.wt	dry weight / dw
dfi	daily food intake
DG	Directorate General
DIN	Deutsche Industrie Norm (German norm)
DNA	DeoxyriboNucleic Acid
DOC	Dissolved Organic Carbon
DT50	Degradation half-life or period required for 50 percent dissipation / degradation

DT90	Period required for 50 percent dissipation / degradation
E	Explosive (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
EASE	Estimation and Assessment of Substance Exposure Physico-chemical properties [Model]
EbC50	Effect Concentration measured as 50% reduction in biomass growth in algae tests
EC	European Communities
EC10	Effect Concentration measured as 10% effect
EC50	median Effect Concentration
ECB	European Chemicals Bureau
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
ECVAM	European Centre for the Validation of Alternative Methods
EDC	Endocrine Disrupting Chemical
EEC	European Economic Communities
EINECS	European Inventory of Existing Commercial Chemical Substances
ELINCS	European List of New Chemical Substances
EN	European Norm
EPA	Environmental Protection Agency (USA)
ErC50	Effect Concentration measured as 50% reduction in growth rate in algae tests
ESD	Emission Scenario Document
EU	European Union
EUSES	European Union System for the Evaluation of Substances [software tool in support of the Technical Guidance Document on risk assessment]
F(+)	(Highly) flammable (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
FAO	Food and Agriculture Organisation of the United Nations
FELS	Fish Early Life Stage
GLP	Good Laboratory Practice
HEDSET	EC/OECD Harmonised Electronic Data Set (for data collection of existing substances)
HELCOM	Helsinki Commission -Baltic Marine Environment Protection Commission
HPLC	High Pressure Liquid Chromatography
HPVC	High Production Volume Chemical (> 1000 t/a)
IARC	International Agency for Research on Cancer
IC	Industrial Category
IC50	median Immobilisation Concentration or median Inhibitory Concentration
ILO	International Labour Organisation
IPCS	International Programme on Chemical Safety
ISO	International Organisation for Standardisation
IUCLID	International Uniform Chemical Information Database (existing substances)

IUPAC	International Union for Pure and Applied Chemistry
JEFCA	Joint FAO/WHO Expert Committee on Food Additives
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
Koc	organic carbon normalised distribution coefficient
Kow	octanol/water partition coefficient
Kp	solids-water partition coefficient
L(E)C50	median Lethal (Effect) Concentration
LAEL	Lowest Adverse Effect Level
LC50	median Lethal Concentration
LD50	median Lethal Dose
LEV	Local Exhaust Ventilation
LLNA	Local Lymph Node Assay
LOAEL	Lowest Observed Adverse Effect Level
LOEC	Lowest Observed Effect Concentration
LOED	Lowest Observed Effect Dose
LOEL	Lowest Observed Effect Level
MAC	Maximum Allowable Concentration
MATC	Maximum Acceptable Toxic Concentration
MC	Main Category
MFO	Mixed Function Oxydase
MITI	Ministry of International Trade and Industry, Japan
MOE	Margin of Exposure
MOS	Margin of Safety
MW	Molecular Weight
N	Dangerous for the environment (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC
NAEL	No Adverse Effect Level
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
NOEC	No Observed Effect Concentration
NTP	National Toxicology Program (USA)
O	Oxidizing (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
OECD	Organisation for Economic Cooperation and Development
OEL	Occupational Exposure Limit
OJ	Official Journal
OSPAR	Oslo and Paris Convention for the protection of the marine environment of the Northeast Atlantic

P	Persistent
PBT	Persistent, Bioaccumulative and Toxic
PBPK	Physiologically Based PharmacoKinetic modelling
PBTK	Physiologically Based ToxicoKinetic modelling
PEC	Predicted Environmental Concentration
PG	Propylene Glycol
pH	logarithm (to the base 10) (of the hydrogen ion concentration $\{H^+\}$
pKa	logarithm (to the base 10) of the acid dissociation constant
pKb	logarithm (to the base 10) of the base dissociation constant
PNEC	Predicted No Effect Concentration
POP	Persistent Organic Pollutant
PPE	Personal Protective Equipment
QSAR	(Quantitative) Structure-Activity Relationship
R phrases	Risk phrases according to Annex III of Directive 67/548/EEC
RAR	Risk Assessment Report
RC	Risk Characterisation
RfC	Reference Concentration
RfD	Reference Dose
RNA	RiboNucleic Acid
RPE	Respiratory Protective Equipment
RWC	Reasonable Worst Case
S phrases	Safety phrases according to Annex III of Directive 67/548/EEC
SAR	Structure-Activity Relationships
SBR	Standardised birth ratio
SCE	Sister Chromatic Exchange
SDS	Safety Data Sheet
SETAC	Society of Environmental Toxicology And Chemistry
SNIF	Summary Notification Interchange Format (new substances)
SSD	Species Sensitivity Distribution
STEL	Short Term Exposure Limit
STP	Sewage Treatment Plant
T(+)	(Very) Toxic (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
TDI	Tolerable Daily Intake
TG	Test Guideline
TGD	Technical Guidance Document
TNsG	Technical Notes for Guidance (for Biocides)
TNO	The Netherlands Organisation for Applied Scientific Research

TWA	Time Weighted Average
UC	Use Category
UDS	Unscheduled DNA Synthesis
UN	United Nations
UNEP	United Nations Environment Programme
US EPA	Environmental Protection Agency, USA
UV	Ultraviolet Region of Spectrum
UVCB	Unknown or Variable composition, Complex reaction products of Biological material
vB	very Bioaccumulative
vP	very Persistent
vPvB	very Persistent and very Bioaccumulative
v/v	volume per volume ratio
w/w	weight per weight ratio
WHO	World Health Organization
WWTP	Waste Water Treatment Plant
Xn	Harmful (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
Xi	Irritant (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)

APPENDIX A

Methods of calculation of consumer exposures

Scenario 2 : Aqueous paints and floor varnishes

WALLPAINT EXPOSURE MODEL (WPEM)

Resident DIY model

Room volume 25m^3

Painted area 28m^2

Air changes 0.5 per hour

Paint quantity:5kg, density 1.3, type: flat

Model type: empirical

Body mass: 60kg

Events per year: 10

Active/total lifetime: 40/70 years

No sinks

PGME content: 11%

Painting time: 133 minutes

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