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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

SECTION 2. TOXICOLOGICAL OVERVIEW

2.1 ACUTE TOXICITY

Oral

The acute oral toxicity of glycol ethers has been studied extensively; glycol ethers and their acetates generally exhibit a low to moderate order of acute oral toxicity in rodents. In the majority of cases, acute oral LD_{50} values in the rat are greater than 2,000 mg/kg. 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 of nine glycol ethers in mice and rats (Krasavage and Terhaar, 1981). The study was performed to GLP standards and provides the most definitive data on the comparative acute oral toxicity of ethylene and diethylene glycol ethers. The acute toxicities of ethylene glycol monoethers were generally greater than that for the corresponding diethylene glycol monoethers in both rats and mice and toxicity was greater in rats than 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 those determined in starved animals. Clinical signs of toxicity included inactivity, laboured breathing, rapid respiration, anorexia, slight to moderate weakness, tremors, prostration and death.

The available evidence (Smyth *et al*, 1941 see also individual Substance Profiles) indicates 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 appear to be less toxic than the secondary ethers.

Dermal

The 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/kg, 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 monoethylene glycol series was inversely

related to alcohol chain length, whereas diethylene glycol monoethers penetrated less rapidly than their monoethylene 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) show 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 laboratory 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 man appears to be 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 have been reported in rodents exposed to high vapour concentrations.

Skin irritancy

Glycol ethers generally do not appear to be appreciably irritating to the skin on acute exposure. Prolonged or repeated skin contact may lead to more severe irritation, consistent with the solvent properties of this chemical class.

Eye irritation

Rabbit eye irritation tests show a range of responses following a single exposure to the undiluted test substance. The majority of glycol ethers showed only slight to moderate irritation (conjunctival redness and swelling) of the eye. EGPhE, DEGDEE, EGiPE, EGnPE, PGBE, EGBE, DEGBE and TEGBE caused more marked eye irritation. Tissue damage and corneal injury have been reported in some studies, although the effects appeared to be reversible following removal of the test substance. Dilution of glycol ethers in water reduced the severity of eye irritation.

Skin sensitization

There is no indication, from a limited number of animal studies, that glycol ethers cause skin

sensitisation.

2.2 REPEATED DOSE TOXICITY

Glycol ethers have been extensively studied for toxic responses following repeated dosing. Studies have been conducted in a variety of laboratory animal species, by different routes of exposure and for different exposure durations.

The toxicity of nine glycol ethers (EGME, EGEE, EGPE, EGBE, ethylene glycol mono-2-ethylhexyl ether, DEGME, DEGEE, DEPGE and DEGBE) was compared following oral administration of equimolar doses to rats 5 d/wk for 6 weeks (Krasavage and Vlaovic, 1982). The general conclusion was that monoethylene glycol ethers produced a larger number of toxic responses that were of greater severity than the corresponding diethylene glycol ethers.

A similar comparative investigation of propylene glycol ethers has not been conducted. Available data indicate that the major effects associated with exposures to monopropylene glycol ethers are non specific effects on the CNS and an adaptive response in the liver. Hyaline droplet formation has been found in the kidneys of male (but not female) rats exposed to DPGEE and 2PG1ME.

Target organ specificity is summarised below to enable (where possible) structure activity comparisons to be made.

2.2.1 Effects on the blood and haemopoietic system

Two distinctly different types of haematological effects have been observed in many species following repeated dosing of a number of ethylene and diethylene glycol ethers and their acetates.

EGME, EGEE and their acetate esters exert a primary effect on the haemopoietic (blood cell formation) system, causing a deficiency of all cell elements of the blood (generalised pancytopenia). This contrasts with the erythrocyte haemolysis induced by exposure to EGBE and EGPhE (and possibly EGiPE, EGnPE and EGnPEA), which results from a direct effect on the erythrocyte membrane causing osmotic fragility and intravascular lysis. Secondary changes have also been reported as a result of intravascular haemolysis.

EGME causes marked histological changes in the haemopoietic tissue of bone marrow of mice and rats. Cellular damage is characterised by a reduction in both myeloid and erythroid elements and in

megakaryocytes (see EGME Substance Profile). Haematology findings in mice, rats and rabbits suggest that EGEE may also damage haemopoietic tissue, although it appears to be less potent than either EGME or EGMEA. A smaller number of studies report similar effects in laboratory animals for some diethylene glycol ethers. Interestingly, inhalation exposure of rats to DEGDME produced bone marrow hyperplasia at high doses, whilst at lower doses haematological findings in male rats were consistent with those of EGME. By contrast, DEGME caused no such effects in rats dosed sub-chronically at the maximum achievable exposure concentration (see Substances Profiles for DEGDME and DEGME). Effects on the haemopoietic system do not appear to have been reported for the ethers of triethylene glycol.

The haematological effect caused by EGBE is erythrocyte haemolysis, where significant species differences have been reported. The rat appears to be the most sensitive species; human erythrocytes appear to be the least sensitive of those investigated and this also appears to be the case for man with certain congenital blood defects (ECETOC, 1994). Young rats appear to be less sensitive to EGBE induced haemolysis than older rats. The age of the circulating rat erythrocyte affects the sensitivity to haemolysis, with old erythrocytes more susceptible to haemolysis than younger erythrocytes. This phenomenon is believed to account for the tolerance to EGBE induced haemolytic anaemia seen in rats dosed repeatedly with this glycol ether. Whilst the mechanism(s) of action is not fully understood, the metabolite 2-butoxyacetic acid (BAA) shows a significantly greater haemolytic effect *in vitro* than EGBE. DEGBE shows considerably less haemolytic activity than EGBE and no haematological effects have been reported in the more limited studies conducted with TEGBE.

EGPhE causes haemolytic anaemia in rabbits exposed orally or (in a more variable manner) 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 to the haemolytic effects of orally administered EGPhE than rabbits. In contrast to EGBE, metabolism of EGPhE to phenoxyacetic acid produces a less potent haemolytic agent and this may explain, in part, the observed species differences.

There are no reports of propylene glycol monoethers being associated with adverse effects on haemopoietic tissue or blood.

2.2.2 Testes

Spermatogenesis is adversely affected by EGME, EGEE and their acetates. There is also an increasing database suggesting that EGDME and some diethylene glycol ethers produce similar effects at higher

doses (see Substances Profiles for EGDME, DEGDME, DEGME, DEGEE). The endocrinal organ of testes (testosterone production) is not significantly affected. The effects appear to be related to the presence of a common metabolic pathway leading to either methoxyacetic acid (MAA) or ethoxyacetic acid (EAA).

MAA is a potent testicular toxicant in rats (Miller *et al*, 1982b). Testicular atrophy (decreased testes weight) is commonly reported. Histopathology of the lesion is described as moderate to severe degeneration of the germinal epithelium in the seminiferous tubules. Rats treated with EGME and DEGDME showed degeneration of spermatocytes, indicative of impairment of the sperm maturation process.

Comparative studies indicate EGME is the most potent glycol ether inducing testicular toxicity. Lesions occur in rat, mouse and rabbit following oral, dermal or inhalation exposure. The most sensitive species appears to be the rabbit, with a minimum effect level of 30 ppm EGME by inhalation; the no effect levels for rats and mice were 100 and 300 ppm respectively. The rank order of potency for testicular toxicity appears to be EGME > EGMEA > EGEE > EGEEA. DEGDME was the most potent of the diethylene glycol ethers and diethers studied; vapour exposure to ca 100 ppm was a minimum effect level in male rats.

Whilst the mechanism(s) of action has yet to be fully elucidated for the testicular effects described above, the morphological development of EGME induced testicular toxicity in the rat has been well characterised. All stages of spermatocyte development, as well as some stages of spermatid development, are affected by EGME exposure, but it is the primary spermatocyte undergoing pachytene development that is the cell type which is initially and most severely damaged. 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 hypothesized that these materials can all donate one carbon unit that may be used in purine base biosynthesis. Reduced availability of bases would be expected to affect late stage pachytene spermatocytes, which are known to be undergoing rapid RNA synthesis (Mebus and Welsch, 1989). It was found that coadministration of serine enantiomers also provides protection against EGME induced teratogenesis in mice (Clarke *et al*, 1991a).

There are also isolated, older reports in the literature that glycol ethers other than those discussed above produce adverse effects on testicular tissue. These are difficult to explain, as often no consistent findings were noted or the response occurred in one or two animals at high doses. There is no convincing evidence from cross species comparisons that higher homologues of EGME or EGEE or

any of the propylene glycol ethers are testicular toxicants.

2.2.3 Kidney

Many studies with ethylene and propylene glycol ethers have reported adverse effects on the kidneys. In the majority of cases, non specific or secondary effects occur at high doses and in the presence of other signs of toxicity (eg reduced weight gain). Glycol ethers causing erythrocyte haemolysis as a primary toxic response (eg EGBE) cause transitory haemoglobinuria or haematuria as a secondary response.

Rats treated with DPGEE showed hyaline droplet formation in the proximal tubule cells. Hyaline droplet formation was diagnosed in the kidneys of male rats exposed to 3,000 ppm of 2PG1ME. It is not known whether hyaline droplet formation in male rats is a more general phenomenon with glycol ethers.

2.2.4 Liver

Repeated dose studies have occasionally reported histological changes in the liver, including cloudy swelling (EGEE, TEGME) and centrilobular enlargement or disruption(DEGEE).

Elevated liver weights have been reported following exposure to EGBE or propylene glycol monoalkyl ethers. In each case the livers were normal histologically and the increased weight was considered to be reversible; the change may have been an adaptive metabolic response to high dose exposure rather than a specific toxic effect.

2.2.5 Lymphatic tissue and immunotoxicity

Toxicity to lymphoid organs and tissues has been reported following repeated exposure of laboratory animals to EGME, DEGDME, DEGME and to the metabolite MAA. Similar effects have not been consistently reported for other ethylene or propylene glycol ethers. A comparative subacute 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 (ca 600 mg/kg/day). Similar effects have been reported elsewhere in rats and rabbits exposed to EGME vapour and in mice following oral administration.

Immunological effects of glycol ethers as a group have not been systematically examined. Administration of high doses of some glycol ethers has been associated with thymic atrophy and effects on white blood cells. It is not clear whether this is a specific effect or a secondary response to stress induced by the general systemic toxicity of the material. Specific immunological effects have only been reported for a few glycol ethers and are detailed below. With the exception of glycol ethers that can give rise to MAA, the large number of subacute studies with other glycol ethers indicates that they are not specifically immunotoxic.

EGME or its metabolite MAA were immunotoxic in rats and, to a lesser extent, mice. Specific antibody reduction and a dose related increase of Natural Killer Cell cytotoxic activity has been reported for rats; inbred Lewis rats were a particularly sensitive strain. The immunotoxicity of EGME is reduced in the presence of the alcohol dehydrogenase inhibitor 4-methylpyrazole, suggesting that conversion of EGME to MAA is a prerequisite for immunotoxicity of EGME. Mechanistic studies indicate that the immune system is a sensitive target for EGME toxicity in the rat and that the proximate immunotoxicant is MAA; EGEE, EGEEA, ethoxyacetic acid (EAA), DEGME and EGBE showed no immunotoxicity using the same test protocol (Smialowicz *et al*, 1991a,b, 1992; Riddle *et al*, 1992). EGME decreases humoral immune responses and increases cell mediated responses; EGEE has shown similar effects and an increase in cell mediated immunity may contribute to the observed antitumour effects of EGEE seen in a 2 year study.

EGBE has been reported to cause thymic atrophy in some studies at high doses. However, no consistent effects on white cells have been reported and the recorded responses for white cells could in part be a secondary response to the stress induced by the red cell haemolysis that occurs 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 white cell measurements (Ghanayem *et al*, 1987a). EGBE had no effect on 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) or its metabolite BAA (1 mMol) (Unilever, 1990).

DEGME has been reported to cause lymphocyte depletion of the thymus following administration of 2,000 mg/kg/day for up to 20 days (Kawamoto *et al*, 1990a).

1PG2MEA has been reported to cause slight thymic atrophy in rats following inhalation exposure to 2,800 ppm for 4 weeks. This is not considered to be particularly significant in view of no effects being reported following oral administration of 2,600 mg/kg/d to rats for 10 days and the absence of any other

effect reported immunological effects for 1PG2ME (BASF, 1982).

2.2.6 Neurological effects

There are few reports describing neurological effects with the glycol ethers. Neurological effects have not been systematically examined for glycol ethers, although the large number of subacute studies did not indicate that these materials produce readily discernible adverse effects on nervous tissue. Administration of high, sublethal doses of glycol ethers have often been associated with general CNS depression and lethargy. EGME and EGPhE have been associated with specific effects on the nervous system in human beings (see Section 2.4).

EGME exposure at high levels has been associated with impairment of nervous function. Rats exposed to 400-500 ppm EGME for 7 days have shown inhibition of the avoidance/escape response and impairment of hind limb motor function (Goldberg *et al*, 1962; Savolainen, 1980).

TEGME produced no adverse neurological effects in a 90 day study in male and female rats that was specifically designed to study neurological effects. TEGME was administered via the drinking water at nominal doses of 0, 0.4, 1.2 or 4.0 g/kg/d for 90 days (Gill and Negley, 1990).

2.2.7 Genotoxicity and carcinogenicity

Genotoxicity

There are a few reports with positive findings in genotoxicity assays with ethylene based glycol ethers, which are detailed below. Propylene based glycol ethers do not appear to have genotoxic potential.

EGMEA was associated with the loss of X chromosomes in *Drosophila* after feeding to young adults in the Zeste test, but not in the FIX test; there was no effect when administered at the larval stage (Osgood *et al*, 1991). These are invalidated tests and their significance is difficult to interpret. In *Saccharomyces cerevisiae*, EGMEA caused aneuploidy without recombination or gene mutation (Zimmermann *et al*, 1985; Whittaker *et al*, 1989). EGMEA increased the SCE rate in CHO cells *in vitro* after metabolic activation (Loveday *et al*, 1990). An *in vivo* Chinese hamster micronucleus test was negative (Basler, 1986).

EGME studies in a wider range of tests do not indicate significant genotoxic potential for this material (see Substance Profile). A non-reproducible response has been reported in a Drosophila test

(McGregor *et al*, 1983). Administration of EGME in the drinking water for 55-65 days post-transplant in an experimental leukaemia model indicated that the material had antileukaemic properties (Dieter *et al*, 1990); this finding was consistent with earlier studies on the effect of EGME on immunocompetence (Houchens *et al*, 1984).

In view of the rapid conversion of EGMEA to EGME *in vivo* (BASF, 1984d), and the wider range of negative test results for EGME compared to EGMEA, it is unlikely that the positive results obtained with EGMEA represent a significant genotoxic hazard for mammalian species.

Administration of EGME has been associated with reduced fertility in rats and abnormal sperm head morphology; there was a weak dominant lethal response McGregor *et al*, 1984; Moss *et al*, 1985). Adverse toxic effects of the EGME metabolite MAA on sperm have been reported *in vitro* (Gray *et al*, 1985). It is probable that the adverse *in vivo* effects of EGME administration are due to testicular toxicity rather than genotoxicity, particularly in view of the negative results for EGME in other genotoxicity assays.

Administration of EGEE has been associated with clastogenic activity at very high dose levels using *in vitro* test systems (SCE and chromosomal aberrations in CHO cells); the effects were reduced or abolished when S9 mix was included (Guzzie *et al*, 1986; Galloway *et al*, 1987). EGEE increased the response to known clastogens *in vitro* when added to the incubation medium after exposure to the clastogen; there is insufficient data in the report to judge the significance of this observation (Elias *et al*, 1992). Point mutation assays *in vitro* (Ames, mouse lymphoma cells and HGPRT assay with CHO cells) and *in vivo* tests (*Drosophila* SLRL test, mouse micronucleus) found no genotoxic activity (Ong, 1980; McGregor, 1984; Shimizu *et al*, 1985; Valencia *et al*, 1985; Guzzie *et al*, 1986; Myrh and Bowers, 1986; Zeiger *et al*, 1985).

An isolated positive response was reported with *Salmonella* strain TA97a (Hoflack *et al*, 1994); all other strains were negative. An equivocal response in an *in vitro* UDS assay with EGBE may have been due to cytotoxicity (Union Carbide, 1989). EGBE increased sister chromatid exchange in an *in vitro* assay with human lymphocytes (Villalabos-Pietrini *et al*, 1989) and also increased the response to known clastogens *in vitro* when added to the incubation medium after exposure to the clastogen (Elias *et al*, 1992); there is insufficient data in the latter report to judge the significance of this observation. Other genotoxicity assays *in vitro* were negative (Kvelland, 1988; Union Carbide, 1989; Zeiger *et al*, 1992).

A dose related increase in mutation frequency in a mouse lymphoma cell assay in the absence of metabolic activation has been reported for DEGBE; no effect was reported 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; Dow, 1987; Zeiger *et al*, 1992) this isolated result does not indicate that DEGBE represents a significant genotoxic hazard for mammalian species.

DEGDME has been associated with a marginal increase in the number of recessive lethal mutations in *Drosophila*. 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, 1983). It is probable that the adverse *in vivo* effects of DEGDME administration are due to testicular toxicity rather than genotoxicity.

Comment

Most of the glycol ethers that have been tested were assessed in the 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 positive findings. 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 invalidated methods or were isolated findings that could not be confirmed with *in vivo* studies. The significance of the recent reports of *in vitro* effects with EGBE in genotoxicity studies could be clarified by *in vivo* studies.

Carcinogenicity

Long term animal studies are only available for two of the glycol ethers considered in this review (NTP has started chronic studies on EGBE in rats and mice).

EGEE administration in the drinking water for 55-65 days post-transplant in an experimental leukaemia model indicated that the material had antileukaemic properties (Dieter *et al*, 1990); this finding was consistent with earlier studies on the effect of EGEE on immunocompetence (Houchens *et al*, 1984). A two-year gavage study has been cited as showing that administration of EGEE prevented the occurrence of spontaneous leukaemia in male and female F344/N rats, where the spontaneous

incidence averages about 25% (NTP unpublished study cited in Dieter *et al*, 1990).

EGEE was administered by gavage to rats and mice at dose levels of 500, 1,000 or 2,000 mg/kg for 5 d/wk for up to 103 weeks (Melnick, 1984). There was high mortality in the 2,000 mg/kg group: early mortality appeared to be due to stomach ulceration and surviving animals were killed at week 18. Testicular atrophy occurred in the high dose male groups and in the middle dose male mice. Male rats in the low and middle dose groups showed enlargement of the adrenal gland and there was a reduction relative to controls in the incidence of spontaneous gross lesions of the spleen, pituitary gland and testes. Additionally there was a reduced incidence of spleen and pituitary enlargement and in subcutaneous masses in the mammary region of female rats. Histopathology from this study has not been published. There was no increase in tumour formation in the treated groups. This is consistent with the finding that *in vitro* clastogenic activity was only observed at very high doses and that the clastogenic effect was reduced or abolished in the absence of S9 mix. It is therefore unlikely that the positive findings with high levels of EGEE *in vitro* represents a significant genotoxic hazard for mammalian species.

DEGEE has not been evaluated in studies specifically designed to assess carcinogenicity. Three 2 year chronic toxicity studies (Morris *et al*, 1942; Hanzlik *et al*, 1947c; Smyth *et al*, 1964) with administration via the drinking water or diet (dose levels up to ca 1,000 mg/kg/day) did not report any tumours. Although these studies have shortcomings they did not indicate any carcinogenic potential of DEGEE.

Comment

Few carcinogenicity studies have been conducted, primarily because of the generally negative results in genotoxicity studies and the priority given to evaluation of the mechanism of toxicity of selected glycol ethers. A further contributing factor is the general similarity of the toxic effects seen following short term or subacute administration of glycol ethers, with no indication of progressive lesion development that may be associated with carcinogenicity. Glycol ethers that do not show specific cellular toxicity would not be expected to be carcinogenic through mechanisms involving cell proliferation.

Available data indicate glycol ethers are unlikely to be carcinogenic.

2.2.8 Developmental and reproductive effects

Structure activity considerations

Developmental toxicity - in the sense of selective toxicity to the foetus or embryo in the absence of maternal toxicity - is a remarkable and well-known feature of a limited number of glycol ethers and their acetates.

EGME and EGMEA, (the most active compounds), EGEE, EGEEA, EGDME, EGDEE, DEGDME, TEGDME, 1PG2ME and 1PG2MEA have been shown to cause developmental toxicity. With the exceptions of 1PG2ME and 1PG2MEA, these materials also produce testicular and bone marrow toxicity. The acetates of EGME, EGEE and 1PG2ME show the same qualitative (and similar quantitative) effects on a molar basis as the parent glycol ethers; this is consistent with their rapid deacetylation.

Ethylene glycol ethers with alkyl chains longer than two carbon atoms and propylene glycol ethers with the exceptions of 1PG2ME and 1PG2MEA do not show developmental toxicity.

Pattern of developmental effects

Glycol ethers based on ethylene glycol and with alkyl chains of more than 2 carbon atoms do not appear to be selectively toxic to the foetus. For EGnPE, EGiPE, EGBE and their acetates foetotoxic effects (increased incidence of common variants, reduced ossification and moderate growth retardation) have been observed in the presence of maternal toxicity (see individual Substances Profiles).

Propylene glycol based glycol ethers are not generally considered to be developmental toxicants if the primary carbon atom carries the ether bond. These materials are secondary alcohols and cannot be oxidized to alkoxy propionic acids (Miller *et al*, 1986). In contrast EGME, EGEE and 1PG2ME and their acetates are metabolised to the corresponding alkoxy acetic acid derivatives, which are widely assumed to be responsible for the developmental effects seen with these materials (see below).

Developmental toxicity has been observed following exposure to the following particular glycol ethers.

EGME (500-1,000 mg/kg by gastric intubation or 300 ppm by inhalation exposure) caused the loss of virtually all litters. At lower levels (eg 50 ppm in rabbits by inhalation), an increase in resorption rates

and malformations involving practically all tissues and organ systems was observed (Hanley *et al*, 1984b).

Exencephaly, paw anomalies, abnormal digits and other skeletal anomalies were observed in mice after gavage administration of EGME (250 mg/kg/d). Horton *et al* (1985) considered the types of malformation appeared to be related to the developmental stage at the time of exposure, with exencephalies being observed after exposure during gestation days 7-10 and paw anomalies after exposure during days 9-12. The externally visible disrupted morphogenesis of paw digits in mice (syndactyly, polydactyly, oligodactyly and stunted digit 1) after administration on days 11-12 was very characteristic and was chosen as endpoint for mechanistic studies with EGME and MAA (Welsch *et al*, 1987; Scott *et al*, 1987). Ventral duplication of the autopod after limb bud periderm damage appears to be a basic mechanism for ventral polydactyly (Scott *et al*, 1987). Skeletal defects in mice were still seen after repeated oral administration at levels as low as 31 mg/kg/day (Nagano, 1979). Exencephalies were observed with EGDME at doses above 250 mg/kg in mice.

EGEE produced pronounced cardiovascular defects, with missing, transposed or fused vessels, ventral wall defects and skeletal variants in rats and rabbits after inhalation exposure (Andrew and Hardin 1984, Doe *et al*, 1984a). Similar cardiovascular effects, and also vertebral malformations, were described after inhalation of EGEEA (Nelson *et al*, 1984a; Doe *et al*, 1984a; Tyl *et al*, 1988).

1PG2ME or 1PG2MEA administration to rabbits was associated with a unique enlargement of sternebrae, which may predispose to impaired breathing during further postnatal development; paw anomalies and heart defects were also observed (Hellwig *et al*, 1994). A 100% incidence of malformations was seen with 1PG2MEA at 550 ppm in rabbits; the no adverse effect level was 145 ppm. No such effects occurred in rats at 550 ppm; mainly dumb-bell shaped notches of the central cartilage of the thoracic vertebrae were observed at 2,800 ppm. No prenatal toxicity was observed in rabbits after dermal administration of 2,000 mg/kg/d under semi-occlusive conditions (Merkle *et al*, 1987).

DEGME is metabolised primarily to methoxyethoxyacetic acid and shows only weak developmental toxicity at maternally toxic dose levels; metabolism to EGME or MAA does not appear to be significant (Doe *et al*, 1984b; Hardin *et al*, 1986; Scortichini *et al*, 1986). Similarly, DEGEE showed no selective developmental toxicity after oral, dermal or inhalation exposure (Schuler *et al*, 1984; Nelson *et al*, 1984b; Hardin *et al*, 1984,1987). DEGDEE would be expected to show developmental toxicity on theoretical grounds and on the basis of a screening study, but studies in mice, rats and rabbits have shown no significant developmental toxicity (NTP, 1987b).

Interspecies considerations

Developmental toxicity of EGME has been demonstrated with all exposure routes and across all test species investigated, including primates. Two cases of hypospadia (a developmental anomaly where the male ureter opens on the underside of the penis or perineum) in man have been attributed to maternal exposure to EGMEA during pregnancy (Bolt and Golka, 1990). EGEE and EGEEA showed developmental toxicity in a number of studies in rats and rabbits; the potency was approximately five fold lower than that reported for EGME and EGMEA.

Rat and rabbit inhalation studies have provided a clear cut NOEL of 50 ppm for EGEE and EGEEA. The NOEL for EGME was as low as 10 ppm in mice, rats and rabbits. Gavage administration of EGME (12 mg/kg/day) in monkeys showed embryolethality and a trend for MAA accumulation with continuous exposure (Scott *et al*, 1989). Extrapolation of animal data to man requires caution in view of the potential for inter- and intra-species differences in the potential for MAA accumulation.

The only two propylene glycol ethers showing developmental toxicity, 1PG2ME and 1PG2MEA, are not commercially available. These showed significant species differences in the level of exposure required for developmental toxicity. 1PG2MEA was teratogenic at non-maternally toxic levels (550 ppm) in rabbits, whereas in rats foetotoxic and teratogenic effects were less pronounced and were only observed at 2,700 ppm in the presence of maternal toxicity (decreased body weight on days 15 and 20). The NOAEL for inhalation exposure to 1PG2ME and 1PG2MEA in rabbits has shown to be 145 ppm (Merkle *et al*, 1987; Hellwig *et al*, 1994).

The role of metabolism

The developmental effects of ethylene glycol ethers are mediated by alkoxy acetic acid metabolites. MAA (from EGME) has been extensively investigated and established as a strong embryotoxicant and teratogen. EAA (from EGEE) showed similar developmental effects to MAA in an *in vitro* study, whereas propoxyacetic acid (PAA) and BAA were only slightly active (Rawlings *et al*, 1985). MAA arises primarily from metabolism of EGME and EGMEA, but may also be formed from EGDME, DEGDME and TEGDME. Whilst there is no conclusive proof, it is reasonable to expect that other glycol ethers showing prenatal developmental toxicity exert their effects by the generation of alkoxy acetic or propionic acids. The rate of alkoxy acid formation, and possibly also detoxification via 2-alkoxy-N-acetylglycine, may influence the observed developmental toxicity and pattern of malformations.

Ethanol (and other inhibitors of ADH) have shown some protection against developmental toxicity by slowing the rate of oxidation to the corresponding alkoxy carboxylic acid (Römer *et al*, 1985; Welsch *et al*, 1987; Sleet *ef al*, 1988).

Whilst monoethylene glycol ethers are mainly oxidized via ADH to the corresponding alkoxy carboxylic acids, the formation of EGME (and hence the developmental toxicant MAA) from EGDME, DEGDME and EGDME appears to be mediated by microsomal oxidation.

Ethylene glycol (EG) is a weak teratogen and may be formed from EGME (and higher homologues) by microsomal oxidation. However, the high dose of EG required for developmental toxicity, the typical pattern of EG induced malformations (Price *et al*, 1985) and the absence of developmental toxicity with the homologues EGiPE or EGBE indicate that EG does not play a significant role in the developmental toxicity seen with EGME or EGEE.

Propylene glycol ethers only show developmental toxicity if the ether bond is present on the secondary carbon atom; this allows the primary alcohol to be oxidised to an alkoxy-propionic acid. 2-methoxypropionic acid is the presumed teratogenic metabolite formed from 1PG2ME and 1PG2MEA. The primary isomer of this material (2PG1ME) has not been tested as a pure substance; inhalation studies with commercial material showed no developmental toxicity (see Substance Profile). Propylene glycol ethers with the ether bond on the primary carbon (eg 1PG2ME, 1PG2EE and 1PG2BE) are secondary alcohols and are not metabolised to alkoxy- propionic acids; these ethers have not shown developmental toxicity.

Mechanistic studies

EGME and its metabolite MAA, have been used as model compounds to elucidate the mechanism of action of developmental toxicity. MAA has shown developmental toxicity at 9 mg/kg and a firm NOEL has not been established; the mechanism of this activity remains inconclusive, despite a number of studies in this area. High concentrations of MAA in the amniotic fluid and a unique derangement of limb periderm cells, with focal shedding, were observed after administration of EGME to pregnant rats on day 12 of gestation (Scott *et al*, 1987); MAA was still detectable after 69 hours. Welsch *et al* (1987) found a 2-fold higher concentration of MAA in embryos and in extraembryonic fluid than in maternal serum following maternal EGME administration. MAA has an affinity for metabolically active tissues and is a relatively strong organic acid which may be specifically attracted by the more basic medium in embryonic tissues. MAA appears to be bound by coenzyme A (Mebus *et al*, 1992) and incorporated into intermediary metabolism as a "false substrate" (Welsch *et al*, 1987; Sumner *et al*, 1991, 1992).

Small physiological compounds generating or consisting in C1 and C2 fragments related to the TCA cycle or to tetrahydrofolate related metabolism attenuated the teratogenic potency of EGME in the mice paw malformation model (Coakley *et al*, 1986; Stedman and Welsch, 1989). Incorporation of ^{3}H-TdR in whole embryo cultures was reduced by MAA; this, affect was also antagonised by small carboxylic acids (Welsch *et al*, 1987). MAA decreases lactate production in Sertoli cells (Beatti *et al*, 1984; Williams and Foster, 1988); this effect has also been observed with TCA cycle inhibitors such as fluoro- or iodo-acetate. Decreased lactate supply to the pachytene spermatocytes, which depend on lactate, has been suggested as a mechanism responsible for testicular effects (Beatti *et al*, 1984; Williams and Foster, 1988). The inhibitory effects of MAA were not seen in rat foetuses (Coakley *et al*, 1986) or other cell types (CHO, V79 or hepatocytes). It is possible that in embryonic tissues either cells only in a specific state of differentiation with certain patterns of stage-specific isoenzymes are affected, or other mechanisms not related to lactate supply such as decreased availability of small carbon units necessary for purine and pyrimidine synthesis may be relevant.

2.3 ABSORPTION, DISTRIBUTION, METABOLISM AND ELIMINATION (ADME)

2.3.1 Absorption and distribution

Glycol ethers and their acetates are readily absorbed and distributed following oral administration or inhalation. Dermal absorption is also an important exposure route; a series of penetration studies with human epidermis *in vitro* have shown a rank order for penetration from liquid contact to be EGME > 2PG1ME > EGEEA > EGEE > EGBE > DEGME > DEGEE > DEGBE (Dugard *et al*, 1984). Recent studies with EGBE have claimed that dermal uptake may account for about 75 % of the total systemic exposure in man during whole body exposure to EGBE vapour (Johanson and Boman, 1991). Further studies are necessary to establish total systemic burden arising from dermal exposure to EGBE vapour and to assess the implications for occupational exposure.

The glycol ethers are readily distributed throughout the body and no substantial accumulation of the parent compound has been observed. However, the alkoxyacetic acid metabolites of EGME and EGEE (MAA and EAA) have shown evidence of accumulation in animals and man (Scott *et al*, 1989; Groeseneken *et al*, 1989a,b; Ghanayem *et al*, 1990; Medinski *et al*, 1990); in contrast, the metabolite of EGBE (BAA) shows no evidence of significant accumulation (see Section 2.4.5).

2.3.2 Metabolism and elimination

Glycol ethers follow two main oxidative pathways of metabolism, either via alcohol dehydrogenase or

the microsomal P450 mixed function oxidase (O-demethylation or O-dealkylation). The first pathway gives rise to the formation and excretion of alkoxyacetic acids whereas the latter mainly leads to the production and exhalation of carbon dioxide via ethylene glycol or propylene glycol, which enter intermediary metabolism via the tricarboxylic acid cycle.

Glycol ether acetates are metabolised 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.

In addition to these pathways, conjugation with sulphate, glucuronic acid or glycine has also been reported.

The pathways of metabolism of the glycol ethers may be considered in 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 (ether on primary or secondary carbon).

The pathways are shown on the following pages (Figures 1-3 respectively).

The di- and tripropylene glycol ethers (DPGME, TPGME) contain four or more isomers. A small percentage of each substance might comprise isomers with a terminal hydroxyl group. These isomers are theoretical substrates for alcohol dehydrogenase, either directly or after O-dealkylation of DPGME or TPGME. The metabolic studies carried out with these substances have not identified the formation of methoxypropionic acid in rats (Breslin *et al*, 1990). 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.

Figure 1 Pathways for the metabolic breakdown of ethylene glycol mono- and di-alkyl ethers and their acetates (EGME, EGMEA, EGEE, EGEEA, EG(i,n)PE, EGnPEA, EGBE, EGBEA, EGPhE, EGDME and EGDEE)

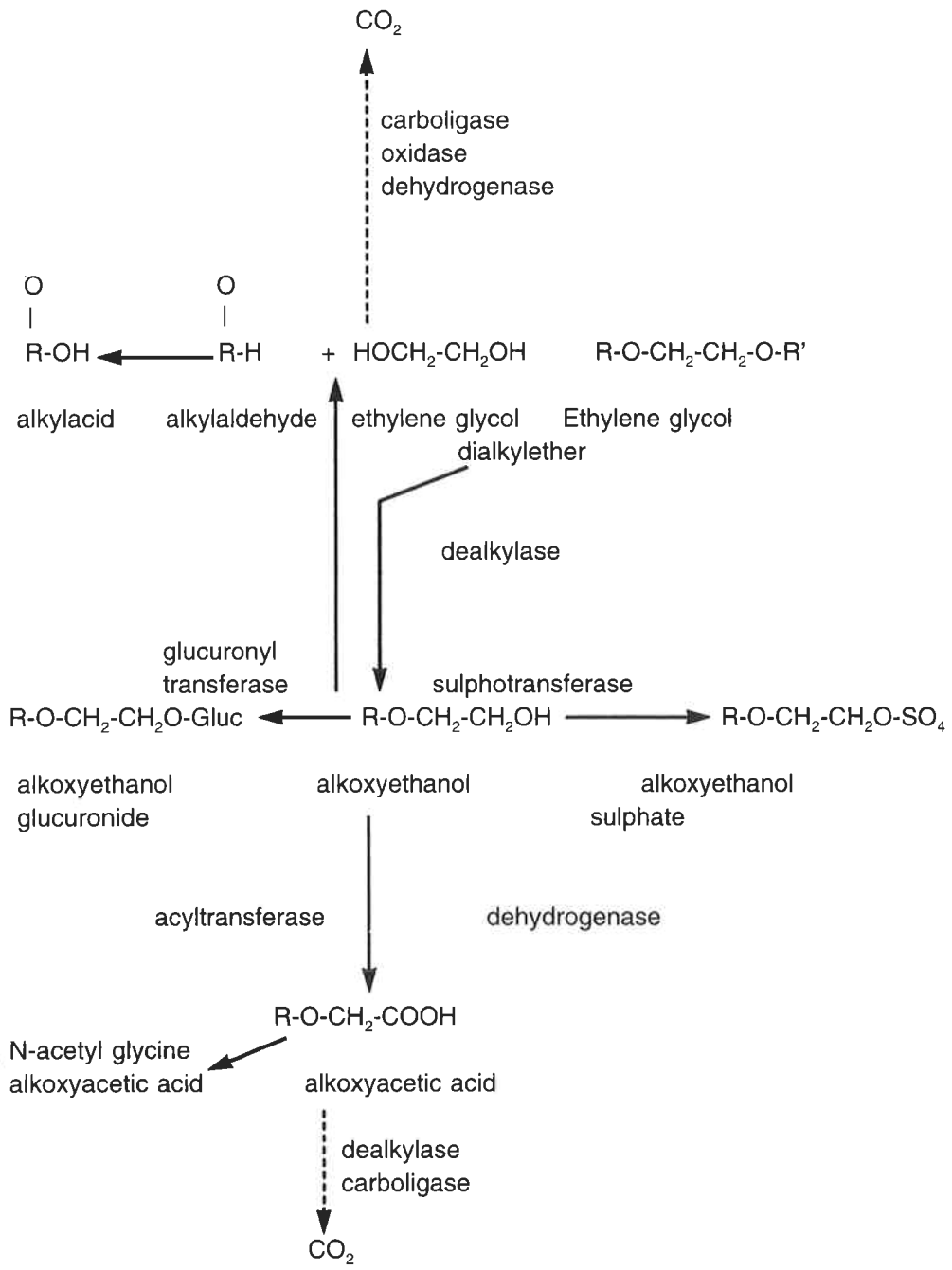


Figure 2 **Pathways for the metabolic breakdown of diethylene glycol mono- and di-alkyl ethers and their acetates (DEGME, DEGEE, DEGEEA, DEGBE, DEGBEA, DEGDME, DEGDEE)**

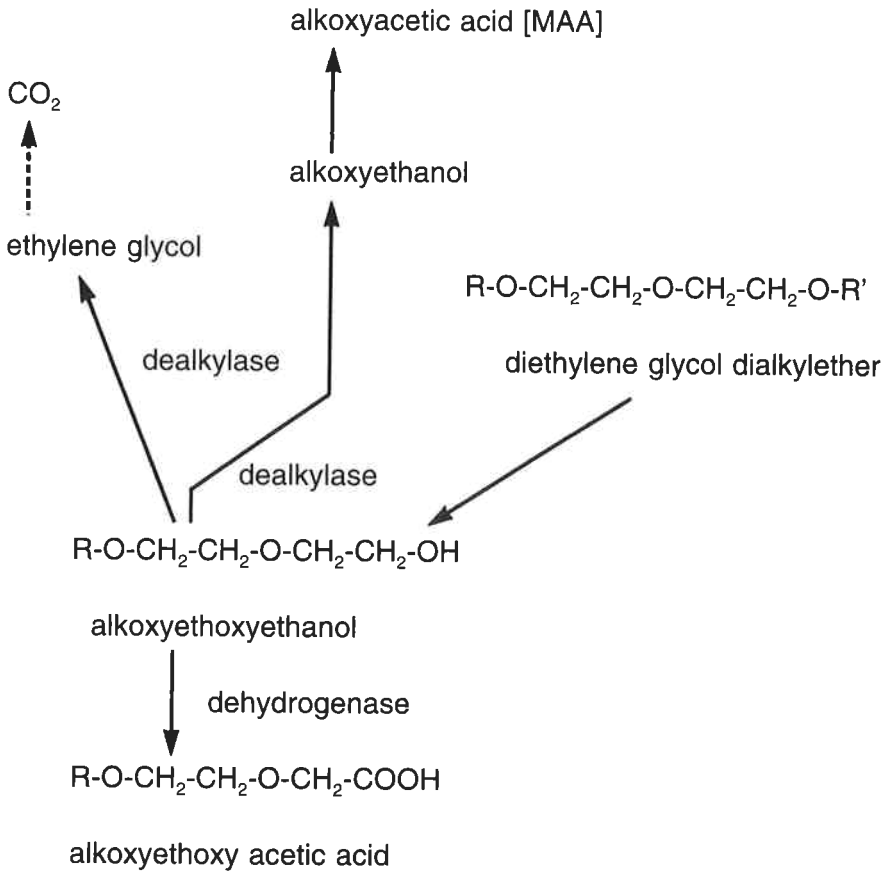


Figure 3a Pathways for the metabolic breakdown of propylene glycol ethers (ether bond on primary carbon) and their acetates (2PG1ME, 2PG1MEA, 2PG1EE, 2PG1EEA, 2PG1BE, 2PG1PhE)

These glycol ethers are secondary alcohols and are primarily metabolised to carbon dioxide. The existing metabolism studies provide no incidence of these materials being metabolised to alkoxy propionic acids.

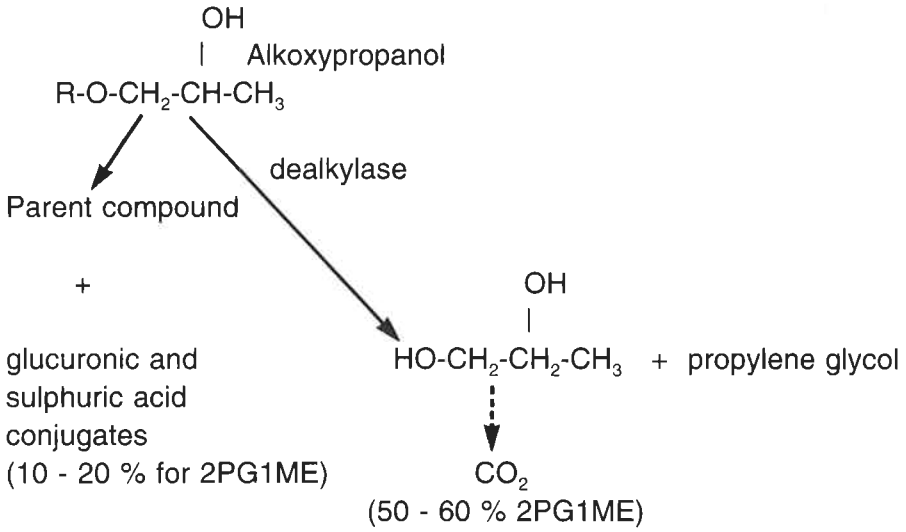
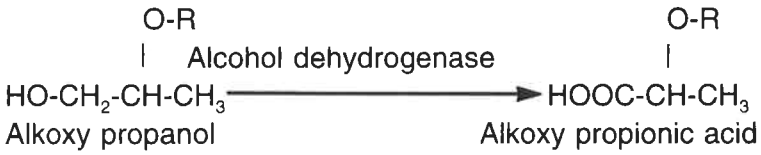


Figure 3b Pathway for the metabolic breakdown of propylene glycol ethers (ether bond on secondary carbon) and their acetates (1PG2ME, 1PG2MEA)

These glycol ethers are primary alcohols and are metabolised to alkoxy propionic acids, presumably by alcohol dehydrogenase (cf ethylene glycol ethers).



2.3.3 Role of Metabolism

A number of glycol ethers and their acetates have been shown to cause haematological, immunological, testicular and developmental toxicity; these toxic effects appear to be dependent on the formation of alkoxy acetic or alkoxy propionic acids. Thus, for example, EGME and EGEE are predominantly metabolised to MAA and EAA, both of which exhibit similar toxicity to the parent compound; EGBE is metabolised to give significant amounts of BAA, which shows significantly greater erythrocyte haemolysis than EGBE.

MAA undergoes further metabolism in laboratory animals and embryos to a glycine conjugate. Identification of 2-methoxy-N-acetylglycine in the urine of EGME exposed mice indicates that MAA first undergoes "activation" to methoxy acetyl coenzyme A (Mebus *et al*, 1992). Sumner *et al* (1991, 1992) identified several metabolites formed by entry of the reactive thioester into the TCA cycle and fatty acid biosynthesis pathways.

It has been proposed that MAA (or further metabolites) may be implicated in the toxicity of EGME. This is based on the observation that simple physiological compounds (eg serine, formate and acetate) that can become involved in the TCA cycle or tetrahydrofolate (THF) metabolism are able to protect against EGME or MAA induced malformations and testicular lesions (Clarke *et al*, 1991a; Welsch *et al*, 1987; Mebus and Welsch, 1989; Mebus *et al*, 1989). These investigations indicate that MAA either affects energy metabolism in the target cells by entering the TCA-cycle as methoxy acetyl Coenzyme A (a "false substrate") and/or affects the availability of small carbon units necessary for purine and pyrimidine base synthesis. Both mechanisms might be expected to disrupt cell proliferation and normal differentiation in the embryo and seminiferous epithelium, but the precise mechanism remains to be elucidated.

The microsomal oxidation of EGME reported in rats administered low amounts of EGME in drinking water (Medinsky *et al*, 1990) has also been shown to occur in pregnant mice (Clarke *et al*, 1991b). This pathway (high affinity/low capacity) is readily saturated by EGME. Approximately 30 % of a 5 mg/kg intravenous dose was oxidised to EG, while only a few percent of a teratogenic dose of EGME (100 mg/kg and above) was metabolised by this route (Clarke *et al*, 1991b). Recently Sabourin *et al* (1992b) showed that dermal application of EGME led to only small amounts of EG being produced in rats. Although EG may be a developmental toxicant in rodents, relatively high doses are required (Price *et al*, 1985; Tyl *et al*, 1988) and the oxidation of a relatively low amount of EGME to EG, rather than to MAA, produces a metabolite with a lower potential of developmental toxicity.

Man and pregnant monkeys also metabolise EGME to MAA, presumably via ADH dehydrogenase as in rodents; MAA was the major urinary metabolite in human volunteers exposed to 5 ppm of EGME (Groeseneken *et al*, 1989a; Scott *et al*, 1989). There is therefore a potential for teratogenic effects in women exposed to EGME.

The above considerations 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 of the toxic metabolites.

   EGDME and EGDEE are potent teratogens which probably act via the formation of EGME (EGEE) and thence MAA (EAA).

2. DEGME and DEGDME are also developmental toxicants in rats and mice, but only at high doses; this may be explained by low level formation of EGME and MAA.

   DEGEE and DEGDEE give rise to low levels of EGEE and EAA, but neither compound caused selective developmental toxicity in rats, mice and rabbits; DEGEE had no effect on fertility. This is plausible in view of the five-fold lower developmental toxicity of EGEE/EAA compared to EGME/MAA.

3. Propylene glycol ethers with the ether bond on the primary carbon (2PG1ME, 2PG1EE, 2PG1BE, 2PG1PhE) are secondary alcohols that are primarily metabolised to carbon dioxide; they do not form alkoxy propionic acids and have not been found to cause selective developmental toxicity.

4. Propylene glycol ethers with the ether bond on the secondary carbon (1PG2ME, 1PG2MEA) are primary alcohols and are predominantly metabolised to methoxypropionic acid. It is presumed that methoxypropionic acid (MPA) is the teratogenic metabolite derived from 1PG2ME.

5. DPGME and TPGME are potentially capable of forming MPA, but metabolism studies have not identified this material in rat urine (Breslin *et al*, 1990).

SECTION 3. HUMAN EXPOSURE AND HEALTH EFFECTS

3.1 HUMAN EXPOSURE

3.1.1 General population 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.

Procter and Gamble (1985) determined potential inhalation and dermal consumer exposure for the use of 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 (146 square feet (15 square metres), volume 10.4 m^3). DEGBE vapour concentrations during the 20 minute washing task were below the detection limit (0.01 ppm), after that it rose steadily to around 0.06 ppm at 1.5 - 3 h and then declined to below the detection limit at 24 hours. *In vitro* human skin penetration studies with a cleaning product containing 4% DEGBE indicated a calculated maximum consumer exposure to DEGBE of 0.047 mg/kg for use over 0.05 hours. Total daily consumer exposure to DEGBE from inhalation and topical exposure was calculated to be 0.059 mg/kg/d.

Gibson *et al* (1991) evaluated consumer inhalation exposure to DEGBE in the home from the use of cleaning products containing up to 9% DEGBE. Several experiments with exposures exceeding those likely to be encountered by consumers found peak airborne concentrations of DEGBE did not exceed 1.6 ppm, with average DEGBE concentrations in the breathing zone below 0.8 ppm.

3.1.2 Occupational exposure

US data on EGME, EGMEA, EGEE and EGEEA exposures showed a wide variation, ranging from 0.31 to 313.9 mg/m^3 (0.1 to 85.3 ppm). Arithmetic means were 0.37-84.90 mg/m^3 (0.10-23.07 ppm) and geometric means 0.04-59.80 mg/m^3 (0.01-16.25 ppm) (WHO, 1990).

Paustenbach (1988) reported on personal and area air samples from 7 different companies in the semiconductor industry. Time weighted average (TWA) samples for EGME were mainly around 0.1 ppm; concentrations of EGMEA were usually lower than 0.01 ppm; the average concentration of EGEE was 0.55 ppm; exposures to EGEEA were generally less than 0.05 ppm.

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

NIOSH (1983) determined occupational exposures to EGME, EGEE, EGMEA and EGEEA. A total of 151 area and personal air samples were collected at 8 survey sites. Only 40% of the samples had detectable levels of glycol ethers, ranging from 0.04-2.77 ppm for long term (approximately 5 to 8 hours) samples and 0.21-11.9 ppm for short term (approximately 15 minutes) samples. Most personal air sampling results complied with the OSHA and ACGIH exposure limits 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 was 50 ppm leading to a maximum uptake of DEGBEA of 190 μg/kg/day.

Summarised data on workplace exposure levels in European glycol ether manufacturing showed TWA personal exposures from 0.12-6.4 ppm for EGME, 0.01-6.5 ppm for EGEE, 0.02-0.2 ppm for EGiPE and 0.01-2.7 ppm for EGBE (ECETOC, 1985).

Veulemans *et al* (1987) reported on 262 ambient air samples from 78 different Belgian plants and workshops. The majority of air samples revealed complex mixtures of glycol ethers with other solvents; the glycol ethers were often minor components. The ethylene glycol ethers most frequently identified were EGEE, EGEEA, EGME, EGMEA and EGBE. Most exposure levels were far below the respective ACGIH (1991) 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 for EGEEA; up to 1,775 mg/m^3 for EGBE; up to 1224 mg/m^3 for EGEE).

Angerer *et al* (1990) reported the following average exposure concentrations in a varnish production plant: 2.8 ppm EGEE, 2.7 ppm EGEEA, 1.1 ppm EGBE, 7.0 ppm 2PG1ME and 2.8 ppm 2PG1MEA.

Samples of 2PG1ME collected during manufacturing of paint, metals and plastics had average levels of 2-3 ppm (Johanson, 1990). Peak levels of 0.5-7 ppm 2PG1ME were reached in apartments painted with water based alkyd and acrylate paints (Kragh-Hansen, cited in Johanson, 1990).

Parquet fitters in Finland were exposed to approximately 35-39 ppm 2PG1ME during undercoat varnishing and 10-63 ppm during varnishing (Johanson, 1990).

A summary of the concentrations of some ethylene glycol ethers in industrial operations is given in Table 3 and the current applicable exposure limits in Table 4.

Table 3: Concentrations (mg/m³) of Ethylene Glycol Ethers Measured in Workplaces of Various Industrial Operations[a]

Operation		EGME TLV[C] = 16mg/m³	EGMEA TLV = 24 mg/m³	EGEE TLV = 19 mg/m³	EGEEA TLV = 27 mg/m³	EGBE TLV = 120 mg/m³	EGBEA TLV = n.a[b] mg/m³
Printing	GM	n.a.	4.3	9.8	16.4	4.1	12.7
	Range.	-	(3.9 - 4.7)	(0.7 - 182.0)	(0.3 - 186.8)	(1.5 - 17.7)	(4.6 - 26.5)
Painting	GM	31.3	n.a.	9.5	9.7	18.8	n.a.
	Range	(5.6 - 136.9)	-	(1.4 - 210.3)	(1.2 - 78.6)	(3.4 - 93.6)	-
Car repair	GM	7.9	2.3	n.a.	8.9	5.9	n.a.
	Range	(3.4 - 15.9)	-	-	(1.5 - 42.1)	-	-
Various	GM	n.a.	11.6	17.1	9.9	8.5	10.6
	Range	-	(0.4 - 143.3)	(3.1 - 1,224)	(0.6 - 819.5)	(0.2 - 1,775)	(8.9 - 11.7)

[a] Data are geometric means (GM); the range is given in parenthesis

[b] n.a. = not available

[C] TLV = Occupational Exposure Limit (TWA) as applicable todate (see table 4)

Table from: Am. Ind. Hyg. Assoc. J. (48), August, 1987.

Ambient air and personal air monitoring studies reported in the literature do not always the actual reflect exposures. There are wide variations in exposure conditions, not only between plants but also in the same plant at different locations and times. Furthermore, glycol ether sampling might have underestimated exposures in general as the glycol ethers could have been unstable on the collection medium (NIOSH, 1983). A further complication of sampling was that many of the uses of glycol ethers also resulted in concomitant exposure to other solvents, which may have interfered with the analysis. Finally, the use of air monitoring to determine body burden also needs to take account of dermal absorption, which can make a significant contribution to overall systemic exposure.

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

3.1.3 Analytical methods for air monitoring

A method has been published for the determination of TWA concentrations of airborne vapours and aerosols of glycol ethers and their acetates in the range 0.5 to 250 mg/m^3 (0.1 to 50 ppm) (HSE, 1988).

3.1.4 Biological monitoring

Human volunteer studies

Healthy male subjects were exposed to EGME, EGEE or EGBE in a number of human volunteer studies.

Groeseneken *et al* (1989a) measured the uptake of EGME and the urinary excretion of its major metabolite methoxyacetic acid (MAA) in seven resting male subjects exposed to 16 mg/m^3 EGME for 4 hours (TLV = 16 mg/m^3). Respiratory uptake was 76% and urine was collected for 120 hours. There was a rapid increase in the urinary excretion of MAA during exposure and elimination half-life averaged 77.1 hours from the first hour. On cessation of exposure, the urinary excretion rate was fairly constant for 4-6 hours and then showed a slow exponential decrease, with the excretion rate about one-third of it's maximal level after 120 hours. Approximately 55% 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.

Five male subjects were exposed at rest to EGEE vapour concentrations of 10, 20 or 40 mg/m^3 (TLV = 19 mg/m^3); a further five male subjects were exposed to EGEE vapour (20 mg/m^3) at rest and during physical exercise (30 or 60 Watt) for four hours (Groeseneken *et al*, 1986a,b). The metabolite EAA was

determined in urine samples collected over 42 hours. Maximal excretion of EAA was reached three to four hours after the end of the exposure period and the elimination half-life of EAA was 21-24 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. In a separate study, similar results were reported after exposure to EGEEA (Groeseneken *et al*, 1987a).

Johanson *et al* (1986b) measured the uptake of EGBE and the excretion of the urinary metabolite butoxyacetic acid (BAA) in 7 male volunteers exposed to 20 ppm EGBE during physical exercise (50 Watt) for two hours. Blood levels of EGBE indicated approximately 57% of inhaled EGBE was absorbed into the blood; the half-life of EGBE in the blood was approximately 40 minutes. EGBE blood concentrations plateaued after about 2 hours at around 900 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.

The above studies indicate an inverse relationship between the elimination half-life of alkoxyacetic acids and the length of the alkyl chain of the glycol ether (BAA: 5.77 hours; EAA: 21-24 h; MAA: 77 h).

The percutaneous absorption of EGBE was investigated by Johanson *et al* (1988). In 12 experiments 5 men kept two or four fingers immersed in undiluted EGBE for 2 hours. Capillary blood samples collected from the unexposed hand were analyzed for EGBE before, during and up to 4 hours after exposure. Urine was collected for 24 hours and analyzed for BAA. The presence of EGBE in blood and of BAA in urine confirmed dermal uptake of EGBE. Percutaneous uptake rates ranged from 7 to 96 nMol/min/cm^2. The results indicated that exposure of large areas of skin to EGBE may result in significant absorption of material by this route.

In further percutaneous absorption studies, Johanson and Boman (1991) exposed four male volunteers to 50 ppm EGBE vapour. In the first study the men were exposed by inhalation only, whilst in the second study only the skin was exposed by sitting naked inside the exposure chamber and wearing a respiratory protection mask supplied with compressed air. Capillary blood samples were collected at regular intervals and analyzed for EGBE. Two experiments separated by at least two weeks were carried out with each volunteer. The average EGBE concentration in blood was 3-4 times higher during dermal exposure than during inhalation exposure. These experiments suggested that dermal uptake of EGBE accounted for about 75% of the total uptake during whole body exposure to EGBE vapour. The blood sampling procedure and methodology has been discussed in ECETOC Special Report n°7 (1994).

Occupational exposure

Several field studies have measured occupational exposure to various glycol ethers by determination of urinary alkoxyacetic acids. Veulemans *et al* (1987) measured the urinary excretion of EAA in a group of 5 women who were exposed daily to a mixture of EGEE and EGEEA. The first measurements were during a 5 day period of normal production and the second measurements were 7 days after a 12 day production stop. Urinary EAA excretion reached a plateau concentration 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. 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). Angerer *et al* (1990) measured exposure to EGEE and EGEEA in 17 workers of a varnish production plant by air monitoring and by urinary EAA determination, and exposures to EGBE by air monitoring and urinary BAA determination. Urine samples were taken pre- and post-shift and post-shift EGBE blood levels were also measured. Measurements were only carried out on the second working day. The highest exposures were found in the 12 workers of the varnish production plant. Exposures to EGEE ranged from <0.1 to 7.8 ppm (mean 2.8 ppm), from <0.1 to 11.1 ppm (mean 2.7 ppm) for EGEEA and from <0.1 to 8.1 ppm (mean 1.1 ppm) for EGBE. Corresponding levels of EAA (combined EGEE and EGEEA exposure) in post-shift urines 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 found 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.

Clapp *et al* (1987) found urinary EAA concentrations in the range of 16 to 163 mg/g creatinine in 7 workers who collected spot urine samples (not timed) on several working days. Separate airborne EGEE levels ranged from non-detectable to 23.8 ppm. Johanson *et al* (1989) found good correlations between EGEEA exposure and urinary EAA excretion in 19 workers and also between EGBE exposure and urinary excretion of BAA.

These studies indicate that analysis of alkoxyacetic acids in urine is a useful method for the biomonitoring of occupational exposure to ethylene glycol ethers. Many of the toxicological effects of ethylene glycol ethers have been attributed to their alkoxyacetic acid metabolites. Alkoxyacetic acids are not normally present in human urine and the extent of urinary excretion of these metabolites may

give a better indication of systemic exposure than airborne measurements of ethylene glycol ethers. Sensitive methods for the quantitative analysis of alkoxyacetic acids in urine have been developed (Johanson *et al*, 1988; Groeseneken *et al*, 1989b; Johanson, 1989).

3.2 HUMAN 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 man 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

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 (area monitoring: 4-20 ppm; personal monitoring: 5.4-8.5 ppm TWA) as compared with 44 non exposed workers (Cook *et al*, 1982).

Cohen (1984) reported low levels of red and white blood cells, platelets, haemoglobin and haematocrit 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). There was also a lower concurrent exposure to methylethyl ketone and commercial PGME.
All haematological parameters had returned to normal values one month after cessation of EGME exposure.

Welch *et al* (1988a) described anaemia and granulocytopenia in shipyard painters exposed to EGME and EGEE. The airborne exposure to EGEE ranged from 0-21.5 ppm TWA (mean 2.6 ppm, median 1.2 ppm) and for EGME ranged from 0-5.6 ppm TWA (mean 0.8 ppm, median 0.4 ppm) (Sparer *et al*, 1988). These effects were consistent with animal studies and other human case reports.

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

Larese *et al* (1992) described mild macrocytic anaemia and leucopenia with an increased proportion of lymphocytes in three 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 to EGME showed normal haematological values in two cases; the erythrocyte count in the third case did not normalise for two years.

Changes in lymphocyte sub-populations were found in nine 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).

EGBE and EGBEA

Erythrocyte osmotic fragility did not change in two men exposed to 114 ppm EGBE for 4 hours, or in two men and two women, exposed to 114 ppm EGBE for 8 hours. This was in contrast to effects on rats under the same experimental conditions, where haemolysis of erythrocytes was reported. Erythrocyte osmotic fragility did not change *in vivo* in two men and one woman exposed to 195 ppm EGBE 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 for 2 hours were approximately two orders of magnitude lower than those causing swelling and haemolysis of human erythrocytes *in vitro*.

DPGME

Cullen *et al* (1983) reported a case of aplastic anaemia 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 six of seven subjects examined; bone marrow hyperplasia was seen in six subjects and an increase in Periodic Acid Schiff (PAS) positive stromal material was seen in three 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-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.

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; Browning, 1965 and WHO 1990). Levels of exposure were poorly documented.

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). There was also lower concurrent exposure to methyl ethyl ketone and 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 demonstrated (Froelich *et al*, 1984).

Morton (1990) reported the cases of three women 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 experienced headache, lightheadedness, slurred speech, euphoria, grogginess and feeling "drunk". Diminished sensation and strength of hands and fingers also occurred, especially in the preferred hand. After one year of exposure, additional symptoms developed, including excessive fatigue, irritability, impaired recent memory, impairment of verbal or visual learning and comprehension, lowered intellectual and mental function, depression, somnolence and impaired concentration. Whilst persistent neuropathy did not develop, neuropsychological testing verified that all three had focal cognitive impairments that persisted up to at least three years after cessation of exposure.

3.2.3 Reproductive effects

Pastides *et al* (1988) reported a 39% higher spontaneous abortion rate in women exposed to glycol ethers (not further specified) and other solvents in semiconductor manufacturing as compared with non-exposed women. Glycol ether exposure levels were well below the occupational exposure standards existing at that time. This was a tentative association, based on the modest sample size and lack of strong evidence about specific work site exposures or practices which may have caused an increased abortion risk.

Windham *et al* (1991) reported a slight association between exposure to glycol ethers (not further specified) and spontaneous abortion.

Schenker *et al* (1992) performed a retrospective and prospective epidemiological study of reproductive health effects among workers employed in the manufacture of semiconductors.
The study suggested a 20-40% increase in spontaneous abortions in women working in fabrication rooms, especially for women who handled photoresist/developer solvents, including glycol ethers. It was not possible to separately analyze for an association with exposure to individual photoresist/developer solvents (particularly ethylene based glycol ethers, xylene and n-butyl acetate) because they were used together in the fabrication room. Whilst the other solvents may have contributed to the miscarriages, the evidence implicated glycol ethers as the most likely cause. The retrospective study showed no statistically significant differences in fertility among male and female employees, or of menstrual cycle characteristics among women associated with the fabrication work. However, the prospective study showed a statistically significant reduction in the probability of conception for those individuals associated with fabrication work.

EGME, EGMEA, EGEE, EGEEA and DEGDME

A study of spontaneous abortions in 200 employees of a book cover manufacturing plant showed an estimated relative risk of spontaneous abortions of women working at the plant of 2.7 (95% confidence interval = 1.36-5.42) (Fidler *et al* 1991). 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.

A study on reproductive health at semi-conductor facilities suggesting an association between exposure to DEGDME and EGEEA and miscarriages awaits publication and further evaluation (Schenker, 1992).

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) (Cook *et al*, 1982).

Welch *et al* (1988b) examined the semen of 73 shipyard painters exposed during the previous 2 to 6 months to EGEE (0-21.5 ppm 8 hour TWA; mean 2.6 ppm, median 1.2 ppm). They also had been exposed in the same period to EGME (0-5.6 ppm 8 hour TWA; mean 0.8 ppm, median 0.44 ppm). It was 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.

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)(Ratcliffe *et al*, 1989).

Veulemans *et al* (1993) compared 1,019 male patients diagnosed as infertile or subfertile on the basis of a spermiogram with 475 controls diagnosed as of normal fertility by the same procedure. Possible exposure to EGME and EGEE or their acetates was assessed by the presence of their respective urinary metabolites MAA and EAA. EAA was detected in 39 patients and six controls (OR: 3.11; $p = 0.004$). MAA was only found in 1 patient and 2 controls. The presence of EAA in urine seemed to be associated with solvent exposure for some groups of occupations, mainly connected with paint products. However, urinary EAA concentrations and various measures of sperm quality were not significantly correlated.

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

3.2.4 Other effects

EGME and EGEE

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

Young and Woolner (1946) reported a case of fatal poisoning when a man drank half a pint of EGME. The kidneys showed degenerative and toxic changes, there was liver fatty degeneration, the pancreas

showed early necrosis and there was acute haemorrhagic gastritis.

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

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

EGBE

Exposure of two men to 114 ppm EGBE 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 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 men and two women to 100 ppm EGBE for 8 hours resulted in vomiting and headaches. All four persons excreted BAA (75 to 250 mg) in their urine (Carpenter *et al*, 1956).

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

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

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

EGPhE

Exposure to EGPhE has been reported to cause hepatitis-like symptoms (Morton, 1990).

DEGME

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

DEGEE

A case report described an alcoholic male who drank a liquid containing approximately 300 ml DEGEE. Central nervous system symptoms, dyspnoea, thirst, acidosis and albuminuria were reported and he recovered with symptomatic treatment (cited in 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 repellant 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).

1PG2ME, 1PG2MEA, 2PG1ME and 2PG1MEA

Steward *et al* (1970) performed a controlled human exposure study in 6 volunteers with commercial PGME (95-99% 2PG1ME, <5% 1PG2ME). Vapour concentrations ranged from 50 to 2,000 ppm. The odour became noticeable at 10 ppm and objectionable above 100 ppm.

Exposure to 250 ppm PGME caused progressive irritation of nose, throat and eyes after 15 minutes. The volunteers were unable to smell PGME after 3 hours exposure to 250 ppm PGME. One person exposed to 2,000 ppm 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.

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 have been described as very disagreeable (Rowe *et al*, 1954). The odour threshold and irritation level for DPGME were reported to be 35 ppm and 74 ppm respectively.

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

2PG1PhE

2PG1PhE has bactericidal properties and is used in medical disinfectants, 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 man.

No human data have been found on following glycol ethers.

EGnPE, EGiPE, EGnPEA, EGDME, EGDEE, DEGEEA, DEGBE, DEGDEE, TEGME, TEGEE, TEGBE, TEGDME, 2PG1EE, 2PG1EEA, 2PG1BE, DPGEE, TPGME

3.3 SUMMARY

The following health effects in man have been associated with glycol ether exposure:

Haematological effects

EGME and EGEE exert a primary effect on haematopoiesis. Whilst no significant haematological effects have been observed in workers exposed to EGME at up to 8.5 ppm (8 hour TWA) (Cook *et al*, 1982), significant effects were found in workers who had received mixed exposures of EGEE (up to 21.5 ppm, 8 hour TWA) and EGME (up to 5.6 ppm, 8 hour TWA) (Welch *et al*, 1988a). These findings are consistent with animal studies and human case reports.

Behavioural and neurological effects

Both EGME (WHO, 1990) and EGPhE (Morton, 1990) have been associated with acute and chronic effects on the central and peripheral nervous system following high level exposure.

Reproductive effects

EGME, EGEE, EGMEA and EGEEA have been associated with adverse effects on spermatogenesis in man.

Lowered sperm counts were found after mixed exposures to EGEE and EGME in one study (Welch *et al*, 1988b). Inconclusive evidence of effects on spermatogenesis was found in other studies (Cook *et al*, 1982; Ratcliffe *et al*, 1989; Veulemans *et al*, 1993).

An increased miscarriage frequency has been reported in women with general solvent exposure (including glycol ethers) and for EGEEA and DEGDME specifically. These associations must be considered tentative in view of factors such as concomitant exposure to other chemicals and insufficient glycol ether exposure data. Publication of a recently conducted study suggesting an association between DEGDME and EGEEA exposure and an increased miscarriage frequency is pending.

3.4 EXPOSURE LIMITS

Exposure limits for glycol ethers applicable in 1992 are summarised in Table 4.

Table 4: Exposure Limits For Glycol Ethers

Glycol Ether (CAS Nr.)	Country	OEL-TWA[1]		STEL[2,5]		SKIN[3]	Pregnancy[4] group
		ppm	mg/m^3	ppm	mg/m^3		
EGME (109-86-4)	Germany	5	15	Category II,1		+	B
	Netherlands	5	16			+	
	Sweden	5					
	United Kingdom	5	16			+	
	USA (ACGIH)	5	16			+	
	USA (OSHA)	25				+	
EGMEA (110-49-6)	Germany	5	25	Category II,1		+	B
	Netherlands	5	24			+	
	Sweden	5					
	United Kingdom	5	24			+	
	USA (ACGIH)	5	24			+	
	USA (OSHA)	25				+	
EGEE (110-80-5)	Germany	20	75	Category II,1		+	B
	Netherlands	5	19			+	
	Sweden	5					
	United Kingdom	10	37			+	
	USA (ACGIH)	5	18			+	
	USA (OSHA)	200				+	
EGEEA (111-15-9)	Germany	20	110	Category II,1		+	B
	Netherlands	5	27			+	
	Sweden	5					
	United Kingdom	10	54			+	
	USA (ACGIH)	5	27			+	
	USA (OSHA)	100				+	

Table 4: Exposure Limits For Glycol Ethers

Glycol Ether (CAS Nr.)	Country	OEL-TWA[1]		STEL[2,5]		SKIN[3]	Pregnancy[4] group
		ppm	mg/m^3	ppm	mg/m^3		
EGiPE (109-59-1)	Germany	5	22	Category II,1		+	C
	Netherlands	10	44				
	Sweden						
	United kingdom						
	USA (ACGIH)	25	106				
EGBE (111-76-2)	Australia	25				+	
	Belgium	25	120			+	
	Denmark	25	120			+	
	Finland	25	120			+	
	France	25	120			+	
	Germany	20	100	Category II,1		+	C
	Italy	25	120			+	
	Japan	50	240			+	
	Netherlands	20	100	40	200	+	
	Norway	20	100			+	
	Sweden	10	50			+	
	Switzerland	25	120			+	
	United Kingdom	25	120			+	
	USA (ACGIH)	25	121			+	
	USA (OSHA)	50				+	
	USA (NIOSH)	5				+	
EGBEA (112-07-2)	Germany	20	135	Category II, 1		+	C
	Netherlands	20	135	40	270	+	
	Sweden	20				+	
	Switzerland	25	120			+	
	United Kingdom	25	120			+	

Table 4: Exposure Limits For Glycol Ethers

Glycol Ether (CAS Nr.)	Country	OEL-TWA[1]		STEL[2,5]		SKIN[3]	Pregnancy[4] group
		ppm	mg/m^3	ppm	mg/m^3		
DEGDME (111-96-6)	Germany (1994)	5	27	Category II, 1		+	B
DEGBE (112-34-5)	Germany	100	100	Category I			C
2PG1ME (PGME Alpha) (107-98-2)	Germany	100	375	Category I			
	Netherlands	100	360				
	Switzerland	100	360	200	720		
	United Kingdom	100	360	300	1080	+	
	France	100	360				
	Belgium	100	369	150	553		
	Denmark	100	360				
	Finland	100	360	150	540		
	Australia	100	360	150	540		
	USA (ACGIH)	100	369	150	553		
	USA (OSHA)	100	360	150	540		
	USA (NIOSH)	100	360	150	540		
2PG1MEA (PGMEA Alpha)(108-65-6)	Germany	50	275	Category I			C
1PG2ME (1589-47-5)	Germany	20	75	Category II,1			B
1PG2MEA (70657-70-4)	Germany	20	110	Category II,1			B
DPGME (34590-94-8)	Germany	50	300	Category I			
	Netherlands	50	300				
	USA (ACGIH)	100	600				

Glossary

1. OEL-TWA: Occupational Exposure Limit - 8 hour Time Weighted Average

2. STEL: Short Term Exposure Limit

   Category II,1:

   Substances with systemic effects (onset of effect ≤ 2 hours; half-life < 2h). Short term exposure is allowed up to 2 times the MAK value for 30 minutes average value and not more than 4 times per shift**.

   Category I:

   Local irritants: Short term exposure is allowed up to 2 times the MAK value, during a maximum period of 5 minutes and with a maximum frequency of 8 times per shift.**

3. Skin: A skin notation is based on variable criteria in different countries and is related to penetration through the skin.

4. Pregnancy Group: Group B:
   According to currently available information, a risk of damage to the developing embryo or foetus must be considered to be probable. Damage to the developing organism cannot be excluded when pregnant women are exposed, even when MAK and BAT values are adhered to **.

   Group C:

   There is no reason to fear a risk of damage to the developing embryo or fetus when MAK and BAT values are adhered to**

** From: Deutsche Forschungsgemeinschaft : MAK- and BAT-Werke-Liste 1992.

SECTION 4. SUBSTANCE PROFILES

In this section the identity, the physical chemical and toxicological data of 35 glycol ethers is summarised in individual product profiles.

Substance Profile: EGME

1. IDENTITY

Name:	Ethylene Glycol (mono) Methyl Ether
Structural formula:	CH_3-O-CH_2-CH_2-OH
Molecular formula:	$C_3H_8O_2$
Molecular weight:	76.09
CAS No.:	109-86-4
IUPAC name:	2-Methoxyethanol
Other components:	Water (max. 0.1%) Methanol (max. 0.1%) Methyldiglycol (max. 0.1%) Ethyleneglycol (max. 0.02%)

2. PHYSICAL CHEMICAL DATA

Conversion factor:	1 ppm = 3.11 mg/m^3 (20°C, 1013hPa) 1 mg/m^3 = 0.322 ppm (20°C, 1013hPa)
Melting point:	- 85.1°C
Boiling point:	124°C at 1013 hPa
Vapour pressure:	6.2 hPa at 20°C 9.7 hPa 25°C
Solubility in water:	Completely soluble

3. TOXICOLOGICAL DATA

3.1. ACUTE TOXICITY

3.1.1 Oral toxicity

Male rats : LD_{50} 2,460 mg/kg. Kidney damage (Smyth *et al*, 1941).

Male rats : LD_{50} 3,250 mg/kg. Narcosis, lung and kidney damage (Carpenter *et al*, 1956).

Female rats : LD_{50} 3,400 mg/kg. Narcosis, lung and kidney damage (Carpenter *et al*, 1956).

After single gavage administration of 200 mg/kg to male F-344 rats the calcium channel blocker verapamil protected against pachytene spermatocyte cell death in stage XIV seminiferous tubules. At 300 mg/kg verapamil was less effective (Ghanayem and Chapin, 1990).

Rawcliffe *et al* (1989) found 48 hours after dosing male rats with a maximum of 500 mg/kg a significant rise in urinary creatinine and 24 hours after dosing a dose-related decrease of creatinine.

Holloway *et al* (1990) found after 5 weeks after single oral administration of 50 mg/kg EGME reduced fertility in rats. This time pattern corresponded to pachytene spermatocyte injury. Higher dose levels (100 and 200 mg/kg) also affected elongated spermatides and, respectively, leptotene and preleptotene spermatocytes, resulting in reduced fertility also after 2 and 3 and up to 10 weeks.

Whereas in CD rats 6 weeks after single oral doses of 750 - 1,500 mg/kg complete sterility was observed, CD-1 mice showed less effect on reproductive capacity under the same treatment regimens, though decreased testes weights were observed after 2 -5 weeks. In rats (500 mg/kg) total sperm count was decreased to about 50%, abnormal sperm was increased from 2.84 to 27.29%, and separated sperm cell heads from 3.74 to 67.28%. Fertility, however, was not much affected at this dose level (Anderson *et al*, 1987).

Mice: Late spermatocytes and early spermatides appeared to be more sensitive than in rats (Anderson *et al*, 1987).

Guinea pigs: LD_{50} 950 mg/kg (Smyth *et al*, 1941 and Carpenter *et al*, 1956).

Rabbits: LD_{50} 890 mg/kg (Carpenter *et al*, 1956).

3.1.2 Dermal toxicity

Rabbits: LD_{50} 1,300 mg/kg (Carpenter *et al*, 1956).

3.1.3 Inhalation toxicity

Rats: 2,000 ppm (7 h) caused increase in osmotic fragility (Carpenter *et al*, 1956). 4-hour inhalation of 1,000; 1,250 and 2,000 ppm caused testicular atrophy and 625 ppm damaged spermatides (Samuels *et al*, 1984).

3.2 IRRITATION/SENSITIZATION

3.2.1 Skin irritation

0.5 ml undiluted material applied to the rabbit on the intact dorsal skin (4 h) was not irritating (Jacobs *et al*, 1987).

3.2.2 Eye irritation

0.1 ml of undiluted material applied into the conjunctival sac of the rabbit was not irritating (Jacobs, 1992).

3.2.3 Sensitization

No data available.

3.3 SUBACUTE/SUBCHRONIC/CHRONIC TOXICITY

3.3.1 Subacute toxicity

Proliferating and/or differentiating tissues are targets of EGME related toxicity in all species investigated (with exception of the intestinal epithelium which remains unaffected); these are:

- the germinal epithelium of testes with pachytene spermatocytes showing as the earliest target and

the greatest sensitivity;

- bone marrow and thymus with depletion of RBC and WBC and alterations in immune competence (immunotoxic and immunomodulating effects);

- embryonic tissues (see chapter 3.5).

In addition, detrimental effects on central and peripheral nervous system which were frequently reported in humans (see chapter 3.9) also appear to be detectable in animals (see chapter 3.7). Savolainen (1980) found glial cell toxicity in rats and Goldberg *et al* (1962 and 1969) could demonstrate a specific loss of active avoidance response in conditioned Wistar
and Carworth rats.

Several oral, inhalation and dermal studies were undertaken.

The results are summarised in Appendix A. Typical results are described in the following :

Oral Studies

Groups of Wistar rats receiving 100 or 300 mg/kg for 1, 2, 5 or 20 d showed moderate decreased of liver, spleen and testes weight and massive decrease of thymus weight after 2 d. After 5 d thymus depletion was nearly complete, after 20 d also testicular weights were massively reduced (Kawamoto *et al*, 1990a).

Repeated oral treatment with 100 and 300 mg/kg/d for 20 d did not induce cytochrome P450, cytochrome b_5 or NADPH cytochrome c reductase in Wistar rats. The activity of cytosolic ADH however was increased (Kawamoto *et al*, 1990b).

Oral administration of 0, 50, 100 and 200 mg/kg for 5 d with post observation periods of up to 7 wk showed the following pattern: at 50 mg/kg no immediate effects were observed; after 3 wk aggregation of detached spermatides; maximum after 4-5 wk; no effects after 7 wk. At 100 and 200 mg/kg dead spermatocytes of different stages in 90% of the tubules; after 7 weeks 50 % repopulated tubules; in the remaining only spermatogonia and Sertoli cells were present; a third population type restored gradually. Prostate and seminal vesicle weight were unaffected (no indication of testosterone shortage) (Chapin *et al*, 1985b).

Inhalation Studies

Inhalation exposure to 300 ppm/3d produced injury initially limited to pachytene and stage XIV spermatocytes of rats. After 1-2 days post exposure other stages became affected. This time pattern did not become apparent after a 2 wk exposure regimen. 20-80% of the tubules showed atrophic germinal epithelium; some tubules only showed single layers of stem cells. Leydig cells were not significantly affected and moved only some hyperplasia and interstitial edema 7 and 14 d post exposure. After 42 d tubular populations restored partially. After 84 days 5% of the tubules were still atrophic (loss of stem cells). Sertoli cells in the post exposure period showed loss of cell-cell contacts and cytoplasmatic vacuolisation (Lee and Kinney, 1989). Ultrastructural effects in Sertoli cells were also reported by Creasy *et al* (1986). Sertoli cells and secondary spermatocytes form a functional unit. Furthermore, Beatti *et al* (1984) showed a decreased lactate production in isolated Sertoli cells after incubation with MAA; lactate forms a nutritional substrate for spermatocytes.

Fischer rats and B6C3F1 mice were exposed to 100; 300 and 1,000 ppm for 9 d/2 wk. Decreased RBC and WBC counts occurred at the two higher levels and testicular atrophy (microscopic changes) at 100 ppm (Miller *et al*, 1981). Similar results were obtained by Doe *et al* (1983), who found testicular atrophy at 300 ppm in Wistar rats after 10 days.

Dermal Studies

Male guinea pigs were dermally exposed to 1,000 mg/kg/d (6 h/d, 5 d/wk, 13 wk), under occlusive conditions. Mild anaemia, lymphopenia and testicular damage were observed (Hobson *et al*, 1986a). Rats exposed to 100 or 1,000 mg/kg/d, (5 d/wk, 4 wk under occlusive conditions showed decreased RBC and WBC, bond marrow cellularity and testicular atrophy. Effects were much weaker under non-occlusive conditions (Fairhurst *et al*, 1989).

Newborn mice receiving 100, 200 or 400 mg/kg/d from day 1-5 p.p. showed in the higher dose group a decrease of cellularity and granulopoietic stem cells in bone marrow after 8 weeks; this was reversible by week 16 (Hong *et al*, 1988).

3.3.2 Subchronic toxicity

5 male and 5 female Fischer rats and New Zealand rabbits were exposed to vapours of 0, 30, 100 and 300 ppm. Death cases occurred among rabbits of the 2 higher levels. Decreased testicular weights were observed at 100 ppm and in 2 animals at 30 ppm. NOAEL for rats was 100 ppm. Severe testicular

atrophy with abnormal sperm cell morphology, thymus atrophy and decreased RBC and WBC, serum proteins and liver weights were obtained at 300 ppm (Miller *et al*, 1983a).

Under the same dose regimen a fertility decrease in males but not in females was noted in rats when bred 13 weeks after last exposure (Rao *et al*, 1983).

10 New Zealand male rabbits were exposed to vapours of 0, 3, 10 or 30 ppm, (6 h/d, 5 d/wk, 13 wk). No effects were observed in this study (Miller *et al*, 1982a).

The results of subchronic studies are summarised in Appendix A.

3.3.3 Chronic toxicity/Carcinogenicity

No data available.

In experimental leukaemia models EGME was found to exert antitumourigenic properties. The studies were conducted with B6C3F1 mice receiving 10 administrations by gavage of 300, 600 and 1,200 mg EGME/kg/d within 2 wk prior to injection of leukaemic cells (Houchens *et al*, 1984) and with Fischer rats receiving 15 and 100 mg EGME/kg/d in drinking water after injection of leukaemic cells (Dieter *et al*, 1990). In the same set of experiments EGEE was 10 fold less active than EGME whereas the non-teratogenic homologues EGPE, EGBE, EGPhE and DEGME were totally ineffective.

3.4 GENOTOXICITY

EGME did not exert substantial genotoxic effects in a battery of *in vitro* and *in vivo* assays (McGregor *et al*, 1983 and McGregor, 1984). The results are summarised in Appendix C.

3.5 REPRODUCTION/DEVELOPMENTAL TOXICITY

EGME exerts pronounced foetotoxic, embryotoxic and teratogenic effects in all species investigated (mice, rats, rabbits, primates) and via all routes of exposure (oral, dermal, inhalation) in the presence and absence of maternal toxicity. This has been demonstrated in many experimental investigations. The results of the studies are summarised in Appendix B.

By gavage administration 7-14 ICL-ICR mice showed developmental effects including malformations of doses as low as 31.25 mg/kg from gestation day (Nagano *et al*, 1984).

Nelson *et al* (1989) exposed pregnant Sprague-Dawley rats to EGME (approximately 16, 31, 73, 140, 198, 290 and 620 mg/kg/d) via a liquid diet from gestation day 7-18. Doses 73 mg/kg/d and higher produced total embryolethality. Lower doses produced cardiovascular malformations. 16 mg/kg/d were not teratogenic, however, mean survivor weights were still reduced. No significant behavioural teratogenicity was observed.

Toraason *et al* (1985) found abnormal QRS complexes after gavage administration of 25 and 50 mg/kg for 11 days in Sprague-Dawley rats.

Nelson *et al* (1984b) exposed rats for 7 h/d from gestation day 7-15 via inhalation. 200 ppm produced complete resorptions in the absence of maternal toxicity. 100 and 50 ppm caused increased incidence of resorptions and skeletal and cardiovascular defects.

Hanley *et al* (1984b,c) exposing rats to 3, 10 or 50 ppm from gestation day 6-15 found skeletal variations but no malformations in the highest exposure group.

10 ppm (6 h/d) were found to be a NOAEL in inhalation studies with Fischer rats and CF1 mice (Hanley *et al*, 1984b,c), whereas 25 ppm (7 h/d) caused behavioral effects in offspring of rats (Nelson *et al*, 1984a). In New Zealand rabbits, exposed to 3, 10 and 50 ppm from gestation day 6-18 a clear teratogenic effect was noted at 50 ppm (mainly cardiovascular, urogenital and skeletal defects). Retarded ossification (in relation to the actual, but not the historical control) was recorded at 10 ppm. Thus, 10 ppm was still defined as a no adverse effect level (Hanley *et al*, 1984b,c).

In the primate *Macaca fascicularis* pregnant females received daily gavage doses of 0.47, 0.32 and 0.16 mmol/kg (12, 24, 36 mg/kg) during the organogenetic gestation period (d 20 -45). At the highest dose material toxicity was pronounced and all 8 pregnancies ended in embryonic death; one of these dead embryos showed an external malformation (missing a digit on each forelimb). At the middle dose 3/10 and in the lowest dose 3/13 pregnancies ended in embryonic death. At the highest dose the animals became severely anorectic and were gavaged with gruel and electrolytes to prevent physical deterioration. After the end of treatment period the animals recovered. Moderate and slight anorexia were found at the lower levels. The major metabolite, MAA, showed biological half-life time of about 20 hours and appeared to accumulate in all dose groups under the continuous exposure throughout the course of the study (Scott *et al*, 1989).

Single and repeated dermal administration under open or occlusive conditions caused developmental effects including external visceral and skeletal malformations in rats (Wickramaratne, 1986; Feuston *et*

al, 1989 and 1990). 250 mg/kg were reported as NOAEL for single exposure between gestation days 10-14.

A reduction of teratogenicity in rats after administration of ethanol (Sleet *et al*, 1986, 1988) or the ADH inhibitor 4-methylpyrazole (Ritter *et al*, 1985) was reported. In another study the teratogenicity in Sprague-Dawley rats uptaking 0.05% and 0.025% of EGME in a liquid diet was not significantly reduced by simultaneous administration of ethanol 16 g/kg/d (Nelson *et al*, 1989).

Protection against EGME induced teratogenicity in mice was also partially achieved with several physiologically compounds such as acetate, formate, glycine, sarcosine and glucose and especially serine enantiomers (Mebus and Welsch, 1989; Clarke *et al*, 1991a).

The metabolite 2-MAA has a long biological half-life and may interfere with the availability of one-carbon units linked to tetrahydrofolate pathways. In fact, 5 mMol MAA produced a 50% reduction of ^{3}H-thymidine incorporation into mouse embryos in serum-free medium. This effect could be counteracted by formate, acetate or sarcosine (Stedman and Welsch, 1989).

Fertility studies/Multigeneration studies

In continuous breeding studies in CD-1 mice receiving 0.03; 0.1; 0.2; 0.3; 0.4; 0.5; 1.0 and 2.0% EGME in the drinking water (20 or 30 animals per sex and dose group; 30 or 40 animals per sex and control group) fertility index was reduced at 0.3% in the F_0 and at 0.1% in the F_1 generation; litter parameters were affected at 0.1% in the F_0 and at 0.03% in the F_1 generation. No viable pups were produced above 0.4%. The NOAEL was below 0.03% in the F_1 generation (Gulati *et al*, 1985a,b; 1988a).

In continuous breeding studies in rats employing 20 male and 20 female Sprague Dawley rats on 0.006; 0.01; 0.012; 0.024; 0.03 and 0.1% EGME in the drinking water a NOAEL of 0.012% was obtained, equivalent to 9.6 and 8.1 mg/kg bw/day for F_0 and F_1 males and 15.3 and 14.2 mg/kg/d for F_0 and F_1 females. At 0.024 and 0.03% the number of viable and surviving pups was reduced; at 0.1% only one litter was obtained; testicular weights, epididymis, prostate and relative kidney weights were reduced at that level in F_0 (and at 0.03 % also in F_1) as well as number and motility of sperm cells. Mating and fertility indices were not affected (Gulati *et al*, 1990a,b).

The same group of authors also performed continuous breeding studies in C57 BL/6 and C3H mice with 0.03; 0.1 and 0.3% EGME in the drinking water. At 0.3% no offspring was obtained in F_1 of C3H and at 0-1% in F_2 of C3H. Fertility index was 25 % in F_1 of C57 BL/6 at 0.3%; in F_2 fertility index was 50%

at 0.03% and 0% at 0.1% (Gulati *et al*, 1988b; 1989).

In an inhalation study in rats F_1-animals were infertile at 30 ppm (30 animals/sex), 100 and 300 ppm (20 animals/sex) for 13 wk (6 h/d; 5 d/wk) and cross-matings with untreated animals (for 2 wk in all groups, for 13 and 19 wk in the top dose) severe reduction of male fertility was noted at 300 ppm; the effect was only partially reversible after 19 weeks; 100 ppm were the NOEC (Rao *et al*, 1983). Feuston *et al* (1989) administered 625; 1,250 or 2,500 mg EGME/kg/d dermally to male Sprague Dawley rats under occlusive conditions in 4 aliquots per day (20 male rats per group). After exposure periods of 4, 7, 10 and 14 wk the animals mated untreated females. Dose related testicular and epididymal weights and histologically visible tubular atrophy and reduced fertility indices were seen in all groups under occlusive conditions. Similar effects were observed under open conditions at higher levels (1,250; 2,500 and 5,000 mg/kg). At 1,250 there was a loss of spermatides but no influence on fertility index.

Single oral administration of 50 mg/kg to male rats resulted in decreased fertility in *in vitro* fertilization after 5 wk. This was reversible by wk 8 after administration. At 100 mg/kg reduced fertility was observable from wk 4.5 - 6.5 after administration, and at 200 mg/kg from wk 2 - 7. This corresponds to the dose dependent impact on different stages of the spermatogenic cycle (Holloway *et al*, 1990).

3.6 TOXICOKINETICS/METABOLISM

EGME is resorbed through human skin *in vitro* at a rate of 1.66 mg/cm^2/h (permeability constant 16.60 x 10^{4}cm/h; damage ratio 3.20; Dugard *et al*, 1984).

Prenatal and subacute/subchronic toxicity studies in Sprague-Dawley rats also demonstrate ready dermal absorption *in vivo* even under non-occlusive conditions (Hobson *et al*, 1986b; Fairhurst *et al*, 1989; Feuston *et al*, 1989 and 1990).

Two major metabolic pathways were observed after drinking water administration of ^{14}C- labelled EGME to male F-344 rats (180 - 2,590 ppm). Within 72 hours 40 - 50% (dose-dependent increase) of the radioactivity was excreted in the urine. Less than 34% of the total dose was oxidized to MAA. 10 - 30% of the dose underwent cleavage of ether bound with production of ethylene glycol and CO_2. The parent compound (< 5%) and its glucuronide were also found in the urine (Medinsky *et al*, 1990).

After a single oral dose of 1 or 8.7 mmol/kg of ^{14}C-labelled EGME to male Fischer rats (label in both glycol C atoms) 12% of the radioactivity was eliminated as $^{14}CO_2$ within 48 hours and MAA was identified as the primary urinary metabolite accounting for 80 - 90% of urinary ^{14}C (Miller *et al*, 1983b;

Miller, 1987).

EGME exerts its toxic activity via its oxidation product MAA. Pretreatment of male Sprague-Dawley rats with the ADH-inhibitor pyrazole protected against EGME induced testicular toxicity and reduced the radioactivity in the 48 h urine for 55-18% (Moss *et al*, 1985).

In primary testicular cell cultures of rats EGME even at 50 mM concentrations for 72 h was not active, due to lack of oxidation to MAA. In contrast, MAA at 2 - 10 mM for 24 - 72 h caused the typical cytotoxic effects (Gray *et al*, 1985).

The oxidation of EGME to MAA is also delayed by ethanol since they both compete for ADH. Ethanol accumulates plasma levels of EGME whereas EGME does not much prevent ethanol degradation (Römer *et al*, 1985). At present, it is difficult to decide whether ethanol suppresses plasma peak levels of MAA after EGME exposure.

3.7 NEUROTOXICITY

Goldberg *et al* (1962) found inhibition of avoidance - escape response in conditioned Wistar rats exposed to 1,555 mg/m^3 (500 ppm) for up to 7 d. The effect was dose and time dependent.

Savolainen (1980) reported partial loss of motor function in hind limbs of Wistar rats and enzyme alterations possibly indicative of glial cell toxicity after 2 wk exposure to 400 ppm. In addition, body weights were reduced in the second week and spleens enlarged. At 50 and 100 ppm no effects were recorded.

3.8 IMMUNOTOXICITY

EGME and its metabolite MAA have been shown to be immunotoxic in Sprague-Dawley rats and - to a lower extent - in mice (Exon *et al*, 1991). In B6C3F1 mice only thymus depletion was significant in one study (House *et al*, 1985) after 10 oral dosages of 250, 500 and 1,000 mg/kg. In rats 10 administrations of 50, 100 and 200 mg/kg caused dose dependent decreases of thymus weights, lymphocyte proliferation response upon B and T cell mitogen stimulation, antibody and interleukin-2 production. Similar effects were noted with MAA (Smialowicz *et al*, 1991a,b).

Thymic atrophy and immunotoxicity with decreased specific antibody reduction were also described by Exon *et al* (1991) who exposed Sprague-Dawley rats via the drinking water (2,000 or 6,000 ppm). Dose-

related increase of natural killer (NK) cell cytotoxic activity, on the other hand, were noted. The study points out the importance of the specific parameter that is applied for the immunological assessments.

Inbred Lewis rats were found to be the most sensitive strain showing immunosuppression at levels as low as 0.66 mM/kg/d EGME or MAA, whereas mice were comparably resistant (Riddle *et al*, 1992).

4. HUMAN DATA

4.1 ACCIDENTAL ORAL EXPOSURE

After accidental oral uptake of 100 ml methoxyethanol by 2 persons Nitter-Hauge (1970) observed high urinary excretion of oxalate levels (see chapter 3.6) in one case. Thus after oral ingestion also ethylene glycol/oxalic acid mediated toxicity (kidney, CNS) has to be taken into account. Ingestion of 400 ml EGME, mixed with brandy, by a 44-year old man was fatal within 5 hours. Coma and severe liver and kidney injury were observed (Young and Woolner, 1946).

4.2 OCCUPATIONAL EXPOSURE

Several reports exist on the central nervous system toxicity of EGME in exposed workers.

Exposure to EGME may lead to a complex neurological disorder diagnosed and described as "toxic encephalopathia" (Donley, 1936; Greenburg *et al*, 1938; Parsons and Parsons, 1938; Groetschel and Schürmann, 1959; Zavon, 1963; Nitter-Hauge, 1970; Ohi and Wegman, 1978). Not all patients showed the same signs and symptoms, but the following pattern is derived from different case studies of persons who were exposed at the work place. The patients suffered from nausea, headache, drowsiness, irritated or burning eyes and impaired vision, deterioration of audition, loss of concentration and interest, states of agitation and in some cases hallucinations. Poor intellectual performance, stupor, disorientation, rigor and hypertonia of muscles, tremor, sometimes ataxia of arms and legs and spastic gait with clonic feet were also observed. In some cases the eye pupils were wide and reacted slowly. Romberg sign was occasionally positive, the reflexes of the abdomen wall absent while patellae reflexes were either increased or decreased. Babinsky reflex was always negative. The patients also lost weight during their illness. Macrocytic anaemia, leucopenia, reactive lymphocytosis and premature leucocytes were diagnosed if investigated.

All signs were gradually reversible after the cessation of exposure. Duration and intensity of exposure in these case reports were varied and ill-defined. Zavon (1963) measured air concentrations under simulated conditions after anaemias and encephalopathias had occurred. He found between 61 and 3,960 ppm, depending of the kind of work. MAA was postulated as metabolite responsible for toxicity (Zavon, 1963).

Greenburg *et al* (1938) measured the concentration in the workroom air after the intoxications had been diagnosed. They found 25 ppm, when the windows were open, 76 ppm, when the windows were partially closed. However, at the time of the intoxications (but not at the time of measurement), the ventilation had been defective.

According to Ohi and Wegman (1978) neurological symptoms were observed in two men exposed to an air concentration of 8 ppm over a period of a few months. Here, the principle source of exposure was thought to be skin contamination.

Macrocytic anaemia has been described in a worker who was exposed for 20 months towards 35 ppm in average (18-58 ppm). Other solvents, methoxyethylketone and PGME, were also used but are unlikely for this effect. After termination of exposure the patient recovered (Cohen, 1984).

In a recent cross-sectional epidemiology study in a chemical plant no signs of encephalopathia were detected among potentially exposed workers. However, smaller testicular size and possibly slight reduction in red and white blood cell counts could not be completely ruled out. The exposure levels monitored were below 20 ppm (Cook *et al*, 1982).

Alterations in the cellular immune response (decrease of T-helper cells, increase of NK cells, B lymphocytes and normal suppressor cells) in 9 workers exposed to EGME, EGEE and other solvents were observed (Denkhaus *et al*, 1986).

7 workers with dermal and respiratory exposure to EGME, EGEE, DPGME and other solvents were examined. 3 of them showed evidence of some bone marrow injury (Cullen *et al*, 1983).

Sparer *et al* (1988), Welch *et al* (1988) and Welch and Cullen (1988) investigated the effect of EGME and EGEE exposure on male reproductive factors and blood in 153 shipyard painters. Increased prevalence of oligo- and azoospermia (73), odds ratio for lower sperm counts, anaemia (10%) and granulocytopenia (5%) were noted. None of these effects occurred in 55 control persons.

4.3 EXPERIMENTAL HUMAN EXPOSURE

Experimental human exposure was investigated by Groeseneken *et al* (1989a and 1989b) employing 7 volunteers inhaling 16 mg/m^3/4 h (total dose 0.25 mg/kg). No toxicological signs or symptoms were found. By this route and at this dose level 85.5% in average of EGME was transformed to MAA. MAA was detected in the urine up to 120 hours after the exposure. The elimination half-life was 66 - 90 h (77.1 $\pm$ 9.5).

Substance Profile: EGMEA

1. IDENTITY

Name:	Ethylene Glycol (mono) Methyl Ether Acetate
Structural formula:	CH_3-O-CH_2-CH_2-O-CO-CH_3
Molecular formula:	$C_5H_{10}O_3$
Molecular weight:	118.1
CAS No.:	110-49-6
IUPAC name:	2-Methoxyethyl acetate
Other components:	Not known

2. PHYSICAL CHEMICAL DATA

Conversion factor:	1 ppm = 4.90 mg/m^3 (20°C, 1013hPa) 1 mg/m^3 = 0.2 ppm (20°C, 1013hPa)
Melting point:	- 65°C
Boiling point:	145°C at 1013 hPa
Vapour pressure:	9.3 hPa at 20°C
Solubility in water:	Completely soluble

3. TOXICOLOGICAL DATA

3.1 ACUTE TOXICITY

3.1.1 Oral toxicity

Rats: LD_{50} 3,930 - 4,300 mg/kg (Smyth *et al*, 1941; BASF, 1966).

Guinea pigs: LD_{50} 1,250 mg/kg (Kirk-Othmer, 1980).

3.1.2 Dermal toxicity

Rabbits: LD_{50} 5,250 - 5,560 mg/kg (Kirk-Othmer, 1980)

3.1.3 Inhalation toxicity

Rats: Vapour saturated air concentrations (< 4,000 ppm) were survived by guinea pigs (1 h) and cats (2-6 h). Exposure at 450 ppm for 8 h were survived by mice and guinea pigs and 1 rabbit, whereas another rabbit and 2 cats died showing kidney injury Gross (1938). Rats survived 4 h at 1,500 ppm, but death causes after 8 h Carpenter *et al* (1956).

3.2 IRRITATION/SENSITIZATION

3.2.1 Skin irritation

Not or slightly irritating to rabbit skin (Carpenter and Smyth, 1946; BASF AG, 1966).

3.2.2 Eye irritation

Whereas no irritation was found by Carpenter and Smyth (1946), irritating effects were observed in another experiment (BASF, 1966).

3.2.3 Sensitization

No data available.

3.3 SUBACUTE/SUBCHRONIC/CHRONIC TOXICITY

3.3.1 Subacute toxicity

Male ICL-ICR mice received by gavage dose levels of 62.5 - 4,000 mg/kg/d (5d/wk, 5 wk). Dose-dependent testicular atrophy and leucopenia was noted (Nagano *et al*, 1979 and 1984) (See Appendix A).

Repeated inhalations (up to 6 d) at 500 and 1,000 ppm were lethal among cats and rabbits, whereas guinea pigs and mice survived, but showed kidney damages. The investigations are fairly old (Gross, 1938).

3.3.2 Subchronic toxicity

No data available.

3.3.3 Chronic toxicity/Carcinogenicity

No data available.

3.4 GENOTOXICITY

Single i.p. injections of 1,333 mg/kg into Chinese hamsters did not cause micronuclei in polychromatic erythrocytes 12, 24, 48 and 72 h after administration (Basler, 1986).

Drosophila melanogaster cytogenetic assay: Loss of X-chromosome after feeding young adults in the ZESTE-Test, but not in the FIX-Test. When applied to the larval stage no effects occurred (Sehgal and Osgood, 1990; Osgood *et al*, 1991).

Increased SCE rates in CHO cells (11). Increased chromosome aberrations in CHO cells after metabolic activation (Loveday *et al*, 1990) and in *Saccharomyces cerevisiae* (Whittacker *et al*, 1989). Aneuploidy in diploid *Saccharomyces cerevisiae*, but no recombination and no gene mutation

(Zimmermann *et al*, 1985).

3.5 REPRODUCTION/DEVELOPMENTAL TOXICITY

Pregnant CD-1 mice received 1,225 mg/kg/d via gavage from day 6 - 13 of gestation. Evaluation followed the Chernoff-Kavlock procedure. Dams appeared to be unaffected. In 31 litters no viable fetus was born (Hardin *et al*, 1987; NTIS, 1984).

In analogy to EGME also EGMEA is to be categorized as a potent teratogen.

3.6 TOXICOKINETICS/METABOLISM

Half-life time in rat plasma (37°C) *in vitro* was found to be 11.75 min with a subsequent formation of EGME (Hoffmann and Jäckh, 1985).

3.7 NEUROTOXICITY

No data available. However, since EGME shows distinct CNS-toxic properties and EGMEA is rapidly cleaved to EGME, this effect may also be assumed for EGMEA.

3.8 IMMUNOTOXICITY

No data available. Immunosuppression was observed with EGMEA metabolites (EGME, MAA).

4. HUMAN DATA

Two cases of hypospadia were attributed to occupational exposure (inhalation and dermal contact) of a woman during 2 pregnancies (Bolt and Golka, 1990).

Central nervous and behavioural effects are known from EGME exposure.

Substance Profile: MAA

1. IDENTITY

Name:	Methoxy-Acetic Acid
Structural formula:	CH_3-O-CH_2-COOH
Molecular formula:	$C_3H_6O_3$
Molecular weight:	90.09
CAS No.:	625-45-6
IUPAC name:	Methoxyacetic acid
Other components:	Not known

2. PHYSICAL CHEMICAL DATA

Conversion factor:	1 ppm = 1.74 mg/m^3 (20°C, 1013 hPa) 1 mg/m^3 = 0.58 ppm (20°C, 1013 hPa)
Melting point:	Approximately 7°C
Boiling point:	202°C at 1013 hPa
Vapour pressure:	1.8 hPa at 20°C 4.8 hPa at 50°C
Solubility in water:	Completely soluble

3. TOXICOLOGICAL DATA

3.1 ACUTE TOXICITY

3.1.1 Oral toxicity

Rats: LD_{50} >1,000 <1,500 mg/kg (aqueous preparation) CNS symptoms (convulsions, paresis, atonia) were recorded (BASF, 1980).

Single oral treatment of 118, 296 and 592 mg MAA/kg were given to 6 male Wistar rats per dose group. The highest level produced after 1, 4 and 14 d of observation lower relative testes weights and damage to germinative epithelium in pachytene, diplotene, diakinetic and secondary spermatocytes. (Under the same conditions 868 mg/kg BAA caused haematuria but no testicular damage). 118 mg MAA/kg still showed some effect after 24 h (Foster *et al*, 1987).

70 d after a single treatment with 650 mg/kg Sodium-MAA testicular morphology appeared to be normal. Serum-FSH was increased on d 1 and 3 and d 21; it was in the normal range at d 14 and from d 28. The increase in FSH was discussed as indicative for altered Sertoli cell function. Serum LH was slightly increased and testosterone in isolated tubules slightly decreased (d 21 > 42) but restored by d 70 (Bartlett *et al*, 1988). Several authors suggest that changes in the Sertoli cells are a sequel to the changes to germ cell complement (Sharpe, 1989; see also Section 3.5).

3.1.2 Dermal toxicity

No data available.

3.1.3 Inhalation toxicity

In a vapour saturated atmosphere at 20°C no lethalities occurred in rats exposed for 7 h (Miller *et al*, 1982b).

3.2 IRRITATION/SENSITIZATION

3.2.1 Skin irritation

Corrosive to rabbit skin (BASF, 1980).

3.2.2 Eye irritation

No data available.

3.2.3 Skin sensitization

No data available.

3.3 SUBACUTE/SUBCHRONIC/CHRONIC TOXICITY

3.3.1 Subacute toxicity

Six male Sprague-Dawley rats received 592 mg/kg/d for 4 consecutive days. Relative body weight, liver and testicular weights were significantly reduced. Histologic examination of testes showed degenerative effects in spermatocytes of the pachytene, diplotene and diakinesis. Sertoli cells, leptotene and zygotene spermatocytes and spermatides were unaffected with the exception of early spermatocytes (Foster *et al*, 1983; Gray *et al*, 1985).

Male Fischer rats (5 animals/group) received daily gavage administrations of 30, 100 and 300 mg/kg for 8 days in 2 weeks. n the two higher dose levels absolute and relative thymus weights, RBC, haemoglobin and haematocrit values were significantly decreased. n the 300 mg/kg group decreased body weights, absolutely and relatively decreased spleen and testicular weights as well as leucopenia were observed. Cellularity of thymus core and germinal epithelium were affected from 100 mg/kg/d and above. Testicular giant cells and reduced cellularity in bone marrow were observed at 300 mg/kg/d, whereas 30 mg/kg/d produced no effects within the observation period (Miller *et al*, 1982b). MAA in the diet (0.4%) of continuously bred CD-1 mice caused decrease of male body weights, loss of sperm and increase of abnormal spermatocytes (Morrissey *et al*, 1988).

The results of subacute studies are summarised in Appendix A.

3.3.2 Subchronic toxicity

No data available.

3.3.3 Chronic toxicity/Carcinogenicity

No data available.

3.4 GENOTOXICITY

No data available. Results with the metabolic precursor EGME suggest that MAA will not exert substantial genotoxic effects (see EGME product profile).

3.5 REPRODUCTION/DEVELOPMENTAL TOXICITY

MAA in postimplantation rat embryonic cultures interfered with normal growth and development of early neurula stage (Yonemoto *et al*, 1984).

Gross structural defects in 9.5 d rat embryos over 48 h in culture were also found (Rawlings *et al*, 1985). In this study EAA did also produce similar defects, whereas the longer chain alkoxy acids n-propoxyacetic acid, n-butoxyacetic acid, 3-methoxypropionic acid and 4-methoxy-propionic acid were only slightly active. 2-methoxypropionic acid, the presumptive metabolite of 1PG2ME was not examined.

The experiments clearly indicate a potential for prenatal toxicity. This was confirmed in *in vivo* experiments (see Appendix B).

Wistar rats were orally treated with 0; 0.16 and 0.32 ml/kg MAA (undiluted) on gestation day 12 (8 animals per group). On gestation day 20 an increase in the number of resorptions (4%, 15.1% and 53.8%) and of malformed foetuses (0; 53.1 and 98.9%), mostly with hydronephrosis, cardiac and limb malformations and shortening of limbs and tails was recorded (Ritter *et al*, 1985).

I.p. injection of 225 mg/kg into Wistar rats on gestation days 8, 10, 12 or 14 showed high fetal mortality for d 8 (93% vs. 0% in the control) and d 10 (61%); significant fetal mortality was also seen after injection on d 12 (16%) and 14 (3%). Malformations occurred at all treatment points with the highest rate on d 12 (92.5% vs. 15.4%). The malformations mostly consisted in skeletal malformations and hydrocephalus. They could be demonstrated in a second experiment employing 9 - 225 mg/kg on

gestation d 10 or 12 at all dose levels down to 9 mg/kg. A NOEL was not obtained (Brown *et al*, 1984).

When administered at 0.03 and 0.014% in a liquid diet of rats (79 and 39 mg/kg/d; day 7-18) MAA showed clear teratogenicity (cardiovascular malformations in 15%) at the lower dose and complete resorption at the higher dose (Nelson *et al*, 1989).

In a 2-generation continuous breeding study (NTP, 1986) CD-1 mice received MAA via the drinking water in concentrations of 0; 0.1; 0.2 and 0.4% (about 140, 240 and 390 mg/kg/d). Fertility index in the F_0 generation in the 0.2% group was 95%; in the 0.4% group no animal became pregnant. In the two lower dose levels the number of litters per pair, the number of viable animals per litter were severely reduced: pub lethality 10.3% at 0%; 75.4% during lactation. Pubs from 0.2% died by d 4. In a subsequent cross-mating experiment the proportion of detected matings was not adversely affected, however, the fertility index at 0.4% MAA was reduced. In the surviving F_1 generation with continuous exposure to 0.1% MAA mating and fertility index was zero. Adjusted weight of kidneys/adrenals, prostate and seminal vesicles were unaffected by the treatment. The body weights were reduced at d 4 at mating (d 74 $\pm$ 0).

Further in vitro studies in mouse whole embryo culture 5 mM MAA in serum-free medium reduced ^{3}H-incorporation; this could be antagonized by some small carboxylic acids (Stedman and Welsch, 1989; Mebus and Welsch, 1989). 5 - 10 mM occur *in vivo* in embryos or extra-embryonic fluid after a single treatment with a teratogenic dose of ME (Stedman and Welsch, 1989 and Scott *et al*, 1987).

Cytotoxicity *in vitro*

In Sertoli cells, MAA at 3 and 10 mM following incubation for 6, 9 and 12 h decreased lactate production (Beatti *et al*, 1984; Williams and Foster, 1988), thereby indirectly influencing nutrition of spermatogenic cells depending on lactate supply.

In rat foetuses (10.5 d), 5.0 mM methoxyacetate did not decrease lactate production. This is in contrast to the effects seen with 0.1 mM iodoacetate (Coakley *et al*, 1986).

Detrimental effects on spermatocytes with a pronounced sensitivity of pachytene spermatocytes including leakage of LDH was found by several investigators (Foster *et al*, 1983; Gray *et al*, 1985; Blackburn *et al*, 1985; Foster *et al*, 1986 and 1987; Bartlett *et al*, 1988). Methoxyacetic aldehyde was even more effective (Foster *et al*, 1986) (BAA at 5 mM was without effect (Foster *et al*, 1987). Following a teratogenic EGME dose (500 mg/kg),

the plasma MAA levels in mice were approx. 5 mM (Welsch *et al*, 1987). Among other alkoxy acids MAA has the least haemolytic activity (Ghanayem *et al*, 1989).

In mitochondria from rat liver and testes 300 µg/ml MAA inhibited oxidative phosphorylation and Cyt.C-oxidase activity (Beatti and Brabec, 1986).

3.6 TOXICOKINETICS/METABOLISM

MAA arises from EGME via alcohol dehydrogenase oxidation (Miller *et al*, 1983b). The toxicity of EGME roughly correlates with MAA. There are indications that MAA is incorporated into the intermediary metabolism. Some of its activity is attenuated by small carboxylic acids (Coakley *et al*, 1986; Welsch *et al*, 1987; Stedman and Welsch, 1989).

MAA is excreted renally in a partially conjugated form. The biological half-life appears to be long (20 hours) with signs of slow accumulation in non-human primates (Scott *et al*, 1989). The concentration of MAA in 12 days old embryos and in extraembryonic fluid after EGME injection (5 mMol/kg i.p.) is twice as high as in maternal serum (Welsch *et al*, 1987).

3.7 NEUROTOXICITY

No data are available. The precursor compound EGME, however, was shown to exhibit behavioural and CNS toxicity in rats and signs of behavioural and neurotoxicity in humans (See EGME product profile).

3.8 IMMUNOTOXICITY

Fischer-344-rats received 10 consecutive oral doses ranging from 50 - 200 mg/kg/d. At 100 and 200 mg/kg thymic involution in the absence of body weight reduction and reduction of lymphoproliferative responses to mitogens (ConA, PHA, pokeweed) were observed. At 200 mg/kg also the in vitro generated cytotoxic T-lymphocyte response was reduced, whereas mixed lymphocyte reaction and NKA were unaffected. The plaque forming cell (PFC) response to trinitrophenyl-lipopolysaccharide (TNP-LPS) was suppressed throughout all dose levels, while increased to SRBC at 50 mg/kg (Smialowicz *et al*, 1991a).

TNP-LPS- and SRBC-immunized rats, dosed with MAA, showed suppression of PFC responses at 100 and 200 mg/kg and 200 and 400 mg/kg respectively. Phenotypic analysis of splenocytes revealed a small (3%) reduction in the percentage of W3/25-positive cells (i.e. CD4, helper/inducer cells). Spleen

cellularity appeared to be unaffected. IL-2 production was decreased in the 150 mg/kg group (Smialowicz *et al*, 1991a).

In B6C3F1 mice treated via gavage for 2 wk (5 d/wk; 10 animals per group) with 25, 50 and 100 mg/kg/d reduced thymus weights were observed at the two higher dose levels, but no influence on cellularity in spleen and bone marrow, plasma blood cell counts, plaque test for IgM antibodies, macrophage and NKA, cytotoxic response of T-lymphocytes, proliferative reaction of spleen cells towards T and B cell mitogens and mortality towards Listeria monocytogens (House *et al*, 1985).

Riddle *et al* (1992) comparing the immunosuppressive activity on the TNP-LPS plaque forming response employing several strains of rats dosed with 0.33 - 2.64 mMol/kg/d for 10 consecutive days and strains of mice dosed with 0.66 - 5.28 mMol/kg/d found no effects in mice and the (inbred) Lewis rat, being the most sensitive strain, showing suppression as low as 0.66 mMol/kg. EGME was equally active.

The studies clearly demonstrate that MAA exerts a significant immunotoxic potential which is more pronounced in rats than mice.

4. HUMAN DATA

No data available.

Substance Profile: EGEE

1. IDENTITY

Name:	Ethylene Glycol (mono) Ethyl Ether
Structural formula:	C_2H_5-O-CH_2-CH_2-OH
Molecular formula:	$C_4H_{10}O_2$
Molecular weight:	90.1
CAS No.:	110-80-5
IUPAC name:	2-Ethoxyethanol
Other components:	Not known

2. PHYSICAL CHEMICAL DATA

Conversion factor:	1 ppm = 3.73 mg/m^3 (20°C, 1013 hPa) 1 mg/m^3 = 0.27 ppm (20°C, 1013 hPa)
Melting point:	< - 80 °C
Boiling point:	135 - 137 °C at 1013 hPa
Vapour pressure:	5 hPa at 20 °C
Solubility in water:	Soluble

3. TOXICOLOGICAL DATA

3.1 ACUTE TOXICITY

3.1.1 Oral toxicity

Rats: LD_{50} 2,125 - 5,487 mg/kg (Laug *et al*, 1939; Smyth *et al*, 1941; Carpenter *et al*, 1956; Stenger *et al*, 1971; Gingell *et al*, 1994; Cheever *et al*, 1984; Pis'ko and Werbilow, 1988). Male animals appear to be more sensitive than female. Main signs of toxicity were dyspnoea, ataxia, loss of righting reflex.

Mice: LD_{50} 2,451 - 4,831 mg/kg (Laug *et al*, 1939; Stenger *et al*, 1971; Kodak, 1982; Pis'ko and Werbilow, 1988).

Rabbits: LD_{50} 1,486 mg/kg (Carpenter *et al*, 1956) and 3,100 mg/kg (Stenger *et al*, 1971).

Guinea pigs: LD_{50} 1,400 mg/kg (Stenger *et al*, 1971); 2,137 mg/kg (Smyth *et al*, 1941) and 2,595 mg/kg (Laug *et al*, 1939).

3.1.2 Dermal toxicity

Rabbits: LD_{50} 3,311 mg/kg (Carpenter *et al*, 1956); 3,900 mg/kg (Daughtrey *et al*, 1984). The studies used undiluted test material, 24 h occluded exposure.

3.1.3 Inhalation toxicity

Rats: LC_{50} 16 mg/l = 4,300 ppm (4 h exposure), 8 mg/l = 2,150 ppm (8 h exposure) (Carpenter *et al*, 1956).

3.2 IRRITATION/SENSITIZATION

3.2.1 Skin irritation

Slight irritating to rabbit skin (4 h non occluded exposure) (Kodak, 1982).

3.2.2 Eye irritation

Slightly irritating to the eye of rabbits (Carpenter and Smyth, 1946; Sanderson, 1959; Kodak, 1982).

3.2.3 Sensitization

No data available.

3.3 SUBACUTE/SUBCHRONIC/CHRONIC TOXICITY

3.3.1 Subacute toxicity

Various studies have been conducted following oral or dermal application in rat and mouse. The main systemic findings were histopathological changes in liver kidney, spleen and testis. Main haematological findings were changes in haemoglobin and haematocrit.

NOAEL-levels after oral application were identified to be 150 mg/kg after 6 wk of exposure in the rat (Hürtt and Zenick, 1986). Following dermal application (undiluted material), doses of 4,428 mg/kg were identified respectively as NOAEL after 10 days in the rat (Hardin *et al*, 1982).

In the mouse a NOAEL of 500 mg/kg was determined following 5 wk oral exposure (Nagano *et al*, 1979).

The results are summarised in Appendix A.

3.3.2 Subchronic toxicity

Similar to the investigations following a subacute toxicity protocol the results of the subchronic studies revealed histopathological changes in liver, kidney, spleen and testis as well as haematological changes as main findings in rats and mice (Barbee *et al*, 1984; Biodynamics, 1983a; Smyth *et al*, 1951; Stenger *et al*, 1971; Werner *et al*, 1943a). In 90-d drinking water studies NOAEL-levels of 210 mg/kg or 109 mg/kg were identified respectively in rats (Smyth *et al*, 1951; NTP, 1992). In a 13-wk inhalation study with rats the NOAEL was 100 ppm (390 mg/m^3). The same NOAEL was found in a 13-wk inhalation study with rabbits (Biodynamics, 1983b; Barbee *et al*, 1984).

The results are summarised in Appendix A.

3.3.3 Chronic toxicity/Carcinogenicity

EGEE has been tested in a life time study in F344 rats and B6C3F1 mice with administration by gavage (Melnick, 1984). Rats and mice (50 m/50 f/group) received doses of 500, 1,000 and 2,000 mg/kg/d (5 d/wk; 103 wk). Due to high mortality in the high dose group all animals were killed following the 18 wk of the test. In the rat a dose dependent decrease of body weight gain was observed, whereas in mice, no decrease was seen. The following conclusions were made for the 2-year study on EGEE:

- repeated administration of EGEE at the 2,000 mg/kg dose level was lethal to rats and mice. Early mortality in the high dose groups of rats and mice appeared to be due to stomach ulceration. EGEE caused testicular atrophy in male rats and mice. This effect was apparent in high dose male rats which died early in the 2-year study and in the medium and high dose male mice.

- gross observations indicated that chronic treatment with EGEE at dose levels of 500 or 1,000 mg/kg caused an apparent enlargement of the adrenal gland in male rats and reduced the occurrence of spontaneous gross lesions of the spleen, pituitary gland and testes that commonly occur in the aging male Fisher-344 rat.

- chronic treatment with EGEE also caused a decrease in the incidences of enlarged spleens and pituitaries and of subcutaneous masses in the mammary gland region in the aging female Fisher-344 rat (further histopathological details are not published) (Melnick, 1984).

For details, see Appendix A

3.4 GENOTOXICITY

A series of *in vivo* and *in vitro* genotoxicity tests are available for EGEE. The *in vivo* studies were conducted with *Drosophila melanogaster* (SLRL-test) and the mouse (Micronucleus test). The results of this battery of *in vivo* studies do not suggest a genotoxic activity (McGregor, 1984; Valencia *et al*, 1985; Guzzie *et al*, 1986).

The *in vitro* investigations showed no genotoxic activity in point mutation assays including the bacterial Ames test as well as the mammalian cell test systems of mouse lymphoma and the HGPRT-test in CHO-cells (Ong, 1980; Shimizu *et al*, 1985; Zeiger *et al*, 1985; Guzzie *et al*, 1986; Myhr and Bowers, 1986).

Some *in vitro* test systems indicating clastogenic activity (SCE and chromosomal aberration in CHO-cells) have been published. However, the applied concentrations were exceedingly high (up to 9,510 µg/ml) and in most cases the clastogenic response was eliminated after addition of S9-Mix, which is in good accordance with the a. m. *in vivo* studies (Galloway *et al*, 1987; Guzzie *et al*, 1986).

The results of genotoxicity studies are summarised in Appendix C.

3.5 REPRODUCTION/DEVELOPMENTAL TOXICITY

Reproductive teratological embryotoxic and foetotoxic effects of EGEE have been studied in the rat, the mouse and the rabbit following oral and dermal exposure and inhalation respectively. At high maternal toxic doses/concentrations testicular atrophy in conjunction with histopathological changes in the testis of males of all species tested were observed. The female fertility was not effected.

Embryotoxicity such as mortality and post implantational losses and foetotoxicity (decreased fetal weight) were observed in all species tested. Teratogenic effects such as increased skeletal and cardiovascular malformations were seen predominantly in rat and rabbit, whereas exencephaly and cleft palate were only seen in the mouse.

In some incidences an increased postnatal mortality was observed (Stenger *et al*, 1971; Nelson *et al*, 1981; Hardin *et al*, 1982; Tinston *et al*, 1983a,b; Andrew and Hardin, 1984; Doe, 1984a; Goad and Cranmer, 1984; Hardin *et al*, 1984; Schuler *et al*, 1984; Chester *et al*, 1986; Wier *et al*, 1987).

Some of these studies were designed to determine NOAEL's for the different species tested. For teratogenic and foetotoxic effects of 50 ppm were determined for rats and rabbits, following inhalation and 23 mg/kg following oral exposure in the rat (Stenger *et al*, 1971; Tinston *et al*, 1983a;b; Doe, 1984a).

The results are summarised in Appendix B.

3.6 TOXICOKINETICS/METABOLISM

Following oral exposure or inhalation 60 to 80 % of the given dose was excreted in the urine by the rat. The main metabolite identified was EAA the second metabolite being EG (Medinsky *et al*, 1990). Approximately 10 % were exhaled as CO_2 whereas 1 to 3 % were exhaled unchanged. 0.5 to 5 % of the dose were excreted by the faeces. Following dermal application EAA was also determined as the

main metabolite. The half-life for the elimination of EAA was approximately 7.2 h (Cheever *et al*, 1984; Groeseneken *et al*, 1988; Medinsky *et al*, 1990; Sabourin *et al*, 1992b).

The oxidation of EGEE to EAA is competitively inhibited in the rat by EtOH. This finding is indicative for the involvement of the liver ADH-enzyme system (Römer *et al*, 1985).

The results of toxicokinetics/metabolic studies are summarised in Appendix D.

3.7 NEUROTOXICITY

No data available.

3.8 IMMUNOTOXICITY

No specific studies were identified (see Section 4).

4. HUMAN DATA

A case of human poisoning by accidental injection of approximately 40 ml EG has been reported (Gingell *et al*, 1994). Main symptoms were cyanosis, edema of the lung and convulsion. The woman recovered after approximately 40 days.

As shown in experimental studies, the main metabolite following inhalation of EGEE was determined to be EAA (Groeseneken *et al*, 1986a,b). The concentration of this metabolite in the urine of exposed workers has been used as a qualitative measure in workplace monitoring studies (Veulemans *et al*, 1987; Ratcliffe *et al*, 1989; Angerer *et al*, 1990).

Some of these occupational studies included investigations of sperm samples. The incidence of oligo spermia was increased in some cases, whereas sperm morphology and sperm motility were not affected (Sparer *et al*, 1988; Welch *et al*, 1988; Welch and Cullen, 1988; Ratcliffe *et al*, 1989). In one investigation on painters a significant proportion of the examined individuals were anaemic (10 %) and granulocytopenic (5 %), compared to none of the controls (Welch and Cullen, 1988).

In a case control study by Veulemans *et al* (1993) 1,019 cases of first-time patients of a clinic for reproduction disorders, defined as patients diagnosed as infertile or subfertile on the basis of a

spermiogram were studied. The investigation suggested a correlation between exposure to EGEE, the occurrence of urinary metabolites (EAA) and impaired sperm morphology. Firm conclusions could not be drawn because of the unknown latency period between exposure and sampling time.

Substance Profile: EGEEA

1. IDENTITY

Name:	Ethylene Glycol (mono) Ethyl Ether Acetate
Structural formula:	C_2H_5-O-CH_2-CH_2-O-CO-CH_3
Molecular formula:	$C_6H_{12}O_3$
Molecular weight:	132.2
CAS No.:	111-15-9
IUPAC name:	2-Ethoxyethyl acetate
Other components:	Not known

2. PHYSICAL CHEMICAL DATA

Conversion factor:	1 ppm = 5.47 mg/m^3 (20°C, 1013hPa) 1 mg/m^3 = 0.183 ppm (20°C, 1013hPa)
Melting point:	- 62 °C
Boiling point:	153 - 159 °C at 1013 hPa
Vapour pressure:	2 hPa at 20 °C
Solubility in water:	235 g/l at 20 °C

3. TOXICOLOGICAL DATA

3.1 ACUTE TOXICITY

3.1.1 Oral toxicity

Rats: LD_{50} 2,900 - 7,500 mg/kg (Smyth *et al*, 1941; Pozzani *et al*, 1959; Truhaut *et al*, 1979). Main signs of toxicity were ataxia and transient haematuria.

Guinea pigs: LD_{50} 1,910 mg/kg (Smyth *et al*, 1941). Main signs of toxicity were ataxia and transient haematuria.

Rabbits: LD_{50} 1,950 mg/kg (Carpenter, 1947). Main signs of toxicity were ataxia and transient haematuria.

3.1.2 Dermal toxicity

Guinea pigs: LD_{50} 1,818 mg/kg; occluded (Carpenter, 1947).
> 19,500 mg/kg; non occluded (Eastman, 1982).

Rabbits: LD_{50} 10,300-10,500 mg/kg; occluded (Carpenter, 1947; Truhaut *et al*, 1979).

3.1.3 Inhalation toxicity

Rats: LC_{50} 8.25 - 12.1 mg/l = 1,500-2,200 ppm (8 h exposure) (Pozzani *et al*, 1959; Tyl *et al*, 1988).

3.2 IRRITATION/SENSITIZATION

3.2.1 Skin irritation

Slightly irritating to rabbit skin (24 h occluded exposure) (Truhaut *et al*, 1979). Similar results have been reported in the guinea pig (Eastman, 1982).

3.2.2 Eye irritation

Slightly irritating to the eye of rabbits (0.1 ml undiluted test material) (von Oettingen and Jirouch, 1931; Carpenter and Smyth, 1946; Truhaut *et al*, 1979; Eastman, 1982; Kennah *et al*, 1989).

3.2.3 Sensitization

No data available.

3.3 SUBACUTE/SUBCHRONIC/CHRONIC TOXICITY

3.3.1 Subacute toxicity

In a subacute oral study in the mouse (5 animals/dose) doses of 500, 1,000, 2,000 and 4,000 mg/kg (5 d/wk; 5 wk) were administered. No compound related changes in the haematological parameters were observed. From 1,000 mg/kg upwards a dose dependent increase of the incidences of testicular atrophy in male animals was found (Nagano *et al*, 1979).

The results are summarised in Appendix A.

3.3.2 Subchronic toxicity

In a comparative study with rats and rabbits with inhalation of EGEEA in a concentration of 200 ppm (1,100 mg/m^3) over the period of 10 months (4 h/d; 5 d/wk) no changes of any haematological parameter was observed in both species. Body weight gain was in the range of the control. Histopathological investigations revealed no increase of incidences of testicular atrophy in the male rabbit and rat. However, in the rabbit and the male rat lesions of tubular nephritis and degeneration of the epithelium with hyaline and granular tubular casts were observed. No appreciable alterations were found in the females (Truhaut *et al*, 1979).

In a 6-months study in the dog inhalation of 600 ppm (3,300 mg/m^3, 7 h/d, 5 d/wk) induced no effects on the haematological parameters and no compound related macroscopic or histopathological variations were observed (Carpenter, 1947).

The results are summarised in Appendix A.

3.3.3 Chronic toxicity/Carcinogenicity

No data were available.

3.4 GENOTOXICITY

A number of *in vivo* and *in vitro* studies including the bacterial Ames test (Hüls, 1989), the HGPRT-test, the SCE-test in CHO-cells and an *in vivo* micronucleus assay in the mouse revealed no genotoxic activity in the test systems used (Slesinski *et al*, 1988).

The results of genotoxicity studies are summarised in Appendix C.

3.5 REPRODUCTION/DEVELOPMENTAL TOXICITY

Feeding Studies

In a multigeneration drinking water study in CD-1 mice following the continuous breeding protocol EGEEA was a reproductive toxicant as evidenced by significant decreases in the number of litters per fertile pair, decreased life pups per litter and decreased proportion of pups born live especially at the medium and highest dose level (1,800 mg/kg, 3,000 mg/kg). The females appeared to be more sensitive to the effects of EGEEA as evidenced by nearly a 50 % drop in fertility index, a decreased number of life pups per litter in the crossover mating group where the treated females were cohabited with control males, but not in the group cohabitating treated males with control females. Sperm parameters, testes weights and the incidence of abnormal sperm did suggest modest effect on male mice. EGEEA treatment at 1 % (1,800 mg/kg) also affected fertility and certain reproductive parameters in the second generation mice but the observed response was not statistically significant. Another significant finding was, that EGEEA treatment resulted in a prominent histopathological changes in the testes of second generation mice (Gulati *et al*, 1985c).

Inhalation Studies

In a number of inhalation studies with rats and rabbits various embryotoxic, foetotoxic and teratogenic effects were observed following exposure to high doses/concentrations of EGEEA. As main embryotoxic effects increased resorptions/litter were found. Main foetotoxic effects were skeletal variations and reduced foetal body weight. The main teratogenic effects were skeletal and cardiovascular malformations (Tinston, 1983; Nelson *et al*, 1984b; Doe, 1984a; Tyl *et al*, 1988).

A clear NOEL for both, rats and rabbits was 50 ppm (275 mg/m^3) (Tyl *et al*, 1988).

Dermal Studies

In a dermal teratogenicity study in the rat (18 f) a dose of 5,923 mg/kg applied on day 7 -16 of gestation also induced an increased number of post-implantational losses as well as an increased incidence of cardiovascular and skeletal malformations (Hardin *et al*, 1984).

The results of reproduction and developmental studies are summarised in Appendix B.

3.6 TOXICOKINETICS/METABOLISM

EGEEA is rapidly absorbed after inhalation. Hydrolysis of the ester group occurs more or less quantitatively and the main route of excretion is the urine. By dermal application approximately 60 to 70 % of the applied dose/concentration is excreted after 24 hours via this route. Only minor amounts are exhaled as CO_2 (approximately 1 %). Absorption rates through human and dog skin were determined to be 0.8 mg/cm^2/h (30 °C) and 2.3 mg/cm^2/h (37°C) respectively (Dugard *et al*, 1984; Guest *et al*, 1984). The half-life of ^{14}C-EGEEA in the blood of dogs following *i.v.* administration was determined to be 7.9 hours (Guest *et al*, 1984).

The results of toxicokinetics/metabolic studies are summarised in Appendix D.

Similar to those findings with EGEE, EtOH inhibited the oxidation of EGEE to EAA when EGEEA was inhaled, indicative for the involvement of the liver ADH enzyme system in the oxidation of EGEE (Römer *et al*, 1985).

3.7 NEUROTOXICITY

No data available.

3.8 IMMUNOTOXICITY

No data available.

4. HUMAN DATA

Following inhalation of EGEEA and absorption via the respiratory system the main metabolite in humans similar to the inhalation of EGEE was identified as EAA. Approximately 24 % of the absorbed EGEEA dose was excreted as EEA with a half-life of 23.6 hours. Only 0.5 % of the absorbed EGEEA was exhaled unchanged (Groeseneken *et al*, 1987a,b). The identification of EEA as main urinary metabolite after EGEEA exposure was used in several studies where occupationally exposed workers were monitored. These studies showed that even low concentrations of EGEEA such as 1 ppm (5.47 mg/m^3) were sufficient to show an increased level of EEA in the urine of the workers (Veulemans *et al*, 1987; Johanson *et al*, 1989; Angerer *et al*, 1990).

Substance Profile: EGnPE

1. IDENTITY

Name:	Ethylene Glycol (mono) n-Propyl Ether
Structural formula:	C_3H_7-O-CH_2-CH_2-OH
Molecular formula:	$C_5H_{12}O_2$
Molecular weight:	104.2
CAS No.:	2807-30-9
IUPAC name:	n-Propoxyethanol
Other components:	Not known

2. PHYSICAL CHEMICAL DATA

Conversion factor:	1 ppm = 4.25 mg/m^3 (25°C, 1013 hPa) 1 mg/m^3 = 0.24 ppm (25°C, 1013 hPa)
Melting point:	approx. -60°C
Boiling point:	150 - 152°C at 1013 hPa
Vapour pressure:	1.3 hPa at 25°C
Solubility in water:	Completely soluble

3. TOXICOLOGICAL DATA

3.1 ACUTE TOXICITY

3.1.1 Oral toxicity

Rats: LD_{50} 3,090 mg/kg (Katz *et al*, 1984). Signs of toxicity were abnormal respiration, haemoglobinuria and tremors.

3.1.2 Dermal toxicity

Guinea pigs: LD_{50} >1<5 ml/kg (24 h occluded) (Katz *et al*, 1984).

3.1.3 Inhalation toxicity

Male rats: LC_{50} 2,132 ppm (6h exposure to vapour saturation) (Katz *et al*, 1984). Haemoglobinuria was observed at 1,121 and 2,132 ppm.

Pregnant rats: 1,600 ppm killed 8/10 dams after 2 exposures (Krasavage and Katz, 1985).

Pregnant rabbits: LC_{50} >500 ppm; 800 ppm were lethal after 2 - 5 exposures (Krasavage *et al*, 1990).

3.2 IRRITATION/SENSITIZATION

3.2.1 Skin irritation

Slightly irritating to guinea pig skin (undiluted test material, 24 h occluded exposure) (Katz *et al*, 1984)

3.2.2 Eye irritation

Moderate to marked irritating to the eye of rabbits (undiluted test material) (Katz *et al*, 1984)

3.2.3 Sensitization

Very weak response in 1/5 guinea pigs (Katz *et al*, 1984) (footpad injection with 0.05 ml Freund's adjuvant with and without 1% of the test material; 1 week later 0.3 ml of 1% solution dosed topically to the depilated dorsal skin).

3.3 SUBACUTE/SUBCHRONIC/CHRONIC TOXICITY

3.3.1 Subacute toxicity

Feeding studies

Groups of 10 male CBOS/CD rats were dosed with 1.88, 3.75, 7.5 and 15 mmol/kg (5d/wk; 6wk) by gavage. Haemoglobinuria was seen at least for one day at all dose levels. There was little effect on feed consumption and body weight gain. With exception of the lowest dose level absolute and relative spleen weights were increased (Katz *et al*, 1984).

Inhalation studies

Pregnant rabbits, exposed to 800 or 1,000 ppm in a probe teratology study, showed haemoglobinuria following the first exposures. After 2 - 5 exposures these dose levels were lethal (Krasavage *et al*, 1990).

Pregnant rats, exposed to 1,600 ppm in a probe teratology study, showed a lethality rate of 8/10 after 2 exposures. 800 ppm produced losses in body weight and in absolute and relative liver weights; feed intake was reduced (Krasavage *et al*, 1990).

Groups of 10 CBOS/CD rats (5 m, 5 f) were exposed via inhalation to 800, 400, 200 and 100 ppm for 11 exposures (6 h/d; 5 d/wk). Initial haemoglobinuria occurred in the males at 400 and 800 ppm and in the females exposed to 800 ppm (Katz *et al*, 1984).

The results of subacute studies are summarised in Appendix A.

3.3.2 Subchronic toxicity

No data available.

3.3.3 Chronic toxicity/Carcinogenicity

No data available.

3.4 GENOTOXICITY

No data available.

3.5 REPRODUCTION/DEVELOPMENTAL TOXICITY

In a probe teratology study with Charles River rats inhalation of 800 ppm caused severe maternal toxicity and fetal resorptions. In the following main study employing 100, 200, 300 and 400 ppm no teratogenicity or significant fetal toxicity was recorded (Krasavage and Katz, 1985).

In a New Zealand rabbit study employing 125, 250, 500 ppm no developmental toxicity was observed (Krasavage *et al*, 1990).

The studies are summarised in Appendix B.

3.6 TOXICOKINETICS/METABOLISM

No data available.

3.7 NEUROTOXICITY

No data available.

3.8 IMMUNOTOXICITY

No data available.

4. HUMAN DATA

No data available.

Substance Profile: EGnPEA

1. IDENTITY

Name:	Ethylene Glycol (mono) n-Propyl Ether Acetate
Structural formula:	C_3H_7-O-CH_2-CH_2-O-CO-CH_3
Molecular formula:	$C_7H_{14}O_3$
Molecular weight:	146.2
CAS No.:	20706-25-6
IUPAC name:	2-Propoxyethyl acetate
Other components:	Not known

2. PHYSICAL CHEMICAL DATA

Conversion factor:	1 ppm = 5.98 mg/m^3 (25°C, 1013 hPa) 1 mg/m^3 = 0.17 ppm (25°C, 1013 hPa)
Melting point:	Not known
Boiling point:	173°C
Vapour pressure:	0.67 hPa at 20°C
Solubility in water:	Approx. 5% w/w at 20°C

3. TOXICOLOGICAL DATA

3.1 ACUTE TOXICITY

3.1.1 Oral toxicity

Rats: LD_{50} 9,456 mg/kg. Signs of toxicity were abnormal respiration, haemoglobinuria and prostration (Katz *et al*, 1984).

3.1.2 Dermal toxicity

Rabbits: LD_{50} > 20 mg/kg (24 h semi-occluded exposure) (Katz *et al*, 1984).

3.1.3 Inhalation toxicity

Rats: LC_{50} > 934 ppm (6 h exposure to saturated vapour) (Katz *et al*, 1984).

3.2 IRRITATION/SENSITIZATION

3.2.1 Skin irritation

Slightly irritating to guinea pig skin (24 h occluded exposure, undiluted test material) (Katz *et al*, 1984).

3.2.2 Eye irritation

Slightly irritating to the eye of rabbits (undiluted test material) (Katz *et al*, 1984).

3.2.3 Sensitization

Non sensitizer in guinea pig (Katz *et al*, 1984).

3.3 SUBACUTE/SUBCHRONIC/CHRONIC TOXICITY

3.3.1 Subacute toxicity

Groups of 10 male COBS/CD rats were dosed with 7.5, 15 and 30 mmol/kg/d (5d/wk; 6 wk) by gavage. Haemoglobinuria and increase of spleen weights was seen at least once at all dose levels. Body weight was reduced at the two high doses and feed intake was reduced at all levels. Histopathological effects occurred in spleen, liver, kidney and testes. The NOEL for liver and kidney effects was 15 mmol/kg, whereas haematological, spleen and kidney effects occurred throughout all dose levels (Katz *et al*, 1984).

In groups of 10 COBS/CD rats (5 m, 5 f per dose level), exposed to 100, 200, 400, 800 ppm (6 h/d; 5 d/wk), for a total of 11 exposures, initial haemoglobinuria occurred in females at 200, 400 and 800 ppm and also in males at 800 ppm. 100 ppm was the NOEL (Katz *et al*, 1984).

The results are summarised in Appendix A.

3.3.2 Subchronic toxicity

No data available.

3.3.3 Chronic toxicity/Carcinogenicity

No data available.

3.4 GENOTOXICITY

No data available.

3.5 REPRODUCTION/DEVELOPMENTAL TOXICITY

No teratogenicity was found in COBS/CD/(SD)BR rats exposed to vapour concentrations of 100, 200, 400 and 800 ppm (6h/d) from day 6 through 15 of gestation. At 400 and 800 ppm the dams showed

haemoglobinuria and at 800 ppm reduced body weight. The incidence of resorptions was significantly increased at 800 ppm. Minor rib anomalies were slightly increased at 400 and 800 ppm and at 200 ppm a slight increase of common skeletal variants was seen (Krasavage and Katz, 1984) (see Appendix B).

The metabolic cleavage product EGnPE was neither teratogenic in rabbits nor in rats (see EGnPE product profile).

3.6 TOXICOKINETICS/METABOLISM

No data available.

In analogy to other glycol ether acetates metabolic cleavage to EGnPE and subsequent oxidation to PAA are assumed to occur.

3.7 NEUROTOXICITY

No data available.

3.8 IMMUNOTOXICITY

No data available.

4. HUMAN DATA

No data available.

Substance Profile: EGiPE

1. IDENTITY

Name:	Ethylene Glycol (mono) iso-Propyl Ether (2-Isopropoxyethanol)
Structural formula:	$(CH_3)_2CH\text{-}O\text{-}CH_2\text{-}CH_2\text{-}OH$
Molecular formula:	$C_5H_{12}O_2$
Molecular weight:	104.2
CAS No.:	109-59-1
IUPAC name:	2-Isopropoxyethanol
Other components:	Not known

2. PHYSICAL CHEMICAL DATA

Conversion factor:	1 ppm = 4.25 mg/m^3 (20°C, 1013hPa) 1 mg/m^3 = 0.24 ppm (20°C, 1013hPa)
Melting point:	< -60°C
Boiling point:	144°C at 1013 hPa
Vapour pressure:	6.9 hPa at 25°C
Solubility in water:	Completely soluble

3. TOXICOLOGICAL DATA

3.1 ACUTE TOXICITY

3.1.1 Oral toxicity

Rats: LD_{50} >500< 1,000 mg/kg (Gingell *et al*, 1994) signs of toxicity were CNS depression, dyspnoea and haemoglobinuria with kidney damage, liver and spleen alterations.

LD_{50} 5,600 mg/kg (Smyth *et al*, 1969).

Mice: LD_{50} 2,300 mg/kg (administration in oil) 2,180 g/kg (administration in water) (Saparmamedov, 1974).

3.1.2 Dermal toxicity

Rabbits: LD_{50} 1,600 mg/kg (undiluted material) (Smyth *et al*, 1969).

3.1.3 Inhalation toxicity

Rats: LC_{50} 4,000 ppm (4 h exposure) (Smyth *et al*, 1969).

Mice: LC_{50} 1,930 ppm (7 h exposure) (Smyth *et al*, 1969).

Haemolytic effects were seen in rats after single inhalation exposure of 62, but not 32 ppm (Carpenter *et al*, 1956) and 80 ppm (Saparmamedov, 1974).

3.2 IRRITATION/SENSITIZATION

3.2.1 Skin irritation

Moderately irritating to rabbit skin (undiluted test material) (Gingell *et al*,1994).

3.2.2 Eye irritation

Irritating to the eyes of rabbits causing iritis and corneal damage (Smyth *et al*, 1969).

3.2.3 Sensitization

No data available.

3.3 SUBACUTE/SUBCHRONIC/CHRONIC TOXICITY

3.3.1 Subacute toxicity

Haemolytic effects were found in 23 Wistar rats exposed for 5 weeks to 390 ppm (7 h/d 5 d/wk). The number of reticulocytes was increased. After the 4th week haematological parameters were nearly in the control range, indicating less sensitivity of the young RBC's (red blood cells) towards EGiPE (Werner *et al*, 1943c).

10 male Wistar rats exposed to 600 or 1,000 ppm through 9 days in 2 weeks showed haemolytic effects. No testicular damage was observed (Doe, 1984b).

Haemolytic effects and signs of haemolytic anaemia were observed in a 28-day inhalation study with Wistar rats exposed to 150, 450 and 900 ppm for 10 m; 10 f/dose group). In the two higher dose groups urinary pH values showed a tendency to lower levels indicating a compensated metabolic acidosis. In addition these dose groups also showed increased spleen weights. No influence on body weight development and dietary consumption was observed and no testicular effect was seen. A subsequent study with concentrations of 10, 30 and 100 ppm showed the NOEL at 30 ppm, since at 100 ppm there was still some haemolytic effect in the females (Reuzel *et al*, 1987).

Inhalation of 100, 300 and 1,000 ppm (6 h/d; 5 d/wk; 3 wk) (4 m, 4 f) initially caused haemoglobinuria in rats and decrease of haemoglobin in plasma and red blood cells (RBC) at the top dose level. The effect was reversible - probably via compensation by increased cellular proliferation (reticulocytes). Irritation of respiratory tract and increase of lung weight was also observed. At 300 ppm there was only a transient reduction of haemoglobin in plasma and RBC's. 100 ppm were without effect (Gage, 1970).

The results of subacute studies are summarised in Appendix A.

3.3.2 Subchronic toxicity

The US-TLV documentation cites a 26-week inhalation study in rats, guinea pigs, rabbits and dogs exposed to 25, 50 and 200 ppm (6 h/d). Haemolytic effects still occurred marginally at 25 ppm, more clearly at 50 ppm and pronouncedly at 200 ppm. No further details were reported (Moffet *et al*, 1976).

An insufficiently described 3-month study reports exposure levels of 1, 3, 10 and 30 mg/m^3 (24 h/d) in male rats. 1 mg/m^3 were without effect. At 3 mg/m^3 RBC was marginally decreased. 10 and 30 mg/m^3 led to a dose-dependent decrease of body weights, RBC's plasma haemoglobin, whole blood cholinesterase activity and increase of C-reactive protein[1] and GPT activity (Lykova *et al*, 1976).

3.3.3 Chronic toxicity/Carcinogenicity

No data available.

3.4 GENOTOXICITY

No data available.

3.5 REPRODUCTION/DEVELOPMENTAL TOXICITY

Artificially inseminated New Zealand rabbits were exposed to 20, 90 and 490 ppm, (6 h/d), from gestation day 6-18. Dams of the highest dose group showed reduced food consumption and weight gain. Haematological parameters indicated also haemolytic effects. There was an increased number of foetuses showing reduced foetal weight and signs of delayed maturation. No teratogenic effect was observed. 90 and 20 ppm were without effect in dams and foetuses (Coder *et al*, 1988).

[1] Liver protein related to unspecific resistance towards bacteria, relative with Ca^{2+} and bacterial polysaccharides

A prenatal toxicity study in Wistar rats showed similarly negative results (Coder *et al*, 1987). The animals were exposed to 50, 150 and 450 ppm, (6 h/d) from gestation day 6 - 15. At the two higher levels the dams showed haemoglobinuria. At 450 ppm the incidence of delayed development was increased.

The results are summarised in Appendix B.

3.6 TOXICOKINETICS/METABOLISM

EGiPE was ^{14}C-labelled in both C-atoms of the ethylene group and *i.p.* injected into Caworth Farm E rats (1 mg/animal). 87% of the radioactivity were recovered within 2 h (73% with the urine and 14% in the expiration air). Urinary metabolites were mainly isopropoxyacetic acid (iPAA), partially conjugated with glycine, as well as acetone and EG. A similar profile was found in a dog receiving 75 mg/kg *i.p.* (Hutson and Pickering, 1971).

3.7 NEUROTOXICITY

No findings of neurotoxicity in a considerable number of studies.

3.8 IMMUNOTOXICITY

No data available.

4. HUMAN DATA

No data available.

Substance Profile: EGBE

1. IDENTITY

Name:	Ethylene Glycol (mono) n-Butyl Ether
Structural formula:	C_4H_9-O-CH_2-CH_2-OH
Molecular formula:	$C_6H_{14}O_2$
Molecular weight:	118.2
CAS No.:	111-76-2
IUPAC name:	2-Butoxyethanol
Other components:	Diethylene glycol (mono)n-butyl ether

2. PHYSICAL CHEMICAL DATA

Conversion factor:	1 ppm = 4.91 mg/m^3 (20°C, 1013 hPa) 1 mg/m^3 = 0.204 ppm (20°C, 1013 hPa)
Melting point:	-77°C
Boiling point:	171°C at 1013 hPa
Vapour pressure:	1.17 hPa at 25°C
Solubility in water:	soluble

3. TOXICOLOGICAL DATA

Note: A comprehensive toxicological review on EGBE has been published as ECETOC Special Report N° 7 (1994).

3.1 ACUTE TOXICITY

3.1.1 Oral toxicity

Rats: LD_{50} 560-3,000 mg/kg (male); 530-2,500 mg/kg (female). The LD_{50} was age and sex dependent, with females and older animals more susceptible to toxicity. Signs of toxicity included congested or haemorrhagic lungs, mottled livers, congested kidneys and haemoglobinuria (Smyth *et al*, 1941; Carpenter *et al*, 1956; Weil and Wright, 1967; Truhaut *et al*, 1979).

Mice: LD_{50} 1,230 mg/kg (male) (Carpenter *et al*, 1956).

Guinea pigs: LD_{50} 950-1,400 mg/kg (Carpenter *et al*, 1956).
LD_{50} 1,414 mg/kg (Shepard, 1994).

Rabbits: LD_{50} 320-3,100 mg/kg (male) (Carpenter *et al*, 1956).

3.1.2 Dermal toxicity

Rats: No data available.

Guinea pigs: LD_{50} 1,200-4,800 mg/kg (1 wk occluded exposure)
(Wahlberg and Boman, 1979).
LD_{50} > 2,000 mg/kg (Shepard, 1994).

LD_{50} 0.23 ml/kg or 0.30 ml/kg on intact and abraded skin respectively (Roudabush *et al*, 1965).

Rabbits: LD_{50} 0.45-0.56 ml/kg (male) (Carpenter *et al*, 1956); 0.11 ml/kg (female) (Duprat and Gradiski, 1979). Effects on liver, spleen, kidney and lung. Haemoglobinuria.

3.1.3 Inhalation toxicity

Rats: LC_{50} 486 ppm (male); 450 ppm (female) (4 h exposure). Effects on kidneys. Haemoglobinuria (Dodd *et al*, 1983).

Mice: LC_{50} 700 ppm (7 h exposure) (Werner *et al*, 1943a).

Guinea pigs: One of six guinea pigs died after exposure (4 h, saturated vapour, actual level not reported); no haemoglobinuria was observed (Carpenter *et al*, 1956).

3.2 IRRITATION/SENSITIZATION

3.2.1 Skin irritation

Slighty irritating to rabbit skin (4 h, non occluded exposure). Moderate irritation reported in percutaneous toxicity studies over 24 h (Tyler, 1984). Occluded patch (0.5 ml for 4 h) was irritating (Rohm and Haas, 1989).

3.2.2 Eye irritation

Severely irritating to the rabbit eye (Tyler, 1984; Rohm and Haas, 1989; Kennah *et al*, 1989).

3.2.3 Sensitization

Non sensitizer in a guinea pig maximisation test (0.5% injection induction, 25% application induction, 10% application challenge) (Unilever, 1989).

3.3 SUBACUTE/SUBCHRONIC/CHRONIC TOXICITY

3.3.1 Subacute toxicity

Erythrocyte damage or destruction was the major feature, with bone marrow, spleen and liver involved in erythrocyte replacement. Liver, lung and kidney effects were essentially sequelae to the primary effect of erythrocyte haemolysis, with the kidney particularly susceptible to damage. Neither EGBE, nor its metabolite 2-butoxyacetic acid (BAA), produced significant testicular toxicity (see Appendix A).

3.3.2 Subchronic toxicity

The toxicity profile was similar to that seen in subacute studies, with older animals more susceptible to haemolytic effects (see Appendix A).

3.3.3 Chronic toxicity/carcinogenicity

No data available. A 2 years carcinogenicity study in rats and mice has been started in July 1993 in the US by NTP.

3.4 GENOTOXICITY

EGBE was not mutagenic in a limited number of *in vitro* studies, apart from an equivocal response in an unscheduled DNA synthesis study (that may have been due to cytotoxicity), a positive response in *Salmonella typhimurium* strain TA97a, and in an *in vitro* sister chromatid exchange assay with human lymphocytes (see Appendix C).

3.5 REPRODUCTION/DEVELOPMENTAL TOXICITY

EGBE was not teratogenic in studies with rat, rabbit or mouse. Toxic doses reduced female (but not male) fertility and caused embryotoxicity and foetotoxicity (see Appendix B).

3.6 TOXICOKINETICS/METABOLISM

The urine was the major route of excretion following administration of EGBE. The major urinary metabolite of EGBE was 2-butoxyacetic acid (BAA) in all species studied (dog, rabbit, rat, guinea pig, monkey and man). Uptake and elimination of inhaled EGBE in rat was essentially linear over the range 4-438 ppm.

Pretreatment with the alcohol dehydrogenase inhibitor pyrazole or the aldehyde dehydrogenase inhibitor cyanamide protected rats against EGBE (500 mg/kg, oral) induced haematotoxicity; cyanamide also protected against butoxyacetaldehyde (BAL) induced haematotoxicity. This protection was associated with significant reductions in the conversion of EGBE to BAA and an increase in EGBE glucuronide and sulphate conjugates. Substitution of methylene group hydrogens on EGBE with deuterium delayed, but did not abolish, the haematotoxic effects of EGBE. These results were consistent with the metabolism of EGBE to BAA being a primary cause of haematotoxicity following administration of EGBE. Comparison of tissue radioactivity levels 48 hours after oral administration of ^{14}C-EGBE (500 mg/kg) showed significantly lower levels of tissue radioactivity in rats where conversion of EGBE to BAA had been blocked (Ghanayem *et al*, 1987b).

The effects of dose, age, inhibition of metabolism and elimination on the toxicokinetics of EGBE and its metabolites have been studied in mature (3-4 months) or old (12-13 months) male rats. EGBE (31.25, 62.5 or 125 mg/kg) was administered by intravenous injection. Only EGBE and BAA were identified in the plasma. The increased sensitivity of older rats to erythrocyte haemolysis was attributed to a number of factors contributing to increased exposure of erythrocytes to BAA, including compromised renal clearance of BAA, increased conversion of EGBE to BAA and reduced degradation of BAA to CO_2. Erythrocytes from older animals were also more susceptible to BAA induced haemolysis than erythrocytes from younger animals (Ghanayem *et al*, 1990). Further studies established that rats developed tolerance to EGBE induced haematolytic anaemia as a result of replacement of old erythrocytes with younger cells (Ghanayem *et al*, 1992).

Concomitant administration of ethanol with EGBE in rats delayed the elimination of EGBE from the blood (Römer *et al*, 1985). Studies on the elimination kinetics of EGBE in perfused rat liver also showed that ethanol inhibited the removal of EGBE (Johanson *et al*, 1986a).

In vitro studies of the metabolic and cellular basis of EGBE induced haemolytic anaemia in rats were used to assess the risk to man (Ghanayem, 1989; Ghanayem *et al*, 1989). EGBE (10 mMol) incubated with rat blood caused no haemolysis of erythrocytes, whereas 20 mMol EGBE caused significant haemolysis. 2-Butoxyacetaldehyde (BAL) and BAA (0.5, 1.0 or 2.0 mMol) caused time and concentration dependent swelling of erythrocytes followed by erthyrocyte haemolysis. ADH potentiated the effect of BAL on erythrocytes. BAA and BAL (but not EGBE) also caused a time and concentration dependent reduction in blood ATP concentration. Partitioning of BAA between plasma and erythrocytes favoured plasma by 6.5:1, but this changed with time to 3.25:1 after 4 hours. It was not clear whether the ATP fall caused the erythrocyte swelling or whether swelling of the erythrocyte led to ATP depletion; the reason for the change in distribution of BAA between plasma and erythrocytes was not defined.

The results of toxicokinetics and metabolism of EGBE are summarised in Appendix D.

3.7 NEUROTOXICITY

No data available.

3.8 IMMUNOTOXICITY

No consistent effects were reported on white blood cells and no reports indicated degenerative change in bone marrow in subacute toxicity studies. EGBE had no significant effect on cellular or humoral measures of immune function (Appendix A). The proliferative activity of guinea pig lymphocytes *in vitro* was not affected by non-cytotoxic doses of BAA (1 mMol) or EGBE (2 mMol) (Unilever, 1990).

4. HUMAN DATA

Two cases of human poisoning by ingestion of household products containing 12-13% EGBE have been reported (Rambourg-Schepens *et al*, 1988; Gijsenbergh *et al*, 1989). The probable doses of EGBE were 30-60 ml or 25-30 ml respectively. Coma and metabolic acidosis were common features, with hypokalaemia and haemoglobinuria following ingestion of the higher dose. Neither patient died, but both required hospitalisation and supportive treatment.

In vitro studies examined the metabolic and cellular basis of EGBE induced haemolytic anaemia in rats and assessed the risk to man (Ghanayem, 1989; Ghanayem *et al*, 1989). Incubation of human blood with BAA (up to 4 mMol) in vitro caused minimal swelling or haemolysis of erythrocytes and there was no reduction in blood ATP (0.5-2.0 mMol BAA produced total rat erythrocyte haemolysis). There was a slight increase in haemolysis of human erythrocytes incubated with 8 mMol BAA. Female erythrocytes were slightly more sensitive than male erythrocytes. The study was conducted with blood from young volunteers. EGBE reduced the deformability of rat erythrocytes *in vitro* and this was proposed as a possible reason for rat erythrocyte haemolysis *in vivo* ; no studies were reported for BAA (Kurantsin-Mills *et al*, 1992). Erythrocyte deformability and haemolysis has been studied with rat and human erythrocytes *in vitro* following exposure to BAA (up to 2.0 mMol for up to 4 h). Human erythrocytes were unaffected, whereas rat erythrocytes were haemolysed and showed decreased deformability. BAA had no effect on abnormal human erythrocytes (sickle cell, hereditary spherocytosis) or erythrocytes from older subjects (Udden, 1992).

EGBE penetrated human abdominal skin in vitro at a rate of 1.67 μmel/cm^2/h (Dugard *et al*, 1984) and human stratum corneum at 2.5 μmel/cm^2/h (Barber *et al*, 1992). EGBE was absorbed at a rate of 1.56 μmel/cm^2/h (range 0.42 to 5.76 μmel/cm^2/h) during immersion of 2 or 4 fingers of volunteers into undiluted EGBE. Exposure of 4 fingers to liquid EGBE was calculated to be approximately equivalent to inhalation exposure at 20 ppm (Johanson *et al*, 1988).

Johanson *et al* (1986b) evaluated the toxicokinetics of inhaled EGBE in man. Volunteers were exposed at 20 ppm during light physical exercise for a period of 2 hours. None of the subjects complained of or showed any signs of adverse effects. The respiratory uptake rate averaged 10 μmel/min., which corresponded to 57% of the inhaled dose. Blood concentrations of EGBE reached a plateau of 74 μmel/l during exposure and fell rapidly at the end of the exposure period with a half life of 40 minutes. Urinary elimination of EGBE and BAA was <0.03% and 41% respectively of the absorbed amount during 24 h post exposure, with the majority appearing within 12 hours. The half life for the decay of BAA in urine from 4 hours after the end of exposure was 5.77 hours.

Johanson (1986) developed a pharmacokinetic model for inhalation of EGBE in man which indicated there was unlikely to be progressive accumulation in workers taking the equivalent of light exercise and exposed to 20 ppm for 8 hours a day. However, the possibility of accumulation by high affinity binding to a specific organ or tissue was not excluded. No data are available on the kinetic behaviour of BAA

in man.

Johanson and Fernstrom (1986) related inhalation studies in man at 20 ppm to dermal penetration studies in guinea pigs. They calculated that placing the hands into EGBE would be equivalent to an inhalation exposure level of 370 ppm of EGBE during light physical exercise or in excess of 1,000 ppm if at rest. On the basis of this calculation, they considered that dermal exposure to EGBE should be avoided.

Johanson and Boman (1991) evaluated systemic exposure to EGBE arising from nose only and whole body (no inhalation) exposure in volunteers exposed to 50 ppm EGBE for 2 hours. Blood EGBE levels were 2-3 times higher following whole body exposure compared to inhalation exposure at 23°C (29 % humidity) and 4-5 times higher at 33°C (71 % humidity). Dermal uptake of EGBE may therefore account for around 75 % of the total systemic body burden of EGBE (as measured by blood EGBE concentrations) following exposure to 50 ppm EGBE vapour.

Carpenter *et al* (1956) reported headaches following inhalation exposure to between 100 and 198 ppm EGBE for 8 hours; women appeared to be more severely affected.

Substance: EGBEA

1. IDENTITY

Name:	Ethylene Glycol (mono)n-Butyl Ether Acetate
Structural formula:	C_4H_9-O-CH_2-CH_2-O-CO-CH_3
Molecular formula:	$C_8H_{16}O_3$
Molecular weight:	160.2
CAS No.:	112-07-2
IUPAC name:	2-n-Butoxyethyl acetate
Other components:	Not known

2. PHYSICAL CHEMICAL DATA

Conversion factor:	1 ppm = 6.65 mg/m^3 (20°C, 1013 hPa) 1 mg/m^3 = 0.15 ppm (20°C, 1013 hPa)
Melting point:	- 64°C
Boiling point:	192°C at 1013 hPa
Vapour pressure:	0.4 hPa at 20°C
Solubility in water:	Slightly soluble (1.5% w/w at 20°C)

3. TOXICOLOGICAL DATA

Note: A comprehensive toxicological review on EGBEA has been published as ECETOC Special Report N° 7 (1994).

3.1 ACUTE TOXICITY

3.1.1 Oral toxicity

Rats: LD_{50} 2,400 mg/kg (female); 3,000 mg/kg (male). Signs of toxicity were haemoglobinuria/haematuria, with extensive renal damage and blood present in the bladder (Truhaut *et al*, 1979).

LD_{50} 7,000 mg/kg (Smyth *et al*, 1962).

Mice: LD_{50} 3,200 mg/kg (Eastman Kodak, 1971: cited in Bibra, 1987).

3.1.2 Dermal toxicity

Rats: No data available.

Rabbits: LD_{50} 1,500 mg/kg (Smyth *et al*, 1962).

LD_{50} approx. 1,500 mg/kg. Deaths after 24-48 h. RBC and haemoglobin were decreased, with blood in the kidneys and bladder; haemoglobinuria/haematuria (Truhaut *et al*, 1979).

3.1.3 Inhalation toxicity

Rats: No mortalities or signs of toxicity in males and females exposed for 4 h (Truhaut *et al*, 1979) or 8 h (Smyth *et al*, 1962) to saturated vapour (nominally 400 ppm).

Rabbits: No mortalities in males and females exposed for 4 h to saturated vapour (nominally 400 ppm). Slight, transient haemoglobinuria and/or haematuria (Truhaut *et al*, 1979).

3.2 IRRITATION/SENSITIZATION

3.2.1 Skin irritation

Not a primary irritant to rabbit skin (Truhaut *et al*, 1979). No significant erythema in rabbits after 4 h covered patch application (Jacobs *et al*, 1989).

3.2.2 Eye irritation

Slightly irritating to the eye of rabbits (Truhaut *et al*, 1979).

3.2.3 Sensitization

No data available.

3.3 SUBACUTE/SUBCHRONIC/CHRONIC TOXICITY

3.3.1 Subacute toxicity

In a 28 day inhalation study (nominally 400 ppm, actual level not reported), rats and rabbits showed haematuria and haemoglobinuria from week 2 (see Appendix A).

3.3.2 Subchronic toxicity

In a 10 month inhalation study (nominally 100 ppm, actual level not reported), rats and rabbits showed no treatment related effects (see Appendix A).

3.3.3 Chronic toxicity/Carcinogenicity

No data available. In view of the rapid conversion of EGBEA to EGBE, the chronic toxicity of EGBEA is likely to be similar to that of EGBE (see EGBE product profile).

3.4 GENOTOXICITY

No data available. In view of the rapid conversion of EGBEA to EGBE, the mutagenic potential of EGBEA *in vivo* is likely to be similar to that of EGBE (see EGBE product profile).

3.5 REPRODUCTION/DEVELOPMENTAL TOXICITY

No data available. In view of the rapid conversion of EGBEA to EGBE, the reproductive and developmental effects of EGBEA are likely to be similar to those of EGBE (see EGBE product profile).

3.6 TOXICOKINETICS/METABOLISM

EGBEA underwent rapid hydrolysis in rat plasma to EGBE (Hoffman and Jäckh, 1985).

3.7 NEUROTOXICITY

No data available. In view of the rapid conversion of EGBEA to EGBE, any neurological effects of EGBEA are likely to be similar to those of EGBE (see EGBE product profile).

3.8 IMMUNOTOXICITY

No data available. In view of the rapid conversion of EGBEA to EGBE, any immunological effects of EGBEA are likely to be similar to those of EGBE (see EGBE product profile).

4. HUMAN DATA

The skin irritation potential of EGBEA under occlusive patch was assessed by determining cutaneous blood flow in human volunteers. EGBEA (48 h patch) or 10% EGBEA in water (3 h patch) did not substantially alter cutaneous blood flow under the conditions of the test (first assessments after 12 h and 1 h respectively). This was in contrast to marked effects seen with toluene, n-hexane and n-butanol. Erythema and other skin responses were not recorded (Jacobs *et al*, 1989).

Substance Profile: EGPhE

1. IDENTITY

Name:	Ethylene Glycol (mono) Phenyl Ether
Structural formula:	C_6H_5-O-CH_2-CH_2-OH
Molecular formula:	$C_8H_{10}O_2$
Molecular weight:	138.2
CAS No.:	122-99-6
IUPAC name:	2-Phenoxyethanol
Other components:	Phenol, diethylene glycol (mono) phenyl ether (8% maximum)

2. PHYSICAL CHEMICAL DATA

Conversion factor:	1 ppm = 5.74 mg/m^3 (20°C, 1013 hPa) 1 mg/m^3 = 0.17 ppm (20°C, 1013 hPa)
Melting point:	13°C
Boiling point:	246°C at 1013 hPa
Vapour pressure:	0.04 hPa at 20°C
Solubility in water:	slightly soluble (2.7 % w/w at 20°C)

3. TOXICOLOGICAL DATA

3.1 ACUTE TOXICITY

3.1.1 Oral toxicity

Rats: LD_{50} 1,300 - 3,400 mg/kg (Smyth *et al*, 1941; Grote and Woods, 1955; (Unilever, 1981a; CIR, 1990).

LD_{50} of cosmetic grade (minimum 92% EGPhE, maximum 8% DEGPhE): 1.26 ml/kg (male); 2.33 ml/kg (female) (CIR, 1990). Dose related decrease in spontaneous activity and reflexes and laboured respiration.

3.1.2 Dermal toxicity

Rats: LD_{50} 2,300 - 14,300 mg/kg (American Cyanamid, 1982; Union Carbide, 1982 and Nipa 1987; all cited in BIBRA, 1988).

Rabbits: LD_{50} 5,000 mg/kg (Union Carbide, 1958; cited in BIBRA, 1988).

3.1.3 Inhalation toxicity

Rats: No signs of toxicity (8 h exposure to saturated vapour; actual level not reported) (American Cyanamid, 1982 and Union Carbide, 1982; cited in BIBRA, 1988).

3.1.4 Intraperitoneal or intramuscular injection toxicity

Rats: Lethal at 575 mg/kg. No further details (Laborit *et al*, 1961).

3.2 IRRITATION/SENSITIZATION

3.2.1 Skin irritation

Slightly irritating to rabbit skin (500 mg) (Union Carbide, 1958; cited in BIBRA, 1988). Repeated application (300-1,000 mg/kg/d for 12 d) produced only slight reddening of rabbit skin (Scortichini *et al*, 1987).

3.2.2 Eye irritation

Moderate to severe irritation in the rabbit eye as quoted in BIBRA, 1988.

3.2.3 Sensitization

EGPhE was not a sensitizer in the Magnusson and Kligman guinea pig maximisation test: 0.5% injection induction, 25% application induction, 5% application challenge (Unilever 1981b; Bruze *et al*, 1988).

3.3 SUBACUTE/SUBCHRONIC/CHRONIC TOXICITY

3.3.1 Subacute toxicity

EGPhE produced erythrocyte haemolysis in rats at high doses (1,000 mg/kg and above). The rabbit was more susceptible to these effects than the rat. Serum alkaline phosphatase concentrations were raised in male rats at high doses. There were no reports of testicular toxicity in subacute studies.

Rat, rabbit and human erythrocyte osmotic resistance to EGPhE was measured *in vitro*. EGPhE had no haemolytic effects at concentrations up to 0.5% in rat and rabbit blood and 1% in human blood (Nipa, 1985). EGPhE was considerably more haemolytic than 2-phenoxyacetic acid (the major metabolite of EGPhE) to female rabbit erythrocytes *in vitro*; 1% EGPhE caused complete erythrocyte lysis (Breslin *et al*, 1991).

The results of subacute studies are summarised in Appendix A.

3.3.2 Subchronic toxicity

No treatment related effects were reported following oral (rat/mouse) or dermal (rabbit) administration of ca 500 mg/kg/day for up to 13 weeks. Higher doses (2000 mg/kg/day) were fatal in some instances and were associated with red cell haemolysis. Serum alkaline phosphatase concentrations were raised in male rats with oral doses at or above 400-500 mg/kg/day (see Appendix A).

3.3.3 Chronic toxicity/Carcinogenicity

No data available.

3.4 GENOTOXICITY

EGPhE was not mutagenic in a range of *in vivo* and *in vitro* tests.
(see Appendix C).

3.5 REPRODUCTION/DEVELOPMENTAL TOXICITY

EGPhE showed no evidence of teratogenic effects at doses that caused maternal and embryo toxicity. Observed effects on reproductive performance in a reproductive toxicity study (primarily neonatal toxicity and possible selective foetotoxicity in F_0 females) were likely to have been secondary to general toxicity (see Appendix B).

3.6 TOXICOKINETICS/METABOLISM

EGPhE was excreted primarily in the urine following oral or dermal administration to rats. The major urinary metabolite was 2-phenoxyacetic acid (see Appendix D).

3.7 NEUROTOXICITY

No data available.

3.8 IMMUNOTOXICITY

No data available.

4. HUMAN DATA

No irritation was reported in human patch testing with 1, 5 or 10% EGPhE in petrolatum. Patch testing of 2736 patients with 1% EGPhE in petrolatum elicited no irritant or allergic reactions at 2 or 4 days. Further patch testing of 130 patients with EGPhE at 1%, 5% or 10% in petrolatum produced no irritant or allergic reactions. A single case of an adverse reaction to an aqueous cream containing 1% EGPhE was reported; this patient gave a positive patch test to 1% EGPhE at 2 and 4 days (Lovell *et al*, 1984).

De Groot *et al* (1986) patch tested 501 consecutive patients with suspected contact dermatitis with 5% EGPhE in petrolatum; one patient gave a positive patch test.

Two repeat insult patch tests with panels of 51 and 138 subjects exposed to 10% EGPhE in petrolatum found no evidence that EGPhE was a primary or cumulative irritant or a sensitizer (CIR, 1990).

Orally administered EGPhE (10.6 mg in water) was recovered quantitatively in the urine of a single male volunteer within 24 h, primarily as 2-phenoxyacetic acid (85% free, 15% as an acid labile conjugate); no EGPhE was detected. Recovery of 2-phenoxyacetic acid in the urine of four hospitalised volunteers (1 male, 3 females) who applied a skin cream containing 1.2% EGPhE was 9-48%. One volunteer excreted 55% of the absorbed dose in urine within 6 h of a single application (Howes, 1988).

Occupational neurotoxicity has been reported for 3 women where EGPhE was used as an anaesthetic for handling small fish at a salmon hatchery (Morton, 1990). It was not possible to determine the extent of exposure to EGPhE. Each worker used about 500 ml of EGPhE a day and was exposed by immersion of the hands in a dilute aqueous solution. The vapour pressure of EGPhE is very low and the main route of systemic exposure was therefore likely to have been by dermal absorption. Peripheral effects were diminished sensation and strength of hands and fingers exposed directly to EGPhE; these effects were short term and did not persist. Other effects recorded during or for a short time after exposure included headache, lightheadedness, slurred speech, euphoria, grogginess and feeling "drunk". After 1-2 years exposure there was onset of constant irritability, forgetfulness and inability to

maintain concentration. Neuropsychological testing confirmed persistent focal cognitive impairment.

Substance Profile: EGDME

1. IDENTITY

Name:	Ethylene Glycol Dimethyl Ether
Structural formula:	CH_3-O-CH_2-CH_2-O-CH_3
Molecular formula:	$C_4H_{10}O_2$
Molecular weight:	90.1
CAS No.:	110-71-4
IUPAC name:	1,2-Dimethoxyethane
Other components:	Not known

2. PHYSICAL CHEMICAL DATA

Conversion factor:	1 ppm = 3.74 mg/m^3 (25°C, 1013 hPa) 1 mg/m^3 = 0.267 ppm (25°C, 1013 hPa)
Melting point:	-58°C to - 71°C
Boiling point:	84°C at 1013 hPa
Vapour pressure:	64 hPa at 20°C
Solubility in water:	soluble

3. TOXICOLOGICAL DATA

3.1 ACUTE TOXICITY

3.1.1 Oral toxicity

Rats: No data available.

Mice: LD_{50} 2,525 mg/kg (Plasterer *et al*, 1985).

3.1.2 Dermal toxicity

No data available.

3.1.3 Inhalation toxicity

No data available.

3.2 IRRITATION/SENSITIZATION

3.2.1 Skin irritation

No data available.

3.2.2 Eye irritation

No data available.

3.2.3 Skin sensitization

No data available.

3.3 SUBACUTE/SUBCHRONIC/CHRONIC TOXICITY

3.3.1 Subacute toxicity

In rats exposed via inhalation, dose dependent behavioural changes, mortalities and haemorrhaging were seen (Goldberg *et al*, 1964). The results are summarised in Appendix A.

3.3.2 Subchronic toxicity

No data available.

3.3.3 Chronic toxicity/Carcinogenicity

No data available.

3.4 GENOTOXICITY

Non mutagenic in bacterial mutagenicity assay (Arimoto *et al*, 1982) (see Appendix C).

3.5 REPRODUCTION/DEVELOPMENTAL TOXICITY

EGDME is teratogenic in mice following a single oral dose or repeated oral doses causing no apparent maternal toxicity (Hardin and Eisenmann, 1987; Uemura, 1980). Specific paw malformations similar to those induced by EGME and DEGDME were reported (Hardin and Eisenmann, 1987). At maternally toxic doses to rats, EGDME caused 100% foetolethality; at oral doses causing no apparent maternal toxicity, retarded ossification but no soft tissue anomalies were seen (Leonhardt *et al*, 1991) (see Appendix B).

3.6 TOXICOKINETICS/METABOLISM

No data available.

3.7 NEUROTOXICITY

Dose dependent and progressive behavioural changes were seen in rats. The effects were reversible (Goldberg *et al*, 1964) (Appendix A).

3.8 IMMUNOTOXICITY

No data available.

4. HUMAN DATA

No adverse effects reported. No data available for evaluation.

Substance Profile: EGDEE

1. IDENTITY

Name:	Ethylene Glycol Diethyl Ether
Structural formula:	C_2H_5-O-CH_2-CH_2-O-C_2H_5
Molecular formula:	$C_6H_{14}O_2$
Molecular weight:	118.2
CAS No.:	629-14-1
IUPAC Name:	1,2-Diethoxyethanol
Other components:	Ethanol; EGEE

2. PHYSICAL CHEMICAL DATA

Conversion factor:	1 ppm = 4.83 mg/m^3 (at 25°C, 1013hPa) 1 mg/m^3 = 0.21 ppm (at 25°C, 1013hPa)
Melting point:	- 74°C
Boiling point:	121°C at 1013 hPa
Vapour pressure:	12.5 hPa at 20°C 16.5 hPa at 25°C
Solubility in water:	20.4% w/w at 20°C

3. TOXICOLOGICAL DATA

3.1 ACUTE TOXICITY

3.1.1 Oral toxicity

Rats : LD_{50} >4,390 mg/kg (10% aqueous solution) (Smyth *et al*, 1941).

Guinea pigs : LD_{50} 2,440 mg/kg (10% aqueous solution) (Smyth *et al*, 1941).

3.1.2 Dermal toxicity

No data available.

3.1.3 Inhalation toxicity

Exposures of 10,000 ppm for 1 h to various species resulted in irritation of mucous membranes, possible narcosis, but no lethalities. The cat is more sensitive than the rabbit, guinea pig or dog (Lehmann and Flury, 1938).

3.2 IRRITATION/SENSITIZATION

3.2.1 Skin irritation

Slightly irritating to the skin of rabbits (4h application, OECD test) (Shell, 1991).

3.2.2 Eye irritation

Slightly irritating to the eye causing an initial pain response. Conjunctival irritation and slight transitory injury of the cornea (Carpenter and Smyth, 1946).

3.2.3 Sensitization

No data available.

3.3 SUBACUTE/SUBCHRONIC/CHRONIC TOXICITY

3.3.1 Subacute toxicity

Preliminary reports of studies conducted in a variety of animal species following EGDEE administration (oral, inhalation or by *s.c.* injection) indicate kidney damage and some mortality in selected species (Lehmann and Flury, 1938; Wiley *et al*, 1938). In some species and via some treatment routes, however, no abnormalities were noted.

The results of subacute studies are summarised in Appendix A.

3.3.2 Subchronic toxicity

No data available.

3.3.3 Chronic toxicity/Carcinogenicity

No data available.

3.4 GENOTOXICITY

No data available.

3.5 REPRODUCTION/DEVELOPMENTAL TOXICITY

Screen developmental toxicity assays have indicated potential adverse developmental effects in mice and rats exposed to EGDEE (Schuler *et al*, 1984; Shell, 1988). In regulatory compliant teratology studies, EGDEE was selectively toxic to the offspring of mice dosed at levels not causing maternal toxicity (George *et al*, 1992). Similar effects were seen in rabbits (George *et al*, 1992). The results are

summarised in Appendix B.

No data are available on which to assess the reproductive toxicity of EGDEE.

3.6 TOXICOKINETICS/METABOLISM

No data available.

3.7 NEUROTOXICITY

No data available.

3.8 IMMUNOTOXICITY

No data available.

4. HUMAN DATA

No adverse effects reported. No data available for evaluation.

Substance Profile: DEGME

1. IDENTITY

Name:	Diethylene Glycol (mono) Methyl Ether
Structural formula:	CH_3-(O-CH_2-CH_2)$_2$-OH
Molecular formula:	$C_5H_{12}O_3$
Molecular weight:	120.1
CAS No.:	111-77-3
IUPAC name:	2,(2-Methoxyethoxy)ethanol
Other components:	Monoethylene glycol, EGME, TEGME

2. PHYSICAL CHEMICAL DATA

Conversion factor:	1 ppm = 4.99 mg/m^3 (20°C, 1013 hPa) 1 mg/m^3 = 0.20 ppm (20°C, 1013 hPa)
Melting point:	-85°C
Boiling point:	190 -196°C at 1013 hPa
Vapour pressure:	0.24 hPa at 25°C
Solubility in water:	Miscible

3. TOXICOLOGICAL DATA

3.1 ACUTE TOXICITY

3.1.1 Oral toxicity

Rats : LD_{50} 9,210 mg/kg (as 50% aqueous solution) (Smyth *et al*, 1941).

Rabbits : LD_{50} 7,200 mg/kg (Gingell *et al*, 1994).

Guinea pigs : LD_{50} 4,200 mg/kg (as 50% aqueous solution) (Smyth *et al*, 1941).

3.1.2 Dermal toxicity

Rats : LD_{50} 20 ml/kg (Browning, 1965).

3.1.3 Inhalation toxicity

Rats : LC_{50} greater than saturated atmosphere (Gingell *et al*, 1994).

3.2 IRRITATION/SENSITIZATION

3.2.1 Skin irritation

Not appreciably irritating to the skin of rabbits (Wolfe, 1954).

3.2.2 Eye irritation

Moderate initial pain response in rabbit eye followed by transitory irritation of conjunctival membranes (Carpenter and Smyth, 1946; Wolfe, 1954).

3.2.3 Sensitization

No data available (see Section 4, HUMAN DATA).

3.3 SUBACUTE/SUBACUTE/CHRONIC TOXICITY

3.3.1 Subacute toxicity

In a limited drinking water study in mice, DEGME apparently was without effect over a 25 day treatment period (Nagano *et al*, 1984). No mortalities were seen in rats receiving DEGME by gavage at doses up to 1,830 mg/kg/d for 30 days. Unspecified microscopic changes were reported in the liver, kidneys and gastrointestinal tract at all dose levels (Smyth and Carpenter, 1948). In a more recent study, DEGME caused treatment-related effects in testes and thymus of rats at oral doses above 500 mg/kg/d (Kawamoto *et al*, 1990a).
The results of subacute toxicity studies are summarised in Appendix A.

3.3.2 Subchronic toxicity

No treatment-related effects were seen in rats exposed for 13 weeks to a maximum achievable DEGME vapour concentration (216 ppm) (Miller *et al*, 1985a). Male guinea pigs treated dermally with DEGME for 13 weeks showed toxicological findings considered to be of minimal significance (Hobson *et al*, 1986a) (see Appendix A).

3.3.3 Chronic toxicity/Carcinogenicity

No data available.

3.4 GENOTOXICITY

DEGME is not a bacterial mutagen in the Ames test. Standard plate test and pre-incubation test with *Salmonella typhimurium* (BASF, 1989).

3.5 REPRODUCTION/DEVELOPMENTAL TOXICITY

DEGME was teratogenic in pregnant Sprague-Dawley rats dosed orally at doses of 720 mg/kg/d and above. Under treatment conditions causing no maternal toxicity, an increased incidence of malformed ribs and malformations of the cardiovascular system were seen, together with reduced foetal body weights and a reduced implantation frequency (Hardin *et al*, 1986). In a recent study (Yamano *et al*, 1993) DEGME was found to be foetotoxic in Wistar rats following oral doses of 600 mg/kg/d, and teratogenic with slight maternal toxicity at 1,800 mg/kg/d. The most sensitive organ to DEGME exposure in this study was the thymus in both adults and foetuses. By contrast, s.c. injection of DEGME in pregnant rats caused no statistically significant treatment-related findings at doses up to 1,000 µl/kg/d (Doe, 1984b). Pregnant rabbits treated dermally with DEGME showed selective foetotoxicity (delayed ossification) under treatment conditions causing no maternal toxicity (Scortichini *et al*, 1986).

The results of reproduction and developmental studies are summarised in Appendix B.

3.6 TOXICOKINETICS/METABOLISM

No studies detailing the metabolic fate of DEGME in animals were located. Studies of the hepatic alcohol/aldehyde dehydrogenase (ADH) and mixed function oxidase (MFO) systems in rats separately pre-treated with DEGME and EGME indicated different substrate responses.

DEGME induced the MFO system, whereas EGME increased the activity of the ADH system (Kawamoto *et al*, 1990b). Further work by Kawamoto *et al* (1991) failed to show induction of rat hepatic microsomal γ-Glutamyl Transpeptidase following single or repeated oral doses of DEGME. Comparative skin penetration studies (Dugard *et al*, 1984) indicate that DEGME crosses human skin *in vitro* at a rate of flux some 10 fold less than that of EGME (see Appendix D).

3.7 NEUROTOXICITY

No data available.

3.8 IMMUNOTOXICITY

No data available.

4. HUMAN DATA

(Penetration of DEGME through excised human skin *in vitro* is described in section 3.6). DEGME, when applied at a concentration of 20% in petrolatum in a closed patch test, caused no irritation nor sensitisation in 25 human subjects (cited in Opdyke, 1974).

Substance Profile: DEGEE

1. IDENTITY

Name:	Diethylene Glycol (mono) Ethyl Ether
Structural formula:	C_2H_5-(O-CH_2-CH_2)$_2$-OH
Molecular formula:	$C_6H_{14}O_3$
Molecular weight:	134.2
CAS No.:	111-90-0
IUPAC name:	2-(2-Ethoxyethoxy)ethanol
Other components:	Ethylene glycol, Diethylene glycol, Triethylene glycol

2. PHYSICAL CHEMICAL DATA

Conversion factor:	1 ppm = 5.57 mg/m^3 (20°C, 1013 hPa) 1 mg/m^3 = 0.179 ppm (20°C, 1013 hPa)
Melting point:	- 76°C
Boiling point:	197-205°C at 1013 hPa
Vapour pressure:	0.19 hPa at 25°C
Solubility in water:	Miscible

3. TOXICOLOGICAL DATA

3.1 ACUTE TOXICITY

3.1.1 Oral toxicity

Rats: LD_{50} 5,400 - 5,500 mg/kg (Laug *et al*, 1939; Berte *et al*, 1986). Signs of toxicity were CNS depression, ataxia, coma and death.

Mice: LD_{50} 5,300 mg/kg (Berte *et al*, 1986).

Guinea pigs: LD_{50} 3,900 mg/kg (Laug *et al*, 1939).

Rabbits: LD_{50} (50% aqueous solution) 3,600 mg/kg (Smyth *et al*, 1941).

3.1.2 Dermal toxicity

Rats: LD_{50} 6,000 mg/kg (Hanzlik *et al*, 1947a). Signs of toxicity were depressed activity, ataxia and coma.

Rabbits: LD_{50} 8,300 mg/kg (Hanzlik *et al*, 1947a).

3.1.3 Inhalation toxicity

No data available.

3.2 IRRITATION/SENSITIZATION

3.2.1 Skin irritation

Slightly irritating to rabbit skin (Draize test 500 mg/24h) (Draize *et al*, 1944).

3.2.2 Eye irritation

Slightly irritating to the rabbit eye. Slight pain response, conjunctival redness, thickening of cornea (Conquet *et al*, 1977; Jacobs and Martens, 1989).

3.2.3 Sensitization

No data available (see Section 4, HUMAN DATA).

3.3 SUBACUTE/SUBCHRONIC/CHRONIC TOXICITY

3.3.1 Subacute toxicity

Several studies have been reported in various species via different dose routes. Kidney damage and treatment-related mortality were reported in cats treated orally (Walther, 1942) and rabbits treated dermally (Hanzlik *et al*, 1947b) with DEGEE. Rats receiving DEGEE in their drinking water showed reductions in food intake, growth and unspecified micropathological changes at all effect dose levels (Smyth and Carpenter, 1948).

The results of subacute toxicity studies are summarised in Appendix A.

3.3.2 Subchronic toxicity

Dietary feeding studies

Dietary feeding to rats of DEGEE at concentrations up to 5% w/w for 90 days caused treatment related kidney damage in high dose group animals (Hall *et al*, 1966; Gaunt *et al*, 1968). Similar effects on the kidney were seen on sub-chronic feeding of DEGEE to other species (Gaunt *et al*, 1968). By contrast, ferrets showed no adverse treatment related effects following dietary feeding with DEGEE at concentrations up to 3 ml/kg/d for 9 months (Butterworth *et al*, 1975).

Inhalation studies

Daily exposure for 12 days to an atmosphere saturated with DEGEE was reported to cause no injuries to mice, rabbits, cats or guinea pigs (Lehmann and Flury, 1943). Continuous DEGEE exposure to rats for 4 months followed by a recovery period resulted in changes in blood cell and blood chemistry profiles (Krotov *et al*, 1981). It is difficult to draw meaningful conclusions from this study given the imprecise reporting of the results.

Dermal studies

Rabbits receiving occluded dermal treatments of repurified DEGEE for 90 days showed no effects on growth, mortality, haematology, clinical chemistry or gross pathology. A treatment related histopathological effect was seen however in the kidneys of animals at the upper dose (Gingell *et al*, 1994).

The results of subchronic studies are summarised in Appendix A.

3.3.3 Chronic toxicity/Carcinogenicity

Several chronic toxicity studies have been performed with DEGEE in the rat. In a 2 year dietary study employing limited pathological examination, effects included testicular atrophy and slight liver damage in the treatment group (Morris *et al*, 1942). Rats receiving DEGEE at concentrations up to 1% in their drinking water and exposed for 2 years (Smyth *et al*, 1964) showed treatment related kidney damage. In another, incomplete study (Hanzlik *et al*, 1947c), DEGEE caused no apparent adverse effects when presented at 1% concentration in the drinking water to rats or mice for up to 23 months (see Appendix A).

3.4 GENOTOXICITY

The weak *in vitro* mutagenic potential seen in bacteria and yeast, was not expressed on testing *in vivo*. DEGEE did not induce micronuclei in mouse bone marrow following two daily *i.p.* treatments at 2 ml/kg (Berte *et al*, 1986) (see Appendix C).

3.5 REPRODUCTION/DEVELOPMENTAL TOXICITY

In a screen assay and several developmental toxicity studies performed with DEGEE in rats and mice, no selective developmental toxicity was seen under treatment conditions not also causing maternal toxicity. Thus DEGEE is not considered a developmental toxicant in laboratory animals exposed orally (Schuler *et al*, 1984; Hardin *et al*, 1987), dermally (Hardin *et al*, 1984), or via inhalation of a maximum achievable vapour concentration (Nelson *et al*, 1984b).

DEGEE had no effect on fertility or reproductive performance of mice exposed at concentrations of up to 2.5% via the drinking water in a study employing a continuous breeding protocol (Williams *et al*, 1990). A significant decrease in the sperm motility was observed in the males exposed at the high dose (equivalent to 4,400 mg/kg/d).

The results of these studies are summarised in Appendix B.

3.6 TOXICOKINETICS/METABOLISM

Anecdotal report on rabbits treated orally or by *s.c.* injection indicate degradation of DEGEE and elimination in the urine as glucuronic acid conjugates (Fellows *et al*, 1947). DEGEE given orally to an adult human (ca 20 mg/kg) resulted in detection of (2-ethoxy- ethoxy)acetic acid as a major (68% dose) metabolite in the urine (Kamerling *et al*, 1977). This appears to be similar to the biotransformation of DEGBE in rats (see DEGBE product profile) where the major metabolite in the urine is 2-(2-butoxyethoxy)-acetic acid.

DEGEE penetrates animal and human skin. Dugard *et al* (1984) determined a rate of penetration through excised human skin for DEGEE that was some six-fold greater than EGEE (see Appendix D).

3.7 NEUROTOXICITY

DEGEE, in common with many other organic solvents, causes depression of the central nervous system at high acute doses (see section 3.1).

3.8 IMMUNOTOXICITY

No data available.

4. HUMAN DATA

In an isolated case report (Browning, 1965), an alcoholic male (aged 44) drank a liquid containing approximately 300 ml DEGEE . Severe symptoms of central nervous and respiratory injury (dyspnoea), thirst and acidosis occurred. The urine contained albumen. He recovered upon symptomatic treatment. In describing the fate of a single oral dose of DEGEE (1.5 g) in a human subject, Kamerling *et al* (1977) provided no information on clinical signs or outcome.

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

Substance Profile: DEGEEA

1. IDENTITY

Name:	Diethylene Glycol Ethyl Ether Acetate
Structural formula:	C_2H_5-(O-CH_2-CH_2)$_2$-O-CO-CH_3
Molecular formula:	$C_8H_{16}O_4$
Molecular weight:	176.2
CAS No.:	112-15-2
IUPAC name:	Ethanol, 2-(2-Ethoxyethoxy)-, acetate
Other components:	Not known

2. PHYSICAL CHEMICAL DATA

Conversion factor:	1 ppm = 7.3 mg/m^3 (20°C, 1013hPa) 1 mg/m^3 = 0.14 ppm (20°C, 1013hPa)
Melting point:	- 25°C
Boiling point:	210 - 220°C at 1013 hPa
Vapour pressure:	0.13 hPa at 20°C
Solubility in water:	Soluble

3. TOXICOLOGICAL DATA

3.1. ACUTE TOXICITY

3.1.1 Oral toxicity

Rats: LD_{50} 11,000 mg/kg (50% aqueous solution) (Smyth *et al*, 1948).

Rabbits: LD_{50} 4,400 mg/kg (50% aqueous solution) (Smyth *et al*, 1948).

Guinea pigs: LD_{50} 3,930 mg/kg (50% aqueous solution) (Smyth *et al*, 1948).

3.1.2 Dermal toxicity

Rabbits: LD_{50} 15,000 mg/kg (Smyth *et al*, 1948).

3.1.3 Inhalation toxicity

Rats and guinea pigs exposed 8 h to saturated atmospheres all survived. But cross autopsy revealed injury to the lungs and kidneys (Smyth *et al*, 1948).

3.2 IRRITATION/SENSITIZATION

3.2.1 Skin irritation

Slight irritation to the rabbit skin (Smyth *et al*, 1948, Hüls, 1990a).

3.2.2 Eye irritation

Slight to moderate irritation to the rabbit eye (0.1 ml undiluted test material) (Smyth *et al*, 1948, Hüls, 1990b).

3.2.3 Sensitization

Not sensitizing in guinea pig in a Magnusson-Kligman maximization test (Hüls, 1990c).

3.3 SUBACUTE/SUBCHRONIC/CHRONIC TOXICITY

3.3.1 Subacute toxicity

No data available.

3.3.2 Subchronic toxicity

No data available.

3.3.3 Chronic toxicity/Carcinogenicity

No data available.

3.4 GENOTOXICITY

In a standard Ames assay DEGEEA showed no mutagenic effect (Hüls, 1990d).

3.5 REPRODUCTION/DEVELOPMENTAL TOXICITY

No data available.

3.6 TOXICOKINETICS/METABOLISM

No data available.

3.7 NEUROTOXICITY

No data available.

3.8 IMMUNOTOXICITY

No data available.

4. HUMAN DATA

Human patch test using undiluted material resulted in a limited number of people developing mild skin irritation. No further details were reported (Gingell *et al*, 1994).

Substance profile: DEGBE

1. IDENTITY

Name:	Diethylene Glycol (mono) n-Butyl Ether
Structural formula:	C_4H_9-(O-CH_2-CH_2)$_2$-OH
Molecular formula:	$C_8H_{18}O_3$
Molecular weight:	162.2
CAS No.:	112-34-5
IUPAC name:	2-(2-n-Butoxyethoxy)ethanol
Other components:	not known

2. PHYSICAL CHEMICAL DATA

Conversion factor:	1 ppm = 6.75 mg/m^3 (20°C, 1013 hPa) 1 mg/m^3 = 0.15 ppm (20°C, 1013 hPa)
Melting point:	- 68°C
Boiling point:	230°C at 1013 hPa
Vapour pressure:	0.057 hPa at 25°C
Solubility in water:	soluble

3. TOXICOLOGICAL DATA

3.1 ACUTE TOXICITY

3.1.1 Oral toxicity

Rats: LD_{50} 7,300 mg/kg (fasted) or 9,600 mg/kg (fed)(Kodak, 1984a).

Mice: LD_{50} 2,400 mg/kg (fasted) or 5,500 mg/kg (fed) (Kodak, 1984a).

Guinea pigs: LD_{50} 2,000 mg/kg (Smyth *et al*, 1941).

Rabbits: LD_{50} 2,200 mg/kg (Gingell *et al*, 1994).

3.1.2 Dermal toxicity

Rats: No data available.

Rabbits: LD_{50} 2,800 mg/kg (Kodak, 1984b).

3.1.3 Inhalation toxicity

Rats: LC_{50} not established; no mortalities occurred following 7 h exposure to saturated vapour (Gingell *et al*, 1994).

3.1.4 Subcutaneous injection toxicity

Rats: 0.5, 1.0 or 1.5 ml/kg caused erythrocyte toxicity and related changes in female rats; older rats were more susceptible (Unilever 1987b).

Guinea pigs: No signs of toxicity at 0.1, 0.5 or 1.0 ml/kg (Unilever, 1984e).

3.2 IRRITATION/SENSITIZATION

3.2.1 Skin irritation

Slightly irritating to rabbit skin upon prolonged or repeated exposure (Gingell *et al*,1994).

3.2.2 Eye irritation

Moderately irritating to the rabbit eye (0.1 ml). Effects were most severe within the first 24 h; the eye returned to normal within 14 days (Ballantyne, 1984a).

3.2.3 Sensitization

Non sensitizer in guinea pig maximisation test (25% injection induction, 100% application induction and application challenge) (Unilever, 1984a).

3.3 SUBACUTE/SUBCHRONIC/CHRONIC TOXICITY

3.3.1 Subacute toxicity

DEGBE was of low toxicity by the oral, dermal or inhalation routes in rat and rabbit. High doses (above 1,000 mg/kg) in the rat showed toxicity consistent with erythrocyte damage (see Appendix A).

15 male and 15 female Fischer 344 rats were exposed to 0, 2, 6 or 18 ppm DEGBE vapour for 6 h/d, 5 d/wk for 5 wk. No treatment-related effects were found in male rats of any exposure group nor in female rats exposed to 2 ppm. A slightly increased degree of hepatocyte vacuolization (apparent fat accumulation) was observed in female rats exposed to 6 or 18 ppm, compatible with slightly increased group mean relative liver weight and paleness of liver in 3 of 10 females in the 18 ppm group. The slight increase of vacuolization observed in the livers of the 6 and 18 ppm females was considered by the authors to be of questionable toxicological significance (Gushow *et al*, 1981).

3.3.2 Subchronic toxicity

DEGBE caused no significant toxicity in the rat over 13 weeks at doses up to 2,000 mg/kg/d (oral or dermal) or 14 ppm (inhalation) (see Appendix A).

3.3.3 Chronic toxicity/Carcinogenicity

No data available.

3.4 GENOTOXICITY

DEGBE was not mutagenic in a range of *in vivo* and *in vitro* tests. An isolated weak positive result in a mouse lymphoma test contrasts with negative results from other studies (see Appendix C).

3.5 REPRODUCTION/DEVELOPMENTAL TOXICITY

Orally (rat and mouse) or dermally (rabbit) administered DEGBE showed no teratogenic, foetotoxic or embryotoxic effects at doses up to 1,000 mg/kg/d. Maternal toxicity (reduced weight gain) was seen in some studies (see Appendix B).

3.6 TOXICOKINETICS/METABOLISM

DEGBE was excreted primarily in the urine following oral, dermal or parenteral administration to rats. The major urinary metabolite was 2-(2-n-butoxyethoxy)acetic acid (see Appendix D). In view of the rapid conversion of DEGBEA to DEGBE, studies on the metabolism of DEGBEA are also relevant (see DEGBEA product profile).

3.7 NEUROTOXICITY

DEGBE produced no signs of neurotoxicity in rats in a 90 day dermal application study at doses up to 2 ml/kg. DEGBE (2 ml/kg, 0.6 ml/kg or 0.2 ml/kg) produced no neurotoxic effects using a functional observational battery or with motor activity testing. Neuropathology found occasional, slight degeneration at various sites in the central and peripheral nervous system, but these were typical of

the strain and were not treatment related (Beyrouty *et al*, 1993) (see Appendix A).

3.8 IMMUNOTOXICITY

No data available.

4. HUMAN DATA

A number of volunteers patch tested with DEGBE developed reddening of the skin (Gingell *et al*, 1994).

In vitro human skin penetration rates from a cleaning product containing 4% DEGBE applied at 100%, 50% and 1.5% dilutions were 0.98, 0.40 and 0.007 μmel/cm²/h respectively. Maximal human inhalation and dermal exposure to DEGBE from using a hard surface cleaner containing 4% DEGBE (used at 1.5% dilution) for 15 minutes was 0.06 mg/kg (Procter and Gamble, 1985 and Gibson *et al*, 1991).

Substance Profile: DEGBEA

1. IDENTITY

Name:	Diethylene Glycol (mono)n-Butyl Ether Acetate
Structural formula:	C_4H_9-(O-CH_2-CH_2)$_2$-O-CO-CH_3
Molecular formula:	$C_{10}H_{20}O_4$
Molecular weight:	204.3
CAS No.:	124-17-4
IUPAC name:	2-(2-butoxyethoxy)ethyl acetate
Other components:	Not known

2. PHYSICAL CHEMICAL DATA

Conversion factor:	1 ppm = 8.48 mg/m^3 (20°C, 1013 hPa) 1 mg/m^3 = 0.12 ppm (20°C, 1013 hPa)
Melting point:	not known
Boiling point:	247°C at 1013 hPa
Vapour pressure:	<0.013 hPa at 20°C
Solubility in water:	Soluble (65 g/l)

3. TOXICOLOGICAL DATA

3.1 ACUTE TOXICITY

3.1.1 Oral toxicity

Rats: LD_{50} 6,500-11,900 mg/kg (Smyth *et al*, 1941; Draize *et al*, 1948).

Rabbits: LD_{50} 2,300-2,700 mg/kg (Draize *et al*, 1944 and 1948).

Guinea pigs: LD_{50} 2,300-2,600 mg/kg (Smyth *et al*, 1941; Draize *et al*, 1948).

Mice: LD_{50} 6,500 mg/kg (Draize *et al*, 1948).

No signs of toxicity were described in these tests.

3.1.2 Dermal toxicity

Rats: No data available.

Rabbits: LD_{50} 5,400 mg/kg (male) (Draize *et al*, 1948);
LD_{50} 14.8 ml/kg (female); signs of toxicity were renal damage (Union Carbide, 1984).

3.1.3 Inhalation toxicity

Rats: LC_{50} 8,693 ppm (4 h exposure). Signs of toxicity were red foci and congestion in the lungs (DuPont 1984). One of six rats died following a single 8 h exposure to saturated vapour (actual level not reported)(Union Carbide, 1984).

3.2 IRRITATION/SENSITIZATION

3.2.1 Skin irritation

Slightly irritating to rabbit skin in a Draize test (Draize *et al*, 1944 and 1948).

3.2.2 Eye irritation

Mild to moderate irritation to the rabbit eye in a Draize test (Carpenter and Smyth, 1946).

3.2.3 Sensitization

No data available.

3.3 SUBACUTE/SUBCHRONIC/CHRONIC TOXICITY

In view of the rapid conversion of DEGBEA to DEGBE, the repeat dose toxicity is likely to be similar to that of DEGBE (see DEGBE product profile).

3.3.1 Subacute toxicity

No data available.

3.3.2 Subchronic toxicity

A 13 week dermal application study in rabbits (Draize *et al*, 1944, 1948) showed a dose related increase in erythrocyte haemolysis, renal damage and haemoglobinuria. Mortality was 50% at 2,000-3,000 mg/kg/d (see Appendix A).

3.3.3 Chronic toxicity/Carcinogenicity

No data available.

3.4 GENOTOXICITY

No data available. In view of the rapid conversion of DEGBEA to DEGBE, the mutagenic potential of DEGBEA *in vivo* is likely to be similar to that of DEGBE (see DEGBE product profile).

3.5 REPRODUCTION/DEVELOPMENTAL TOXICITY

No data available. In view of the rapid conversion of DEGBEA to DEGBE, the reproductive toxicity and teratogenic potential of DEGBEA is likely to be similar to that of DEGBE (see DEGBE product profile).

3.6 TOXICOKINETICS/METABOLISM

DEGBEA underwent rapid hydrolysis in rat blood to DEGBE (Deisinger and Guest,1989). The urine was the major route of excretion. The major metabolite was 2-(2-butoxyethoxy) acetic acid (see Appendix D).

3.7 NEUROTOXICITY

No data available. In view of the rapid conversion of DEGBEA to DEGBE, any neurological effects of DEGBEA are likely to be similar to those of DEGBE (see DEGBE product profile).

3.8 IMMUNOTOXICITY

No data available.

4. HUMAN DATA

Dawson *et al* (1989) reported a single case of allergic dermatitis following occupational exposure over a 20 year period.

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

Substance Profile: DEGDME

1. IDENTITY

Name:	Diethylene Glycol Dimethyl Ether
Structural formula:	CH_3-(O-CH_2-CH_2)$_2$-O-CH_3
Molecular formula:	$C_6H_{14}O_3$
Molecular weight:	134.2
CAS No.:	111-96-6
IUPAC name:	Bis(2-methoxyethyl)ether
Other components:	not known

2. PHYSICAL CHEMICAL DATA

Conversion factor:	1 ppm = 5.57 mg/m^3 (20°C, 1014 hPa) 1 mg/m^3 = 0.18 ppm (20°C, 1014 hPa)
Melting point:	-68°C

Boiling point: 162°C at 1013 hPa

Vapour pressure:	2.27 hPa at 20°C
Solubility in water:	Miscible

3. TOXICOLOGICAL DATA

3.1 ACUTE TOXICITY

3.1.1 Oral toxicity

Rats: LD_{50} 5,000 mg/kg (US-EPA, 1982).

Mice: LD_{50} 2,980 mg/kg (Plasterer *et al*, 1985).

3.1.2 Dermal toxicity

No data available.

3.1.3 Inhalation toxicity

Rats: LC_{50} approx. 4,300 ppm male 4 h exposure (Dupont, 1987).

3.2 IRRITATION/SENSITIZATION

3.2.1 Skin irritation

Not irritating to rabbit skin (US-EPA, 1982).

3.2.2 Eye irritation

Not irritating to the eye of the rabbit (US-EPA, 1982).

3.2.3 Sensitization

No data available.

3.3 SUBACUTE/SUBCHRONIC/CHRONIC TOXICITY

3.3.1 Subacute toxicity

Repeated inhalation exposure or oral dosing of DEGDME to rats causes testicular atrophy, adverse effects on the blood and blood forming organs (Cheever *et al*, 1985 and 1989a; Dupont 1988a,b; Lee *et al*, 1989). Mice appear to be more sensitive than rats to the lethal effects of repeated inhalation exposures of DEGDME (McGregor *et al*, 1983). The similarity of toxic effects seen, and knowledge of the metabolic fate of DEGDME, indicate that the formation of EGME and the alkoxyacetic acid metabolite, methoxyacetic acid (MAA), contributes significantly to the toxic effects observed in rodents exposed to DEGDME.

The results of subacute toxicity studies are summarised in Appendix A.

3.3.2 Subchronic toxicity

No data available.

3.3.3 Chronic toxicity/Carcinogenicity

No data available.

3.4 GENOTOXICITY

DEGDME has been tested in a battery of *in vitro* and *in vivo* genotoxicity tests designed to address various genetic endpoints (McGregor *et al*, 1983). The results indicate no adverse genotoxic response but a strong antifertility effect (see Appendix C).

3.5 REPRODUCTION/DEVELOPMENTAL TOXICITY

DEGDME has been shown to be a reproductive toxicant in male and to be developmentally toxic in female rats (Plasterer *et al*, 1985; Cheever *et al*, 1989a; Lee *et al*, 1989) and mice (McGregor *et al*, 1983; Plasterer *et al*, 1985; Price *et al*, 1987). Studies in mice with a variety of glycol ether substrates indicated similar characteristic paw malformations in offspring of mice dosed orally with DEGDME or EGME (Hardin and Eisenmann, 1987). In rabbits, foetal resorption and skeletal malformations of offspring occurred only in mothers also showing signs of maternal toxicity (NTP, 1987a) (see

AppendixB).

The proximate reproductive and developmental toxicant in rodents is MAA (Cheever *et al*, 1988; Daniel *et al*, 1986 and 1991).

3.6 TOXICOKINETICS/METABOLISM

Considerable metabolic data exist for DEGDME in rodents (Cheever *et al*, 1988; Daniel *et al*, 1991). The principal pathway of biotransformation of DEGDME involves O-demethylation with subsequent oxidation to form (2-methoxy- ethoxy) acetic acid (MEAA). In addition, cleavage (O-dealkylation) of the central ether bond results in formation of 2-methoxyethanol, which is subsequently oxidised to the toxic metabolite, methoxyacetic acid (MAA). The major route of elimination is through the urine. Repeated doses of DEGDME or of phenobarbitone, an inducer of cytochrome P450, increases the rate of cleavage of the central ether bond resulting in an increased formation of MAA (Cheever *et al*, 1989b). Thus in conditions where mixed function oxidase induction may occur, the toxic effects of MAA may be more apparent (see Appendix D).

3.7 NEUROTOXICITY

No data available.

3.8 IMMUNOTOXICITY

No data available.

4. HUMAN DATA

No adverse effects reported. No data available for evaluation.

Substance Profile: DEGDEE

1. IDENTITY

Name:	Diethylene Glycol Diethyl Ether
Structural formula:	C_2H_5-(O-CH_2-CH_2)$_2$-O-C_2H_5
Molecular formula:	$C_8H_{18}O_3$
Molecular weight:	162.2
CAS No.:	112-36-7
IUPAC name:	Bis (2-ethoxyethyl)ether
Other components:	Not known

2. PHYSICAL CHEMICAL DATA

Conversion factor:	1 ppm = 6.64 mg/m^3 (25°C, 1013 hPa) 1 mg/m^3 = 0.15 ppm (25°C, 1013 hPa)
Melting point:	-
Boiling point:	189°C at 1013 hPa
Vapour pressure:	0.67 hPa at 25°C
Solubility in water:	Miscible

3. TOXICOLOGICAL DATA

3.1 ACUTE TOXICITY

3.1.1 Oral toxicity

Rats: LD_{50} 4,970 mg/kg (Union Carbide, 1984).

Guinea pigs: LD_{50} 1,850 mg/kg (Smyth *et al*, 1941).

Mice: LD_{50} 3,670 mg/kg (Plasterer *et al*, 1985).

3.1.2 Dermal toxicity

No data available.

3.1.3 Inhalation toxicity

No data available.

3.2 IRRITATION/SENSITIZATION

3.2.1 Skin irritation

No data available.

3.2.2 Eye irritation

Moderate irritating to the eye of the rabbit following instillation of 50 mg (Union Carbide, 1984).

3.2.3 Sensitization

No data available.

3.3 SUBACUTE/SUBCHRONIC/CHRONIC TOXICITY

3.3.1 Subacute toxicity

Repeated exposure of rats to a saturated DEGDEE vapour (400 ppm) resulted in restlessness and, at necropsy, no remarkable findings. No further details were provided (Gage, 1970) (see Appendix A).

3.3.2 Subchronic toxicity

No data available.

3.3.3 Chronic toxicity/Carcinogenicity

No data available.

3.4 GENOTOXICITY

No data available.

3.5 REPRODUCTION/DEVELOPMENTAL TOXICITY

Results from screen developmental toxicity assays suggested possible adverse effects of DEGDEE, warranting further study (Schuler *et al*, 1984; Plasterer *et al*, 1985). Follow up teratology studies in mice and rabbits (NTP, 1987b,c) failed to show any adverse effects on embryonic or foetal development, even at maternally toxic doses (see Appendix B).

3.6 TOXICOKINETICS/METABOLISM

No data available.

3.7 NEUROTOXICITY

No data available.

3.8 IMMUNOTOXICITY

No data available.

4. HUMAN DATA

No adverse effects reported. No data available for evaluation.

Substance Profile: TEGME

1. IDENTITY

Name:	Triethylene Glycol (mono) Methyl Ether
Structural formula:	CH_3-(O-CH_2-CH_2)$_3$-OH
Molecular formula:	$C_7H_{16}O_4$
Molecular weight:	164.2
CAS No.:	112-35-6
IUPAC name:	2-[2-(2-methoxyethoxy)ethoxy]-ethanol
Other components:	< 10% 2-ethoxy-1-propyl acetate

2. PHYSICAL CHEMICAL DATA

Conversion factor :	1 ppm = 6.72 mg/m^3 (20°C, 1013 hPa) 1 mg/m^3 = 0.15 ppm (20°C, 1013 hPa)
Melting point:	- 44°C
Boiling point:	249.2°C at 1013 hPa
Vapour pressure:	< 0.013 hPa at 20°C
Solubility in water:	Soluble

3. TOXICOLOGICAL DATA

3.1. ACUTE TOXICITY

3.1.1 Oral toxicity

Rats: LD_{50} 11,800 mg/kg (Smyth *et al*, 1962).

3.1. Dermal toxicity

Rabbits: LD_{50} 7,400 mg/kg (Smyth *et al*, 1962).

3.1.3 Inhalation toxicity

Rats: No significant signs of toxicity (8 h exposure to saturated vapour - actual level not reported) (Smyth *et al*, 1961).

3.2 IRRITATION/SENSITIZATION

3.2.1 Skin Irritation

No data available.

3.2.2 Eye Irritation

No data available.

3.2.3 Sensitization

No data available.

3.3 SUBACUTE/SUBCHRONIC/CHRONIC TOXICITY

3.3.1 Subacute toxicity

A dose of 1,000 mg/kg TEGME was applied daily to the shaved skin of groups of 5 male and 5 female New Zealand white rabbits, under an occlusive dressing, 6 h/d for 21 d (Leber *et al*, 1990). The only effect reported that could be attributed to treatment was slight irritation at the site of application.

A two week study was conducted to investigate the palatability of TEGME in the diet or drinking water of male and female Sprague Dawley rats. Concentrations providing an intake of 5,000 mg/kg were reported to be without effect (Gill and Hurley, 1990).

The results of subacute toxicity studies are summarised in Appendix A.

3.3.2 Subchronic toxicity

TEGME applied to the shaved skin of male and female Sprague Dawley rats under an occlusive dressing, 6 h/d 5 d/wk for 13 wk at dose levels of 0, 400, 1,200, or 4,000 mg/kg/d produced focal irritation only on skin areas abraded by the clippers. There was no evidence of systemic toxicity (Corley *et al*, 1990) (see Appendix A).

3.3.3 Chronic toxicity/Carcinogenicity

No data available.

3.4 GENOTOXICITY

TEGME was tested for gene mutation in *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, and TA 1537 using a preincubation protocol. There was no evidence of gene mutation in any of the tester strains either in the presence or absence of an S9 fraction (Samson and Gollapudi, 1990).

A study for gene mutation at the HGPRT locus in Chinese Hamster Ovary cells was similarly negative at concentrations of 2,000-5,000 μg/ml (Linscombe and Gollapudi, 1990).

A micronucleus test was conducted in mice using dose levels of 500, 1,667, and 5,000 mg/kg. There was no evidence of an increase in the incidence of micronucleated polychromatic erythrocytes at any

of the dose levels compared with controls (McClintock and Gollapudi, 1990).

The results of genotóxicity studies are summarised in Appendix C.

3.5 REPRODUCTION/DEVELOPMENTAL TOXICITY

The teratogenicity of TEGME has been investigated in rats and rabbits.

In a screening study TEGME, TEGEE or TEGBE were administered by gavage to pregnant rats at doses of 250 or 1,000 mg/kg/d. The animals were allowed to litter and the growth and viability of the offspring assessed at days 1 and 5 post partum. No adverse effects were reported in either the dams or their offspring (Hoberman 1990a).

A full study was conducted in pregnant Crl:CD(SD)BR rats using oral doses of 0, 625, 1,250, 2,500 or 5,000 mg TEGME/kg/d, administered from d 6-16 of gestation. Maternal death and embryo-foetal lethality were reported at the 5,000 mg/kg dose level. There was a slightly reduced food consumption in the dams and delayed foetal ossification at doses of 1,250 mg/kg/d and above but no evidence of abnormal development at any dose level (Hoberman, 1990a).

A study in pregnant New Zealand white rabbits (Hra: (NZW)SPF) was carried out at dose levels of 250, 500, 1,000 and 1,500 mg/kg/d of TEGME, administered orally from d 6-19 of gestation. At 1,500 mg/kg various signs of maternal toxicity were reported, including death and elevated incidences of angulated hyoid alae and delayed ossification of the xiphoid in the progeny. At 1,000 mg/kg one death was reported, possibly related to treatment, but no foetal effects (Hoberman, 1990b).

There was no evidence of selective toxicity to the foetus including teratogenesis in either study. The results are summarised in Appendix B.

3.6 TOXICOKINETICS/METABOLISM

The skin penetrability of TEGME; TEGEE and TEGBE was compared with EGME (ethylene glycol monomethyl ether) using isolated human epidermis. The mean steady state absorption from undiluted applications were : EGME 2.2 mg/cm^2/h; TEGME 0.034 mg/cm^2/h; TEGEE 0.024 mg/cm^2/h; TGBE 0.022 mg/cm^2/h (Leber *et al*, 1990).

No information is available on the metabolism TEGME.

3.7 NEUROTOXICITY

Groups of male and female Sprague-Dawley CD rats were given TEGME in the drinking water giving nominal doses of 0, 400, 1,200 and 4,000 mg/kg/d for 90 d (Gill and Negley, 1990). The study was conducted specifically to investigate possible neurotoxicity and included observation for behavioural changes and detailed pathological examination of the nervous system. Food consumption, body weight and body weight gain were reduced in both sexes at the top dose and to a lesser extent at the mid-dose. There was a decreased water consumption only in the females at the higher dose. Dose related increases in mean weight and evidence of hepatocellular hypertrophy in the livers of the male rats at all three dose levels were reported. Testicular atrophy was also observed in most male rats from the high dose group. There was no evidence of neurotoxicity in this study.

3.8 IMMUNOTOXICITY

No information available.

4. HUMAN DATA

No data are available.

Substance Profile: TEGEE

1. IDENTITY

Name:	Triethylene Glycol(mono) Ethyl Ether
Structural formula:	C_2H_5-(O-CH_2-CH_2)$_3$-OH
Molecular formula:	$C_8H_{18}O_4$
Molecular weight:	178.2
CAS No.:	112-50-5
IUPAC name:	2-[2-(2-Ethoxyethoxy)ethoxy]ethanol
Other components:	Not known

2. PHYSICAL CHEMICAL DATA

Conversion factor:	1 ppm = 8.66 mg/m^3 (20 °C, 1013 hPa) 1 mg/m^3 : 0.12 ppm (20 °C, 1013 hPa)
Melting point:	- 30°C
Boiling point:	235 - 280°C at 1013 hPa
Vapour pressure:	< 0,01 hPa at 20 °C
Solubility in water:	Soluble

3. TOXICOLOGICAL DATA

3.1 ACUTE TOXICITY

3.1.1 Oral toxicity

Rats: LD_{50} 8,500 mg/kg. Signs of toxicity were lethargy, ataxia and piloerection (EPA, 1982a).

LD_{50} 10,610 mg/kg. Signs of toxicity not specified. (Smyth and Carpenter, 1948).

3.1.2 Dermal toxicity

Rabbits: LD_{50} 8,200 mg/kg. (No details given) Smyth *et al* (1951). At a single dose of 2,000 mg/kg no signs of toxicity were observed (EPA, 1982b).

3.1.3 Inhalation toxicity

Rats: No signs of toxicity or mortality were observed (1 h exposure to nominal concentration of 200 mg/l) (EPA, 1982c).

3.2 IRRITATION/SENSITIZATION

3.2.1 Skin irritation

Not irritating to rabbit skin (24 h 0.5 ml undiluted test material, semi-occluded patch exposure) (Smyth and Carpenter, 1948; EPA, 1982d).

3.2.2 Eye irritation

Not irritating to the eye of the rabbit (0.1 ml undiluted test material) (EPA, 1982e; Smyth and Carpenter, 1948).

3.2.2.1 Skin irritation in man

Slightly irritating to human volunteers skin (2 h, 0.03 ml semi-occluded patch of undiluted test material). Very slight erythema (EPA, 1982f).

3.2.3 Sensitization

No data available.

3.3 SUBACUTE/SUBCHRONIC/CHRONIC TOXICITY

3.3.1 Subacute toxicity

Groups of ten rats were given doses of TEGEE in the drinking water in concentrations of 0, 0.12, 0.5, 2 an 8 % for 30 d. The actual doses were 0, 180, 750, 3,300 and 13,290 mg/kg/d. The rats drinking an 8 % solution consumed only 25 % of the control value. All of them died in 6 to 24 d mainly because of liver and kidney injury. There was no mortality in rats drinking a 2 % solution, but a decreased body weight gain and liver and kidney lesions were observed occasionally. At a drinking water concentration of 0.5 % or 0.12 % solutions no animal showed any abnormalities (EPA, 1985).

In a 21-day dermal study in New Zealand White rabbits (5 m/5 f/group) a limit dose of 1,000 mg/kg TEGEE was applied for 6 hours daily. The chemical did not produce any systemic toxicity in male or female animals. Observations at the application site indicated that TEGEE produced slight erythema and edema starting on day 6 or 7 of treatment. Erythema continued throughout the study whereas edema was not observed after day 18 (Leber *et al*, 1990).

The results are summarised in Appendix A.

3.3.2 Subchronic toxicity

No data available.

3.3.3 Chronic toxicity/Carcinogenicity

No data available.

3.4 GENOTOXICITY

No data on TEGEE are available. However, studies with TEGME (Ames, HGPRT and Micronucleus Test) showed no mutagenic activity (see product profile TEGME).

3.5 REPRODUCTION/DEVELOPMENTAL TOXICITY

TEGEE was screened in rats for potential developmental toxicity following a modified Chernoff-Kavlock assay. Groups of ten mated female Wistar rats were administered daily doses of 250 and 1,000 mg/kg by gavage on days 6 - 15 of gestation. No significant changes in clinical conditions or body weights were seen in maternal rats following exposure to TEGEE. All rats in the control and treated groups were pregnant and delivered live foetuses. The number of life pups on day 1 and 5 postpartum were also comparable in these groups indicating no chemically induced developmental effects (Leber *et al*, 1990) (see Appendix B).

3.6 TOXICOKINETICS/METABOLISM

Human abdominal whole skin (2.54 cm^2) was mounted in a glass diffusion apparatus and the diffusion of TEGEE into the donor chamber was monitored during a 12 h-period using gas chromatography. The diffusion rate of TEGEE was determined to be 0.125 $\mu mel/cm^2/h$ indicating a low skin permeability of the compound (Leber *et al*, 1990) (see Appendix D).

3.7 NEUROTOXICITY

No data available.

3.8 IMMUNOTOXICITY

No data available.

4. HUMAN DATA

No data available.

Substance Profile: TEGBE

1. IDENTITY

Name:	Triethylene Glycol (mono)n-Butyl Ether
Structural formula:	C_4H_9-(O-CH_2-CH_2)$_3$-OH
Molecular formula:	$C_{10}H_{22}O_4$
Molecular weight:	206.3
CAS No.:	143-22-6
IUPAC name:	2-[2-(2-Butoxyethoxy)ethoxy]ethanol
Other components:	Not known

2. PHYSICAL CHEMICAL DATA

Conversion factor:	1 ppm = 10 mg/m^3 (20°C, 1013hPa) 1 mg/m^3 = 0.1 ppm (20°C, 1013hPa)
Melting point:	- 35°C
Boiling point:	255 - 295 °C at 1013 hPa
Vapour pressure:	< 0,01 hPa at 20°C
Solubility in water:	Soluble

3. TOXICOLOGICAL DATA

3.1 ACUTE TOXICITY

3.1.1 Oral toxicity

Rats: LD_{50} 6,730 mg/kg and 5,300 mg/kg (Smyth *et al*, 1962; EPA, 1982h). Signs of toxicity were loss of righting reflex and flaccid muscle tone.

3.1.2 Dermal toxicity

Rabbits: LD_{50} 3,540 mg/kg (single application of undiluted test material) (Smyth *et al*, 1962).
LD_{50} > 2,000 mg/kg (single application of undiluted test material) (EPA, 1982i).

3.1.3 Inhalation toxicity

Rats: No signs of toxicity were observed; all animals (10 males) survived after 1 h exposure to saturated vapour (EPA, 1982c).

3.2.1 Dermal irritation

No significant irritating effect to the rabbit skin (Smyth *et al*, 1962; EPA, 1982j).

3.2 IRRITATION/SENSITIZATION

3.2.2 Eye irritation

Irritating to the eye of the rabbit (Smyth *et al*, 1962; EPA, 1982k).

3.2.3 Sensitization

No data available.

3.3 SUBACUTE/SUBCHRONIC/CHRONIC TOXICITY

3.3.1 Subacute toxicity

In a 21-day dermal study in New Zealand White rabbits (5 m/5 f/group) a limit dose of 1,000 mg/kg TEGBE was applied for 6 h daily. The chemical did not produce any systemic toxicity in male or female animals. Observations at the application site indicated that TEGBE produced slight erythema and edema starting on day 6 or 7 of treatment. Erythema continued throughout the study whereas edema was not observed after day 18 (Leber *et al*, 1990) (see Appendix A).

3.3.2 Subchronic toxicity

No data available.

3.3.3 Chronic toxicity/Carcinogenicity

No data available.

3.4 GENOTOXICITY

No data on TEGBE is available. However studies with TEGME (Ames, HGPRT and Micronucleus Test) showed no mutagenic activity (see product profile TEGME).

3.5 REPRODUCTION/DEVELOPMENTAL TOXICITY

TEGBE was screened in rats for potential developmental toxicity following a modified Chernoff-Kavlock assay. Groups of 10 mated female Wistar rats were administered daily doses of 250 and 1,000 mg/kg by gavage on days 6 - 15 of gestation. No significant changes in clinical conditions or body weights were seen in maternal rats following exposure to TEGBE. All rats in the control and treated groups were pregnant and delivered live foetuses. The number of life pups on day 1 and 5 postpartum were also comparable in these groups indicating no chemically induced developmental effects (Leber *et al*, 1990) (see Appendix B).

3.6 TOXICOKINETICS/METABOLISM

Human abdominal whole skin (2,54 cm^2) was mounted in a glass diffusion apparatus and the diffusion

of TEGBE into the donor chamber was monitored during a 12 h-period using gas chromatography. The diffusion rate of TEGBE was determined to be 0.1 μmel/cm^2/h indicating a low skin permeability of the compound (Leber *et al*, 1990) (see Appendix D).

3.7 NEUROTOXICITY

No data available.

3.8 IMMUNOTOXICITY

No data available.

4. HUMAN DATA

No data available.

Substance Profile: TEGDME

1. IDENTITY

Name:	Triethylene Glycol Dimethyl Ether
Structural formula:	CH_3-(O-CH_2-CH_2)$_3$-O-CH_3
Molecular formula:	$C_8H_{18}O_4$
Molecular weight:	178.2
CAS No.:	112-49-2
IUPAC name:	2,5,8,11-Tetraoxadodecane
Other components:	purity >99 %

2. PHYSICAL CHEMICAL DATA

Conversion factor:	1 ppm = 7,3 mg/m^3 (20°C, 1013hPa) 1 mg/m^3 = 0.14 ppm (20°C, 1013hPa)
Melting point:	- 40°C
Boiling point:	210-230°C at 1013 hPa
Vapour pressure:	1.2 hPa at 20°C
Solubility in water:	Completely soluble

3. TOXICOLOGICAL DATA

3.1 ACUTE TOXICITY

3.1.1 Oral toxicity

Rats: LD_{50} 5,877 mg/kg (female) (Hofmann *et al*, 1992).

3.1.2 Dermal toxicity

No data available.

3.1.3 Inhalation toxicity

No data available.

3.2 IRRITATION/SENSITIZATION

3.2.1 Skin irritation

No data available.

3.2.2 Eye irritation

No data available.

3.2.3 Sensitization

No data available.

3.3 SUBACUTE/SUBCHRONIC/CHRONIC TOXICITY

3.3.1 Subacute toxicity

Wistar rats were administered oral doses of 0, 62.5, 250 or 1,000 mg/kg/d for 28 d. Retardation in

growth rate, reduced water consumption, reductions in testes and thymus weight and thrombocytopenia were reported for the male animals given 1,000 mg/kg. Histopathological examination showed degenerative changes in the seminiferous epithelium and atrophy of the thymus similar to that observed in animals treated with methoxyacetic acid. At doses of 250 mg/kg reductions in thymus weight in the absence of any histopathological changes were reported. The NOEL in this study was 62.5 mg/kg (Hofmann *et al*, 1992).

3.3.2 Subchronic toxicity

No data available.

3.3.3 Chronic toxicity/carcinogenicity

No data available.

3.4 GENOTOXICITY

No data available.

3.5 REPRODUCTION/DEVELOPMENTAL TOXICITY

Administration of 3,500 mg/kg/d orally to time mated, pregnant CD-1 mice on d 7-14 gestation resulted in a 4% maternal mortality and 100% resorption of implantations in the surviving animals (Schuler *et al*, 1984).

The reproductive performance of CD-1 mice was evaluated following the administration of TEGDME in the drinking water at levels of 0.25, 0.5 and 1.00 % (estimated daily dose 440, 880 and 1,630 mg/kg) using the continuous breeding protocol. During the continuous breeding phase there were statistically significant decreases in the mean number of litters and live pups per pair at the high dose and in the proportion of pups born alive and live pup weights at both the high and mid doses. A reduced fertility index was reported during the cross over mating trial, in which treated females (1,850 mg/kg/d) were mated with control males. The proportion of live pups and the mean pup weight (live births) were also reduced (Morrissey *et al*, 1989).

Time mated CD-1 mice were given a single equimolar oral dose (4 mMol/kg) of either EGME, EGDME, DEGDME or TEGDME (713 mg/kg) on d 11 of gestation. Foetuses were examined on day 18 for

gross, soft tissue and skeletal abnormalities. There were no signs of maternal toxicity or effects on intrauterine survival in any of the treated animals. Characteristic paw malformations were seen in all but the TEGDME groups (Hardin and Eisenmann, 1987).

TEGDME was administered to time mated mice at doses of 0, 250, 500 or 1,000 mg/kg/d from d 6-15 of gestation. An increased incidence of malformed foetuses, mainly neural tube, craniofacial and axial skeletal defects, occurred at 1,000 mg/kg. A significant increase in maternal relative liver weight occurred at doses of 500 and 1,000 mg/kg but otherwise there were no signs of maternal toxicity (George *et al*, 1987).

Oral administration of TEGDME at doses of 175 or 250 mg/kg to New Zealand rabbits during organogenesis was also reported to effect foetal development. Maternal body weight was also reduced at these doses (George *et al*, 1990).

The results of reproduction/developmental studies are summarised in Appendix B.

3.6 TOXICOKINETICS/METABOLISM

No specific data are available. The reported developmental effects and subchronic toxicity of this material are consistent with those of EGME and MAA suggesting that both dealkylation and oxidation occur (see EGME and MAA product profile).

3.7 NEUROTOXICITY

There was no evidence of any specific effects of TEGDME on either the central or peripheral nervous system of rats given daily oral doses up to 1,000 mg/kg for 28 d (Hofmann *et al*, 1992).

3.8 IMMUNOTOXICITY

Evidence of thymic involution was reported among rats given oral doses of 250 and 1,000 mg/kg TEGME for 28 d (Hofmann *et al*, 1992).

4. HUMAN DATA

No data available.

Substance Profile: 2PG1ME

1. IDENTITY

Name:	2-Propylene Glycol 1-Methyl Ether
Structural formula:	CH_3-CH(OH)-CH_2-O-CH_3
Molecular formula:	$C_4H_{10}O_2$
Molecular weight:	90.1
CAS No.:	107-98-2
IUPAC name:	1-Methoxy-2-propanol
Other components:	≤ 0.5% 2-Methoxy-1-propanol

2. PHYSICAL CHEMICAL DATA

Conversion factor:	1 ppm = 3.75 mg/m^3 (20°C, 1013hPa) 1 mg/m^3 = 0.267 ppm (20°C, 1013hPa)
Melting point:	- 96°C
Boiling point:	120°C at 1013 hPa
Vapour pressure:	12.0 hPa at 20°C
Solubility in water:	Completely soluble

3. TOXICOLOGICAL DATA

3.1 ACUTE TOXICITY

3.1.1 Oral toxicity

Rats: LD_{50} 6,100 mg/kg (Rowe *et al*, 1954).

Dogs: LD_{50} 9,200 mg/kg (Shideman and Procita, 1951).

Central nervous system depression preceded the mortality. Signs of toxicity were dyspnoea, somnolence, uncoordinated gait, ataxia in rats and nausea, vomiting, diarrhoea and respiratory arrest in dogs (Rowe *et al*, 1954).

3.1.2 Dermal toxicity

Rats: No data available.

Rabbits: LD_{50} 12,000 mg/kg. Signs of toxicity were central nervous system depression and incomplete anaesthesia were observed at dose levels above 10,000 mg/kg (Rowe *et al*, 1954).

3.1.3 Inhalation toxicity

Rats: LC_{50} 15,000 ppm (4 h exposure) (Rowe *et al*, 1954).

Guinea pigs: LC_{50} 15,000 ppm (10 h exposure) (Rowe *et al*, 1954).

Signs of toxicity were irritation of the respiratory tract at high concentrations (Rowe *et al*, 1954).

3.2 IRRITATION/SENSITIZATION

3.2.1 Skin irritation

Slightly irritating to the rabbit skin even upon prolonged and repeated contact. No skin corrosion (Rowe

et al, 1954).

3.2.2 Eye irritation

Slightly irritating to the eyes of the rabbit (undiluted test material). May cause slight transient opacity of the cornea (Rowe *et al*, 1954) .

3.2.3. Sensitization

Non sensitizing to guinea pig (undiluted material in modified Maguire test) (Carreon *et al*, 1984).

3.3 SUBACUTE/SUBCHRONIC/CHRONIC TOXICITY

3.3.1 Subacute toxicity

Groups of 5 male rats that received repeated oral doses of 100, 300 or 1,000 mg/kg/d over a period of 7 weeks showed no ill effects as judged by appearance, growth, organ weights and histopathological examination of the organs. Under the same conditions, 3,000 mg/kg/d produced only minor effects in the liver and kidneys (Rowe *et al*, 1954).

In a 3-week dermal study, New Zealand and white rabbits received 1,000 mg/kg/d. Only slight skin irritation occurred. No signs of systemic toxicity were seen. No haematological, gross or histopathological effects were observed (Calhoun *et al*, 1984).

In an inhalation study, male Wistar rats were exposed to 200 or 600 ppm 6 h/d for 10 days. No alteration in testicular weight or histopathology and no changes in haematology were observed (Doe *et al*, 1983).

In a 9-day inhalation study in male and female Fischer 344 rats and B6C3F1 mice, rats at 3,000 ppm were sedated and also had a slight increase in liver weights. No haematological or testicular effects were observed. No effects occurred at 300 or 1,000 ppm. In female mice, liver weight was also slightly increased at 3,000 ppm (Miller *et al*, 1981).

Female CFE rats (Carworth Faims Elias) were exposed to concentrations of 2,500; 5,000 and 10,000 ppm 4h/d, 5d/wk for 2 wk, in order to study the effect of inhalation on behaviour. There was a transient nonspecific depression of behaviour for the first several exposures to 5,000 and 10,000 ppm. However

there was a rapid development of tolerance. Decreased growth rate was seen at 10,000 ppm (Goldberg *et al*, 1964).

The results of subacute studies are summarised in Appendix A.

3.3.2 Subchronic toxicity

Inhalation studies

There were no observable treatment-related effects in Fischer 344 rats or New Zealand white rabbits repeatedly exposed to 300 or 1,000 ppm for 6 h/d, 5 d/wk for 13 wk. At 3,000 ppm, apart from sedation and lower bodyweight gain, transient CNS depression in both species and slightly increased liver weights were observed in rats (Landry *et al*, 1983) (see Appendix A).

In a 1,2 or 13-wk exposure of male Fischer 344 rats and B6C3F1 mice to 3,000 ppm 2PG1ME, the initial hepatic cell proliferation in week 1 returned to normal in the second week.
The cell proliferation in the male rat kidneys was 4 fold over the remaining dosing period, consistent with observed α - 2 μ globulin accumulation (Bus *et al*, 1992).

When animals were subjected to repeated seven-hour vapour exposures, 5 d/wk for 6 months, guinea pigs tolerated 3,000 ppm, rats tolerated 1,500 ppm, and monkeys and rabbits tolerated 800 ppm without adverse effects (Rowe *et al*, 1954).

Dermal studies

Repeated dermal application (65 times) of 5 ml/kg (4,595 mg/kg) produced some liver and kidney changes in rabbits (Rowe *et al*, 1954).

3.3.3 Chronic toxicity/Carcinogenicity

No data available.

3.4 GENOTOXICITY

2PG1ME was not mutagenic in the *Ames Salmonella* assay, in the CHO metaphase analysis test and negative in the rat hepatocyte unscheduled DNA synthesis assay (Kirkland *et al*, 1983, Kirkland and

Verschuuren, 1983, Mendrala and Schumann, 1983c).

The results are summarised in Appendix C.

3.5 REPRODUCTION/DEVELOPMENTAL TOXICITY

No teratogenic effect was observed in pregnant Fischer 344 rats or New Zealand white rabbits in an inhalation study at exposure concentrations of 500; 1,500 and 3,000 ppm. Slight foetotoxicity among rats, in the form of delayed sternebral ossification, was observed at 3,000 ppm (Hanley *et al*, 1984a).

In another inhalation study, pregnant Wistar rats were exposed to 200 or 600 ppm, 6 h/d on days 16-17 of gestation. No effects were noted on maternal body weight gain or the number, weight or viability of pups (Doe *et al*, 1983).

No teratogenic effects in CFLP mice, CFE rats and Yellow Silver rabbits were seen in mixed oral and subcutaneous routes at dose levels up to 1,850 mg/kg in mice, 924 mg/kg in rabbits and 740 mg/kg in rats. In rats at this dose level, toxicity was manifested as delayed ossification of the skull bones, at 370 mg/kg no effects were observed (Stenger *et al*, 1972).

In a continuous breeding study in CD-1 mice, 2PG1ME was administered up to 2% in the drinking water for 2 generations. No effects on fertility or reproduction were observed, although, in essence, at this dose level, 2PG1ME was moderately toxic, showing reduced pup weight (Gulati *et al*, 1986).

The results of reproduction/developmental studies are summarised in Appendix B.

3.6 TOXICOKINETICS/METABOLISM

During the 6-h exposure of Fischer 344 rats 300 or 3,000 ppm 2PG1ME, the blood concentration increased throughout, indicating that absorption was limited by respiration. The end of exposure blood concentrations were not proportional to the exposure concentrations, and the clearance was best described as a zero order process. After the 10th exposure to 3,000 ppm, the end of exposure blood concentrations were 50% lower versus the first day. This indicates clearly an increased elimination capacity in these rats (Morgott and Nolan, 1987).

After oral gavage, 10-20% of a high and low dose was eliminated as glucuronate or sulfate in the urine of Fischer 344 rats in 2 days. At the same time, 50-60% was eliminated with the expired air as carbon

dioxide, following metabolism to propylene glycol. Amongst the metabolites of 2PG1ME, no methoxypropionic acid was identified (Miller *et al*, 1983b).

In a comparative study, rats and mice were administered orally and intravenously 1 and 5 mmol/kg. The extent and rate of exhalation of $^{14}CO_2$ were similar following *p.o.* and *i.v.* administration of the same dose in the same species. The rate of exhalation of $^{14}CO_2$ was faster in mice than in rats. In addition, mice metabolized and eliminated 2PG1ME faster than rats (Ferrala *et al*, 1992).

The results of these studies are summarised in Appendix D.

3.7 NEUROTOXICITY

Perceptible odour at and above 100 ppm. Intolerable odour at 1,000 ppm and anaesthetic effects at still higher exposure levels (Stewart *et al*, 1970).

3.8 IMMUNOTOXICITY

The available studies provide no indication for an immunologic effect. No specific further studies are available.

4. HUMAN DATA

Apart from a volunteer study by Stewart *et al* (1970) no other data on human volunteers are available (see chapter 3.7).

Twenty-two persons (20 men and 2 women) were examined for their external and internal exposure to 2PG1ME during production, leak testing and mounting of brakehoses. For the measurement of external exposure, personal air monitoring was the method of choice. Average concentrations of 2PG1ME of 82.2 mg/m^3 (22.3 ppm), 68.6 mg/m^3 (18.6 ppm) and 11.3 mg/m^3 (3.1 ppm) were found in the air of the brakehose production, leak test and mounting areas, respectively. For the estimation of internal exposure to 2PG1ME, this glycol ether was measured in both urine and blood. The biological samples were taken post-shift. The highest internal exposure levels were found in the brakehose production section and in the leak test area. The average post-shift concentrations for 2PG1ME in workers in the brakehose production section were 4.6 mg/l in urine and 13.5 mg/l in blood; the corresponding figures for workers in the leak test area were 4.2 mg/l in urine and 11.0 mg/l in blood. In blood and urine

samples of workers engaged in the mounting area, 2PG1ME levels were below the detection limits. The elimination kinetics of 2PG1ME were also studied in three highly exposed persons, and mean excretion half-lives of approximately 4.4 h were found (Hubner *et al*, 1992).

Substance Profile: 2PG1MEA

1. IDENTITY

Name:	2-Propylene Glycol 1-Methyl Ether Acetate
Structural formula:	CH_3-CH(O-CO-CH_3)-CH_2-O-CH_3
Molecular formula:	$C_6H_{12}O_3$
Molecular weight:	132.2
CAS No.:	108-65-6
IUPAC name:	1-Methoxy-2-acetoxypropane
Other components:	< 2.5% 2-Methoxy-1-acetoxypropane

2. PHYSICAL CHEMICAL DATA

Conversion factor:	1 ppm = 5.4 mg/m^3 (20°C, 1013hPa) 1 mg/m^3 = 0.185 ppm (20°C, 1013hPa)
Melting point:	< - 67°C
Boiling point:	145.8°C at 1013 hPa
Vapour pressure:	4.9 hPa at 20°C
Solubility in water:	19% w/w at 20°C

3. TOXICOLOGICAL DATA

3.1 ACUTE TOXICITY

The main symptoms after acute high oral and/or dermal dosage are lethargy, anorexia, shallow breathing and excess salivation.

3.1.1 Oral toxicity

Rats: LD_{50} 8,532 mg/kg (Henck *et al*, 1980).

3.1.2 Dermal toxicity

Rats: No data available.

Rabbits: LD_{50} >5,000 mg/kg (Henck *et al*, 1980).

3.1.3 Inhalation toxicity

Rats: LC_{50} >4,345 ppm; 6 h exposure (Henck *et al*, 1980).

No signs of toxicity were seen during exposure or upon gross pathological examination (Henck *et al*, 1980).

3.2 IRRITATION/SENSITIZATION

3.2.1 Skin irritation

Undiluted test material was not irritating to the rabbit skin (Henck *et al*, 1980).

3.2.2 Eye irritation

Undiluted test material caused conjunctival redness in rabbits, slight conjunctival swelling, slight iritis and corneal opacity. The eye returned to normal within 7 d (Henck *et al*, 1980).

3.2.3 Sensitization

Non sensitizing in guinea pigs (10% aqueous solution, modified Maguire test) (Carreon *et al*, 1980).

3.3 SUBACUTE/SUBCHRONIC/CHRONIC TOXICITY

3.3.1 Subacute toxicity

In a 9-d vapour inhalation study in Fischer 344 rats and B6C3F1 mice at 0, 300, 1,000 and 3,000 ppm slight increase in relative liver weight in male rats without histopathological changes and kidney effects with reticulated appearance at 1,000 and 3,000 ppm. Also metaplasia in the olfactory epithelium in mice at all dose levels and in rat at 3,000 ppm. In the cytoplasm of the proximal tubules, an increased degree of normally occurring eosinophilic granularity was observed in the male rats of 3,000 ppm and in 1 out of 5 at 1,000 ppm (Miller *et al*, 1984) (see Appendix A).

3.3.2 Subchronic toxicity

No data available.

3.3.3 Chronic toxicity/Carcinogenicity

No data available.

3.4 GENOTOXICITY

The *Salmonella-Ames* test, with and without metabolic activation was negative (Mendrala and Schumann, 1983a). The unscheduled DNA synthesis test with rat hepatocytes was also negative (Mendrala and Schumann, 1983b) (see Appendix C).

3.5 REPRODUCTION/DEVELOPMENTAL TOXICITY

In an inhalation study (Asaki and Houpt, 1990) pregnant female Sprague-Dawley rats (20 animals per group) were exposed for 6h/d during day 6-15 of pregnancy to 0, 500, 2,000 and 4,000 ppm. Dyspnoea was observed in the 4,000 ppm group and in one animal of the 2,000 ppm group. Food consumption and body weight were reduced in the 4,000 and 2,000 ppm group. In the 500 ppm group no signs of toxicity were observed. No teratological or other developmental effects were seen in foetuses in any

of the dose levels (see Appendix B).

3.6 TOXICOKINETICS/METABOLISM

Acetate esters of aliphatic alcohols are rapidly hydrolysed by enzymes in the respiratory epithelium, lungs, liver and blood of rats, rabbits, hamsters (Stott and McKenna, 1984, 1985; Dahl *et al*, 1987).

Miller *et al* (1984) compared the metabolism of 2PG1ME and 2PG1MEA in rats and confirmed that 2PG1MEA has the same metabolism pattern as 2PG1ME. After inhalation 53% and after oral gavage of 8.7 mmol/kg body weight, 64% of the radioactivity was exhaled as CO_2 in 48 h. In the urine the same metabolite species as found for 2PG1ME were recovered after oral gavage (24 %) and after inhalation exposure (26 %) (see Appendix D).

3.7 NEUROTOXICITY

No data available.

3.8 IMMUNOTOXICITY

The available studies provide no indication for an immunological effect. No specific further studies are available.

4. HUMAN DATA

No data available.

Substance Profile: 2PG1EE

1. IDENTITY

Name:	2-Propylene Glycol (mono) 1-Ethyl Ether
Structural formula:	CH_3-CH(OH)-CH_2-O-C_2H_5
Molecular formula:	$C_5H_{12}O_2$
Molecular weight:	104.2
CAS No.:	1569-02-4
IUPAC name:	1-Ethoxy-2-propanol
Other components:	<10% 2-Ethoxy-1-propanol

2. PHYSICAL CHEMICAL DATA

Conversion factor:	1 ppm = 4.25 mg/m^3 (20°C, 1013 hPa) 1 mg/m^3 = 0.235 ppm (20°C, 1013 hPa)
Melting point:	- 90°C
Boiling point:	132°C at 1013 hPa
Vapour pressure:	10 hPa at 20°C
Solubility in water:	Completely soluble

3. TOXICOLOGICAL DATA

3.1 ACUTE TOXICITY

3.1.1 Oral toxicity

Rats: LD_{50} (m and f) >5 ml/kg. Signs of toxicity were indicative of mild CNS depression between one and 6 h after treatment. These effects were fully reversible. Oral doses of 2 ml/kg were without effect (BP, 1983a).

3.1.2 Dermal toxicity

Rabbits: LD_{50} 9 ml/kg (estimated) by percutaneous absorption under occlusive dressing. Signs of toxicity following administration of large doses were marked central nervous system depression. Deaths occurred within 48 h. There was no appreciable skin irritation (Dow, 1947).

3.1.3 Inhalation toxicity

Rats: No mortality (4 h whole body exposure to atmospheres containing 14,200 mg/m^3 = 3,337 ppm or nose exposure to 9,500 mg/m^3 = 2,232 ppm). Signs of toxicity were CNS-depression at both concentrations, salivation and lachrymation at the higher concentration. All effects were reversible. (BP, 1981a and 1983b).

Rats: Exposure to 10,000 ppm (4 h) showed signs of marked irritation and CNS depression (Gingell *et al*, 1994).

Mice: No evidence of effect on respiratory rate, and by implication sensory irritation, in mice exposed nose only to vapour concentrations of 2,800 - 7,200 mg/m^3 (BP, 1983c).

3.2 IRRITATION/SENSITIZATION

3.2.1 Skin Irritation

Mildly irritating to rabbit skin (24 occluded or 4 h semi occluded) (BP, 1981b and 1984a).

3.2.2 Eye irritation

Not severely irritating to the eye of the rabbit (discomfort, conjunctival irritation and corneal reactions only). The effects were fully reversible within 7 d (BP, 1981b and 1984b).

3.2.3 Sensitization

No specific information available. Guinea pig Maximisation Test on the acetate (see 2PG1EEA product profile) was negative suggesting that the parent glycol would also be unlikely to possess skin sensitizing potential (BP, 1986g).

3.3 SUBACUTE/SUBCHRONIC/CHRONIC TOXICITY

3.3.1 Subacute toxicity

Groups of 6 m and 6 f rats were given 10 consecutive oral doses of 2 ml/kg. The treatment was well tolerated by all animals although the body weight gain of the males was slightly reduced compared to controls. A slight increase in liver weight was seen in both sexes and minor haematological changes reported in the males only (BP, 1983d).

Groups of 6 m and 6 f rats were exposed, nose only to atmospheres containing 1,400 or 8,900 mg/m^3 6 h/d for 9 d . The test animals grew at a similar rate to controls. Initial exposure resulted in sedation, the effect becoming less marked as the study progressed. The only effect that could be related to treatment was a small increase in liver weight in both sexes exposed to the higher concentrations. The livers were histologically normal (BP, 1983e). The results of subacute studies are summarised in Appendix A.

3.3.2 Subchronic toxicity

The effects of repeated exposure were studied in rats over 90-d. Groups of 15 m and 15 f rats (Crl: Cobs C.D (S.O) BR Strain - Charled River UK) were exposed 6 h/d, 5 d/wk for 13 wk (65 exposures) to atmospheres containing nominally 0, 100, 300 or 2,000 ppm (BP, 1986b). Irritation of the eyes and nose were observed at the highest concentration. These effects were minimal and readily reversible. There was evidence of a slight increase in liver weight in the females exposed to the highest concentration. The livers were histologically normal. An increase in urine volume was found in both male and female rats exposed to the high concentration during wk 1 and to the high and intermediate

concentrations during wk 12. There were no detectable changes in the composition of either the urine or serum, or histological changes indicative of a toxic effect on the kidney. There was a small increase in focal macrophage aggregation in the lungs of the male and female rats exposed to the highest concentration. There were no effects from this study to indicate any adverse effects on either the testes, haemopoietic tissues or blood (see Appendix A).

3.3.3 Chronic toxicity/Carcinogenicity

No data available.

3.4 GENOTOXICITY

2PG1EE has been examined for its potential to produce point mutations using the *Salmonella typhimurium* reverse mutation (Ames) test. Five histidine requiring strains, TA 98, TA 100, TA 1535, TA 1537 and TA 1538 were used both in the presence and in the absence of rat liver post mitochondrial fraction. There was no evidence of mutation induction in any of the five tester strains, either in the presence or absence of the metabolic activation system, at doses up to 5,000 µ/plate (BP, 1988a).

Cultured human lymphocytes were used to evaluate the chromosome damaging potential of 2PG1EE. The cell cultures were treated, both in the presence and absence of post-mitochondrial fraction (S9) with doses up to 5,000 µg/ml. The frequency of aberrations in cells treated with 2PG1EE were similar to those in the solvent controls and within the range of the historical solvent controls (BP, 1988b).

The results of genotoxicity studies are summarised in Appendix C.

3.5 REPRODUCTION/DEVELOPMENTAL TOXICITY

The effects of 2PG1EE on the developing embryo has been investigated in both rats and rabbits (see Appendix B).

Groups of 25 mated rats (Crl: COBS CO (SD) BR Strain - Charles river UK) were exposed, whole body, 6 h/d from d 6-15 inclusive of pregnancy to nominal vapour concentrations of 0, 100, 450 or 2,000 ppm. Signs of maternal toxicity consisting of reduced body weight gain and food consumption were observed in animals exposed to 2,000 ppm. The body weight gain of the dams exposed 44 to 450 ppm was also slightly reduced compared to controls and signs of possible irritation also observed. There was no evidence of maternal toxicity at 100 ppm. At all exposure concentrations litter size and weight, the

number of pre and post implantation losses and mean foetal weights were indistinguishable from control values. There was also no evidence of any effects on foetal development as assessed by incidences of malformations, anomalies or skeletal variants (BP, 1986b).

Groups of 22 mated New Zealand White Rabbits were exposed, whole body, 6 h/d from days 6-18 inclusive of pregnancy, to nominal vapour concentrations 0, 100, 350 or 1,200 ppm. Slight maternal toxicity was evident among the animals exposed to the highest vapour concentration, manifested as slight reduction in mean food consumption and a retardation in body weight gain between days 6 and 10 of pregnancy. There was no evidence of maternal toxicity in the dams exposed to 350 or 100 ppm and no evidence of any treatment related effects on litter size and weight, pre- and post- implantation losses and mean foetal weights. Although the overall incidences of malformations were slightly higher in the treated animals compared to the controls they were not dose related and all incidences were within the range of the historical control incidences (BP, 1986c).

3.6 TOXICOKINETICS/METABOLISM

No specific data available.

In common with other glycol ethers 2PG1EE would be expected to be readily absorbed across the skin and alveolar membrane. By analogy with propylene glycol methyl ether metabolism to propylene glycol and carbon dioxide is likely to be the principal pathway of the secondary isomer (see 2PG1ME product profile).

3.7 NEUROLOGICAL DATA

No studies have been conducted specifically to examine the neurological effects of 2PG1EE. Both oral and inhalation sub-acute studies have provided evidence of a reversible depression of the central nervous system at high doses or concentrations. A 90 d inhalation study on rats provided no evidence of any effects on CNS and peripheral nervous system as could be detected from daily routine observations and from conventional histopathological examination of the brain and sciatic nerves at exposure concentrations up to 2,000 ppm (BP, 1986b).

3.8 IMMUNOLOGICAL DATA

No tests to specifically examine the effects of 2PG1EE on the immune system have been carried out. The results of studies on the effects of repeated exposure have not suggested any effects on lymphoid

tissue or other elements of the immune system.

4. HUMAN DATA

No data available.

Substance Profile: 2PG1EEA

1. IDENTITY

Name:	2-Propylene Glycol 1-Ethyl Ether Acetate
Structural formula:	CH_3-CH(O-CO-CH_3)-CH_2-O-C_2H_5
Molecular formula:	$C_7H_{14}O_3$
Molecular weight:	146.2
CAS No.:	54839-24-6
IUPAC name:	1-Ethoxy-2-acetoxypropanol
Other components:	< 10% 2-ethoxy-1-acetoxypropanol

2. PHYSICAL CHEMICAL DATA

Conversion factor:	1 ppm = 6.09 mg/m^3 (20°C, 1013hPa) 1 mg/m^3 = 0.16 ppm (20°C, 1013hPa)
Melting point:	- 89°C
Boiling point:	158°C at 1013 hPa
Vapour pressure:	2.026 hPa at 20°C
Solubility in water:	soluble

3. TOXICOLOGICAL DATA

3.1 ACUTE TOXICITY

3.1.1 Oral toxicity

Rats: LD_{50} >5 ml/kg. Signs of toxicity were non-specific including lethargy, salivation and pallor of the extremities. All animals were reported as normal by d 4 (BP, 1985a).

3.1.2 Dermal toxicity

No data available.

3.1.3 Inhalation toxicity

Rats: No mortality (5 m and 5 f, 4 h exposure to 6.99 ml/kg the highest achievable droplet free vapour concentration). Only effects observed were indicative of irritation of the eyes and nose (BP, 1985b).

3.2 IRRITATION/SENSITIZATION

3.2.1 Skin irritation

Low potential of irritancy to the rabbit skin following OECD guidelines (BP, 1986e).

3.2.2 Eye Irritation

Mildly irritating to the eye of the rabbit (initial hyperaemia of the conjunctival membranes) recovered by day two. There were no effects on either the cornea or iris (BP, 1986f).

3.2.3 Sensitization

No evidence of delayed contact hypersensitivity in guinea pig treated by the method of Magnusson and Kligman (BP, 1986g).

3.3 SUBACUTE/SUBCHRONIC/CHRONIC TOXICITY

3.3.1 Subacute toxicity

Groups of 5 m and 5 f rats were exposed 6 h/d, 5 d/wk over a period of 28 d to atmospheres containing 0, 102, 292 or 1,176 ppm 2PG1EEA (BP, 1986h). 1176 ppm was the highest droplet free vapour concentration achievable. The study was carried out following OECD guidelines. The only effect observed during the study was a reduced response to external stimuli in those animals exposed to the high and intermediate concentrations. At the end of the study, comprehensive gross post mortem and histopathological examination did not provide any evidence of local or systemic toxicity (see Appendix A).

3.3.2 Subchronic toxicity

No specific study has been carried out on 2PG1EEA. A 90 d inhalation toxicity study in rats of the parent glycol ether (BP, 1986b) provided evidence of sedation, local irritation of the respiratory tract and slight liver enlargement, in the absence of histological changes, in animals exposed to 2,000 ppm only (see 2PG1EE product profile).

3.3.3 Chronic toxicity/Carcinogenicity

No data available.

3.4 GENOTOXICITY

2PG1EEA has been tested in the reverse mutation (Ames) test using *Salmonella typhimurium* strains TA 98, TA 100, TA 1353, TA 1537 and TA 1538, in the presence and in the absence of a liver post-mitochondrial fraction (S9). There was no increase in revertants in any of the strains tested at doses up to 5,000 µg/plate (BP, 1985c).

Cultured Chinese Hamster Ovary cells were exposed to 2PGEEA concentrations up to 2,300 µg/ml in the presence and absence of a metabolic activation system (S9). There was no evidence of an increase in the proportion of metaphase figures containing aberrant chromosomes when compared to concurrent controls at any dose level with or without metabolic activation (BP, 1985d).

The results of genotoxicity studies are summarised in Appendix C.

The parent glycol ether 2PG1EE has also been tested for its ability to induce point mutations in bacteria and chromosome damage in mammalian cell culture; both tests were negative (BP, 1988a,b).

3.5 REPRODUCTION/DEVELOPMENTAL TOXICITY

No specific studies have been carried out.

Teratology studies in rats and rabbits, carried out on the parent glycol ether 2PG1EE (BP, 1986b,c) have provided evidence that the material is not selectively toxic to the foetus. In view of the likely ready metabolism of ethoxy propyl acetate to ethoxy propanol the former is not expected to adversely effect the developing embryo (see 2PG1EE product profile).

3.6 TOXICOKINETICS/METABOLISM

No specific data available.

3.7 NEUROLOGICAL DATA

There have been no studies carried out to specifically examine the neurological effects of 2PG1EEA. The sub-acute studies reported above and the 90 d study on 2PG1EE do not suggest any effect of this material on the CNS, other than reversible depression at high concentrations.

3.8 IMMUNOLOGICAL DATA

No tests to specifically examine the effects of 2PG1EEA on the immune system have been carried out. The results of studies on the effects of repeated exposure have not suggested any effects on lymphoid tissue or other elements of the immune system.

4. HUMAN DATA

No data are available.

Substance Profile: 2PG1BE

1. IDENTITY

Name:	2-Propylene Glycol 1-n-Butyl Ether
Structural formula:	CH_3-CH(OH)-CH_2-O-$(CH_2)_3$-CH_3
Molecular formula:	$C_7H_{16}O_2$
Molecular weight:	132.2
CAS No.:	5131-66-8 29387-86-8 (mixture of isomers)
IUPAC name:	1-Butoxy-2-propanol
Other components:	< 5% 2-Butoxy-1-propanol

2. PHYSICAL CHEMICAL DATA

Conversion factor:	1 ppm = 5.49 mg/m^3 (20°C, 1013hPa) 1 mg/m^3 = 0.182 ppm (20°C, 1013hPa)
Melting point:	< - 75°C
Boiling point:	170.2°C at 1013 hPa
Vapour pressure:	0.8 hPa at 20°C
Solubility in water:	6% w/w at 20°C

3. TOXICOLOGICAL DATA

3.1 ACUTE TOXICITY

3.1.1 Oral toxicity

Rats: LD_{50} 3,300 mg/kg. Signs of toxicity were lethargy, CNS depression, coma, hypnopnoea and dacryorrhea (Reijnders *et al*, 1987).

3.1.2.Dermal toxicity

Rats: LD_{50} >2,000 mg/kg. There were no signs of systemic toxicity and no abnormalities of the treated skin surface (Reijnders and Verschuuren, 1987).

3.1.3 Inhalation toxicity

Rats: No signs of toxicity during 4 h exposure to saturated vapour atmosphere (Corley *et al*, 1989a).

3.2 IRRITATION/SENSITIZATION

3.2.1 Skin irritation

Moderately irritating to the rabbit skin during 4 h exposure to undiluted or as 75% dilution in water. Slightly irritating during 4 h exposure to 50 % dilution in water. Non irritating during 4 h exposure to 25 % dilution in water (Weterings *et al*, 1987a,b).

3.2.2 Eye irritation

The undiluted material was moderately irritating to the eye of the rabbit. Transient corneal opacity was observed (Weterings *et al*, 1987c).

3.2.3 Skin sensitization

Not sensitising to guinea pig (40% in propylene glycol) in the modified 3-induction epicutaneous Buehler test (Vankerkom and Verschuuren, 1987).

3.3 SUBACUTE/SUBCHRONIC/CHRONIC TOXICITY

3.3.1 Subacute toxicity

Daily oral dosing for 14 consecutive days at levels of 0, 100, 200 and 400 mg/kg/d, caused neither a haematologic effect nor any other adverse health problem in Sprague-Dawley rats (Debets and Verschuuren, 1987).

Fischer 344 rats exposed 9 times over 2 wk to the maximum attainable vapour concentration of 700 ppm for 6 h/d did not show any haematologic or other adverse effect (Corley *et al*, 1989b).

In repeated inhalation studies male and female rats were exposed to 600 ppm for 7 h/d, 5 d/wk for a total of 31 exposure days. The only effects seen were increased liver weights in the female rats (Pozzani and Carpenter, 1965).

In a further repeated inhalation study, male and female Fischer 344 rats and male and female Sprague-Dawley rats received whole-body exposure at 0, 10, 100, 300 or 600 ppm for 6 h/d on 9 d over an 11-d period. The only exposure-related effects reported were increased liver weights without histopathologic liver lesions in the 600 ppm group of Fischer 344 rats and low incidence of mild eye lesion in the 600 ppm group of Fischer 344 rats (Klonne *et al*, 1989).

The results of these studies are summarised in Appendix A.

3.3.2 Subchronic toxicity

Dermal Studies

13 wk repeated dermal applications of 0, 0.1, 0.3 and 1.0 ml/kg/d (0, 88, 264 and 880 mg/kg/d) to Wistar rats did only give rise to local skin effects, but no haematologic or other systemic effects were observed (Jonker *et al*, 1988).

Similarly, 13-wk repeated dermal applications of 0, 11.4, 114 and 1,140 mg/kg/d to New Zealand albino rabbits for 7 h/d, 5 d/wk, did not produce any haematologic, nor other systemic toxicity effects (Innis *et al*, 1990).

Oral Studies

In a 13 wk study, test material was administered to Fischer 344 rats with drinking water at concentrations of 0, 100, 350 and 1,000 mg/kg/d. At 1,000 mg/kg/d, drinking water became unpalatable ensuing lower water consumption, food consumption and body weight and secondary alterations in clinical chemistry, electrolytes, haematology and urinalysis. At 1,000 mg/kg/d, absolute and relative liver weights were higher in male rats and absolute and relative kidney weights were higher in female rats. No gross or histopathologic alterations were associated with PnB administration. No effects attributable to test material were evident in male and female rats administered 100 or 350 mg/kg/d (Grandjean *et al*, 1992).

The results of subchronic studies are summarised in Appendix A.

3.3.3 Chronic toxicity/Carcinogenicity

No data available.

3.4 GENOTOXICITY

2PG1BE was evaluated in the *in vitro Salmonella*/mammalian-microsome bacterial mutagenicity assay (Ames test) using a pre-incubation modification of the standard method. The test was conducted in the presence and absence of a metabolic activation system (S9-mix from Aroclor induced rat liver) using *Salmonella typhimurium* bacterial tester strains TA 98, TA 100, TA 1535 and TA 1537. The test material was assayed two times in each tester strain up to a maximum concentration of 5,000 µg/plate. 2PG1BE did not induce a mutagenic response in any of the tester strains (Bruce *et al*, 1987).

2PG1BE was also evaluated in the *in vitro* chromosomal aberration assay utilizing Chinese hamster ovary (CHO) cells. The clastogenicity of the test material was assessed in the absence and presence of a metabolic activation system (S9-mix) at dose levels of 500, 1,667 and 5,000 µg 2PG1BE/ml of culture medium. Cultures treated with 1,242 µg/ml ethyl methane sulfonate and 14 µg/l cyclophosphamide served as positive controls for the non-activation and activation assays, respectively. There was no statistically significant increase in the frequencies of cells with aberration (Gollapudi *et al*, 1988).

The result of genotoxicity studies are summarised in Appendix C.

3.5 REPRODUCTION/DEVELOPMENTAL TOXICITY

No embryo/foetotoxicity or teratogenic effects in mated Wistar rats treated dermally with 0, 0.3 and 1.0 ml/kg/d (0, 264 and 880 mg/kg/d) during d 6-16 of gestation (Waalkens-Berendsen *et al*, 1989).

No embryo/foetotoxicity or teratogenicity and no maternal toxicity were observed in New Zealand White rabbits treated dermally with 0, 10, 40 or 100 mg/kg/d during d 7-18 of gestation (Gibson *et al*, 1989).

The results of these studies are summarised in Appendix B.

3.6 TOXICOKINETICS/METABOLISM

No data available.

3.7 NEUROLOGICAL DATA

No data available.

3.8 IMMUNOLOGICAL DATA

The available studies provide no indication for an immunological effect. No specific further studies are available.

4. HUMAN DATA

No data available.

Substance Profile: 2PG1PhE

1. IDENTITY

Name:	2-Propylene Glycol 1-Phenyl Ether
Structural formula:	CH_3-CH(OH)-CH_2-O-C_6H_5
Molecular formula:	$C_9H_{12}O_2$
Molecular weight:	152.2
CAS No.:	770-35-4
IUPAC name:	1-Phenoxy-2-propanol
Other components:	≤ 7% Dipropylene glycol phenyl ether

2. PHYSICAL CHEMICAL DATA

Conversion factor:	1 ppm = 6.33 mg/m^3 (20°C, 1013hPa) 1 mg/m^3 = 0.158 ppm (20°C, 1013hPa)
Melting point:	appr. 13°C
Boiling point:	242.7°C at 1013 hPa
Vapour pressure:	0.05 hPa at 25°C
Solubility in water:	1% w/w at 20°C

3. TOXICOLOGICAL DATA

3.1 ACUTE TOXICITY

3.1.1 Oral toxicity

Rats: Males LD_{50} 2,830 mg/kg; females LD_{50} 3,730 mg/kg. No specific symptoms were observed (Norris and Olson, 1968).

3.1.2 Dermal toxicity

Rats: No data available.

Rabbits: LD_{50} >2,000 mg/kg. No signs of toxicity were observed (Norris and Olson, 1968).

3.1.3 Inhalation toxicity

Rats: No signs of toxicity during 7 h exposure to saturated vapour concentration (Norris and Olson, 1968).

3.2 IRRITATION/SENSITIZATION

3.2.1 Skin irritation

Slightly irritating to the rabbit skin (repeated, prolonged skin contact, undiluted test material) (Norris and Olson, 1968). PGPhE is not considered corrosive, according to the criteria of the US Department of Transport (DOT) (Rampy *et al*, 1973).

3.2.2 Eye irritation

Slight conjunctival irritation and slight transient corneal injury to the eye of the rabbit (undiluted test material) recovering within a few days (Norris and Olson, 1968).

3.2.3 Skin sensitization

No data available.

3.3 SUBACUTE/SUBCHRONIC/CHRONIC TOXICITY

3.3.1 Subacute toxicity

Dermal Studies

Female rabbits were exposed to 14 daily dermal applications of 1,000 mg/kg/d with no obvious adverse effects which could be related to treatment. No haemolytic anaemia was observed (Phillips *et al*, 1985).

In an 28 d dermal study groups of 5 rabbits/sex/dose received 19 daily dermal applications of 0, 100, 300, or 1,000 mg/kg. No evidence of systemic toxicity was observed in body weights, organ weights, clinical laboratory studies, gross or histopathologic examinations. The only treatment-related effect seen was mild transient dermal irritation (Calhoun *et al*, 1986c).

The results of these studies are summarised in Appendix A.

3.3.2 Subchronic toxicity

No data available.

3.3.3 Chronic toxicity/Carcinogenicity

No data available.

3.4 GENOTOXICITY

PGPhE was evaluated in the *in vitro Salmonella*/ bacterial mutagenicity assay (Ames test). The test was conducted in the presence and absence of a metabolic activation system (S9-mix from Aroclor induced rat liver) using *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537. The test material was assayed two times in each tester strain up to a maximum concentration of 5,000 µg/plate. PGPhE did not induce a mutagenic response in any of the tester strains (Bootman and May, 1985).

PGPhE was also evaluated *in vitro* chromosomal aberration assay, utilizing human peripheral lymphocytes. The clastogenicity of the test material was assessed in the absence and presence of a metabolic activation system (S9-mix) at dose levels up to 400 µg of PGPhE/ml of culture medium. Cultures treated with 400 µg/ml ethyl methanesulfonate and 6 µg/ml cyclophosphamide served as positive controls for the non-activation and activation assays, respectively. There were no statistically significant increase in the frequencies of cells with aberrations (Bootman, 1986).

The results of these studies are summarised in Appendix C.

3.5 REPRODUCTION/DEVELOPMENTAL TOXICITY

No data available.

3.6 TOXICOKINETICS/METABOLISM

No data available.

3.7 NEUROLOGICAL DATA

No data available.

3.8 IMMUNOLOGICAL DATA

The available studies provide no indication for an immunologic effect. No specific further studies are available.

4. HUMAN DATA

PGPhE has bactericidal properties and is used as a preserver in medical disinfectants, in cleansing and cosmetic formulations. It is mentioned as an antibacterial agent in pharmaceutical compositions for acne treatment (Roberts, 1986). No other data are available.

Substance Profile: 1PG2ME

1. IDENTITY

Name:	1-Propylene Glycol 2-Methyl Ether
Structural formula:	$H_3C\text{-}CH(OCH_3)\text{-}CH_2\text{-}OH$
Molecular formula:	$C_4H_{10}O_2$
Molecular weight:	90.1
CAS No.:	1589-47-5
Chemical name:	2-Methoxypropanol-1
Other components:	Not known

2. PHYSICAL CHEMICAL DATA

Conversion factor:	1 ppm = 3.74 mg/m^3 (20°C, 1013 hPa) 1 mg/m^3 = 0.267 ppm (20°C, 1013 hPa)
Melting point:	< - 50°C
Boiling point:	130 - 133°C at 1013 hPa
Vapour pressure:	5.5 hPa (20°C)
Solubility in water:	Completely soluble

3. TOXICOLOGICAL DATA

3.1 ACUTE TOXICITY

3.1.1 Oral toxicity

Rats: LD_{50} >5,000 mg/kg (BASF, 1979a).

3.1.2 Dermal toxicity

No data available.

3.1.3 Inhalation toxicity

Rats: LC_{50} >6 mg/l (4 exposure) (BASF, 1979b).

3.2 IRRITATION/SENSITIZATION

3.2.1 Skin irritation

Undiluted material (24 h, occlusive) was not irritant to intact and scarified rabbit skin. Draize test (BASF, 1979a).

3.2.2 Eye irritation

Undiluted material was not irritant to rabbit eye. Draize test (BASF, 1979a).

3.2.3 Skin sensitization

No data available.

3.3 SUBACUTE/SUBCHRONIC/CHRONIC TOXICITY

3.3.1 Subacute toxicity

5 male Wistar rats, receiving 10 administrations of 1,800 mg/kg/d by gavage 10 times within 2 weeks, showed a slight decrease of erythrocyte numbers and haemoglobin content. No testicular damage and no leucopenia were observed; rats receiving ethoxyethanol under equimolar conditions showed pronounced RBC and WPC depletion, thymus involution and lowed tested weights. A marginal decrease of RBC and total Hb concentration were the only effects observed with 1PG2ME (BASF, 1982) (see Appendix A).

No data are available on subacute inhalation toxicity; however, a 28-day inhalation study was carried out with 1PG2MEA, which has a very similar toxicological profile (see 1PG2MEA product profile).

3.3.2 Subchronic toxicity

No data available.

3.3.3 Chronic toxicity/Carcinogenicity

No data available.

3.4 GENOTOXICITY

No mutagenic effects were observed in *Salmonella typhimurium* with or without metabolic activation (BASF, 1988a) (see Appendix C).

3.5 REPRODUCTION/DEVELOPMENTAL TOXICITY

Screening experiments with a limited number of rats (5 animals per dose group) exposed to 1,000; 2,000 and 3,000 ppm from gestation days 6 - 15 (6 h/d) showed thoracic vertebral incisions and split vertebrae at the highest level and to a slight extend (only incisions) at 1,000 and 2,000 ppm. The dams showed slight sedation and at higher dose levels also irritation (Merkle *et al*, 1987).

Himalayan rabbits (12 animals per dose group) were exposed to 145, 225, 350 and 545 ppm from gestation days 6 - 18 (6 h/d). Maternally toxic effects were recorded only at the highest level (decrease

ot weight gain and uterine weight at the end of the post-exposure period; placental weights were increased). Increased fetal resorptions were observed, and fetal weights were decreased. Two animals aborted. Malformations occurred in a dose-related manner at 545, 350 and to a marginal extent at 225 ppm. The anomalies mostly consisted in anomalies in the sternebrae; fused ribs and swollen rib cartilage were also observed; 2 fetuses at 350 ppm had cleft palate; at 545 ppm several other types of anomalies were observed including truncus arteriosus communis, missing gall bladder, and aplasia of phalanges). At 225 ppm also the numbers of variations in ribs and sternebrae were slightly increased. 145 ppm was without effects (BASF, 1988b and Hellwig *et al*, 1994).

Teratogenicity studies with the isomeric 2PG1ME in rats containing 1.32% of 1PG2ME as an impurity did not show effects at the 3,000 ppm level, which is equivalent to 40 ppm of 1PG2ME (Hanley *et al*, 1984a,c).

The results are summarized in Appendix B.

3.6 TOXICOKINETICS/METABOLISM

Male Fischer 344 rats dosed with 1.0 or 8.7 mmol/kg of ^{14}C-labelled material (at C-atom 2) eliminated 70-80% of the radioactivity with the urine and only 10-20% were recovered as $^{14}CO_2$. 2-Methoxypropionic acid accounted for 79-93% of the urinary radioactivity (Miller *et al*, 1986).

3.7 NEUROLOGICAL DATA

No data available.

3.8 IMMUNOLOGICAL DATA

The available studies provide no indication for immunologic effects. No specific further studies are available.

4. HUMAN DATA

No data available.

Substance Profile: 1PG2MEA

1. IDENTITY

Name:	1-Propylene Glycol 2-Methyl Ether Acetate
Structural formula:	CH_3-CH(O-CH_3)-CH_2-O-CO-CH_3
Molecular formula:	$C_6H_{12}O_3$
Molecular weight:	132.2
CAS No.:	70657-70-4
IUPAC name:	2-Methoxy-1-acetoxypropane
Other components:	Not known

2. PHYSICAL CHEMICAL DATA

Conversion factor:	1 ppm = 5.49 mg/m^3 (20°C, 1013 hPa) 1 mg/m^3 = 0.182 ppm (20°C, 1013 hPa)
Melting point:	appr. <-20°C
Boiling point:	150 - 151°C at 1013 hPa
Vapour pressure:	2.9 hPa
Solubility in water:	Completely soluble

3. TOXICOLOGICAL DATA

3.1 ACUTE TOXICITY

3.1.1 Oral toxicity

Rats: LD_{50} >5,000 mg/kg. Signs of toxicity were CNS depression (BASF, 1984a).

3.1.2 Dermal toxicity

Rabbits: LD_{50} >2,000 mg/kg. No symptoms were observed (Merkle *et al*, 1987).

3.1.3 Inhalation toxicity

Rats: No data available

Rabbits and dogs: LC_{50} >400 ppm (6 h exposure). Signs of toxicity in dogs were initially increased salivation and eyelid movement (BASF, 1984b).

3.2 IRRITATION/SENSITIZATION

3.2.1 Skin irritation

Undiluted material showed no irritation on rabbit skin (BASF, 1984a).

3.2.2 Eye irritation

Vapours at 400 ppm caused slight irritation to the eye of the rabbit (BASF, 1984b).

3.2.3 Skin sensitization

No data available.

3.3 SUBACUTE/SUBCHRONIC/CHRONIC TOXICITY

3.3.1 Subacute toxicity

5 male Wistar rats received 10 gavage administrations of 2,600 mg/kg in 2 weeks. No effects were found in macroscopical investigations or in routine clinical-chemistry. Ethoxyethanol (EGEE) at equimolar doses caused testicular damage and leucopenia (BASF, 1982).

In a 28 d inhalation experiment Wistar rats were exposed to 100, 560 and 2,800 ppm (4 h/d; 4 h/d; 4 d/wk). No effects occurred at 110 ppm. At 560 ppm slight irritation was observed. 2,800 ppm (14.5 mg/l) caused marked irritation, reduced weight gain, slight thymic atrophy, and in males increase of absolute liver weights. No testicular or myelotoxic effects were observed (BASF, 1984c).

The results are summarised in Appendix A.

3.3.2 Subchronic toxicity

No data available.

3.3.3 Chronic toxicity/Carcinogenicity

No data available.

3.4 GENOTOXICITY

No data available.

3.5 REPRODUCTION/DEVELOPMENTAL TOXICITY

Inhalation

Pregnant Wistar rats (25 f/dose group) were exposed to concentrations of 110, 550 and 2,700 ppm from gestation days 6-15. Maternal effects (irritation, sedation, decreased body weights between days 15 and

20) were observed at 2,700 ppm and, slightly, at 550 ppm. At 2,700 ppm there was an increased rate of fetal resorptions and a slight decrease of fetal weights. 12/189 fetuses showed thoracic vertebral incisions (Merkle *et al*, 1987).

Pregnant Himalayan rabbits (15 f/dose group) were exposed to 36, 145 and 550 ppm from gestation days 6-18. No maternal effects were observed. At 560 ppm all fetuses investigated showed malformations of sternum, paws, major blood vessels and heart. No treatment-related effects occurred at 145 and 36 ppm (Merkle *et al*, 1987).

Dermal

Pregnant Himalayan rabbits (10 f/dose group) were dermally exposed to 1,000 and 2,000 mg/kg/d from gestation days 6-18. The test material was undiluted and administered under semiocclusive conditions for 6 h daily on an area of 22 x 9 cm on the cleaved back skin. No adverse effects were observed (Merkle *et al*, 1987).

The results are summarised in Appendix B.

3.6 TOXICOKINETICS/METABOLISM

In vitro half-life time in rat plasma (cleavage of the ester bond) was 10 minutes (BASF, 1984d). The resulting 1PG2ME is oxidized to 2-methoxypropionic acid and excreted via the urine (Miller *et al*, 1986).

3.7 NEUROTOXICITY

No data were identified.

3.8 IMMUNOTOXICITY

No data are available. The thymic atrophy observed at 2,800 ppm in Wistar rats in the 4-week inhalation study (see Section 3.3.1.) might be interpreted as indicative of immunotoxic effect after repeated uptake of high dose levels.

4. HUMAN DATA

No data available.

Substance Profile: DPGME

1. IDENTITY

Name:	Dipropylene Glycol (mono)Methyl Ether
Structural Formula:	CH_3-$(OC_3H_6)_2$-OH
Molecular formula:	$C_7H_{16}O_3$
Molecular weight:	148.2
CAS No.:	34590-94-8
IUPAC name:	-
Other components:	Mixture of 4 isomers

2. PHYSICAL CHEMICAL DATA

Conversion factor:	1 ppm = 6.2 mg/m^3 (20°C, 1013 hPa) 1 mg/m^3 = 0.016 ppm (20°C, 1013 hPa)
Melting point:	-83°C
Boiling point:	184-197°C at 1013 hPa
Vapour pressure :	1 hPa at 20°C
Solubility in water:	Completely soluble

3. TOXICOLOGICAL DATA

3.1. ACUTE TOXICITY

3.1.1 Oral toxicity

Rats: LD_{50} 5.50 ml/kg (male); 5.45 ml/kg (female). Signs of toxicity were depression of the CNS (Rowe *et al*, 1954).

Dogs: LD_{50} 7,500 mg/kg. Mortality within 48 h. Signs of toxicity were respiratory paralysis. (Shideman and Procita, 1951).

3.1.2 Dermal toxicity

Rabbits: LD_{50} 10,000 - 14,000 mg/kg (Browning, 1965). Transient narcosis were observed at doses of 20 ml/kg (occluded) (Draize *et al*, 1944)..

3.1.3 Inhalation toxicity

Rats: Exposure (3 groups of 3 m/group) for 7 h to 500 ppm (vapour and aerosol atmosphere) produced mild narcosis (Rowe *et al*, 1954).

3.2 IRRITATION/SENSITIZATION

3.2.1 Skin irritation

Slightly irritating (slight scaliness) to rabbit skin over a 90 d period (repeated application). Human patch tests provided no evidence of primary irritation or immune mediated hypersensitivity of the skin (Draize *et al*, 1944).

3.2.2 Eye irritation

Irritating to the eye of the rabbit (0.1 ml undiluted test material). Signs were irritation to the

conjunctivae and margins of the eyelid. These effects declined in severity over 24 h and had completely resolved by 7 days. Measurement of corneal thickness and intra ocular pressure showed minor changes indicating minimal effects on the corneal epithelium (Ballantyne, 1984).

Application of 0.04 ml of a 20% aqueous solution to human eyes produced mild transient sensory irritation, hyperaemia of conjunctival vessels and a small increase in intra ocular pressure. All effects disappeared within 2 h (Ballantyne, 1984b).

Mild transitory irritation of the conjunctival membranes was observed in the rabbit eye after 5 daily applications of undiluted test material (Rowe *et al*, 1954).

3.2.3 Skin Sensitization

No evidence of skin sensitisation was reported in human patch tests (Rowe *et al*, 1954).

3.3 SUBACUTE/SUBCHRONIC/CHRONIC TOXICITY

3.3.1 Subacute toxicity

Application to the shaved skin of rabbits, 5 times/wk for 90 d at dose levels of 1.0-10 ml/kg resulted in narcosis and deaths at doses of 10 and 5 ml/kg. An increase in hydropic degeneration of the kidney was reported for animals in the 10 ml/kg dose group (Rowe *et al*, 1954).

Open or occluded application of daily doses of 100 or 1,000 mg/kg, 5 d/wk for 4 wk to the shaved skin of rats produced no significant changes in clinical chemistry, haematology or pathology (Fairhurst *et al*, 1989).

Rats, guinea pigs and monkeys were exposed 7h/d, 5d/wk for periods of up to 8 months to essentially saturated atmospheres (reported to be 300 ppm). The only observed effects were in rats and consisted of slight narcosis in the first weeks of exposure and as light increase in liver weight at the end of the study. No significant effects were observed in the other species (Rowe *et al*, 1954).

DPGME administered to rats as daily *i.p.* doses of 1,000 mg/kg, 5 times/wk for 2 wk produced minimal changes in the urinary excretion of N-acetyl-β-D-glucosaminidase β_2 microglobulin and albumin and was therefore judged to have no effect on renal function (Bernard *et al*, 1989).

The results of subacute studies are summarised in Appendix A.

3.3.2 Subchronic toxicity

Small increases in relative liver weight were observed in rats and mice exposed 6 h/d for 9 d to atmospheres of 50, 140 or 330 ppm. These changes occurred in the absence of any histopathological changes and were considered adaptive (Landry *et al*, 1981).

When rats and mice were exposed to atmospheres of 15, 50, or 200 ppm; 6 h/d; 5 d/wk; 13 wk no effects were seen in either species at any concentration (Landry and Yano, 1984).

The results of subchronic studies are summarised in Appendix A.

3.3.3 Chronic toxicity/Carcinogenicity

No data available.

3.4 GENOTOXICITY

DPGME has been studied for mutagenic activity in *Salmonella typhimurium* strains TA 1535, T 1537, TA 1538, TA 98 and TA 100 (Kirkland and Varley, 1983) and for clastogenic activity in CHO cells (Kirkland, 1983). In both studies negative results were obtained both in the presence and absence of metabolic activation.

No unscheduled DNA synthesis was observed in rat hepatocytes (Mendrala, 1983).

The results of genotoxicity studies are summarised in Appendix C.

3.5 REPRODUCTION/DEVELOPMENTAL TOXICITY

Studies of the developmental toxicity in rats and rabbits provided no evidence of any selective toxicity to the foetus (Breslin *et al*, 1990).

3.6 TOXICOKINETICS/METABOLISM

Following oral administration of ^{14}C labelled DPGME, 60% of the label was excreted in the urine, most within the first 24 h, 27% in the expired air and <3% in the faeces. DPGME, PGME, propylene glycol, dipropylene glycol and the sulphates and glucuronides of DPGME were identified in the urine (Miller, 1987).

3.7 NEUROLOGICAL DATA

No specific data are available. Acute, sub-acute and subchronic studies in experimental animals have shown that exposure to high concentrations or extensive and prolonged skin contact may produce depression of the central nervous system leading to narcosis. Death following massive exposures has been ascribed to respiratory paralysis. The CNS effects produced by sub-lethal concentrations appear to fully reversible and conventional histopathological examination of the CNS and peripheral nerves have not indicated any structural changes (see chapters 3.3.1 and 3.3.2).

3.8 IMMUNOLOGICAL DATA

No specific data are available. Studies on the effects of repeated exposure in animals have not provided evidence of any effects on the immune system (see chapters 3.3.1 and 3.3.2).

4. HUMAN DATA

Patch tests conducted on 250 human subjects produced no evidence of either primary skin irritation or sensitisation (Rowe *et al*, 1954).

Airborne concentrations of between 300-400 ppm have been described as very disagreeable to humans (Rowe *et al*, 1954).

Substance Profile: DPGEE

1. IDENTITY

Name:	Dipropylene Glycol (mono) Ethyl Ether
Structural formula:	C_2H_5-(O-C_3H_6)$_2$-OH
Molecular formula:	$C_8H_{18}O_3$
Molecular weight:	162.2
CAS No.:	300025-38-8
IUPAC name:	Propanol, (2 ethoxy-methylethoxy) (all isomers)
Other components:	1-Ethoxy-2-propanol 1-5% Ethoxypropoxy propanol 0.5-5%

2. PHYSICAL CHEMICAL DATA

Conversion factor:	1 ppm = 4.25 mg/m^3 (20°C, 1013 hPa) 1 mg/m^3 = 0.235 ppm (20°C, 1013 hPa)
Melting point:	< - 50°C
Boiling point:	188.3°C at 1013 hPa
Vapour pressure:	56.67 hPa at 20°C
Solubility in water:	completely soluble

3. TOXICOLOGICAL DATA

3.1 ACUTE TOXICITY

3.1.1 Oral toxicity

Rats: LD_{50} 5 ml/kg (male and female). The lowest dose producing mortality was 2.76 ml/kg (f) and 5.4 ml/kg (m). Signs of toxicity were lethargy, ataxia and breathing irregularities. Death generally occurred within the first day. Surviving animals had recovered completely by day 3 (BP, 1986a).

3.1.2 Dermal toxicity

Rats: No signs of toxicity after a single application of 2,000 mg/kg to the shaved skin of 5 m and 5 f (BP, 1990a).

3.2 IRRITATION/SENSITIZATION

3.2.1 Skin irritation

Slightly irritating to the rabbit skin (4 h, semi-occluded) (BP, 1985e).

3.2.2 Eye irritation

Conjunctival irritation and diffuse corneal opacity were reported following application to the rabbit eye (BP, 1985f). These reactions did not meet the criteria for classification as an eye irritant, according to the EC Dangerous Substances Directive.

3.2.3 Sensitization

Non sensitising in guinea pigs by the test method of Magnusson and Kligman (BP, 1985g).

3.3 SUBACUTE/SUBCHRONIC/CHRONIC TOXICITY

3.3.1 Subacute toxicity

The sub-acute toxicity of DPGEE has was investigated in Sprague Dawley rats (BP, 1990b). Groups of 5 m and 5 f rats were given daily oral doses of 0, 50, 225 or 1,000 mg/kg/d for 28 d. The protocol was in accordance with OECD Guidelines. There were no effects on either growth rate or general behaviour of the animals. At the end of the study absolute and relative liver weights were increased in both male and female animals given 1,000 mg/kg without any associated histopathological changes. Minimal to slight hyaline droplet formation (HRE Strain) was observed in the proximal tubular cells of the kidneys of all male animals given 1,000 mg/kg and in 2 of 5 animals given 225 mg/kg (see Appendix A).

3.3.2 Subchronic toxicity

No data available.

3.3.3 Chronic toxicity/Carcinogenicity

No data available.

3.4 GENOTOXICITY

DPGEE was examined for mutagenic activity in five histidine-dependant strains of *Salmonella typhimurium*, TA 98, TA 100, TA 1535, TA 1537, TA 1538, in the presence and in the absence of a post-mitochondrial fraction of rat liver (S9). There was no increase in the number of revertants at any of the dose levels employed, ranging from 50 - 5,000 µ/plate (BP, 1985h).

Cultured human lymphocytes were used to evaluate the chromosome damaging potential of DPGEE. Cell cultures were treated both in the presence and absence of a post-mitochondrial fraction of rat liver (S9) at concentrations up to 1,000 µ/ml. Under these conditions DPGEE did not induce chromosome aberrations in the presence or absence of metabolic activation (BP, 1990c).

The results of genotoxicity studies are summarised in Appendix C.

3.5 REPRODUCTION/DEVELOPMENTAL TOXICITY

No data available.

3.6 TOXICOKINETICS/METABOLISM

No specific data available.

In common with other glycol ethers percutaneous absorbtion is likely.

A single dose of 2,000 mg/kg applied to the shaved skin of rats was not absorbed in amounts sufficient to produce any signs of systemic toxicity. Metabolism is likely to proceed in a manner similar to DPGME with formation of PGEE dipropylene glycol, propylene glycol and their conjugates. (BP, 1990a).

There are no data available on the metabolism of DPGEE.

3.7 NEUROLOGICAL DATA

There have been no studies carried out specifically to examine the neurological effects of DPGEE.

Single oral doses of about 5 ml/kg produced signs consistent with depression of the central nervous system in rats. Repeated daily oral administration to rats did not however produce overt signs of dysfunction of either the central or peripheral nervous system doses up to 1,000 mg/kg. Histopathological examination did not include nervous tissue. (BP, 1986a and 1990b).

3.8 IMMUNOLOGICAL DATA

No tests to specifically examine the effects of DPGEE on the immune system have been carried out. The results of studies on the effects of repeated exposure have not suggested any effects on lymphoid tissue or other elements of the immune system.

4. HUMAN DATA

No data are available.

Substance Profile: TPGME

1. IDENTITY

Name:	Tripropylene Glycol (mono)Methyl Ether
Structural formula:	CH_3-$(O$-$C_3H_6)_3$-OH
Molecular formula:	$C_{10}H_{22}O_4$
Molecular weight:	206.3
CAS No.:	25498-49-1
IUPAC name:	Mixture of Isomers
Other components:	< 2.5% Ethers of mono-, di- and tetrapropylene glycols

2. PHYSICAL CHEMICAL DATA

Conversion factor:	1 ppm = 8.62 mg/m^3 (20°C, 1013 hPa) 1 mg/m^3 = 0.116 ppm (20°C, 1013 hPa)
Melting point:	-78°C
Boiling point:	242.2°C at 1013 hPa
Vapour pressure:	0.03 hPa at 20°C
Solubility in water:	Completely soluble

3. TOXICOLOGICAL DATA

3.1 ACUTE TOXICITY

3.1.1 Oral toxicity

Rats: LD_{50} 3,300 mg/kg. Signs of toxicity were narcosis (Rowe *et al*, 1954).

Dogs: LD_{50} 4,800 mg/kg. Signs of toxicity were CNS depression with death at large doses due to respiratory failure (Shideman and Procita, 1951).

3.1.2 Dermal toxicity

Rats: No data available.

Rabbits: LD_{50} >19,220 mg/kg. No signs of toxicity (Rowe *et al*, 1954).

3.1.3 Inhalation toxicity

Rats: No signs of toxicity during 7 h exposure to saturated vapour atmosphere (Rowe *et al*, 1954).

3.2 IRRITATION/SENSITIZATION

3.2.1 Skin irritation

Mildly irritating to the rabbit skin (undiluted test material under occlusion) (Rowe *et al*, 1954).

3.2.2 Eye irritation

Not irritating to the eye of the rabbit after repeated instillation of the undiluted test material (Rowe *et al*, 1954).

3.2.3 Sensitization

No data available.

3.3 SUBACUTE/SUBCHRONIC/CHRONIC TOXICITY

3.3.1 Subacute toxicity

In a 2 wk aerosol inhalation study (Miller *et al*, 1985b) Fisher 344 rats and B6C3F1 mice were exposed to concentrations of 0, 0.15, 0.36 and 1.01 mg/l 6 h/d for 9 d. An increase in liver weights in both species was the only exposure-related effect. No gross or histopathologic changes in the liver occurred. No changes in testes or haematology nor any other systemic effects were observed at any concentration, at 0.15 mg/l only the male mice still showed an increase in liver weight (see Appendix A).

3.3.2 Subchronic toxicity

In a 13 wk dermal study (Rowe *et al*, 1954) rabbits received repeated (65) doses of 0, 1, 3, 5, and 10 ml/kg (0, 965, 2,895, 4,825 or 9,650 mg/kg). Kidney injury was observed at all dose levels tested. At 5 and 10 ml/kg, narcosis occurred, which lead to the death of 7 out of 8 animals in the 10 ml/kg group (see Appendix A).

3.3.3 Chronic toxicity/carcinogenicity

No data available.

3.4 GENOTOXICITY

TPGME was evaluated in the *in vitro Salmonella*/mammalian microsome bacterial mutagenicity assay (Ames test) using a pre-incubation modification of the standard method (Mendrala and Schumann, 1982a). The test was conducted in the presence and absence of a metabolic activation system (S-9 mix from Aroclor induced rat liver) using *Salmonella typhimurium* bacterial tester strains TA 98, TA 100, TA 1535, TA 1537 and TA 1538. The test material was assayed three times in each tester strain up to a maximum concentration of 100,000 µg/plate. TPGME did not induce a mutagenic response in any of the tester strains (see Appendix C).

TPGME was also evaluated in the rat hepatocyte unscheduled DNA synthesis (UDS) assay (Mendrala and Schuman, 1982b) at concentrations of 1×10^{-4} to 1×10^{-1} M (half-log intervals). TPGME failed to elicit significant UDS at any of the concentrations tested (see Appendix C).

3.5 REPRODUCTION/DEVELOPMENTAL TOXICITY

Groups of female mated Sprague-Dawley rats were exposed by aerosol inhalation for 6 h/d to 0.3, 0.9, 2.7 and 8.2 mg/l during d 6-15 of gestation in a range finding study (Breckenridge *et al*, 1985a). The NOEL was 0.9 mg/l. Maternal liver weight increases and tremors occurred at 2.7 mg/l. No embryotoxicity was observed at any concentration level (see Appendix B).

When groups of mated female Sprague-Dawley rats were exposed by aerosol inhalation for 6 h/d during d 6-15 of gestation at doses of 0.1, 0.3 or 1.0 mg/l, there was maternal toxicity at 1.0 mg/l. No embryotoxicity, foetotoxicity or teratogenic effects were observed at any concentration level (Breckenridge *et al*, 1985b) (see Appendix B).

3.6 TOXICOKINETICS/METABOLISM

Studies in male Fischer 344 rats indicate that TPGME is extensively metabolized (Calhoun *et al*, 1986a,b; Miller, 1987). The urine contained 5% unchanged TPGME. Dipropylene glycol methyl ether was also identified as a metabolite. In general, the disposition and types of other metabolites identified were similar to those of DPGME. Urine was the predominant route of elimination after oral doses of 1 or 4 mMol/kg ^{14}C-TPGME. At the high dose, about 75% of the dose was recovered in urine within 48 h; 69% of the low dose was recovered within 48 h. It was noted that 2-methoxypropionic acid was not identified as a metabolite of TPGME (see Appendix D).

3.7 NEUROLOGICAL DATA

No effects were found that are specific for this compound (Rowe *et al*, 1954).

3.8 IMMUNOLOGICAL DATA

The available studies provide no indication for an immunologic effect. No specific further studies are available.

4. HUMAN DATA

No data available.

SECTION 5. APPENDICES. TOXICOLOGICAL DATA OF GLYCOL ETHERS

In the following appendices, the toxicological data is tabulated to allow easy comparison of effects between the different glycol ethers as follows:

Appendix A: Systemic Toxic Effects

Appendix B: Reproduction and Development Studies

Appendix C: Genotoxicity Studies

Appendix D: Absorption Distribution, Metabolism and Elimination Studies

APPENDIX A: Systemic Toxic Effects

Compound	Species (Strain)	Route	Animals per dose level	Exposure conc. or dose	Time	Response	Reference
EGME	rats (Fischer 344)	oral	24 m	100 mg/kg 500 mg/kg; sacrificed	once per d for 4 d	↓ WBC largely reversible on d 22. ↓ WBC largely reversible on day 22. ↓ Hb, Hct and RBC.	Grant *et al* (1985)
	rats (Sprague-Dawley)	oral	36 m	50 mg/kg 100 mg/kg 250 mg/kg 500 mg/kg	11 d	NOEL. Degeneration of pachytene at 24 h. " " " " " ; ↓ testicular weight. " " " " " ; ↓ testicular weight.	Foster *et al* (1983)
	rats (Fischer 344)	oral	5-6 m per treatment period (1,2,4,7, 10 d)	150 mg/kg	up to 10 d	Spermatocytes degeneration at d 1; ↓ testes weight at d 2.	Chapin and Lamb (1984)
	rats (Fischer 344)	oral	20 m	50 mg/kg 100 mg/kg 200 mg/kg	for 5 d, then mated with 2 f rats/wk for 8 wk; after 8 wk interval, mated again for 5 d	↓ sperm numbers. ↓ fertility and pups/litter (wk 2 and 5) abnormal sperm/morphology (wk 5). ↓ number of live foetuses (wk 4-16); pre-implantation loss (wk 3-16); abnormal sperm morphology (wk 6).	Chapin *et al* (1985a)
	rats (Sprague-Dawley)	oral	6 m, 6 f	2,000 or 6,000 ppm in drinking water	21 d	Dose-dependent thymus depletion. ↓ testicular toxicity at higest concentration. ↓ humoral and ↑ NK cell immunity.	Exon *et al* (1991)
	rats (Fischer 344)	oral	6-8 m	50 mg/kg 100 mg/kg 200 mg/kg	10 d	Impact on immune system. Impact on immune system. ↓ testes weights and ↑ serum testosterone.	Smialowicz *et al* (1991a)

APPENDIX A: Systemic Toxic Effects

Compound	Species (Strain)	Route	Animals per dose level	Exposure conc. or dose	Time	Response	Reference
EGME	rats (Wistar)	oral (gavage)	4 m	100 mg/kg/d	20 d	↓ body weight; ↓ rel.thymus weights; ↓ rel.testes weights.	Kawamoto *et al* (1990a)
				300 mg/kg/d	1 d	↓ body weight.	
					2 d	↓ body weight; ↓ rel.thymus weights; ↓ rel.testes weights; ↓ rel.liver, kidney, spleen and heart weights.	
					5 d 20 d	Additionally strong depletion of lymphocytes in thymus cortex.	
	rats	inhalation	6 f	32 - 2,000 ppm	4 h	↑ osmotic fragility.	Carpenter *et al* (1956)
	rats (Fischer)	inhalation	10 m/10 f	100 ppm 300 ppm 1,000 ppm	6 h/d for 9 d	No effects. Some thymic atrophy. Lymphoid depletion in thymus cortex, spleen and lymph nodes; testicular degeneration, ↓ bone marrow cellularity.	Miller *et al* (1981)
	rats	inhalation	30 m/30 f 20 m/20 f	30 ppm 100 ppm 300 ppm	6 h/d, 5 d/wk for 13 wk, then paired with unexposed animals for breeding	No effects. No effects. ↓ male fertility, partially reversed when bred 13 and 19 wk after exposure.	Rao *et al* (1983)
	rats (Wistar)	inhalation	10 m	100 ppm 300 ppm	6 h/d for 10 d	No effects. Testicular atrophy.	Doe *et al* (1983)

APPENDIX A: Systemic Toxic Effects

Compound	Species (Strain)	Route	Animals per dose level	Exposure conc. or dose	Time	Response	Reference
EGME	rats (Wistar)	inhalation	20 m	150 ppm 300 ppm 625 ppm 1,250 ppm 2,500 ppm 5,000 ppm	4 h; sacrified on d 14	No effects. No effects. Damaged spermatids. Microscopic testicular changes and atrophy; damaged spermatids. Microscopic testicular changes and atrophy; damaged spermatids. Microscopic testicular changes and atrophy; damaged spermatids.	Samuels *et al* (1984)
	rats (Wistar)	inhalation	90 m	1,000 ppm 2,500 ppm	4 h; sacrificed on day 1, 2, 3, 4, 5, 8, 10, 15, and 19 post exposure	↓ testes weight at 48 h; testicular atrophy on d 1-19, at both exposure levels.	Samuels *et al* (1984)
	rats (Sprague-Dawley)	inhalation	10 m/10 f	30 ppm 100 ppm 300 ppm	6 h/d, 5 d/wk for 13 wk	No effects. No effects. ↓ WBC, platelets, Hb, total protein, albumin and globulin; thymic and testicular atrophy.	Miller *et al* (1983a)
	rats (Wistar and Carworth)	inhalation	(not reported)	125 ppm 250 ppm 1,000 ppm 2,000 ppm 4,000 ppm	4 h/d, up to 14 d	Dose and exposure time related inhibition on conditioned avoidance-escape behaviour.	Goldberg *et al* (1962)
	rats (Porton-Wistar)	dermal (open and occluded)	8 m	100 mg/kg 1,000 mg/kg	5 d/wk for 4 wk	No effects. Testicular and bone marrow damages; more pronounced under occluded conditions.	Fairhurst *et al* (1989)
	rats (Sprague-Dawley)	dermal (open and occluded)	20 m	0; 625; 1,250; 2,500 mg/kg 0; 1,250; 2,500; 5000 mg/kg	single dose	Dose-related↓ in sperm and spermatid count; ↑ abnormal sperm morphology; ↓ fertility.	Feuston *et al* (1989)

APPENDIX A: Systemic Toxic Effects

Compound	Species (Strain)	Route	Animals per dose level	Exposure conc. or dose	Time	Response	Reference
EGME	rats (CD) and mice (CD-1)	oral	10 m	500 mg/kg 750 mg/kg 1,000 mg/kg 1,500 mg/kg	single dose; sacrifice after weekly intervals	↓ testes weights at wk 2-5; abnormal spleen morphology. ↓ testes weights at wk 2-5; abnormal spleen morphology. ↓ testes weights at wk 2-5; abnormal spleen morphology. ↓ testes weights at wk 2-5; abnormal spleen morphology.	Anderson *et al* (1987)
	mice (ICL-ICR)	oral	5 m (20 m in control)	62.5 mg/kg 125 mg/kg 250 mg/kg 500 mg/kg 1,000 mg/kg 2,000 mg/kg	5 times/wk for 5 wk	No effects. No effects. Testicular atrophy. ↓ WBC, RBC and PCV; testicular effects. ↓ WBC, RBC and PCV; testicular effects, no germ cells. Died before completion.	Nagano *et al* (1979)
	mice (B6C3F1)	oral	10 f	250 mg/kg 500 mg/kg 1,000 mg/kg	10 times during 2 wk	No effects. Cellularity ↓ in thymus and spleen. ↓ WBC, platelets and Hb; thymic atrophy after 4 and 12 wk.	House *et al* (1985)
	mice (B6C3F1)	oral (gavage)	7 m 7 f	50 mg/kg/d 100 mg/kg/d 250 mg/kg/d	4 d (postobservation = 1, 5, 14 d)	After 5 d postobservation: ↓ leukocytes in male ↓ granulopoetic stem cells already 1 d postobservation. ↓ female erythropoetic stem cells (1 d postobservation). After 1 d postobservation: ↓ rel.testes weights, loss of germinal epithelium, no other histopathological lesions.	Hong *et al* (1988)
	mice (B6C3F1)	inhalation	5 m/5 f	100 ppm 300 ppm 1,000 ppm	6 h/d for 9 d	No effects. Some thymic atrophy. Testicular degeneration; ↓ bone marrow cellularity, WBC and RBC.	Miller *et al* (1981)

APPENDIX A: Systemic Toxic Effects

Compound	Species (Strain)	Route	Animals per dose level	Exposure conc. or dose	Time	Response	Reference
EGME	guinea pigs	oral	3 m	250 and 500 mg/kg	5 d/wk for 5 wk	↓ WBC at both concentrations. testicular atrophy.	Nagano *et al* (1984)
	guinea pigs	dermal (occluded)	6 m	1,000 mg/kg	6 h/d, 5 d/wk for 13 wk	Severe testicular atrophy, degeneration of seminiferous tubulus with complete loss of spermatogenic cells; ↓ spleen weights, lymphopenia; ↓ RBC with ↑ MCV.	Hobson *et al* (1986a)
	rabbits (New Zealand)	inhalation	5 m/5 f	30 ppm 100 ppm 300 ppm	6 h/d, 5 d/wk for 13 wk	Dose-related increase incidence and severity of testicular lesions. Dose-related increase incidence and severity of testicular lesions. ↓ body weights, thymus weights and testicular weights; microscopic lesions.	Miller *et al* (1983a)
	rabbits (New Zealand)	inhalation	10 m /10 f	3 ppm 10 ppm 30 ppm	6 h/d, 5 d/wk for 13 wk	No effects. No effects. ↓ WBC, platelets and Hb : thymic atrophy after 4 and 12 wk.	Miller *et al* (1982a)
	hamsters (Syrian)	oral	4 m	62.5 mg/kg 125 mg/kg 250 mg/kg 500 mg/kg	5 d/wk for 5 wk	No effects. ≥ 125 mg/kg dose dependent testicular atrophy.	Foster *et al*, 1983
	hamsters (Syrian, golden)	oral	4 m	62.5 mg/kg 125 mg/kg 500 mg/kg	5 d/wk for 5 wk	No effects. No effects. ↓ WBC	Nagano *et al* (1984)
	dogs	inhalation	2 treated 2 control	3,091 mg/m3 (750 ppm)	7 h/d, 5 d/wk for 12 wk	↓ RBC, Hb, and PCV; microcytosis, hypochromia, and polychromatophilia; immature granulocytes and ↓ osmotic fragility.	Werner *et al* (1943b)

APPENDIX A: Systemic Toxic Effects

Compound	Species (Strain)	Route	Animals per dose level	Exposure conc. or dose	Time	Response	Reference
EGMEA	mice (ICL-ICR)	gavage	5 m	62.5 mg/kg 125 mg/kg 250 mg/kg 1,000 mg/kg 2,000 mg/kg	5 times/wk for 5 wk	Dose-dependent testicular atrophy; leukopenia.	Nagano *et al* (1979 and 1984)
MAA	rats (Wistar)	oral	6 m	118 mg/kg 296 mg/kg 592 mg/kg	single treatment 1-14 d observation	Testicular damage (pachytene spermatides).	Foster *et al* (1987)
	rats	oral	?	650 mg/kg	single treatment 70 d observation	↓ serum testosterone and serum FSH.	Bartlett *et al* (1988)
	rats (Sprague-Dawley)	oral	6 m	592 mg/kg	4 times/4 d	Testicular damage (pachytene, diplotene, diakinesis).	Foster *et al* (1983); Gray *et al* (1985)
	rats (Fischer)	oral	5 m	30 mg/kg 100 mg/kg 300 mg/kg	8 d in 2 wk	NOEL ↓ testicular weights, cellularity, thymus weights and core cellularity. ↓ bone marrow cellularity and RBC.	Miller *et al* (1982b)
	rats (Fischer 344)	oral	10 m	50-200 mg/kg	10 d	Thymic involution, immunosuppression.	Smialowicz *et al* (1991b)
	mice (B6C3F1)	oral	10 f	25 mg/kg 50 mg/kg 100 mg/kg	2 wk	↓ Spleen, bone marrow and thymus cellularity . No effects on NK cell activity .	House *et al* (1985)
EGEE	rats	oral (drinking water)	10 m/10 f	52-1,890 mg/kg	90 d	NOEL : 210 mg/kg From 740 mg/kg upwards: ↓ body weight and food consumption; histopathological changes in liver, kidney spleen and testes.	Smyth *et al* (1951)

APPENDIX A: Systemic Toxic Effects

Compound	Species (Strain)	Route	Animals per dose level	Exposure conc. or dose	Time	Response	Reference
EGEE	rats Fischer 344/N)	oral (drinking water)	10 m/10 f	1 250 ppm (109 mg/kg) 2 500 ppm (205 mg/kg) 5 000 ppm (400 mg/kg) 10 000 ppm (792 mg/kg) 20 000 ppm (2 240 mg/kg)	90d	NOEL ↓ body weight for m and f from 5 000 ppm Anemia in m and f from 2 500 ppm upwards ↓ thymus weight in m and f from 2 500 upwards Testicular degeneration from 5 000 ppm upwards Survival : 5/10 (m) 3/10 (f)	NTP (1992)
	rats (Fischer 344/N)	oral (drinking water)	5 m/5 f	200 mg/kg 600 mg/kg 900 mg/kg 1 500 mg/kg 2 500 mg/kg	14d	↓ bw for m in all treated groups. ↓ bw for f from 1500 mg/kg upwards. Degeneration of testis (mild). Degeneration of testis (marked).	NTP (1992)
	rats (Wistar)	oral (gavage)	5 m/5 f	46 mg/kg 93 mg/kg (372 mg/kg from d. 59) 186 mg/kg (743 mg/kg from d. 59)	13 wk	No changes. NOEL. Histopathological changes in testes and spleen. ↓Hb and Hct.	Stenger *et al* (1971)
	rats (Sprague-Dawley)	oral (gavage)	36 m	250 mg/kg 500 mg/kg 1,000 mg/kg	11 d	NOEL. Histopathological changes in testes of animals of both dose groups.	Foster *et al* (1983) Foster *et al* (1984)
	rats (Long Evans)	oral (gavage)	9 m	936 mg/kg	6 wk	Abnormal morphology of spermatocytes; ↓Hb and Hct.	Oudiz and Zenick (1986)
	rats (Long Evans)	oral (gavage)	11-13 m	150 mg/kg 300 mg/kg	6 wk	NOEL Abnormal morphology of spermatocytes; ↓ testes weight and number of spermatocytes.	Hürtt and Zenick (1986)
	rats (Fischer 344/N)	oral (gavage)	50 m/50 f	500 mg/kg 1 000 mg/kg 2 000 mg/kg	2 y	Enlargement of adrenal gland in m Testicular atrophy (at 1 000 and 2 000 mg/kg) High mortality (Termination at week 18) due to stomach ulcers	Melnick (1984)

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Compound	Species (Strain)	Route	Animals per dose level	Exposure conc. or dose	Time	Response	Reference
EGEE	rats (Wistar)	inhalation (whole body)	15 f/15 m	93 mg/m3 390 mg/m3 1,480 mg/m3	6 h/d, 5 d/wk for 13 wk	↓ spleen weight (f). ↓ spleen weight (f). ↓ spleen weight (f). no histopathological correlations were found.	Barbee *et al* (1984) Biodynamics (1983a)
	rats	inhalation		17,000 mg/m3	single dose	Testicular atrophy, haematuria.	Doe (1984a)
	rats (Sprague-Dawley)	dermal	5 f	1,552 mg/kg 2,214 mg/kg 3,100 mg/kg 4,428 mg/kg 6,200 mg/kg 8,857 mg/kg	10 d	No changes. No changes. No changes. NOEL. Ataxia. Ataxia.	Hardin *et al* (1982)
	mice (B6C3F1)	oral (drinking water)	5 m/5 f	300 mg/kg 600 mg/kg 900 mg/kg 1,500 mg/kg 2,500 mg/kg	14d	No microscopic examination of the tissues was performed ↓ relative testis weight	NTP (1992)
	mice (B6C3F1)	oral (drinking water)	10 m/10 f	2,500 mg/kg 5,000 mg/kg 10,000 mg/kg 20,000 mg/kg 40,000 mg/kg	90d	Hypertrophy of adrenal gland in f in all close groups Haematopoeiesis in spleen of f from 10,000 ppm upwards ↓ bw, testicular degeneration ↓ bw, testicular degeneration	NTP (1992)
	mice (B6C3F1)	oral (gavage)	50 m/50 f	500 mg/kg 1,000 mg/kg 2,000 mg/kg	2y	Testicular atrophy (1 000 and 2 000 mg/kg); High mortality due to stomach ulcers (Termination week 18).	Melnick (1984)
	mice (ICL-ICR)	oral	5 m	500 mg/kg 1,000 mg/kg 2,000 mg/kg 4,000 mg/kg	5 wk	NOEL. Testicular atrophy. Testicular atrophy. Testicular atrophy.	Nagano *et al* (1979)

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Compound	Species (Strain)	Route	Animals per dose level	Exposure conc. or dose	Time	Response	Reference
EGEE	rabbits (New Zealand)	inhalation (whole body)	10 m/10 f	93 mg/m3 390 mg/m3 1,480 mg/m3	6 h/d, 5 d/wk for 13 wk	No changes except ↑ lacrimation. NOEL. ↓ testes weight, histopathological changes in testes.	Barbee *et al* (1984) Biodynamics (1983b)
	dogs	oral	3 m/3 f	46 mg/kg 93 mg/kg 186 mg/kg	13 wk	No changes. NOEL. histopathological changes in testes.	Stenger *et al* (1971)
	dogs	inhalation (whole body)	2 m/2f	3,142 mg/m3	7 h/d, 5 d/wk for 12 wk	↓Hb and Hct.	Werner *et al* (1943b)
EGEEA	rats (Wistar)	inhalation	10 m/10 f	0 mg/m3 1,100 mg/m3	4 h/d, 5 d/wk for 10 months	- Renal lesions (not specified) no testicular and haematological effects.	Truhaut *et al* (1979)
	mice (ICL-ICR)	oral	5 m/5 f	0 mg/kg 500 mg/kg 1,000 mg/kg 2,000 mg/kg 4,000 mg/kg	5 wk	- No effects. Testicular atrophy and ↓ number of Leukocytes. Testicular atrophy and ↓ number of Leukocytes. Testicular atrophy and ↓ number of Leukocytes.	Nagano *et al* (1979)
	rabbits (New Zealand)	inhalation	2 m/2 f	0 mg/m3 1,100 mg/m3	4 h/d, 5 d/wk for 10 months	- Renal lesions (not specified) no testicular and haematological effects.	Truhaut *et al* (1979)
	dogs	inhalation	3 m/3 f	0 mg/m3 3,300 mg/m3	7 h/d, 5 d/wk for 6 months	- No effects.	Carpenter (1947)
EGnPE	rats (CBOS/CD/ (SD)BR)	gavage	10 m	1.88 mmol/kg 3.75 mmol/kg 7.5 mmol/kg 15 mmol/kg	6 wk	NOEL. Haemoglobinuria; ↑ spleen weight. Haemoglobinuria; ↑ spleen weight. Haemoglobinuria; ↑ spleen weight.	Katz *et al* (1984)

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Compound	Species (Strain)	Route	Animals per dose level	Exposure conc. or dose	Time	Response	Reference
EGnPE	rats (CBOS/CD/ (SD)BR)	inhalation	5 m/5 f	100 ppm 200 ppm 400 ppm 800 ppm	11 d	No effects. NOEL. Initial haemoglobinuria. Initial haemoglobinuria.	Katz *et al* (1984)
EGiPE	rats (Wistar)	inhalation	23m/23 f	390 ppm	7 h/d, 5 d/wk for 5 wk	Haemolytic effects; ↑ reticulocytes and are less sensitive.	Werner *et al* (1943c)
	rats (Wistar; Alderley Park)	inhalation	10 m	600 ppm 1,000 ppm	6 h/d in 9 d	Haemolytic effects. Haemolytic effects.	Doe (1984b)
	rats (Wistar)	inhalation	10 m/10 f	10 ppm 30 ppm 100 ppm 150 ppm 450 ppm 900 ppm	6 h/d for 28 d	NOAEL. NOAEL. Haemolytic effects in female. Haemolytic effects; ↑ spleen weights. Haemolytic effects; ↑ spleen weights. Haemolytic effects; ↑ spleen weights.	Reuzel *et al* (1987) Arts *et al* (1988)
	rats (Wistar; Alderley Park)	inhalation	4 m/4 f	100 ppm 300 ppm 1,000 ppm	6 h/d, 5d/wk for 3 wk	NOEL. Transient haemolytic effects. Haemolytic effects; ↑ reticulocytes and lung weights.	Gage (1970)
EGnPEA	rats (COBS/CD/ (SD)BR)	oral	10 m	7.5 mmol/kg 15 mmol/kg 30 mmol/kg	5 d/wk	Spleen and kidney affected. Spleen and kidney affected. Spleen, kidney, liver and testes affected.	Katz *et al* (1984)
	rats (COBS/CD/ (SD)BR)	inhalation	5 m/5 f	100 ppm 200 ppm 400 ppm 800 ppm	11 exp. (5 per wk)	Haemoglobinuria in females. Haemoglobinuria in females. Haemoglobinuria in females. Haemoglobinuria in males and females.	Katz *et al* (1984)

APPENDIX A: Systemic Toxic Effects

Compound	Species (Strain)	Route	Animals per dose level	Exposure conc. or dose	Time	Response	Reference
EGBE	rats (Fischer 344)	oral	≥ 5 m at ages 4-5, 9-13, 22-26 or 69 wk	32 mg/kg 63 mg/kg 125 mg/kg 250 mg/kg 500 mg/kg	single dose	Dose and age related erythrocyte haemolysis and haemoglobinuria, with all the oldest rats showing haemoglobinuria at 32 mg/kg and all the youngest rats at 250 mg/kg.	Ghanayem *et al* (1987a)
	rats (Fischer)	oral	24 m	500 mg/kg 1,000 mg/kg	4 d with 1, 4, 8 or 22 d recovery	↑ liver/spleen weights to d 8; bone marrow hyperplasia, splenic EMH (to d4); lymphocyte depletion of thymus (to d1). ↓ RBC, Hb and lymphocytes; ↑ MCV, MCH and reticulocytes. Slow recovery to d22. ↑ liver/spleen weights to d22, bone marrow hyperplasia; splenic EMH (to d4); lymphocyte depletion of thymus (to d1). ↓ RBC, Hb, Hct and lymphocytes; ↑ MCV, MCH, reticulocytes. Slow recovery to d22.	Grant *et al* (1985)
	rats (COBS CD)	oral	10 m	222 mg/kg 443 mg/kg 885 mg/kg	5 d/wk for 6 wk	↓ Hb and RBC; ↑ MCH. Splenic congestion. Minor histopathological changes. ↑ Relative liver weight. 1 death. ↓ Hb and RBC; ↑ MCV, MCH and MCHC. Haemoglobinuria. ↑ liver, spleen, kidney, heart and brain relative weights. ↑ serum ALP. Focal haemosiderin in liver and kidney pct. Splenic congestion. 2 deaths. Changes as for 443 mg/kg group plus ↑ serum ALT and ↓ glucose. No testicular effects.	Krasavage (1986)

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Compound	Species (Strain)	Route	Animals per dose level	Exposure conc. or dose	Time	Response	Reference
EGBE	rats (Fischer 344)	oral (gavage)	6 m (8-10 wk)	50, 100 or 200 mg/kg 400 mg/kg	2d	No significant effect in primary antibody response (plaque forming cell response to trinitrophenyl-lipopolysaccharide). 1 died, 1 moribund (200 mg/kg). All died.	Smialowicz *et al*, 1992
	rats (Fischer 344/N)	oral (drinking water)	8-10 m	3 or 6 mg/ml	55-65 d	2 groups ± leukaemic cell line at d0. No effect on leukaemia development. Haematototoxicity (no details) in controls.	Dieter *et al*, 1990
	rats (Sprague-Dawley)	oral (drinking water)	6 m 6 f	180 mg/kg 506 mg/kg 204 mg/kg 444 mg/kg	21 d	Dose related ↓ bw. No significant effect on weight of spleen, kidney, thymus, testis or liver. Slight ↑ NK cytotoxic reponse. ↓ water intake. No effect on IgG antibody production, delayed type hypersensitivity response, cytokine production or splenocyte numbers. ↓ bw. No significant effect on weight of spleen, kidney, thymus, or liver. Slight ↑ - NK cytotoxic response. ↓ water intake. No other effects.	Exon *et al*, 1991

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Compound	Species (Strain)	Route	Animals per dose level	Exposure conc. or dose	Time	Response	Reference
EGBE	rats (Fischer 344/N)	oral (drinking water)	5 m 5 f	13-346 mg/kg 77-265 mg/kg	14 d	Trend for ↓ water consumption. ↓ bw in top dose females. No chemical related gross lesions. No histopathological change in testes/epididymes (only tissues studied). No deaths.	NTP, 1992
			10 m 10 f	69-452 mg/kg 82-470 mg/kg	90 d 90 d	Dose related anaemia and erythrocyte haemolysis with liver, spleen, kidney and bone marrow effects associated with disposal/ renewal of erythrocytes. Dose related ↓ bw, ↓ thymus weight at top 2 doses (m) top dose (f). Uterine atrophy at top 2 doses (363/470 mg/kg). No deaths.	
			10 m	124-443 mg/kg	60 d, recovery to 90 d	↓ bw at d 60 and d 90 in top dose. No other significant effects.	
	rats (Fischer)	inhalation	8 m/8 f	20 ppm 86 ppm 245 ppm	6 h/d; 5 d + 4 d	No effects. ↓ body weight (f), Hb; ↑ MCV. ↓ body weight, RBC, Hb and MCHC; ↑ WBC, MCV, reticulocytes and nucleated erythrocytes.	Dodd *et al* (1983)
	rats (Fischer)	inhalation	16 m/16 f	5 ppm 25 ppm 77 ppm	6 h/d, 5 d/wk for 90 d	No effects. No effects. ↓ RBC, Hb and MCH.	Dodd *et al* (1983)
	rats (Wistar)	*i.v.*	4 m	25-62.5 mg/kg 75 mg/kg	single dose	No haemolysis. Some haemolysis	Bartnik *et al* (1987)
		dermal	6 m/6 f 3 f	200 mg/kg 260 mg/kg 320 mg/kg 375 mg/kg 500 mg/kg	single dose	No haemolysis. 2 serum haemolysis, 1 haemoglobinuria. 3 serum haemolysis, 3 haemoglobinuria. 1 serum haemolysis, 1 haemoglobinuria. 3 serum haemolysis, 1 haemoglobinuria.	

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Compound	Species (Strain)	Route	Animals per dose level	Exposure conc. or dose	Time	Response	Reference
EGBE	mice (ICL-ICR)	oral	5 m	500 mg/kg 1,000 mg/kg 2,000 mg/kg	5 d/wk for 5 wk	↓ RBC. ↓ RBC. Testicular atrophy (1/5), not considered significant. All animals died.	Nagano *et al* (1979, 1984)
	mice (Swiss CD-1)	oral (drinking water)	20 m/20 f	0.5% (approx. 700 mg/kg) 1% (approx. 1,300 mg/kg) 2% (approx. 2,100 mg/kg)	14 wk	1 f died. ↑ kidney (m/f) and liver (f) weights in F_1 animals. 6 f died. ↑ kidney (m/f) and liver (f) weights. ↓ body weight (f). 13 f died.	Heindel *et al* (1990)
	mice (B6C3F1)	oral (drinking water)	5 m 5 f 10 m 10 f	93-627 mg/kg 150-1364 mg/kg 118-694 mg/kg 185-1306 mg/kg	14 d 14 d 90 d 90 d	No biologically significant effects No biologically significant effects Slightly ↓ bw gain. No other biologically significant adverse effects. Slightly ↓ bw gain. No other biologically significant adverse effects.	NTP 1992
	guinea pigs	*s.c.*	3 f	0.1 ml/kg 0.5 ml/kg 1.0 ml/kg	single dose	No effects. No effects. No effects.	Unilever (1984e)
	rabbits (NZ white)	dermal	10 m/10 f	10 mg/kg 50 mg/kg 150 mg/kg	5 d/wk for 90 d	No effects. No effects. No effects.	Mayhew *et al* (1983)
EGBEA	rats (Wistar)	inhalation	10 m/10 f	100 ppm	4 h/d, 5 d/wk for 10 months	No effects.	Truhaut *et al* (1979)
	rats (Wistar)	inhalation	10 m/10 f	saturated vapour (400 ppm est)	4 h/d, 5 d/wk for 28 d	Slight haematuria and/or haemoglobinuria from week 2. No other effects.	Truhaut *et al* (1979)

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Compound	Species (Strain)	Route	Animals per dose level	Exposure conc. or dose	Time	Response	Reference
EGBEA	rabbits (NZ white)	inhalation	2 m/2 f	100 ppm	4 h/d, 5 d/wk for 10 months	No effects.	Truhaut *et al* (1979)
	rabbits (NZ white)	inhalation	2 m/2 f	saturated vapour (400 ppm est)	4 h/d, 5 d/wk for 28 d	Haematuria and/or haemoglobinuria from week 2. ↓RBC and Hb after 3 weeks, slightly (2) or severely (2). The latter 2 died in wk 4; kidneys were hypertrophic and swollen with blood; bladders were filled with blood.	Truhaut *et al* (1979)
BAA	rats (Sprague-Dawley)	oral	6 m	868 mg/kg	4 d (consecutive)	No effect on testes.	Gray *et al* (1985)
	rats (Wistar Alderley Park)	oral	24 m	174 mg/kg 434 mg/kg 868 mg/kg	single dose kills at 1, 2, 4, 14 d	No effect on reproductive organs. No effect on reproductive organs. Haematuria. No effect on reproductive organs.	Foster *et al* (1987)
EGPhE	rats (Fischer)	oral	3 f	1,250 mg/kg 2,500 mg/kg	7 d/wk for 2 wk	No red cell haemolysis; ↓ PCV in 1 animal. No red cell haemolysis.	Dow (1986)
	rats (Wistar)	oral (diet)	10 m/10 f	50 mg/kg 100 mg/kg 200 mg/kg 500 mg/kg (calculated 550 mg/kg)	7 d/wk for 4 wk	No significant effects. No significant effects. No significant effects. ↓ body weight gain; ↑ plasma ALP (m). No other significant effects.	Unilever (1991a)
	rats (Wistar)	oral (diet)	15 m/15 f 20 m/20 f (5 m/f recovery)	50 mg/kg 100 mg/kg 200 mg/kg 500 mg/kg	7 d/wk for 13 wk	No significant effects. No significant effects. No significant effects. ↓ food efficiency (m), present after 5 wk recovery. ↓ cholesterol, still present (m) after 5 wk recovery. ↓ serum protein (m), not present after 5 wk recovery. ↓ platelets, still present (f) after 5 wk recovery. ↓ hepatic parenchymal lipid (m), not present after 5 wk recovery. ↑ serum ALP (m).	Unilever (1991b)

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Compound	Species (Strain)	Route	Animals per dose level	Exposure conc. or dose	Time	Response	Reference
EGPhE	rats (CD)	oral	15 m/15 f	80 mg/kg 400 mg/kg 2,000 mg/kg	7 d/wk for 13 wk	No effects. ALP elevated (m) at wk 4, not wk 13. Some renal damage (m). Deaths (4 f). ↓ RBC (f wk 4, m/f wk 13), ↓ Hb/PCV (f wk 4, m/f wk 13), ↓ Hb/PCV (m/f wk 13). ↑ urea/glucose at wk 4, not wk 13. ↑ ALP/SGPT (m, wk 4), ↑ ALP (m, wk 13). ↑ urine volume, cells present. Renal damage (m/f). 4/15 m some testicular atrophy.	Nipa (1977)
	rats (Fischer 344/N)	oral (drinking water)	8-10 m	2.5, 5.0 or 10.0 mg/ml	55-65 d	2 groups, one ± leukaemic cell line at d 0. No effect on leukaemic development. Haematotoxicity (no details) in controls.	Dieter *et al*, 1990
	rats	inhalation	6 f	approaching saturation	4 h	No increase in osmotic fragility of erythrocytes.	Carpenter *et al* (1956)
	mice (ICL-ICR)	oral	5 m	500 mg/kg 1,000 mg/kg 2,000 mg/kg	5 d/wk for 5 wk	No significant effects on testes of vesicular and coagulating gland weights, RBC, PCV, Hb or white cell count. All died before examination.	Nagano *et al* (1979)
	mice (Swiss CD1)	oral (diet)	20 m/20 f	0.25% (400 mg/kg m) 1.25% (2,000 mg/kg m) 2.5% (4,000 mg/kg m)	14 wk	No effects observed. No effects in m, 1 f died. 2 f died. ↓ slight body weight (m) and liver weight.	Heindel *et al* (1990)
	rabbits (NZ white)	oral	3 f	800 mg/kg	1 dose	↑ erythrocyte fragility after 1h and 3h. Red urine. 2 animals had splenic congestion, erythrophagocytosis, Hb in renal tubules.	Breslin *et al* (1991)

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Compound	Species (Strain)	Route	Animals per dose level	Exposure conc. or dose	Time	Response	Reference
EGPhE	rabbits (NZ white)	oral	3 f	100 mg/kg	10 d (consecutive)	Slight ↓ in body weight, RBC, PCV and Hb. ↑ WBC, platelets, reticulocytes. Minor urinary changes. Slight erythroid hyperplasia, splenic extramedullary haematopoeisis	Breslin *et al* (1991)
				300 mg/kg		1 dead at d 10. Anorexia, lethargy. Slight ↓ in body weight, RBC, PCV, Hb, WBC and platelets; ↑ reticulocytes. Indication of renal tubule damage. Bone marrow erythroid hyperplasia, splenic necrosis (1 animal). Some necrosis of gastric glandular mucosa.	
				600 mg/kg		1 died, 2 killed (moribund) on days 3 and 6. Anorexia, lethargy, red urine. ↓ RBC, PCV, Hb; ↑ WBC, platelets and retoculocytes. Kidney/spleen dark and enlarged, renal tubule damage. Bone marrow erythroid hyperplasia, splenic congestion and erythrophagocytosis. Some necrosis of gastric glandular mucosa.	
				1,000 mg/kg		1 died, 2 killed (moribund) on day 2. Anorexia, lethargy, red urine. ↓ RBC, PCV and Hb; ↑ WBC and platelets. Kidney/spleen dark and enlarged, renal tubule damage. Splenic congestion and erythrophagocytosis. Some necrosis of gastric glandular mucosa.	

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Compound	Species (Strain)	Route	Animals per dose level	Exposure conc. or dose	Time	Response	Reference
EGPhE	rabbits (NZ white)	dermal	25 f (pregnant)	300 mg/kg 600 mg/kg 1,000 mg/kg	13 d (consecutive)	Occasional red skin at application site. 5 dead or moribund with haemoglobinuria, jaundice, dark kidneys. ↓ RBC, PCV and Hb. ↑ reticulocytes. Skin dark at application site (4 animals). 9 dead or moribund with haemoglobinuria, jaundice, dark kidneys. ↓ RBC, PCV and Hb. ↑ reticulocytes. Skin dark at application site (3 animals).	Scortichini *et al* (1987)
	rabbits (NZ white)	dermal	10 f	1,000 mg/kg	14 d (consecutive)	3 deaths, 4 moribund and killed after 5-8 applications. ↓ RBC, PCV and Hb in decendents. ↑ nucleated RBCs, reticulocytes and leukocytes. Skin dark at application site. Pale livers, dark kidneys/spleen. Haemoglobinuria.	Dow (1985)
	rabbits (NZ white)	dermal	10 m/10 f	50 mg/kg 150 mg/kg 500 mg/kg	6 h/d, 5 d/wk for 13 wk	No effects observed. No effects observed. Sporadic erythema/scaling at application site. No other effects.	Breslin *et al* (1991)
EGDME	rats (CFE)	inhalation	8-10 f	0 ppm 1,000 ppm 2,000 ppm 4,000 ppm 8,000 ppm	4 h/d, 5 d/wk for 10 exp. d	Dose dependent and progressive behavioural changes. Effects were reversible at low doses. ↓ growth in all treatment groups. Post exposure mortality in 8,000 and 4,000 ppm dose groups; surviving animals in these groups showed haemorrhaging of the lungs and GI-tract.	Goldberg *et al* (1964)
EGDEE	mice	inhalation	5	500 ppm	8 h/d for 12 d	No abnormalities reported.	Lehmann and Flury (1938)

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Compound	Species (Strain)	Route	Animals per dose level	Exposure conc. or dose	Time	Response	Reference
EGDEE	rabbits	oral	1	1.0 ml/kg (0.9 g/kg)	6 times within one wk	No signs of toxicity were noted (urine was not investigated).	Lehmann and Flury (1938)
	rabbits	inhalation	2	500 ppm	8 h/d for 12 d	1 animal died 10 days after the last exposure.	Lehmann and Flury (1938)
	guinea pigs	inhalation	1	500 ppm	8 h/d for 12 d	No abnormalities reported.	Lehmann and Flury (1938)
	guinea pigs	*s.c.* injection	?	0.5 ml/kg (400 mg/kg) 1.0 ml/kg (800 mg/kg)	7 injections	Marked weight loss; kidney injury (perenchylatous and interstial nephritis) was seen at necropsy. Death after 7 injections, preceded by narcosis and prostration.	Lehmann and Flury (1938)
	dogs	oral	1	1.0 ml/kg (900 mg/kg)	6 times within one wk	No signs of toxicity were noted (urine was not investigated).	Lehmann and Flury (1938)
	dogs	*s.c.* injection	2	9.5 ml/kg (7,600 mg/kg)	7 d	No adverse clinical signs. At necropsy, injury to vasculature, liver, brain, testes, and particularly to the kidney.	Wiley *et al* (1938)
	cats	oral	1	1.0 ml/kg (900 mg/kg)	4 times	Animal died within 2 days of last dose. Serious intoxication was noted after each dose.	Lehmann and Flury (1938)

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Compound	Species (Strain)	Route	Animals per dose level	Exposure conc. or dose	Time	Response	Reference
EGDEE	cats	inhalation	2	500 ppm	8 h/d for 12 d	Both animals died within 2 days of the last exposure. Microscopic kidney damage and, in one animal, purulent inflammation of the trachea.	Lehmann and Flury (1938)
DEGME	rats	oral	5	190-1,830 mg/kg (4 dose levels)	30 d	↓ growth at 1,440 mg/kg/d, inappetence at 740 mg/kg/d and unspecified micropathological changes seen at all dose levels. Damage to liver, kidneys and gastrointestinal tract. No mortality.	Smyth and Carpenter (1948)
	rats (Wistar)	oral	Dose response study: 4 m; (8 m control) Time course study: 4 m (8 m control)	0, 500, 1,000, 2,000 mg/kg 2,000 mg/kg	 1, 2, 5, 20 d	Time- and dose-dependent effects on relative organ weights. Effects on thymus, testes, spleen, liver and kidney. NOEL 500 mg/kg/d. Lymphocyte depletion in thymus.	Kawamoto *et al* (1990a)
	rats (Fischer 344)	inhalation (whole body)	10 m/10 f	0, 30, 100, 216 ppm,	6h/d, 5 d/wk for 13 wk	NOEL 216 ppm established. No adverse treatment related effects seen at any dose level.	Miller *et al* (1985a)
	mice (ICL-ICR)	drinking water	5 m	0, 2%	25 d	No adverse treatment-related effects. Study limited to examination of body weight, testis weight, seminal residue and coagulating gland weight, and mean WBC count.	Nagano *et al* (1984)
	guinea pigs (Hartley)	dermal (Undiluted occluded)	6 m; (7 m control)	0, 40, 200, 1,000 mg/kg.	6h/d 5 d/wk for 13 wk	No treatment related effects on body weight. ↓ spleen weights at 200 and 1,000 mg/kg/d. Fatty change in liver in all test treatment groups. NOEL not established.	Hobson *et al* (1986a)

APPENDIX A: Systemic Toxic Effects

Compound	Species (Strain)	Route	Animals per dose level	Exposure conc. or dose	Time	Response	Reference
DEGEE	rats	drinking water	5 or 10 m (13 controls) 5 or 9 f (8 controls)	1%	23 months	No apparent effects noted, incomplete assessment	Hanzlik *et al* (1947c)
	rats	drinking water	5 sex not specified	210 - 3,880 mg/kg/d	30 d	NOEL approx. 490 mg/kg/d. No mortalities. ↓ food intake and growth.	Smyth and Carpenter (1948)
	rats	inhalation	15 Sex?	1.5 and 25 mg/m3 continuous exposure	4 months, followed by recovery period	CNS effects, anaemia, changes in blood/clinical chemistry.	Krotov *et al* (1981)
	mice	diet	5-20 sex?	5%	21 months	No apparent effects noted, incomplete assessment.	Hanzlik *et al* (1947c)
	rabbits	dermal (100 cm3 uncovered, chipped skin)	3 sex not specified	20 - 490 mg/kg	1h/d for 30 d. 30 d recovery.	NOEL between ca. 40-80 mg/kg/d. Weight loss, CNS depression, kidney damage.	Hanzlik *et al* (1947b)
	rabbits	dermal (open)	Not specified	50 or 70% aqueous solution, continuous contact with open wound.	up to 23 d	No systemic injury, no effect on wound healing.	Cranch *et al* (1942)
	ferrets	diet	3 m 2 m	0, 0.5, 2.0, 3.0 ml/kg	9 months	NOEL 3.0 ml/kg/d. No adverse effects on weight gain, organ weights, haematology or histopathology.	Butterworth *et al* (1975)
	cats	oral	8	0, 300, 500, 1,000, 4,900 mg/kg as 20% v/v solution	2 - 52 d	NOEL approx. 300 mg/kg for 8 d. Mortalities at high dose after 2 d. Albuminuria, kidney damage in lower dose groups.	Walther (1942)

APPENDIX A: Systemic Toxic Effects

Compound	Species (Strain)	Route	Animals per dose level	Exposure conc. or dose	Time	Response	Reference
DGEE (<0.2% MEG)	rats	drinking water	8 m/8 f	0, 0.01, 0.04, 0.2, 1.0%	2 years	↓ weight gain, kidney damage.	Smyth *et al* (1964)
DEGEE (0.4% MEG)	rats (Wistar)	diet	12 m/12 f	0, 0.25, 1.0, 5.0% (Equivalent to approx. 0, 125, 500, 2,500 mg/kg)	90 d	NOEL approx. 500 mg/kg/d. ↓ weight gain, damage to liver, kidney and testes at high dose.	Hall *et al* (1966)
	rats	diet	20 m/20 m	0, and 2.16%	2 years	Testicular and liver tissue damage. A NOEL was not established.	Morris *et al* (1942)
	rats (CFE)	diet	15 m/25 f	0, 0.5, 5.0% (equivalent to approx. 0, 250 and 2,500 mg/kg).	90 d	NOEL approx. 250 mg/kg. ↓ weight gain, anaemia, kidney damage in high dose animals.	Gaunt *et al* (1968)
	mice (CD1)	diet	20 m/20 f	0, 0.2, 0.6, 1.8, 5.4% (equivalent to approx. 0, 300, 900, 2,800, 8,000 mg/kg).	90 d	NOEL approx. 900 mg/kg. ↓ RBC count; liver and kidney damage.	Gaunt *et al* (1968)
	pigs (Large white)	diet	3 m/3 f	167, 500, 1,500 mg/kg. Top dose reduced to 1,000 mg/kg after 3 wk of treatment	90 d	NOEL approx. 167 mg/kg/d. ↓ CNS, kidney and liver effects at the two high doses.	Gaunt *et al* (1968)
DEGEE (repurified)	rabbits	dermal	not specified	0, 100, 300, 1,000 mg/kg. Occluded.	5x/wk for 90 d	NOEL approx. 300 mg/kg/d. Kidney damage at high dose.	Drill (1950)
DEGBE	rats	oral	5 m/5 f	51 - 1,830 mg/kg	30 d	NOEL 51 mg/kg. Slight changes in liver, kidney spleen or testis at 650 mg/kg (no details of which organs were affected).	Smyth and Carpenter (1948)

APPENDIX A: Systemic Toxic Effects

Compound	Species (Strain)	Route	Animals per dose level	Exposure conc. or dose	Time	Response	Reference
DEGBE	rats (CD)	oral	25 m/25 f	250 mg/kg 500 mg/kg 1,000 mg/kg	60 d (m) or 14 d (f) consecutive prior to mating	No effects on male fertility. No effects on male fertility. No effects on male fertility. Small ↑ in post-implantation losses; small ↓ in implantation sites and delivered pups (not statistically significant);↓ in mean body weight of pups.	Procter and Gamble (1985)
	rats (CD)	oral	10 m	891 mg/kg 1,781 mg/kg 2,564 mg/kg	7 d/wk for 6 wk	No effects. ↓ RBC, Hb and MCHC; ↑ MCV and MCH. ↑ liver/spleen weight (relative and absolute). Spleen and kidney lesions. ↓ RBC, Hb and MCHC; ↑ MCV and MCH. ↑ liver/spleen weight (relative and absolute). Spleen and kidney lesions.	Gushow *et al* (1981)
	rats (Fischer)	oral	16 m	65 mg/kg 327 mg/kg 1,630 mg/kg	7 d/wk for 13 wk	slight ↑ liver weight, no other effects. slight ↑ liver/spleen weight, no other effects. slight ↑ liver weight; ↓ body weight. Very high mortality (dosing accidents).	Hobson *et al* (1986b)
	rats (Fischer)	oral	16 f	51 mg/kg 254 mg/kg 1,270 mg/kg	7 d/wk for 13 wk	slight ↓ lymphocytes, no other effects. slight ↓ lymphocytes, no other effects. slight ↓ lymphocytes, ↓ body weight. Very high mortality (dosing accidents).	Hobson *et al* (1986b)

APPENDIX A: Systemic Toxic Effects

Compound	Species (Strain)	Route	Animals per dose level	Exposure conc. or dose	Time	Response	Reference
DEGBE	rats (Fischer 344)	inhalation	15 m/15 f	2 ppm 6 ppm 18 ppm	6 h/d, 5 d/wk for 5 wk	No effects. Males: No effects Females: Slight increase of hepatocyte vacuolisation Males: No effects Females: Slight increase of hepatocyte vacuolisation	Gushow *et al* (1981)
	rats (Wistar)	s.c.	4 f (6-8 wk old) 8 f (6-8 wk old) 4 f (6-8 wk old) 4 f (13-14 wk old) 4 f (13-14 wk old) 4 f (13-14 wk old)	0.5 ml/kg 1.0 ml/kg 1.5 ml/kg 0.5 ml/kg 1.0 ml/kg 1.5 ml/kg	1 d 1 d 1 d 1 d 1 d 1 d	Lethargy, minor haematological changes. Lethargy, haemoglobinuria (1/8). ↓ RBC, Hb and PCV; ↑ MCV. Minor renal and hepatic changes. Lethargy for 24 hours. Haemoglobinuria (3/4) and ↑ urine volume. Markedly ↓ RBC, Hb and PCV; ↑ MCV and reticulocytes. ↑ RBC osmotic fragility. Liver, kidney and spleen changes. Lethargy, minor haematological changes. ↑ RBC osmotic fragility. Lethargy for 24 hours, haemoglobinuria (4/4). ↓ RBC, Hb, PCV (markedly); slightly ↓ WBC, reticulocyes. ↑ RBC osmotic fragility. Liver, kidney and spleen changes. Similar changes to those at 1.0 ml/kg.	Unilever (1987b)
	rats (Sprague-Dawley)	dermal	12 m/12 f (2 studies)	0.2 ml/kg 0.6 ml/kg 2.0 ml/kg	6h/d, 5d/wk, 13 wk	No systemic or neurotoxic effects. No systemic or neurotoxic effects. Renal tubular epithelium degeneration in 2 m. No other systemic or neurotoxic effects.	Beyrouty *et al* (1993)

APPENDIX A: Systemic Toxic Effects

Compound	Species (Strain)	Route	Animals per dose level	Exposure conc. or dose	Time	Response	Reference
DEGBE	rats (CD)	dermal	10 m/10 f	200 mg/kg 666 mg/kg 2,000 mg/kg	6h/d, 5d/wk, 13 wk	No effects. Transient haematuria (1f). No other effects. Transient haematuria (1f). No other effects.	Auletta *et al* (1993)
	guinea pigs	*s.c.*	3 f	0.1 ml/kg 0.5 ml/kg 1.0 ml/kg	1 d (killed at d 5)	No effects. No effects. No effects.	Unilever (1984e)
	rabbits (NZ white)	dermal	3 m/3 f	2 ml/kg	5 d/wk for 4 wk	No effects.	Procter and Gamble (1985)
DEGBEA	rabbits	dermal	not reported	0.5 - 3.9 g/kg	7 d/wk for 13 wk	Dose related erythrocyte haemolysis, renal damage and haemoglobinuria. 50% mortality at 2-3 g/kg/d. NOEL not reported. No gross skin irritation.	Draize *et al* (1944, 1948)
DEGDME	rats (Crt:CD (SD)BR)	oral	90 m	0, 684 mg/kg	Daily up to 20 d. Animals (5m/group sacrificed at 2 day intervals during dosing, and at weekly intervals to 8 weeks post exposure.	Primary and secondary spermatocyte degeneration and spermatidic giant cells were observed after 6-8 treatments. ↓ testes to bodyweight ratio by 10th day of treatment, continued to be depressed 8 weeks post exposure. Testicular LDH-X activity, a pachytenespermatocyte marker enzyme, was decreased in animals by 18th day of treatment.	Cheever *et al* (1989a)
	rats (Alderley Park)	inhalation	4 m /4 f	0 ppm 200 ppm 600 ppm	15 x 6 h exposures	- NOEL (Uncertainty whether test wre examined); no toxic signs, blood and urine tests normal; autopsy; organs normal. Irregular ↑ weight; blood and urine tests normal; autopsy: atrophied thymus, congested adrenal.	Gage (1970)

APPENDIX A: Systemic Toxic Effects

Compound	Species (Strain)	Route	Animals per dose level	Exposure conc. or dose	Time	Response	Reference
DEGDME	rats (Crl:CDBR)	inhalation (nose only)	20 m	0 ppm 3.1 ppm 9.9 ppm 30 ppm 98 ppm	6 h/d, 5 d/wk for 2 wk. 10 rats/group necropsied immediately, 10 rats/group were maintained for a recovery period of 2 wk.	- No effects. No effects. NOEL. ↓ body weight and some lower doses, not considered compound-related. Testicular atrophy both immediately post exposure and after 2 wk.	Dupont, (1988b)
	rats (Crl: CDBR)	inhalation (nose only)	20 m	0, 110, 370, 1,100 ppm	6 h/d, 5 d/wk. Positive control group exposed to EGME at 300 ppm. Necropsies performed at 2 wk (end of exposure) and at 14, 42, 84 d post exposure.	Testicular atrophy affecting all stages of spermatogenesis at 1,100 ppm DEGDME and 300 ppm EGME. Some reversibility of response seen. Testicular effects at lower DEGME doses less marked. A NOEL not established.	Lee *et al* (1989)
DEGDEE	rats (Alderley Park)	inhalation	4 m	400 ppm (saturated atmosphere)	17 x 17 h exposure	Restlessness, organs normal at necropsy.	Gage (1970)
TEGME	rats	drinking water	15 m/15 f	400 mg/kg 1,200 mg/kg 4,000 mg/kg	90 d	↑ liver weight. Testicular atrophy. ↓ food intake, and body weight ↑ liver weight. ↓ food intake and body weight. ↓ motor activity. ↑ liver weight.	Gill and Negley (1990)
	rats (Wistar Alderley Park)	dermal (occluded)	5 m/5 f	1,000 mg/kg	6 h/d for 21 d	Slight local irritation.	Leber *et al* (1990)

APPENDIX A: Systemic Toxic Effects

Compound	Species (Strain)	Route	Animals per dose level	Exposure conc. or dose	Time	Response	Reference
TEGME	rats (Sprague-Dawley)	dermal (occluded)	10 m/10 f	400 mg/kg 1,200 mg/kg 4,000 mg/kg	6 h/d, 5 d/wk for 13 wk	No effect. No effect. Local irritation.	Corley *et al* (1990)
TEGEE	rats	oral (drinking water)	10 sex?	180 mg/kg 750 mg/kg 3,300 mg/kg 13,290 mg/kg	30 d	No effect. No effects. ↓ bw; liver and kidney injury. Lethality.	EPA (1985)
	rabbits (New Zealand White)	dermal	5 m/5 f	1,000 mg/kg	6 h/d for 21 d	Slight edema and erythema at site of application. No systemic effects.	Leber *et al* (1990)
TEGBE	rabbits (New Zealand White)	dermal	5 m/5 f	1,000 mg/kg	6 h/d for 21 d	Slight edema and erythema at site of application. No systemic effects.	Leber *et al* (1990)
2PG1ME	rats (Wistar)	inhalation	10 m	200 ppm 600 ppm	6 h/d for 10 d	No effects. No effects.	Doe *et al* (1983)
	rats (Fischer 344)	inhalation	5 m/5 f 5 m/ 5 f 10 m/ 10 f	300 ppm 1,000 ppm 3,000 ppm	6 h/d for 9 d	No effects. No effects. ↓ CNS, ↑ liver weight.	Miller *et al* (1981)
	rats (CFE)	inhalation	8-10 f	2,500 ppm 5,000 ppm 10,000 ppm	4 h/d, 5 d/wk for 2 wk	No effects. ↓ behaviour, ↑ tolerance. ↓ behaviour, ↑ tolerance. ↓ growth rate	Goldberg *et al* (1964)

APPENDIX A: Systemic Toxic Effects

Compound	Species (Strain)	Route	Animals per dose level	Exposure conc. or dose	Time	Response	Reference
2PG1ME	rats (Fischer 344)	inhalation	10 m/10 f	300 ppm 1,000 ppm 3,000 ppm	6 h/d, 5 d/wk for 13 wk	No effects. No effects. ↓ CNS; ↑ liver weight; hepatocellular hypertrophy.	Landry *et al* (1983)
	mice (B6C3F1)	inhalation	5 m/5 f 5 m/5f 10 m 10 f	300 ppm 1,000 ppm 3,000 ppm 3,000 ppm	6 h/d for 9 d	No effects. No effects. No effects. ↑ liver weight.	Miller *et al* (1981)
	rabbits (New Zealand White)	inhalation	7 m/7 f	300 ppm 1,000 ppm 3,000 ppm	6 h/d, 5 d/wk for 13 wk	No effects. No effects. ↓ CNS.	Landry *et al* (1983)
	rabbits (New Zealand White)	dermal	5 m/5 f	1,000 mg/kg	daily; 5 d/wk for 3 wk	Slight local effects.	Calhoun *et al* (1984)
2PG1MEA	rats (Fischer 344)	inhalation	5 m/5 f	300 ppm 1,000 ppm 3,000 ppm	6 h/d, 9 exp./11 d	No effects. ↑ Granularity of kidney tubular cells (m). ↑ Relative liver weight, granularity of kidney tubular cells (m); degenerative changes in olfactory mucosa (m).	Miller *et al* (1984)
	mice (B6C3F1)	inhalation	5 m/5 f	300 ppm 1,000 ppm 3,000 ppm	6 h/d, 9 exp./11d	1 (f), olfactory mucosa replaced by respiratory mucosa in nose. All (m) and (f), olfactory mucosa replaced by respiratory mucosa in nose. All (m) and (f) olfactory mucosa replaced by respiratory mucosa in nose	
2PG1EE	rats	oral	6 m/6 f	2 ml/kg	10 d	Slight ↑ in liver weight. Minor blood effect males only.	BP (1983d)

APPENDIX A: Systemic Toxic Effects

Compound	Species (Strain)	Route	Animals per dose level	Exposure conc. or dose	Time	Response	Reference
2PG1EE	rats	inhalation (nose only)	6 m/6 f	1,400 mg/m^3 8,900 mg/m^3	6 h/d for 9 d	No effect. Sedation. Slight ↑ liver weight.	BP (1983e)
	rats	inhalation (whole body)	15 m/15 f	100 ppm 300 ppm 2,000 ppm	6 h/d, 5 d/wk for 13 wk	No effects. Slight ↑ in urine volume. Irritation of eyes and nose. Slight ↑ in liver weight and slight in urine volume.	BP (1986b)
2PG1EEA	rats	inhalation	5 m/5 f	102 ppm 292 ppm 1,176 ppm	6 h/d, 5 d/wk 28 d	No effects. No effects. Sedation.	BP (1986h)
2PG1BE	rats (Sprague-Dawley)	oral	6 m/6 f	100 mg/kg 200 mg/kg 400 mg/kg	daily once 14 d	No effects. No effects. No effects.	Debets and Verschuuren (1987)
	rats (Fischer 344)	drinking water	10 m/10 f	100 mg/kg 350 mg/kg 1,000 mg/kg	daily 13 wk	No effects. No effects. Inpalatability of water, ↓ water and food consumption and body weights, secondary alterations in clinical parameters. ↑ liver (m) and kidney (f) weights without histopathologic alterations.	Grandjean *et al* (1992)
	rats (Wistar)	dermal	10 m/10 f	88 mg/kg 264 mg/kg 880 mg/kg	5 times/wk for 13 wk	Only local effects. Only local effects. Only local effects. No systemic effects.	Jonker *et al* (1988)
	rats (Fischer 344)	inhalation	5 m/5 f	50 ppm 200 ppm 700 ppm	6 h/d, 9x, 2 wk	No effects. No effects. ↑ liver weight without histopathologic lesions or changes in clin. chem. parameters.	Corley *et al* (1989b)

APPENDIX A: Systemic Toxic Effects

Compound	Species (Strain)	Route	Animals per dose level	Exposure conc. or dose	Time	Response	Reference
2PG1BE	rats	inhalation	6m 6 f	600 ppm	7 h/d, 5 d/wk for 31 d	No effects. ↑ liver weight (f).	Pozzani and Carpenter (1965)
	rats (Fischer 344)	inhalation	10 m/10 f	10 ppm 100 ppm 300 ppm 600 ppm	6 h/d, 5 d/wk, 9 exposure d	No effects. No effects. No effects. ↑ liver weight without histopathologic lesions. Low incidence of mild eye lesions	Klonne *et al* (1989)
	rats (Sprague-Dawley)	inhalation	10 m/10 f	10 ppm 100 ppm 300 ppm 600 ppm	6 h/d, 5 d/wk; 9 exposure d	No effects. No effects. No effects. No effects.	Klonne *et al* (1989)
	rabbits (New Zealand)	dermal	5 m/5 f	11.4 mg/kg 114 mg/kg 1,140 mg/kg	7 h/d, 5 d/wk for 13 wk	Only local effects. Only local effects. Only local effects. No systemic effects.	Innis *et al* (1990)
2PG1PhE	rabbits	percuta-neous	10 f	1,000 mg/kg	7 d/wk for 2 wk	No effects.	Phillips *et al* (1985)
	rabbits	percuta-neous	5 m/5 f	100 mg/kg 300 mg/kg 1,000 mg/kg	5 d/wk for 4 wk	No effects. No effects. No effects.	Calhoun *et al* (1986c)
1PG2ME	rats (Wistar)	gavage	5 m	1,800 mg/kg	10 d	↓ numbers of erythrocytes and Hb. No testicular effects, no leukopenia. (EGEE equimolar level as positive control).	BASF (1982)
1PG2MEA	rats (Wistar)	gavage	5 m	2,600 mg/kg	10 d	No effects.	BASF (1982)

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Compound	Species (Strain)	Route	Animals per dose level	Exposure conc. or dose	Time	Response	Reference
1PG2MEA	rats	inhalation	5 m/5 f	110 ppm 560 ppm 2,800 ppm	4 wk	No effects. No effects. Slight ↓ in liver and thymus weight; ↑ adrenal weight; ↓ blood glucose; ↑ serum albumin; ↓ thromboplastin time; ↓ serum urea; ↑ AP activity. Some clinical parameters supportive of liver damage.	BASF (1984c)
	rats	inhalation	5 m/5 f	50 ppm 140 ppm 330 ppm	6 h/d, 7 d over 9 d period	↑ liver weight (m).	Landry *et al* (1981)
	rats	inhalation	7 m/f 2 m/f 10 m/f	15 ppm 50 ppm 200 ppm	6 h/d, 5 d/wk for 13 wk	No effects. No effects. No effects.	Landry and Yano (1984)
	rats	inhalation	20 m/20 f	300 ppm	14 d/7 h exp. over 200 d	Slight narcosis; ↑ in liver weight.	Rowe *et al* (1954)
DPGME	rats	*ip*	5 f	1,000 mg/kg	5 d/wk for 2 wk	No effects.	Bernard *et al* (1989)
	rats	dermal (open) dermal (occluded)	8 8	100 mg/kg (open) 1,100 mg/kg (open) 100 mg/kg (occl) 1,100 mg/kg (occl)	5 d/wk for 4 wk	No effects. No effects. No effects. No effects.	Fairhurst *et al* (1989)

APPENDIX A: Systemic Toxic Effects

Compound	Species (Strain)	Route	Animals per dose level	Exposure conc. or dose	Time	Response	Reference
DPGME	rats	inhalation	5 m/5 f	50 ppm 140 ppm 330 ppm	6 h/d, 7 d 9 d period	No effects. No effects. No effects.	Landry *et al* (1981)
	rats	inhalation	7 m/f 2 m/f 10 m/f	15 ppm 50 ppm 200 ppm	6 h/d, 5 d/wk for 13 wk	No effects. No effects. No effects.	Landry and Yano (1984)
	rabbits	inhalation	2 m/2 f	300 ppm	156 x 7 h over 221 d	No significant effects.	Rowe *et al* (1954)
	rabbits	dermal	5	1 ml/kg 2 ml/kg 3 ml/kg 4 ml/kg 5 ml/kg 7 ml/kg 10 ml/kg	5 d/wk for 90 d	No effects. No effects. No effects. No effects. No effects. No effects. Narcosis, death.	Rowe *et al* (1954)
	guinea pigs	inhalation	8 m/8 f	300 ppm	130 x 7 h over 184 d	No significant effects.	Rowe *et al* (1954)
	monkeys	inhalation	1 m/1 f	300 ppm	156 x 7 h over 221 d	No significant effects.	Rowe *et al* (1954)
DPGEE	rats (Sprague-Dawley)	oral	5 m/5 f	50 mg/kg 225 mg/kg 1,000 mg/kg	28 d	No effects. Hyaline droplet accumulation in kidney (m). ↑ in liver weight. Hyaline droplet accumulation in kidney (m).	BP (1990b)
TPGME	rats (Fischer 344)	inhalation (aerosol)	5 m/5 f	0.15 mg/l 0.36 mg/l 1.01 mg/l	6 h/d, 9 d/2wk	↑ in liver weight at all dose levels. No gross or histopathologic changes in the liver. No changes in testes or haematology nor any other systemic effects (for both species).	Miller *et al* (1985b)

APPENDIX A: Systemic Toxic Effects

Compound	Species (Strain)	Route	Animals per dose level	Exposure conc. or dose	Time	Response	Reference
TPGME	mice (RGC3F1)	inhalation (aerosol)	5 m/5 f	0.15 mg/l 0.36 mg/l 1.01 mg/l	6 h/d, 9 d/2wk	↑ in liver weight at all dose levels. No gross or histopathologic changes in the liver. No changes in testes or haematology nor any other systemic effects (for both species).	Miller *et al* (1985b)
	rabbits	percuta-neous	> 5 m	965 mg/kg 2,895 mg/kg 4,825 mg/kg 9,650 mg/kg	5 d/wk for 13 wk	Kidney injury. Kidney injury. Kidney injury; narcosis. Kidney injury; narcosis resulting in deaths in 7/8 animals.	Rowe *et al* (1954)

APPENDIX B: Reproduction and Developmental Studies

Compound	Species (strain)	Route	Animals per dose level	Exposure conc. or dose	Time	Response	Reference
EGME	rats (Fischer 344)	oral (gavage)	20 m mated to 40 untreated f	50 mg/kg 100 mg/kg 200 mg/kg	5 d	≥ 100 mg/kg ↓ of fertility index and viable offspring.	Chapin *et al*, (1985a)
	rats (Sprague-Dawley)	oral (drinking water)	20 m-20 f	0.01% 0.03% 0.1%	2 gen. study 22 wk	↓ number of viable offspring in F_1. ↓ number of viable offspring in F_0. marginal fertility in F_0.	Gulati (1990a)
	rats (Sprague-Dawley)	oral (drinking water)	20 m-20 f	0.006% 0.012% 0.024%	2 gen. study 20 wk	No effects. No effects. ↓ number of viable litter in F_0 and F_1.	Gulati (1990b)
	rats (Sprague-Dawley)	oral (liquid diet)	10-12 9 10	0.0% 0 mg/kg 0.006% 16 mg/kg 0.012% 31 mg/kg 0.025% 73 mg/kg 0.05% 140 mg/kg 0.1% 198 mg/kg 0.25% 290 mg/kg 0.5% 620 mg/kg 0.025% plus ETOH 0.05% plus ETOH	g.d. 7-18	- NOAEL. Skeletal and cardiovascular malformation rate 4% among survivors. Malformation rate 40%. 100% resorption. 100% resorption. 100% resorption. 100% resorption. 1% malformations. 25% malformations.	Nelson *et al*, (1989)
	rats (Sprague-Dawley)	oral	13 f 40 f	25 mg/kg 25 mg/kg 50 mg/kg 75 mg/kg	g.d. 7-13 or 13-19 g.d. 6-12	No effects. No effects. ↑ foetotoxicity. ↑ foetotoxicity.	Toraason *et al*, (1986)
	rats (Wistar)	oral	6 f (13 in control)	158 mg/kg 315 mg/kg	g.d. 12	19.3% foetal death; 45.2% malformations 15.1% foetal death; 100% malformations	Ritter *et al*, (1985)

APPENDIX B: Reproduction and Developmental Studies

Compound	Species (strain)	Route	Animals per dose level	Exposure conc. or dose	Time	Response	Reference
EGME	rats (Sprague-Dawley)	oral	8 f (11 in control)	25 mg/kg 50 mg/kg 100 mg/kg	g.d. 7-13 and 9-15	↑ foetuses with aberrant QRS complexes. Cardiovascular defects. 100% resorption.	Toraason *et al*, (1985)
	rats (Sprague-Dawley)	inhalation	11-38 f	50 ppm 100 ppm 200 ppm	g.d. 7-15 (7 h/d)	↑ malformation and fetotoxicity. ↑ malformation and fetotoxicity. No litters.	Nelson *et al*, (1984b)
	rats (Wistar)	inhalation	20 f	100 ppm 300 ppm	g.d. 6-17 (6 h/d) then litters delivered	↓ prolonged gestation and number of pups and live pups. ↓ maternal body weight gain; 100% embryonic death.	Doe *et al* (1983)
	rats (Sprague-Dawley)	inhalation	15-18 f	25 ppm	g.d. 7-13 or 14-20 (7 h/d)	Significant differences in avoidance conditioning of offspring from mothers exposed on g.d. 7-13; neurobehavioral deviations in offspring.	Nelson *et al*, (1984a)
	rats (Fischer)	inhalation	30-31 f	3 ppm 10 ppm 50 ppm	g.d. 6-15	no effects. no effects. Minor skeletal variations.	Hanley *et al*, (1984a,c)
	rats (Wistar)	i.p.	11	5 mM/kg	g.d. 12	28% resorptions; 86/87 foetuses showed limb malformations; 11% ventral duplication of handlimb digits.	Scott *et al*, (1987)
	rats (Wistar)	dermal	10 f	3% 10% 30% 100% (solutions at 10 ml/kg)	g.d. 6-17 (6 h/d)	No effects. ↓ litter sizes. Foetal deaths. Maternal death rate: 100%.	Wickramaratne (1986)
	rats (Sprague-Dawley)	dermal (occlusive)	20 m mated to untreated f	625 mg/kg 1,250 mg/kg 2,500 mg/kg	5 d	↓ of testicular weight and sperm numbers: ↓ fertility for all doses	Feuston *et al*, (1989)

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Compound	Species (strain)	Route	Animals per dose level	Exposure conc. or dose	Time	Response	Reference
EGME	rats (Sprague-Dawley)	dermal (undiluted; non-occlusive)	8-10 f	250 mg/kg 500 mg/kg 1,000 mg/kg 2,000 mg/kg	g.d. 12 g.d. 10, 11, 12, 13, or 14	No effects. ↓ maternal body weight gain; ↑ external, visceral, or skeletal malformations. ↓ maternal body weight gain; external visceral or skeletal malformations; ↓ foetal weights. ↑ resorptions and mean percentage resorptions (g.d. 10); ↓ foetal weights (g.d. 10 and 12).	Feuston *et al* (1990)
	rats (Wistar)	dermal (occluded) 6 h/d	45-50	0.5 ml/kg 0.8 ml/kg 1.0 ml/kg 0.3 ml/kg 0.1 ml/kg 0.05 ml/kg	d 6-15 p.c.	↓ maternal body weight, no litters, 100 % resorption. ↓ maternal body weight, no litters, 100 % resorption. ↓ maternal body weight, no litters, 100 % resorption. 99.4% postimplantation losses, 5 malformed. foetuses 26.5% postimplantation losses, ↑ malformations; ↓ maternal weight gain. ↑↑ malformation: feto- and embryotoxicity; no maternal effects.	Hellwig, (1993)
	mice (ICL-ICR)	oral	21-24 f	31.25 mg/kg 62.5 mg/kg 125 mg/kg 250 mg/kg 500 mg/kg 1,000 mg/kg	g.d. 7-14	Skeletal malformations. Skeletal malformations. Skeletal malformations. Gross anomalies and skeletal malformations (≥250 mg/kg embryonic death. Embryonic death. Up to 100% death.	Nagano *et al* (1984)
	mice (CD-1)	oral	30 f	1,400 mg/kg	g.d. 7-14	100% embryonic death.	Schuler *et al* (1984)

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Compound	Species (strain)	Route	Animals per dose level	Exposure conc. or dose	Time	Response	Reference
EGME	mice (CD-1)	oral	9-12 f	250 mg/kg 250 or 500 mg/kg	g.d. 7-14, 7-9, 8-10, or 9-11 g.d. 7-8, 9-10, 10-11, 12 or 13	Exencephaly and paw lesions; ↓ foetal weights; embryo-lethality in all dosage groups except single 500 mg/kg on g.d. 12 or 13.	Horton *et al* (1985)
	mice (CD-1)	oral	9-11 f (16 in control)	100 mg/kg 175 mg/kg 250 mg/kg 300 mg/kg 350 mg/kg 400 mg/kg 450 mg/kg	g.d. 11	NOAEL. Digit anomalies in all doses above 175 mg/kg.	Horton *et al* (1985)
	mice (CD-1)	oral	9-12 f	250 mg/kg	several intervals between g.d. 7-14 (sacrifice g.d. 18)	Gross malformations (exencephaly and paw lesions).	Horton *et al* (1985)
	mice (CD-1)	oral	16 f	4 mmol/kg (304 mg/kg);	g.d. 11 (sacrifice g.d. 18)	No maternal toxicity; paw malformations (68.5% of foetuses in 87.5% of litters).	Hardin and Eisenmann (1987)
	mice (CD-1)	oral	2-3 f per time point	100 mg/kg 250 mg/kg 350 mg/kg	g.d. 11, then sacrificed 2, 6, 24, or 48 h later and embyros removed	No effects. No effects. No maternal toxicity; forelimb - bud cytotoxicity as early as 2 h post EGME treatment, with maximum effect at 6 h.	Greene *et al* (1987)
	mice (CF-1)	oral	16-18 f	100 mg/kg 175 mg/kg 250 mg/kg 300 mg/kg 350 mg/kg 400 mg/kg 450 mg/kg 500 mg/kg	g.d. 11, and embryos removed 6 or 24 h later	No effects. Paw malformations induced in dose-dependent manner (175-500 mg/kg).	Greene *et al* (1987)

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Compound	Species (strain)	Route	Animals per dose level	Exposure conc. or dose	Time	Response	Reference
EGME	mice (CD-1)	oral (drinking water)	30 m-30 f	0.03% 0.1% 0.3%	2 gen. study 18 wk	↓ number of viable litter in F_1. No fertility in F_1. No fertility in F_0.	Gulati *et al* (1988a)
	mice (CD-1)	oral (drinking water)	20 m-20 f	0.1% 0.2% 0.4%	2 gen. study 18 wk	↓ number of viable offspring. Marginal fertility in F_1. Marginal fertility in F_0; no viable litters.	Gulati *et al* (1985a)
	mice (CD-1)	oral (drinking water)	20 m-20 f	0.5% 1.0% 2.0%	98 wk continuous breeding	Fertility index 0%.	Gulati *et al* (1985b)
	mice (CF-1)	inhalation	30-32 f	0 ppm 10 ppm 50 ppm	g.d. 6-15 (sacrificed g.d. 18)	- No effects Slight foetotoxicity; minor skeletal variations.	Hanley *et al* (1984a,c)
	rabbits (New Zealand)	inhalation	29-30 f	3 ppm 10 ppm 50 ppm	g.d. 6-18	No effects. NOEL. ↓ maternal body weight gain; ↑ absolute liver weight; ↑ resorptions; ↓ foetal body weight; ↑ skeletal and visceral malformations.	Hanley *et al* (1984a,c)
	monkey (Macaca fascicu-laris)	oral	8-14 f (6 in control)	12 mg/kg 24 mg/kg 36 mg/kg	g.d. 20-45	Embryonic death : - 3/13 (23%) - 3/10 (30%) - 8/8 (100%) 1 embryo was missing one digit on each forelimb.	Scott *et al* (1989)
EGMEA	mice (CD-1)	gavage	49 f	1,225 mg/kg	g.d. 6-13	In 31 litters no viable foetuses.	Hardin *et al* (1987) NTIS (1984)
MAA	rats (Wistar)	oral	8 f	0.16 mg/kg 0.32 mg/kg	g.d. 12	4; 15.1; 53.8% resorptions. 0; 53.1; 98.9% malformed foetuses.	Ritter *et al* (1985)

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Compound	Species (strain)	Route	Animals per dose level	Exposure conc. or dose	Time	Response	Reference
MAA	rats (Wistar)	*i.p.*	8-10 f	225 mg/kg	g.d. 8, 10, 12 or 14	d 8: 93% foetal mortality. d 10: 61% foetal mortality. d 12: 92.5% malformations.	Brown *et al* (1984)
			5 f	9-225 mg/kg	g.d. 10 or 12	Dose-dependent teratogenic response at all dose levels.	
	mice (CD-1)	oral (drinking water)		0.1% 0.2% 0.4%	2 generations	↓ litters, foetal weights and viable foetuses (all exposures). No pregnancies.	NTP (1986)
EGEE	rats	oral (drinking water)	no details reported	0 mg/kg 210 mg/kg 270 mg/kg 400 mg/kg 550 mg/kg	g.d. 1-21	- No maternal toxicity. Embryomortality 31%. Embryomortality 69%; ↓ foetus weight. Delayed development of foetuses. Embryo mortality.	Chester *et al* (1986)
	rats	oral (gavage)	20-39 f	0 mg/kg 12 mg/kg 23 mg/kg 46 mg/kg 93 mg/kg 186 mg/kg 372 mg/kg	g.d. 1-21	- No effects. NOEL. ↓ number of foetuses and implantations. ↑ skeletal variations (21%). ↑ skeletal variations (90%). -	Stenger *et al* (1971)
	rats	oral (gavage)	no details reported	200 mg/kg	g.d. 7-9 g.d. 10-12 g.d. 13-15 g.d. 7-15	5 %) 11 %) cardiovascular abnormalities. 1 %) ↓ foetal weight. 24 %) ↑ prenatal mortality.	Goad and Cranmer (1984)

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Compound	Species (strain)	Route	Animals per dose level	Exposure conc. or dose	Time	Response	Reference
EGEE	rats	inhalation (whole body)	24 f	0 mg/m3 37 mg/m3 187 mg/m3 935 mg/m3	g.d. 6-15 (6 h/d)	- No effects. No effects. ↓ Hb and Hct; ↑ skeletal variations.	Doe (1984a) Tinston *et al* (1983a)
	rats	inhalation (whole body)	2-6 f	1,122 mg/m^3 2,244 mg/m^3 3,366 mg/m^3 4,488 mg/m^3	g.d. 7-13 (7 h/d)	No resorption, no foetomortality; 9 resorptions + 3 life pups/dam; 100 % postimplanational losses.	Nelson *et al* (1981)
	rats	inhalation (whole body)	2-6 f	0 mg/m^3 748 mg/m^3 1,122 mg/m^3 2,244 mg/m^3 3,366 mg/m^3 4,488 mg/m^3	g.d. 14-20 (7 h/d)	- ↑ postnatal mortality. ↑ postnatal mortality. Postnatal mortality (100 %).	Nelson *et al* (1981)
	rats	inhalation (whole body)	35-38 f	0 mg/m^3 755 mg/m^3 2,869 mg/m^3	3 weeks preexposure and/or g.d. 1-19 (7 h/d)	- No effect on female fertility. No effect on female fertility. ↑ of skeletal variations and cardiovascular malformations.	Andrew and Hardin (1984)
	rats	dermal	25 f	0 mg/kg 3,445 mg/kg 6,889 mg/kg	g.d. 7-16	- ↓ of live foetuses/litter; ↓ of foetal body weight. ↑ of skeletal variations and cardiovasular malformations. Embryomortality 100%.	Hardin *et al* (1982)
	rats	dermal	18 f	3,875 mg/kg	g.d. 7-16	Skeletal, cardiovascular, renal malformations.	Hardin *et al* (1984)

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Compound	Species (strain)	Route	Animals per dose level	Exposure conc. or dose	Time	Response	Reference
EGEE	rats	*s.c.*	20 f	0 mg/kg 23 mg/kg 46 mg/kg 93 mg/kg	g.d. 1-21	- No effects. No effects. ↑ skeletal variations.	Stenger *et al* (1971)
	mice (CD-1)	oral (drinking water)	40 m/40 f	0 mg/kg 800 mg/kg 1,500 mg/kg 2,600 mg/kg	g.d. 8-14	- Dose related ↑ of testicular atrophy (m). No effects on female fertility.	Wier *et al* (1987)
	mice (CD-1)	oral (gavage)	50 f	0 mg/kg 3,605 mg/kg	g.d. 7-14	- 100% postimplantational losses.	Schuler *et al* (1984)
	mice (CD-1)	oral (gavage)	6 f	0 mg/kg 1,000 mg/kg 1,800 mg/kg 2,600 mg/kg 3,400 mg/kg 4,200 mg/kg	g.d. 8-14	- ↑ postimplantational losses. ↑ teratogenic effects. (Exencephaly, cleft palate). ↑ teratogenic effects. (Exencephaly, cleft palate). ↑ teratogenic effects. (Exencephaly, cleft palate). 100 % Embryolethality.	Wier *et al* (1987)
	mice (CD-1)	oral (gavage)	20 f	0 mg/kg 800 mg/kg 1,200 mg/kg	g.d. 8-14	- ↓ number of life pups; ↓ birth weight of foetuses. ↑ number of pups with kinked tail.	Wier *et al* (1987)
	mice (Swiss)	*s.c.*	22 f	0 mg/kg 46 mg/kg	g.d. 1-18	- No effects.	Stenger *et al* (1971)
	rabbits	inhalation (whole-body)	24 f	0 mg/m3 37 mg/m3 187 mg/m3 655 mg/m3	g.d. 6-18 (6 h/d)	- No effects. No effects. ↑ of skeletal variations.	Doe (1984a) Tinston *et al* (1983b)

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Compound	Species (strain)	Route	Animals per dose level	Exposure conc. or dose	Time	Response	Reference
EGEE	rabbits	inhalation (whole -body)	29 f	0 mg/m3 598 mg/m3 2,308 mg/m3	g.d. 1-18	- ↑ of skeletal variations and cardiovasular malformations. Embryo mortality 100 %.	Andrew and Hardin (1984)
	rabbits	*s.c.*	15 f	0 mg/kg 23 mg/kg	g.d. 7-16	- No effects.	Stenger *et al* (1971)
EGEEA	rats (Sprague-Dawley)	inhalation (whole body)	9-20 f	0 mg/m^3 715 mg/m^3 2,145 mg/m^3 3,300 mg/m^3	g.d. 7-15 (7 h/d)	- Skeletal variations. ↑ resorption/litter; skeletal and visceral malformations. 100 % resorptions.	Nelson *et al* (1984b)
	rats (Fischer 344)	inhalation (whole body)	30 f	0 mg/m^3 275 mg/m^3 550 mg/m^3 1,100 mg/m^3 1,650 mg/m^3	g.d. 6-15 (6 h/d)	No effects. ↑ resorption/litter; ↑ skeletal variations. ↓ foetal weight; ↑ visceral and skeletal malformations. ↓ foetal weight; ↑ visceral and skeletal malformations.	Tyl *et al* (1988)
	rats	dermal	18 f	0 mg/kg 5,923 mg/kg	g.d. 7-16	- ↑ postimplatational losses. ↑ cardiovascular and skeletal malformations.	Hardin *et al* (1984)
	mice (CD-1)	oral (drinking water)	20 m/20 f	0 mg/kg 900 mg/kg 1,800 mg/kg 3,000 mg/kg	Multigeneration study	- No effects. F_2: testicular atrophy. F_1: ↓ life pups/litter; ↓ litter/fertile pair; ↓ pups born alive; ↓ female fertility.	Gulati *et al* (1985c)

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Compound	Species (strain)	Route	Animals per dose level	Exposure conc. or dose	Time	Response	Reference
EGEEA	rabbits (New Zealand)	inhalation	8 f	0 mg/m^3 550 mg/m^3 1,375 mg/m^3 2,475 mg/m^3	g.d. 6-18 (6 h/d)	- ↑ pre- and postimplantational losses; ↓ foetal weight. ↑ pre- and postimplantational losses; ↓ foetal weight. ↑ pre- and postimplantational losses; ↓ foetal weight.	Tinston (1983)
	rabbits (New Zealand)	inhalation	24 f	0 mg/m^3 275 mg/m^3 550 mg/m^3 1,100 mg/m^3 1,650 mg/m^3	g.d. 6-18 (6 h/d)	- No effects. Skeletal and visceral variations. ↓ number life pups; skeletal and visceral malformations. ↓ number life pups; skeletal and visceral malformations.	Tyl *et al* (1988)
	rabbits (Dutch)	inhalation	24 f	0 mg/m^3 138 mg/m^3 550 mg/m^3 2,200 mg/m^3	g.d. 6-18 (6 h/d)	- No effects. ↓ foetal weight; ↑ postimplatational losses skeletal and visceral variations. ↓ foetal weight; ↑ postimplatational losses skeletal malformations.	Doe (1984a)
EGnPE	rats (Charles River)	inhalation	24-29 f	100 ppm 200 ppm 300 ppm 400 ppm	g.d. 6-15 (6h/d)	↓ reticulocytes. ↑ maternal spleen weights, ↓ RBC; ↑ reticulocytes; initial hemoglobinuria. With exception of ↑ in common variations at 200, 300 and 400 ppm, no foetal effects.	Krasavage and Katz (1985)
	rats (Wistar)	inhalation	not known	50 ppm 150 ppm 450 ppm	g.d. 6-15 (6h/d)	- 450 ppm: more immature foetuses maternal hemolytic effects also at 150 ppm. No teratogenicity.	Koeter *et al* (1987)

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Compound	Species (strain)	Route	Animals per dose level	Exposure conc. or dose	Time	Response	Reference
EGnPE	rabbits (New Zealand)	inhalation	15 f	125 ppm 250 ppm 500 ppm	g.d. 6-18, (6h/d)	Mildly ↓ maternal body weight gain; no foetal effects at all 3 concentrations.	Krasavage *et al* (1990)
EGnPEA	rats COBS/CD/ (SD)BR	inhalation	20-23 f per group	100 ppm 200 ppm 400 ppm 800 ppm	g.d. 6-15 (6 h/d)	No teratogenic response. Slight embryo/foetotoxicity. Slight embryo/foetotoxicity. Foetotoxicity.	Krasevage and Katz (1984)
EGiPE	rats (Wistar)	inhalation	21-23 f	50 ppm 50 ppm 450 ppm	g.d. 6-15 (6h/d)	NOEL haemolytic effects in the dams. ↑ incidences in delayed development.	Koeter *et al* (1987)
	rabbits (New Zealand)	inhalation	18 f	20 ppm 90 ppm 490 ppm	g.d. 6-18 (6 h/d)	No effects. No effects. ↓ haemolytic effects in the dams; foetal weight ↓; ↓ maturation.	Koeter *et al* (1988)
EGBE	rats	inhalation	15-16 f	150 ppm 200 ppm	g.d. 7-15 (6 h/d)	No effects. Haematuria.	Nelson *et al* (1984b)
	rats	inhalation	36 f	25 ppm 50 ppm 100 ppm 200 ppm	g.d. 6-15 (6 h/d)	No effects. No effects. Maternal-, embryo- and foeto-toxicity. Maternal toxicity, embryolethality and foetotoxicity.	Tyl *et al* (1984)
	rats	dermal	9 f	0.12 ml/kg	g.d. 7-16, 4x/d	No effects.	Hardin *et al* (1984)

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Compound	Species (strain)	Route	Animals per dose level	Exposure conc. or dose	Time	Response	Reference
EGBE	rats (CD)	*s.c.* injection	20 f	0.05 ml/kg 0.1 ml/kg 0.2 ml/kg	g.d. 6-15	Slight ↑ in rib defects, slightly retarded ossification. Initial maternal toxicity (weight loss and haemoglobinuria). Slight ↑ in rib defects, slightly retarded ossification. Initial maternal toxicity (weight loss and haemoglobinuria). Slight ↑ in rib defects, slightly retarded ossification.	Unilever (1976)
	mice (CD-1)	oral	6 f	350 mg/kg 650 mg/kg 1,000 mg/kg 1,500 mg/kg 2,000 mg/kg	g.d. 8-14	No effects. No effects. ↑ Resorptions; cleft palate in 1/5 litters (4/43 foetuses). 3/6 mothers died. ↑ resorptions, cleft palate in 1/3 litters (1/25 foetuses). 6/6 mothers died. No effect on number of implanation sites.	Wier *et al* (1987)
	mice (CD-1)	oral (drinking water)	20 f	0.5% (approx 700 mg/kg) 1% (approx 1,300 mg/kg) 2% (approx 2,100 mg/kg)	14 wks	1 mother died; no other effects on mothers (continuous breeding) or on reproductive performance of offspring. Slight ↓ in live pup weight. Offspring fertility normal. Maternal toxicity (6 deaths); fewer litters, pups and ↓ pup weight; ↑ pup mortality. ↓ female fertility. Maternal toxicity (13 deaths); fewer litters, pups and ↓ pup weight; ↑ pup mortality. ↓ female fertility.	Heindel *et al* (1990)
	rabbits	inhalation	24 f	25 ppm 50 ppm 100 ppm 200 ppm	g.d. 6-18 (6 h/d)	No effects. No effects. No effects. Maternal- and embryo-toxicity.	Tyl *et al* (1984)

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Compound	Species (strain)	Route	Animals per dose level	Exposure conc. or dose	Time	Response	Reference
EGPhE	rats	*s.c.* injection	30 f	0.1 ml/kg 0.2 ml/kg 0.4 ml/kg	g.d. 6-15	No embryotoxic, foetotoxic, teratogenic effects. Slight maternal toxicity; no embryotoxic, foetotoxic or teratogenic effects. Maternal and embryo toxicity; no foetotoxicity or teratogenic effects.	Unilever (1984f)
	mice (Swiss CD1)	oral (diet)	20 f	0.25% (approx. 400 mg/kg) 1.25% (approx. 2,000 mg/kg) 2.5% (approx. 4,000 mg/kg)	14 wks	No effects on mothers (continuous breeding) or on reproductive performance of offspring. 1 mother died; no effects on mothers (continuous breeding); ↑ neonate and pup mortality. 2 mothers died, foetotoxicity indicated; ↓ fertility; severe neonatal toxicity.	Heindel *et al* (1990)
	rabbits (New Zealand White)	dermal	25 f	300 mg/kg 600 mg/kg 1,000 mg/kg	g.d. 6-18	No embryotoxic, foetotoxic, teratogenic effects. Maternal toxicity (5 deaths); no embryotoxic, foetotoxic or teratogenic effects. Severe maternal toxicity (9 deaths); 5 survived to gestation before group was terminated. No evidence of adverse effects on conception.	Scortichini *et al* (1987)
EGDME	rats (Sprague-Dawley)	oral	6-28 f	0, 30, 60, 120, 250, 500, 1,000 mg/kg	g.d. 8-18 sacrifice d. 19	Maternal mortality at 1,000 mg/kg. Maternal toxicity in dose groups 120 to 1,000 mg/kg; also 100% foetolethality. Foetotoxicity (retarded ossification; ↓ pup body weight) at 60 and 30 mg/kg.	Leonhardt *et al* (1991)
	mice	oral	23-28 f	0, 250, 350, 490 mg/kg	g.d. 7-10	No maternal toxicity. Dose-related foetal mortality. Dose-related external deformations seen in offspring. A developmental NOEL was not established.	Uemura (1980)
	mice (CD1)	oral	20 f	0, 361 mg/kg	g.d. 11-18 sacrifice d. 18	No maternal toxicity noted. ↓ foetal body weight; paw malformations noted.	Hardin and Eisenmann (1987)

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Compound	Species (strain)	Route	Animals per dose level	Exposure conc. or dose	Time	Response	Reference
EGDEE	mice (CD1)	oral	22-24 f	0, 50, 150, 500 1,000 mg/kg	g.d. 6-15 Sacrifice d. 17	NOEL level for maternal toxicity 500 mg/kg/d. ↓ body weight in high dose animals. Exencephaly and fused ribs in offspring from 150, 500 and 1,000 mg/kg/d groups. NOEL for developmental toxicity 50 mg/kg/d.	George *et al* (1992)
	rabbits (New Zealand White)	oral	26-32 f	0, 25, 50, 100 mg/kg	g.d. 6-19 Sacrifice d. 30	No overt maternal toxicity. (NOEL 100 mg/kg/d). ↑ of malformed foetuses at 50 mg/kg/d, and ↑ in resorptions at 100 mg/kg/d. NOEL for developmental toxicity = 25 mg/kg/d.	George *et al* (1992)
DEGME	rats (Sprague-Dawley) Cr[1]:CD (SD)BR)	oral	9 f finding study	Finding study : 0, 1,000, 1,495, 2,235, 3,345, 5,175 mg/kg).	Exposure duration = 10 d. On g.d. 7 through 16. Sacrifice d 21. Study duration = 21 d	Maternal mortality at high dose, maternal toxicity at 3,345 mg/kg/d considered minimal. Skeletal ossification impaired at 1,495 mg/kg/d and higher doses.	Hardin *et al* (1986)
			12-13 f teratology study.	Teratology study: 0, 720, 2,165 mg/kg (dose levels based on dose range finding study).	Exposure duration = 10 d. On g.d. 7 through 16. Sacrifice d 21. Study duration = 21 d	At 2,165 mg/kg, ↓ maternal weight; ↓ foetal weight and litter size; skeletal malformations (rudimentary cervical ribs and bilateral wavy ribs). Developmental LOEL = 720 mg/kg/d. Maternal NOEL = 720 mg/kg/d.	
	rats (Alpk/Ap Wistar-derived)	*s.c.* injection	14/15 f	0, 250, 500, 1,000 µl/kg	Exposure duration = 15 d. On g.d. 6-20. Sacrifice on g.d. 24. Study duration = 24 d	No maternal toxicity. Slight but not statistically significant reduction in pup survival at 1,000 µl/kg/d.	Doe (1984b)

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Compound	Species (strain)	Route	Animals per dose level	Exposure conc. or dose	Time	Response	Reference
DEGME	rabbits (New Zealand White)	dermal	25 f	0, 50, 250, 750 mg/kg. Dose levels selected on basis of results of dose range finding study.	Exposure duration = 13 d on g.d. 6 throught 18. Sacrifice on g.d. 29 Study duration = 29 d	No treatment related clinical signs nor maternal toxicity at 50 and 250 mg/kg/d. ↓ maternal weight gain; ↓ in RBC and packed cell volumes at 750 mg/kg/d. Embryo/foetotoxicity seen at 750 mg/kg/d and of less significance at 250 mg/kg per day. Maternal NOEL = 250 mg/kg/d. Developmental NOEL = 50 mg/kg/d.	Scortichini *et al* (1986)
DEGEE	rats	drinking water		3 generations study with up to 1%	up to 2 y	Early cessation of breeding at 1%. Animals displayed severe kidney damage.	Smyth *et al* (1964)
	rats (Sprague-Dawley)	inhalation	15 f	0, 100 ppm (highest achievable vapour conc.)	10 d 7h/d exposure (g.d. 7-15). Necropsy on d 20	No maternal toxicity. No adverse effects on offspring.	Nelson *et al* (1984b)
	rats (Sprague-Dawley)	dermal	13 f (17 controls)	0, 0.35 ml 4x/d (approx. 6,000 mg/kg)	10 d exposure (g.d. 7-16). Necropsy on d 21	↓ maternal body weight. No adverse effects on offspring.	Hardin *et al* (1984)
	mice (CD-1)	drinking water	20 m/20 f (40 m and 40 f controls)	0, 0.25, 1.25, 2.5% (equivalent to approx. 0, 440, 2,200, 4,400 mg/kg/d)	Continuous breeding assay. Exposures to breeding pairs over 14 wks	No effects on reproduction in F_0 and F_1 generations. ↓ in sperm motility at top dose.	Williams *et al* (1990)
DEGBE	rats (Wistar)	oral	14-16 f	25 mg/kg 115 mg/kg 633 mg/kg	g.d. 0-20 (killed d. 20)	Maternal toxicity (↓ weight gain), no other effects. Maternal toxicity (↓ weight gain), no other effects. Maternal toxicity (↓ weight gain), no other effects.	Ema *et al* (1988)
	rats (CD)	oral	22-24 f	250 mg/kg 500 mg/kg 1,000 mg/kg	14 d to g.d. 13 (killed d. 13) 14 d to d. 21pp (killed d. 21)	No effects. No effects. No maternal or foetal effects; ↓ pup weight d 14 pp.	Nolen *et al* (1985)

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Compound	Species (strain)	Route	Animals per dose level	Exposure conc. or dose	Time	Response	Reference
DEGBE	rats (Wistar)	*s.c.*	20 f	0.125 ml/kg 0.25 ml/kg 0.5 ml/kg 0.75 ml/kg	g.d. 6-15 (killed d. 21)	No effects. No effects. Maternal toxicity (↓ weight gain). Maternal toxicity (↓ weight gain); transient haemogobinuria. Foetotoxicity.	Unilever (1987a)
	rats (CD)	dermal	25 m, 25 f	200 mg/kg 666 mg/kg 2,000 mg/kg	6h/d, 5d/wk13 wk prior to mating and to g.d. 20 in f.	No adverse effects on reproductive performance or fertility in any group.	Auletta *et al* (1993)
	mice	oral	50 f	500 mg/kg	g.d. 7-14	No effect on maternal mortality, viable litters, pup survival; body weight or weight gain.	Schuler *et al* (1984)
	rabbits (New Zealand White)	dermal	20 f	100 mg/kg 300 mg/kg 1,000 mg/kg	g.d. 7-18 (killed d. 29)	No effects. No effects. No effects.	Nolen *et al* (1985)
DEGDME	mice Crl:CD-1 (1CR) BR Swiss Albino	oral	13-15 f	0, 62.5, 125, 500 mg/kg on g.d. 6 through 15. Necropsy on g.d. 17.	Exposure 10 d, study duration 17 d.	No maternal toxicity. ↓ foetal body weight/litter at 125 mg/kg/d. Significant ↑ percentage of post implantation loss/litter and of malformed live foetuses/litter at 250 mg/kg/d. Developmental effects involved neural tube, limbs, digits, cranio facial structures, abdominal wall, cardiovascular system, urogenital organs, and both the axial and appendicular skeleton. Developmental NOEL = 62.5 mg/kg/d.	Price *et al* (1987)
	mice (CD1)	oral	20 f	0, 537 mg/kg	g.d. 11-18 Sacrifice g.d. 18.	No maternal toxicity. No effect of foetal body weight in the test group. Gross foetal malformations (paw defects) similar to those of structurally related glycol ethers.	Hardin and Eisenmann (1987)

APPENDIX B: Reproduction and Developmental Studies

Compound	Species (strain)	Route	Animals per dose level	Exposure conc. or dose	Time	Response	Reference
DEGDME	rabbits (New Zealand White)	oral	15-22 f	0, 25, 100, 175 mg/kg on g.d. 6 through 19. Necropsy on g.d. 30.	exposure 14 d study duration 30 d	Maternal mortality (15%) at 175 mg/kg/d. Maternal toxicity, (↓ body weight gain), at 50 mg/kg/d. Maternal NOEL 25 mg/kg/d. At 100 and 175 mg/kg/d, ↑ incidence of resorptions and malformed live foetuses. Malformations affected development of digits, cranio facial structures, abdominal wall, cardio-vascular system, urogenital organs and axial skeletal. Developmental NOEL of 25 mg/kg/d.	NTP (1987a)
DEGDEE	mice (CD1)	oral	7 f	0, 300, 1,500, 3,000, 4,500 mg/kg	Exposure duration 10 d on g.d. 6 through 15. Sacrificed g.d. 17. Study duration 17d.	Maternal NOEL = 300 mg/kg/d. Developmental NOEL = 1,500 mg/kg/d.	NTP (1987b)
	rabbits (New Zealand White)	oral	27-31 f	0, 50, 200, 400 mg/kg	Exposure duration 14 d on g.d. 6 through 19. Sacrificed g.d. 30. Study duration 30 d.	Maternal NOEL = 200 mg/kg/d. Developmental NOEL = 400 mg/kg/d.	NTP (1987c)
TEGME	rats (CrL:CD)	oral	10 f	1,000 mg/kg	d 6-15	No effects.	Hoberman (1990a)
	rats (CrL:CD)	oral	25 f	625 mg/kg 1,250 mg/kg 2,500 mg/kg 5,000 mg/kg	d 6-16	No effect. ↓ maternal food intake. ↓ maternal food intake and body weight. Delayed ossification. ↑ skeletal variations. Death. ↓ maternal food intake and body weight. ↑ embryo lethality. Delayed ossification. ↑ skeletal variations.	Hoberman (1990a)

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Compound	Species (strain)	Route	Animals per dose level	Exposure conc. or dose	Time	Response	Reference
TEGME	rabbits (New Zealand White)	oral	20 f	250 mg/kg 500 mg/kg 1,000 mg/kg 1,500 mg/kg	g.d. 6-18	No effects. ↑ food intake and body weight gain (post dosing). Maternal death. Maternal death. Marked clinical signs. ↓ maternal body weight and food intake. Delayed ossification, absorptions.	Hoberman (1990b)
TEGEE	rats (Alpk Wistar)	oral (gavage)	10 f	250 mg/kg 1,000 mg/kg	g.d. 6-15 (Chernoff-Kavlock Screening assay)	No effects observed. No effects observed.	Leber *et al* (1990)
TEGBE	rats (Alpk Wistar)	oral (gavage)	10 f	250 mg/kg 1,000 mg/kg	g.d. 6-15 (Chernoff-Kavlock Screening assay)	No effects observed. No effects observed.	Leber *et al* (1990)
TEGDME	mice (CD-1)	drinking water	20 m/20 f	440 mg/kg 880 mg/kg 1,630 mg/kg 1,850 mg/kg	continuous breeding protocol cross over mating	No effects. ↓ pup weight live births. ↓ pup weight and live birth and litters. ↓ pup weight and live births.	Morrissey *et al* (1989)
	mice (CD-1)	oral	20	713 mg/kg	single on g.d. 11	No effects.	Hardin and Eisenmann (1987)
	mice (CD-1)	oral	50	3,500 mg/kg	daily g.d. 7-14	Maternal death (2/50); 100% resorption.	Schuler *et al* (1984)
	mice (CD-1)	oral	29-30	250 mg/kg 500 mg/kg 1,000 mg/kg	g.d. 6-15	No effect. ↑ maternal liver at ↓ foetal pup weight. ↑ maternal liver weight; ↓ foetal weight malformations.	George *et al* (1987)

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Compound	Species (strain)	Route	Animals per dose level	Exposure conc. or dose	Time	Response	Reference
TEGDME	rabbits (New Zealand White)	oral	27-32	75 mg/kg 125 mg/kg 175 mg/kg 250 mg/kg	g.d. 6-19	No effects. No effects. ↓ maternal pup weight; ↑ external and visceral malformation. ↓ maternal pup weight; ↑ external and visceral malformation.	George *et al* (1990)
2PG1ME	rats (CFE)	oral	20 f	46 mg/kg 92 mg/kg 185 mg/kg 370 mg/kg 740 mg/kg	g.d. 1-18 daily	No effects. No effects. No effects. No effects. Delayed ossification.	Stenger *et al* (1972)
	rats (Fischer 344)	inhalation	29-32 f	500 ppm 1,500 ppm 3,000 ppm	g.d. 6-15 6 h/d	No effects. No effects. Delayed ossification; Mild lethargy in dams in the first 2 d of exposure.	Hanley *et al* (1984a)
	rats (Wistar)	inhalation	20 f	200 ppm 600 ppm	g.d. 6-17 6 h/d	No effects. No effects.	Doe *et al* (1983)
	rats (CFE)	injection *s.c.*	20 f	46 mg/kg 92 mg/kg 185 mg/kg 370 mg/kg 740 mg/kg	g.d. 1-21 daily	No effects. No effects. No effects. No effects. Delayed ossification.	Stenger *et al* (1972)
	mice (CFLP)	oral	20 f	460 mg/kg 924 mg/kg 1,850 mg/kg	g.d. 1-18 daily	No effects. No effects. No effects.	Stenger *et al* (1972)

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Compound	Species (strain)	Route	Animals per dose level	Exposure conc. or dose	Time	Response	Reference
2PG1ME	mice (CD1)	drinking water	1st generation 20 m/20 f 2nd generation	0.5% in water 1.0% in water 2.0% in water 2.0% in water	continuous breeding	No effects. No effects. ↓ pup weights. ↓ right epididymal and prostate gland weights.	Gulati *et al* (1986)
	mice (CFLP)	injection *s.c.*	20 f	46 mg/kg 92 mg/kg 185 mg/kg 370 mg/kg	g.d. 1-18 (daily)	No effects. No effects. No effects. No effects.	Stenger *et al* (1972)
	rabbits (Silver Yellow)	oral	15 f	230 mg/kg 460 mg/kg 924 mg/kg	g.d. 6-18 (daily)	No effects. No effects. No effects.	Stenger *et al* (1972)
	rabbits (New Zealand White)	inhalation	29-32 f	500 ppm 1,500 ppm 3,000 ppm	g.d. 6-18 (6 h/d)	No effects. No effects. Mild lethargy in dams on the first 2 d of exposure.	Hanley *et al* (1984a)
	rabbits (Silver Yellow)	injection *s.c.*	15 f	46 mg/kg 92 mg/kg	g.d. 6-18 (daily)	No effects. No effects.	Stenger *et al* (1972)
2PG1MEA	rats (Sprague-Dawley)	inhalation	20 f	500 ppm 2,000 ppm 4,000 ppm	g.d. 6-15	No effects. Dispnoea in 1 animal. ↓ Food consumption; ↓ Body weight. Dispnoea. ↓ Food consumption; ↓ Body weight.	Asaki and Houpt (1990)
2PG1EE	rats (CRL: COBS)	inhalation (whole body)	25 f	100 450 2,000	d. 6-15 (6 h/d)	No effects. Slight ↓ maternal weight gain. ↓ maternal weight gain and food consumption.	BP (1986b)

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Compound	Species (strain)	Route	Animals per dose level	Exposure conc. or dose	Time	Response	Reference
2PG1EE	rabbits (New Zealand White)	inhalation (whole body)	22 f	100 350 1,200	d. 6-18 (6 h/d)	No effects. No effects. ↓ maternal but gain and food consumption.	BP (1986c)
1PG2ME	rats (Wistar)	inhalation	5	1,000 ppm 2,000 ppm 3,000 ppm	g.d. 6-15 (6 h/d)	↑ in thoracic vertebral anomalies (dumb-bell-shaped notches of central cartilage). ↑ in thoracic vertebral anomalies (dumb-bell-shaped notches of central cartilage). ↑ in thoracic vertebral anomalies (dumb-bell-shaped notches of central cartilage).	Merkle *et al* (1987)
	rabbits (Himalayan)	inhalation	10-11	145 ppm 225 ppm 350 ppm 545 ppm	g.g. 6-18 (6 h/d)	1 sternebral malformation. ↑ malformations. ↑ malformations. ↑ malformations.	Hellwig *et al* (1994)
1PG2MEA	rats (Wistar)	inhalation	25 f	0.6 mg/l 110 ppm 3.0 mg/l; 550 ppm 14.9 mg/l; 2,700 ppm	g.d. 6-15	No effects. No foetal effects (maternal CNS depression; maternal weight). Abnormalities (spit vertebrae thoracicae); dead implantations.	Merkle *et al* (1987)
	rabbits (Hima-layan)	inhalation	15 f	0.2 mg/l; 36 ppm 0.8 mg/l; 145 ppm 3.0 mg/l; 550 ppm	g.d. 6-18	No effects. No effects. All foetuses (63) severely malformed in the absence of clear maternal toxicity.	Merkle *et al* (1987)
	rabbits	dermal (200 cm^2; undiluted; semi-occlusive)	15 f	1,000 mg/kg 2,000 mg/kg	g.d. 6-18	No effects. No effects.	Merkle *et al* (1987)

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Compound	Species (strain)	Route	Animals per dose level	Exposure conc. or dose	Time	Response	Reference
2PG1BE	rats (Wistar)	dermal	25 f	264 mg/kg 880 mg/kg	g.d. 6-16	No effects. Only dermal effects no foetotoxic or teratogenic effects.	Waalkens-Berendsen *et al* (1989)
	rabbits (New Zealand White)	dermal	20 f	10 mg/kg 40 mg/kg 100 mg/kg	g.d. 7-18	No effects. No effects. No effects.	Gibson *et al* (1989)
TPGME	rats (Sprague-Dawley)	inhalation (aerosol)	7 f	0.3 mg/l 0.9 mg/l 2.7 mg/l 8.2 mg/l	g.d. 6-15 (6 h/d)	No effects. No effects. Maternal toxicity. No embryotoxicity. Maternal toxicity. No embryotoxicity.	Breckenridge *et al* (1985a)
	rats (Sprague-Dawley)	inhalation (aerosol)	25 f	0.1 mg/l 0.3 mg/l 1.0 mg/l	g.d. 6-15 (6 h/d)	No effects. No effects. Maternal toxicity; no embryotoxicity; no foetotoxicity; no teratogenicity.	Breckenridge *et al* (1985b)

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Compound	Type of test	Test Species/Conditions	Results	Reference
EGME *In vitro*	Bacterial mutation	*Salmonella typhimurium* TA98, 100, 1535, 1537, 1538; +/- S9	Negative.	McGregor *et al* (1983)
	Bacterial mutation	- TA 102	Negative.	McGregor (1984)
	Mutation	*Schizoshaccaromyces pombe P1* ; +/- S9	Negative. No cytotoxicity at 48 mg/l	Abbondandolo *et al* (1980)
	Mutation	Mouse lymphoma; + S9 (0.01-100 mg/ml)	Negative.	McGregor (1984)
	UDS	Human fibroblasts; +/- S9	Negative. No cytotoxicity at 9,663 µg/ml	McGregor *et al* (1983)
	Cytogenetic	Rats (10 m/10 f) 7 h inhalation, 25 and 500 ppm -dito for 5 d	Negative.	McGregor *et al* (1983)
In vivo	Dominant lethal assay	Rats and mice (10 m), single oral administration 500, 750, 1,000 and 1,500 mg/kg	Pre-end postimplantation losses after 4-5 wk; sterility after 6 wk. No DL-effects	Anderson *et al* (1987)
	Dominant lethal assay	Rats (20-30 m and f) inhalation 13 wk; 30, 100 and 300 ppm	↓ fertility, no litters. No DL-effects	Rao *et al* (1983)
	Dominant lethal assay	Rats (10 m) 5 inhalation of 25 and 500 ppm	Preimplantation losses at 500 ppm.	McGregor *et al* (1983)
	Mutation (SLRL-test)	*Drosophila Melanogaster* 1h 25 ppm inhalation 0.25h 500 ppm inhalation 48 ppm, 7 h, 7 d 240 ppm, 7 h, 5 d 120 ppm, 7 h, 6 d 36 ppm, 7 h, 10 d	 Unclear. Unclear. Positive. Positive. Positive. Negative.	McGregor *et al* (1983)
	Clastogenicity in bone marrow	B6C3F1 mice 35-2500 mg/kg	Negative	Au *et al* (1993)

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Compound	Type of test	Test Species/Conditions	Results	Reference
EGMEA *In vitro*	Cytogenetic assay Aneuploidy	*Saccharomyces cerevisiae*	Positive (Aneuploidy; mitotic chromosome loss)	Zimmermann *et al* (1985) Whittacker *et al* (1989)
	Cytogenetic assay	CHO cells; +/- S9 mix	Positive (+ S9 mix)	Loveday *et al* (1990)
	Sister chromatid exchange	CHO cells; +/- S9 mix	Positive	Loveday *et al* (1990)
EGMEA *In vivo*	Cytogenetic assay	*Drosophila melanogaster* (f) oral feed; larves and adults 3,200 ppm FIX test 32,000 ppm FIX test 500 ppm ZESTE test 4,200 ppm ZESTE test 5,000 ppm ZESTE test 42,000 ppm ZESTE test	Negative Positive (X-chromosome losses in offspring generations of young adults)	Osgood *et al* (1991) Sehgal and Osgood (1990)
	Micronucleus assay	Chinese Hamster 1,333 mg/kg i.p. sacrifice after 12, 24, 48, 72 h	Negative	Basler (1986)

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Compound	Type of test	Test Species/Conditions	Results	Reference
EGEE	Bacterial mutation	*Salmonella typhimurium* TA 98, 100, 1535, 1537 0-23 mg/plate; +/- S9	Negative in all strains.	Ong (1980)
		Salmonella typhimurium TA 98, 100, 1535, 1537, 1538 5-5,000 µg/plate; +/- S9	Negative in all strains.	Shimizu *et al* (1985)
		Salmonella typhimurium TA 98, 100, 1535, 1537 100-1,000 µg/plate; +/- S9	Negative in all strains.	Zeiger *et al* (1985)
		No details reported 0-93,3 mg/plate; +/- S9	Negative response.	Guzzie *et al* (1986)
		Salmonella typhimurium TA 1535, TA 1537, TA 97n TA 18, TA 100; +/- S9 (rat, hamster)	Negative in all strains.	Zeiger *et al* (1992)
	Mammalian mutation	Mouse Lymphoma L51784 TK +/-; Conc. not specified; +/- S9	Negative with and without S9.	Myhr *et al* (1986)
		HGPRT- Test; CHO-Cells 0-42 mg/ml; +/- S9	Negative with and without S9.	Guzzie *et al* (1986)
	Mammalian chromosomal SCE	CHO-Cells 951-9,510 µg/ml; +/- S9	Positive with and without S9.	Galloway *et al* (1987)
		CHO-Cells Conc. not specified; +/- S9	Positive with and without S9.	Guzzie *et al* (1986)
	Chromosomal aberration	CHO-Cells 4,780-9,510 µg/ml; +/- S9	Positive with and without S9.	Galloway *et al* (1987)
		CHO-Cells Conc. not specified; +/- S9	Positive with and without S9.	Guzzie *et al* (1986)

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Compound	Type of test	Test Species/Conditions	Results	Reference
EGEE	Chromosomal aberration augmentation *in vitro*	Human lymphocytes, 48 h	Negative response.	Villalabos - Pietrini *et al* (1989)
	Mammalian *in vitro* SCE	Humam lymphocytes, 48 h	Positive response.	Villalabos - Pietrini *et al* (1989)
	Micronucleus test	Mice; *i.p.* 647, 1,295, 2,071 mg/kg (30, 48, 72h)	Negative at all dose levels.	Guzzie *et al* (1986)
	SLRL-Test	*Drosophila melanogaster* Injection, 50,000 mg/l	Negative and positive response.	Valencia *et al* (1985)
		Drosophila melanogaster Injection, conc. not specifed	Negative response.	McGregor (1984)
		Drosophila melanogaster Oral feed, 20,000 mg/l	Negative response.	Valencia *et al* (1985)
		Drosophila meanogaster Oral feed, conc. not specified	Negative response.	McGregor (1984)
EGEEA	Micronucleus (bone marrow)	Mice *i.p.* Conc. not specified	Negative.	Slesinski *et al* (1988)
	Bacterial, mutation	*Salmonella typhimurium* TA 98, 100, 1535, 1538 5-5,000 µg/plate; +/- S9	Negative at all dose levels .	Huels (1989)
	Mammalian	*Salmonella typhimurium* +/- S9 Conc. not specified	Negative response.	Slesinski *et al* (1988)
	HGPRT-Test	CHO-Cells +/- S9 Conc. not specified	Negative response.	Slesinski *et al* (1988)

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Compound	Type of test	Test Species/Conditions	Results	Reference
EGEEA	SCE	CHO-Cells +/- S9 Conc. not specified	Negative response.	Slesinski *et al* (1988)
EGBE	Mammalian *in vitro* UDS	Primary hepatocyte Scintillation. 1-1000 ppm	Unclear; not reproducible.	Union Carbide (1989)
	Mammalian *in vitro* SCE	CHO cells; +/- S9 0.016 - 0.25 %	Negative response.	Union Carbide (1989)
	Mammalian *in vitro* point mutations	CHO cells, HGPRT locus, 0.03 - 0.5 %; + S9 0.06 - 1 %; - S9	Negative response.	Union Carbide (1989)
	Bacterial mutation	*Salmonella typhimurium* TA1535, TA1537, TA1538, TA98, TA100; +/-S9 (rat, hamster). Up to 10,000 µg/plate. 20-111 µl/ml.	Negative at all dose levels.	Zeiger *et al* (1992)
	Bacterial mutation	*Salmonella typhimurium* TA 97a, TA 98, TA 100, TA 102; +/- S9 (rat) up to 9,000 µg/plate.	Positive response in TA 97a at 2,250 and 9,000 µg/plate. No effect in other strains.	Hoflack *et al* (1994)
	Bacteriophage mutation	Bacteriophage T4D with E. Coli B, CR63 and K12 (lambda h). 20-111µl/ml.	Negative response. Significant phage toxicity.	Kvelland (1988)
	Chromosomal aberration augmentation *in vitro*	Clastogenic response to MMS, MMC and bleomycin in V79 cells and human lymphocytes preincubated with EGBE (2 mg/ml).	↑ Response to clastogen. Summary report, insufficient data for full assessment. Response at high, non physiological dose levels.	Elias *et al* (1992)
	Mammalian *in vitro* SCE	Human lymphocytes, 0-3,000 ppm	Positive response.	Villalabos-Pietrini *et al* (1989)
	Chromosomal aberration *in vitro*	Human lymphocytes, 48 h, 0-3,000 ppm	Negative response.	Villalobos -Pietrini *et al* (1989)

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Compound	Type of test	Test Species/Conditions	Results	Reference
EGPhE	Bacterial mutation	*Salmonella typhimurium* TA1535, TA1537, TA1538, TA998, TA100 50-5,000 µg/plate; +/-S9.	Negative in all strains.	Nipa (1982a)
	Mouse micronucleus	Oral administration at 300, 600 or 1,200 mg/kg (total dose: 2 equal doses were given 24 h apart).	No effects at all dose levels.	Nipa (1982b)
	Rat bone marrow cytogenetics	Oral administration at 280, 933 or 2,800 mg/kg. Sampling at 6, 24 and 48 h.	No effects at all dose levels.	Dow (1988)
	Mammalian *in vitro* chromosomal aberrations	CHO-cells 125-1,000 µg/ml; no S9 CHO-cells 500-3,000 µg/ml; +S9	Some mitotic inhibition at 1,000 µg/ml. No mitotic inhibition at 3,000 µg/ml.	Unilever (1985)
	Mammalian *in vitro* forward mutation	CHO-HGPRT 2,500-3,500 µg/ml (no S9) 2,000-3,500 µg/ml; +S9	Negative response. Negative response.	Dow (1987)
EGDME	Point mutation in: bacteria	*Salmonella typhimurium* TA100 50, 200, 500 µg/plate; +/-S9 in plate incorporation assay. 50, 100, 500 µg/plate; +/-S9 in pre-incubation test. Positive control B(a)P.	Inconsistencies in reporting of dose levels/results. EGDME alone was without obvious effects in either test.	Arimoto *et al* (1982)
DEGEE	Bacterial mutation in: bacteria	*Salmonella typhimurium* TA97, TA100, TA102, TA1535, TA1537, TA1538. 0.01, 0.1, 1.0 ml/plate; +/-S9	(+/-) in TA1535, TA1537, TA1538 (+/-S9). (-) in all other strains (+/-S9).	Berté *et al* (1986)
	Mutation	*Saccharomyces cerevisiae* D7 1%, 10% for 4h	(+/-) convertants and revertants at 10%. (-) cross overs/aberrants.	Berté *et al* (1986)
	In vivo mouse micronucleus	Male Swiss CD1 mice. 5 animals/group (2 ml/kg) i.p.	(-) No micronuclei induced.	Berté *et al* (1986)

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Compound	Type of test	Test Species/Conditions	Results	Reference
DEGEEA	Ames	Standard	Negative	Hüls (1990d)
DEGBE	Bacterial, mutation	*Salmonella typhimurium* TA1535, TA1537, TA1538, TA98, TA100; Exposure to vapour at up to 0.7 mg/l during 72 h incubation at 37°C; +/-S9	Negative in all strains.	Thompson *et al* (1984) Unilever (1984c) Unilever (1984d)
	Mammalian *in vitro* UDS	Primary hepatocyte, grain counts 0.26 - 10 µl/ml	No effects.	Thompson *et al* (1984)
	Mammalian *in vitro* chromosomal aberrations	CHO cells; +/- S9 0.1 - 0.79 µl/ml	No effects.	Thompson *et al* (1984)
	Mammalian *in vitro* CHO/HGPRT forward mutation	CHO cells; +/- S9 1,000-5,000 µg/ml	No effects.	Gollapudi *et al* (1993)
	Mammalian mutations	Mouse lymphoma L5178Y 0.42 - 10 µl/ml	Weak response.	Thompson *et al* (1984)
	Drosophila, SCRL-Test	3d old males Feeding and injection	No effects.	Thompson *et al* (1984)
	Mouse micronucleus	Oral administration (single dose) at 330, 1,100 or 3,300 mg/kg. Groups (5 m, 5 f) killed at 24, 48, 72 h.	No effects.	Gollapudi *et al* (1993)
DEGDME	Sperm abnormality test	Mice (B6C3F1) 10 m/group. 250 or 1,000 ppm, 7 h/d for 4 d, by inhalation. Mice killed 35 day after completion of treatment. EMS was used as a positive control substance.	Positive. Sperm abnormalities were significantly ($p<0.001$) increased (from 5.14 to 32.30%) only in the 1,000 ppm exposed group. All categories of abnormalities were increased, particularly those with amorphous heads.	McGregor *et al* (1983)

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Compound	Type of test	Test Species/Conditions	Results	Reference
DEGDME	Dominant lethal test	Rats (CD) 10 m/group. 250 or 1,000 ppm, 7 h/d for 5 d, by inhalation. Male animals were serially mated (1 m : 2 f) at weekly intervals for 10 wk. F were examined 17 days after first caging with the m.	Equivocal. Pregnancies were reduced 4-9 weeks after exposure for the 1,000 ppm exposure group, with total implantations significantly reduced ($p<0.01$) in weeks 6 and 7. Since the high proportion of early deaths can be partly explained in terms of low implantation frequency, it is not possible to demonstrate conclusively that a dominant lethal effect occurred at 1,000 ppm. Control and 250 ppm groups were normal with the exception of a statistically significant decrease in early death frequency at week 7 in 250 ppm group.	McGregor *et al* (1983)
	Bacterial mutation	*Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98, TA100 Plate incorporation assay. Doses up to 94 mg plate; +/- S9	Negative responses seen at all dose levels in presence and in absence of rat liver S9.	McGregor *et al* (1983)
	UDS	Human embryonic intestinal fibroblasts. Inclubations (3h at 37°C);conc. up to 19 mg/ml.	No increased UDS observed at any test concentration either in the presence or absence of rat liver S9.	McGregor *et al* (1983)
	SLRL test	*Drosphophila melanogaster* ORK m; M-5 f. Exposed by inhalation at 250 ppm for 2.75h. Positive control substance EMS (0.4%) was exposed for 5 h. Treated m were mated with 2 virgin f on 3 separate 2 d periods, starting on days 1, 4 and 9 following exposure. The three broods of each of the F2 and F3 generations were examined after brother:sister mating of the F1 generation.	Test concentration was a maximum tolerated dose established by a preliminary study. Two independent tests were performed using different stocks of flies. In one test, 6 recessive lethals were found. In the other test one recessive lethal was found. The negative controls showed recessive lethals of 3 and 2, respecitively in the F2 generation. In the F3 generation, 6 recessive lethals were seen in one experiment while none were seen in the other test exposure or in control air samples. Test data are difficult to interpret.	McGregor *et al* (1983)
	In vivo bone marrow cytogenetics	10 m - 10 f CD rat/group, 250 or 1,000 ppm 7 h/d for 1 or 5 d, by inhalation. Rats were killed 6, 24 or 48 h after the end of exposure for 1 d, or 6 h after completion of 5 d of exposure.	Negative. In male rats only at 250 ppm exposure concentration, there was a small increase in total aberrations not dose related. EMS was a positive control substance.	McGregor *et al* (1983)

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Compound	Type of test	Test Species/Conditions	Results	Reference
TEGME	Bacterial mutation	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537 preincubation protocol 2-5,000 µg/plate; +/-S9	Negative in all strains at all dose levels.	Samson and Gollapudi (1990)
	Mammalian cell gene mutation	CHO cells/HGPRT locus 2,000-5,000 µg/ml; +/-S9	Negative at all dose levels.	Linscombe and Gollapudi (1990)
	In vivo micronucleus	Mice 500; 1,667; 5,000 mg/kg single oral gavage	No effects at all dose levels.	McClintock and Gollapudi (1990)
2PG1ME	Bacterial mutation	*Salmonella typhimurium* TA1535, TA1537, TA1538, TA98, TA100 2 - 6,250 µg/plate; +/- S9	Negative in all strains.	Kirkland *et al* (1983)
	Mammalian *in vitro*, UDS	Primary hepatocyte, grain counts	No effects.	Mendrala and Schumann (1983a)
	Mammalian *in vitro*, chromosomal aberrations	CHO cells 1.25, 2.5, 5.0, 10.0 mg/ml	Negative response.	Kirkland and Verschuuren (1983)
2PG1MEA	Bacterial mutation	*Salmonella typhimurium* TA1535, TA1537, TA1538, TA98, TA100; 100-50,000 µg/plate; +/- S9	Negative in all strains.	Mendrala and Schumann (1983b)
	Mammalian *in vitro* UDS	Primary hepatocyte, grain counts	No effects.	Mendrala and Schumann (1983c)
2PG1EE	Bacterial mutation	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537, TA1538 5,000 µg/plate; +/- S9	Negative in all strains.	BP (1988a)
	Mammalian *in vitro* cytogenetics	Human lymphocytes 0-5,000 µg/plate; +/- S9	Negative response.	BP (1988b)

APPENDIX C: Genotoxicity Studies

Compound	Type of test	Test Species/Conditions	Results	Reference
2PG1EEA	Bacterial mutation	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537, TA1538 50-5,000 µg/plate; +/- S9	Negative in all strains.	BP (1985c)
	Mammalian *in vitro* cytogenetics	CHO cells 230-2,300 µg/plate; +/- S9	Negative response.	BP (1985d)
2PG1BE	Bacterial mutation	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537 (pre-incubation modification); 5; 15.8; 50; 158; 500; 1,580; 5,000 µg/plate; +/- S9;	Negative in all strains .	Bruce *et al* (1987)
	Mammalian *in vitro* chromosomal aberrations	CHO cells 500; 1,667; 5,000 µg/ml	Negative response.	Gollapudi *et al* (1988)
2PG1PhE	Bacterial mutation	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537; 50-5,000 µg/plate; +/- S9	Negative in all strains.	Bootman and May (1985)
	Mammalian *in vitro* chromosomal aberrations	Human peripheral lymphocytes 100-400 µg/ml	No effects.	Bootman (1986)
1PG2ME	Bacterial mutation	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537, TA1538; up to 5,000 mg/plate; +/- S9	No effects.	BASF (1988a)
DPGME	Bacterial mutation	*Salmonella typhimurium* TA1535, TA1537, TA1538, TA98, TA100; +/- S9	Negative in all strains.	Kirkland and Varley (1983)
	Mammalian *in vitro* cytogenetics	CHO cells; +/- S9	Negative response.	Kirkland (1983)
	Mammalian *in vitro* UDS	Primary hepatocyte, grain counts	No effects.	Mendrala (1983)

APPENDIX C: Genotoxicity Studies

Compound	Type of test	Test Species/Conditions	Results	Reference
DPGEE	Bacterial mutation	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537, TA1538 50-5,000 µg/plate; +/- S9	Negative in all strains.	BP (1985h)
	Mammalian *in vitro* cytogenetics	Human lymphocytes 50-1,000 µg/plate; +/- S9	No effects at all dose levels.	BP (1990c)
TPGME	Bacterial mutation	*Salmonella typhimurium* TA1535, TA1537, TA1538, TA98, TA100 10; 100; 1,000;10,000;100,000 µg/plate; +/- S9	Negative in all strains.	Mendrala and Schumann (1982a)
	Mammalian *in vitro* uscheduled DNA sythesis	Primary hepatocyte	No effects.	Mendrala and Schumann (1982b)

APPENDIX D: Absorption, Distribution, Metabolism and Elimination Studies (ADME)

Compound	Species (Strain)	Route	Animals per dose level	Exposure conc. or dose	Time	Results	Reference
EGME	rats (Wistar)	oral	4 or 8 m	100 mg/kg 300 mg/kg	1-20 d	↓ Liver weight at high dose (20 days). ↑ Cytosolic ADH, but no effect on other enzyme parameters.	Kawamoto *et al* (1990b)
	rats (Fischer)	oral	2 x 3 m	662 mg/kg	single dose	48 h later 80-90% of the radioactivity was eliminated. 80-90% of this was identified as MAA in the urine; 10-12% were exhaled as CO_2.	Miller *et al* (1983b)
	rats	oral	12 m	500 mg/kg	single dose	58.5% of radioactivity was eliminated in urine within 24 h; 70% within 48 h. Relative amounts: 73% MAA; 15% EGME; 8% unidentified.	Foster *et al* (1984)
	rats (Fischer)	oral (drinking water)	4 m	180 ppm (12.2 mg/kg) 450 ppm (26.2 mg/kg) 1,620 ppm (110.3 mg/kg)	24 h	72 h urine collection; 40-50% of radioactivity recovered in urine. Relative amounts: 34-35% MAA; 42-60% Ethylene glycol; 6-8% EGME. ↑ relative amounts of MAA with dose, ↓ ethylene glycol; 20-30 % were exhaled as CO_2 and 5% as EGME.	Medinsky *et al* (1990)
	rats (Fischer)	dermal (semi-occlusive)	4 m	35 mg/kg 109 mg/kg 321 mg/kg	72 h (exposure and concomitant sampling).	19.4-26.9% of radioactivity resorbed, 51-61% evaporated. 67-72% of resorbed activity excreted in urine; 8.8-10% in faeces; 14-16% remained in the carcass. In urine 23-46% MAA; 8.6-11% as Ethylene glycol; 32-58% unidentified ↑ with dose related.	Sabourin *et al* (1992b)
	rats (Sprague-Dawley)	*i.p.*	? m	250 mg/kg 250 mg/kg Pyrazol prior to EGME injection	single injection single injection	24 h urine collection: 40.4% recovery in urine; 48 h urine collection: 55.2% recovery; 50-60% identified as MAA, 18-25% as MAA glycin . Only 18% recovery after 48 h; ↑ EGME plasma elimination half-time from 0.6 to 42.6 h; ↑ radioactivity plasma elimination half-time from 19.7 to 51.0 h.	Moss *et al* (1985)

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Compound	Species (Strain)	Route	Animals per dose level	Exposure conc. or dose	Time	Results	Reference
EGME	rats (Sprague-Dawley)	Inhalation (whole body exposure)	3 f	1,600 ppm 1,600 mg/kg + 20 mmol/kg Ethanol *i.p.* prior to injection	2 h	in blood: 86 µg/ml EGME 243 µg/ml	Römer *et al* (1985)
	Pregnant Maccaca fascicularis	oral	3-6 f	 12 mg/kg/d 24 mg/kg/d 36 mg/kg/d	25 d	Blood sampling on d 1, 8, 15 and 22; 2, 4, 7.5 and 25 h after each administration. Maximal MAA concentration already after 2 h; 50% ↓ after 24 h. ↑ MAA levels measured (µg/ml) : d 1 (2 h)~16 d 15 (2 h)~43 d 22 (2 h)~ 38 (24 h)~12 (24 h)~16 (24)~20 d 1 (2 h)~41 d 15 (2 h)~86 d 22 (2 h)~85 (24 h)~20.5 (24 h)~34.5 (24)~46 d 1 (2 h)~75 d 15 (2 h)~200 d 22 (2 h)~191.5 (24 h)~25 (24 h)~98.5 (24)~107	Scott *et al* (1989)
EGEE	rats (Sprague-Dawley)	oral	a) 4m b) 5 m	230 mg/kg	single dose, 96h collection	a) 2-ethoxyethanol (1,2 ^{14}C). b) 2-ethoxyethanol (ethoxy-1-^{14}C). - Recovery: a) 99.3% b) 99.4% - Urinary excretion 76-80% of ^{14}C. - Major urinary metabolites : ethoxy acetic acid N-ethoxy-acetyl-glycine. - $^{14}CO_2$ expiration: a) 4.61% b) 11.7% - Biological half-time: a) 12.5 h b) 9.9 h	Cheever *et al*, (1984)

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Compound	Species (Strain)	Route	Animals per dose level	Exposure conc. or dose	Time	Results	Reference
EGEE	rats (Wister)	oral	5 m	0.5; 1; 5; 10; 50;100 mg/kg	single dose, 60 h collection	- Recovery increasing with dose from 13.4%-36.8%. - Major urinary metabolites : ethoxy acetic acid N-ethoxy-acetyl-glycine. - Biological half-time: 7.2 h	Groeseneken *et al* (1988)
	rats (Fischer 344/N)	oral (drinking water)	4 m	10;20;120 mg/kg	24 h; 72 h collection	- Recovery: 27%, 59%, 32% for the corresponding doses. - Major urinary metabolites ethoxy acetic acid (25-40%) ethylene glycol (18%). - CO_2 expiration (20%).	Medinsky *et al* (1990)
	rats (Fischer 344/N)	dermal (non occluded)	4 m	12; 24; 60 mg/kg (absorbed dose)	single dose; 72 h collection	- Dermal absorption of administered dose : 20-25%. - Major urinary metabolites ethoxy acetic acid (50%) ethylene glycol (18%). - CO_2 expiration (10%).	Sabourin *et al* (1992b)
	human	Inhalation	5 volunteers	10, 20, 40 mg/m^3	4 h	- Absorption 70% of inhaled compound. - Major urinary metabolite : ethoxy acetic acid (EAA) (23% of absorbed compound). - Biological half-time of EAA approx. 21-24 h.	Groeseneken *et al* (1986a, 1986b)
EGEEA	dogs (beagle)	dermal	3	14.6 mg	single dose 30-60 min. 24h collection	- Absorption rate : 29 or 14.5 µg/cm^2/min. - Approximately 60% of dose excreted via urine within 24 h; 1% CO_2.	Guest *et al* (1984)
	dogs (beagle)	*i.v.*	3	1 mg	single dose 24 h collection	- Approximately 60% of dose excreted via urine within 24 h; 1.6% CO_2. - Biological half-time of EGEEA in blood : approx. 7.9 h.	
	human	inhalation	5 volunteers	14,28,50 mg/m^3	4 h	- Major urinary metabolite: ethoxy acetic acid (EAA) (22% of absorbed compound). - Biological half-time of EAA: approx. 23 h.	Groeseneken *et al* (1987a, 1987b)
	human	skin penetration (*in vitro*)	Excised human skin (1.2 cm^2)	Dose 5 ml/diffusion cell	8 h	- Penetration rate 0,8 mg/cm^2/h.	Dugard *et al* (1984)

APPENDIX D: Absorption, Distribution, Metabolism and Elimination Studies (ADME)

Compound	Species (Strain)	Route	Animals per dose level	Exposure conc. or dose	Time	Results	Reference
EGBE	rats (Fischer 344)	oral	3m	125 mg/kg	Single dose, 48 h collection	Recovery ca 92%; 70% urine, 2% faeces, 18% CO_2, <2% exhaled. Urinary metabolites were n-butoxyacetic acid (>75%), glucuronide and sulphate conjugates of EGBE and <5% of an unidentified metabolite. Radiolabel localised in glandular stomach at 48h, ^{14}C higher than blood level in liver, kidney, skin.	Ghanayem *et al* (1987c)
	rats (Fischer 344)	oral	3m	500 mg/kg	single dose, 48h collection	Recovery 55%; 40% urine, 3% faeces, 10% CO_2, <2% exhaled. Urinary metabolites were n-butoxyacetic acid (>75%), EGBE glucuronide and <1% of an unidentified metabolite. Radiolabel localised in glandular stomach, ^{14}C higher than blood level in liver.	
	rats (Fischer 344)	oral	3m	500 mg/kg	single dose, 8h collection of bile	8% excreted in bile, primarily as EGBE glucuronide. Some EGBE in bile up to 2h after dose, with n-butoxyacetic acid excretion in bile increasing steadily.	
	rats (Fischer 344)	oral	3m, 4-5wk and 3m, 9-13wk	500 mg/kg	single dose, 48h collection	Radiolabel excreted more quickly in urine of younger rats (>60% vs <40%), with higher amounts of EGBE glucuronide and an unidentified metabolite and lower amounts of n-butoxyacetic acid. CO_2 exhalation higher in younger rats (>20% vs ca 11%).	Ghanayem *et al* (1987a)
	rats (Fischer 344/N)	oral (drinking water)	4m	28 mg/kg 47 mg/kg 140 mg/kg	over 24h, 72h collection	Details of percentage recoveries not given. No significant differences in excretion pattern for 3 doses. Urine major route of excretion (50-60% of dose as n-butoxyacetic acid), with 8-10% as CO_2 and 10% as ethylene glycol.	Medinsky *et al* (1990)

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Compound	Species (Strain)	Route	Animals per dose level	Exposure conc. or dose	Time	Results	Reference
EGBE	rats (Fischer 344/N)	Inhalation , nose only	29 m, 11-12 wk 9 m, 11-12 wk 9 m, 11-12 wk	43 ppm 49 ppm 438 ppm	6 h, 66h collection	Essentially linear uptake and metabolism. Majority of absorbed dose excreted in urine (64-76%), 1-2% in faeces, 7-9% as exhaled CO_2, 13-20% in carcass and 2-5% as exhaled EGBE. Major urinary metabolite BAA (57-68%), lesser amounts of EGBE glucuronide (5-16%), ethylene glycol (12-25%) and unidentified metabolites.	Sabourin *et al* (1992a)
	rats (Fischer 344/N)	dermal, non occluded	4 m, 11-12 wk	4.4 mg/kg 13 mg/kg 21.4 mg/kg	6 h, 72h collection	78%-90% recovery, 21-26% absorbed irrespective of dose. 83% of absorbed dose recovered in urine, primarily as BAA. EGBE glucuronide a lesser metabolite, with small amounts of ethylene glycol and CO_2. BAA major plasma metabolite.	Sabourin *et al* (1992b)
	rats (hairless), pig or man	dermal, *in vitro*	3 samples	210-5,400µg/cm^2, 3.5%, 10%. Isopropanol or sodium dodecyl benzene sulphorate (LAS), 100 %	1,6 or 16 h	Penetration rapid, faster for aqueous EGBE than would be predicted from rate for EGBE. Penetration 3x faster for hairless rats than pig/man. Penetration rate not significantly altered by isopropanol or LAS.	Bartnik *et al* (1987)
	rats (Sprague Dawley)	dermal, *in vitro*	12 m	undiluted	single dose , 8 h	Penetration rate 4.3 µmol/cm^2/h.	Barber *et al* (1992)
	rats (Wistar)	dermal	6 m, 6 f	200 mg/kg over 12 cm^2, no occlusion	single dose, 48 h collection	20-23% urine, 18-23% application site (only samples taken).	Bartnik *et al* (1987)
	rats (Wistar)	*sc*	3m	118 mg/kg	single dose, 72h collection	Recovery 97%; 80% urine,<1% faeces, 10% CO_2, 2% expired, 5% carcass. Radiolabel localised in spleen, thymus and liver.	Bartnik *et al* (1987)
	guinea pigs	dermal	10f	1 ml in 3.14 cm^2 glass ring	single dose, blood sampled up to 2 h	Penetration rate 15 µmol/cm^2/h.	Johanson and Fernstrom (1986)

APPENDIX D: Absorption, Distribution, Metabolism and Elimination Studies (ADME)

Compound	Species (Strain)	Route	Animals per dose level	Exposure conc. or dose	Time	Results	Reference
EGBE	guinea pigs	dermal	10f	1 ml in 3.14 cm^2 glass ring of 100%, 80%, 40%, 20% or 5% (n=2) or 10% (n=4) EGBE in water	single dose, blood sampled up to 2h	Penetration rates 2.3, 5.2, 6.2, 5.9, 4.5 and 4.4 µmol/cm^2/h for 100%, 80%, 40%, 20%, 10% and 5% EGBE in water respectively. Penetration rate for 100% EGBE in second exposure (n=10) was 7.9 µmol/cm^2/h. Blood levels were 1.8-14.2 µmol/l.	Johanson and Fernstrom (1988)
	guinea pigs	*iv*	10f	10.8 mg/kg	single dose, blood sampled up to 2 h	Average Clearance 128 ml/min/kg, mean residence time 4.7 min.	Johanson and Fernstrom (1986)
EGPhE	rats (Wistar)	oral	4m	15.6 mg/kg	single dose, 96h collection	Recovery 96%; 94% urine, 0.8% faeces, 1.3% CO_2 and 1.1% carcass.	Howes (1988)
			4m	27.4 mg/kg	single dose, 96h collection	Recovery 97%; 94% urine, 0.9% faeces, 1.5% CO_2 and 1.3% carcass.	
			4m	160.7 mg/kg	single dose, 96h collection	Recovery 98%; 94% urine, 1.3% faeces, 1.3% CO_2 and 1.3% carcass.	
			4f	27.4 mg/kg	single dose, 96h collection	Recovery 95%; 91% urine, 1.3% faeces, 2.2% CO_2 and 1.2% carcass.	

APPENDIX D: Absorption, Distribution, Metabolism and Elimination Studies (ADME)

Compound	Species (Strain)	Route	Animals per dose level	Exposure conc. or dose	Time	Results	Reference
EGPhE	rats (Wistar)	dermal	4m,4f	18 mg/kg over 10 cm^2, occlusive	single dose, 48h collection	Recovery 76%(m) or 65%(f); 55-60% urine, 0.6-1% faeces, 1.1-1.3% CO_2, 2-2.5% carcass and 6.5-11% skin/patch.	Howes (1988)
			4m,4f	24 mg/kg over 10 cm^2, occlusive	single dose, 48h collection	Recovery 73%(m) or 67%(f); 55-58% urine, 1.7-2.2% faeces, 1.5-1.6% CO_2, 2.3-2.4% carcass and 6.5-8% skin/patch.	
			4f	6.3 mg/kg over 10 cm^2, oil in water cream, occlusive	single dose, 48h collection	Recovery 93%; 80% urine, 3.1% faeces, 2.2% CO_2, 3.7% carcass and 5% skin/patch.	
			4f	7.2 mg/kg over 10 cm^2, water in oil, cream, occlusive	single dose, 48h collection	Recovery 98%; 84% urine, 1.5% faeces, 2.2% CO_2, 3.1% carcass and 6.6% skin/patch.	
			3f	6.2 mg/kg over 10 cm^2 in 50% anionic shampoo base, rinsed after 1, 5 or 10 min, occluded	single dose, 48h collection	Recovery >99%; 94-99% in rinsings, 1.1-2.5% skin/patch, 0.5% (1 min) 1.2% (5 min) or 2% (10 min) in urine, <0.1% faeces and 1-1.2% carcass.	
	rats (Wistar)	oral/dermal	3/4m or f	6.2-160 mg/kg	single dose, 48/96h collection	Analysis of urinary radioactivity from above studies identified 2 major components (2-phenoxyacetic acid (>75%) and EGPhE) and 2 minor components.	Howes (1988)
	rabbits (NZ white)	oral	3f	800 mg/kg	single dose	2-phenoxyacetic acid at ca 1,000 µg/ml identified in serum up to 25h after dosing. EGPhE 25 µg/ml at ca 1h after dosing, not detectable at 3h.	Breslin *et al* (1991)

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Compound	Species (Strain)	Route	Animals per dose level	Exposure conc. or dose	Time	Results	Reference
DEGME	rats (Wistar)	oral	4 or 8	0 mg/kg 500 mg/kg 1000 mg/kg 2000 mg/kg	1,2,5 or 20 d	↓ liver weight at high dose (20 days). ↑ hepatic microsomal protein content and induction of cytochrome p450. No effect on cytosolic ADH-Cyt C reductase.	Kawamoto *et al* 1990b)
	human	skin penetration *in vitro*	excised human abdominal skin (area 1.8 cm^2)	1 or 5 ml per diffusion cell	8 h	Permeability constant = 2.06 cm/h x 10^4. Rate of penetration 0.206 mg/cm^2/h.	Dugard *et al* (1984)
DEGEE	human (sex unknown)	oral	one	ca. 20 mg/kg	-	12h urine sample contained metabolite (2-ethoxy-ethoxy) acetic acid (68% dose)	Kamerling *et al* (1977)
	human	skin penetration *in vitro*	excised human abdominal skin (area 1.8 cm^2)	1 or 5 ml per diffusion cell	8h	Permeability constant = 1.32 cm/h x 10^4. Rate of penetration 0.125 mg/cm^2 per h.	Dugard *et al* (1984)
DEGBE	human	dermal, *in vitro*	-	undiluted	8h	Penetration rate 0.22 µmol/cm^2/h.	Dugard *et al* (1984)
	rats (Wistar)	oral, *ip* and *sc*		7 mg/kg	single dose, 96h collection	Excretion pattern similar for all routes. Recovery 90 - 93% : 78-86% urine (66-75% within 6h); 0.5-1.3% faeces, 6.7-11% CO_2, 1% or less carcass.	Unilever (1984b)
	rats (Wistar)	dermal		730 mg/kg over 10 cm^2, clipped or unclipped, occluded patch	single dose, 48h collection	Excretion pattern similar for clipped and unclipped animals. Recovery 67 - 73% : 37% urine, 1.7% faeces, 4-6% CO_2, 3% carcass, 20-26% skin/patch. Major urinary matabolite was not DEGBE. Penetration rate was 0.55 µmol/cm^2/h.	Unilever (1984b)
	rats (Sprague-Dawley)	dermal	4 m, 4 f	200 mg/kg or 2,000 mg/kg	single dose, occluded for 24 h	Recovery : 83-89%. Major urinary metabolite 2-(2-butoxyethoxy) acetic acid; 5.2-8.2% of urinary radioactivity was labile to β-glucuronidase, releasing DEGBE. Traces of 2-butoxyacetic acid were not quantified. Penetration rate was 4.5 µmol/cm^2/h (m) or 9 µmol/cm^2/h (f).	Boatman *et al* (1993)

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Compound	Species (Strain)	Route	Animals per dose level	Exposure conc. or dose	Time	Results	Reference
DEGBEA	rats (Sprague-Dawley)	oral	5m	200 mg/kg	single dose, 72h collection	97% recovery; 83% urine, 2% faeces, 5% CO_2,4% carcass. 59% urinary radiolabel was 2-(2-butoxy-ethoxy) acetic acid, 15% aryl sulphatase labile conjugates, 12% diethylene glycol,12% 2-(2-,(3- or 4-hydroxybutoxy)-ethoxy) ethanol, 2% acid labile. No DEGBEA or DEGBE in urine, no significant metabolism to EGBE or 2-butoxyacetic acid.	Deisinger and Guest (1989)
				2,000 mg/kg	single dose, 72h collection	101% recovery; 84% urine, 3% faeces, 5% CO_2, 4% carcass. 53% urinary radiolabel was 2-(2-butoxyethoxy)acetic acid, 32% diethyleneglycol + 2-(2-,(3- or 4-hydroxybutoxy)-ethoxy) ethanol, 7% aryl sulphatase labile conjugates, 8% acid labile. No DEGBEA or DEGBE in urine, no significant metabolism to EGBE or 2-butoxyacetic acid.	
	rats (Sprague-Dawley)	blood, *in vitro*	5m	5 mM, 37°C	Samples taken 0-14 min.	94% hydrolysis of DEGBEA to DEGBE after 10 minutes.	Deisinger and Guest (1989)
	rats (Sprague-Dawley)	dermal	4m, 4 f	200 mg/kg or 2,000 mg/kg	Single dose, occluded for 24 h	Recovery 80-88 %. Major urinary metabolite 2-(2-butoxyethoxy) acetic acid. Penetration rate was 7.7 µmol/cm^2/h (m) or 6.3 µmol/cm^2/h (f).	Boatman *et al* (1993)
DEGDME	mice (CD-1 Swiss) Time mated	oral	60f	3.73 mmol/kg (500 mg/kg)	Dose administered gd.11. Excreta samples collected for 48h postdose.	Rapid elimination of radioactivity via urine (63% dose in 0-48h). Two principal metabolites in 0-48h urine: (2-methoxyethoxy) acetic acid (63% dose) and methoxy acetic acid (28% dose).	Daniel *et al* (1991)
	rats (Sprague-Dawley)	oral	10 m	Single dose of 0.051 or 5.1 mmol/kg (6.84 and 684 mg/kg)	0-96h	Rapid elimination of administered radioactivity at both dose levels. 0-24h urine samples contained >70% of dose. Profile of metabolites in urine similar at each dose level. Major metabolite was (2-methoxyethoxy)-acetic acid (ca 70% dose). A second metabolite (ca 6% dose) was identified as methoxyacetic acid.	Cheever *et al* (1988)

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Compound	Species (Strain)	Route	Animals per dose level	Exposure conc. or dose	Time	Results	Reference
DEGDME	rats	oral	5m per treatment group	Single dose of 5.1 mmol/kg (684 mg/kg) ^{14}C DEGDME to naive rats and to rats pretreated with (a) phenobarbitone (0.1% in drinking water) or (b) non radio-active DEGDME (5.1 mmol/kg per day) for 22 days.	0-96h	Urine was major route of elimination in each case. Metabolic profile qualitatively similar in naive and pretreated animals. Quantitative increase seen in methoxyacetic acid content of 0-96h urine between naive rats 6.2% dose and rats pretreated with DEGDME (10% dose) phenobarbitone (13.4% dose).	Cheever *et al* (1989b)
TEGEE	human	Skin penetration *in vitro*	excised human skin (2.5 cm^3)	undiluted test substance	12 h	Skin penetration rate < 0.125 mol/cm^2/h.	Leber *et al* (1990)
TEGBE	human	Skin penetration *in vitro*	excised human skin (2.5 cm^3)	undiluted test substance	12 h	Skin penetration rate < 0.125 mol/cm^2/h.	Leber *et al* (1990)
2PG1ME	rats (Fischer 344)	oral	3 m	90 mg/kg 780 mg/kg	single dose 48 h collection	50-60 % exhaled as CO_2 10-20 % excreted in urine as: unchanged 2PG1ME, propylene glycol and sulfate and glucuronate conjugates of 2PG1ME.	Miller *et al* (1983b)
	rats (Fischer 344)	inhalation (nose-only) (whole body)	2 m/2 f 6 m/6 f	300 ppm 750 ppm 1,500 ppm 3,000 ppm 3,000 ppm 3,000 ppm	6 h/d 1 d 6 h/d 1 or 10 d	↑ blood concentration without reaching a plateau: absorption limited by respiration, not saturated . End of exposure blood concentrations not proportional to exposure concentration. Clearance best described with pseudo zero order kinetics. Elimination practically completed within 24 h.	Morgott and Nolan (1987)

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Compound	Species (Strain)	Route	Animals per dose level	Exposure conc. or dose	Time	Results	Reference
2PG1ME	rats (Fischer 344) and mice (B6C3F1)	oral and injection *i.v.*	no indication	90 mg/kg 450 mg/kg	single dose	43-77 % exhaled as CO_2 7-16 % excreted in urine. Rate of exhalation of CO_2 faster in mice than in rats. Metabolism and excretion faster in mice than in rats.	Ferrala *et al* (1992)
2PG1MEA	rats (Fischer 344)	oral	3 m	1,150 mg/kg (8.7 mmol/kg)	Single dose 48 h collection	64 % exhaled as CO_2; 24% excreted in urine as: 2PG1ME, propylene glycol and sulfate and glucuronate conjugates of 2PG1ME.	Miller *et al* (1984)
	rats (Fischer 344)	inhalation	6 m	3,000 ppm	6 h/d 1 d 48 h collection	53 % exhaled as CO_2; 26 % excreted in urine as: 2PG1ME, proprylene glycol and sulfate and glucuronate conjugates of 2PG1ME.	Miller *et al* (1984)
TPGME	rats (Fischer 344)	oral	3 m	206 mg/kg (1 mmol/kg) 825 mg/kg (4 mmol/kg)	Single dose 48 h collection	16 % exhaled as CO_2 69 % excreted in urine as tripropylene glycol (TPG) and dipropylene glycol methyl ether (DPGME) and subsequent degradation products, but no 2-methoxypropionic acid. 16 % exhaled as CO_2 75 % excreted in urine. Same metabolites as at 1 mmol/kg. Only 5% of unchanged TPGME.	Calhoun *et al* (1986a,b) Miller (1987)

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