The Toxicology of Glycol Ethers and its Relevance to Man (Fourth Edition) Volume I

Technical Report No. 95

ISSN-0773-8072-95
Brussels, February 2005

ECETOC TECHNICAL REPORT No. 95

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CONTENTS - VOLUMES I AND II

EXECUTIVE SUMMARY

This report provides an update of an earlier ECETOC review [a] of a number of important ethylene and propylene glycol mono-ethers and di-ethers (glymes). It includes substantial new information concerning the human health consequences of exposure to this class of chemicals. The report presents toxicity data profiles for each individual compound.

Glycol mono-ethers are liquids that combine the solubility characteristics of ethers and alcohols since both functional groups are present. As a result, they are widely used in solvent applications, including formulations such as paints, inks and cleaning fluids. Non-solvent applications include uses as anti-icing agents in jet fuel, hydraulic system fluids and as chemical intermediates.

The hazard assessment of several glycol ethers can be based on short-term exposure studies because long-term exposure have not lead to more severe or different systemic effects. Glycol ethers have the potential to penetrate the skin (as a liquid or vapour) and this, therefore, represents a potentially significant route of exposure.

The majority of glycol ethers are of low acute toxicity; the main effect seen in laboratory animals at high doses is narcosis, typical of many solvents. Some glycol ethers are eye irritants. Overall, numerous studies with glycol ethers show that they do not exhibit genotoxic activity. The results of carcinogenicity studies with glycol ethers are consistent with this lack of genotoxic activity.

The systemic toxicity of the ethylene-based glycol ethers is mediated by their metabolism to the corresponding alkoxyacetic acids. Methyl- and ethyl-substituted ethylene glycol ethers can cause bone marrow depression, testicular atrophy, developmental toxicity, and immunotoxicity in animals. It should be noted that methyl- and ethyl-ethers of ethylene glycol are not used in consumer products in Europe. In contrast, the longer chain ethylene glycol ethers (ethylene glycol butyl ether, -propyl ether, -isopropyl ether and -phenyl ether) do not cause any of these effects. Toxicity commonly associated with the longer chain homologues involves red blood cell haemolysis (anaemia), to which humans are resistant. The alkoxyacetic acid metabolites of glycol ethers are responsible for the haemolysis.

None of the ethylene-bond effects have been observed for the propylene glycol ethers (α-isomers in commercial products); they are secondary alcohols and cannot be metabolised to their corresponding alkoxypropionic acids. Propylene glycol ethers are dealkylated to propylene glycol and then oxidised. The only change observed with propylene glycol ethers is an adaptive liver response and male rat kidney toxicity, which is not considered relevant to humans.

[a] ECETOC. 1995. The toxicology of glycol ethers and its relevance to man. Technical Report 64. European Centre for Ecotoxicology and Toxicology of Chemicals, Brussels, Belgium [ISSN-0773-8072-64]

Reports of a number of effects in humans have been associated with glycol ether exposure, such as anaemia, granulocytopenia and leukopenia, increased risk of abortion or reduced sperm count in painters. Many such reports relate to methyl- and ethyl-substituted glycol ethers and are confounded by simultaneous exposures to other chemicals as well as limited information on exposure levels, which do not allow firm conclusions to be made concerning the contribution of glycol ethers to the observed effects. The toxicological findings reported to date indicate that, except for haemolytic anaemia and the liver and kidney effects in long-term studies, the effects seen in animals are also relevant to humans.

SUMMARY AND CONCLUSIONS

Glycol mono-ethers are liquids that combine the solubility characteristics of ethers and alcohols since both functional groups are present in the molecule. They are therefore widely used in solvent applications, including formulations such as paints, inks and cleaning fluids. Non-solvent applications include uses as anti-icing agents in jet fuel, hydraulic system fluids and as chemical intermediates.

The majority of glycol ethers are of low acute toxicity. Clinical signs of acute intoxication in animals are consistent with non-specific depression of the central nervous system, which is typical of many solvents. Lethargy and haemoglobinuria have been observed in glycol ethers that produced haemolysis in rodents. Although some glycol ethers are irritant to the eye, most are not, and none are appreciably irritant to the skin on acute exposure. As with other solvents, prolonged or repeated skin exposure may lead to a severe skin irritation. It is recognised that the glycol ether class lacks specific determinants for either genotoxicity or carcinogenicity. Negative results obtained in conventional genotoxicity assays, both *in vivo* and *in vitro*, confirm the lack of genotoxic activity for this class of solvents. Some glycol ethers have been tested in life-time studies in rats and mice, including ethylene glycol ethyl ether, ethylene glycol *n*-butyl ether, diethylene glycol ethyl ether, 2-propylene glycol 1-methyl ether and propylene glycol *tert*-butyl ether. However, the tumour responses seen in these cases were probably caused by mechanisms that are species-specific or reflect a mode of action to which humans are resistant. Overall, glycol ethers do not pose a significant genotoxic or carcinogenic risk to humans.

For the ethylene-based glycol ethers, the major route of metabolism is via alcohol and aldehyde dehydrogenases to the corresponding alkoxyacetic acids. A secondary route involves O-dealkylation to ethylene glycol and its oxidation metabolites. The metabolism of propylene-based glycol ethers varies with the isomer type. The α-isomers, which are used commercially, cannot be oxidised to acids, and O-dealkylation by microsomal cytochrome P450 (CYP) is the predominant route of metabolism. The minor impurity β-isomers are, like the ethylene glycol ethers, substrates for alcohol and aldehyde dehydrogenases, producing the corresponding propoxyacetic acids. They may also undergo O-dealkylation. This explains the main difference in the toxicities of the ethylene-based and propylene-based glycol ethers.

Within the ethylene-based series, the short chain ethers, including methyl- and ethyl-ethers of ethylene glycol and their acetates, show different toxicity effects from the higher propyl and butyl homologues. Methyl- and ethyl-substituted ethylene glycol ethers and derivatives have been shown to cause bone marrow depression, testicular atrophy, developmental toxicity, and immunotoxicity in animals. The toxicological effects observed are due to the alkoxyacetic acid metabolites, methoxyacetic acid and ethoxyacetic acid, which show relatively slow excretion rates especially in larger animals. In contrast, the longer chain ethylene glycol ethers (ethylene

glycol butyl ether, -propyl ether, -isopropyl ether and -phenyl ether) do not cause these effects because methoxyacetic and ethoxyacetic acid are not formed. Methyl and ethyl ethers of ethylene glycol are not used in consumer products in Europe.

The toxicity commonly associated with the longer chain ethylene-series homologues involves red blood cell haemolysis with secondary effects relating to this haemosiderin accumulation in the spleen, liver and kidney, and a compensatory haematopoiesis displayed in bone marrow. Ethylene glycol butyl ether, the most studied in this series, produces haemolytic anaemia in rats, rabbits and mice, showing greater sensitivity than other species, including guinea pigs. Those glycol ethers that cause haemolytic effects are more toxic than the other glycol ethers in respective susceptible species. Humans exhibit a resistance to glycol ether-induced haemolytic anaemia.

The toxicity of the propylene glycol ethers with the alkoxy group at the primary position (α-isomers, main isomers found in commercial products) is quite different from that of the ethylene glycol ethers. These ethers cannot be metabolised to their corresponding alkoxypropionic acids. None of the effects mentioned above have been reported and the only evidence of toxicity is towards liver and kidney. In the case of propylene glycol methyl ether, developmental effects have been reported when the primary position is occupied by a hydroxyl group (β-isomer). The β-isomer is not produced as a commercial product, and is found as a minor component (< 0.5%) of commercial propylene glycol methyl ether.

Target organ toxicity for the lower molecular weight ethylene-series glycol ethers in animals has been related to the extent of formation of methoxyacetic acid or ethoxyacetic acid, which may affect one or more of testes, bone marrow, thymus or developing offspring. For example, administration of ethylene glycol methyl ether in rats produces thymic and testicular atrophy, lymphocytopenia, and neutropenia with a near complete failure of blood cell precursor development in the bone marrow. Methoxypropionic acid has also been shown to produce developmental effects. With the exception of the developmental toxicity, these adverse effects are reversed upon removal of exposure. In sharp contrast, ethylene glycol butyl ether does not produce these effects, but produces haemolytic anaemia in rodents, accompanied by a compensatory bone marrow hyperplasia. Butoxyacetic acid has been shown to induce haemolysis in several animal species. An exception in the ethylene glycol ether series is ethylene glycol phenyl ether (phenoxyethanol), which is a more potent haemolytic agent (in the rabbit) than its metabolite, phenoxyacetic acid.

The liver has frequently shown an increased weight, in the absence of significant pathological change, following high doses of ethylene- and propylene-series glycol ethers. This has been interpreted as an adaptive change. Kidney weight changes and histopathological changes have been identified following dipropylene glycol ethyl ether and 2-propylene glycol methyl ether administration. These changes are associated with the accumulation of $\alpha_{2\mu}$-globulin in the case of

2-propylene glycol 1-methyl ether only in male rats. Based on information from several other hazard assessments of chemicals, they are considered not to be relevant for humans. This is also most likely the case for dipropylene glycol ethyl ether, but definitive analytical confirmation is not available.

The hazard assessment of several glycol ethers can be based on systemic changes found in short-term exposure studies, such as haematological effects and organ weight changes. These effects do not appear to increase in studies of long-term duration. This observation, together with the overall absence of genotoxic effects, indicates that long-term exposure is unlikely to lead to more severe or different effects. In the specific case of ethylene glycol butyl ether, hepatic oxidative stress due to haemolysis has led to tumours following lifetime exposure. Repeated oral dosing of ethylene glycol butyl ether in mice resulted in irritation of the forestomach. Irritation has also been observed in inhalation studies, probably due to oral ingestion from grooming and muco-ciliary transfer, which progressed to hyperplasia and forestomach tumours on prolonged exposure in a cancer bioassay.

Glycol ethers have the potential to penetrate the skin and this, therefore, represents a potentially significant route of exposure. In studies conducted in animals, dermal exposures result in toxicities similar to those following oral administration. Some comparative *in vitro* data show that the degree of penetration varies with chemical structure, with the rate decreasing with increasing molecular weight. Recent studies with ethylene glycol butyl ether indicate that dermal absorption from the vapour phase is a minor but not insignificant component of total systemic exposure.

Systemic health effects in humans have been reported to be associated with exposures to ethylene glycol methyl ether, ethyl ether and their acetates and also diethylene glycol dimethyl ether based on evaluation of worker populations and case reports. Ethylene glycol methyl and ethyl ethers exposure has been associated with anaemia, granulocytopenia and leukopenia. All such reports of human related effects are confounded by simultaneous exposures to other chemicals as well as limited information of exposure levels. The number of observations and the limited information on the level of exposure do not allow firm conclusions to be made concerning the contribution of glycol ethers to the observed effects. Although the available literature concerning human exposures to ethylene glycol methyl ether, -ethyl ether and the acetates do not provide conclusive evidence, the data reported to date indicate that, with the exception of haemolytic anaemia and the liver and kidney changes seen in some of the carcinogenicity bioassay studies, effects seen in animals are likely to be relevant to humans.

Several epidemiological studies have investigated the possible association between exposure to glycol ethers and aspects of the male and female reproductive system. Some of these studies have found increased risks in workers exposed to glycol ethers. However overall conclusions are difficult to draw because of the strong inter-correlation between exposure to other agents, the

possibility of recall bias and the variety of endpoints investigated. Further epidemiological studies are needed to confirm or refute these findings.

Overviews of the hazards and available data on glycol ethers are presented in Table 2 and 3. The toxicological information on individual glycol ethers is detailed in their substance profiles (Section 4.1 to 4.44). The following abbreviations are used for the names of glycol ether compounds (Table 1).

Table 1: List of glycol ethers and abbreviations

Abbreviation	Name
Ethylene-based	
DEGBE	Diethylene glycol butyl ether
DEGBEA	Diethylene glycol (mono) *n*-butyl ether acetate
DEGDEE	Diethylene glycol diethyl ether
DEGDME	Diethylene glycol dimethyl ether
DEGEE	Diethylene glycol (mono) ethyl ether
DEGEEA	Diethylene glycol ethyl ether acetate
DEGHE	Diethylene glycol (mono) hexyl ether
DEGME	Diethylene glycol (mono) methyl ether
EGBE	Ethylene glycol (mono) *n*-butyl ether
EGBEA	Ethylene glycol (mono) *n*-butyl ether acetate
EGDEE	Ethylene glycol diethyl ether
EGDME	Ethylene glycol dimethyl ether
EGEE	Ethylene glycol ethyl ether
EGEEA	Ethylene glycol (mono) ethyl ether acetate
EGHE	Ethylene glycol (mono) *n*-hexyl ether
EGiPE	Ethylene glycol (mono) isopropyl ether
EGiPEA	Ethylene glycol (mono) isopropyl ether acetate
EGME	Ethylene glycol (mono) methyl ether
EGMEA	Ethylene glycol (mono) methyl ether acetate
EGnPE	Ethylene glycol (mono) *n*-propyl ether
EGnPEA	Ethylene glycol (mono) *n*-propyl ether acetate
EGPhE	Ethylene glycol (mono) phenyl ether
MAA	Methoxyacetic acid [a]
TEGBE	Triethylene glycol (mono) *n*-butyl ether
TEGDME	Triethylene glycol dimethyl ether
TEGEE	Triethylene glycol (mono) ethyl ether
TEGME	Triethylene glycol (mono) methyl ether
Propylene-based	
1PG2ME	1-Propylene glycol 2-methyl ether
1PG2MEA	1-Propylene glycol 2-methyl ether acetate
2PG1BE	2-Propylene glycol 1-*n*-butyl ether
2PG1EE	2-Propylene glycol (mono) 1-ethyl ether
2PG1EEA	2-Propylene glycol 1-ethyl ether acetate
2PG1ME	2-Propylene glycol 1-methyl ether
2PG1MEA	2-Propylene glycol 1-methyl ether acetate
2PG1PhE	2-Propylene glycol 1-phenyl ether
DPGBE	Dipropylene glycol (mono) *n*-butyl ether
DPGEE	Dipropylene glycol (mono) ethyl ether
DPGME	Dipropylene glycol (mono) methyl ether
DPGPE	Dipropylene glycol (mono) propyl ether
DPGTBE	Dipropylene glycol *tert*-butyl ether
PGPE	Propylene glycol *n*-propyl ether
PGTBE	Propylene glycol *tert*-butyl ether
TPGBE	Tripropylene glycol (mono) *n*-butyl ether
TPGME	Tripropylene glycol (mono) methyl ether

[a] Not a glycol ether, but has similar toxicity

Table 2: Summary of hazards[a] posed by glycol ethers

Section	Compound	CAS[b] number	Haemolysis	Haematopoietic toxicity	Testicular toxicity	Reproductive toxicity	Developmental toxicity	Immuno-toxicity	Geno-toxicity	Carcinogenicity	Other effects
	Ethylene-series										
4.1	EGME	109-86-4	–ve	+ve	+ve	+ve	+ve	+	–ve	No data	CNS[c]/behavioural effects
4.2	EGMEA	110-49-6	–ve	+ve	+ve	+ve (limited data)	+ve	+	–ve	No data	
4.3	EGDME	110-71-4	No data	No data	+ve	+ve	+ve	No data	–ve	No data	CNS/behavioural effects
4.4	DEGME	111-77-3	–ve	–ve	+ve	No data	+ve (weak)	–ve	–ve	No data	
4.5	DEGDME	111-96-6	–ve	+ve	+ve	+ve	+ve	No data	–ve	No data	
4.6	TEGME	112-35-6	–ve	–ve	–ve	No data	–ve	No data	–ve	No data	
4.7	TEGDME	112-49-2	–ve	–ve	+ve	+ve	+ve	(+ve)	No data	No data	
4.8	MAA[a]	625-45-6	–ve	+ve	+ve	+ve	+ve	+	–ve	No data	
4.9	EGEE	110-80-5	–ve	+ve	+ve	No data	+ve	–ve	–ve	–ve (limited data)	
4.10	EGEEA	111-15-9	–ve	+ve (limited data)	+ve	+ve	+ve	–ve	–ve	No data	
4.11	EGDEE	629-14-1	–ve	No data	No data	No data	+ve	–ve	No data	No data	
4.12	DEGEE	111-90-0	–ve	–ve	+ve	–ve	–ve	–ve	–ve	No data	
4.13	DEGEEA	112-15-2	No data	No data	No data	No data	No data	No data	–ve	No data	
4.14	DEGDEE	112-36-7	No data	No data	No data	No data	–ve	No data	No data	No data	
4.15	TEGEE	112-50-5	–ve	–ve	–ve	No data	–ve	No data	No data	No data	
4.16	EGiPE	109-59-1	+ve	–ve	–ve	No data	–ve	No data	-ve	No data	
4.17	EGiPEA	91598-97-9	No data	No data	No data	No data	No data	No data	No data	No data	
4.18	EGnPE	2807-30-9	+ve	–ve	–ve	No data	–ve	No data	No data	No data	
4.19	EGnPEA	20706-25-6	+ve	–ve	–ve	No data	–ve	No data	No data	No data	
4.20	EGPhE	122-99-6	+ve (rabbits)	–ve	–ve	–ve	–ve	No data	–ve	No data	

Table 2: Summary of hazards[a] posed by glycol ethers (cont'd)

Section	Compound	CAS [b] number	Haemolysis	Haematopoietic toxicity	Testicular toxicity	Reproductive toxicity	Developmental toxicity	Immuno-toxicity	Geno-toxicity	Carcinogenicity	Other effects
	Ethylene-series (cont'd)										
4.21	EGBE	111-76-2	+ve	–ve	–ve	–ve	–ve	–ve	–ve	±	
4.22	EGBEA	112-07-2	+ve	–ve	–ve (limited data)	No data	No data	No data	No data	No data	
4.23	DEGBE	112-34-5	–ve	–ve	–ve	–ve	–ve	No data	–ve	No data	
4.24	DEGBEA	124-17-4	+ve	–ve	No data	No data	No data	No data	No data	No data	
4.25	TEGBE	143-22-6	–ve	–ve	–ve	No data	–ve	No data	No data	No data	
4.26	EGHE	112-25-4	-ve	–ve	–ve	No data	–ve	No data	–ve	No data	
4.27	DEGHE	112-59-4	–ve	–ve	No data	No data	No data	No data	–ve	No data	
	Propylene-series										
4.28	2PG1ME	107-98-2	–ve	–ve	–ve	–ve	–ve	–ve	–ve	–ve	
4.29	2PG1MEA	108-65-6	–ve	–ve	–ve	–ve	–ve	No data	–ve	No data	
4.30	1PG2ME	1589-47-5	–ve	–ve	–ve	No data	+ve	No data	–ve	No data	
4.31	1PG2MEA	70657-70-4	–ve	–ve	–ve	No data	+ve	No data	No data	No data	
4.32	DPGME	34590-94-8	–ve	–ve	–ve	No data	–ve	No data	–ve	No data	
4.33	TPGME	25498-49-1	–ve	–ve	–ve	No data	–ve	No data	–ve	No data	
4.34	2PG1EE	1569-02-4	–ve	–ve	–ve	No data	–ve	No data	–ve	No data	
4.35	2PG1EEA	54839-24-6	–ve	–ve	–ve	No data	No data	No data	–ve	No data	
4.36	DPGEE	30025-38-8	–ve	–ve	–ve	–ve	No data	No data	–ve	No data	
4.37	PGPE	1569-01-3	–ve	–ve	–ve	No data	–ve	No data	–ve	No data	
4.38	DPGPE	29911-27-1	–ve	–ve	–ve	No data	No data	No data	–ve	No data	
4.39	2PG1PhE	770-35-4	–ve	–ve	–ve	No data	No data	No data	–ve	No data	
4.40	2PG1BE	5131-66-8	–ve	–ve	–ve	No data	–ve	No data	–ve	No data	

[a] Not a glycol ether, but has similar toxicity

Table 2: Summary of hazards[a] posed by glycol ethers (cont'd)

Section	Compound	CAS[b] number	Haemolysis	Haemato-poietic toxicity	Testicular toxicity	Reproductive toxicity	Developmental toxicity	Immuno-toxicity	Geno-toxicity	Carcinogenicity	Other effects
	Propylene-series (cont'd)										
4.41	DPGBE	29911-28-2	–ve	–ve	–ve	No data	–ve	No data	–ve	No data	
4.42	TPGBE	55934-93-5	–ve	–ve	–ve	No data	No data	No data	–ve	No data	
4.43	PGTBE	57018-52-7	–ve	–ve	–ve	–ve	–ve	No data	–ve	+ve	
4.44	DPGTBE	132739-31-2	–ve	–ve	–ve	No data	No data	No data	–ve	No data	

[a] –ve, negative: no effects, +ve, positive: effects on organ or system; ±, equivocal; (–ve) or (+ve), insufficient data

[b] Chemicals Abstracts Service

[c] Central nervous system

Table 3: Summary of available [a] data on glycol ethers

Section	Compound	CAS number	Acute toxicity	Irritation	Sensitisation	Reproductive toxicity	Developmental toxicity	Repeated-dose toxicity	Genotoxicity	Carcinogenicity	Other [b]
	Ethylene-series										
4.1	EGME	109-86-4	+	+	-	+	+	+	+	-	K/M, N, Im, H
4.2	EGMEA	110-49-6	+	+	-	-	+ (limited)	+ (limited)	+	-	Im, H
4.3	EGDME	110-71-4	+ (oral)	-	-	-	+	+ (limited)	+ (limited)	-	K/M, N
4.4	DEGME	111-77-3	+	+	-	-	+	+	+	-	Im
4.5	DEGDME	111-96-6	+	+	+	+	+	+	+	-	K/M, H
4.6	TEGME	112-35-6	+	-	-	-	+	+	+	-	K/M, N
4.7	TEGDME	112-49-2	+ (oral)	-	-	+	+	+	-	-	
4.8	MAA [c]	625-45-6	+	+ (skin)	-	+	+	+	+	-	K/M, Im, H
4.9	EGEE	110-80-5	+	+	-	+	+	+	+	+ (limited)	K/M, N, Im, H
4.10	EGEEA	111-15-9	+	+	+	+	+	+	+	-	K/M, Im
4.11	EGDEE	629-14-1	+	+	-	-	+	+ (limited)	-	-	K/M
4.12	DEGEE	111-90-0	+	+	-	+	+	+	+	+ (limited)	K/M, H
4.13	DEGEEA	112-15-2	+	+	+	-	-	-	+	-	
4.14	DEGDEE	112-36-7	+ (oral)	+ (eye)	-	-	+	+ (limited)	-	-	
4.15	TEGEE	112-50-5	+	+	-	-	+	+	-	-	K/M
4.16	EGiPE	109-59-1	+	+	+	-	+	+	+	-	K/M
4.17	EGiPEA	91598-97-9	-	-	-	-	-	-	-	-	
4.18	EGnPE	2807-30-9	+	+	+	-	+	+	-	-	K/M, N
4.19	EGnPEA	20706-25-6	+	+	+	-	+	+	-	-	K/M
4.20	EGPhE	122-99-6	+	+	+	+	+	+	+	-	K/M
4.21	EGBE	111-76-2	+	+	+	+	+	+	+	+	K/M, N, Im, H
4.22	EGBEA	112-07-2	+	+	-	-	-	+ (limited)	-	-	H

Table 3: Summary of available[a] data on glycol ethers (cont'd)

Section	Compound	CAS number	Acute toxicity	Irritation	Sensitisation	Reproductive toxicity	Developmental toxicity	Repeated-dose toxicity	Genotoxicity	Carcinogenicity	Other[b]
4.23	DEGBE	112-34-5	+	+	+	+	+	+	+	-	K/M, N, H
4.24	DEGBEA	124-17-4	+	+	-	-	-	+ (limited)	-	-	K/M
4.25	TEGBE	143-22-6	+	+	-	-	+	+ (limited)	-	-	K/M
4.26	EGHE	112-25-4	+	+	-	-	+	+	+	-	
4.27	DEGHE	112-59-4	+	+	-	-	-	+ (limited)	+	-	
	Propylene-series										
4.28	2PG1ME	107-98-2	+	+	+	+	+	+	+	+	K/M, N, H
4.29	2PG1MEA	108-65-6	+	+	+	-	+	+ (limited)	+	-	K/M
4.30	1PG2ME	1589-47-5	+	+	-	-	+	+	+	-	K/M
4.31	1PG2MEA	70657-70-4	+	+	-	-	+	+	-	-	
4.32	DPGME	34590-94-8	+	+	+	-	+	+	+	-	K/M
4.33	TPGME	25498-49-1	+	+	-	-	+	+	+	-	
4.34	2PG1EE	1569-02-4	+	+	-	-	+	+	+	-	
4.35	2PG1EEA	54839-24-6	+	+	+	-	-	+	+	-	
4.36	DPGEE	30025-38-8	+	+	+	+	-	+	+	-	K/M, N
4.37	PGPE	1569-01-3	+	+	-	-	+	+	+	-	
4.38	DPGPE	29911-27-1	+	+	-	-	-	+	+	-	
4.39	2PG1PhE	770-35-4	+	+	-	-	-	+	+	-	K/M
4.40	2PG1BE	5131-66-8	+	+	+	-	+	+	+	-	K/M
4.41	DPGBE	29911-28-2	+	+	+	-	+	+	+	-	K/M
4.42	TPGBE	55934-93-5	+	+	+	-	-	+	+	-	
4.43	PGTBE	57018-52-7	+	+	+	+	+	+	+	+	K/M
4.44	DPGTBE	132739-31-2	+	+	+	-	-	+	+	-	K/M, N

[a] +, data are available; -, no data are available

[b] Abbreviations: K/M, kinetics; N, neurotoxicity; Im, immunotoxicity; H, human data

[c] Not a glycol ether, but has similar toxicity

Recommendations for further work

Several glycol ethers are part of the International Council of Chemical Associations (ICCA) programme on High Production Volume chemicals, which requires a base set of data to be available on all chemical substances registered on the ICCA tracking system. Glycol ethers covered in several submissions that have been developed for the ICCA programme are: ethylene glycol phenyl ether, ethylene glycol propyl ether, ethylene glycol *n*-hexyl ether, diethylene glycol ethyl ether, diethylene glycol hexyl ether, ethylene glycol butyl ether acetate, diethylene glycol butyl ether acetate, triethylene glycol butyl ether, propylene glycol butyl ether and propylene glycol phenyl ether. The reports have been submitted to the US-EPA and OECD for review.

The overall evaluation of these compounds indicates certain knowledge gaps and the need to:

- Develop biological action levels for ethylene glycol methyl ether and/or methoxyacetic acid that are based on biomonitoring data and which will help control dermal exposure situations. This would be based on the no-observed adverse effect level for methoxyacetic acid, which may require more data to derive a definitive value.
- Determine the role of haemolytic anaemia in inducing oxidative stress that could lead to toxicological effects, especially in the liver.
- Further validate biological monitoring methods, focusing on the relationship of biological effects to airborne exposure values.
- Obtain exposure and/or use data from downstream users and consumer groups covering both qualitative (for example frequency, duration and control measures used) and quantitative determinants that address personal air measurements and biological monitoring.

1. INTRODUCTION

This report collects and assesses available toxicity and human health related information on selected ethylene and propylene glycol mono-ethers and di-ethers (glymes) that are of regulatory and/or commercial interest. It provides a critical update of a previous ECETOC (1995) review, published as Technical Report No. 64 [a], and identifies gaps in knowledge and proposals for research.

Following an overview of production and use (Section 1.2), the report presents an evaluation of the toxicity database (Section 2) and significant new information on human exposure (Section 3.1) of glycol ethers. The available information on adverse human health effects is discussed in Section 3.2, followed by an overview of current occupational exposure limit (OEL) values (Section 3.3). Individual toxicity data profiles are presented for each of the ethylene glycol ethers in Section 4.1 to 4.27, and for propylene glycol ethers in Section 4.28 to 4.44. Abbreviated names of compounds are given in Table 1 above; special abbreviations are listed at Appendix A.

1.1 Conversion factors and physico-chemical properties

Conversion factors for concentrations in air at standard conditions (20°C and 1,013 hPa) are given for each compound (toxicity profile) in Section 4. The generic formula is given in Appendix B. In this report, converted values are given in parentheses. The relative density (D_4^{20}) of a compound (compared to that of water at 4°C = 1,000 kg/m^3) is given as required. Data on the physico-chemical properties of each compound are given at the above standard conditions, unless stated otherwise.

1.2 Production and use

1.2.1 Manufacture of ethylene-series glycol ethers

Ethylene glycol mono-ethers are produced in closed continuous processes by reacting ethylene oxide with an anhydrous alcohol (usually methyl, ethyl or butyl alcohol). Temperature, pressure, reactant molar ratios and catalysts are selected to yield the required product mix. For example, high ratios of alcohol to ethylene oxide are used when ethers of mono-ethylene glycol are manufactured, whereas lower ratios favour the production of diethylene-, triethylene- and higher glycol ethers. Although most diethylene- and triethylene glycol mono-methyl ethers are co-produced *in situ* with the corresponding mono-ethylene glycol ether, they can also be made

[a] That in itself updated earlier ECETOC reviews from 1982 and 1985.

through the specific reaction of ethylene oxide with an isolated ethylene glycol mono-ether. Because of the large difference in boiling points, mixtures of glycol ethers are typically separated by distillation.

The ethylene-series glycol ether acetates are produced by the reaction of glycol ether and acetic acid in the presence of a catalyst. The reaction is carried out at elevated temperature followed by separation and purification and is carried out in either a batch or continuous mode.

1.2.2 Manufacture of propylene-series glycol ethers

Production of propylene glycol mono-ethers follows the generalised scheme described above for ethylene-series products. They are produced by the catalysed reaction of propylene oxide and an alcohol. As a result, propylene glycol mono-alkyl ethers are the primary products, with some di- and tri-propylene glycol mono-alkyl ethers formed from the further reaction of the mono-alkyl ether with excess propylene oxide. However, while reaction kinetics favour the production of 1-alkoxy-2-propanol (secondary or α-isomer), trace amounts of the corresponding 2-alkoxy-1-propanol (primary or β-isomer) are also formed. By further manipulating the reaction conditions, the proportion of α-isomer can be increased to 99% or more of the final stream. The process can be carried out either in a batch or continuous mode.

The propylene-series glycol ether acetates are produced by the reaction of glycol ether and acetic acid in the presence of a catalyst. The reaction is carried out at elevated temperature followed by separation and purification and is carried out in either a batch or continuous mode.

1.2.3 Uses

Glycol mono-ethers combine the solubility characteristics of ethers and alcohols since both functional groups are present in the molecule. They are therefore widely used in solvent applications, including formulations such as paints, inks and cleaning fluids. Non-solvent applications include uses as anti-icing agents in jet fuel, hydraulic system fluids and as chemical intermediates.

Total use of glycol ethers in western Europe during 1999 was 422 kt. This volume comprised 233 kt for the ethylene-series and 189 kt for the propylene-series (Chinn *et al*, 2000) (Table 4).

Table 4: Western Europe consumption of glycol ethers by end-use in 1999

	%	kt
Ethylene-series		**233**
Brake fluids	27	
Surface coatings (as glycol ethers)	29	
Surface coatings (as glycol ether acetates)	12	
Pesticides, printing inks, jet fuel additives	6	
Industrial cleaners	4	
Other	21	
Propylene-series		**189**
Surface coatings (as glycol ethers)	32	
Surface coatings (as glycol ether acetates)	24	
Leather, pesticides, electrical, industrial cleaners, resins	23	
Printing inks	12	
Other	9	
Total:		**422**

[a] Chinn *et al*, 2000

A number of glycol ethers are worthy of specific mention due to their specific usage patterns.

Four commercially available glycol ethers have shown reproductive and developmental effects in laboratory animals. These are ethylene glycol ethyl ether (EGEE) and ethylene glycol methyl ether (EGME) and their acetates (EGEEA and EGMEA). The usage of these materials is restricted to jet fuel de-icing and pharmaceutical production. Sales of products containing these substances to the general public are forbidden in the EU (INSERM, 1999).

Diethylene glycol methyl ether (DEGME) is mainly used as an anti-icing fluid in jet fuel and a chemical intermediate, a processing solvent and as a solvent in paints and floor polishes. Diethylene glycol butyl ether (DEGBE) is used as a solvent in paints, dyes, inks, detergents and cleaners. Both DEGME and DEGBE have undergone risk assessment in the EU under the Existing Substances Regulation and the uses of these materials are subject to appropriate controls (European Chemical Bureau, 2000, 2001).

Glymes (glycol diethers) are specialised materials used in a variety of industrial processes as solvents, in chemical reactions involving metals, inorganic salts and organo-metallics (Ferro, 2002).

Methoxy acetic acid (MAA) is a specialised substance used mainly in the production of pharmaceuticals where it is used to separate racemic mixtures.

2. TOXICOLOGICAL OVERVIEW

2.1 Acute toxicity

Oral

The acute oral toxicity of many glycol ethers and their acetates has been studied extensively; they generally exhibit a low to moderate order of acute oral toxicity in rodents. In the majority of cases, LD_{50} values are greater than 2,000 mg/kgbw, excluding those compounds that produce haemolysis (Section 2.3.1 below). Much of the data are historical and this makes quantitative comparison of glycol ether toxicity difficult because of inter- and intra-laboratory variations.

An early study by Smyth *et al* (1941) is supported by a more recent and comprehensive comparative research programme on nine glycol ethers in mice and rats (Krasavage and Terhaar, 1981a). The study was performed according to good laboratory practice (GLP) standards and provides the most definitive data on the comparative acute oral toxicity of ethylene and diethylene glycol ethers. The acute toxicity of mono-ethylene glycol mono-ethers was generally higher than that of the corresponding diethylene glycol mono-ethers in both rats and mice, while systemic toxicity was greater in rats than in mice. Generally, within each series of ethylene and diethylene glycol ethers, the toxicity of the compound increased with increasing molecular weight; those materials causing significant haemolysis (EGBE, EGPhE) showed more marked acute toxicity in rodents. LD_{50} values were generally higher in fed animals than in starved animals. Clinical signs of toxicity included inactivity, laboured breathing, rapid respiration, anorexia, slight to moderate weakness, tremors, prostration and death.

The available data indicate that propylene or dipropylene glycol ethers are less toxic by the oral route in rats than the corresponding ethylene or diethylene glycol ethers. The primary ethers of propylene glycol are considered to be less toxic than the secondary ethers.

Dermal

Glycol ethers and their acetates generally exhibit a low to moderate order of acute dermal toxicity in laboratory animals. In the majority of cases, the acute dermal LD_{50} values are greater than 2,000 mg/kgbw, although a moderate order of dermal toxicity is exhibited by EGBE, EGBEA and EGiPE. Studies *in vitro* with excised human skin have demonstrated that glycol ethers penetrate the cutaneous barrier at different rates of flux. The rate of penetration within the mono-ethylene glycol series was inversely related to alcohol chain length. Diethylene glycol mono-ethers penetrated less rapidly than their mono-ethylene counterparts.

Inhalation

Acute inhalation toxicity data for a number of glycol ethers show a range of toxic responses. Glycol ethers of relatively low volatility (typically di-, triethylene and propylene glycol ethers) have a low order of acute inhalation toxicity and laboratory animals appear able to tolerate acute exposures to saturated vapour with little or no adverse toxicological effects.

Moderate toxicity is seen in animals exposed by inhalation to EGME, EGEE and EGBE. Testicular damage has been observed after acute inhalation exposure to EGME or EGEE. Haemolytic effects were observed in rats exposed to EGBE by inhalation; rats are particularly sensitive to EGBE induced haemolysis, whereas humans are more resistant to this effect. In general, the propylene glycol based mono ethers do not exhibit haemolytic or testicular toxicity on acute inhalation exposure. Depression of the CNS and increased liver weight has been reported in rodents exposed to high vapour concentrations.

2.2 Irritation and sensitisation

Skin irritation

The majority of glycol ethers do not cause significant skin irritation upon acute exposure; however, severe irritation has been associated with prolonged or repeated skin contact.

Eye irritation

Standard laboratory eye irritation tests have yielded a range of responses following single exposure to the undiluted test material. Many of the glycol ethers caused slight to moderate eye irritation, typically conjunctival redness and swelling. A number of compounds, primarily the higher alkyl derivatives (EGPhE, DEGDEE, EGiPE, EGnPE, PGBE, EGBE, DEGBE, TEGBE and EGHE) induced more marked eye irritation. Some studies have reported tissue damage and corneal injury with recovery following removal of the test compound. Severity of the eye irritation was reduced by dilution of the glycol ether in water.

Skin sensitisation

Data available from a limited number of studies indicate that glycol ethers are not skin sensitisers.

2.3 Repeated-dose toxicity

Glycol ethers have been extensively investigated for their specific toxicity profiles and target organs following repeated administration. Studies have been conducted in a variety of laboratory animal species, by different routes of exposure and exposure durations.

Generally, the target organs and toxicity profiles of all glycol ethers are detectable shortly after administration. Many effects are notable after single exposure. There is minimal difference between the effects following subacute (up to 28 days) and subchronic (up to 90 days) exposure, either in qualitative or in quantitative terms. Administration routes are of minor importance for the effects observed.

There are few species differences in response to glycol ethers. The most important differences are the lack of haemolytic effects of EGBE and its metabolite 2-butoxyacetic acid (BAA) in humans, in contrast to rodents, and the greater sensitivity of rats than mice to immunotoxicity of EGME and MAA. Short chain alkoxy acetic acids (MAA, ethoxyacetic acid [EAA]) and methoxypropionic acid (MPA) are excreted more slowly in larger organisms, including humans, than in rodents. The significance of this difference in species sensitivity is not known. The elimination rate of the alkoxy acetic acids in rabbits is slower than in rats; this might be a factor in the more pronounced effects in rabbits compared to rats (EGME, 1PG2ME).

A limited number of glycol ethers can cause adverse effects in the bone marrow and the germinal epithelium of the testes. These are: EGME, EGMEA, EGEE, EGEEA, EGDME and DEGDME. In the case of 1PG2ME, data on the rabbit, a sensitive species, are not available and hence no overall conclusion can be drawn. Biotransformation to their respective metabolites is responsible for all their specific effects. The same compounds are also selectively toxic to the foetus. All other glycol ethers do not exert such effects. Furthermore EGME, but not EGEE, exerts a specific CNS effect (loss of avoidance-escape response), which has been observed in humans and in animal models, most likely mediated by the metabolite MAA.

Ethylene glycol ethers of medium chain length (EGPE, EGBE and their acetates; to some extent also EGPhE) may cause haemolytic effects in rodents, but not in humans. For EGBE, the metabolite BAA was shown to be responsible for this effect. In the specific case of EGPhE, it is considered to be the parent compound and not a metabolite that causes haemolysis.

2.3.1 Effects on the haematopoietic system and the peripheral blood

Two distinctly different types of haematological effects have been observed with glycol ethers, depending on their chain length.

EGME, EGEE and their acetate esters exert detrimental effects on the haematopoietic system in the bone marrow (blood cell formation) and cause a deficiency of all cell elements (red and white) of haematopoiesis (generalised pancytopenia) in rats, mice and rabbits. Similar effects are also observed with EGDME and DEGDME. The toxicity to the haematopoietic system is observable in all species investigated, including humans. 1PG2ME does not cause adverse effects in rats or mice, but data in rabbits, which are generally considered a more sensitive species, are not available.

The cellular damage is characterised by a reduction in both myeloid and erythroid elements and in mega-karyocytes. Haematology findings in mice, rats and rabbits suggest that EGEE is less potent than EGME and EGMEA. Significant effects on the haematopoietic system have not been reported for the ethers of triethylene glycol.

In contrast, EGnPE, EGiPE, EGBE, EGBEA and EGPhE exert detrimental effects only to mature peripheral RBCs; the erythrocyte membranes show increased osmotic fragility and are subject to intravascular lysis. Secondary changes may occur as a result of intravascular haemolysis. The haemolytic effect does not directly affect the white blood cell (WBC) count and is species-specific (mice, rats and rabbits show haemolysis; guinea pigs are more resistant): it does not occur in humans.

In vitro investigations with EGBE and BAA including human erythrocytes showed both the mediation of the EGBE effects by BAA and the resilience of human erythrocytes towards BAA even at high concentrations. This low sensitivity to haemolysis was also shown for erythrocytes from humans with certain congenital blood defects, such as sickle cell anaemia. Young rats appear to be less sensitive to EGBE- (BAA-) induced haemolysis than adult rats because old rats also tend to have a higher number of old erythrocytes that are more susceptible to haemolysis than younger erythrocytes. When, after the first administration(s), old erythrocytes are replaced by younger erythrocytes, rats become less sensitive and higher doses are needed to induce haemolysis. DEGBE does not show haemolytic activity; furthermore, no haematological effects have been reported in the more limited studies conducted with TEGBE.

EGPhE may cause haemolytic anaemia in rabbits exposed orally or via the skin. Increased erythrocyte fragility and signs of intravascular haemolysis are similar to the effects reported for EGBE, although in this case rats appear to be less susceptible than rabbits (EGPhE). In contrast to EGBE, the metabolism of EGPhE to phenoxyacetic acid (PhAA) produces a less potent haemolytic agent, which may explain, in part, the observed species difference.

Propylene glycol mono-ethers (2-propylene glycol 1-methyl ether [2PG1ME], 2-propylene glycol 1-ethyl ether [2PG1EE], 2-propylene glycol 1-*n*-butyl ether [2PG1BE] and 2-propylene glycol

1-phenyl ether [2PG1PhE]) neither exhibit adverse effects on haematopoiesis nor produce haemolytic anaemia.

Evaluation

In summary, low molecular weight ethylene glycol ethers, through their metabolites, produce pancytopenia. In contrast, higher molecular weight ethylene-based molecules, through their metabolites, produce a compensatory haemolysis of peripheral red blood cells to which humans are resistant. Propylene-based glycol ethers have no haematological actions.

2.3.2 Testes

EGME, EGEE and their acetates adversely affect spermatogenesis. There is an increasing database suggesting that DEGDME and EGDME, and to a limited extent DEGME, may also produce similar effects. Leydig cells, responsible for testosterone production, are not affected. These testicular effects require the formation of MAA or EAA.

MAA is a potent testicular toxicant in rats (Miller *et al*, 1982b). The testicular atrophy is characterised by decreased testes weight and histological lesions showing apoptosis and degeneration of the germinal epithelium in the seminiferous tubules with a specific impact on pachytenic and subsequently also on other stages of the spermatogenic cycle (Sections 4.1.4.3 and 4.8.4.3). At higher doses or prolonged exposure all stages of spermatogenesis may be adversely affected.

Comparative studies indicate that EGME is the most potent glycol ether inducing testicular toxicity. Lesions were observed in rats, mice and rabbits following all routes of exposure (oral, dermal or inhalation). The most sensitive species is considered to be the rabbit, with a minimum effect level of 30 ppm EGME vapour (95 mg/m^3) over 90 days (Miller *et al*, 1982a, 1983a). For DEGDME vapour, exposure to 98 ppm (550 mg/m^3) was a minimum effect level in male rats (Du Pont, 1988b).

A range of simple physiological compounds (such as serine, acetate, sarcosine, glycine, and D-glucose) administered concurrently with EGME reduced or prevented the degenerative changes in the testes. It is hypothesised that MAA may interfere with one-carbon unit pathways and that these "antagonists" can donate a carbon unit that may be used in purine nucleotide biosynthesis. Reduced availability of bases might predominantly affect late stage pachytene spermatocytes, which are known to be undergoing rapid RNA synthesis (Mebus and Welsch, 1989). Co-administration of serine enantiomers may provide protection against EGME induced teratogenesis in mice (Clarke *et al*, 1991a).

2.3.3 Kidney

A number of studies with ethylene and propylene glycol ethers have reported adverse effects on the kidneys. In general, effects were confined to the high dose and in the presence of other signs of toxicity such as reduced weight gain. There are two distinct effects: those exacerbated through the metabolite, mono-ethylene glycol (MEG) and, secondly, a male rat-specific nephropathy.

MEG is a potential metabolite of ethylene glycol ethers as shown in the case of EGME. MEG is more nephrotoxic in dogs, rabbits and humans than in mice and rats. This has to be taken into account for glycol ethers exerting low systemic toxicity but which are potentially metabolised to MEG. The metabolic pathways of EGBE have been clearly elucidated, which shows that, in addition to BAA also some metabolic transformation to MEG potentially occurs. Thus, subsequent oxaluria (excess of calcium oxalate in urine) may be regarded as an additional candidate for biomonitoring in humans.

Male rats treated with DPGEE showed some hyaline droplet formation in the proximal tubule cells (BP, 1990b). Elevated deposition of $\alpha_{2\mu}$-globulin and cell proliferation were also seen in the kidneys of male rats exposed to 2PG1ME (11,200 mg/m^3) (Cieszlak *et al*, 1996a; Spencer *et al*, 2002) and PGTBE (Doi *et al*, 2004; NTP, 2004). This male rat-specific kidney response is not relevant to human hazard assessment (US-EPA, 1991).

2.3.4 Liver

Repeated-dose studies have occasionally reported histological changes in the liver, including cloudy swelling and centrilobular enlargement (e.g. EGEE, TEGME). Chronic exposure to EGBE, 2PG1ME and PGTBE produced a centrilobular hypertrophy in mice. These effects are more representative for adaptive phenomena and enzyme induction than cytotoxicity.

Elevated liver weights at high-doses have been also reported following exposure to EGBE or propylene glycol mono-alkyl ethers. The increased weight is considered to be reversible, reflecting an adaptive metabolic response rather than a specific organ toxicity as judged by an expert panel within the US-National Toxicology Program study on EGBE (NTP, 2000). The total incidence of hepatic tumours (adenoma and carcinoma) in mice was not altered following lifetime exposure to EGBE, but there was an indication of a progression from hepato-adenoma to carcinoma in males, which may reflect oxidative stress.

2.3.5 Lymphatic tissue and immunotoxicity

Toxicity to lymphoid organs and tissues, including pronounced thymus weight reduction, has been reported following repeated exposure of laboratory animals to EGME, DEGDME and DEGME, and to the metabolite MAA (rats more than mice). Similarly pronounced effects have not been reported in comparable tests for other ethylene or propylene glycol ethers. A comparative 28-d drinking water study with EGME and EGBE in rats (Exon *et al*, 1991) found that EGME, but not EGBE, caused a dose-related reduction in thymus weight. Microscopic examination confirmed overall atrophy and loss of the clear demarcation between the cortex and medulla within the thymus lobules in high dose animals (approximately 600 mg/kgbw/d). Similar effects have been reported also in rabbits exposed to EGME vapour and in mice following oral administration.

Specific antibody reduction and a dose related increase of natural killer (NK) cell cytotoxic activity has been reported for rats after administration of EGME and its metabolite MAA. Inbred Lewis rats were a particularly sensitive strain. The immunotoxicity of EGME was reduced in the presence of the alcohol dehydrogenase (ADH) inhibitor 4-methylpyrazole, suggesting that MAA is a prerequisite for immunotoxicity of EGME (Smialowicz, 1996).

The decreases in humoral immune responses and increases in cell-mediated responses may have contributed to the observed anti-tumour effects of EGME in tumour inoculation experiments and of EGEE seen in a 2-year study. On the other hand, EGEE, EGEEA, and the metabolite EAA showed no immunotoxicity using the same test protocol as for EGME and MAA (Smialowicz *et al*, 1991a,b, 1992; Riddle *et al*, 1992). DEGME was also devoid of such effects in this protocol but has been reported to cause lymphocyte depletion of the thymus following oral administration of 2,000 mg/kgbw/d for up to 20 days (Kawamoto *et al*, 1990a).

EGBE has been reported to cause decreased thymus weights or thymic atrophy in some studies that have used high doses. However, no consistent effects on white cells have been reported and the recorded responses could also be secondary or stress-induced effects in the sequel of the RBC haemolysis following administration of EGBE. It has also been reported that the large number of immature erythrocytes that appear in the blood following EGBE administration can affect WBC counts (Ghanayem *et al*, 1987a). EGBE had no effect on immunoglobulin class G (IgG) antibody production or primary antibody response, delayed type hypersensitivity, cytokine production or splenocyte numbers (Exon *et al*, 1991; Smialowicz *et al*, 1992). The proliferative activity of guinea pig lymphocytes *in vitro* was not affected by non-cytotoxic doses of EGBE (2 mmol/l) or its metabolite BAA (1 mmol/l) (Unilever, 1990).

1PG2MEA caused some thymic atrophy in rats at inhalation exposure to 2,800 ppm (15,400 mg/m^3) for 4 weeks (BASF, 1984d; Ma-Hock *et al*, 2005). However, since the metabolite

2-MPA is excreted slower in rabbits than in rats and rabbit studies on this endpoint are not available, a final assessment is not possible.

On balance, with the exception of those glycol ethers that may produce MAA, the large number of other glycol ethers investigated in subacute/subchronic studies are not considered to be specifically immunotoxic.

2.3.6 Neurological effects

Reversible neurological effects have been reported in humans with EGME, which appear to be typical and most likely mediated by MAA (Section 4.1.5.2). In rats exposed to 400 to 500 ppm EGME (1,270 - 1,580 mg/m^3) for 7 days, an inhibition of the avoidance-escape response and impairment of hind limb motor function was observed. This behavioural change is different to the transient CNS depression, which results from inhalation of other organic solvents (Goldberg *et al*, 1962; Savolainen, 1980).

TEGME produced no adverse neurological effects in a 90-day drinking water study in male and female rats that was specifically designed to study neurological effects at nominal doses of 0, 400, 1,200 or 4,000 mg/kgbw/d (Gill and Negley, 1990).

Neurological effects have not been systematically examined for other glycol ethers, although the large number of subacute/subchronic studies do not indicate that these materials in general produce adverse effects on nervous tissue. At high, sublethal doses, a reversible CNS depression was seen, which is a general feature of solvent toxicity.

2.4 Genotoxicity and cell transformation

There are some reports with positive findings in genotoxicity assays with ethylene-based glycol ethers, which are detailed below. However, the majority of studies undertaken with the ethylene-based chemicals is negative, demonstrating an overall lack of genotoxicity. Studies on the propylene- based glycol ethers do not indicate a genotoxic potential.

EGME studies in a wide range of *in vitro* and *in vivo* tests do not indicate significant genotoxic potential for this material. A few studies have produced effects and these are mentioned in Section 4.1.4.4.

Results of numerous *in vitro* and *in vivo* assays have shown that EGBE is non-genotoxic. A few studies have found effects and these are summarised in Section 4.21.4.4. Reviews by Elliot and Ashby (1997) as well as by the US-NTP (2000) have concluded that EGBE is non-mutagenic.

For DEGBE, a dose-related increase in mutation frequency in the mouse lymphoma cell assay in the absence of metabolic activation has been reported; no effect was seen in the presence of metabolic activation (Thompson *et al*, 1984). However, in view of the level of response and the uniformly negative results from a number of other genotoxicity assays (Thompson *et al* 1984; Unilever, 1984c,d; Zeiger *et al*, 1992; Gollapudi *et al*, 1993), this isolated result does not indicate that DEGBE represents a significant genotoxic hazard for mammals.

DEGDME has been associated with a marginal increase in the number of recessive lethal mutations in *Drosophila melanogaster*. However, other genotoxicity tests were negative and the *Drosophila* data are not considered to indicate that DEGDME represents a significant genotoxic hazard for mammalian species (McGregor *et al*, 1983).

Administration of DEGDME has been associated with reduced fertility in rats and abnormal sperm head morphology; there was an equivocal dominant lethal response (McGregor *et al*, 1983). It is probable that the adverse *in vivo* effects of DEGDME administration are due to testicular toxicity rather than genotoxicity.

2.4.1 Evaluation

Most of the glycol ethers that have been assessed were tested in *Salmonella typhimurium* (Ames test); whilst the test protocols were not always to current standards, none of the studies indicated a mutagenic potential. Also the vast majority of other genotoxicity assays with glycol ethers have not reported any mutagenic activity.

The occasional positive genotoxicity results are not considered to indicate a significant genotoxic hazard for these glycol ethers. Reported positive findings were generally either obtained with non-validated methods or were isolated findings that could not be confirmed with validated test systems.

2.5 Chronic toxicity and carcinogenicity

Lifetime studies with EGBE (NTP, 2000), 2PG1ME (Spencer *et al*, 2002) and PGTBE (Doi *et al*, 2004; NTP, 2004) have been conducted in rats and mice. A study with EGEE has also been undertaken although histopathology data were not reported, thus limiting its utility (Melnick, 1984).

Rats were exposed to EGBE by inhalation at 31.2, 62.5 or 125 ppm (153, 307 or 614 mg/m^3), while mice were exposed at 62.5, 125 or 250 ppm (307, 614 or 1,230 mg/m^3). Significant haematological effects were reported, in both species, consisting of a concentration-dependent

compensatory anaemia resulting from RBC haemolysis and present at 3, 6 and 12 months of exposure. Treatment-related non-neoplastic lesions were reported in the olfactory epithelium (hyaline degeneration in rats at all doses) and spleen at 125 ppm in both species. A dose-related increase in Kupffer-cell pigmentation was present in livers of all exposed animals. Female animals were more affected than males for both species. In female rats exposed to 125 ppm, benign or malignant phaeochromocytomas of the adrenal glands were not statistically increased but exceeded the historic control range (NTP, 2000).

In mice, significant non-neoplastic lesions were present in the bone marrow, olfactory and respiratory epithelia, and the urogenital system. Ulcers and epithelial hyperplasia of the forestomach were present in mice with effects more severe in females. In female mice at 250 ppm, the incidence of combined squamous-cell papilloma of the forestomach was increased, and a single case of forestomach carcinoma occurred. This forestomach finding is associated with prolonged, exposure-induced, irritation leading to hyperplasia and papilloma formation. Liver neoplasms (in particular haemangiosarcoma) were observed in male mice but not female mice (NTP, 2000). Subsequent research indicates that this tumorigenic response is likely to be a consequence of oxidative stress subsequent to RBC haemolysis and haemosiderin deposition in the liver (Boatman *et al*, 2004).

Inhalation studies with 2PG1ME vapour were undertaken in rats and mice, both exposed to 0, 300, 1,000 or 3,000 ppm (0, 1,125, 3,745 or 11,250 mg/m^3) for 2 years, to characterise its chronic toxicity/carcinogenicity. Primary treatment-related effects included: initial sedation of animals exposed to 3,000 ppm; elevated mortality in high-exposure male rats and mice; elevated deposition of $\alpha_{2\mu}$-globulin and associated nephropathy in male rat kidneys and increased occurrence/severity of eosinophilic foci of altered hepatocytes in male rats. No toxicologically relevant, statistically significant increases in neoplasia occurred in either species. A numerical increase in the incidence of kidney adenomas occurred in intermediate-exposure male rats; however, the association with $\alpha_{2\mu}$-globulin nephropathy, a male rat specific effect, indicated a lack of relevance for human risk assessment (Spencer *et al*, 2002).

Inhalation studies with PGTBE have been conducted in rats and mice exposed to 0, 75, 300 and 1,200 ppm (0, 410, 1,650, 6,600 mg/m^3) for 2 years. Survival, haematology and clinical chemistry were unaffected and decreases in body weight occurred in both species at the top dose. Clinical signs were observed in mice at 1,200 ppm. The main target organs were the liver and kidney. Liver adenomas were increased in male rats: the incidence of hepatocellular adenoma/carcinoma increased in top dose male and female mice. Renal tubular degenerations were seen in male rats in all dose groups, with accompanying increases in $\alpha_{2\mu}$-globulin. Marginal increases in the incidences of renal tumours were reported at 300 and 1,200 ppm in male rats (Doi *et al*, 2004; NTP, 2004).

EGEE administered by gavage to rats and mice at dose levels of 0, 500, 1,000 or 2,000 mg/kgbw for 103 weeks produced a high mortality at the highest dose, probably associated with stomach ulceration and this top dose group was terminated after 18 weeks. Testicular atrophy was observed in mice dosed with 1,000 and 2,000 mg/kgbw. Enlargement of the adrenals and reductions in spontaneous gross lesions of the spleen, pituitary and testes compared to controls were seen at 500 and 1,000 mg/kgbw. Chronic treatment with EGEE also caused a decrease in the incidences of enlarged spleens and pituitaries and of subcutaneous (s.c.) masses in the mammary gland region in the aging female rats. Histopathology data are not published for this study, although there was no increase in tumour incidence reported for treated groups (Melnick, 1984). Studies with EGEE did not show leukaemogenic potential (Dieter, 1990).

2.5.1 Evaluation

In conclusion, the six recent studies with glycol ethers have shown some evidence of tumour formation in rats and mice. The predominant mode of action of EGBE is to produce haemolysis, which has resulted in oxidative stress in mouse liver that can be related to haemangiosarcoma. The mouse forestomach response is secondary to a local irritative effect. The four studies with the propylene glycol ethers, 2PG1ME and PGTBE produced male rat specific nephropathy with a low level of related renal tumours. PGTBE also caused an increase in liver hypertrophy and tumours, probably secondary to metabolic adaptation. Each of the tumour responses seen in rats or mice has a mechanism that is either species-specific or reflects a mode of action to which humans are resistant. IARC (2004) concluded that EGBE and PGTBE are not classifiable as to their carcinogenicity to humans (Group 3) on the basis of limited evidence in experimental animals and inadequate evidence in humans.

2.6 Reproductive and developmental toxicity

Several glycol ethers have been evaluated for potential effects on fertility and the developing offspring, with a significant structure-activity relationship emerging. The relationship between structure and reproductive or developmental toxicity of the glycol ethers and their acetates follows the broad principles established for other toxicity endpoints. Oxidation to the respective alkoxyacetic acid is a prerequisite for the expression of both developmental toxicity and testicular atrophy, thus secondary propylene glycol ethers are not toxic. Furthermore, the potency of the toxic glycol ethers decreases as the lengths of the alkyl and alkoxy chains increase; EGME and MAA are the most potent.

EGME, EGMEA, EGEE, EGEEA, EGDME, EGDEE, DEGME, DEGDME, TEGDME, 1PG2ME, and 1PG2MEA have all been shown to cause developmental toxicity, with EGME and EGMEA being the most potent. EGMEA, EGEEA, and 1PG2MEA have a similar degree of

developmental toxicity (both qualitatively and, on a molar basis, quantitatively) as the respective glycol ethers, underlining their rapid de-acetylation. Ethylene glycol ethers with alkyl chains of three or more carbon atoms, and propylene glycol ethers other than 1PG2ME and its acetate, do not express developmental toxicity.

The pattern of developmental effects in a number of species is characterised by a range of structural anomalies (affecting the development of the cardiovascular system, CNS and urogenital system, as well as the skeleton), with foetotoxicity and embryo lethality occurring at higher doses. In the case of the ethylene glycol methyl ethers EGME (and EGMEA), EGDME, DEGME, DEGDME and TEGDME, the developmental effects are mediated by the common metabolite MAA, a conclusion that is supported by the commonality of the effects elicited, and the relationship between potency and conversion to the acid and the developmental toxicity of MAA itself.

Effects upon fertility are largely related to testicular atrophy, characterised by selective degeneration of pachytenic spermatocytes in rodents. As with developmental toxicity, EGME and EGMEA are the most potent of the ethylene glycol ethers, and the effects are all mediated via conversion to MAA. However, the effects of treatment upon the testis generally appear to be reversible on cessation of exposure.

2.6.1 Evaluation

In summary, those glycol ethers that can be metabolised to the low-molecular-weight alkoxy acids can cause developmental effects in animals. Metabolites of the higher molecular weight glycol ethers, such as EGBE, do not produce developmental toxicity. The testicular toxicity of MAA and EAA will alter fertility and, in the absence of these testicular effects, no reproductive toxicity is associated with glycol ethers.

2.7 Absorption, distribution, metabolism and elimination

2.7.1 Absorption and distribution

Glycol ethers and their acetates are readily absorbed following oral administration or inhalation. Dermal absorption is also an important exposure route; penetration rates in human epidermis *in vitro* have shown a rank order for liquid contact: EGME > 2PG1ME > EGEEA > EGEE > EGBE > DEGME > DEGEE > DEGBE (Dugard *et al*, 1984). For EGBE, dermal uptake may account for about 75% of the total systemic exposure in humans during whole-body exposure to EGBE vapour (Johanson and Boman, 1991). Further work provided a lower estimate of 15 to 27% of total systemic exposure through dermal uptake (Corley *et al*, 1997) are necessary to

establish total systemic burden arising from dermal exposure to EGBE vapour and to assess the implications for occupational exposure.

Once absorbed, glycol ethers are readily distributed throughout the body; no substantial accumulation of the parent compound has been observed. However, the alkoxyacetic acid metabolites of EGME (MAA) and EGEE (EAA) have shown evidence of accumulation in animals and humans (Scott *et al,* 1989; Groeseneken *et al,* 1989a,b; Ghanayem *et al,* 1990; Medinsky *et al,* 1990); in contrast, the metabolite of EGBE (BAA; half-life of elimination 5.77 h) shows no evidence of significant accumulation (Johanson *et al,* 1986a).

2.7.2 Metabolism and elimination

Glycol ethers follow two main oxidative pathways of metabolism, either via ADH or the microsomal CYP mixed function oxidase (MFO) (O-demethylation or O-dealkylation). The first pathway gives rise to the formation and excretion of alkoxyacetic acids. The second mainly leads to the production and exhalation of carbon dioxide (CO_2) via ethylene glycol (MEG) or propylene glycol, which enter intermediary metabolism via the tricarboxylic acid (TCA) cycle. In addition to these two pathways, conjugation with sulphate, glucuronic acid or glycine has also been reported.

Glycol ether acetates are rapidly hydrolysed *in vivo* to the parent glycol ethers by plasma esterases; this is consistent with the view that the metabolism of the acetates is similar to that of the parent glycol ether.

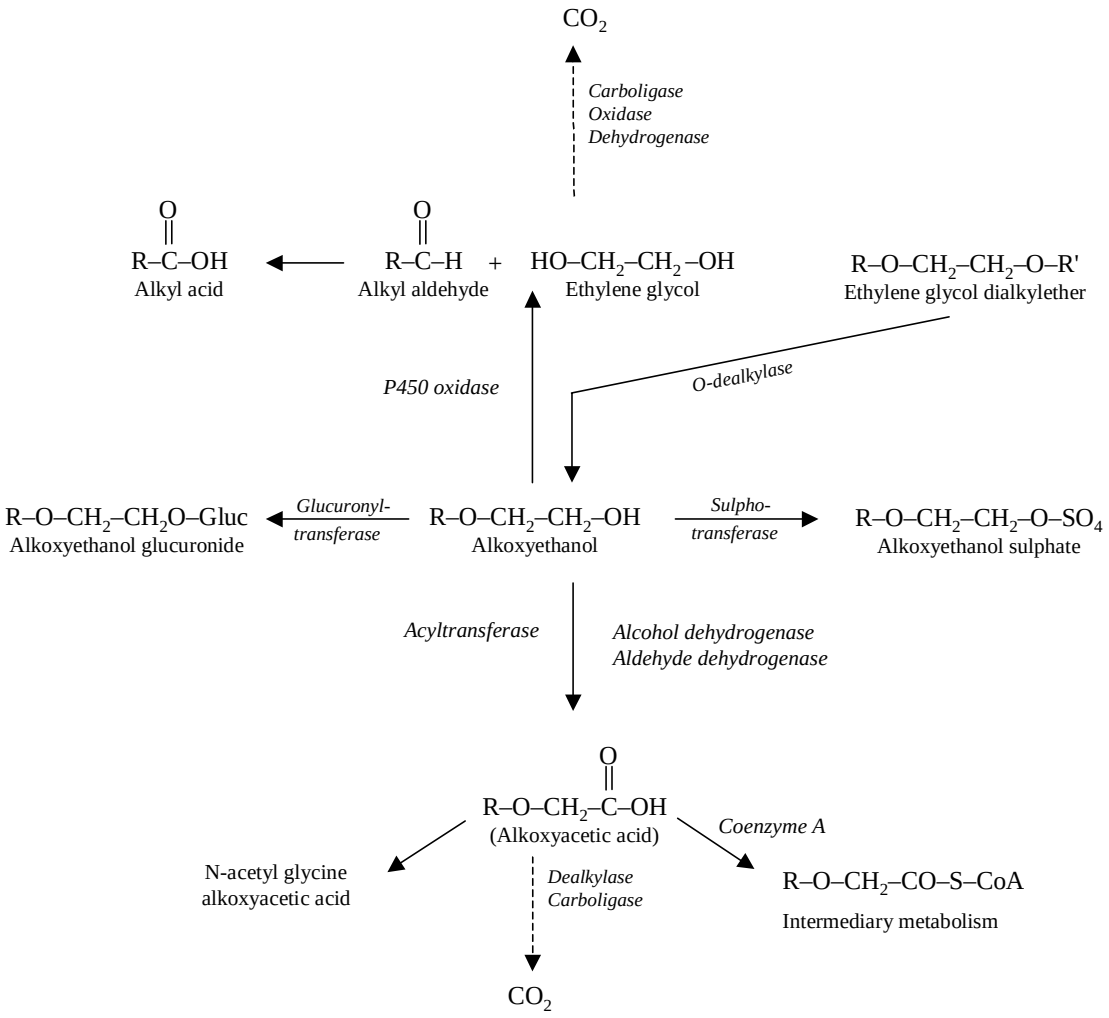
According to their pathways of metabolism, the glycol ethers may be divided into three groups:

- Ethylene glycol mono- and di-alkyl ethers and their acetates;
- diethylene glycol mono- and di-alkyl ethers and their acetates;
- propylene glycol ethers.

Mono-ethylene glycol ethers

All mono-ethylene glycol ethers bearing a primary OH-group (alkoxyethanols) are primary alcohols that are oxidised via ADH and aldehyde dehydrogenase (ALDH) to their corresponding alkoxyacetic acids. Thus, for example, EGME and EGEE, and their corresponding acetates, are predominantly metabolised to MAA and EAA; EGBE is metabolised to BAA (Figure 1, starting at centre). It is noted that mono-propylene glycol mono-alkyl ethers with a primary OH function (*n*-alkoxypropanols) follow similar pathways yielding alkoxypropionic acid (Figure 3) (this section, below).

Figure 1: Metabolic pathways of mono-ethylene glycol mono-alkyl ethers (alkoxyethanols)[a] and mono-ethylene glycol di-alkyl ethers[b]



[a] EGME (EGMEA), EGEE (EGEEA), EGiPE, (EGiPEA), EGnPE (EGnPEA), EGPhE and EGBE (EGBEA)

[b] Glymes: EGDME and EGDEE (below)

The toxicity profiles of these acids are very similar to their parent compounds. Investigations *in vivo* and *in vitro* have shown that nearly all effects of this group of glycol ethers are mediated by these metabolites. The only exception, so far, is PhAA that appears to be less haemolytic *in vitro* than the parent substance EGPhE. In the case of EGBE and EGPE (*i*- and *n*-) it was shown that the parent compounds are practically devoid of haemolytic activity. It is the bioavailability of MAA and EAA (in terms of peak concentration and area under the curve [AUC]) that determines the myelotoxic, spermatotoxic and developmentally toxic properties of EGME and EGEE. Likewise, the same appears to be true for 2-MPA as the active metabolite of 1PG2ME.

The bioavailability of these metabolites depends largely on the dose but also the metabolic rate and species. There is evidence that MAA, and to a lesser extent also EAA, are fairly slowly excreted and that the excretion rates appear to be slower in larger organisms (such as rabbits or primates) than in rats and mice. This slow excretion rate is presumably the major reason why 1PG2ME and thus 2-MPA are more teratogenic in rabbits than in rats.

To some extent, MAA undergoes further metabolism. The identification of 2-methoxy-N-acetylglycine in the urine of EGME-exposed mice indicates that MAA may bind to coenzyme A (Mebus *et al*, 1992) and is incorporated into the intermediary metabolism. Sumner *et al* (1991, 1992) identified several metabolites after entry of the reactive thio-ester into common cellular pathways (TCA cycle; fatty acid biosynthesis). Though MAA is not overtly cytotoxic, the pattern of *in vivo* effects indicated that at least specific target cells may be affected, either by interference with the energy metabolism in the TCA-cycle as a "false substrate" and/or a reduced availability of small carbon units necessary for purine and pyrimidine nucleotide synthesis. Such mechanisms might be expected to disrupt cell proliferation and normal differentiation in critical stages, but the precise mechanism remains to be elucidated. Interestingly, simple physiological compounds (e.g. serine, formate and acetate) that may be introduced into the TCA cycle or tetrahydrofolate (THF) metabolism are able to protect against EGME/MAA-induced malformations and testicular lesions (Welsch *et al*, 1987; Mebus and Welsch, 1989; Mebus *et al*, 1992**;** Clarke *et al*, 1991a).

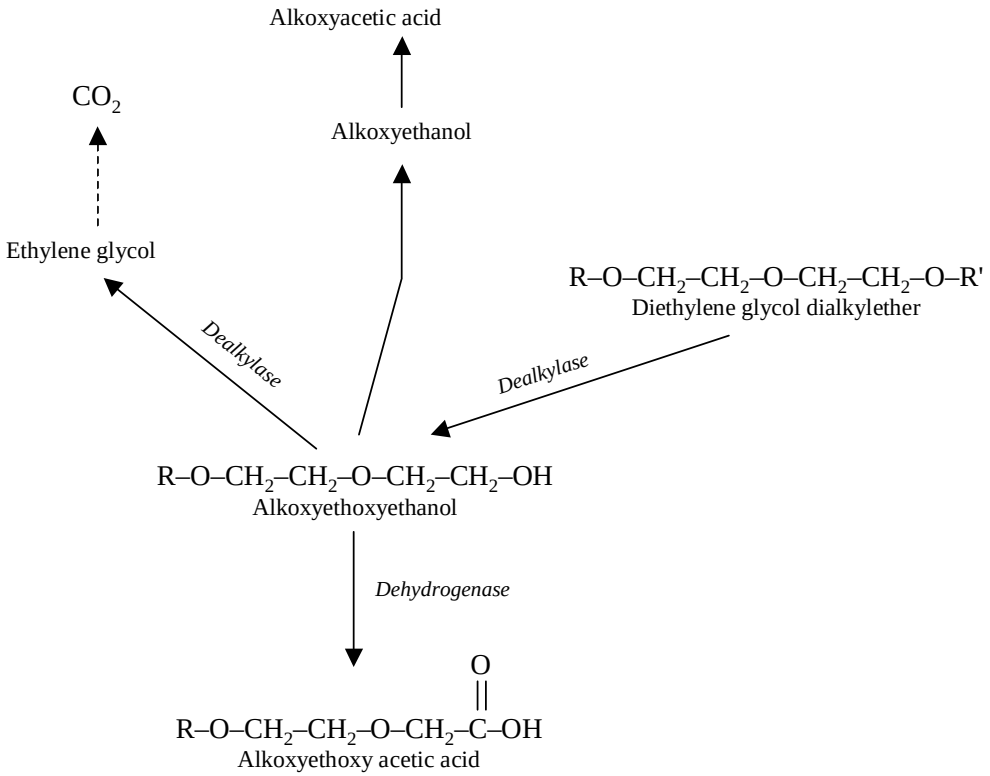
In addition to ADH-mediated oxidation of glycol ethers bearing a primary alcohol function, microsomal oxidation (catalysed by CYP MFO: O-demethylation or O-dealkylation) may also occur in male rats (Medinsky *et al*, 1990) or in pregnant mice (Clarke *et al*, 1991b) and lead to cleavage of the ether bond (Figure 1). This pathway has a rather low capacity and may be saturated but possibly also induced by repeated administrations. At a single dose of 5 mg/kgbw i.v., approximately 30% of EGME underwent oxidative cleavage to MEG; with a high single or repeated (and teratogenic) dose of EGME (100 mg/kgbw and above) only a few percent was metabolised by this route (Clarke *et al*, 1991b; Sabourin *et al*, 1992b). Though MEG itself exerts some developmental toxicity in rodents at high doses (≥ 500 mg/kgbw/d) (Price *et al*, 1985; Tyl *et al*, 1988), this pathway has no significance for the developmental and other typical effects of EGME.

Alkoxyacetic and alkoxypropionic acids are the most relevant biomonitoring parameters in exposed humans (Section 3.1.4.1). MAA was the major urinary metabolite in human volunteers exposed to 16 mg EGME/m^3 (5 ppm) (Groeseneken *et al*, 1989a; Scott *et al*, 1989). Some investigations showed that MAA and EAA concentrations in exposed individuals have a tendency to increase over the course of a working week and decrease to some extent over the weekend. This is consistent with the respective half-lives of elimination of 77.1 (Groeseneken *et al*, 1989a) and 24 hours (Groeseneken *et al*, 1986a, 1987a).

Di-ethylene glycol ethers

Diethylene glycol ethers being etherified at only one OH function (alkoxy-ethoxy-ethanols) such as DEGME, may undergo a low level formation of ether cleavage and formation of alkoxyacetic acids such as MAA (Figure 2, centre). DEGME is a weak developmental and testicular toxicant that may act via such a mechanism. DEGEE has not shown these effects.

Figure 2: Metabolic pathways of diethylene glycol mono-alkyl ethers (alkoxy-ethoxy-ethanols)[a] and diethylene glycol di-alkyl ethers[b]



[a] DEGME, DEGEE (DEGEEA) and DEGBE (DEGBEA)
[b] Glymes: DEGDME and DEGDEE

Glymes

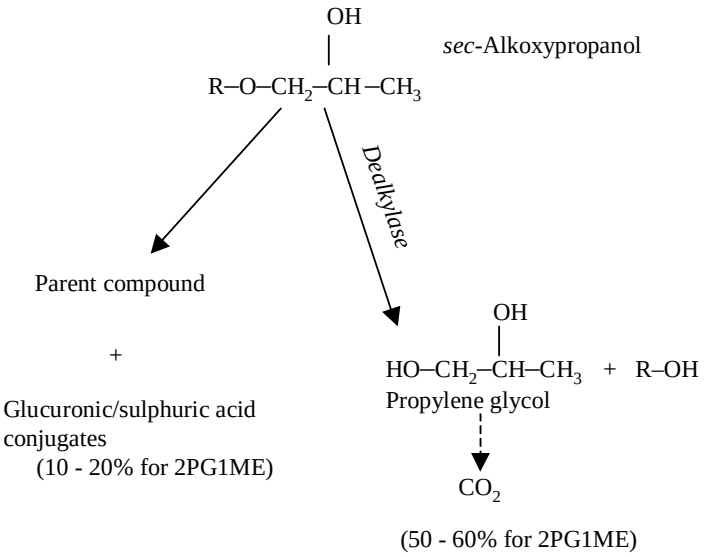
Glycol ethers with both alcohol groups etherified (so-called glymes) may undergo oxidative ether cleavage to the mono-etherified compounds and alkoxy acids (upper right in Figure 1 for mono-ethylene glycol dialkyl ethers; Figure 2 for diethylene glycol dialkyl ethers). This process appears to be much dependent on metabolic status and has a higher capacity following enzyme induction; thus it is facilitated either by repeated administration or by co-administration of other enzyme

inducers. The propensity to produce MAA after oxidative cleavage is the reason why EGDME and DEGDME are developmental and testicular toxicants; MAA is the main metabolite. EGDEE and DEGDEE did not cause selective testicular or developmental toxicity in rats, mice or rabbits though one would expect the formation of EAA. This could be due to EAA having a 5-fold lower developmental and testicular toxicity as EGME/MAA. Dipropylene glycol dialkyl ethers are presumed to be metabolised by similar pathways.

Propylene glycol ethers

Mono-propylene glycol mono-alkyl ethers etherified at the primary carbon (*sec*-alkoxypropanols) are secondary alcohols that cannot be metabolised to alkoxypropionic acids (Figure 3). These compounds are either renally excreted after conjugation or, to some extent may form ketones that may enter the intermediary metabolism via the TCA cycle, eventually to CO_2. Propylene-based glymes may apparently bond to the formation of β-isomers (and 2-MPA and homologues). Also di- and tri-propylene glycol ethers such as DPGME and TPGME contain four or more isomers and are theoretically capable of forming 2-MPA, but metabolism studies have shown that this does not occur at a toxicologically hazardous level. The main metabolic route is therefore via dealkylation. The parent compound, DPGME, dipropylene glycol and the sulphates and glucuronides of DPGME have been identified as main urinary metabolites (Calhoun *et al*, 1986a,b; Miller, 1987).

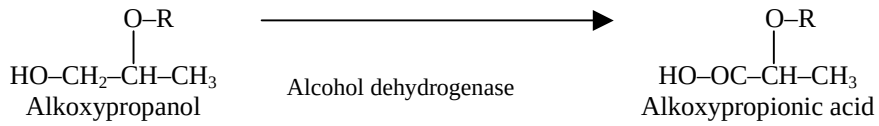
Figure 3: Metabolic pathways of propylene glycol mono-alkyl ethers with primary ether bond [a]



[a] 2PG1ME (2PG1MEA), 2PG1EE (2PG1EEA), 2PG1PhE and 2PG1BE

Mono-propylene glycol mono-alkyl ethers etherified at the secondary carbon (*n*-alkoxypropanols) are again primary alcohols, that can be oxidised via ADH to their corresponding alkoxypropionic acids (Figure 4), then following similar pathways as in Figure 1. Thus, for example, 1PG2ME (the primary or β-isomer) and its acetate are oxidised to 2-MPA.

Figure 4: Initial metabolic pathways of propylene glycol ethers with secondary ether bond [a]



[a] 1PG2ME (1PG2MEA)

2.7.3 Summary and conclusions

Glycol ethers and their acetates are readily absorbed following oral administration or inhalation. Dermal absorption is also an important exposure route. Once absorbed, glycol ethers are readily distributed throughout the body; no substantial accumulation of the parent compound has been observed.

The above considerations on metabolism and elimination allow the following generalisations to be made:

1. Compounds capable of giving rise to EGME, EGEE and/or their corresponding alkoxyacetic acids (MAA and EAA) exhibit bone marrow depression, and characteristic developmental, testicular and immunological toxicity. Realisation of this potential depends on the extent of formation and retention of the alkoxy acid metabolites.
2. EGDME and EGDEE are potent developmental toxicants which probably act via the formation of EGME (EGEE) and then MAA (EAA).
3. DEGME and DEGDME are also developmental toxicants in rats and mice, but only at high doses; this may be explained by the low level of EGME and MAA formed.
4. DEGEE and DEGDEE give rise to low levels of EGEE and EAA, but neither compound caused selective developmental toxicity in rats, mice or rabbits; DEGEE had no effect on fertility. This is plausible in view of the 5-fold lower developmental toxicity of EGEE/EAA compared to EGME/MAA.
5. Propylene glycol ethers with the ether bond on the primary carbon (2PG1ME, 2PG1EE, 2PG1BE, 2PG1PhE) are secondary alcohols that are primarily metabolised to CO_2; they do

not form alkoxy propionic acids and have not been found to cause selective developmental toxicity.

6. Propylene glycol ethers with the ether bond on the secondary carbon (1PG2ME) are primary alcohols and are predominantly metabolised to 2-MPA. It is presumed that 2-MPA is the developmentally toxic metabolite derived from 1PG2ME.
7. DPGME and TPGME are potentially capable of forming 2-MPA, but metabolism studies have not identified this material in rat urine.
8. Following extensive physiological-based pharmacokinetic (PBPK) modelling of EGBE (Section 4.21.4.7), it was shown that humans do not produce BAA at a faster rate than rats nor do they excrete BAA at a slower rate. Thus, there are no indications of accumulation of BAA in humans. The resistance of human erythrocytes to BAA (in contrast to rodents), therefore, is not considered to be related to a kinetic difference, but to a difference in terms of toxicodynamics and species susceptibility at the cellular level.
9. Glycol ether acetates (esters) are rapidly hydrolysed to their corresponding parent glycol ethers.

2.8 Cardiac sensitisation

Cardiac sensitisation, linked to an increased responsiveness of the heart to the arrythmogenic effects of endogenous catecholamines, has been reported following inhalation of a number of organic solvents (Boon, 1987; Kristensen, 1989). In humans, the condition may be fatal and occurs following deliberate solvent abuse or accidental over-exposure to aliphatic, aromatic or chlorinated solvents (Kristensen, 1989). The underlying mechanism(s) of cardiac sensitisation has not been well elucidated (Baskin, 1995).

A literature search did not reveal any references to published data implicating glycol ethers in cardiac sensitisation (Copestake, 2002).

2.9 Neurotoxicity

EGME has been well recognised for effects on the central and peripheral nervous systems in humans. No such effects have been reported for EGEE or other glycol ethers. The only exception appears to be a single communication on EGPhE, suggesting peripheral nerve effects in humans after high dermal exposures (Morton, 1990) (Section 3.2.2), but this report has a number of confounding factors (Schmuck *et al*, 2000).

EGME (and EGDME) caused behavioural effects in an animal experiment in which inhalation exposure at fairly low levels inhibited active avoidance behaviour in trained rats (Goldberg *et al*, 1964).

No other glycol ether has shown neurological or behavioural effects as far as investigated in specifically designed studies or in the course of normal subchronic studies.

3. HUMAN EXPOSURE AND HEALTH EFFECTS

3.1 Human exposure

The main routes of human exposure to glycol ethers and their acetates are through inhalation and/or the skin. Dermal exposure may occur as a result of contact with both liquid and vapours forms. For some glycol ethers skin penetration is so efficient that dermal absorption is equal to or even exceeds inhalation exposure in contribution to the total systemic exposure (Section 3.1.1)**.** This is accentuated as the vapour pressure of all glycol ethers is generally below 1 kPa at ambient temperature (20 - 25°C), and often considerably lower, reducing the potential for airborne concentrations unless an aerosol is generated or the compound is heated during use. As a consequence, no correlation exists between ambient air concentrations of glycol ethers and body burden in many instances. Hence, biological monitoring that determines systemic exposure, regardless of the route, plays an important role in the assessment of exposure to glycol ethers. For most glycol ethers biological monitoring methods have been developed. Unfortunately, with a few exceptions for the most commonly used glycol ethers, such as EGME(A), EGEE(A) and EGBE(A), most of the available biological monitoring methods have not been adequately validated (Section 3.1.4).

Further work is recommended with respect to validating biological monitoring methods, in particular in relation to (i) correlation with airborne values and (ii) the availability of good reference materials such as metabolite standards and appropriate biological limit values. In addition, only limited exposure data are currently available to characterise exposure of downstream users and consumers. It is advised to obtain data for these groups covering both qualitative (e.g. frequency, duration and control measures used) and quantitative exposure determinants which address personal air measurement and biological monitoring.

3.1.1 Human volunteer studies

In a number of human volunteer studies, healthy subjects were exposed to EGME, EGEE, EGBE or 2PG1ME to determine and compare inhalation and dermal exposure.

The respiratory uptake of EGME and the urinary excretion of its major metabolite MAA were measured in 7 resting male subjects exposed to 16 mg/m^3 EGME (5 ppm) for 4 hours (cf. TLV [a] of 16 mg/m^3, Section 3.3). The total dose was 0.25 mg EGME/kgbw; respiratory uptake was 76%. There was a rapid increase in the urinary excretion of MAA during exposure and elimination half-life averaged 77.1 hours (range 66 - 90 h), i.e. much longer than in the rat where the half-life was 9 to 13 hours [Aasmoe *et al*, 1999] [Section 4.8.4.7]). On cessation of exposure,

[a] Threshold limit value

the urinary excretion rate was fairly constant for 4 to 6 hours and then showed a slow exponential decrease, with the excretion rate about one third of its maximal level after 120 hours. Approximately 85.5% of the absorbed EGME was excreted as MAA up to 120 hours after exposure, with half of this being excreted during the first 48 hours (Groeseneken *et al*, 1989a).

The dermal uptake of EGME and EGEE, both as liquid and as vapour, was measured in 5 resting volunteers (2 males, 3 females). The forearm and hand (skin surface area approximately 1,000 cm^2) were exposed to EGME at 4,000 mg/m^3 (1,260 ppm) or to EGEE at 3,700 mg/m^3 (990 ppm) for 45 minutes. An area of 27 cm^2 on the forearm was exposed simultaneously to liquid EGME or EGEE for 15 minutes. For comparison to the dermal uptake, a reference inhalation exposure was performed in the same individuals. Each volunteer was exposed through a mouthpiece to vapours of EGME (48 mg/m^3 [15.2 ppm]) and or EGEE (57 mg/m^3 [15.2 ppm]) for 4 x 15 minutes, 10 minutes apart. Uptake was measured by determination of urinary MAA or EAA. Respiratory uptake was about 80%. Vaporised as well as liquid EGME and EGEE were both readily absorbed through the skin. EGME penetrates the skin more rapidly than EGEE, both as vapour (36 versus 19 $mg/cm^2/h$) and as liquid (2.9 versus 0.7 $mg/cm^2/h$). The elimination half-life for MAA and EAA averaged 72 and 42 hours, respectively. Forty-eight hours after exposure only 12% of the absorbed EGME was recovered as MAA, and 14% of the EGEE as EAA. A strong circadian rhythm was observed in the urinary excretion, which was judged due to protein binding of MAA and EAA in the blood and renal re-absorption. It was calculated by the authors (theoretical calculation based on pure EGME or EGEE), that exposure of both hands and forearms to liquid EGME or EGEE during 1 hour would exceed the respiratory uptake at the 8-hour TLV (5 ppm, 16 and 19 mg/m^3 respectively; Section 3.3) by about 100-fold for EGME and by about 20-fold for EGEE. In the case of whole-body and inhalation exposure to vapour, the contribution of the skin to the total uptake would amount to 32 to 55% for EGME and to 40 to 42% for EGEE (Kežić *et al*, 1997).

Five male subjects were exposed (whole-body, closed chamber) at rest to EGEE vapour concentrations of 10, 20 or 40 mg/m^3 (2.7, 5.3 or 10.7 ppm) (TLV 5 ppm, 19 mg/m^3); a further 5 male subjects were exposed to EGEE vapour (20 mg/m^3) at rest and during physical exercise (30 or 60 Watt) for 4 hours. EAA was determined in urine samples collected over 42 hours. Maximal excretion of EAA was reached 3 to 4 hours after the end of the exposure period and the elimination half-life of EAA was 21 to 24 hours; around 23% of the absorbed EGEE was excreted as EAA within 42 hours. The excretion of urinary EAA was dose-related to EGEE uptake and also to pulmonary ventilation rate during physical exercise (Groeseneken *et al*, 1986a,b). In a separate study, similar results were reported for EGEEA (Groeseneken *et al*, 1987a,b).

The uptake of EGBE and the excretion of the urinary metabolite BAA were measured in 7 male volunteers exposed to 20 ppm EGBE (100 mg/m^3) for 2 hours during light physical exercise

(50 Watt). The respiratory uptake rate averaged 10 µmol/min, and blood levels of EGBE indicated that approximately 57% of inhaled EGBE was absorbed; the half-life of EGBE in the blood was approximately 40 minutes. EGBE blood concentrations flattened out after about 2 hours at around 7.4 µmol/l (870 µg/l). Maximal urinary excretion of BAA was recorded 5 to 12 hours after the start of exposure, with an elimination half-life of 5.77 hours. Less than 0.03% of the absorbed dose was excreted in the urine as EGBE (Johanson *et al*, 1986a).

The percutaneous absorption of EGBE was investigated in 12 experiments using 5 men who kept 2 or 4 fingers immersed in undiluted EGBE for 2 hours. Capillary blood samples collected from the unexposed hand were analysed for EGBE before, during and up to 4 hours after exposure. Urine was collected for 24 hours and analysed for BAA. The presence of EGBE in blood and of BAA in urine confirmed dermal uptake of EGBE. Percutaneous uptake rates ranged from 0.42 to 5.76 µmol/cm^2/h (mean 1.56 µmol/cm^2/h). The results indicated that exposure of large areas of skin to EGBE may result in significant absorption of the material by this route (Johanson *et al*, 1988).

In further dermal absorption studies, 4 male volunteers were exposed by inhalation only or whole-body (naked) without inhalation to 50 ppm EGBE vapour (245 mg/m^3). Capillary blood samples were collected at regular intervals and analysed for EGBE. Two experiments separated by at least two weeks were carried out with each volunteer. Blood EGBE levels were 2 to 3 times higher following whole-body exposure compared to inhalation exposure at 23°C (29% humidity) and 4 to 5 times higher at 33°C (71% humidity). Dermal uptake of EGBE might, according to the authors, therefore account for about 75% (45 - 85% in individual experiments) of the total uptake during whole-body exposure (Johanson and Boman, 1991). This relatively high estimate of the dermal contribution to the total exposure would be expected for exposure to liquid EGBE but is quite unexpected for exposure to EGBE vapour. This is based on the anatomical structure and physiological properties of the lung and the skin with regard to vapour exchange (lungs receive 100% of the cardiac output and skin only 3% and the surface area of the lungs (30 - 100 m^2), which is much larger than that of the skin, approximately 1.9 m^2).

The most likely explanation is that the authors made a wrong assumption in considering blood collected from a fingertip prick to represent systemic arterial ("general") blood. It is more likely that such blood samples represent venous blood drained from the skin prior to dilution with pooled venous blood. Based on this assumption, a PBPK model predicted that dermal exposure to EGBE vapour would contribute no more than 20% to the systemic dose (Corley *et al*, 1994). Further modelling, based on blood and urine concentrations of EGBE, BAA, and BAA conjugates predicted that even under worst-case circumstances (no clothing, 100% of the body exposed) no more than 15 to 27% of the total uptake (depending on temperature and relative humidity) could be attributed to dermal uptake when exposed for 8 hours to 25 ppm EGBE (123 mg/m^3). During moderate physical exercise (50 - 100 Watt), i.e. taking into account more

realistic exposure conditions, the percentage of dermal contribution to total uptake would drop to 5 to 9% (Corley *et al*, 1997).

Six volunteers (4 males and 2 females) were exposed to 100 ppm 2PG1ME vapour (375 mg/m^3) for 8 hours including a 30-min break after 4 hours. Blood, breath and urine samples for the determination of 2PG1ME were collected from all volunteers before, during and up to 24 hours after the exposure. 2PG1ME was readily absorbed with rapid alveolar uptake and elimination. A steady state for 2PG1ME in alveolar air was reached within 1 hour. 2PG1ME was rapidly cleared from the lungs. Blood levels of 2PG1ME rose steadily throughout the exposure. Post-exposure blood levels of up to 103 μmol/l were attained. The mean elimination half-life was 93 minutes (range 81 - 111 min). Urinary levels of 2PG1ME ranged from 78 to 110 μmol/l (average 92 μmol/l) at the end of exposure. Results were more consistent when expressed in μmol/l than when corrected for urine volume or creatinine. The urinary half-life averaged 120 minutes (range 50 - 151 min) and elimination was virtually complete after 16 hours (Jones *et al*, 1997).

In another study, 4 volunteers were exposed to 2PG1ME vapour at a concentration of 100 ppm (375 mg/m^3) for 4 hours, on two different occasions (at least a week apart), once without and once with respiratory protection (air-fed half-masks). Samples collected to determine the exposure included blood, before and immediately after the exposure (0 and 4 h), breath (0 and 4 h and then every 15 min for up to 7 h) and urine (0 and 4 hours and then at intervals up to 22 h). All samples were analysed for 2PG1ME. The percentage dermal uptake was calculated from the 4-hour blood sample, the combined breath samples from the first 0.5 hour after exposure, and the combined urine samples over the total collection period. There was considerable inter-individual and intra-individual variation, which was largest for breath and blood samples and smallest for urine samples. The relative contribution of dermal uptake was 4.2 ± 1.7% based on the urine samples, and approximately 10% based on blood or breath samples. The mean urinary half-life was 1.5 hour (range 1.1 - 2.0 h) after whole-body exposure compared to 2.7 hour (range 1.3 - 4.3 h) after skin-only exposure. This more prolonged elimination following dermal uptake is also found with other solvents (Brooke *et al*, 1998).

The above human volunteer studies indicate an inverse relationship between the urinary elimination half-life of alkoxyacetic acids and the length of the alkyl chain of the glycol ether (BAA 5.77 h, EAA 21 - 42 h, MAA 72 - 77 h) and are suggestive of a similar relationship between the blood half-life of the glycol ethers and the length of their alkyl chain (EGBE 42 min, 2PG1ME 93 min).

A consistent urinary sampling pattern is important when using urinary alkoxyacetic acids as biomarkers for exposure to glycol ethers to reduce the variability in results. This is further commented on under Section 3.1.4.

3.1.2 Consumer exposure

Consumer products containing certain glycol ethers are widespread and many people in the general population may be exposed to a limited number of these materials, although actual exposure data are difficult to obtain. Sometimes, occupational exposure data may be read across to consumers, with appropriate adjustment factors to take account of the significantly lower exposure frequency and duration of consumers, resulting in lower overall exposures. Particular reference is made to the surveys of Vincent *et al* (1993) on window cleaning (EGBE), Vincent *et al* (1994) on paint stripping (EGEEA), Vincent *et al* (1996 cited by INSERM, 1999) on car washing (EGBE), cleaning (EGBE) and house painting (EGBE and EGBEA), and Norbäck *et al* (1996) on house painting (DEGBE, DEGEE, EGBE, DPGME, DEGME and DEGBEA) (Section 3.1.3). Other surveys specifically identifying consumer exposure are given below.

Procter and Gamble (1985) determined potential inhalation and dermal consumer exposure from the use of a hard surface cleaner containing DEGBE. The cleaner was diluted to 1.5% (0.06% DEGBE) and used to wash the floor, wall tiles, window and mirror of a typical bathroom with sealed room openings (area 146 square feet [15 m^2], volume 10.4 m^3) for 20 minutes. DEGBE vapour concentrations during the washing task were below the detection limit (0.01 ppm). Thereafter it rose steadily to around 0.06 ppm at 1.5 to 3 hours and then declined to below the detection limit at 24 hours. *In vitro* human skin penetration studies with cleaning product containing 4% DEGBE indicated a calculated maximum consumer exposure to DEGBE of 0.047 mg/kgbw for use of 3 minutes. Total daily consumer exposure to DEGBE from inhalation and topical exposure was estimated to be 0.059 mg/kgbw/d.

Using *in vitro* human skin penetration data, the maximum consumer exposure from hands-only use of an undiluted cleaning product containing 4% DEGBE for 3 minutes was estimated to be 0.047 mg/kgbw. Use of diluted cleaner (1.5% dilution) for 30 min/d would result in a dermal exposure of 0.0025 mg/kgbw. The maximum overall exposure by inhalation and topical contact was calculated to be 0.06 mg DEGBE/kgbw/d (Gingell *et al*, 1993). An estimate of consumer exposure to paint containing 0.6% of the acetate ester, DEGBEA, was 0.01 mg/kg/d for an 80-minute daily application (Gingell *et al*, 1993).

Gibson *et al* (1991) simulated domestic exposure of consumers by inhalation of DEGBE from the use of cleaning products containing up to 9% DEGBE. Several experiments with exposures exceeding those likely to be encountered by consumers found that peak airborne concentrations of DEGBE did not exceed 1.6 ppm (10.7 mg/m^3), with average DEGBE concentrations in the breathing zone below 0.8 ppm (5.3 mg/m^3).

A systemic dose for consumers (assuming 100% skin penetration) was estimated for EGPhE used as preservative in cosmetics at 180 mg/person/d, DEGEE as a cosmetic component at

30 mg/person/d, and DEGBE and EGBE, both as used in hair dyes, at 45 and 8 mg/person/application (1 x/4 - 8 wk) respectively. The data were based on these glycol ethers being present at the following maximum concentrations in the relevant products: EGPhE 1% and DEGEE 2% in leave-on and rinse-off cosmetics, DEGBE 9% and EGBE 2% in rinse-off hair dyes (Féderation des Industries de la Parfumerie (2002).

3.1.3 Occupational exposure

The following information comprises workplace exposures in terms of airborne (personal and area) concentrations and biological monitoring data, as far as they are available. The data are presented chronologically according to the date of publication of the source article. Exposure information contained in articles reviewed since the ECETOC (1995) report has been tabulated, where practicable, to assist in subsequent review. Where both airborne measurements and biological monitoring were performed at the same time, these have been included in tandem in the same table. Information on the exposure measurement methods used is summarised in Section 3.1.4.

NIOSH (1983) determined occupational exposures to EGME, EGEE, EGEEA and EGMEA at 8 survey sites in the USA; a total of 151 area and personal air samples were collected and analysed. Only 40% of the samples had detectable levels of glycol ethers, ranging from 0.04 - 2.77 ppm (0.13 - 8.76, 0.15 - 10.37, 0.22 - 15.22 and 0.20 - 13.6 mg/m^3, respectively) for long-term (5 - 8 h) workshift samples and 0.21 to 11.9 ppm (0.66 - 37.7, 0.79 - 44.6, 1.15 - 65.4 and 1.03 - 58.4 mg/m^3, respectively) for short-term (15 min) samples. Most personal concentrations results complied with the US Occupational Safety and Health Administration (OSHA) and American Conference of Governmental Industrial Hygienists (ACGIH) exposure limit values current at the time of the study.

Guest *et al* (1985) reported ambient air concentrations of DEGBEA arising from indoor application of paint containing approximately 0.58% DEGBEA. During painting for 6.33 hours, the maximum exposure concentration was 50 ppm (425 mg/m^3), leading to a maximum uptake of DEGBEA of 190 µg/kgbw/d.

Earlier summarised data on workplace exposure levels in the manufacture of glycol ethers in European plants showed time-weighted average (TWA) personal exposure concentrations ranging from 0.12 to 6.4 ppm EGME (0.38 - 20.2 mg/m^3), 0.01 to 6.5 ppm EGEE (0.04 - 24.3 mg/m^3), 0.02 to 0.2 ppm EGiPE (0.09 - 0.9 mg/m^3) and 0.01 to 2.7 ppm EGBE (0.05 - 13 mg/m^3) (ECETOC, 1985).

The majority of 262 ambient air samples from 78 different Belgian plants and workshops revealed complex mixtures of ethylene glycol ethers with other solvents; the glycol ethers were often minor components. The most frequently identified compounds were EGEE, EGEEA, EGME, EGMEA and EGBE. Most personal exposure levels were far below the respective ACGIH (1984 as cited) occupational exposure limits, but approximately 25% were higher than the TLV. Most excursions were slight (< 1.5 x TLV) or moderate (2 - 2.5 x TLV), although some serious excursions above the TLV were observed (up to 819.5 mg/m^3 [150 ppm] for EGEEA; up to 1,775 mg/m^3 [360 ppm] for EGBE; up to 1,224 mg/m^3 [327 ppm] for EGEE). These latter excursions were recorded in a mirror manufacturing plant but no information to explain the high results were noted (Veulemans *et al*, 1987) (Table 5).

Table 5: Workplace concentrations[a] (mg/m^3) of ethylene glycol ethers in various Belgian industries, with TLVs[b] (mg/m^3) applicable at that time (1984) (Veulemans *et al*, 1987)

Glycol ether	**EGME**	**EGMEA**	**EGEE**	**EGEEA**	**EGBE**	**EGBEA**
Operation / TLV	**16**	**24**	**19**	**27**	**120**	**-**
Printing	-	4.3 (3.9-4.7)	9.8 (0.7 - 182.0)	16.4 (0.3 - 186.8)	4.1 (1.5 - 17.7)	12.7 (4.6-26.5)
Painting	31.3 (5.6 - 136.9)	-	9.5 (1.4 - 210.3)	9.7 (1.2 - 78.6)	18.8 (3.4-93.6)	-
Car repair	7.9 (3.4 - 15.9)	2.3	-	8.9 (1.5 - 42.1)	5.9	-
Various	-	11.6 (0.4 - 143.3)	17.1 (3.1 -1,224)	9.9 (0.6 - 819.5)	8.5 (0.2 - 1,775)	10.6 (8.9-11.7)

[a] Geometric mean and range

[b] Threshold limit values

Clapp *et al* (1987) found urinary EAA concentrations in the range of 16 to 163 mg/g creatinine in 7 workers exposed to EGEE who collected spot urine samples (not timed) on several working days. Separate personal airborne EGEE levels ranged from non-detectable to 23.8 ppm (89.1 mg/m^3).

In 5 women with daily exposure to a mixture of EGEE and EGEEA the urinary excretion of EEA was measured during a 5-day period of normal production and 7 days following a 12-day production stop. Urinary EAA excretion flattened out after the third working day. Elimination of EAA was not complete after the weekends, and traces of EAA could still be detected in the urine even after a non-exposure period of 12 days. (This observation is consistent with the long apparent urinary half-life of EAA found by Kežic *et al*, 1997). A good linear correlation was found between average combined EGEE and EGEEA air levels over 5 days (14.4 mg/m^3) and EAA excretion at the end of the week (106 mg/g creatinine). It was estimated that repeated 5-day

full-shift exposure to either EGEE or EGEEA corresponded to a urinary concentration of 150 ± 35 and 32 mg EEA/g creatinine at the end of the shift or 16 hours after the end of exposure, respectively (Veulemans *et al*, 1987).

Johanson *et al* (1989) found good correlations between EGEEA and EGBE exposure and urinary EAA and BAA excretion, respectively, in 19 workers**.**

Paustenbach (1988) reported on personal and area air samples from 7 different companies in the semi-conductor industry. TWA concentrations of EGME were mainly around 0.1 ppm (0.3 mg/m^3); concentrations of EGMEA were usually lower than 0.01 ppm (0.05 mg/m^3); the average concentration of EGEE was 0.55 ppm (2.06 mg/m^3) and of EGEEA generally less than 0.05 ppm (0.27 mg/m^3).

Sparer *et al* (1988) evaluated exposures of 36 shipyard painters to EGME and EGEE. EGEE exposures ranged from 0 to 80.5 mg/m^3 (TWA), with a mean of 9.9 mg/m^3 and a median of 4.4 mg/m^3. EGME exposures ranged from 0 to 17.7 mg/m^3 (0 - 5.6 ppm) (TWA), with a mean of 2.6 mg/m^3 (0.82 ppm) and a median of 1.6 mg/m^3 (0.5 ppm).

Samples of 2PG1ME collected during manufacturing of paint, metals and plastics had average levels of 2 to 3 ppm (7 - 11 mg/m^3) (Johanson, 1990). Peak levels of 0.5 to 7 ppm 2PG1ME (2 - 26 mg/m^3) were reached in apartments painted with water based alkyd and acrylate paints (Kragh-Hansen, cited by Johanson, 1990). Parquet fitters in Finland were exposed to approximately 35 to 39 ppm 2PG1ME (131 - 146 mg/m^3) during undercoat varnishing and 10 to 63 ppm (37 - 236 mg/m^3) during varnishing (Johanson, 1990).

EGEE and EGEEA concentrations were measured in 17 workers of a varnish production plant by personal air sampling and urinary EAA determination, and EGBE levels by air sampling and urinary BAA determination. Urine samples were taken pre- and post-shift; post-shift EGBE blood levels were also measured. Measurements were only carried out on the second working day. The highest exposures were observed in 12 workers of the varnish production plant. Exposures to EGEE ranged from < 0.1 to 7.8 ppm (mean 2.8 ppm) (< 0.4 - 29.2, 10.5 mg/m^3), EGEEA from < 0.1 to 11.1 ppm (mean 2.7 ppm) (< 0.5 - 61, 14.8 mg/m^3) and EGBE from < 0.1 to 8.1 ppm (mean 1.1 ppm) (< 0.5 - 39.8, 5.4 mg/m^3). Corresponding levels of EAA (combined EGEE and EGEEA exposure) in post-shift urine ranged from 50 to 497 mg/l (mean 168 mg/l) and of BAA from 0.6 to 30 mg/l (mean 10.5 mg/l). EGBE blood levels ranged from non-detectable to 570 μg/l (mean 121 μg/l). High urinary EAA levels (mean 129 mg/l) were measured in pre-shift urine samples, resulting from EGEE and EGEEA exposure the previous day and consistent with the slow elimination rate of EAA. Residual urine levels of BAA (3.3 mg/l) in pre-shift urine were lower than for EAA, consistent with the faster rate of elimination of BAA. There was no significant correlation between concentrations of these glycol ethers in air and levels of glycol

ethers or their metabolites in blood or urine (Angerer *et al*, 1990). In the documentation to the German Biologische Arbeitsstofftoleranzwerte (BAT) [a] values, Angerer states that this is due to extensive dermal contact of the workers and that BAT (and other biological exposure limits) are best based on human volunteer studies where skin contact is carefully avoided (Angerer, 1993).

Personal exposure concentrations of several ethylene glycol ethers were reported across a number of industries in the USA. Monitoring results at several of the sites (particularly aerospace, electronics, automotive, and glycol ether formulation) indicated that airborne concentrations of the glycol ethers were generally non-detectable in all or most areas. This was generally attributed to infrequent usage and handling of only small quantities (often present in low percentages in preparations), the effectiveness of engineering controls (such as local exhaust ventilation, enclosures, dual mechanical seals on pumps and automation) and conscientious work practices (including frequent cleaning/maintenance and proper chemical storage). Job categories with the highest exposure potential were reported as including activities related to transfer and manual handling of glycol ether compounds, e.g. sampling, drum filling and spray application of paints and coatings. The highest reported short-term (15 min) task level of 11.9 ppm EGEEA (65.4 mg/m^3) was noted for spray painting in airline maintenance, however, in this case the use of respiratory protection was observed (Piacitelli *et al*, 1990) (Table 6).

Table 6: Workplace concentrations of some glycol ethers in the USA (Piacitelli *et al*, 1990)

Job	**Glycol ether**	**Number of TWA (task) samples**	**8-h TWA concentration**		**Short-term (15 min) range**	
			(ppm)	**(mg/m^3)**	**(ppm)**	**(mg/m^3)**
Aerospace	EGME	8 (3)	≤ 0.27	(≤ 0.85)	≤ 0.65 -1.04	(≤ 2.06 - 3.3)
Aerospace	EGEE	5	≤ 0.22	(≤ 0.82)	-	-
Aerospace	EGEEA	15 (3)	≤ 0.23	(≤ 1.26)	≤ 0.33 - 0.86	(≤ 1.81 - 4.7)
Electronics	EGEEA	8 (2)	≤ 0.02	(≤ 0.11)	≤ 0.12	(≤ 0.66)
Airline maintenance	EGEEA	13 (5)	0.29 - 2.69	(1.59 - 14.8)	1.73 - 11.9	(9.5 - 65.4)
Coating manufacturing	EGEEA	6 (7)	0.07 - 0.35	(0.38 - 1.92)	0.41 - 1.85	(2.25 - 10.2)
Automotive manufacturing	EGEEA	12 (2)	≤ 0.02 - 0.05	(≤ 0.11 - 0.27)	≤ 0.61	(≤ 3.35)
Fuel distribution	EGME	10 (5)	≤ 0.03 - 0.34	(≤ 0.09 - 1.08)	0.21 - 6.86	(0.66 - 21.7)
Paperboard manufacturing	EGME	9 (3)	≤ 0.04 - 1.06	(≤ 0.13 - 3.35)	≤ 0.22 - 5.25	(≤ 0.70 - 16.6)
Glycol ether manufacturing	EGME	(2)	-	-	≤ 0.20 - 2.45	(≤ 0.63 - 7.75)
Glycol ether manufacturing	EGEEA	31(2)	≤ 0.02 - 0.44	(≤ 0.11 - 2.4)	-	-

2PG1ME was measured in ambient air, blood and urine of operators in a brake-hose production facility (Hubner *et al*, 1992) (Table 7).

[a] Biological tolerance values for working materials

Table 7: 2PG1ME exposure of operators during brake-hose manufacturing (Hubner *et al*, 1992)

Job (number of air samples) / Airborne concentration, 8-h TWA		**Number of samples / Urinary concentration**				**Number of samples / Blood concentration**	
(mg 2PG1ME/m^3)		**(mg 2PG1ME/l)**		**(mg 2PG1ME/g creatinine)**		**(mg 2PG1ME/l)**	
Mean ± sd [a]	**Range**	**Mean ± sd**	**Median, range**	**Mean ± sd**	**Median, range**	**Mean ± sd**	**Median, range**
Actual production (5)		5		6		6	
82.2 ± 31.1	48.0 - 116.6	4.6 ± 3.4	3.2, 1.7 - 9.6	8.5 ± 12.7	3.1, 1.6 - 34.1	13.5 ± 4.4	14.6, 7.3 - 17.7
Leak testing (7)		8		8		8	
68.6 ± 54.0	18.0 - 184.0	4.2 ± 2.1	4.4, 1.3 - 7.2	6.5 ± 6.4	3.8, 0.6 - 14.7	11.0 ± 4.4	10.0, 7.3 - 20.1
Mounting (6)		8		8		8	
11.3 ± 4.4	5.5 - 17.0	ND [b]	ND	ND	ND	ND	ND

[a] Standard deviation

[b] Not detected, assuming 0.5 mg/l limit of detection

The mean excretion half-life of 2PG1ME as determined in the three highest exposed individuals was 4.4 hours. A tentative biological exposure limit of 38 to 109 mg 2PG1ME/l blood or 10 to 31 mg/l urine was established, corresponding to an 8-h TWA air concentration of 375 ppm 2PG1ME (1,404 mg/m^3) (Hubner *et al*, 1992).

Hallock *et al* (1993) reported on worker exposure to EGEEA and EGME in microelectronics manufacture. Full-shift personal air concentrations for EGEEA ranged from 0.001 to 0.64 ppm (0.005 - 3.5 mg/m^3) while short-term task-based exposures were between < 0.002 and 0.043 ppm (< 0.01 - 0.24 mg/m^3). For EGME full-shift exposures were 0.003 to 0.53 ppm (0.009 - 1.68 mg/m^3) and task exposures < 0.002 and 2.3 ppm (< 0.006 - 7.3 mg/m^3).

In a study of 30 silk-screen painters exposed to EGEEA, the 8-h TWA airborne concentration of EGEEA was 12 ppm (range 2.9 - 34 ppm) (66, 16 - 187 mg/m^3) in 12 press operators; in other jobs the levels ranged from 0.7 to 7.6 ppm (3.8 - 42 mg/m^3). The urinary excretion of EAA corresponded well with the air concentrations and ranged from 1.1 to 27 mg EAA/g creatinine in specimens collected at the end of the shift in the second half of the working week. The results indicated that dermal absorption of EGEEA was not a significant problem in that facility (Lowry *et al*, 1993).

Ethylene glycol exposure was studied in 19 workers in a varnish production plant (Table 8) and a group of 14 workers in the ceramic industry (Table 9). In 17 workers (all 14 workers in the ceramics industry and 3 of the varnish manufacturers), the kinetics of EAA were studied during an exposure-free weekend. The median half-life value for excretion was calculated as 57.4 or 63.4 hours, without or with creatinine correction, respectively (Söhnlein *et al*, 1993).

Table 8: Exposure of 19 workers in a varnish production plant (Söhnlein *et al*, 1993)

Workplace (number of operators / Glycol ether	**Average (range) airborne concentration**				**Average (range) urinary metabolite concentration**	
	Monday		**Tuesday**		**Monday**	**Tuesday**
Varnish production (12)	(ppm)	(mg/m^3)	(ppm)	(mg/m^3)	(mg EAA/l)	(mg EAA/l)
EGEE	2.9 (< 0.6 - 15.2)	(11, < 2.2 - 57)	2.1 (< 0.1 - 6.2)	(8, < 0.4 - 23)	53.2 (2.3 - 180)	53.8 (11.1- 43.7)
EGEEA	0.5 (< 0.1 - 3.7)	(2.7, < 0.5 - 20.3)	0.1 (< 0.1 - 0.4)	(0.5, < 0.5 - 2.2)		
Store (2)						
EGEE	< 0.1	(< 0.4)	< 0.1, 0.2	(< 0.4, 0.7)	3.1 (1.9 - 4.3)	3.4 (2.6 - 4.2)
EGEEA	< 0.1	(< 0.5)	< 0.1	(< 0.5)		
Laboratory (4)						
EGEE	< 0.1	(< 0.4)	< 0.1	(< 0.4)	4.4 (1.9 - 6.0)	5.1 (3.9 - 7.6)
EGEEA	0.3 (< 0.1 - 0.4)	(1.6, < 0.5 - 2.2)	0.3 (0.2 - 0.3)	(1.6, 1.1 - 1.6)		
Office (1)						
EGEE	< 0.1	(< 0.4)	< 0.1	(< 0.4)	7.7	9.8
EGEEA	< 0.1	(< 0.5)	< 0.1	(< 0.5)		
Varnish production (12)					(mg BAA/l)	(mg BAA/l)
EGBE	0.5 (< 0.1 - 1.4)	(2.5, < 0.5 - 6.9)	0.6 (< 0.1 - 1.0)	(2.9, < 0.5 - 4.9)	0.2 (< 0.02 - 1.3)	16.4 (0.8 - 60.6)
Store (2)						
EGBE	< 0.1	(< 0.5)	0.1	(0.5)	0.09 (0.05 - 0.12)	0.9 (0.4 - 1.4)
Laboratory (4)						
EGBE	< 0.1	(< 0.5)	< 0.1	(< 0.5)	0.04 (< 0.02 - 0.12)	1.6 (0.1 - 5.1)
Office (1)						
EGBE	< 0.1	(< 0.5)	< 0.1	(< 0.5)	< 0.02	0.9

Table 9: Urinary excretion of EEA in 17 workers (14 in ceramic industry and 3 in varnish production) (Söhnlein *et al*, 1993)

	Average (median)		Range	
Concentration	**(mg/l)**	**(mg/g creatinine)**	**(mg/l)**	**(mg/g creatinine)**
Friday, post-shift urine	44.8 (29.8)	41.3 (27.6)	4.5 - 196.9	2.0 - 156.3
Monday, pre-shift urine	19.3 (10.7)	17.1 (11.6)	3.1 - 85.1	1.3 - 79.2
Calculated half-life	**(h)**	**(h)**	**(h)**	**(h)**
	74.3 (57.4)	82.0 (63.4)	69.6 - 250.7	24.8 - 240.1

A good correlation was observed between urinary BAA collected in 6 workers in a semi-conductor factory, engaged in polymerisation of resin dissolved in EGBE, at the end of the shift and airborne concentrations of EGBE during the shift. The airborne concentrations correlated better to the total BAA (r = 0.76, after acid hydrolysis of the conjugates) than to the either free BAA (r = 0.50) or conjugated BAA (r = 0.72). Creatinine correction slightly ameliorated the correlation (r = 0.78). The percentage of conjugated versus total BAA varied from 44% to 92% and decreased over the working week. Hydrolysis of the urine samples prior to analysis to determine free BAA seems essential for more reliable determination of the total body burden (Sakai *et al,* 1994), an observation also found by other investigators (Rettenmeier *et al*, 1993; Corley *et al*, 1997).

Occupational airborne exposures to EGBE and post-shift urine concentrations of BAA during use of window cleaning products were reported by Vincent *et al* (1993) (Table 10).

Table 10: Concentrations of EGBE in personal air and BAA in post-shift urine in window cleaners (Vincent *et al*, 1993)

Job (No. of operators)	**Airborne EGBE concentration, 8-h TWA**				**Urinary BAA**	
	Mean ± sd [a] (No. of samples)		**Range**		**Mean ± sd (No. of samples)**	**Range**
	(ppm)	**(mg/m^3)**	**(ppm)**	**(mg/m^3)**	**(mg/g creatinine)**	
Cleaning new car windows (7)	2.33 ± 2.44 (15)	(11.4 ± 12)	< 0.10 - 7.33	(< 0.49 - 36)	111.3 ± 99.1 (12)	12.7 - 371
Cleaning used car windows (6)	0.36 ± 0.41 (15)	(1.77 ± 2.0)	< 0.10 - 1.52	(< 0.49 - 7.47)	6.3 ± 6.7 (11)	< 2 - 24.4
Office cleaner of windows, half shifts (8)	0.32 ± < 0.1 (32)	(1.57 ± < 0.5)	< 0.30 - 0.73	(< 1.47 - 3.59)	2.1 ± < 1 (32)	2 - 3.3

[a] Standard deviation

A log-log correlation between EGBE exposure and BAA in urine was poor (r = 0.603), but statistically significant ($p < 0.001$). A better (r = 0.963, $p < 0.001$) log-log correlation was observed between BAA in urine and the quantity of cleaning product used, suggesting that dermal exposure was the most significant route of exposure as protective gloves were used only by 2 of 29 persons sampled (Vincent *et al*, 1993). These results may also be applicable as an indicator of consumer exposure albeit at lower levels (Section 3.1.2).

During paint stripping and painting operations a group of workers exposed to a variety of organic solvents, including EGEEA, was monitored by personal air sampling and biological monitoring

of EAA (Vincent *et al*, 1994) (Table 10). These results may also be applicable as an indicator of consumer exposure albeit at lower levels (Section 3.1.2).

Table 11: Exposure to EGEEA in paint strippers and painters (Vincent *et al*, 1994)

Day	Number of operators	Airborne concentration (mg/m^3, 8-h TWA)		Uninary concentration (mg EAA/g creatinine)			
				Pre-shift		Post-shift	
		Mean ± sd	Range	Mean ± sd	Median, range	Mean ± sd	Median, range
1	5	110 ± 29	81 - 150	125 ± 100	106, 55 - 297	117 ± 72	99, 25 - 197
2	9	63 ± 29	29 - 144	109 ± 52	81, 59 - 200	150 ± 59	139, 81 - 237
3	9	73 ± 27	38 - 127	98 ± 37	98, 38 - 160	141 ± 49	133, 82 - 215

Full-shift exposures to 2PG1EE solvent contaminated with 1-propylene glycol 2-ethyl ether (1PG2EE) (8%) during colour rotagravure printing were 6.5 to 34.1 mg 2PG1EE/m^3 (median 15.3 mg/m^3) and 0.9 to 3.9 mg 1PG2EE/m^3 (median 1.9 mg/m^3). Post-shift urine sampling showed levels of 2PG1EE of 0.2 to 2.8 mg/l (median 0.8 mg/l), without significant correlation with low airborne exposure to 2PG1EE; levels of 2-ethoxypropionic acid (2-EPA) of 2.8 to 37.2 mg/l (median 21.9 mg/l) showed a fair correlation ($r = 0.657$, $p < 0.05$) with airborne exposure to 1PG2EE (Bader *et al*, 1996).

Hammond *et al* (1996) reported full-shift and short-term task exposures to EGEEA and 2PG1MEA during micro-electronics manufacture (Table 12).

Table 12: Exposure to EGEEA and 2PG1MEA during micro-electronics manufacture (Hammond *et al*, 1996)

Glycol ether	Number of TWA (task) samples	Airborne concentration, 8-h TWA				Short-term concentration	
		Mean ± sd		Geometric mean ± sd		Range	
		(ppb)	(µg/m^3)	(ppb)	(µg/m^3)	(ppb)	(µg/m^3)
EGEEA	23 (12)	64 ± 148	(352 ± 813)	22 ± 3.7	(121 ± 20.3)	< 2 - 110	(< 11 - 605)
2PG1MEA	20 (46)	12 ± 14	(66 ± 77)	8 ± 2.5	(44 ± 14)	< 2 - 2,300	(< 11 - 12,640)

Vincent *et al* (1996 cited by INSERM, 1999) reported further surveys for a range of glycol ethers across a number of industries. The airborne glycol ether and urinary metabolite concentrations are shown in Table 13. The data on car washing (EGBE), cleaning (EGBE) and house painting (EGBE and EGBEA) may also be applicable as an indicator of consumer exposure albeit at lower levels (Section 3.1.2).

Table 13: Further surveys of industrial exposure to glycol ethers (Vincent *et al*, 1996 cited by INSERM, 1999)

Job (number of operators)	Glycol ether	Airborne concentration, 8-h TWA mean (range)		Biomarker	Urinary concentration, mean (range)	Remark
		(ppm)	(mg/m^3)		(mg/g creatinine)	
Aerospace (20)	EGEEA	14.8 (5.4 - 27.6)	(81.3, 29.7 - 151.7)	EAA	109 (2 - 237.4)	Respiratory protection equipment worn: exposure mostly dermal to liquid and vapour
Car washing (13)	EGBE	- (0.1 - 7.2)	(- , 0.5 - 35.4)	BAA	96.5 (7.4 - 371)	
Printed circuit manufacturing (13)	EGME	2.3 (0.1 - 18.1)	(7.3, 0.3 - 57.3)	MAA	39.2 (2 - 121.4)	
Cataphoresis (12)	EGBE	0.8 (0.1 - 6.2)	(3.9, 0.5 - 30.5)	BAA	17.9 (ND - 210)	Dermal route major contributor to exposure
Silk screen printing (110)	EGEEA	2.6 (0.1 - 20.6)	(14.3, 0.5 - 113)	EAA	- (0.1 - 20.6)	Dermal route major contributor to exposure
Cleaning (17)	EGBE	- (< 0.1 - 0.4)	(< 0.5 - 2.0)	BAA	- (< 0.1 - 0.4)	May duplicate some data from Vincent *et al* (1993)
Can coating (143)	EGEE(A)	-		EAA	10	
Metal frameworks (23)	EGEE(A)	-		EAA	9.6	
Paint manufacturing (248)	EGEE(A)	-		EAA,	10.1	
	EGBE(A)			BAA,		
	EGME			MAA		
Furniture manufacturing (50)	EGEE(A)	-		EAA,	9.1	
	EGBE(A)			BAA,		
	EGME			MAA		
Metallic packaging (79)	EGEE(A)	-		EAA,	7.5	
	EGBE(A)			BAA		
Auto paint(20)	EGEE(A)	-		EAA	7.1	
Plastics manufacturing (19)	EGEE(A)	-		EAA	6.9	
Pad printing (29)	EGEE(A)	-		EAA,	4.8	
	EGBE(A)			BAA		
Use of cutting fluids (13)	EGBE	-		BAA	3.2 (< 2 - 8.3)	

Table 13: Further surveys of industrial exposure to glycol ethers (cont'd) (Vincent *et al*, 1996 cited by INSERM, 1999)

Job (number of operators)	Glycol ether	Airborne concentration, 8-h TWA mean (range)		Biomarker	Urinary concentration, mean (range)	Remark
		(ppm)	(mg/m^3)		(mg/g creatinine)	
Offset printing (11)	EGBE(A)	-		BAA	2.2	
House painting (63)	EGBE(A)	-		BAA	< 2 (< 2 - 13.2)	

ND, not detected

Norbäck *et al* (1996) reported full-shift exposures for a range of glycol ethers during (industrial) house painting with water-based paints (Table 14). These results may also be applicable as an indicator of consumer exposure albeit at lower levels (Section 3.1.2).

Table 14: Personal full-shift air concentrations (mg/m³) of glycol ethers in house painters using water-based paints (Norbäck *et al*, 1996)

	Number of samples	Range	Mean	Geometric mean
DEGBE	20	< 0.01 - 8.1	0.8	0.02
DEGEE	20	< 0.01 - 4	0.2	0.007
EGBE	20	< 0.01 - 0.7	0.05	0.008
DPGME	20	< 0.01 - 3.2	0.2	0.009
DEGME	< 20	< 0.01 - 0.02	0.002	-
DEGBEA	< 20	< 0.01 - 0.16	0.001	-

Wesolowski and Gromiec (1997) reported exposures to various glycol ethers used by different paint and lacquer manufacturers (Table 15).

Table 15: Mean personal air concentrations (mg/m³) during paint and lacquer manufacturing (Wesolowski and Gromiec, 1997)

Glycol ether	Type of plant				
	Airtight mill	Old mill, limited space	Non-airtight mill, primitive solvent handling	Small plant, ball mill, old resin plant	Modern plant, high volume production
Number of samples:	**23**	**28**	**27**	**26**	**75**
2PG1MEA	0.1	ND	ND	ND	ND
EGBE	0.3	0.4	0.3	0.2	0.1
EGEE	0.1	0.1	0.1	0.1	0.1
EGEEA	0.3	0.1	0.1	0.1	0.1
EGMEA	0.1	0 [sic]	0.1	0.1	0.1

ND, not detected

The correlation between EGME exposure and urinary excretion of MAA was studied in operators of a circuit board manufacturing plant. Daily personal air samples and urine samples were collected on 6 consecutive days from 18 operators and 30 non-exposed controls. No MAA was found in the urine of the non-exposed workers. In exposed workers, highly significant correlations were observed between the urinary MAA at the end of the shift on the 5th working

day and the average exposure over the 5 preceding days (r = 0.702, p = 0.001) and between the weekly increase of urinary MAA and the average exposure over the 5 preceding days (r = 0.741, p = 0.0007). Biological exposure limits, corresponding to exposure (8 h/d) to 5 ppm EGME for 5 days, were 40 mg/g creatinine at the end of the shift or a weekly increase of MAA of 20 mg/g creatinine (Shih *et al*, 1999a).

Two groups of shipyard painters experienced low (n = 30) or high exposure (n = 27) to solvents, including EGEEA as determined by means of personal air and biological monitoring. The mean personal air concentration to EGEEA was 1.8 ppm (range ND - 8.1 ppm) (9.9 mg/m^3, ND - 44.5 mg/m^3) and 3.0 ppm (ND - 18.3 ppm) (16.5 mg/m^3, ND - 100.6 mg/m^3) in the low and high exposure group, respectively. The corresponding geometric mean/geometric standard deviation urinary levels of EAA were 9.2 ± 5.6 mg/l (range ND - 227 mg/l) or 0.6 ± 11.3 (ND - 15.1) mg/g creatinine in urine samples collected at the end of the shift. In unexposed controls urinary EAA was 0.1 ± 2.6 (ND - 1.5) mg/g creatinine (Kim *et al*, 1999).

Exposure of 3 male workers to 2PG1ME involved in cleaning of vats in an ink factory, was assessed by personal air monitoring and by determination of urinary 2PG1ME. Air concentrations were between 20 and 40 ppm (75 - 150 mg/m^3) and correlated well with the urinary 2PG1ME after 5 hours of exposure. 2PG1ME was rapidly cleared from the body and 40 to 60% of the total urinary 2PG1ME was present as conjugates (Devanthéry *et al*, 2000).

Commercial, technical grade propylene glycol ethers may be contaminated with a small percentage of their β-isomer. Since β-isomers have a primary alcohol function, they can be metabolised to the corresponding 2-alkoxypropionic acids (Section 2.7.2.4), which can be determined in the urine of exposed individuals. Indeed, small amounts of 2-MPA and 2-EPA could be determined in the urine of 54 silkscreen printers with occupational exposure to various glycol ethers, including 2PG1MEA and 2PG1EEA. The urinary excretion of 2-MPA and 2-EPA immediately after the end of the shift was linearly dependent on the preceding personal airborne exposure to the technical grade 2PG1MEA and 2PG1EEA, respectively (Laitinen, 1997).

Exposure to 2PG1ME and DPGME and a variety of other solvents including DEGEE was measured in 38 workers involved in the removal of graffiti. Exposure was assessed by personal air monitoring as well as by biological monitoring through the determination of the glycol ethers or their metabolites in blood and urine. Exposure to glycol ethers was well below the Swedish permissible exposure levels and none of the glycol ethers could be detected in the urine of the workers. EAA and 2-MPA, however, were detected in almost every urine sample, including those of non-exposed controls. 2-Methoxy-ethoxyacetic acid (2-MEAA) was found in only a few workers. Urinary EAA, but not 2-MPA, was significantly lower in workers using gloves. There was no correlation between the concentration of the glycol ethers in air and the excretion of acid metabolites (Anundi *et al*, 2000).

3.1.4 Measurement methods

In air

It should be noted that ambient air and personal air monitoring data reported in the literature do not always reflect the actual exposures. There are normally wide variations in exposure conditions, not only between industrial plants but also within the same plant between different locations and times. Furthermore, sampling might have generally underestimated airborne concentrations as the glycol ethers could have become unstable on the collection medium (US-NIOSH, 1983). Measurement was further complicated in that many of the uses of glycol ethers also involved simultaneous exposure to other solvents, which may have interfered with the analysis. Finally, the use of air monitoring to determine body burden is insufficient to take account of dermal absorption, which can make a significant contribution to overall systemic body burden.

In view of their potentially greater sensitivity, the application of biological monitoring techniques may permit a more complete and accurate assessment of worker exposure to low concentrations of glycol ethers.

The majority of reported measurements were made using US-OSHA Method 53, or variations thereof, involving collection of the glycol ether vapour on a charcoal adsorbent, followed by solvent desorption and analysis by a gas chromatograph (GC) equipped with a flame-ionisation detector (FID) (US-OSHA, 1985). The techniques used are summarised in Table 16.

Table 16: Air measurement methods used

Sample collection	Extraction (desorbent)	Analysis	Reference
Drawing known volume of air through 100/50 mg charcoal tube and also using 3M and Dräger passive (diffusion) samplers	5% ethanol in CS_2	GC-FID	Veulemans *et al*, 1987a
OSHA 53 Drawing known volume of air through charcoal tube	DCM [a] in ethanol	GC-FID	Piacitelli *et al*, 1990
OSHA 53 Drawing known volume of air through charcoal tube	5% DCM in methanol	GC-FID	Hallock *et al*, 1993
Drawing known volume of air through 100/50 mg charcoal tube	DCM	GC-FID	Vincent *et al*, 1993, 1994
OSHA 53 Drawing known volume of air through charcoal tube	5% methanol in DCM	GC-FID	Hammond *et al*, 1996
Dräger ORSA 5 diffusion tube	DCM in CS_2	GC-FID	Bader *et al*, 1994
Drawing known volume of air through XAD7 resin tube	DCM	GC-FID	Norbäck *et al*, 1996

Table 16: Air measurement methods used (cont'd)

Sample collection	Extraction (desorbent)	Analysis	Reference
Drawing known volume of air through 100/50 mg charcoal tubes	Methylene chloride	GC, detector NS	Vincent *et al*, 1996 cited by INSERM 1999
Drawing known volume of air through 100/50 mg charcoal tube	CS_2	GC-FID	Wesolowski and Gromiec, 1997

[a] Dichloromethane
NS, not specified

Additional methods have been published, for example, US-OSHA (1990a) Method 79 on EGME, EGEE, EGMEA and EGEEA (this is a revision to OSHA 53 method to allow for the measurement of lower airborne vapour concentrations), US-OSHA (1990b) Method 83 on EGBE and EGBEA, and US-NIOSH (1994) Method 1403 on EGBE, that may be adapted for EGBEA. The UK Health and Safety Executive (HSE) has published a method for the determination of hazardous substances (MDHS 72) on glycol ether acetate vapours in air: volatile organic compounds in air, laboratory method using pumped solid sorbent tubes, thermal desorption and gas chromatography (HSE, 1993) and MDHS 96 on volatile organic compounds in air, laboratory method using pumped solid sorbent tubes, solvent desorption and gas chromatography (HSE, 2000).

Biological monitoring

Glycol ethers with a *primary* alcohol and their acetates, such as the ethylene glycol ethers (and certain propylene glycol ethers, e.g. 1PG2ME), are rapidly metabolised to the corresponding alkoxy acetic (or alkoxypropionic) acids and their conjugates, and excreted in the urine. Uptake is therefore usually measured by determination of urinary metabolites of these glycol ethers. Occasionally the concentration of the glycol ethers themselves are determined in blood, urine or exhaled air. Glycol ethers with a *secondary* alcohol, such as most propylene glycol ethers, are metabolised primarily by *O*-dealkylation, yielding propylene glycol and carbon dioxide (Section 2.7.2.1 and 2.7.2.4). As a consequence, uptake of these glycol ethers is normally assessed by determination of the glycol ethers themselves in urine, blood or exhaled air.

Numerous studies in occupational settings indicate that urinary analysis for alkoxycarboxylic acids is a useful method for the biological monitoring of occupational exposure to glycol ethers. Alkoxycarboxylic acids are not normally present in human urine and, in general, the extent of urinary excretion of these metabolites gives a much better indication of systemic exposure than airborne measurements of glycol ethers. An overview of the methods used in the literature is given in Table 17.

Table 17: Biological monitoring methods used

Biomarker	Specimen and sampling	Extraction and solvent [a] or reference	Analysis	Reference
BAA	Urine	Methylation, solid phase XAD-4 resin	GC-FID	Begerow *et al*, 1988
MAA, EAA, BAA	Urine	Pentafluorobenzoylation, DCM/TBAS	GC-ECD	Johanson, 1989
EAA	Urine	Acidification, DCM or pentafluorobenzoylation	GC-ECD	Begerow and Angerer, 1990
EAA	Urine, post-shift, second half of working wk	Groeseneken *et al*, 1989b		Lowry *et al*, 1993
EAA	Urine, pre-shift d 1 and post-shift d 2 of working wk	Begerow and Angerer, 1990		Söhnlein *et al*, 1993
BAA	Urine, pre-shift d 1 and post-shift d 2 of working wk	Begerow *et al*, 1988		Söhnlein *et al*, 1993
BAA and its glutamine conjugate	Urine, post-shift last d and pre-shift d 1 of working wk	Acidification, ethyl acetate extraction, derivatisation with 4-nitrobenzylbromide and 18-crown-6-ether	HPLC-UV	Rettenmeier *et al*, 1993
BAA (free and conjugated)	Urine, spot samples and post-shift	Acid hydrolysis, DCM/IPA (2:1), trimethyl-silylation	GC-FID	Sakai *et al*, 1994
2PG1EE	Urine, post-shift	Acetone elution, solid phase+ DCM	GC-FID	Bader *et al* (1996)
EPA	Urine, post-shift	As EAA according to Söhnlein *et al*, 1993		Bader *et al* (1996)
MAA, EEA, BAA	Urine, post-shift	Groeseneken *et al*, 1989b		Vincent *et al* (1993, 1994 and 1996)
MAA, EAA	Urine	Groeseneken *et al*, 1989b		Kežič *et al*, 1997
MAA, EAA, BAA, MPA, EPA	Urine, post-shift	Acid hydrolysis, ethyl acetate, methylation	GC-FID	Laitinen, 1997
2PG1ME	Urine	Ethyl acetate, trimethyl-silylation	GC-MS	Jones *et al*, 1997
2PG1ME	Urine, blood	Jones *et al*, 1997		Brooke *et al*, 1998
MAA, EAA, BAA	Urine	Acid hydrolysis, DCM/IPA 2:1	GC-MS	Shih *et al*, 1999b
EAA	Urine, post-shift	Sakai *et al*, 1994		Kim *et al*, 1999
EAA, BAA, MPA, MEAA	Urine, post-shift	Johanson, 1989		Anundi *et al*, 2000
PGME	Urine, during- and post-shift	Solid phase (LC-18) + ethyl acetate, trimethyl-silylation	GC-FID	Devanthéry *et al*, 2000

[a] DCM, dichloromethane; IPA, iso-pentyl alcohol; LC-18, type of silica gel; TBAS, tetra-*n*-butyl-ammonium hydrogen sulphate, XAD-4, type of Amberlite resin

A consistent urinary sampling pattern is important when using urinary alkoxyacetic acids as biomarkers for exposure to glycol ethers to reduce the variability in results. This sampling pattern should be related to the urinary half-life of the respective alkoxyacetic acid, e.g. for BAA, which has a relatively short urinary half-life of about 6 hours, sampling at the end of the shift would be

most appropriate. For MAA, which has a much longer urinary half-life of about 3 days lead to significant build up over the working week, sampling at the end of the working week would be more appropriate.

Sensitive techniques for the quantitative analysis of alkoxyacetic acids in urine have been developed in the late eighties (Johanson *et al*, 1988; Groeseneken *et al*, 1989b; Johanson, 1989) and have been adapted to recent developments in analytical chemistry (Laitinen 1997; Shih *et al*, 1999b; Johanson, 2000).

So far, only for EAA (Lowry, 1996) and for BAA (Angerer and Gündel, 1994) has the methodology been validated and have biological exposure limits been established (Table 18).

Table 18: Biological exposure limits

Biomarker	US-NIOSH (1990a,b)	Finnish Institute of Occupational Health (Laitinen, 1998)		DFG (2000)	ACGIH (2001)
	(mg/g creatinine)	(mmol/mol creatinine)	(mg/g creatinine)	(mg/l)	(mg/g creatinine)
MAA	-	3 [b]	(270)	-	Recommended, no value [a]
EAA	5 [c]	50 [b]	(5,200)	50 [a]	100 [a]
BAA	60	70 [c]	(8,300)	100 [a]	-

[a] In post-shift urine collected at the end of the working week
[b] In urine collected 14 - 16 h after exposure
[c] In post-shift urine

An external quality control programme is available for MAA, EAA and BAA. The method for EEA is basically a validation of the methodology developed by Groeseneken *et al* (1989b), which therefore may be considered retrospectively validated.

3.2 Health effects

Widespread exposure to glycol ethers in consumer products such as paints, inks, lacquers, surface coatings and cleaning products has provided no conclusive data on adverse health effects in the general population.

Limited information available on adverse health effects of glycol ethers in humans has come from case reports on accidental or intentional poisoning, workplace exposures, controlled short-term exposure studies and a few epidemiological studies.

3.2.1 Haematological effects

EGME and EGEE

Five workers believed to have been exposed to 61 to 3,960 ppm of EGME (193 - 12,530 mg/m^3) suffered from anaemia and, in one case, hypocellular bone marrow (Zavon, 1963). In a seperate report, substitution of acetone for EGME as an industrial cleaning agent resulted in 2 cases of poisoning. Signs included neurobehavioural abnormalities and were reversible (Ohi and Wegman, 1978).

A cross-sectional, epidemiological study of employees engaged in the manufacture and packaging of EGME reported inconclusive evidence of toxic effects on haematological parameters among 53 workers exposed to EGME vapour (area monitoring 4 - 20 ppm [13 - 63 mg/m^3]; personal monitoring 5.4 - 8.5 ppm TWA [17 - 27 mg/m^3]) as compared with 44 non-exposed workers (Cook *et al*, 1982).

Low levels of RBC and WBC, platelets, haemoglobin (Hb) and haematocrit (Hct) were reported in an employee after 1 year of repeated respiratory and skin exposure to EGME. The average ambient air levels of EGME were approximately 35 ppm (range 18.2 - 57.8 ppm) (110, 58 - 183 mg/m^3). There was also a lower concurrent exposure to methyl-ethyl ketone and commercial PGME (mixture of α-isomer 2PG1ME with < 0.5% β-isomer 1PG2ME). All haematological parameters had returned to normal values one month after cessation of EGME exposure (Cohen, 1984).

Welch and Cullen (1988) described anaemia and granulocytopenia in shipyard painters exposed to EGME and EGEE. The airborne exposure to EGEE ranged from 0 to 21.5 ppm TWA (mean 2.6 ppm, median 1.2 ppm) (0 - 81, mean 9.7, median 4.5 mg/m^3) and for EGME ranged from 0 to 5.6 ppm TWA (mean 0.8 ppm, median 0.4 ppm) (0 - 17.7, mean 2.5, median 1.3 mg/m^3) (Sparer *et al*, 1988).

Questel (1992) evaluated a possible association between haemopathies reported as occupational disease and exposure to glycol ethers but did not demonstrate causality.

Mild macrocytic anaemia and leukopenia with an increased proportion of lymphocytes was described in 3 otherwise healthy young women dipping pieces of cellulose glass frames in a

mixture of acetone (70%) and EGME (30%) in a frame factory; exposure was probably predominantly by the dermal route. Examination 1 year after cessation of exposure showed normal haematological levels in 2 cases; the erythrocyte count in the third case did not normalise for 2 years (Larese *et al*, 1992).

Changes in lymphocyte sub-populations were reported in 9 parquet floor makers exposed to a variety of solvents including EGME, EGEE and EGBE. The exposure in this group was high and variable (Denkhaus *et al*, 1986).

Acute exposure of humans to EGEE caused depression of the CNS and metabolic acidosis. Chronic effects included CNS dysfunction (Section 3.2.2), bone marrow suppression, anaemia, and granulocytopenia (Browning and Curry, 1994).

EGBE

Erythrocyte osmotic fragility did not change in 2 men exposed to 114 ppm EGBE (560 mg/m^3) for 4 hours, or in 2 men and 2 women, exposed to 114 ppm EGBE (560 mg/m^3) for 8 hours. This was in contrast to effects on rats under the same exposure conditions, where haemolysis of erythrocytes was reported. Erythrocyte osmotic fragility did not change *in vivo* in 2 men and 1 woman exposed to 195 ppm EGBE (958 mg/m^3) for 8 hours (Carpenter *et al*, 1956).

Johanson and Johnsson (1991) demonstrated that EGBE concentrations in the blood of 5 male volunteers who were exposed to 20 ppm EGBE (98 mg/m^3) for 2 hours were approximately two orders of magnitude lower than those causing swelling and haemolysis of human erythrocytes *in vitro.*

DPGME

Aplastic anaemia was reported in a worker employed in offset printing and potentially exposed to a range of organic solvents (including EGEE and DPGME), insoluble pigments and acrylic and epoxy resins. In a study of other workers in the same plant, bone marrow abnormalities were diagnosed in 6 of 7 subjects examined; bone marrow hyperplasia was seen in 6 subjects and an increase in periodic acid Schiff (PAS)-stained positive stromal material was seen in 3 individuals. Although the myeloid/erythroid ratio in these subjects was lower than in the normal population, the other reported bone marrow changes (reduced cellularity, the presence of ringed sideroblasts and PAS-stained positive stromal material) were difficult to interpret in view of the absence of adequate controls and the fact that the cellular content of the peripheral blood was entirely normal (Cullen *et al*, 1983). Since the workers were exposed to many different chemicals, with no

measure of individual skin or inhalation exposure to any one material, it is impossible to draw any conclusions from this study about a possible association between bone marrow changes and glycol ether exposure.

3.2.2 Behavioural and neurological effects

EGME

Early reports stated that repeated human exposure to solvents containing EGME could result in headache, lethargy, weakness, dizziness, ataxia, toxic encephalopathy and pathological reflexes (Donley, 1936; Parsons and Parsons, 1938; Greenburg *et al*, 1938; Groetschel and Schürmann, 1959; Browning, 1965; IPCS, 1990; Zavon, 1963; Nitter-Hauge, 1970; Ohi and Wegmann, 1978). Levels of exposure were poorly documented in most cases.

Cohen (1984) reported apathy, fatigue and tiredness in an employee after 1 year of repeated respiratory and dermal exposure to EGME. The average vapour exposure level was around 35 ppm (range 18.2 - 57.8 ppm) (68.2 - 216.5 mg/m^3). There was also lower concurrent exposure to methyl ethyl ketone and (commercial) PGME.

EGPhE

Medical students dissecting human anatomical specimens preserved in a 1% solution of EGPhE in water complained of tiredness, dizziness and headache. Causality was not established (Froelich *et al*, 1984).

Retrospectively, 3 women were reportedly exposed (primarily by skin contact) to EGPhE, which was used as anaesthetic for handling fish at a salmon hatchery. During use of EGPhE the fish handlers reported headache, light-headedness, slurred speech, euphoria, grogginess and "feeling drunk". The workers also reported diminished sensation and strength of hands and fingers, especially in the preferred hand. After 1 year of exposure, additional symptoms developed without correlation with time and frequency of exposure, including excessive fatigue, irritability, impaired recent memory and of verbal or visual learning and comprehension, lowered intellectual and mental function, depression, somnolence and impaired concentration, some detected only 4 years after cessation of exposure. Persistent neuropathy did not develop, but neuropsychological testing verified that all 3 women had focal cognitive impairments that persisted up to at least 3 years after cessation of exposure. The author concluded that immediate and delayed effects of EGPhE on the CNS resemble those of other organic solvents (Morton, 1990). Information on exposures, status of other workers (who were not affected) or lifestyle confounders such as alcohol are lacking; comments on this article have been published (Schmuck *et al*, 2000).

3.2.3 Reproductive effects

An epidemiological survey was conducted in the semi-conductor industry in the USA. The study focussed on possible reproductive effects, such as infertility, complications during pregnancy, pregnancy outcomes, spontaneous abortions, preterm delivery and congenital malformations. Employees were interviewed about the occurrence of these possible effects. On the basis of the industrial process and the jobs held by the study subjects, sub-classifications were made according to exposure to chemicals or groups of chemicals. The researchers observed an association between chemical exposure to glycol ethers and the occurrence of spontaneous abortions (rate of 35% in manufacturing jobs compared to 18% in non-manufacturing workers). However, the researchers concluded, given the lack of quantifiable exposure data on glycol ethers and other chemicals the current association should be regarded as tentative until confirmed by studies which are able to discriminate the numerous chemical and physical exposures found in the semi-conductor industry (Pastides *et al*, 1988).

The study of Pastides *et al* (1988) was followed by a larger epidemiological study in the semi-conductor industry in the USA. This latter study consisted of a cross-sectional component, a retrospective component and a prospective component, with the retrospective and prospective components focussing mainly on reproductive effects. Most employees were exposed to a range of chemical and physical circumstances such as exposure to electromagnetic fields. In both the prospective and the retrospective components small increases in the occurrence of spontaneous abortions were seen, reaching a level of statistical significance, and showing a positive dose-response relationship with the use of solvents, including glycol ethers. Adjustment for known factors that are related to spontaneous abortions, such as smoking, age, ethnicity, stress and socio-economic status did not essentially alter the findings (Schenker *et al*, 1995)[a]. There was an association between spontaneous abortion rate and the exposures to various agents (15% in fabrication jobs compared to 10% in non-fabrication workers). However, it was not possible to accurately study the effect on the occurrence of spontaneous abortions by each individual agent.

In a review on the effects of glycol ethers on the reproductive health of occupationally exposed individuals, Figà-Talamanca *et al* (1997) concluded that the evidence accumulated at that time supports the hypothesis of an increased risk for spontaneous abortion among women in jobs involving exposure to glycol ethers, particularly among photo-lithography and diffusion workers in the semi-conductor industry.

In Europe, a large multi-centre case/control study was conducted to investigate possible occupational risk factors for congenital malformations. The study comprised 984 cases of congenital malformations that compared to 1,134 controls matched for place and date of birth. Information on jobs held during pregnancy was collected by interviewing the mothers of the

[a] See also editorial and specific reports in *American Journal of Industrial Medicine* 28:635 (1995), special issue.

cases and controls. Data on other variables such as smoking, alcohol use and medical history were also collected. The case and control groups were matched for age, socio-economic status, employment during pregnancy, prior reproductive status (parity, previous spontaneous abortion and previous stillbirth), as well as tobacco and alcohol use. The job descriptions were then rated by a chemist with respect to the likelihood of exposure to glycol ethers. Within the total study group a small but statistically significant association was found between reported exposure to glycol ethers and congenital malformations, specifically for three subcategories of malformations (Cordier *et al*, 1997).

Windham *et al* (1991), in a case-control study of 1,926 respondents, reported an association between exposure to a number of solvents and spontaneous abortion with glycol ethers (not further specified) showing a slight association.

In a reproductive health study of male and female employees (and wives of male employees) of two semi-conductor manufacturing plants, a significant trend in spontaneous abortion rates was observed for female employees working in processes with the highest potential exposures to glycol ethers. Sub-fertility and conception delays were also reported. There was no positive trend in spontaneous abortion rates among wives of exposed male workers (Gray *et al*, 1993).

Swan *et al* (1995) analysed these epidemiology studies and concluded that there was an increase in spontaneous abortion rates associated with semi-conductor manufacture, which – on the basis of unspecified toxicological information – might be associated with glycol ethers.

Lamm *et al* (1996) have summarised the results of three epidemiology studies (Pastides *et al*, 1988; Schenker *et al*, 1992 [subsequently published by Schenker *et al*, 1995]; Gray *et al*, 1993; Corn and Cohen, 1993), conducted on workers in the semi-conductor industry, and concluded that increased risk of spontaneous abortion appears to be associated with exposure during the photolithography process, but cannot be attributed to any specific chemical.

Cordier *et al* (1997) interviewed 984 mothers whose children had major malformations and 1,134 matched controls from 4 European countries. On the basis of the interviews, potential exposure to glycol ethers was estimated; other workplace practices and exposure to other materials were not considered. An association between presumed glycol ether exposure and a number of specific malformations was reported.

The reports of the increased prevalence of spontaneous abortions in female workers in the semi-conductor industry led to a study by the UK Health and Safety Executive in the Scottish semi-conductor industry. No differences in prevalence of spontaneous abortions were noted as a result of occupational conditions, including exposure to glycol ethers (Elliot *et al*, 1998).

In another case-control study occupational exposure in the peri-conceptional period to glycol ethers and derivatives did not increase the risk for neural tube defects (Shaw *et al*, 1999).

The Occupational Exposure and Congenital Malformation Working Group investigated the possible association of maternal occupational exposure during pregnancy with the occurrence of oral clefts in a European case-referent study using 6 congenital malformation registers between 1989 and 1992. The occupational exposure of 851 women, including 100 mothers of babies with oral clefts and 751 mothers of healthy referent. The analysis suggested that exposures to several chemical classes were associated with orofacial clefts, whereby the glycol ethers had the lowest odds ratio (1.7, 95% confidence interval 0.9 - 3.3) (Lorente *et al*, 2000).

In a case-control study in Slovakia 196 mothers of live or stillborn babies with a major malformation or foetuses from therapeutic abortion were interviewed about various risk factors and compared with a control group. Potential exposure to various product families containing glycol ethers was identified in 15 women, 7 containing EGEE and 4 EGBE or its acetate. The overall risk of congenital anomalies was elevated (odds ratio 2.3, confidence interval 0.7 - 7.0) (Cordier *et al*, 2001).

EGME, EGMEA, EGEE, EGEEA and DEGDME

A cross-sectional, epidemiological study of employees manufacturing and packaging EGME reported no conclusive evidence of toxic effects on fertility indices among 53 workers exposed to EGME as compared with 44 non-exposed workers (area monitoring 4 - 20 ppm, personal monitoring 5.4 - 8.5 ppm TWA) (area 13 - 63, personal 17 - 27 mg/m^3) (Cook *et al*, 1982).

The semen of 73 shipyard painters was examined following exposure to EGEE (0 - 21.5 ppm 8-h TWA; mean 2.6 ppm, median 1.2 ppm) (0 - 81, mean 9.7, median 4.5 mg/m^3) for the previous 2 to 6 months. The painters also had been exposed to EGME (0 - 5.6 ppm 8-h TWA; mean 0.8 ppm, median 0.44 ppm) (0 - 17.7, mean 2.5, median 1.4 mg/m^3) during the same period. The authors concluded that exposure to EGME and EGEE lowered sperm count in this group of painters, as compared with a control group of 55 non-exposed workers. This was consistent with an effect of these glycol ethers on spermatogenesis (Welch *et al*, 1988).

EGEE exposure had no effect on semen quality in metal casting workers exposed to EGEE (full-shift breathing zone measurement 0 - 24 ppm, geometric mean 6.6 ppm) (0 - 90 and 24.7 mg/m^3, respectively) (Ratcliffe *et al*, 1989).

Bolt and Golka (1990) reported hypospadia (a developmental anomaly whereby the male urethra opens on the underside of the penis or perineum) in 2 young boys whose mother had experienced intensive (mainly dermal) occupational exposure to EGMEA during both pregnancies.

A study of spontaneous abortions in 200 employees of a book cover manufacturing plant showed an estimated relative risk among pregnant women working at the plant of 2.7 (95% confidence interval 1.35 - 5.42). An industrial hygiene survey reported that exposures to EGEEA were well below the TLV. In addition, it identified exposures to other toxicants reported to have adverse effect on reproduction and foetal development (Fidler *et al*, 1991).

In 1993, the results of a case-control study on patients from a reproductive disorders clinic were reported. The study consisted of 1,019 males with an abnormal spermiogram and 475 controls with a normal spermiogram; the case and control groups were matched for age, socio-economic status, smoking and alcohol consumption. Urine samples of the study subjects were collected and tested for the presence of MAA and EAA, as measures of exposure to EGME and EGEE respectively, and their acetates. EAA was detected in 39 cases and 6 controls, with a highly significant ($p = 0.004$) odds ratio of 3.11; MAA was detected in only 1 case and 2 controls. However, there was no correlation between urinary EAA concentration and sperm quality parameters, or between the case and control groups, although this might be related to the latency of the effects (Veulemans *et al*, 1993).

Low-level exposures to EGEEA had no effect on menstrual cycle period or duration in women employed in the liquid crystal display industry (Chia *et al*, 1997).

Saavedra *et al* (1997) described congenital malformations (with most of the manifestations in the craniofacial, musculoskeletal, and central nervous system) with varying degrees of mental retardation in 44 patients whose mothers have been occupationally exposed during pregnancy to EGME and MEG through cutaneous, oral, and respiratory routes in a Mexican factory. A subsequent “case-and-control” study revealed causality with the EGME and MEG exposure.

In exposed workers anaemic effects of EGME exposure were observed and correlated with the biological monitoring of urinary MAA. Spermatotoxic effects were not noted (Shih *et al*, 2000a).

El-Zein *et al* (2002) investigated 41 offspring children of 28 women occupationally exposed to EGME for an average duration of 4.6 years. Six children of 5 women exposed during pregnancy showed characteristic dysmorphic features that were not observed among 35 children of 23 women who had no exposure during pregnancy. No data on the height of exposure are presented.

EGBE, 1PG2ME and others

A number of congenital malformations including cleft lip reportedly correlated with maternal occupational exposures to glycol ethers. Women exposed were divided primarily into two groups: those exposed to EGBE and EGPE and their acetates; and those exposed to 1PG2ME and its acetate, as well as polyethylene and polypropylene compounds. These authors suggest this represents evidence of the human teratogenicity of EGBE and compounds of the propylene glycol series. It is also suggested that EGBE, rather than a causative agent, is acting as a marker for a wider range of occupational exposures (Cordier *et al*, 1997). This study suffers from several methodological problems and a lack of biological plausibility, since implicated agents have tested negative in animal studies. Selection and recall bias may have also contributed to these findings (Maldonado *et al*, 2003).

3.2.4 Other effects, including poisoning

EGME, EGEE and EGEEA

No cases of skin irritation, sensitisation or eye irritation have been reported in humans.

Young and Woolner (1946) reported a case of fatal poisoning when a man drank an estimated 200 ml of EGME (193 g) mixed with rum. The urine from this individual contained ethanol but no methanol, supporting the contention that EGME was not significantly metabolised through ether cleavage. The kidneys showed degenerative and toxic changes, there was liver fatty degeneration, the pancreas showed early necrosis and there was acute haemorrhagic gastritis.

Consumption of EGEE (40 ml [37 g]) by a woman led to dizziness, loss of consciousness, metabolic acidosis and renal and liver damage. She recovered after 6 weeks (Fucik, 1969 cited by Boatman, 2001).

Nitter-Hauge (1970) reported 2 cases of men who drank EGME (100 ml [97 g]). Symptoms included agitation, confusion, nausea, cyanosis, hyperventilation, tachycardia and metabolic acidosis. One case showed slight renal failure. Both cases recovered within 4 weeks.

No cytogenetic effects were noted in varnish production workers exposed to EGBE, EGEE, and EGEEA (Söhnlein *et al*, 1993).

Laitinen *et al* (1994) reported a relationship between decreased urinary levels of succinate dehyrogenase and excretion of urinary oxalic acid and alkoxyacetic acids in workers exposed to glycol ethers (including EGEE). Ammonia excretion by exposed workers was doubled compared with control values.

Saavedra *et al* (1997), in a study on women exposed during pregnancy to EGME and MEG through cutaneous, oral, and respiratory routes in a Mexican factory, reported that they sometimes suffered to varying degrees from symptoms of intoxication, from strong headaches or cutaneous rash to repeated vomiting with dehydration, temporal loss of consciousness and coma. In the severe cases, intra-hospital treatment was needed. No analytical data on the height of exposure are presented but the described exposure and intoxication scenarios suggest high exposure.

In the above study of El-Zein *et al* (2002) (Section 3.2.3), all 6 dysmorphic children, from mothers occupationally exposed to EGME, exclusively had increased levels of chromosome aberrations, including breaks, polyploid and endoreduplicated cells, but no translocations and inversions. The authors explain the pattern of their cytogenetic findings as a disposition for genetic instability characterised by a delay in cell division. No data on the height of exposure are presented.

EGBE

Exposure of two men to 114 ppm EGBE (560 mg/m^3) for 4 hours resulted in nasal and eye irritation and a metallic taste in the mouth (Carpenter *et al*, 1956).

Exposure of two men and one woman to 195 ppm EGBE (958 mg/m^3) for 8 hours resulted in discomfort, irritation of the nose, throat and eyes and disturbed taste; the woman also developed a headache. The woman excreted 300 mg of BAA, one man excreted 175 mg of BAA and the other man excreted only traces of BAA in urine collected for 24 hours after exposure (Carpenter *et al*, 1956).

Exposure of two male and female volunteers to either 100 or 195 ppm EGBE (491 or 958 mg/m^3) for up to 8 hours resulted in varying degrees of discomfort ranging from headaches to emesis. All excreted BAA (75 to 250 mg) in their urine (Carpenter *et al,* 1956). There were no signs of haemolysis or any other systemic effects noted.

Browning (1965) reported 1 case of haematuria and 2 cases of eye/nose irritation and headache in workers exposed to EGBE.

A number of cases of human poisonings with EGBE have been summarised and reviewed by Udden (1996). Three of 4 cases of adult human poisonings with EGBE involved probable doses of EGBE of 25 to 60 g. Coma and metabolic acidosis were common features, with hypokalaemia and haemoglobinuria following ingestion of the higher doses. None died as a result of EGBE

ingestion, but all required hospitalisation and supportive treatment (Rambourg-Schepens *et al*, 1988; Gijsenbergh *et al*, 1989; Bauer *et al*, 1992; Litovitz *et al*, 1991).

A 50-year old woman ingested 250 to 500 ml of window cleaner containing 12% EGBE. Coma, metabolic acidosis, hypokalaemia, an increase in serum creatinine haemoglobinuria and progressive erythropenia were reported. She improved gradually with supportive treatment (Rambourg-Schepens *et al*, 1988).

Gijsenbergh *et al* (1989) reported a suicide attempt with 500 ml of a window cleaner containing EGBE and alcohol (percentages unknown). This resulted in coma, hypotension and metabolic acidosis.

A case of respiratory distress syndrome in a 53-year old man was reported following EGBE intoxication. Metabolic acidosis, shock, and non-cardiogenic pulmonary oedema resolved following supportive treatment. It is not clear whether the pulmonary effects reported were a consequence of EGBE or the unstable conditions of the patient. Such effects have not been reported in other poisonings (Bauer *et al*, 1992).

Massive ingestion of EGBE by a 19-year old, mentally retarded patient produced hypotension and hypoxia, believed to account for neurological injury that persisted following recovery (Burkhart and Donovan, 1998). An 18-year old male who ingested cleaner containing 22% EGBE on two separate occasions. Estimated doses received were 1.0 to 1.34 g/kgbw. Minimal hepatic abnormalities following the first episode were not seen following the second ingestion. Acid-base imbalance responded rapidly to haemodialysis and ethanol treatment. No haematological or renal abnormalities were present following either incident (Gualtieri *et al*, 1995).

Dean and Krenzelok (1992) reported that of 24 children ingesting EGBE-containing household cleaners, 2 required gastric emptying or lavage followed by hospitalisation, with recovery uneventful. All others were given fluids at home.

McKinney *et al* (2000) reported a 51-year old female who ingested up to 8 ounces (0.24 litre) of a cleaner (EGBE and isopropanol). She developed prolonged hyper-chloraemic metabolic acidosis and mental depression and received ethanol treatment but not haemodialysis. There was no renal dysfunction, oxaluria, or haemolysis present in this patient during the course of treatment and she was discharged without apparent sequelae.

Udden (1996) has suggested that haemo-dilution, as a result of i.v. fluid therapy, may have contributed to the haemolytic anaemia reported in some cases of human poisonings with EGBE.

EGBE did not cause skin sensitisation in human subjects exposed dermally to 10% aqueous solutions of EGBE, the highest level used in cosmetics (Greenspan *et al*, 1995).

Haufroid *et al* (1997) reported slight but significant decreases in Hct levels and increases in mean cell haemoglobin (MCHb) concentration in workers exposed to low levels of EGBE. Urinary BAA excretion was low in these latter studies. Low level exposure to EGBE in foundry workers has been correlated with increased D-glucaric acid excretion (Collinot *et al*, 1996). This latter effect may be an adaptive rather than toxic response.

EGPhE

Exposure of unknown degree to EGPhE coincided with a transient liver enlargement and tenderness in one worker. No laboratory or other clinical data were reported (Morton, 1990).

EGPhE tested negative in human clinical trials for skin irritation, sensitisation or phototoxicity (CIR, 1990). This glycol ether is considered safe as a cosmetic ingredient at concentrations less than 1%.

DEGME

20% DEGME in petrolatum caused no irritation or sensitisation in patch testing in 25 human subjects (cited by Opdyke, 1974).

DEGEE

A case report described an alcoholic male who drank a liquid containing approximately 300 ml DEGEE. CNS symptoms, dyspnoea, thirst, acidosis and albuminuria were reported and he recovered with symptomatic treatment (cited by Browning, 1965).

DEGEE was reported to be neither a primary irritant nor a skin sensitiser in humans (Cranch *et al*, 1942; Meininger, 1948; Opdyke, 1974).

DEGEE and DEGBEA

Repeated applications over several months of an insect repellent containing 50% DEGBEA, 15% DEGEE, 28% ethanol, 7% corn oil and a trace of lavender oil produced kidney failure in a 3-year old child (Hoehn, 1945; Draize *et al*, 1948).

A female office worker reported symptoms of irritation of the upper airways, erythema of the face, and swollen eyelids. Patch testing was positive for DEGBE and a paint additive containing DEGBE (Berlin *et al*, 1995). Lack of workplace monitoring information does not allow confirmation of DEGBE as the causative agent in this case.

1PG2ME, 1PG2MEA, 2PG1ME and 2PG1MEA

During controlled exposure of 6 human volunteers with commercial PGME (95 - 99% 2PG1ME, < 5% 1 PG2ME) at vapour concentrations from 50 to 2,000 ppm (190 - 7,500 mg/m^3), the odour became noticeable at 10 ppm (37 mg/m^3) and objectionable above 100 ppm (370 mg/m^3) (Stewart *et al*, 1970).

Exposure to 250 ppm PGME (940 mg/m^3) caused progressive irritation of nose, throat and eyes after 15 minutes; the volunteers were unable to smell PGME after 3 hours at that concentration. One person exposed to 2,000 ppm (7,500 mg/m^3) did not show any neurological impairment. Blood cell count, erythrocyte sedimentation rate and serum chemistry did not differ in pre- and 16- hour post-exposure blood samples.

Emmen (1997, 2003) reported a level of 150 ppm PGME vapour (560 mg/m^3) to be without irritant effect on the eyes of human subjects based on the lack of significant impact on a number of objective and subjective parameters measured before and following exposures.

DPGME

Patch tests with DPGME on 250 persons indicated no evidence of either skin irritation or sensitisation (Rowe *et al*, 1954).

DPGME levels in air of 300 to 400 ppm (1,850 - 2,465 mg/m^3) have been described as very disagreeable. The odour threshold and irritation level for DPGME were reported to be 35 ppm and 74 ppm (216 and 456 mg/m^3), respectively (Rowe *et al*, 1954).

A 20% solution of DPGME (0.04 ml) was applied to one eye of 10 human male volunteers; this caused a minor stinging sensation for 30 to 45 seconds, slight lachrymation for about a minute, mild conjunctival vascular injection and an increase in intra-ocular tension for 1 hour (Ballantyne, 1984a,b).

TEGME

Soldiers who drank brake fluid containing TEGME in place of alcoholic beverages required hospitalisation for gastric lavage and blood dialysis in the case of one individual. Otherwise, recovery from symptoms was rapid (Sprague, 1992 cited by Boatman and Knaak, 2001).

2PG1PhE

2PG1PhE has bactericidal properties and is used in medical disinfectants, and cleansing and in cosmetic formulations; it is mentioned as an antibacterial agent in pharmaceutical compositions of acne treatment (Roberts, 1986). No data are available on untoward effects in humans.

Other glycol ethers

No human data are available on the following glycol ethers: EGDME, TEGDME, EGDEE, DEGDEE, DEGEEA, TEGEE, EGiPE, EGnPE, EGnPEA, TEGBE, 2PG1EE, 2PG1EEA, DPGEE, TPGME and 2PG1BE.

3.3 Occupational exposure limit values

Several countries have adopted OEL values (Appendix C). The justification of some OELs takes account of critical effects on the reproductive system.

4. SUBSTANCE PROFILES (VOLUME II/CD)

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In addition, for PGPE, PTBE and DPGTBE the Toxicology Literature Online Databank (TOXLINE) of the US National Library of Medicine was searched on the internet (http://toxnet.nlm.nih.gov).

Similarly, the reference lists contained in the 5th edition of Patty's Toxicology chapters (Boatman, 2001; Boatman and Knaak, 2001) were updated by searching in the cluster on STN and in the Chemical Information Systems (CIS) in the USA, including MEDLINE, NIOSHTIC, TOXCENTER and BIOSIS, and in TOXLINE on the internet.

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APPENDIX A: SPECIAL ABBREVIATIONS

ADH	Aldehyde dehydrogenase
ADME	Absorption distribution metabolism elimination
ALP or AP	Alkaline phosphatase
ALT	Alanine aminotransferase
ATP	Adenosine triphosphate
AUC	Area under the curve
BAA	2-Butoxy acetic acid
BAL	2-Butoxy acetaldehyde
BAT	Biologischer Arbeitsstoff-Toleranz-Wert [a]
BEAA	2-(2-butoxyethoxy)acetic acid
bw	Body weight
CHL	Chinese hamster lung
CHO	Chinese hamster ovary
CNS	Central nervous system
Con A	Concanavalin A
CYP	Cytochrome P450
d	Day
D_4^{20}	Relative density
DCM	Dichloromethane
DNA	Deoxyribonucleic acid
EAA	Ethoxy acetic acid
EG	Ethylene glycol
EMH	Extramedullary haemopoiesis
EPA	Ethoxypropionic acid
F	Female
F344	Fischer 344
FSH	Follicle stimulating hormone
FOB	Functional observation battery
GC	Gas chromatography
g.d.	Gestation day
GI-tract	Gastrointestinal tract
GLP	Good laboratory practice
GSH	Glutathione
h	Hour
Hb	Haemoglobin
Hct	Haematocrit
HGPRT	Hypoxanthine-guanine-phosphoribosyl transferase

[a] Biological tolerance value at the workplace

APPENDIX A: SPECIAL ABBREVIATIONS (CONT'D)

^{3}H -TdR	^{3}H -Thymidine reduction
IgG	Immunoglobulin class G
IgM	Immunoglobulin class M
i.p.	Intraperitoneal
i.v.	Intravenous
LC_{50}	Lethal concentration for 50% of the exposed animals
LD_{50}	Lethal dose for 50% of the exposed animals
LDH	Lactate dehydrogenase
LH	Luteinising hormone
LO(A)EL	Lowest observed (adverse) effect level
LP	Lymphoproliferative
M	Male
MAALD	2-Methoxyacetaldehyde
MAK	Maximale Arbeitsplatzkonzentration [a]
MCHb	Mean cell haemoglobin
MCV	Mean corpuscular volume
MEAA	(2-Methoxy-ethoxy) acetic acid
MEG	Monoethylene glycol
MEL	Maximum exposure limit
MFO	Mixed function oxidase
mg	Milligramme
mmol	Millimole
ml	Millilitre
MAA	Methoxy acetic acid
MPA	Methoxy propionic acid
NA	Not available
NCE	Normochromatic erthyrocytes
ND	Not detected
n	Number of samples or subjects
NK	Natural killer
NKA	Natural killer (cell) activity
NO(A)EL	No-observed (adverse) effect level
NS	Not specified, not stated
NZW	New Zealand white
OEL	Occupational exposure limit (value)
PAS	Periodic acid Schiff
PBPK	Physiologically-based pharmacokinetic

[a] Maximum workplace concentration

APPENDIX A: SPECIAL ABBREVIATIONS (CONT'D)

PCE	Polychromatic erthyrocytes
PCT	Proximal convoluted tubule
PD	Protective dose
PFC	Plaque-forming cell
PHA	Phytohaemagglutinine
PHAA	Phenoxy acetic acid
PNPH	p-Nitrophenol
ppm	Parts per million
PROD	Pentoxyresorufin O-dealkylase
PWN	Poak wead nitrogen
RBC	Red blood cell(s)
S9	Supernatant of centrifuged 9,000 x g liver homogenate
s.c.	Subcutaneous
sd	Standard deviation
SD	Sprague-Dawley
SCE	Sister chromatid exchange
SGPT	Serum glutamic pyruvic transaminase
SHE	Syrian hamster embryo
SRBC	Sheep red blood cell(s)
ST	Sulfphotransferase
STEL	Short-term exposure limit
TCA	Tricarboxylic acid
TK	Thymidine kinase
TLV	Threshold limit value
TNP-LPS	Trinitrophenyl-lipopolysaccharide
TPG	Tripropylene glycol
TWA	Time-weighted average
UGT	UDP- glucuronosyl transferase
WBC	White blood cell(s)
wk	Week
+/–	With or without, in the presence or absence of
–ve	Negative: no effects
+ve	Positive: effects (on organ or system)
±ve	Equivocal
↓	Decrease
↑	Increase
µmol	Micromole
µg	Microgramme

APPENDIX B: CONVERSION FACTORS FOR VAPOUR CONCENTRATIONS IN AIR

Conversion factors for vapour concentrations in air can be calculated from the molar volume of an ideal gas at 0°C: 22.4136 litre.

$$1\ mg/m^3 = 22.4136/Mw \times 1{,}013.25/P \times (273+T)/273\ ppm \quad \text{.....(Eq. B.1)}$$

$$1\ ppm = Mw/22.4136 \times P/1{,}013.25 \times 273/(273+T)\ mg/m^3 \quad \text{.....(Eq. B.2)}$$

where Mw = molecular weight, T = temperature (°C) and P = pressure (hPa).

For European standard conditions, 20°C and 1,013.25 hPa (=1 atm = 760 mm Hg), the formulae become

$$1\ mg/m^3 = 24.0556/Mw\ ppm \quad \text{.....(Eq. B.3)}$$

$$1\ ppm = Mw/24.0556\ mg/m^3 \quad \text{.....(Eq. B.4)}$$

In the USA and other countries 25°C is used, and the formulae are:

$$1\ mg/m^3 = 24.4661/Mw\ ppm \quad \text{.....(Eq. B.5)}$$

$$1\ ppm = Mw/24.4661\ mg/m^3 \quad \text{.....(Eq. B.6)}$$

APPENDIX C: OCCUPATIONAL EXPOSURE LIMIT VALUES

Several countries have adopted OEL values (Table C.1). The justification of some OELs (also) takes account of critical effects on the reproductive system.

Table C.1: OEL values [a,b]

Country [c]	Concentration, 8-h [d] TWA		STEL, 15-min		Skin notation	Pregnancy group
	(ppm)	(mg/m^3) [e]	(ppm)	(mg/m^3) [e]		
1. Ethylene glycol methyl ether (EGME), CAS No. 109-86-4, structural formula: $CH_3–O–CH_2–CH_2–OH$						
Austria	5	15	10	30	Yes	
Belgium	5	16	-	-	Yes	
Denmark	5	16	-	-	Yes	
EU	-	-	-	-	-	May impair fertility (R60), May cause harm to the unborn child (R61), Toxic for reproduction (Category 2)
Finland	0.5	1.6	-	-	Yes	
France	5	16	-	-	Yes [f]	
Germany	5	16	20	64	Yes	Toxic for reproductive purposes
Ireland	5	16	-	-	Yes	Category 2 reproductive toxins: toxic for reproduction for humans
Italy	5	16	-	-	Yes	
Netherlands	0.3	1	-	-	Yes	Toxic to reproduction
Norway	5	16	-	-	Yes	Reproduction damaging substance
Portugal	-	-	-	-	-	
Spain	5	16	-	-	Yes	Substance that can and should be considered harmful for the fertility of human beings or should be considered toxic for their development.
Sweden	0.1	-	-	-	Yes	Reproduction-disturbing substances. Observation list: properties impairing reproduction.

Table C.1: OEL values[a,b] (cont'd)

Country [c]	Concentration, 8-h[d] TWA		STEL, 15-min		Skin notation	Pregnancy group
	(ppm)	(mg/m^3) [e]	(ppm)	(mg/m^3) [e]		
Switzerland	5	15	10	30	Yes	Harm to the foetus is possible even when the MAK value is complied with.
UK	5	16	-	-	Yes	
US-ACGIH	5	-	-	-	Yes	Critical effect: reproductive
US-NIOSH	0.1	0.3	-	-	-	Reproductive and developmental effects
US-OSHA	25	80	-	-	Yes	
Japan	5	16	-	-	Yes	
2. Ethylene glycol methyl ether acetate (EGMEA), CAS No. 110-49-6, structural formula $CH_3–O–CH_2–CH_2–O–CO–CH_3$						
Austria	5	25	10	50	Yes	
Belgium	5	24	-	-	Yes	
Denmark	5	24	-	-	Yes	
EU	-	-	-	-	-	May impair fertility (R60), May cause harm to the unborn child (R61), Toxic for reproduction (Category 2)
Finland	0.5	2.5	-	-	Yes	
France	5	24	-	-	Yes [f]	
Germany	5	25	20	100	Yes	Toxic for reproductive purposes
Ireland	5	24	-	-	Yes	Category 2 reproductive toxins: toxic for reproduction for humans
Italy	5	24	-	-	Yes	

Table C.1: OEL values[a,b] (cont'd)

Country [c]	Concentration, 8-h[d] TWA		STEL, 15-min		Skin notation	Pregnancy group
	(ppm)	(mg/m^3) [e]	(ppm)	(mg/m^3) [e]		
Netherlands	0.3	1.5	-	-	Yes	Toxic to reproduction
Norway	5	22	-	-	Yes	Reproduction damaging substance
Spain	5	24	-	-	Yes	Teratogen Category TR2: Substance that can and should be considered harmful for the fertility of human beings or should be considered toxic for their development.
Sweden	0.1	-	-	-	Yes	Group B: reproduction-disturbing substances. Observation list: properties impairing reproduction.
Switzerland	5	25	10	50	Yes	Harm to the foetus is possible even when the MAK value is complied with.
UK	5	25	-	-	Yes	
US-ACGIH	5	-	-	-	Yes	Critical effect: reproductive
US-NIOSH	0.1	0.5	-	-	Yes	Reproductive and developmental effects
US-OSHA	25	120	-	-	Yes	
Japan	5	24	-	-	Yes	
3. Ethylene glycol dimethyl ether (EGDME), CAS No. 110-71-4, structural formula: $CH_3–O–CH_2–CH_2–O–CH_3$						
	-	-	-	-	-	
4. Diethylene glycol methyl ether (DEGME), CAS No. 111-77-3, structural formula: $CH_3–(O–CH_2–CH_2)_2–OH$						
Denmark	25	-	-	-	-	
EU	-	-	-	-	-	Possible risk of harm to the unborn child (R63), Toxic for reproduction (Category 3)

Table C.1: OEL values[a,b] (cont'd)

Country [c]	Concentration, 8-h[d] TWA		STEL, 15-min		Skin notation	Pregnancy group
	(ppm)	(mg/m^3) [e]	(ppm)	(mg/m^3) [e]		
Netherlands	9	45	-	-		Toxic to reproduction
5. Diethylene glycol dimethyl ether (DEGDME), CAS No. 111-96-6, structural formula: CH_3–(O–CH_2–CH_2)$_2$–O–CH_3						
Austria	5	27	20	108	-	
Germany	5	28	20	112	Skin	
Netherlands	5	27	-	-		
Norway	-	-	-	-	-	Reproduction damaging substance
Switzerland	5	27	10	54	-	
6. Triethylene glycol methyl ether (TEGME), CAS No. 112-35-6, structural formula: CH_3–(O–CH_2–CH_2)$_3$–OH						
	-	-	-	-	-	
7. Triethylene glycol dimethyl ether (TEGDME), CAS No. 112-49-2, structural formula: CH_3–(O–CH_2–CH_2)$_3$–O–CH_3						
	-	-	-	-	-	
8. Methoxy-acetic acid (MAA), CAS No. 625-45-6, structural formula: CH_3–O–CH_2–COOH						
Netherlands	5	19	-	-	-	
EU	-	-	-	-	-	May impair fertility (R60), May cause harm to the unborn child (R61), Toxic for reproduction (Category 2)
Switzerland	5	19	10	38	-	Harm to the foetus is possible even when the MAK value is complied with.

Table C.1: OEL values[a,b] (cont'd)

Country [c]	Concentration, 8-h[d] TWA		STEL, 15-min		Skin notation	Pregnancy group
	(ppm)	(mg/m^3) [e]	(ppm)	(mg/m^3) [e]		
9. Ethylene glycol ethyl ether (EGEE), CAS No. 110-80-5, structural formula: $C_2H_5–O–CH_2–CH_2–OH$						
Austria	5	19	20	76	Yes	
Belgium	5	18	-	-	Yes	
Denmark	5	18.5	-	-	Yes	
EU	-	-	-	-	-	May impair fertility (R60), May cause harm to the unborn child (R61), Toxic for reproduction (Category 2)
France	5	19	-	-	Yes [f]	
Finland	2	7.5	-	-	Yes	
Germany	5	19	20	76	Yes	Substances which are Carcinogenic, Mutagenic or Toxic for Reproductive Purposes
Ireland	5	18	-	-	Yes	Substance should be regarded as if it is toxic for reproduction for humans (Category 2 reproductive toxins).
Italy	5	18	-	-	Yes	
Netherlands	5	19	-	-	Yes	Substances toxic to reproduction
Norway	5	18	-	-	Yes	Reproduction Damaging Substance
Spain	5	18	-	-	Yes	Substance that can and should be considered harmful for the fertility of human beings or should be considered toxic for their development)
Sweden	5	19	10	40	Yes	Substance has reproduction-disturbing effects. Properties impairing reproduction.

Table C.1: OEL values[a,b] (cont'd)

Country [c]	Concentration, 8-h[d] TWA		STEL, 15-min		Skin notation	Pregnancy group
	(ppm)	(mg/m^3) [e]	(ppm)	(mg/m^3) [e]		
Switzerland	5	19	10	38	Yes	Harm to the foetus is possible even when the MAK value is complied with.
UK	10	37	-	-	Yes	
US-ACGIH	5	-	-	-	Yes	Critical Effect(s): Reproductive
US-NIOSH	0.5	1.8	-	-	Yes	Reproductive and developmental effects
US-OSHA	200	740	-	-	Yes	
Japan	5	18	-	-	Yes	
10. Ethylene glycol ethyl ether acetate (EGEEA), CAS No. 111-15-9, structural formula: $C_2H_5–O–CH_2–CH_2–O–CO–CH_3$						
Austria	5	27	20	108	Yes	
Belgium	5	27	-	-	Yes	
Denmark	5	27.0	-	-	Yes	
EU	-	-	-	-	-	May impair fertility (R60), May cause harm to the unborn child (R61), Toxic for reproduction (Category 2)
France	5	27	-	-	Yes [f]	
Finland	2	11	-	-	Yes	
Germany	5	27	20	108	Yes	Substances which are carcinogenic, mutagenic or toxic for reproductive purposes
Ireland	10	54	-	-	Yes	Substance should be regarded as if it is toxic for reproduction for humans (Category 2 reproductive toxins).
Italy	5	27	-	-	Yes	

Table C.1: OEL values[a,b] (cont'd)

Country [c]	Concentration, 8-h[d] TWA		STEL, 15-min		Skin notation	Pregnancy group
	(ppm)	(mg/m^3) [e]	(ppm)	(mg/m^3) [e]		
Norway	5	27	-	-	Yes	Reproduction damaging substance
Spain	5	27	-	-	Yes	Substance that can and should be considered harmful for the fertility of human beings or should be considered toxic for their development
Sweden	5	30	10	50	Yes	Substance has reproduction-disturbing effects. Properties impairing reproduction
Switzerland	5	27	10	54	Yes	Harm to the foetus is possible even when the MAK value is complied with
Netherlands	5	27	-	-	Yes	Substances toxic to reproduction
UK	10	55	-	-	Yes	
US-ACGIH	5	-	-	-	Yes	Critical Effect(s): Reproductive
US-NIOSH	0.5	2.7	-	-	Yes	Reproductive and developmental effects
US-OSHA	100	540	-	-	Yes	
Japan	5	27	-	-	Yes	
11. Ethylene glycol diethyl ether (EGDEE), CAS No. 629-14-1, structural formula: C_2H_5–O–CH_2–CH_2–O–C_2H_5						
	-	-	-	-	-	
12. Diethylene glycol ethyl ether (DEGEE), CAS No. 111-90-0, structural formula: C_2H_5–(O–CH_2–CH_2)$_2$–OH						
Netherlands	32	180	-	-	Yes	
Sweden	15	80	30	170	Yes	
US-AIHA	25	140	-	-	-	

Table C.1: OEL values[a,b] (cont'd)

Country [c]	Concentration, 8-h[d] TWA		STEL, 15-min		Skin notation	Pregnancy group
	(ppm)	(mg/m^3) [e]	(ppm)	(mg/m^3) [e]		
13. Diethylene glycol ethyl ether acetate (DEGEEA), CAS No. 112-15-2, structural formula: $C_2H_5–(O–CH_2–CH_2)_2–O–CO–CH_3$						
Sweden	15	110	30	220	Yes	
14. Diethylene glycol diethyl ether (DEGDEE), CAS No. 112-36-7, structural formula: $C_2H_5–(O–CH_2–CH_2)_2–O–C_2H_5$						
	-	-	-	-	-	
15. Triethylene glycol(mono) ethyl ether (TEGEE), CAS No. 112-50-5, structural formula: $C_2H_5–(O–CH_2–CH_2)_3–OH$						
	-	-	-	-	-	
16. Ethylene glycol isopropyl ether (EgiPE), CAS No. 109-59-1, structural formula: $(CH_3)_2CH–O–CH_2–CH_2–OH$						
Austria	5	22	10	44	Yes	
Belgium	25	108	-	-	Yes	
Denmark	5	22	-	-	Yes	
France	25	105	-	-	Yes [f]	
Germany	5	22	20	88	Yes	If the MAK and BAT values are complied with, there should be no risk for the foetus
Ireland	25	106	-	-	Yes	
Italy	25	106	-	-	Yes	
Netherlands	10	44	-	-	Yes	
Norway	20	80	-	-	-	
Sweden	10	45	20	90	Yes	

Table C.1: OEL values[a,b] (cont'd)

Country [c]	Concentration, 8-h[d] TWA		STEL, 15-min		Skin notation	Pregnancy group
	(ppm)	(mg/m^3) [e]	(ppm)	(mg/m^3) [e]		
Switzerland	5	22	10	44	Yes	The foetus will not be harmed if the MAK value is complied with.
US-ACGIH	25	-	-	-	Yes	
17. Ethylene glycol isopropyl ether acetate (EGiPEA), CAS No. 91598-97-9, structural formula: $(CH_3)_2CH–O–CH_2–CH_2–O–CO–CH_3$						
	-	-	-	-	-	
18. Ethylene glycol *n*-propyl ether (EgnPE), CAS No. 2807-30-9, structural formula: $C_3H_7–O–CH_2–CH_2–OH$						
Denmark	25	110	-	-	-	
Germany	20	86	20	86	Yes	If the MAK and BAT values are complied with, there should be no risk for the foetus
Netherlands	10	44	-	-	Yes	
Sweden	10	45	20	90	Yes	
Switzerland	20	85	40	170	Yes	The foetus will not be harmed if the MAK value is complied with.
19. Ethylene glycol *n*-propyl ether acetate (EGnPEA), CAS No. 20706-25-6, structural formula: $C_3H_7–O–CH_2–CH_2–O–CO–CH_3$						
Germany	20	120	20	120	Yes	If the MAK and BAT values are complied with, there should be no risk for the foetus
Netherlands	10	60	-	-	Yes	
Switzerland	20	120	40	240	Yes	The foetus will not be harmed if the MAK value is complied with.

Table C.1: OEL values[a,b] (cont'd)

Country [c]	Concentration, 8-h[d] TWA		STEL, 15-min		Skin notation	Pregnancy group
	(ppm)	(mg/m^3) [e]	(ppm)	(mg/m^3) [e]		
20. Ethylene glycol phenyl ether (EGPhE), CAS No. 122-99-6, structural formula: $C_6H_5–O–CH_2–CH_2–OH$						
Germany	20	110	20	110	-	If the MAK and BAT values are complied with, there should be no risk for the foetus
Netherlands	20	110	-	-	-	
Switzerland	20	110	40	220	Yes	The foetus will not be harmed if the MAK value is complied with.
21. Ethylene glycol *n*-butyl ether (EGBE), CAS No. 111-76-2, structural formula: $C_4H_9–O–CH_2–CH_2–OH$						
Austria	20	100	40	200	Yes	
Belgium	25	123	-	-	Yes	
Denmark	20	98	-	-	Yes	
EU	20	98	50	246	Yes	
Finland	20	98	50	250	Yes	
France	25	120	-	-	Yes [f]	
Germany	20	98	80	392	Yes	If the MAK and BAT values are complied with, there should be no risk for the foetus
Ireland	25	120	-	-	Yes	
Italy	20	97	-	-	Yes	
Netherlands	20	100	50	246	Yes	
Norway	10	50	-	-	Yes	
Spain	20	98	-	-	Yes	

Table C.1: OEL values[a,b] (cont'd)

Country [c]	Concentration, 8-h[d] TWA		STEL, 15-min		Skin notation	Pregnancy group
	(ppm)	(mg/m^3) [e]	(ppm)	(mg/m^3) [e]		
Sweden	10	50	20	100	Yes	
Switzerland	20	100	40	200	Yes	
UK	25	123	-	-	Yes	
US-ACGIH	20	-	-	-	Yes	
US-NIOSH	5	24	-	-	Yes	
US-OSHA	25	120	-	-	Yes	
22. Ethylene glycol *n*-butyl ether acetate (EGBEA), CAS No. 112-07-2, structural formula: $C_4H_9–O–CH_2–CH_2–O–CO–CH_3$						
Austria	20	135	40	270	Yes	
Denmark	20	130	-	-	Yes	
EU	20	133	50	333	Yes	
Finland	20	130	50	330	Yes	
Germany	20	130	80	520	Yes	If the MAK and BAT values are complied with, there should be no risk for the foetus
Netherlands	20	135	50	333	Yes	
Norway	10	65	-	-	Yes	
Spain	20	133	50	333	Yes	
Sweden	10	70	20	140	Yes	
Switzerland	20	135	40	270	Yes	
US-ACGIH	20	-	-	-	-	
US-NIOSH	5 [g]	33	-	-	-	

Table C.1: OEL values[a,b] (cont'd)

Country [c]	Concentration, 8-h[d] TWA		STEL, 15-min		Skin notation	Pregnancy group
	(ppm)	(mg/m^3) [e]	(ppm)	(mg/m^3) [e]		
23. Diethylene glycol butyl ether (DEGBE), CAS No. 112-34-5, structural formula: C_4H_9–(O–CH_2–CH_2)$_2$–OH						
Austria	15	100	15	100	-	
Denmark	-	100	-	-	-	
Germany	-	100	-	100	-	If the MAK and BAT values are complied with, there should be no risk for the foetus
Netherlands	9	50	-	-	Yes	
Sweden	15	100	30	200	-	
Switzerland	-	100	-	100	-	The foetus will not be harmed if the MAK value is complied with.
24. Diethylene glycol butyl ether acetate (DEGBEA), CAS No. 124-17-4, structural formula: C_4H_9–(O–CH_2–CH_2)$_2$–O–CO–CH_3						
Netherlands	15	130	30	250	-	
Sweden	15	130	30	250	-	
25. Triethylene glycol *n*-butyl ether (TEGBE), CAS No. 143-22-6, structural formula: C_4H_9–(O–CH_2–CH_2)$_3$–OH						
	-	-	-	-	-	
26. Ethylene glycol (mono) *n*-hexyl ether (EGHE), CAS No. 112-25-4, structural formula: C_6H_{13}–O–CH_2–CH_2–OH						
	-	-	-	-	-	
27. Diethylene glycol (mono) hexyl ether (DEGHE), CAS No. 112-59-4, structural formula: C_6H_{13}–(O–CH_2–CH_2)$_2$–OH						
	-	-	-	-	-	

Table C.1: OEL values[a,b] (cont'd)

Country [c]	Concentration, 8-h[d] TWA		STEL, 15-min		Skin notation	Pregnancy group
	(ppm)	(mg/m^3) [e]	(ppm)	(mg/m^3) [e]		
28. 2-Propylene glycol 1-methyl ether (2PG1ME), CAS No. 107-98-2, structural formula: $CH_3–CH(OH)–CH_2–O–CH_3$						
Austria	50	187	50	187	Yes	
Belgium	100	374	150	561	-	
Denmark	50	185	-	-	-	
EU	100	375	150	568	Yes	
France	100	360	-	-	- [f]	
Finland	100	370	150	560	-	
Germany	100	370	100	370	-	If the MAK and BAT values are complied with, there should be no risk for the foetus
Ireland	100	360	300	1,080	Yes	
Italy	100	369	150	553	-	
Netherlands	100	375				
Norway	50	180	-	-	Yes	
Spain	100	374	200	748	Yes	
Sweden	50	190	75	300	Yes	
Switzerland	100	360	200	720	-	The foetus will not be harmed if the MAK value is complied with.
UK	100	375	300	1,120	Yes	
US-ACGIH	100	-	150	-	-	
US-NIOSH	100	360	150	540	-	

Table C.1: OEL values[a,b] (cont'd)

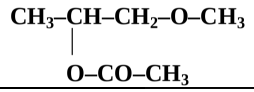
Country [c]	Concentration, 8-h[d] TWA		STEL, 15-min		Skin notation	Pregnancy group
	(ppm)	(mg/m^3) [e]	(ppm)	(mg/m^3) [e]		
29. 2-Propylene glycol 1-methyl ether 2-acetate (2PG1MEA), CAS No. 108-65-6, structural formula:						
Austria	50	275	100	550	-	
Belgium	50	275	100	550	Yes	
Denmark	50	270	-	-	-	
EU	50	275	100	550	Yes	
Finland	50	270	100	550	Yes	
Germany	50	270	50	270	-	If the MAK and BAT values are complied with, there should be no risk for the foetus
Ireland	50	275	100	550	Yes	
Italy	50	275	100	550	-	
Netherlands	100	550	-	-	-	
Norway	50	270	-	-	Yes	
Spain	50	275	100	550	Yes	
Sweden	50	250	75	400	Yes	
Switzerland	50	275	50	275	-	The foetus will not be harmed if the MAK value is complied with.
UK	50	274	150	822	-	
Canada	50	75	-	-	Yes	

Table C.1: OEL values[a,b] (cont'd)

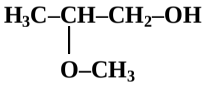
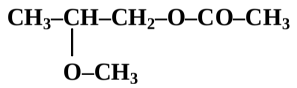
Country [c]	Concentration, 8-h[d] TWA		STEL, 15-min		Skin notation	Pregnancy group
	(ppm)	(mg/m^3) [e]	(ppm)	(mg/m^3) [e]		
US-AIHA	100	541	-	-	-	
US-California	100	541	150	811	-	
30. 1-Propylene glycol 2-methyl ether (1PG2ME), CAS No. 1589-47-5, structural formula:						
Austria	20	75	40	150	-	
Denmark	20	75	-	-	-	
EU						May cause harm to the unborn child (R60), Toxic for reproduction (Category 2)
Germany	20	75	80	300	-	
Netherlands	-	-	-	-	-	Substances toxic to reproduction
Norway	20	75	-	-	Yes	Reproduction damaging substance
Spain	20	75	-	-	-	
Sweden	50	190	75	300	Yes	
Switzerland	20	75	40	150	Yes	Harm to the foetus is possible even when the MAK value is complied with
Canada	20	-	40	-	-	Possible reproductive toxin
31. 1-Propylene glycol 2-methyl ether 1-acetate (1PG2MEA), CAS No. 70657-70-4, structural formula:						
Austria	20	110	40	220	-	

Table C.1: OEL values[a,b] (cont'd)

Country [c]	Concentration, 8-h[d] TWA		STEL, 15-min		Skin notation	Pregnancy group
	(ppm)	(mg/m^3) [e]	(ppm)	(mg/m^3) [e]		
Denmark	20	110	-	-	-	
EU	-	-	-	-	-	May cause harm to the unborn child (R61), Toxic for reproduction (Category 2)
Germany	20	110	80	440	-	
Netherlands	-	-	-	-	-	Substances toxic to reproduction
Norway	20	110	-	-	Yes	Reproduction damaging substance
Switzerland	20	110	40	220	Yes	Harm to the foetus is possible even when the MAK value is complied with
Canada	20	-	40	-	-	Possible reproductive toxin
32. Dipropylene glycol methyl ether (DPGME), CAS No. 34590-94-8, structural formula:					**$CH_3–(O–CH_2–CH(CH_3))_2–OH$**	
Austria	50	307	100	614	-	
Belgium	50	308	-	-	Yes	
Denmark	50	300	-	-	Yes	
EU	50	308	-	-	Yes	
Finland	50	310	-	-	Yes	
France	100	600	-	-	- [f]	
Germany	50	310	50	310	-	
Ireland	100	606	150	909	Yes	
Italy	50	308	-	-	Yes	

Table C.1: OEL values[a,b] (cont'd)

Country [c]	Concentration, 8-h[d] TWA		STEL, 15-min		Skin notation	Pregnancy group
	(ppm)	(mg/m^3) [e]	(ppm)	(mg/m^3) [e]		
Netherlands	50	300				
Norway	50	300	-	-	Yes	
Spain	50	308	-	-	Yes	
Sweden	50	300	75	450	Yes	
Switzerland	50	300	50	300	Yes	
UK	50	308	-	-	Yes	
Canada-Alberta	100	606	150	909	Yes	
Canada, British Columbia	100	-	150	-	Yes	
Canada, Ontario	100	605	150	910	Yes	
Mexico	100	600	150	900	Yes	
US-ACGIH	100	-	150	-	Yes	
US-NIOSH	100	600	-	-	Yes	
US-OSHA	100	600	-	-	Yes	
US-California	100	600	150	900	Yes	
US-North Carolina	100	600	150	900	Yes	
33. Tripropylene glycol methyl ether (TPGME), CAS No. 25498-49-1, structural formula:					$CH_3–(O–CH_2–\underset{\displaystyle CH_3}{\underset{\vert}{CH}})_3–OH$	
	-	-	-	-	-	

Table C.1: OEL values[a,b] (cont'd)

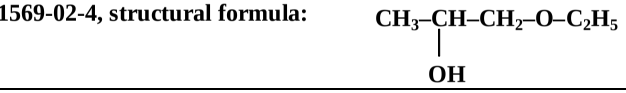
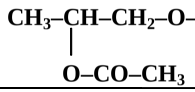
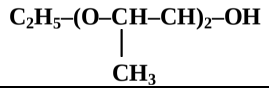
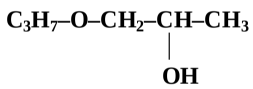
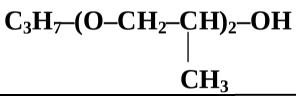
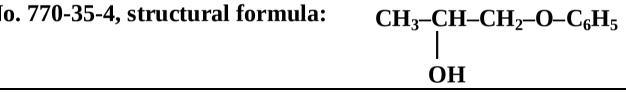
Country [c]	Concentration, 8-h[d] TWA		STEL, 15-min		Skin notation	Pregnancy group
	(ppm)	(mg/m^3) [e]	(ppm)	(mg/m^3) [e]		
34. 2-Propylene glycol 1-ethyl ether (2PG1EE), CAS No. 1569-02-4, structural formula: 						
Denmark	100	-	-	-	-	
35. 2-Propylene glycol 1-ethyl ether 2-acetate (2PG1EEA), CAS No. 54839-24-6, structural formula: 						
	-	-	-	-	-	
36. Dipropylene glycol ethyl ether (DPGEE), CAS No. 30025-38-8, structural formula: 						
	-	-	-	-	-	
37. Propylene glycol *n*-propyl ether (PGPE), CAS No. 1569-01-3, structural formula: 						
Denmark	100	-	-	-	-	
38. Dipropylene glycol *n*-propyl ether (DPGPE), CAS No. 29911-27-1, structural formula: 						
	-	-	-	-	-	
39. 2-Propylene glycol 1-phenyl ether (2PG1PhE), CAS No. 770-35-4, structural formula: 						
	-	-	-	-	-	

Table C.1: OEL values[a,b] (cont'd)

Country [c]	Concentration, 8-h[d] TWA		STEL, 15-min		Skin notation	Pregnancy group
	(ppm)	(mg/m^3) [e]	(ppm)	(mg/m^3) [e]		
40. 2-Propylene glycol 1-n-butyl ether (2PG1BE), CAS No. 5131-66-8, structural formula:					$C_4H_9–O–CH_2–CH(CH_3)–OH$	
Denmark	100	-	-	-	-	
41. Dipropylene glycol 1-butyl ether (DPGBE), CAS No. 29911-28-2, structural formula:					$C_4H_9–(O–CH_2–CH(CH_3))_2–OH$	
	-	-	-	-	-	
42. Tripropylene glycol 1-butyl ether (TPGBE), CAS No. 55934-93-5, structural formula:					$C_4H_9–(O–CH_2–CH(CH_3))_3–OH$	
	-	-	-	-	-	
43. Propylene glycol *tert*-butyl ether (PGTBE), CAS No. 57018-52-7, structural formula:					$CH_3–CH(OH)–CH_2–O–C(CH_3)_3$	
	-	-	-	-	-	
44. Dipropylene glycol *tert*-butyl ether (DPGTBE), CAS No. 132739-31-2, structural formula:					$C_6H_{13}–O–CH_2–CH_2–OH$	
	-	-	-	-	-	

[a] The value may be advisory or official (tentative or legally binding)

[b] Ariel Research, 2002

[c] For additional EU national information, see: http://europe.osha.eu.int/good_practice/risks/ds/oel/
For EU OEL activities, see: http://europe.eu.int/comm/employment_social/hands/areas/oels_en.htm
For Japan, see: http://joh.med.uoeh-u.ac.jp/oel/index.html.

[d] NIOSH 10-h TWA

[e] Some agencies use (slightly) different conversion factors based on variations in temperature, pressure and/or normal gas volume, cf. Appendix C.

[f] Affections engendrées par les solvants organiques liquides à usage professionnel: …, glycols et leurs éthers … (France, 1985)

[g] Recommended value (EGBEA)

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Acknowledgement

The contribution of A. Margary (Shell Chemicals, UK - London) to Section 3.1 of this report and the editorial input from J. Kelsey (BP Chemicals, UK - Sunbury-on-Thames) are gratefully acknowledged.

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