NEG and NIOSH basis for an occupational health standard:

Propylene Glycol Ethers and Their Acetates

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NEG and NIOSH Basis for an Occupational Health Standard:

Propylene Glycol Ethers and Their Acetates

Gunnar Johansson

ARBETS MILJÖ INSTITUTET
NATIONAL INSTITUTE OF OCCUPATIONAL HEALTH

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PREFACE

A memorandum has been signed between the Centers for Disease Control, National Institute for Occupational Safety and Health (NIOSH), USA, and the Nordic Expert Group for Documentation of Occupational Exposure Limits (NEG). The purpose of the memorandum is to exchange information and expertise in the area of occupational safety and health. One product of this agreement is the development of documents to provide scientific basis for establishing recommended occupational exposure limits. The exposure limits will be developed separately by each country according to the different national policies.

This document on the health effects of occupational exposure to propylene glycol ethers and their acetates is the first product of that agreement. The document was written by Gunnar Johanson, Dr Med Sc (Department of Occupational Medicine, University Hospital, Uppsala, and Swedish National Institute of Occupational Health, Solna), and was reviewed by NEG and the Division of Standards Development and Technology Transfer (DSDTT), NIOSH.

Richard W. Niemeier
Director/DSDTT
National Institute for Occupational
Safety and Health
USA

Per Lundberg
Chairman/NEG
National Institute of
Occupational Health
Sweden

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ABBREVIATIONS

CNS	central nervous system
DPGME	dipropylene glycol methyl ether
DSDTT	Division of Standards Development and Technology Transfer (NIOSH, USA)
FID	flame ionization detection
FTIR	Fourier transform infrared (spectrometry)
GC	gas chromatography
MS	mass spectrometry
NEG	Nordic Expert Group for Documentation of Occupational Exposure Limits
NIOSH	National Institute for Occupational Safety and Health (USA)
NMR	nuclear magnetic resonance (spectroscopy)
PGME	1-methoxy-2-propanol (alpha isomer)
PGMEA	1-methoxy-2-propyl acetate (alpha isomer)
ßPGME	2-methoxy-1-propanol (beta isomer)
ßPGMEA	2-methoxy-1-propyl acetate (beta isomer)

1 INTRODUCTION

This document deals with the propylene glycol ethers most commonly used in industry, namely methoxypropanol, methoxypropyl acetate and dipropylene glycol monomethyl ether. Both alpha and beta isomers are present in commercial methoxypropanol and methoxypropyl acetate. These isomers differ in toxicity and are therefore treated separately.

The propylene glycol ethers are colorless liquids at room temperature. They have a sweet, etherlike odor and are completely miscible with water and a number of organic solvents.

2 PHYSICAL AND CHEMICAL PROPERTIES

2.1 Methoxypropanol, alpha isomer

Chemical name:	1–methoxy–2–propanol
CAS number:	107–98–2 (alpha isomer) 1320–67–8 (unspecified isomer)
Synonyms:	propylene glycol monomethyl ether, propylene glycol methyl ether, PGME
Molecular formula:	$C_4H_{10}O_2$
Structural formula:	$CH_3 - O \quad OH$ $\quad CH_2 - CH - CH_3$
Molecular weight:	90.1
Boiling point (101.3 kPa):	119.6 °C (41)
Melting point:	-96 °C (3)
Vapor pressure (25°C):	1.6 kPa (11.8 mm Hg) (41)
Saturation concentration (25°C):	15500 ppm (41)
Relative evaporation rate: (n–butyl acetate=1)	0.7 (47)
Vapor density (25°C, air=1):	3.11 (41)
Liquid density (25°C/4°C):	0.917 (41)
Flash point:	38°C (100°F) (41)
Miscibility with water:	∞
Conversion factors:	1 ppm = 3.68 mg/m^3 1 mg/m^3 = 0.272 ppm

Propylene glycol ethers are commercially prepared by reacting propylene oxide with methyl alcohol in the presence of a catalyst. Two isomers, often designated by alpha (1–methoxy–2–propanol) and beta (2–methoxy–1–propanol, ßPGME), are obtained. The commercial product (PGME) contains mainly alpha (95–99 %), the remainder (1–5 %) being beta isomer. One report, for example, states that 95 % is

alpha isomer (12). In another report the manufacturer's declaration of 98.2 % alpha and 1.8 % beta isomer was confirmed by gas chromatography - mass spectrometry (GC–MS). The purity was > 99.9 % (24). The commercial product Dowanol® PM contains at least 97.5 % alpha isomer and no more than 2.5 % beta isomer, according to the manufacturer (3). The product used in human experiments conducted by Stewart *et al.* (51) was stated to contain 98 % PGME, 0.4 % water and 1.6 % corrosion inhibitors.

An odor threshold for PGME of 10 ppm (36 mg/m^3) is given in two reports (1, 39). The origin of this value may be a study in which male volunteers placed in a truck cab in a controlled exposure situation reported detectable odor at 10 ppm PGME (51).

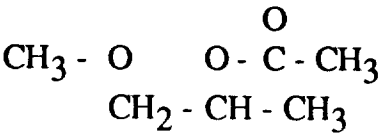
2.2 Methoxypropanol, beta isomer

Chemical name:	2–methoxy–1–propanol
CAS number:	not available for beta isomer 1320–67–8 (unspecified isomer)
Synonyms:	propylene glycol monomethyl ether, propylene glycol methyl ether, ßPGME
Molecular formula:	$C_4H_{10}O_2$
Structural formula:	OH O - CH_3 CH_2 - CH - CH_3
Molecular weight:	90.1
Conversion factors:	1 ppm = 3.68 mg/m^3 1 mg/m^3 = 0.272 ppm

Small amounts (1–5 %) of the beta isomer 2–methoxy–1–propanol (ßPGME) are present in technical methoxypropanol, the main component of which is the alpha isomer (1–methoxy–2–propanol).

There are no data on the odor threshold of ßPGME.

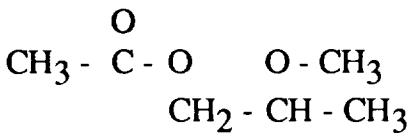
2.3 Methoxypropyl acetate, alpha isomer

Chemical name:	1–methoxy–2–propyl acetate
CAS number:	108–65–6 (alpha isomer) 84540–57–8 (unspecified isomer)
Synonyms:	propylene glycol monomethyl ether acetate, propylene glycol methyl ether acetate, PGMEA
Molecular formula:	$C_6H_{12}O_3$
Structural formula:	
Molecular weight:	132.1
Boiling point (101.3 kPa):	145.8°C (4)
Melting point:	< -67°C (4)
Vapor pressure (20°C):	0.5 kPa (3.7 mm Hg) (4)
Vapor density (air=1):	4.55 (4)
Liquid density:	0.97 (4)
Flash point:	42.2°C (4)
Miscibility with water:	≈ 19 % (w/w) (4)
Conversion factors:	1 ppm = 5.40 mg/m^3 1 mg/m^3 = 0.185 ppm

Technical methoxypropyl acetate (PGMEA) consists mainly of the alpha isomer (1–methoxy–2–propyl acetate). In one study it was stated that the alpha isomer of PGMEA used was of at least 95 % purity (28). The remainder is largely beta isomer (2–methoxy–1–propyl acetate, ßPGMEA).

There are no data on the odor threshold of PGMEA.

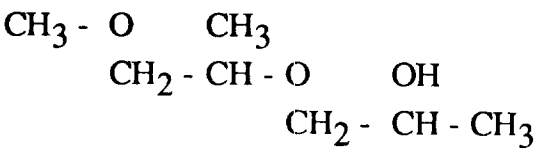
2.4 Methoxypropyl acetate, beta isomer

Chemical name:	2–methoxy–1–propyl acetate
CAS number:	70657–70–4 (beta isomer) 84540–57–8 (unspecified isomer)
Synonyms:	propylene glycol monomethyl ether acetate, propylene glycol methyl ether acetate, ßPGMEA
Molecular formula:	$C_6H_{12}O_3$
Structural formula:	
Molecular weight:	132.1
Conversion factors:	1 ppm = 5.40 mg/m^3 1 mg/m^3 = 0.185 ppm

Small amount of the beta isomer 2-methoxy-1-propyl acetate (ßPGMEA) are present in technical grade methoxypropyl acetate.

There are no data on the odor threshold of ßPGMEA.

2.5 Dipropylene glycol methyl ether

Chemical name (main isomer):	1–(2–methoxy–1–methylethoxy)–2–propanol (additonal isomers are given in Table 1)
CAS number:	34590–94–8 (unspecified isomer)
Synonyms:	dipropylene glycol monomethyl ether, dipropylene glycol methyl ether, DPGME
Molecular formula:	$C_7H_{16}O_3$
Structural formula:	
Molecular weight:	148.2
Boiling point (101.3 kPa):	189.6°C (41)
Melting point:	-80°C (41)
Vapor pressure (25°C):	0.05 kPa (0.38 mm Hg) (41)
Saturation concentration (25°C):	510 ppm (41)
Vapor density (air=1):	5.14
Liquid density (25°C/4°C):	0.948 (41)
Flash point:	85°C (185°F) (41)
Miscibility with water:	∞
Conversion factors:	1 ppm = 6.06 mg/m^3 1 mg/m^3 = 0.165 ppm

Four structural isomers can theoretically be formed in the propylene oxide based production of dipropylene glycol methyl ether. The main isomer as well as the technical product are abbreviated as DPGME in this document. There are two asymmetrical carbon atoms in the molecule, hence configurational isomers may also exist.

Landry and Yano isolated four isomers in the commercial product Dowanol® DPM and were able to identify the structure of two of them (Table 1) (25). The main isomer was a mixture of two enantiomers constituting 35.4 % and 49.1 %,

respectively. Radiolabelled DPGME containing 93.2 % of the main isomer was used in a metabolic study (30). The same authors found four isomers in Dowanol® DPM but reported the identity only of the main isomer. In Table 1 the identities of the other three isomers are assumed to be the same as those reported by Landry and Yano. In other studies the composition of DPGME was not reported.

The odor threshold for DPGME was reported in a review to be 35 ppm (210 mg/m^3) (44).

Table 1. *Composition of commercial DPGME (Dowanol ® DPM).*

Isomer[a]	Relative proportion (%)	
	GC–FID[b]	GC–MS[c]
1–(2–methoxy–1–methylethoxy)–2–propanol	84.5	87.4
2–(2–methoxy–1–methylethoxy)–1–propanol	0.5 or 1.6[d]	0.1 or 1.3[e]
2–(2–methoxy–2–methylethoxy)–1–propanol	0.5 or 1.6[d]	0.1 or 1.3[e]
1–(2–methoxy–2–methylethoxy)–2–propanol	13.0	11.2[e]
Purity (%)	99.2	>98

[a]identity established with NMR (25)
[b]proportion and purity determined by GC–FID (25)
[c]proportion determined by GC–MS (30)
[d]structure not identified
[e]identity not reported

3 USES AND OCCURRENCE

3.1 Uses

Propylene glycol ethers are used industrially as solvents for paints, lacquers, resins, oils and fat. DPGME is often used in cosmetics (41). About 329000 employees (100000 of them females) are potentially exposed to PGME in the United States. About 306000 employees (36000 females) are potentially exposed to PGMEA and 184000 (17000 females) to DPGME (National occupational exposure survey, 1981-1983: Estimated total and female employees, actual observation and trade-named exposure to PGME. Unpublished provisional data as of January 1, 1990. NIOSH, Cincinnati, Ohio).

According to the Products Register at the Swedish Chemicals Inspectorate, PGME occurred in 421 chemical products present on the Swedish market in July 1989 (Table 2). The estimated annual use was 480–5800 tons. PGMEA occurred in 187 products (280–4500 tons/year) and DPGME in 123 products (240–2500 tons/year).

The use of propylene glycol ethers appears to have increased considerably from 1985 to 1989. One important reason for the increase is probably the replacement of ethylene glycol ethers by propylene glycol ethers because of the reproductive toxicity associated with the former group of solvents.

The beta isomers of the propylene glycol ethers were declared to be present in a few products only. According to the register ßPGME and ßPGMEA occurred in 4 products each in 1989 (Table 2). The estimated annual quantity ranged between 9 and 150 tons for ßPGME. The beta isomers are treated in this document as they are present as impurities in technical PGME and PGMEA.

Table 2. *Occurrence of propylene glycol ethers in Swedish chemical products (source: Ulf Rick, The Products Register, Swedish Chemicals Inspectorate).*

Glycol ether	October 1985			July 1989		
	number[a] of products	min[b] (ton/year)	max[c] (ton/year)	number[a] of products	min[b] (ton/year)	max[c] (ton/year)
PGME	112	90	290	421	480	5800
PGMEA	0	-	-	187	280	4500
ßPGME	0	-	-	4	9	150
ßPGMEA	0	-	-	4	-	-
DPGME	42	50	170	123	240	2500

[a]number of products in the register with a declared content of the compound
[b]estimated minimum annual use [c]estimated maximum annual use

3.2 Ambient air levels at the workplace

Only a few records of occupational exposure measurements have been published.

Since 1985 the Norwegian National Institute of Occupational Health has collected in a data base the results of their analyses of volatile organic compounds in personal air samples (Tables 3 and 4). As of 1988, 5500 samples had been analyzed. PGME was detected in 687, or 12 % of them. The sample with the highest level of PGME, 1030 ppm, was collected during solvent cleaning in a paint factory. The highest average levels were associated with paint manufacturing, printing and silk screen printing. PGMEA was detected in 260 samples, or 5 %. The highest average levels were measured around metal production and air-craft lacquering. Relatively low levels were measured in silk screen printing. The beta isomer of methoxypropanol was detected in 2 %, or 127 of the samples. Samples collected around manufacturing of paint, metal and plastics had average levels of 2–3 ppm. The highest level of ßPGME, 14 ppm, was associated with cleaning in a paint factory. The other propylene glycol ethers discussed in this document were not identified. These data should be interpreted with caution, as the number of analyses aimed at finding propylene glycol ethers is not documented. In addition, the detection limits are not given and may vary.

Peak levels of 0.5–7 ppm (2–26 mg/m^3) PGME were reached in apartments painted with water-based alkyd and acrylate paints (23).

In a survey covering several work places parquet fitters in Finland were exposed to approximately 35–39 ppm PGME during undercoat varnishing and 10–63 ppm during varnishing with urea-formaldehyde based products (Riita Riala, personal communication).

Table 3. *Propylene glycol ethers found in 5500 personal air samples collected in Norway 1985–1988 (source: Per Einar Fjeldstad, Norwegian National Institute of Occupational Health).*

Glycol ether	Number of samples with presence of glycol ether					
	> det. limit	> 1 ppm	> 5 ppm	> 10 ppm	> 50 ppm	> 100 ppm
PGME	687	419	174	79	20	5
PGMEA	260	89	50	40	8	1
ßPGME	127	39	4	1		
ßPGMEA	0					
DPGME	0					

3.3 Analytical methods for air monitoring

Standardized methods for sampling and analysis of ambient air levels specific for propylene glycol ethers have not been published. However, the methods used for ethylene glycol ethers might be applicable. Samples are taken either actively with adsorption tubes or passively with diffusive samplers containing either activated charcoal or Amberlite XAD–7. Diethyl ether or a mixture of methanol and methylene chloride is used for desorption, and analysis is made by gas chromatography with flame ionization detection (GC–FID) (2, 5, 13). In the presence of other gaseous polar substances, for example water vapor, the adsorption and/or desorption efficiency may be reduced (36). Langhorst analyzed PGME in the range 0.2–300 ppm and DPGME in the range 0.7–57 ppm after adsorption on activated charcoal and desorption by a mixture of water and carbon disulfide. The yield for PGME was 96–99 % in the solvent phase and 1.7–3.1 % in the aqueous phase; for DPGME yields were 79–84 % and 9–14 %, respectively (26).

Propylene glycol ether vapors may also be monitored by infrared spectrophotometry (24, 51). The detection limits for ethylene and diethylene glycol ethers monitored by this method range from 0.03–0.08 ppm according to one instrument manufacturer (Foxboro, Redhill Surrey, Great Britain). Another manufacturer (Brüel & Kjær, Nærum, Denmark) states that its instrument, which is equipped with a photoacoustic detector, has detection limits of 0.1–0.3 ppm for various ethylene glycol ethers. Fourier transform infrared (FTIR) spectrometry may improve resolution, component identification and analytical sensitivity. Ying *et al.* reported detection limits of about 0.01–0.1 ppm for various solvent vapors measured by FTIR with a spectral resolution of 2 cm^{-1}. The detection limit for 2–ethoxyethanol was 0.012 ppm (55).

Table 4. *Job activities associated with exposure to propylene glycol ethers (source: Per Einar Fjeldstad, Norwegian National Institute of Occupational Health).*

Job activity	Maximum concentration (ppm)	Average concentration (ppm)	Standard deviation (ppm)	Number of samples
		PGME		
Paint manufacturing	1030	20	98	157
Printing	80	10	18	87
Silk screen printing	61	9	13	132
		PGMEA		
Metal production	103	18	33	21
Air-craft lacquering	91	12	19	83
Silk screen printing	12	0.9	1.9	94
		βPGME		
Solvent cleaning	13.9	2.0	3.6	24

4 TOXICOKINETICS

4.1 Uptake

Due to the solubility of the propylene glycol ethers a high uptake may be expected for all routes of exposure. The relative respiratory uptake in anesthetized rats was 87 % for PGME (exposure level 1000 ppm) and 85 % for PGMEA (exposure level 1000 ppm) (52). For comparison, the relative respiratory uptake of the ethylene glycol ethers 2–butoxyethanol, 2–ethoxyethanol, 2–ethoxyethyl acetate, 2–methoxyethanol and 2–propoxyethyl acetate ranged between 50 and 79 % in man and dog (15–18, 21).

The blood/air partition coefficient of PGME is 12400 according to one study (20) and 403 according to another (52). The high affinity to blood suggests that pulmonary ventilation, and not the equilibration between air and blood, is the rate-limiting factor for the uptake of PGME. This hypothesis is supported by experiments in which the blood PGME concentration in rats increased continuously during 6 hr of exposure to 300–3000 ppm (35).

The percutaneous uptake of neat PGME *in vitro* (isolated human epidermis) of 1.2 $mg \cdot cm^{-2} \cdot hr^{-1}$ (12) is relatively high compared with other organic solvents. Among the glycol ethers studied only 2–methoxyethanol had a higher percutaneous uptake rate. No data regarding *in vivo* skin uptake of propylene glycol ethers were found in the literature. Skin uptake was indirectly indicated by toxic effects observed in rabbits and rats after dermal application of PGME and DPGME (40, 48).

4.2 Probable routes of human exposure

The propylene glycol ethers may enter the body by the respiratory as well as the dermal route. For DPGME with its lower vapor pressure the respiratory route may be of less importance relative to the dermal route. Both exposure routes are of special concern in cases of aerosol formation during spray painting with products containing propylene glycol ethers.

4.3 Distribution

PGME was detected in blood from rats exposed for 6 hours to 300–3000 ppm (35); concentrations ranged from 1.2 to 23.4 mM (109–2113 µg/g).

No studies on the distribution of propylene glycol ethers in the body were found in the literature. The low olive oil/blood partition coefficient of 0.056 (20) suggests that PGME does not accumulate in adipose tissue.

In a number of studies Miller and coworkers have investigated the distribution of

radioactivity in rats following oral administration or vapor exposure to ^{14}C–labeled PGME (31), PGMEA (32), ßPGME (34) and DPGME (30). In general, major fractions of the radioactivity remaining in the body 48 hours after exposure were recovered in the skin and the liver. There were no indications of accumulation of radioactivity in adipose tissue, testes or main body tissues.

4.4 Biotransformation

The major metabolic pathways of propylene glycol ethers can be summarized as follows: 1) acetate esters are rapidly hydrolyzed to the corresponding ether alcohol, 2) ether alcohols, both alpha and beta isomers, are conjugated with sulphate and glucuronic acid, 3) beta isomers, being primary alcohols, are also oxidized to carboxylic acids, 4) alpha isomers, being secondary alcohols, are also oxidized to carbon dioxide after cleavage of the ether bond (Figures 1–3).

PGME

When rats were given an oral dose of ^{14}C–labeled PGME (1 mmol/kg body weight), 11 % of the administered radioactivity was found in the urine and 0.9 % in the feces within 48 hours after the dosage. Most (66 %) of the given dose was recovered in the expired air. Most of the exhaled radioactivity (63 %) was carbon dioxide. After a higher dose of PGME (8.7 mmol/kg) the recovery in urine increased to 19–25 %. The predominant urinary metabolite was the glucuronic acid conjugate of PGME, followed by the sulphate conjugate, propylene glycol (1,2–propanediol) and unchanged PGME (31). It is known from previous studies that propylene glycol is oxidized to lactic and pyruvic acids, and subsequently enters the normal carbohydrate metabolism of the body to finally end up as carbon dioxide (42, 43, 54). The metabolism of PGME is depicted in Figure 1.

PGMEA

Rats given an oral dose (8.7 mmol/kg body weight) of ^{14}C–labeled PGMEA excreted 24 % of the radioactivity in urine, 1.8 % in feces, and 66 % in expired air (64 % as carbon dioxide) within 48 hours. The half time of the radioactivity in the urine was 5.5 hr after an oral dose and 7.0 hr after 6 hr of exposure to 3000 ppm. The urinary metabolite pattern was in agreement with that observed for PGME (32). The metabolism of PGMEA is summarized in Figure 1.

Acetate esters of aliphatic alcohols are rapidly hydrolyzed by enzymes in the respiratory epithelium, lungs, liver and blood (10, 53). PGMEA in the body would therefore be rapidly converted to PGME. A comparison of the metabolism of PGME (31) and PGMEA (32) supports this hypothesis. Hence, at equimolar doses the two compounds may be expected to act similarly with respect to kinetics as well as toxicity. At very high doses of PGMEA, however, the acetic acid formed in the hydrolysis may have adverse effects.

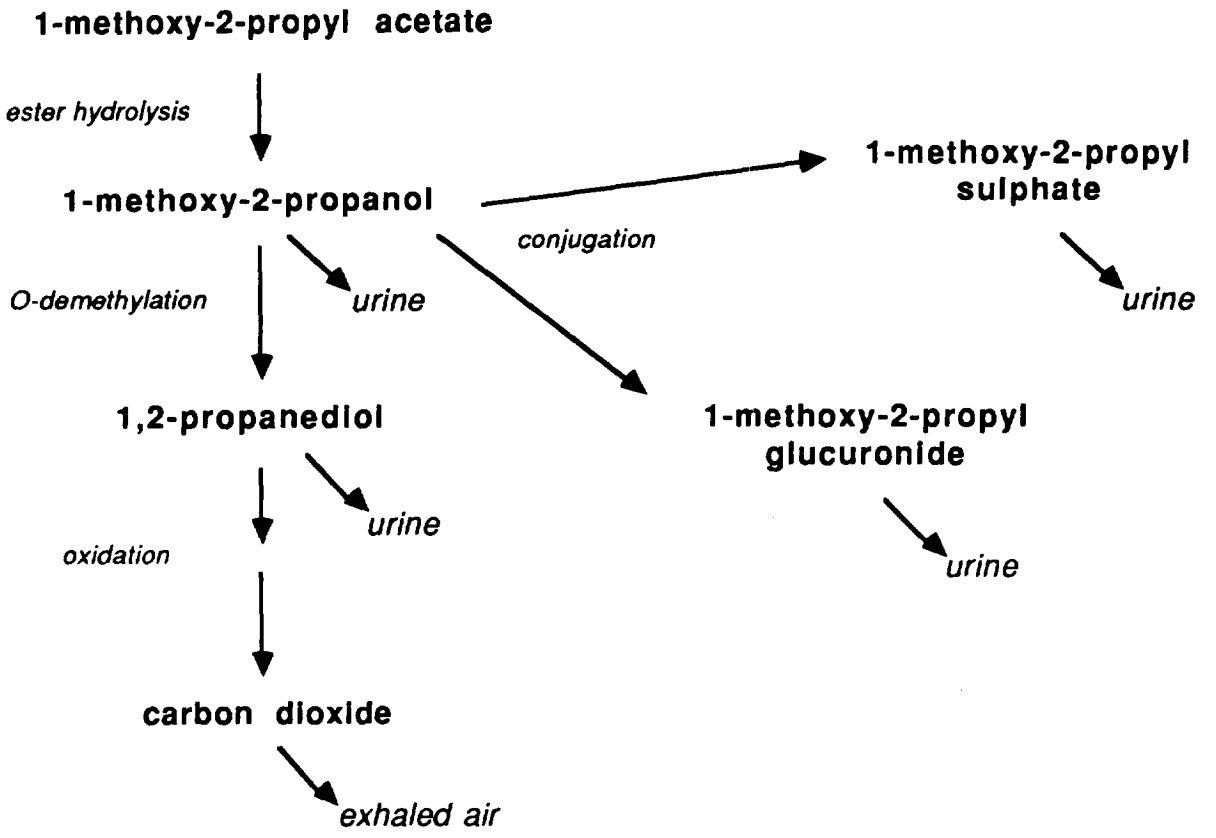


Figure 1. *The metabolism of the alpha isomers of methoxypropanol and methoxypropyl acetate.*

ßPGME

Rats given an oral dose (1 mmol/kg body weight) of ^{14}C–labeled ßPGME excreted 70 % of the radioactivity in urine, 1.6 % in feces and 16.7 % in expired air (16.6 % as carbon dioxide) within 48 hours. After a higher dose (8.7 mmol/kg) the recovery in urine increased to 77 %. The major metabolite was 2–methoxypropionic acid. The glucuronic acid conjugate and unchanged ßPGME were also found (34). The metabolism of ßPGME is summarized in Figure 2.

DPGME

When rats were given an oral dose (8.7 mmol/kg body weight) of ^{14}C–labeled DPGME 60 % of the radioactivity was recovered in urine, 2.7 % in feces and 27.2 % in expired air (26.6 % as carbon dioxide) within 48 hours. The half time of radioactivity in the urine was 5.9 hr. The predominant urinary metabolite was dipropylene glycol, but sulphate and glucuronic acid conjugates, propylene glycol , PGME and unchanged DPGME were also identified (30). The metabolism of DPGME is given in Figure 3.

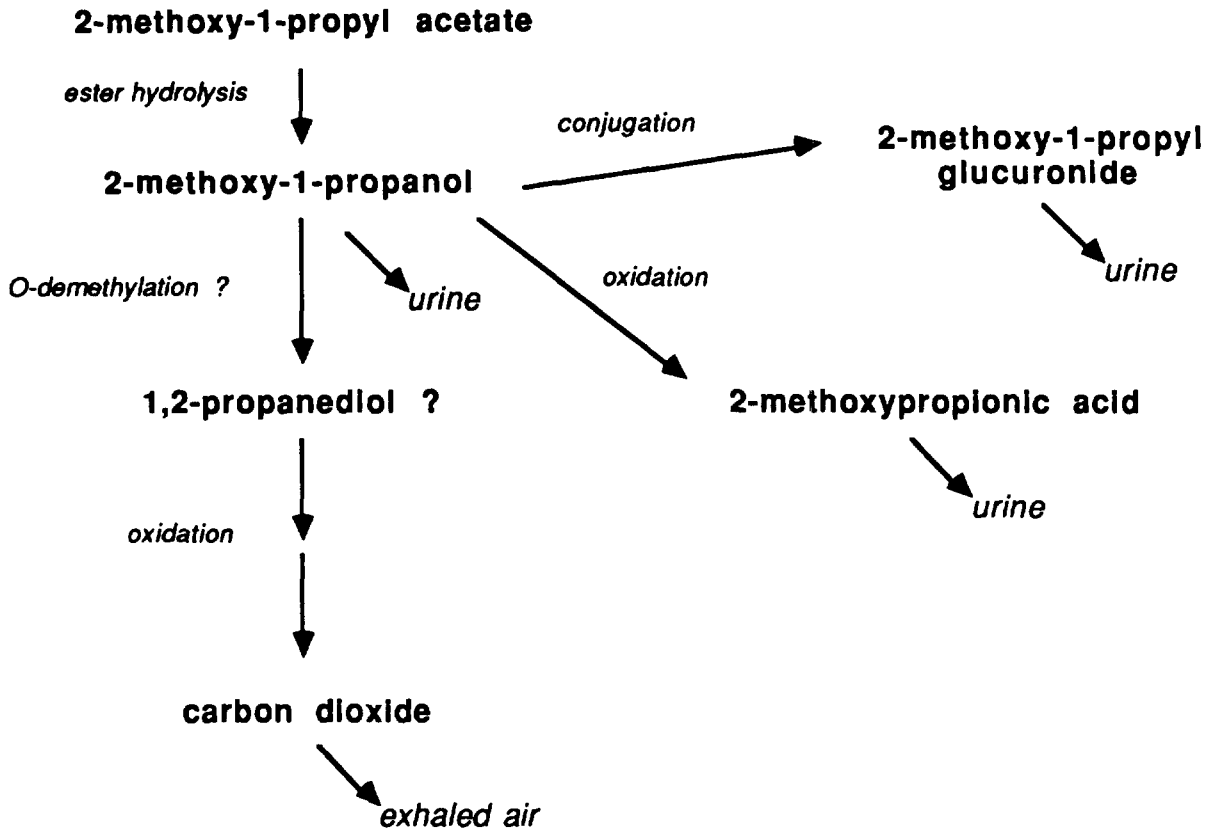


Figure 2. *The metabolism of the beta isomers of methoxypropanol and methoxypropyl acetate.*

4.5 Elimination

In rats of both sexes exposed to 300–3000 ppm PGME for 6 hours the elimination kinetics were nonlinear. At a tenfold increase in exposure level the blood levels increased 20 times. The half time of the blood PGME concentration was 2.4 hr after the lowest exposure level and 15.7 hr after the highest. Assuming a constant volume of distribution of 0.9 l/kg body weight, the total blood clearance of PGME was calculated to 3.1 $ml \cdot min^{-1} \cdot kg^{-1}$ at the lowest and 0.5 $ml \cdot min^{-1} \cdot kg^{-1}$ at the highest level. The post exposure decay of blood PGME levels followed zero order rather than first order kinetics (35). These results indicate saturation of the PGME metabolism.

4.6 Biological exposure indicators

No studies on biological monitoring of exposure to propylene glycol ethers are available.

Unchanged PGME or DPGME as well as a number of metabolites in urine and/or blood are candidates for biological exposure indicators. Morgott and Nolan analyzed by gas chromatography the parent compound and the metabolite 1,2–propanediol in rats exposed to PGME (35). Using ion exclusion

chromatography - mass spectrometry Miller and coworkers identified the sulphate and glucuronic acid conjugates of PGME, 1,2–propanediol and unchanged PGME in the urine of rats given high doses of PGME or PGMEA (31, 32). Rats dosed with DPGME excreted dipropylene glycol, 1,2–propanediol, PGME, sulphate and glucuronic acid conjugates, and unchanged DPGME (30). Rats given ßPGME excreted 2–methoxypropionic acid, ßPGME-glucuronide and unchanged ßPGME (34).

The compounds listed above were detected in experimental animals after high doses of propylene glycol ether. To detect these compounds at levels expected after occupational exposure, more sensitive methods will probably be needed.

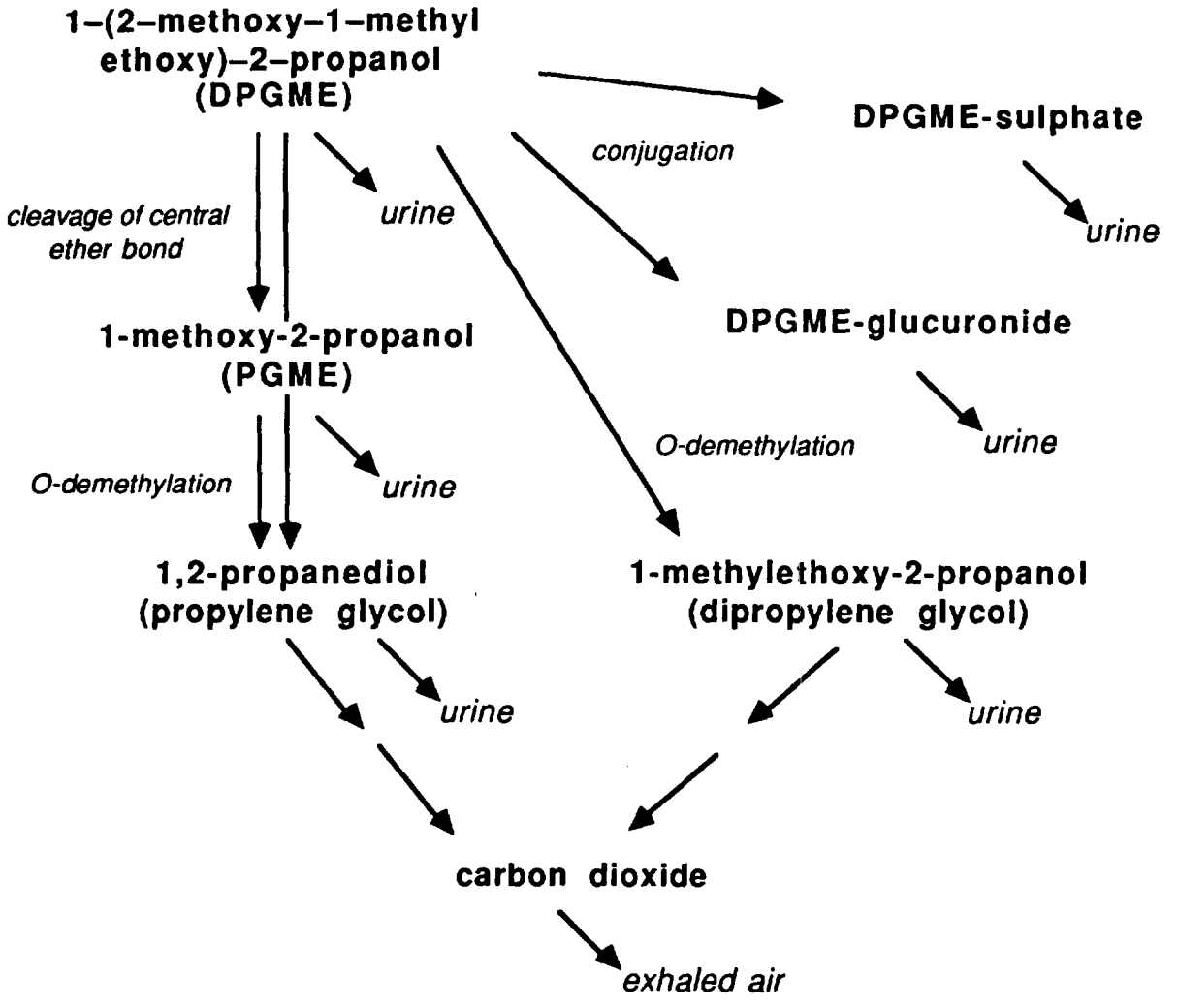


Figure 3. *The metabolism of dipropylene glycol methyl ether.*

5 GENERAL TOXICOLOGY

5.1 Toxic mechanisms and *in vitro* studies

The ethylene glycol ether 2–methoxyethanol is teratogenic and has testicular and hematologic effects. The adverse effects have been attributed to the major metabolite methoxyacetic acid (7, 38, 56) or to further metabolism of methoxyacetic acid (46). In parallel with the metabolism of 2–methoxyethanol to yield methoxyacetic acid, ßPGME is metabolized to 2–methoxypropionic acid. It might therefore be suspected that the toxicity of these two glycol ethers would also be similar. Accordingly, ßPGME (and ßPGMEA) would have teratogenic, hematological and testicular effects. This hypothesis gained support in a study by Merkle *et al.*, who found ßPGMEA to be slightly teratogenic in the rat and more so in the rabbit (28).

PGMEA is rapidly hydrolyzed to PGME and acetic acid by carboxylases in the nasal mucosa (53). The liberated acetic acid may be responsible for the damage to the olfactory epithelium observed in laboratory animals exposed to PGMEA (32) (see Section 6.1).

Jäckh *et al.* investigated the cytotoxicity of various glycol ethers and their acid metabolites in Chinese hamster ovary cells without metabolic activation. The ethylene glycol ethers 2–methoxyethanol and 2–ethoxyethanol and the propylene glycol ethers PGME and ßPGME exhibited similar cytotoxicity, with EC_{50} values (defined as the the concentration allowing 50 % of seeded cells to form colonies after 16 hr of incubation with the test substance) ranging from 0.2 to 0.5 mmol/ml. Methoxypropionate (EC_{50} = 0.1 mmol/ml) was more cytotoxic than its parent compound ßPGME (EC_{50} = 0.3 mmol/ml) but less toxic than methoxy–, ethoxy– and butoxyacetate (EC_{50} = 0.04–0.05 mmol/ml), the oxidation products of the ethylene glycol ethers (22).

3–Methoxypropionate, a structural isomer of 2–methoxypropionate, retarded growth and produced abnormalities in post-implantation rat embryo cultures at concentrations of 2 and 5 mM. Methoxyacetate and ethoxyacetate were more potent than 3–methoxypropionate, while the nonteratogenic butoxyacetate was less potent at the same concentrations (37).

5.2 Factors influencing toxicity

As the exposure level of PGME increases from 300 to 3000 ppm, the elimination rate decreases in rats (see also Section 4.5). The decrease seems to be due to saturation of the O–demethylation capacity while conjugation increases in relative terms (35). Due to metabolic saturation, the relationship between ambient air exposure level and blood PGME concentration, and possibly also the toxic effects, will not be linear but curve upwards.

PGME may induce its own metabolism in rats. Following 10 days of exposure at 3000 ppm (6 hr/d) an increased elimination rate was shown by lowered end-of-exposure blood levels (from 1816 to 1002 μg/g), shortened half time (from 15.7 to 9.7 hr) and increased blood clearance (from 0.5 to 0.8 $ml \cdot min^{-1} \cdot kg^{-1}$ body weight) of PGME. Both liver weight and the amount of cytochrome P–450 in the liver increased significantly. In addition, hepatic microsomal aniline hydroxylase and p–nitroanisole–O–demethylase activities doubled or tripled (35). Induction of the metabolism of propylene glycol ethers is a possible explanation of the transient effects on the central nervous system, liver, urine, and blood chemistry (these effects are described in the following section).

Sex differences in the metabolism of PGME have been observed in rats. The end-of-exposure concentration of PGME in blood was about 40 % higher in male rats than in female rats exposed to 3000 ppm for 6 hours. After 24 hr the blood PGME levels were nearly 8 times greater in males than in females. In addition, males had about 30 % longer half time of PGME in blood, and their blood propylene glycol levels were approximately double those of the females (35).

5.3 General effects

The propylene glycol ethers are of low and approximately equal acute toxicity. The LD_{50} ranges from 4 to 14 g/kg body weight for all routes of administration (oral, intraperitoneal and dermal) except the intravenous in the mouse, rat, rabbit and dog (Table 5).

In amounts close to lethal doses in animals the propylene glycol ethers have a depressant action on the central nervous system and the heart and may produce eye, nose and lung irritation. Signs of intoxication included: anxiety, vomiting, diarrhea, dyspnea, ataxia, hypotension, ventricular and auricular arrhythmia, respiratory depression and narcosis (40, 45).

With repeated exposure of animals to sublethal doses of PGME or DPGME, the initial signs of intoxication gradually disappear. Initially, rats and rabbits exposed to PGME at 3000 ppm became sedated and lost weight. These effects disappeared gradually during continued exposure and were completely gone after 14 days (19, 24, 29, 33, 40). Rats repeatedly exposed to DPGME at 300–400 ppm (7 hr/d) were also affected during the first weeks of exposure but appeared normal thereafter (40).

PGME

A number of organs were examined for gross pathological or histopathological changes following inhalation exposure of rats and rabbits to 3000 ppm PGME for 13 weeks (6 hr/d, 5 d/wk). Apart from minor effects in some organs, reported in the following pages, no changes attributed to this treatment were observed (24).

PGMEA

Various organs and tissues from rats and mice of both sexes exposed to 3000 ppm PGMEA for two weeks were investigated microscopically. No adverse effects were observed, except in the nasal epithelium (discussed in Section 6.1) and kidneys (Section 6.4) (32).

DPGME

Various organs from 10 rats and 7 rabbits of each sex were examined for gross pathological or histopathological changes following inhalation exposure to 200 ppm DPGME for 13 weeks (6 hr/d, 5 d/wk). There was no histopathological evidence of damage in any of the examined tissues, and no change in urine ketones was observed (25).

Table 5. Acute toxicity of propylene glycol ethers expressed as LD_{50} values (g/kg body weight).

Species	Number of animals	Route of administration					Reference
		oral	intra-venous	intra-peritoneal	sub-cutaneous	dermal	
				PGME			
mouse	5 females 5 males	10.7	4.9				(50)
rat	170 both sexes	6.1					(40)
rat	10 males	7.5					(49)
rat	5 males	5.2					(48)
rat	5 females 5 males	7.9	3.9	3.9	7.2		(50)
rabbit	4 males					12.9	(48)
rabbit	3 females 3 males	5.2	1.1		4.6		(50)
dog	3 females	~5–6					(50)
dog	3 males		~2–2.5				(50)
				ßPGME			
rat	10 males	5.7					(49)
				PGMEA, ßPGMEA			
				no data			
				DPGME			
rat	169 both sexes	5.1					(40)
rat	5 males	5.4					(48)
rabbit	4 females					9.5	(48)

6 ORGAN EFFECTS

6.1 Skin and mucous membranes

PGME

In a series of experiments Stewart and coworkers investigated the adverse effects of PGME in male volunteers. An unspecified number of subjects detected the odor of PGME vapor in a truck cab at 10 ppm but not at 5 ppm. Exposure to 300 ppm for 5 min produced mild irritation of eyes, nose and throat. At 750 ppm the PGME vapor was judged to be extremely irritating (51).

The effects of PGME in males were further investigated in experimental chamber exposures. The effects studied in these experiments are listed in Table 6. One man exposed to 50 ppm experienced flushing of the cheeks after 7 min in the exposure chamber and was not used in the following experiments. Four of six males stated immediately upon exposure to 95 ppm PGME that the odor was too strong to be tolerated and wished to terminate the experiment. However, odor tolerance developed within 25 min. One of the subjects complained of mild eye irritation after one hour of exposure to 95 ppm, and two complained after two hours. A total of 23 men were exposed to 231–249 ppm PGME for 1–7 hr. After 15 to 30 minutes eight men experienced eye irritation, three had nose irritation, one had a headache and one was nauseated. After 45 to 60 minutes 20 of the 23 males had developed eye irritation and increased blinking, 15 complained of nose irritation, two of throat irritation and one had a headache. Eight of ten men remaining in the chamber after 2 hr complained of eye irritation and five had nasal irritation. Of the four subjects remaining in the chamber for 7 hr, all had eye irritation and lacrimation, but none of them was still able to detect the odor of PGME (51).

In the last experiment two subjects were exposed to a PGME concentration steadily increasing from 1 to 2050 ppm over a 2-hr period. The subjects noted the odor at less than 25 ppm, reported objectionable odor at 50-75 ppm, light-headedness and mild eye irritation at 300-400 ppm, eye, nose and throat irritation at 500 ppm and lacrimation and rhinorrhea at 700 ppm. One of the subjects became incapacitated by eye irritation at 1000 ppm and was removed from the chamber. The second subject stayed in the chamber until 2050 ppm of PGME was reached. He experienced severe lacrimation, blepharospasm and throat irritation and was unwilling to breathe through his nose because of pain. The nose and throat pain disappeared within 15 min following exposure. The eye irritation disappeared in about 1 hr, while nasal congestion was present for 24 hr (51).

In a study of the ability of chemicals to cause injury to the rabbit eye PGME scored 4 in one study and 3 in a later study. The injury was scored from 1 to 10 based on the amount and concentration of chemical needed to cause keratoconus, iritis, corneal opaqueness and corneal necrosis. The scores 3 and 4 indicate that instillation of 0.1 and 0.02 ml, respectively, of undiluted PGME causes severe injury (8, 48).

Table 6. *Clinical and laboratory parameters investigated by Stewart et al. (51) in their studies on acute effects of PGME vapor. Various exposure protocols were used. One man was exposed to 47 ppm for 1 hr, six to 95 ppm for 3.5 hr and 23 men were exposed to 231–249 ppm for 1–7 hr. Two men were exposed to a PGME concentration steadily increasing from 1 to 2050 ppm in 2 hr. One of these men terminated the experiment at 1000 ppm. The effects are further described in Sections 6.1 and 6.8.*

Parameter studied	Effect observed	Parameter studied	Effect observed
Physical examination		***Subjective responses***	
Body temperature	no	Detection of odor	yes
Blood pressure	no	Odor intensity	yes
Pulse rate	no	Headache	yes
Respiratory rate	no	Irritability	yes
Vital capacity	no	Light-headedness	yes
Tidal volume	no	Nausea	yes
Electrocardiogram	no	Eye, nose or throat irritation	yes
		Sleepiness	no
Blood analysis		Speech difficulty	no
Blood cell count	no	Chest discomfort	no
Sedimentation rate	no	Abdominal pain	no
Serum glutamic oxaloacetic transaminase	no	Loss of apetite	no
Serum glutamic puryvic transaminase	no		
Lactic dehydrogenase	no	***Neurological tests***	
Serum alkaline phosphatase	no	Modified Romberg	yes
Blood urea nitrogen	no	Brake reaction-time	no
Serum creatinine	no	Heel-to-toe	no
		Finger-to-nose	no
Urine analysis		Crawford manual dexterity	no
24–hr creatinine excretion	no	Flannagan	no
Urobilinogen	no		
Catecholamines	no		

PGME scored 2 on a 10–step scale with respect to skin injury. The scores 1 and 2 correspond to no irritation and to the least visible capillary injection, respectively. A score of 10 indicates necrosis from a 0.01 % solution (48).

One drop of PGME placed in the rabbit eye for five consecutive days caused a mild transitory irritation of the conjunctiva. There was no cumulative effect and no indication of corneal injury (40). Gross and histological examination of the skin of rabbits exposed daily by dermal application for up to 13 weeks (5 d/wk), with doses between 1 and 10 ml PGME per kg body weight revealed some animals with scaling and erythema. However, there was no significant difference between PGME-treated animals and controls treated with water (40).

PGMEA

Degeneration of the olfactory epithelium was observed in three of five male rats and in one of five female rats exposed to 3000 ppm PGMEA for two weeks (6 hr/d; 5 d first week, 4 d second week). In mice exposed to 300, 1000 or 3000 ppm at the same schedule this degeneration was observed to be dose-related. The authors suggested that the effect was related to acetic acid resulting from hydrolysis of PGMEA in the nasal epithelium (32).

DPGME

The irritating concentration of DPGME in man was reported in a review paper to be 74 ppm (450 mg/m^3), or about twice the odor threshold (44).

Application of 0.04 ml of a 20 % aqueous solution of DPGME to one eye of each of ten human male volunteers caused a minor stinging sensation for 30–45 sec, and was accompanied by slight excess lacrimation and blepharospasm for about 1 min. A mild injection of the conjunctival vessels and a minor increase in intraocular tension were observed during the first hour (6).

DPGME scored 2 on a 10–step scale with respect to eye injury in the rabbit. This score means that 0.5 ml of undiluted PGME causes severe eye injury. DPGME caused no skin irritation in rabbits (48).

One drop of DPGME placed in the rabbit eye on each of five consecutive days caused a mild transitory irritation of the conjunctiva. There was no cumulative effect and no indication of corneal injury (40).

In a more recent experiment, 0.1 ml of undiluted DPGME instilled into the inferior conjunctival sac caused moderately severe conjunctoblepharitis in all six female rabbits. The effect peaked after about 6 hr and disappeared within a week. A 40 % aqueous solution of DPGME produced mild conjunctival irritation and a 20 % solution was without effects. There was a dose-related increase of intraocular tension and corneal thickness in the exposed rabbit eyes (6).

No studies on ßPGME or ßPGMEA were found.

6.2 Respiratory system

PGME

Rats exposed to 10000 ppm PGME for 6 hr developed microscopic changes revealing slight local irritation and congestion in the lungs (40). The same observation was made in rats exposed to 6000 ppm for 16 weeks and in a small number of monkeys and rabbits exposed to 1500 ppm or more for 5-29 weeks (see Table 10 for details). No effects on the lungs were seen in rabbits or monkeys exposed to 800 ppm (40).

No gross pathological or histopathological effects were seen in the lungs or respiratory tracts of rats and mice of both sexes exposed to 3000 ppm PGME for two weeks (6 hr/d; 5 d first week, 4 d second week) (29). A 13–week study with rats and rabbits of both sexes exposed to 300, 1000 or 3000 ppm (6 hr/d, 5 d/wk) was also negative (24).

PGMEA

No changes in lung weight, gross pathology or histology were observed in rats and mice exposed to 3000 ppm PGMEA for 2 weeks (6 hr per day) (32).

DPGME

Rats, rabbits, guinea pigs and monkeys of both sexes were exposed to 300–400 ppm DPGME for 26–31 weeks (7 hr/d, 5 d/wk). Judging by organ weight and macroscopic and histological examination , there were no effects on the lungs in any of the species studied (40).

Histological examination of lungs and trachea from rats and rabbits of both sexes exposed to up to 200 ppm DPGME for 13 weeks (6 hr/d, 5 d/wk) revealed no exposure-related effects (25).

No studies on ßPGME or ßPGMEA were found.

6.3 Liver

PGME

Stewart *et al.* exposed a total of 32 male volunteers to PGME vapor in various short-term (1–7 hr) inhalation experiments at concentrations ranging from 47 to approximately 1000 ppm (see Section 6.1 and Tables 6 and 7 for details). All subjects had normal values with respect to clinical chemistry (Table 6), and there was no difference between preexposure and postexposure values (51).

Both the absolute and the relative liver weights of male rats and the relative liver weights of female rats and female mice were higher than that of controls after two weeks of exposure (6 hr/d; 5 d first week, 4 d second week) to 3000 ppm PGME. Six weeks after termination of the PGME exposure the liver weights had returned to normal. There were no treatment-related changes in either rats or mice exposed to up to 3000 ppm PGME with respect to liver histology, serum glutamic-pyruvic transaminase activity, urea nitrogen, glucose, total protein, albumin, globulins or total bilirubin. Serum alkaline phosphatase activity was statistically significantly lower than controls ($p<0.05$) in male rats exposed to 3000 ppm and in female rats exposed to 300, 1000 or 3000 ppm (6 hr/d; 5 d first week, 4 d second week). According to the authors, however, these depressions were probably related to the nutritional status of the animals (29).

Rats exposed to 3000 ppm PGME for 13 weeks (6 hr/d, 5 d/wk) exhibited small increases (6 to 8%) in liver weight relative to controls. Hepatocellular swelling without degenerative changes was observed in the female but not in the male rats. In addition, the female rats exhibited slightly increased serum glutamic pyruvic transferase activities. Slightly elevated alkaline phosphatase activities ($p<0.05$) were observed in rabbits exposed to 3000 ppm PGME for 13 weeks (6 hr/d, 5 d/wk). These enzyme acitivities were, however, not higher than values observed in control animals in recent studies in the same laboratory (24).

Miller and coworkers also observed increased liver weights in rats of both sexes and hepatocellular swelling in female but not male rats exposed to 3000 ppm PGME for 13 weeks (6 hr/d, 5 d/wk). Clinical chemistry analyses were not conducted (33).

A series of inhalation experiments (7 hr/d, 5 d/wk) was conducted by Rowe and colleagues with PGME. Increased liver weights were observed in monkeys and rabbits after exposure to 1500 ppm and higher for 26-29 weeks, in guinea pigs after exposure to 6000 ppm for 16 weeks and in rats after exposure to 3000 ppm and higher for 17 weeks. Microscopic examination revealed slight (unspecified) changes in the livers from female rabbits exposed to 1500 ppm or higher for 13-26 weeks and guinea pigs of both sexes exposed to 6000 ppm for 16 weeks. Only 3 of 10 female and 6 of 10 male rats survived exposure 6000 ppm for 17 weeks. Increased liver weights were observed in the surviving animals. Increased liver weights and unspecified microscopic changes in the liver were also observed in male rats after exposure to 6000 ppm for 4 days (40).

PGMEA

In rats and mice of both sexes exposed to 0, 300, 1000 or 3000 ppm PGMEA 6 hr/d for two weeks (5 d first week, 4 d second week), liver weights were unaffected, except in female rats in the highest exposure group; these had a significantly higher mean relative liver weight compared to controls. However, the weight change was not accompanied by any other gross or histopathological finding. Further, clinical chemistry analyses — serum glutamic-pyruvic transaminase and alkaline phosphatase activities, urea nitrogen, glucose, total bilirubin, total protein, albumin and globulins — revealed no adverse effects (32).

DPGME

Female guinea pigs and rabbits and monkeys of both sexes exposed to 300–400 ppm DPGME for 26–31 weeks (7 hr/d, 5 d/wk) exhibited slight but definite changes of granulation in the cytoplasm and numerous vacuoles in the liver cells. These changes were not seen in rats of either sex (40).

There were no statistically significant hepatic effects in rats and rabbits of both sexes exposed to up to 200 ppm DPGME for 13 weeks (6 hr/d, 5 d/wk). The parameters investigated were liver weight and histology, alkaline phosphatase and serum glutamic pyruvic transaminase activities, serum proteins (total protein, albumin and globulin) and urobilinogen (25).

6.4 Kidneys

PGME

Kidneys with a normal appearance by gross examination and normal blood urea levels were observed in male rabbits that survived 13 weeks of daily (5 d/wk) dermal doses of 2 ml (5 of 6 survived), 4 ml (5 of 7 survived) or 7 ml (1 of 9 survived) PGME per kg body weight. Interstitial nephritis and tubular necroses were observed in 3 of 19 male rabbits that died during 13 weeks of exposure to 7 or 10 $ml \cdot kg^{-1} \cdot d^{-1}$ (40). Other rabbits that died exhibited only a slight granular degeneration in the tubules.

Rats of both sexes exposed to 10000 ppm PGME (17 weeks, 2 hr/d, 5 d/wk; or a single 6–hr exposure) and male rats and guinea pigs of both sexes exposed to 6000 ppm (16 weeks; 7 hr/d, 5 d/wk) had increased kidney weights but normal blood urea levels, and the histological appearance of the kidneys was normal (40).

There were no effects on absolute or relative weight, gross pathology or histology in the kidneys of rats and mice exposed to 300, 1000 or 3000 ppm PGME for two weeks (6 hr/d; 5 d first week, 4 d second week). At the highest exposure level of 3000 PGME urine pH was increased and there was a tendency to a decrease in specific gravity. The effects gradually regressed and had disappeared 6 weeks after exposure (29). In a 13–week study exposure of rats and rabbits to 100, 300 and 3000 ppm (6 hr/d, 5 d/wk) had no effect. However elevated urine pH was observed in male rats after 4 weeks, but not after 12 weeks, of exposure to 3000 ppm (24).

PGMEA

All five male and two of five female rats exposed to 3000 ppm PGMEA for two weeks (6 hr/d) had slightly reticulated (pale, honeycombed) kidneys and a slight increase in the eosinophilic granularity of the proximal convoluted tubules of the kidneys. The effect was not seen in any sex of mice after similar exposure. Other renal parameters, kidney weight and blood urea, were within normal limits (32).

DPGME

Kidneys with a normal appearance by gross examination, and normal blood urea levels were observed in all rabbits surviving 13 weeks of daily (5 d/wk) dermal doses of 1 ml (all 5 males survived), 3 ml (9 of 11 males survived), 5 ml (6 of 11 males survived) or 10 ml (1 of 7 males survived) DPGME per kilogram of body weight (40).

Rats and rabbits of both sexes exposed to up to 200 ppm DPGME for 13 weeks (6 hr/d, 5 d/wk) showed no statistically significant effects compared to controls with respect to kidney weight and histology, urea nitrogen and urine specific gravity, but female rabbits exposed to 200 ppm had 14 % higher relative kidney weight. However, both the relative and absolute kidney weights of the DPGME-treated animals were within the range of historical controls. As there were no signs of nephrotoxicity, the increased kidney weights were thought to be unrelated to the exposure to DPGME (25).

No studies on ßPGME or ßPGMEA are reported.

6.5 Gastrointestinal tract

Apart from signs of irritation on the gastric epithelium following high oral doses of PGME or DPGME (40) no adverse effects on the gastrointestinal tract have been observed after exposure to PGME, PGMEA or DPGME.

No studies on ßPGME or ßPGMEA are reported.

6.6 Circulatory system

PGME or DPGME (≥ 0.3 ml/kg body weight) intravenously administered to anesthetized dogs induced transitory changes in the electrocardiogram, accompanied by hypotension. Ventricular asystole and auricular fibrillation occurred at higher doses (0.8 ml/kg body weight). This effect persisted for as long as five minutes (45). No reports mention any effects on the heart or blood circulation at lower exposure levels.

No studies on PGMEA, ßPGME or ßPGMEA are reported.

6.7 Hematological system

PGME

There were no treatment-related changes in packed cell volume, erythrocyte count, hemoglobin or total leukocyte count in rats of both sexes exposed to PGME at up to 3000 ppm for a total of 9 days (6 hr/d). The mean platelet counts were elevated, but this change was considered to be of uncertain toxicologic significance in view of the variability of this parameter in the control animals. There were no statistically significant changes in the animals in the recovery group, including platelet counts, when sacrificed 6 weeks after termination of exposure. No hematological effects were observed in either male or female mice (29).

White cell counts in female rats exposed to 300 ppm PGME for 13 weeks (6 hr/d, 5 d/wk) were reported to be higher than in controls. On the other hand, the white cell counts were reduced in the female rats exposed to 3000 ppm in the same experiment. The significance of these findings is difficult to evaluate since neither the number of animals or the levels of significance are given. The investigators consider the deviations in white cell count to be sporadic occurrences unrelated to exposure. No other hematologic effects were found in either rats or rabbits (33).

Rats and rabbits of both sexes were exposed to 300, 1000 and 3000 ppm PGME for 13 weeks (6 hr/d, 5 d/wk). No hematological effects (bone marrow, thymus and lymph node histology, packed cell volume, erythrocyte count, hemoglobin, total and differential leukocyte count) were observed in either species (24).

PGMEA

There were no effects on thymus and spleen weights, histology of bone marrow or thymus or hematology parameters (not specified) in mice and rats of both sexes exposed to 300, 1000 or 3000 ppm PGMEA for two weeks (6 hr/d; 5 d first week, 4 d second week) (32).

ßPGMEA

A 4–week inhalation study with ßPGMEA in male Wistar rats showed no bone marrow effects. The highest exposure level was 2800 ppm (internal report by Klimisch *et al.* 1984, cited by Merkle *et al.* 1987 (28)).

DPGME

DPGME has been suggested as one possible cause of bone marrow injury observed in seven lithographers working with multicolor offset and ultraviolet curing printing. Personal and area samples revealed air levels of 0.6–6.4 ppm DPGME. Neither benzene nor ethylene glycol monomethyl ether, known inducers of bone marrow injury, were found in the products used. Gloves were used only intermittently and frequent and prolonged skin contact with wash solutions occurred during clean-up. The products used contained a number of other organic solvents,

including ethylene glycol monoethyl ether, methyl ethyl ketone, and aromatic and halogenated hydrocarbons (9). Thus, exposure to ethylene glycol monoethyl ether cannot be excluded as a cause of bone marrow injury. In view of the negative findings in animal experiments, it seems highly unlikely that DPGME could cause the bone marrow injury observed in the lithographers.

There were no statistically significant hematologic effects in rats and rabbits of both sexes exposed to up to 200 ppm DPGME for 13 weeks (6 hr/d, 5 d/wk). The parameters investigated were bone marrow, thymus and lymph node histology, packed cell volume, hemoglobin, erythrocyte count, total and differential leukocyte count and platelet count (25).

6.8 Central nervous system

PGME

In a series of experiments Stewart and coworkers investigated acute effects of PGME vapor on male volunteers (see Section 6.1 and Tables 6 and 7 for details). There was no deterioration in vision, coordination, neurological responses or brake reaction time during 3.5 hr of exposure at 100 ppm and 7 hr of exposure at 250 ppm. Two subjects were exposed to a PGME concentration rising steadily from 1 to 2050 ppm over a 2–hr interval. At 300–400 ppm both subjects reported that they felt slightly light-headed. After one hour, when the concentration had reached 1000 ppm, one of the subjects was unable to perform a normal modified Romberg test (*i.e.* to balance on one foot with his eyes closed and both arms at his sides). He was then severely affected by eye, nose and throat irritation and was removed from the exposure chamber (irritant properties are described in Section 6.1). After an additional hour in the chamber, when the concentration had reached 2050 ppm, the second subject completed the tests with normal pre-exposure scores (51).

PGME vapor produced a transient nonspecific depression of behavior in female rats exposed at 5000 or 10000 ppm, but not at 2500 ppm (4 hr/d for 10 days). The substance was judged to be ineffective with regard to the conditioned avoidance-escape behavior of the rats (14). In a number of rat experiments a transient sedative effect of PGME has been noted during exposure at 3000 ppm. The effect disappeared after 1–2 weeks. Less pronounced sedation has been noted in mice, guinea pigs and rabbits (19, 24, 29, 33).

No weight changes or histopathological deviations were observed in the brains of rats and rabbits of both sexes exposed to 3000 ppm PGME for 13 weeks (6 hr/d, 5 d/wk) (24).

DPGME

No adverse effects (weight change and histology) were observed in the brains of rats and rabbits of both sexes exposed to 200 ppm DPGME for 13 weeks (6 hr/d, 5 d/wk) (25).

6.9 Peripheral nervous system

There are no reports on any effects on the peripheral nervous system.

7 IMMUNOTOXICITY AND ALLERGY

DPGME

Undiluted DPGME was applied to the backs of 200 subjects (100 men and 100 women) and allowed to remain in contact with the skin for five days. Three weeks later the compound was applied again to the backs of the same subjects and allowed to remain for 48 hr. In a second experiment, DPGME was tested in 50 subjects (25 men and 25 women). This time the material was applied to the backs of the subjects and allowed to remain for 4–8 hr every other day until 10 applications had been made. After three weeks DPGME was reapplied for 24–48 hr. None of the subjects exhibited any evidence of irritation or sensitization at any time (40). Although these experiments were not conducted in accordance with modern test protocols, the results seem to indicate that DPGME is not a skin sensitizer.

There are no studies on the other propylene glycol ethers.

8 MUTAGENICITY, GENOTOXICITY

PGME

The genetic toxicology of the glycol ethers was reviewed by McGregor in 1984. PGME was negative in a bacterial mutation test with *S. typhimurium*, with and without metabolic activation. Furthermore, PGME did not increase unscheduled DNA synthesis in hepatocytes, nor the number of chromosomal aberrations in Chinese hamster ovary cells (unpublished report cited by McGregor (27)).

There is no information about the other propylene glycol ethers.

Most studies have been conducted with 2–methoxyethanol and 2–ethoxyethanol. Although a few tests have yielded positive responses the available evidence is sufficient to conclude that, in general, the glycol ethers are not strongly genotoxic (27).

9 CARCINOGENICITY

No studies on the carcinogenicity of propylene glycol ethers are available.

10 REPRODUCTIVE TOXICITY

PGME

There were no changes in testis weight or histology in rats or mice exposed to PGME containing 4 % beta isomer at levels up to 3000 ppm for two weeks (6 hr/d; 5 d first week, 4 d second week) (29). A second study, extended to 13 weeks of exposure at levels up to 3000 ppm PGME containing 1.8 % ßPGME, and including rabbits, was also negative (24).

Exposure of pregnant Wistar rats to PGME (content of ßPGME not specified) at 200 and 600 ppm for 6 hr per day from day 6 through 17 of gestation had no effect on litter size, pup weight, viability or external appearance. Male rats exposed for 10 days at the same levels showed no reduction in testes weight or atrophy of the seminiferous tubules, an effect seen after exposure to 2–methoxyethanol (11).

Pregnant rats and rabbits were exposed (6 hr/d) to 500, 1500 and 3000 ppm PGME containing 1.32 % ßPGME during organogenesis (days 6 through 15 and 6 through 18, respectively). There were mild signs of maternal toxicity, lethargy and decreased weight gain in both species and fetal toxicity and delayed sternal ossification in rats at 3000 ppm, but no signs of teratogenic effects at any exposure level (19).

ßPGME

Miller and coworkers state that no testicular effects were seen in rats and mice after a 2–week exposure to a PGME mixture containing up to 18 % beta isomer. The highest exposure concentration was 3000 ppm. No further details of these unpublished experiments were given (34).

Results from an unpublished pilot study with ßPGME demonstrated the same embryotoxic profile in the rat as ßPGMEA (see below). The details of the pilot study are not given (28).

3– Methoxypropionic acid, a structural isomer of 2–methoxypropionic acid, the common metabolite of ßPGME and ßPGMEA, retarded growth and caused abnormalities in post-implantation rat embryo cultures (see Section 5.1 for details).

ßPGMEA

Pregnant Wistar rats exposed to 110, 550 or 2700 ppm ßPGMEA for 6 hr/d on gestation days 6–15 exhibited maternal toxicity at the 550 ppm level and maternal and fetal toxicity at the 2700 ppm level. The effects reported include slight sedation, pulsative respiration, decreased body weight gain ($p=0.01$), reduced uterus weight ($p=0.05$ at 2700 ppm), reduced number of live fetuses at 2700 ppm ($p=0.05$), weights of female and male fetuses at 2700 ppm ($p=0.01$), increased percentage of dead implantations at 2700 ppm ($p=0.05$) and increased percentage of fetuses with anomalies at 2700 ppm (not significant). At the highest exposure level

of 2700 ppm ßPGMEA a few fetuses had skeletal anomalies of the thoracic vertebrae—dumbbell-shaped or bipartite notches of the cartilage. At 550 ppm one fetus had bipartite notches. These anomalies were not seen in the control group and at the lowest exposure level and were interpreted as signs of a slight teratogenic effect (28).

The teratogenicity was more pronounced in Himalayan rabbits. These were exposed to 0, 36, 145 or 550 ppm (6 hr/d) ßPGMEA from gestation days 6 through 18. There were no signs of maternal toxicity except a slight decrease in body weight gain at day 18 of gestation ($p=0.05$) which had disappeared by day 29. Fetal toxicity was manifested as increased percentage of dead implantations at 550 ppm ($p=0.05$), reduced female fetuses weight at 145 ppm ($p=0.05$) and reduced female and male fetuses weight at 550 ppm ($p=0.01$). No anomalous fetuses were seen at 0 and 145 ppm. At 36 ppm 3 anomalies (diaphragmatic hernia, absent gall bladder and scoliosis) were observed in 65 fetuses. At 550 ppm all 62 fetuses from 13 litters had anomalies. These anomalies included: anarsacra (1 fetus), cleft palate (3 fetuses), hernia umbilicalis (2 fetuses), digit anomalies (17 fetuses), internal hydrocephalus (1 fetus), heart defects (4 fetuses), hydroureter (2 fetuses) and sternal anomalies (53 fetuses) (28).

Dermal exposure of rabbits to 1000 and 2000 mg/kg ßPGMEA from gestation days 6 through 18 did not produce any maternal or fetal effects (28).

A 4–week inhalation study with ßPGMEA in male Wistar rats showed no testicular effects even at the highest dose level of 2800 ppm. The details of the experiment have not been published (28).

DPGME

There were no changes in testes weight or testicular histology in rats or rabbits exposed to 15, 50 or 200 ppm DPGME for 13 weeks (6 hr/d, 5 d/wk) (25).

There are no reports of teratogenic effects of DPGME.

11 DOSE-EFFECT AND DOSE-RESPONSE RELATIONSHIPS

11.1 Short-term exposure

Table 7. *Dose-effect relationships for short-term inhalation exposures to PGME.*

Exposure (ppm)	Number of subjects/animals	Exposure schedule	Reference	Effects
			Man	
2050	1 man	1 to 2050 in 2 hr	(51)	severe lacrimation and blepharospasm, pain and congestion of nose
1000	2 men	1 to 2050 in 2 hr	(51)	severe eye irritation in 1 man
750	? men	5 min, single	(51)	extremely irritating
700	2 men	1 to 2050 in 2 hr	(51)	lacrimation, rhinorrhea
300	? men	5 min, single	(51)	irritation of eyes, nose and throat
240	23 men	1–7 hr, single	(51)	irritation of eyes, nose and throat
95	6 men	3.5 hr, single	(51)	strongly objectionable odor initially, odor tolerance within 25 min, slight eye irritation in 2 men after 2 hr
47	1 man	1 hr, single	(51)	flushing of cheeks after 7 min
10	? men	5 min, single	(51)	odor detected
5	? men	5 min, single	(51)	odor not detected
			Monkey	
10000	1 male	6 hr, single	(40)	CNS depression, eye and nasal irritation
			Rabbit	
15000	8 both sexes	4–7 hr, single	(40)	CNS depression, unconsciousness, death
10000	8 both sexes	4–7 hr, single	(40)	CNS depression
3000	33 females	6 hr/d, d 6–18 of gestation	(19)	CNS depression, decreased weight gain, no embryotoxic or teratogenic effects
			Guinea pig	
15000	45 both sexes	6–10 hr, single	(40)	CNS depression, unconsciousness, death
			Mouse	
3000	5 females 5 males	6 hr/d, 2 wk	(29)	CNS depression, increased liver weight in females

Table 7 (continued). *Dose-effect relationships for short-term inhalation exposures to PGME (selected data).*

Exposure (ppm)	Number of animals	Exposure schedule	Reference	Effects
		Rat		
15000	40 both sexes	2–8 hr, single	(40)	CNS depression, unconsciousness, death
15000	75 both sexes	1 hr, single	(40)	CNS depression
10000	105 both sexes	3–8 hr, single	(40)	CNS depression, unconsciousness, death
10000	15 females 15 males	6 hr, single	(40)	increased liver, kidney and lung weight, lung irritation
10000	5 males	2 hr, single	(40)	increased liver weight
10000	50 both sexes	1.5–2 hr, single	(40)	CNS depression
7000	40 both sexes	4–6 hr, single	(40)	CNS depression, unconsciousness, death
7000	30 both sexes	3 hr, single	(40)	CNS depression
6000	10 males	7 hr/d, 4 d in 5 d	(40)	1 died, increased liver and kidney weights, changes in liver and lung histology
5000	8–10 females	4 hr/d, 2 wk	(14)	transient CNS depression, no effect on conditioned avoidance-escape behavior
3000	10 males	7 hr, single	(40)	no observed effects
3000	28 females	6 hr/d, d 6–15 of gestation	(19)	CNS depression, decreased weight gain, delayed sternebral ossification, no embryotoxic or teratogenic effects
3000	5 females 5 males	6 hr/d, 5+4 d in 11 d[a]	(29)	CNS depression, increased liver weight, decreased urine specific gravity, increased urine pH, elevated platelet count, lowered alkaline phosphatase activity
1000	5 females 5 males	6 hr/d, 5+4 d in 11 d[a]	(29)	lowered alkaline phosphatase activity in females
600	20 females	6 hr/d, d 6–17 of gestation	(11)	no effect on offspring
600	10 males	6 hr/d, 10 d	(11)	no effect on testicles or hematology
300	5 females 5 males	6 hr/d, 5+4 d in 11 d[a]	(29)	lowered alkaline phosphatase activity

[a]5 d of exposure first week, 4 d second week, 2 d interruption during weekend

Table 8. *Dose-effect relationships for short-term inhalation exposures to PGMEA.*

Exposure (ppm)	Number of animals	Exposure schedule	Reference	Effects
			Rat	
3000	5 females 5 males	6 hr/d, 2 wk 5+4 d in 11 d[a]	(32)	increased liver weight in females, changes in kidney histology, degeneration of olfactory epithelium
1000	idem	idem	(32)	degeneration of olfactory epithelium
300	idem	idem	(32)	no observed effects
			Mouse	
3000	idem	idem	(32)	degeneration of olfactory epithelium
1000	idem	idem	(32)	no observed effects
300	idem	idem	(32)	no observed effects

[a]5 d of exposure first week, 4 d second week, 2 d interruption during weekend

Table 9. *Dose-effect relationships for short-term inhalation and dermal exposures to βPGMEA.*

Exposure (ppm)	Number of animals	Exposure schedule	Reference	Effects
		Rabbit, inhalation exposure (ppm)		
550	15 females	6 hr/d, d 6–18 of gestation	(28)	slightly reduced maternal weight gain, reduced fetal body weight, increased number of dead implantations, anomalies in all 63 fetuses
145	15 females	idem	(28)	no observed maternal effects, reduced fetal weight
36	15 females	idem	(28)	no observed maternal effects, anomalies in 3 of 65 fetuses
		Rat, inhalation exposure (ppm)		
2710	25 females	6 hr/d, d 6–15 of gestation	(28)	CNS depression, reduced maternal weight gain, reduced uterus weight, reduced fetal body weight, increased number of dead implantations, vertebral fusion defects
550	25 females	idem	(28)	CNS depression, reduced maternal weight gain
110	25 females	idem	(28)	no observed maternal or fetal effects
		Rabbit, dermal exposure ($mg \cdot kg^{-1} \cdot d^{1}$)		
2000	16 females	daily, d 6–18 of gestation	(28)	no observed maternal or fetal effects
1000	15 females	idem	(28)	no observed maternal or fetal effects

Table 10. *Dose-effect relationships for short-term inhalation exposures to DPGME.*

Exposure (ppm)	Number of animals	Exposure schedule	Reference	Effects
		Man		
74	not given	not given	(1)	irritation
35	not given	not given	(1)	odor threshold
		Rat		
500	9 males	7 hr, single	(40)	CNS depression

11.2 Long-term exposure

Table 11. *Dose-effect relationships for long-term inhalation exposures to PGME.*

Exposure (ppm)	Number of animals	Exposure schedule	Reference	Effects
			Monkey	
10000	1 females 2 males	4 hr/d, 5–13 wk	(40)	CNS depression, decreased final body weight, increased liver weight, changes in liver and lung histology
3000	2 females	7 hr/d, 29 wk	(40)	increased liver weight, changes in liver and lung histology
1500	1 female	7 hr/d, 29 wk	(40)	increased liver weight, changes in lung histology
800	1 female 1 male	7 hr/d, 29 wk	(40)	no observed effects
			Rabbit	
6000	1 female	7 hr/d, 16 wk	(40)	CNS depression, decreased weight gain, increased liver and lung weight, changes in lung histology
3000	7 females 6 males	6 hr/d, 13 wk	(24)	CNS depression first 2 wk, increased alkaline phosphatase activity
3000	?	6 hr/d, 13 wk	(33)	no observed effects
3000	1 female 1 male	7 hr/d, 26 wk	(40)	increased liver weight, changes in liver (female) and lung (male) histology
1500	2 females 2 males	7 hr/d, 26 wk	(40)	increased liver weight, changes in liver and lung histology in females
1000	7 females 6 males	6 hr/d, 13 wk	(24)	no observed effects
800	2 females 1 male	7 hr/d, 26 wk	(40)	no observed effects

Table 11 (continued). *Dose-effect relationships for long-term inhalation exposures (5 d/wk) to PGME.*

Exposure (ppm)	Number of animals	Exposure schedule	Reference	Effects
			Guinea pig	
6000	5 females 5 males	7 hr/d, 16 wk	(40)	CNS depression, decreased body weight, increased liver and kidney weight, changes in liver and lung histology
3000	8 females 8 males	7 hr/d, 26 wk	(40)	no observed effects
1500	idem	idem	(40)	no observed effects
			Rat	
10000	5 females 5 males	2 hr/d, 17 wk	(40)	increased liver and kidney weight
10000	idem	1 hr/d, 15 wk	(40)	CNS depression
10000	idem	0.5 hr/d, 15 wk	(40)	no observed effects
6000	10 females 10 males	7 hr/d, 16 wk	(40)	7 females and 4 males died, CNS depression, increased liver weight, increased kidney weight in males
3000	20 females 20 males	7 hr/d, 28 wk	(40)	CNS depression first week, increased liver weight
3000	10 females 10 males	6 hr/d, 13 wk	(24)	CNS depression first wk, increased liver weight, hepatocellular swelling in females, increased serum glutamic pyruvic transaminase activity in females, increased urine pH after 4 wk in males
3000	?	6 hr/d, 13 wk	(33)	CNS depression first wk, increased liver weight, reduced white cell count in females, hepatocellular swelling in females
1500	20 females 20 males	7 hr/d, 28 wk	(40)	no observed effects
1000	10 females 10 males	6 hr/d, 13 wk	(24)	no observed effects
1000	?	6 hr/d, 13 wk	(33)	no observed effects
300	?	6 hr/d, 13 wk	(33)	increased white cell count in females

Table 12. *Dose-effect relationships for long-term inhalation exposures (5 d/wk) to DPGME.*

Exposure (ppm)	Number of animals	Exposure schedule	Reference	Effects
			Monkey	
300–400	1 female 1 male	7 hr/d, 31 wk	(40)	changes in liver histology
			Rabbit	
300–400	2 females 2 males	7 hr/d, 31 wk	(40)	changes in liver histology
200	7 females 7 males	6 hr/d, 13 wk	(25)	increased kidney weight in females
50	idem	idem	(25)	increased body and kidney weight in females
15	idem	idem	(25)	no observed effects
			Guinea pig	
300–400	5 females 7 males	7 hr/d, 26 wk	(40)	changes in liver histology in females
			Rat	
300–400	17 females 13 males	7 hr/d, 28 wk	(40)	CNS depression first week, increased liver weight
200	10 females 10 males	6 hr/d, 13 wk	(25)	no observed effects
50	idem	idem	(25)	no observed effects
15	idem	idem	(25)	no observed effects

12 RESEARCH NEEDS

The irritant property of propylene glycol ethers to man is described in only one paper, and for PGME only (51). This effect needs to be studied in more detail and in the other propylene glycol ethers as well.

Only one study concerning the reproductive toxicity of the beta isomers was found in the scientific literature (28). The study dealt with the effects of ßPGMEA in female rats and Himalayan rabbits. There is a need for additional investigations involving ßPGME, male reproductive toxicity of both beta isomers and testing in other animal species.

The toxicokinetics of the propylene glycol ethers have not been studied in humans. Such studies are valuable in order to assess respiratory and dermal uptake, distribution, metabolism and excretion. The possibility of dose-dependent kinetics in man should be investigated, as this has been observed for PGME in laboratory animals (35). Dermal uptake may contribute largely to the body burden of propylene glycol ethers. Methods for biological monitoring are therefore needed. The acid metabolite of ßPGME, 2–methoxypropionic acid, is a strong candidate for biological monitoring of exposure to ßPGME for the following reasons: 2–methoxypropionic acid is closely related to the teratogenic potential of ßPGME, it is to a large extent excreted in urine, and it probably has a long urinary half time.

To make possible toxicokinetic studies and to develop methods for biological monitoring sensitive analytical methods for the propylene glycol ethers and their metabolites in biological material will have to be developed.

13 DISCUSSION AND EVALUATION

The five propylene glycol monoalkyl ethers reviewed here are all of low acute toxicity. The main effect exerted at high doses is depression of the central nervous system. This effect has been clearly observed in animals exposed to PGME at 3000 ppm or more (14, 19, 24, 29, 40), to ßPGMEA at 550 ppm or more (28), and to DPGME at 300–400 ppm (40), but not at lower exposure levels. In the DPGME experiment a mist was present in the exposure chamber, and the internal dose may have been higher due to dermal deposition and uptake. One man acutely exposed to about 1000 ppm PGME exhibited a tendency to CNS effects, but exhibited no effects at lower exposure levels (51). There are no signs of subacute or chronic organ specific damage at levels below 1500 ppm PGME, 1000 ppm PGMEA and 300–400 ppm DPGME. Furthermore, there are no indications of mutagenicity or genotoxicity from any of the five glycol ethers, although such effects have only been studied to a limited extent. No carcinogenicity studies are reported. The alpha isomers of PGME and PGMEA, as well as DPGME, seem to lack reproductive toxicity. The critical effect of these three compounds appears to be irritation to the eyes and mucous membranes. Two of six men experienced eye, nose and throat irritation after 2 hr of exposure to 95 ppm PGME (51).

The beta isomer of PGMEA is embryotoxic and teratogenic in laboratory animals (28). The effects were seen in the offspring of rats after exposure at 2710 but not at 550 ppm and in rabbits at 550 but not at 145 ppm. Considering the metabolism of ßPGMEA, it is very likely that ßPGME is also teratogenic. The common metabolite of ßPGME and ßPGMEA is 2-methoxypropionic acid. The structural isomer 3-methoxypropionic acid caused growth retardation and abnormalities in post-implantation rat embryo cultures (37). These observations are analogous to those made for methoxyacetic acid, common metabolites of 2-methoxyethanol and 2-ethoxyethyl acetate (7, 38, 56). Thus, the critical effect of ßPGME and ßPGMEA appears to be the teratogenic potential. The teratogenic potential of beta isomers present in technical PGME and PGMEA must be kept in mind, and these impurities should be monitored and kept as low as possible.

14 SAMMANFATTNING

Arbete och Hälsa 1990:32, sid 1–47.
Kritisk genomgång och värdering av den litteratur som är relevant som underlag för fastställande av hygieniskt gränsvärde för propylenglykolmonometyleter och propylenglykolmonometyleteracetat inklusive deras betaisomerer, samt dipropylenglykolmonometyleter. Rekommendation av de effekter (irritation och reproduktionsstörning) som kan läggas till grund för ett sådant ställningstagande. 56 referenser.

Nyckelord: dipropylenglykolmonometyleter, hygieniskt gränsvärde, irritation, 1–metoxi–2–propanol, 2–metoxi–1–propanol, 1–metoxi–2–propylacetat, 2–metoxi–1–propylacetat, 1–(2–metoxi–1–metyletoxi)–2–propanol, propylenglykolmonometyleter, propylenglykolmonometyleteracetat, reroduktionsstörning, yrkesmässig exponering.

15 SUMMARY

Arbete och Hälsa 1990:32, p. 1–47.
Survey of the literature on propylene glycol monomethyl ether, propylene glycol monomethyl ether acetate, including their beta isomers, and dipropylene glycol monomethyl ether. The document is to be used as background for discussion of occupational exposure limits. The effects irritation and reproductive toxicity are recommended to be used in this discussion. 56 references.

Key words: dipropylene glycol methyl ether, irritation, 1–methoxy–2–propanol, 2–methoxy–1–propanol, 1–methoxy–2–propyl acetate, 2–methoxy–1–propyl acetate, 1–(2–methoxy–1–methylethoxy)–2–propanol, occupational exposure, occupational exposure limits, propylene glycol methyl ether, propylene glycol methyl ether acetate, reproductive toxicity

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