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CONTENTS

SUMMARY

A previous ECETOC review (1985) discussed the toxicological effects of ethylene and propylene glycol alkyl ethers and explained the toxicological observations in the context of metabolism. The current report includes a larger number of glycol ethers, presents the updated relevant toxicological information in animals and man, and reviews the knowledge of mechanisms underlying the observed toxicology.

Glycol ether acetates have the same systemic toxicological effects as their parent glycol ethers and it is reasonable to consider that their toxicity is equivalent on a molar basis.

Consideration of new data and other glycol ethers has not fundamentally altered the previously known toxicological effects exhibited by some members of this chemical group. The short chain ethylene glycol methyl and ethyl ethers (and their acetates), as well as other glycol ethers capable of being converted to ethylene glycol methyl or ethyl ethers, cause testicular atrophy, teratogenicity/foetotoxicity and bone marrow depression. In contrast, longer chain ethylene glycol ethers (ethylene glycol butyl ether, - propyl ether, - isopropyl ether and - phenyl ether) do not cause these effects, but do cause erythrocyte fragility in rats; human erythrocytes are significantly less sensitive for haemolysis than the rodent erythrocytes. The immunological effects, particularly for ethylene glycol methyl ether have now been studied in more detail.

The toxicity of propylene glycol ethers with the alkoxy group at the primary position is quite different to that of the ethylene glycol ethers. None of the effects mentioned above have been reported and the only evidence of toxicity is towards liver and kidney. Teratogenic effects (but no testicular or bone marrow effects) have been reported when the primary position is occupied by a hydroxyl group (1-propylene glycol 2-methyl ether or acetate, neither of which are commercially available).

The principle clinical signs of acute intoxication in animals are consistent with the non-specific CNS depression commonly seen with organic solvents. Those glycol ethers that cause haemolytic effects have lower LD_{50} or LC_{50} values than the other glycol ethers. Glycol ethers generally do not appear to be appreciably irritating to the skin on acute exposure. Consistent with the solvent properties of these materials, prolonged or repeated exposure may lead to more severe skin irritation. There is no evidence from animal experiments or human observations that glycol ethers are skin sensitisers.

Glycol ethers have the potential to penetrate the skin and this therefore represents a potentially significant route of exposure. Some comparative *in vitro* data show that the degree of penetration varies with chemical structure. Recent studies with ethylene glycol butyl ether indicate that dermal

absorption from the vapour phase can contribute significantly to total systemic exposure.

Target organ toxicity has been related to the extent of formation of the following metabolites: methoxy- and ethoxy-acetic acid (affecting testes, bone marrow, thymus and embryonic tissue) and butoxyacetic acid (erythrocyte haemolysis). A similar relation is presumed for methoxypropionic acid (embryonic tissue). In contrast, ethylene glycol phenyl ether (phenoxyethanol) is a more potent haemolytic agent than the metabolite phenoxyacetic acid.

Apart from target organ toxicity, the liver has frequently shown an increased weight (in the absence of pathological change) following high doses of 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 1-methyl ether administration. These changes are diagnosed for 2-propylene glycol 1-methyl ether to result from the accumulation of alpha 2 microglobulin. They occurred only in male rats and are not considered relevant for man. This is also most likely the case for dipropylene glycol ethyl ether but definitive analytical confirmation is not available.

The database on mutagenicity tests has been significantly enlarged, with the majority of tests indicating no genotoxic activity. Whilst *in vitro* tests for clastogenic action showed an increase in chromosomal aberrations (eg for ethylene glycol ethyl ether), this effect could not be confirmed with mammalian *in vivo* test systems.

The general conclusion that glycol ethers, when tested according to internationally accepted test protocols, do not pose a significant genotoxic risk to man is still valid.

The characteristic toxic effects of specific glycol ethers have all been observed following short term exposure and do not increase in severity in studies of longer duration. This observation, together with the absence of significant genotoxic effects, indicates that long-term exposure is not likely to lead to more severe or different effects, relevant for the risk assessment for human beings. The few long-term studies available support the contention that glycol ethers are not likely to be potential human carcinogens.

Metabolism plays a key role in explaining the different toxicological effects observed in structurally related compounds. The main metabolic route is oxidation via alcohol dehydrogenase when a terminal hydroxyl group is available, leading to the formation of the alkoxy-acetic or alkoxy-propionic acids.

The toxic effects observed correlate with the extent of metabolite formation and its elimination rate.

A second important route of metabolism is oxidation by the microsomal P450 mixed function oxidase (O-dealkylation). This leads to the production of ethylene glycol or propylene glycol, which enter into the tricarboxylic acid cycle and are partially excreted as carbon dioxide.

Significant adverse systemic health effects in man have been reported for ethylene glycol methyl ether, ethyl ether and their acetates and diethylene glycol dimethyl ether based on evaluation of worker populations exposures and case reports. Ethylene glycol methyl and ethyl ethers exposure has been associated with anaemia, granulocytopenia and leucopenia and several reports have indicated an association between exposure and increased risk of abortion. Ethylene glycol methyl and ethyl ethers have also been associated with reduced sperm count in painters. The number of observations and the limited information on the level of exposure do not allow firm conclusions to be made.

A single case report has associated significant occupational dermal exposure to ethylene glycol phenyl ether with nervous system effects in 3 women. Data on aplastic anaemia in lithographers are considered to be related to exposure to ethylene glycol ethyl ether, rather than to the confounding presence of dipropylene glycol methyl ether.

Although the individual literature references on ethylene glycol methyl ether, - ethyl ether and acetate do not provide conclusive evidence, the multitude of data on effects in man is compatible with the experimental data in several animal species and suggests at least a similar sensitivity in man for the effects described in animals. The data on haemolytic effects with ethylene glycol butyl ether and - phenyl ether indicate that man is significantly less sensitive to this effect than some animal species.

This evidence indicates that metabolites are of great importance in the toxicology of the glycol ethers. Linked to this is the clear observation that small differences in glycol ether structure can significantly affect toxicity. Structural comparisons may be misleading if applied separately from a knowledge of the metabolism of the material being considered.

SECTION 1. INTRODUCTION

ECETOC earlier reviewed the toxicology of ethylene glycol ethers (and 2-propylene glycol-1-methyl ether) (ECETOC, 1982). This was further extended and updated, when the toxicology and its relevance for health effects in man of 26 glycol ethers, 19 of which were based on ethylene glycol and 7 on propylene glycol were examined (ECETOC, 1985). A number of new studies have become available since 1985, published either in the open literature or from other sources, and it was considered desirable to update the earlier reviews to take account of the substantial amount of new information.

The present report considers 35 glycol ethers, 24 of which are based on ethylene glycol and 11 on propylene glycol. Glycol ethers were selected for review on the basis of either commercial interest or their significance in understanding the toxicology of these materials.

An overview of the important elements of the toxicology of the glycol ethers and a review of human exposure and health effects have been brought together in a separate chapter.
The key toxicological data for each of the glycol ethers have been summarised in individual Substance Profiles. Toxicological data have been tabulated to allow easy comparison of effects between different glycol ethers (appendices A,B,C,D).

1.1 LIST OF GLYCOL ETHERS

A systematic survey of the glycol ethers considered in this review including descriptive names, abbreviations, structural formula and CAS numbers is given in Table 1.

1.2 LIST OF ABBREVIATIONS

The abbreviations used in this report are listed in Table 2.

Table 1: List of Glycol Ethers

	Name	Structural Formula	CAS-No.
EGME	Ethylene Glycol(mono) Methyl Ether	CH_3-O-CH_2-CH_2-OH	109-86-4
EGMEA	Ethylene Glycol(mono) Methyl Ether Acetate	CH_3-O-CH_2-CH_2-O-CO-CH_3	110-49-6
MAA	Methoxy-Acetic Acid	CH_3-O-CH_2-COOH	625-45-6
EGEE	Ethylene Glycol(mono) Ethyl Ether	C_2H_5-O-CH_2-CH_2-OH	110-80-5
EGEEA	Ethylene Glycol(mono) Ethyl Ether Acetate	C_2H_5-O-CH_2-CH_2-O-CO-CH_3	111-15-9
EGnPE	Ethylene Glycol(mono) n-Propyl Ether	C_3H_7-O-CH_2-CH_2-OH	2807-30-9
EGnPEA	Ethylene Glycol(mono) n-Propyl Ether Acetate	C_3H_7-O-CH_2-CH_2-O-CO-CH_3	20706-25-6
EGiPE	Ethylene Glycol(mono) iso-Propyl Ether	$(CH_3)_2$CH-O-CH_2-CH_2-OH	109-59-1
EGBE	Ethylene Glycol(mono) n-Butyl Ether	C_4H_9-O-CH_2-CH_2-OH	111-76-2
EGBEA	Ethylene Glycol n-Butyl Ether Acetate	C_4H_9-O-CH_2-CH_2-O-CO-CH_3	112-07-2
EGPhE	Ethylene Glycol(mono) Phenyl Ether	C_6H_5-O-CH_2-CH_2-OH	122-99-6
EGDME	Ethylene Glycol Dimethyl Ether	CH_3-O-CH_2-CH_2-O-CH_3	110-71-4
EGDEE	Ethylene Glycol Diethyl Ether	C_2H_5-O-CH_2-CH_2-O-C_2H_5	629-14-1
DEGME	Diethylene Glycol(mono) Methyl Ether	CH_3-(O-CH_2-CH_2)$_2$-OH	111-77-3
DEGEE	Diethylene Glycol(mono) Ethyl Ether	C_2H_5-(O-CH_2-CH_2)$_2$-OH	111-90-0
DEGEEA	Diethylene Glycol Ethyl Ether Acetate	C_2H_5-(O-CH_2-CH_2)$_2$-O-CO-CH_3	112-15-2
DEGBE	Diethylene Glycol(mono) Butyl Ether	C_4H_9-(O-CH_2-CH_2)$_2$-OH	112-34-5
DEGBEA	Diethylene Glycol Butyl Ether Acetate	C_4H_9-(O-CH_2-CH_2)$_2$-O-CO-CH_3	124-17-4
DEGDME	Diethylene Glycol Dimethyl Ether	CH_3-(O-CH_2-CH_2)$_2$-O-CH_3	111-96-6
DEGDEE	Diethylene Glycol Diethyl Ether	C_2H_5-(O-CH_2-CH_2)$_2$-O-C_2H_5	112-36-7
TEGME	Triethylene Glycol(mono) Methyl Ether	CH_3-(O-CH_2-CH_2)$_3$-OH	112-35-6
TEGEE	Triethylene Glycol(mono) Ethyl Ether	C_2H_5-(O-CH_2-CH_2)$_3$-OH	112-50-5
TEGBE	Triethylene Glycol(mono) n-Butyl Ether	C_4H_9-(O-CH_2-CH_2)$_3$-OH	143-22-6
TEGDME	Triethylene Glycol Dimethyl Ether	CH_3-(O-CH_2-CH_2)$_3$-O-CH_3	112-49-2
2PG1ME	2-Propylene Glycol 1-Methyl Ether	CH_3-CH(OH)-CH_2-O-CH_3	107-98-2
2PG1MEA	2-Propylene Glycol 1-Methyl Ether 2-Acetate	CH_3-CH(O-CO-CH_3)-CH_2-O-CH_3	108-65-6

Table 1: List of Glycol Ethers (Cont.)

	Name	Structural Formula	CAS-No.
2PG1EE	2-Propylene Glycol 1-Ethyl Ether	CH_3-CH(OH)-CH_2-O-C_2H_5	1569-02-4
2PG1EEA	2-Propylene Glycol 1-Ethyl Ether 2-Acetate	CH_3-CH(O-CO-CH_3)-CH_2-O-C_2H_5	54839-24-6
2PG1BE	2-Propylene Glycol 1-n-Butyl Ether	CH_3-CH(OH)-CH_2-O-$(CH_2)_3$-CH_3	5131-66-8/ 29387-86-8
2PG1PhE	2-Propylene Glycol 1-Phenyl Ether	CH_3-CH(OH)-CH_2-O-C_6H_5	770-35-4
1PG2ME	1-Propylene Glycol 2-Methyl Ether	H_3C - CH(OCH_3) - CH_2-OH	1589-47-5
1PG2MEA	1-Propylene Glycol 2-Methyl Ether 1-Acetate	CH_3-CH(O-CH_3)-CH_2-O-CO-CH_3	70657-70-4
DPGME	Dipropylene Glycol (mono) Methyl Ether	CH_3-(O-CH_2-CH(CH_3))$_2$-OH	34590-94-8
DPGEE	Dipropylene Glycol(mono) Ethyl Ether	C_2H_5-(O-CH(CH_3)-CH)$_2$-OH	300025-38-8
TPGME	Tripropylene Glycol (mono) Methyl Ether	CH_3-(O-CH_2-CH(CH_3))$_3$-OH	25498-49-1

Table 2: List of Abbreviations

ACGIH	American Conference of Governmental Industrial Hygienists
ADH	Aldehyde Dehydrogenase
ADME	Absorption Distribution Metabolism Elimination
ALP or AP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ATP	Adenosine Triphosphate
BAA	Butoxy Acetic Acid
BAL	Butoxy Acetaldehyde
BAT	Biologischer Arbeitsstoff-Toleranz-Wert*
CAS	Chemicals Abstracts Service
CHO	Chinese Hamster Ovary Cell
CNS	Central Nervous System
Con A	Concanavalin A
Cyt C	Cytochrome C
d	Day
DL-effect	Dominant Lethal
DNA	Deoxyribonucleic acid
EAA	Ethoxy Acetic Acid
EG	Ethylene Glycol
EMH	Extramedullary Haemopoiesis
ETOH	Ethanol
f	Female
FSH	Follicle Stimulating Hormone
gd	Gestation Day
GI-tract	Gastrointestinal Tract
GLP	Good Laboratory Practice
GSH	Glutathione

* Biological Tolerance Values at the Workplace

Table 2: List of Abbreviations (Cont.)

h	Hour
Hb	Haemoglobin
Hct	Haematocrit
HGPRT	Hypoxanthine-Guanine-Phosphoribosyl- Transferase
^{3}H - TdR	^{3}H - Thymidine Reduction
IL-2	Interleukin 2
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
LDHX	A Patchytenespermatocyte Marker Enzyme
LH	Luteinizing Hormone
m	Male
MAK	Maximale Arbeits Platz-Konzentration*
MCH or MCHb	Mean Cell Haemoglobin
MCHC	Mean Cell Haemoglobin Concentration
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
mM	Millimolar
MPA	Methoxy Propionic Acid

* Maximum Workplace Concentration

Table 2: List of Abbreviations (Cont.)

NK	Natural Killer Cell
NKA	Natural Killer Cell Activity
NOEL	No Observed Effect Level
OSHA	Occupational Safety and Health Administration
p.p.	Post Partum
PCT	Proximal Convoluted Tubule
PCV	Packed Cell Volume
PFC	Plaque Forming Cell
PHA	Phyto Haem Agglutinin
ppm	Parts per million
RBC	Red Blood Cell
s.c.	Subcutaneous
SRBC	Sheep Red Blood Cells
SCE	Sister Chromatid Exchange
SGPT	Serum Glutamic Pyruvic Transaminase
SLRL-test	Sex Linked Recessive Lethal Assay
STEL	Short Term Exposure Limit
TCA	Tricarboxylic Acid
TLV	Threshold Limit Value
TNP - LPS	Trinitrophenyl - Lipopolysaccharide
TPG	Tripropylene Glycol
TWA	Time Weighted Average
UDS	Unscheduled DNA Synthesis
WBC	White Blood Cell
wk	Week
↓	Decrease
↑	Increase
µmel	Micromole
µg	Microgramme