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The Toxicology of Ethylene Glycol Monoalkyl Ethers and its Relevance to Man

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THE TOXICOLOGY OF ETHYLENE GLYCOL MONOALKYL ETHERS AND ITS RELEVANCE TO MAN

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SUMMARY

1. Glycol ethers are a group of chemicals used widely as co-solvents and marketed under a variety of trade names. The current recommended exposure limits are mainly based on human case histories from the 1930's, but the results of recent animal studies have prompted a re-evaluation of their hazards. ECETOC set up a working group : to evaluate studies relevant to the toxicity to man of glycol ethers in general, and ethylene glycol monomethyl (EGME) and monoethyl (EGEE) ethers in particular, including evidence from human exposure; to advise on the significance for human exposure; to recommend studies which may be necessary to clarify the situation.

2. EGME and EGEE have been shown in experimental animals to cause haematological effects characterised by reductions in the numbers of circulating red and white blood cells, bone marrow and lymph node depression, testicular atrophy, foetotoxicity and teratogenicity. These effects have been observed in two or more animal species exposed by inhalation, dermal and oral routes. EGME appears to be two or three times more potent than EGEE. No-effect levels for inhalation and for oral exposure have yet to be defined for the effects of these compounds.

3. Ethylene glycol monoisopropyl (EGiPE) and ethylene glycol monobutyl (EGBE) ethers appear to have a different spectrum of activity. Their major effect on the blood is haemolysis. Effects on the testes are absent or less severe than with EGME and EGEE. There are no data on their teratogenic activity.

4. Case histories of human over-exposure have shown that EGME can cause haematological and also neurological effects similar to those seen in experimental animals. There are no comparable data for EGEE.

5. Consideration of the similarity in several animal species of the nature of the effects and of the exposure levels at which they occur, coupled with evidence that haematological effects of EGME are also seen in man, suggests that it would be unreasonable to disregard the evidence provided by the animal studies. It is prudent to assume, in the absence of evidence to the contrary, that in addition to the adverse effects on the haemapoietic system of man the effects on the testes and the developing embryo will also occur in exposed humans. No-effect-levels have not yet been found for either the testicular or teratogenic effects. The exposure levels at which these

effects have been found in animals suggest that the present recommended exposure control limits may not afford adequate safety margins for man.

6. Studies are being sponsored by the Chemical Manufacturers'Association to establish no-effect-levels for EGME and EGEE and to investigate the teratogenicity of EGBE.

7. Recommendations for improving our understanding of the situation have been made by the Working Group. The conclusions in this report should be reviewed when new data are available.

CONTENTS

A. INTRODUCTION

Glycol ethers are widely used chemicals. The monoalkyl ethers are usually produced by reacting ethylene oxide with the appropriate alcohol or by direct alkylation of a selected glycol with agents such as dialkyl sulfate. Ethylene glycol monoalkyl ethers are extensively used as co-solvents and are marketed under a variety of names. As they are miscible with water and a large number of organic solvents they are especially useful as co-solvents in many oil-water compositions. They are used as solvents for various resins, lacquers, paints, varnishes, dyes, inks, printing pastes, cleaning compositions, liquid soap and cosmetics. They are also used widely as chemical intermediates.

Glycol ethers are colourless liquids with mild ethereal odours and with boiling points, vapour pressures and evaporation rates dependent on the type of glycol and alkyl moiety. More detailed information about the production, properties and uses of glycol ethers is given in Appendix 1.

The current recommended exposure control limits (cf.Appendix 2) are mainly based on human studies such as those by Greenburg et al.(1938) which showed that overexposure of humans to ethylene glycol monomethyl ether was associated with disorders of the blood and central nervous system. These effects were later confirmed in animal studies. Attention has recently been focussed on glycol ethers as the result of studies demonstrating adverse effects on the reproductive processes of animals, namely testicular atrophy and foetal development. Since glycol ethers are widely used it was considered important to assess the available data. A Glycol Ether Working Group (WG; see list of members in H) was set up by ECETOC, with the following terms of reference :

"To evaluate studies relevant to the toxicity to man of glycol ethers in general and ethylene glycol monomethyl and monoethyl ethers in particular, including evidence from human exposure; to advise on the significance of such evidence for human exposure;to recommend studies which may be necessary to clarify the situation".

In this report the WG gives an assessment of the available data on ethylene glycol ethers. Some data on propylene glycol ethers have been included for comparison. The working group is aware of studies in progress but believes that the conclusions reached in this report are unlikely to be invalidated by the

results of these studies. Abbreviations of the names of the glycol ethers used in this report are given in Table 1.

Table 1

Names		Abbreviations	CAS-No.
ethylene glycol-methyl ether	$HO-CH_2CH_2-O-CH_3$ 2-methoxyethanol	EGME	109-86-4
ethylene glycol-ethyl ether	$HO-CH_2CH_2-OCH_2CH_3$ 2-ethoxyethanol	EGEE	110-80-5
ethylene glycol-isopropyl ether	$HO-CH_2CH_2-O-CH(CH_3)_2$ 2-isopropoxyethanol	EGiPE	109-59-1
ethylene glycol-n-propylether	$HO-CH_2CH_2-O-CH_2CH_2CH_3$ n-propoxyethanol	EGnPE	2807-30-9
ethylene glycol-butyl ether	$HO-CH_2CH_2-O-CH_2CH_2CH_2CH_3$ 2-butoxyethanol	EGBE	111-76-2
ethylene glycol-phenyl ether	$HO-CH_2CH_2-O-C_6H_5$ 2-phenoxyethanol	EGPhE	122-99-6
2-Propylene glycol-methyl ether	$CH_3-CH(OH)CH_2-O-CH_3$ 1-methoxypropanol-2	PGME	107-98-2
Ethylene glycol	$HO-CH_2CH_2-OH$	EG	107-21-1
Ethylene glycol-acetate	$HO-CH_2CH_2OOC-CH_3$	EGAc	542-59-6
Ethylene glycol methyl-ether acetate	$CH_3COOCH_2CH_2-O-CH_3$	EGMEAc	110-49-6
Ethylene glycol ethyl-ether acetate	$CH_3COO-CH_2CH_2-O-C_2H_5$	EGEEAc	111-15-9

B. TOXICOLOGY OF GLYCOL ETHERS

1. Haematological and Testicular Effects.

The adverse effects of EGME on the testes and bone marrow of experimental animals have been known for many years. Since both tissues contain rapidly dividing cells it was considered appropriate to review the effects of glycol ethers on both systems in parallel.

1.1. Historical Data

1.1.1. Human data

a) Haematological effects. The first report of haematological changes ascribed to EGME intoxication appears to have been that made by Donley (1936) in which a 45 year old caucasian woman, in addition to exhibiting neurological symptoms, was found to have anaemia (red blood cell count $3.5 \times 10^6 mm^{-3}$, and a haemoglobin value of 85%).* The white blood cells were unaffected. Whether EGME caused these changes is uncertain; the woman had been exposed to a solvent containing 3% EGME and 74% isopropyl alcohol.

Parsons & Parsons (1938) described two cases of exposure to EGME in which the predominant symptom was fatigue. Both subjects had reduced erythrocyte and leucocyte counts and were diagnosed as having aplastic anaemia. In the same year, Greenburg et al.(1938) reported a variety of haematological abnormalities in workers employed in a collar-fusing plant in which EGME was used as a 33% solution in denatured alcohol. In 19 subjects there was a general immaturity of neutrophils with some abnormal forms, and in the majority of cases a lower number of platelets. Blood haemoglobin concentrations were high in relation to the number of erythrocytes which, together with a slightly higher mean corpuscular volume, suggested a macrocytic type of anaemia. Since the reticulocyte counts were normal and serum bilirubin concentrations generally low, the abnormal blood picture was ascribed to an effect on the bone marrow rather than on the blood itself. The solvent mixture used in this factory contained EGME, ethyl alcohol and small amounts of ethyl acetate and methyl alcohol. Since ethyl alcohol has never been associated with such effects and the exposure levels to ethyl acetate

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* In this report the UK system for numbers is used, ie. ten thousand is 10,000 and one point two is 1.2

and methyl alcohol were so low,it seems unlikely that these substances could be responsible for the observed effects. All the subjects were in their late teens or early twenties and the duration of exposures quoted ranged from 1 to 12 months.Atmospheric concentrations at the time of intoxication were not measured although later investigations suggested that they were in the order of EGME 76 ppm, ethyl alcohol 215 ppm, methyl alcohol 16 ppm, ethyl acetate 5 ppm and petroleum naphtha 1 ppm.

Zavon (1963) presented case histories of 5 workers exposed to EGME. All had worked in a printing department where the floor and the printing machines were cleaned with EGME. Estimations of atmospheric EGME in simulated conditions gave concentrations ranging from 61 to 3960 ppm. Erythrocyte counts and haemoglobin levels were generally below normal and a bone marrow smear on one subject showed hypoplasia with a reduced number of erythroid elements. All patients experienced weakness and lethargy which may have originated from either their anaemia or the central nervous depressant effects of the solvent.

Ohi & Wegman (1978) described two cases of poisoning believed to have resulted from skin contamination with EGME. Both showed signs of anaemia. There was no increase in the numbers of reticulocytes in either case and a study of bone marrow biopsies revealed hypoplasia. In one patient slight haemoglobinuria was also observed,suggesting a haemolytic process.

b)Testicular Effects.There have been no reports of an association between exposure to glycol ethers and adverse effects on human testes. One of the subjects investigated by Zavon (1962) complained of impotence but this may have been a manifestation of general debility resulting from anaemia and CNS effects.

1.1.2. Experimental data

a)Haematological effects.Haematological changes similar to those described in humans have been found in cats exposed to 1.1 to 1.3 mg/l (350 ppm) of EGME vapour several hours per day for 6 days(Flury & Wirth, 1933) and in rats exposed to atmospheres containing between 300 and 400 ppm of either EGME, EGEE, EGnPE, EGiPE or EGBE, 7 hours per day, 5 days per week for 5 weeks (Werner et al.,1943a). The exposure conditions were not sufficient to produce any overt signs of toxicity.

A summary of the histological and haematological findings is given in Table 2 :

Table 2

	decreased RBC(1)	decreased Hb(2)	increased retics(3)	increased juvenile granulocytes	bone marrow hypoplasia	haemo-siderosis spleen	decreased extra medullary haema-poiesis
EGME	-	-	+	+	+	-	-
EGEE	-	-	+	+	+	+	-
EGiPE	+	+	+	+	+	-	+
EGnPE	+	+	+	+	-	-	+
EGBE	+	+	+	+	-	-	+
Control	-	-	-	-	-	-	-

(1) Red Blood Cell Count
(2) Haemoglobin Concentration in Blood
(3) Reticulocyte Count

+ present
- absent

A reduction in erythrocytes and haemoglobin concentration and a compensatory elevation in reticulocytes, occurred with the n-propyl, isopropyl and butyl ethers after one week of treatment,followed by a gradual return to normal. These changes which suggested a haemolytic process were absent in animals exposed to equimolecular concentrations of the methyl and ethyl ethers. This evidence of a haemolytic effect following exposure to EGiPE, EGnPE and EGBE was supported by the observation of haemoglobinuria in mice exposed to these compounds (Werner et al., 1943-a). In terms of in vitro haemolytic activity, the order of potency was EGBE, EGiPE, EGnPE, EGEE, EGME, which parallels their order of efficacy in reducing the surface tension of water. Although there was no appreciable change in the leukocyte count with any of the solvents tested, the percentage of juvenile granulocytes increased. Examination of bone marrow from the middle of the femoral shaft showed replacement of fat by active marrow in some animals from all treatment groups.

Werner et al.,(1943-b) exposed groups of two dogs to atmospheres containing EGME (750 ppm), EGEE (840 ppm) or EGBE (415 ppm), 7 hrs/day, 5 days/week for 12 weeks. All three materials caused a decrease in the haemoglobin concentration, erythrocyte count and haematocrit value which were maximal after 4 to 6 weeks. On cessation of treatment there was a gradual recovery. Examination of blood smears showed marked microcytosis and hypochromia in the animals treated with EGME and EGEE and a similar but less pronounced effect in animals treated with EGBE. A reduction in total white cells noted in the EGEE group at the end of the first week was attributed to a decrease in the number of lymphocytes.An increase in the number of juvenile granulocytes similar to that found previously in rats was noted for both EGME and EGEE between 1 and 8 weeks. Although all three materials were shown to produce anaemia in the dog there was no evidence, even for EGBE, that this was the result of a haemolytic process.

It would therefore appear that there is some similarity between the effects of EGME in dogs and man in that the erythroid elements are affected as well as the white cells.In rodents it is the white cell population that is predominantly affected.

Carpenter et al.(1956) demonstrated an increase in osmotic fragility of erythrocytes in rats, mice and rabbits and to a lesser extent in guinea pigs, rhesus monkeys and humans exposed to EGBE. Repeated inhalation exposure in rodents and dogs resulted in : haemoglobinuria; reduced erythrocyte counts; reduced haemoglobin concentration; increased reticulocytes; and haemolytic anaemia. The haemolytic effects of a number of other glycol ethers were investigated following a four-hour inhalation exposure in rats. The lowest concentrations causing increased erythrocyte fragility were EGME 2000 ppm, EGnPE 62 ppm, EGiPE 62 ppm, and EGBE 62 ppm. A concentration of EGPhE approaching saturation did not increase fragility. Potency was similar to that established by Werner et al.(1943-a). A further experiment was described in which 3 humans and 3 rats were simultaneously exposed for 8 hours in one day to an atmospheric concentration of 195 ppm. The osmotic fragility of the rat erythrocytes increased throughout the exposure, whereas the human erythrocytes were unaffected.

Repeated oral administration of PGME at doses from 1 to 6ml/kgbw/day* in mice, rats and dogs for 2, 13 and 14 weeks respectively, showed no clear or consistent effects on the haemapoietic system (Stenger et al.,1972).

A dose-related increase in Heinz bodies found in mice given 1 to 6ml/kgbw/day of PGME was considered "biologically irrelevant" because of the high doses used. In view of the lack of detail in this report it is impossible to judge the significance of these findings. There was no indication of Heinz-body formation in the rat or dog, or of haemolytic anaemia in any of the three species. Irrespective of the above findings, PGME clearly does not possess the same type of activity as EGME.

b) Testicular effects. The first report of degenerative changes in the seminiferous epithelium was made by Wiley et al.(1938). Two rabbits administered EGME showed degenerative changes and desquamation of the germinal epithelium, with giant cell formation. Degenerative lesions of the testes were also noted in 3 of 4 rabbits administered EG or EGAc. The precise doses and route of administration employed are not clear from the report, although it was stated that the animals were "injected". There were no reported effects on the blood or lymphoid organs .

A 90-day feeding study carried out in 1960 (Tyler,1981) in which rats were fed diets containing 0.01, 0.05, 0.25 and 1.25% EGBE caused testicular atrophy at the two highest levels. There was no mention of any haematological abnormalities.

Stenger et al.(1971) described testicular oedema in rats given subcutaneous doses of EGEE of approx. 200 and 400mg/kgbw/day for 4 weeks. Similar lesions were also reported in the testes of dogs given oral doses of approximately 50 to 200 µl/kgbw/day for 13 weeks. A reduction in haemoglobin concentration and haematocrit value was also noted.

Stenger et al.(1972) administered PGME to rats in doses up to 4 ml/kgbw per day (about 4000 mg/kgbw/day) for four weeks subcutaneously or 13 weeks orally. No testicular atrophy was reported. Three dogs treated with 2 or 3 ml/kgbw PGME, 5 days per week for 14 weeks were described as

* kgbw : kilogram body weight.

having an "abundance of spermiophages in the apertures of the epididymis". The meaning of these histological changes are not clear. They were not reported in the other species examined and cannot be equated with the gross testicular damage produced by EGME.

1.2. Recent Information

Nagano et al.(1979) reported the results of a series of experiments to investigate the testicular effects of a number of glycol ethers and glycol ether acetates when administered by gavage 5 times per week for 5 weeks to groups of 5 adult male mice. EG, EGEE and EGEEAc were given at doses of 500, 1000, 2000 and 4000 mg/kgbw; EGME or EGMEAc at 62.5, 125, 250, 500, 1000 and 2000 mg/kgbw; and EGBE or EGPhE at 500, 1000 and 2000 mg/kgbw. Dose-related decreases in testicular weight were found at a dose of 250 µg/kgbw for EGME, 500 mg/kgbw for EGMEAc and 1000 mg/kgbw for EGEE and its acetate. The effects were most pronounced with EGME and least with EGEEAc. Histologically, the testes showed atrophic changes with a loss of germinal epithelium. Although there were no reported effects on the interstitial cells there was a reduction in weight of accessory glands. One animal in each of the groups administered 1000 mg/kgbw EGBE and EGPhE was reported to have "atrophied seminiferous tubules". The significance of these lesions is, however, questionable in view of their low incidence and their occurrence in untreated animals.

The most striking haematological changes were also found with EGME, EGEE and their respective acetates. These effects consisted of a significant decrease in leukocyte count with a less marked reduction in erythrocytes, haematocrit value and the haemoglobin concentrations. A reduction in erythrocytes only was found in the groups given 500 or 1000 mg/kgbw EGBE. The acetates appear to be equipotent on a molar basis.

Table 3 shows the lowest dose level at which the testicular and haematological effects of the compounds studied were seen.

TABLE 3

Lowest dose levels (mg/kgbw) for testicular and haematological effects in mice (Nagano et al., 1979)

COMPOUNDS	TESTICULAR ATROPHY	REDUCED NUMBER OF RED BLOOD CELLS	REDUCED NUMBER OF WHITE BLOOD CELLS	REDUCED HAEMO-GLOBIN LEVEL	REDUCED HAEMA-TOCRIT
EGME	250	1000	500	1000	no effect
EGEE	1000	no effect	2000	no effect	no effect
EGMEAc	500	no effect	1000	2000	no effect
EGEEAc	1000	no effect	2000	no effect	4000
EGBE	1000*	500	no effect	no effect	no effect
EGPhE	1000*	no effect	no effect	no effect	no effect
EG	no effect	no effect	no effect	no effect	no effect

* equivocal data

Although erythrocyte count and haemoglobin concentration were reduced, there were no effects such as haemoglobinuria, splenomegaly or haemosiderosis indicating a haemolytic process. Reticulocyte counts were not made. These findings support the view that bone marrow suppression is most pronounced with the methyl and ethyl ethers.

A series of short-term inhalation and skin-application studies on EGBE carried out by Union Carbide (summarised by Tyler,1981) corroborated some of the previously-reported haematological changes caused by EGBE. Fischer 344 rats were exposed to 20, 86 and 245 ppm of EGBE vapour, six hours per day for 5 days, and for a further 4 days following 2 days without exposure. Haemoglobinuria was found after 2 days of treatment in the female rats exposed to 245 ppm. This effect was transitory and was not found in any other treatment group. Haematological changes were found in both male and female rats exposed to 245 ppm, although these were not specified. A decreased haemoglobin concentration and an increased mean corpuscular volume were seen in both sexes at 86 ppm EGBE.

The percutaneous toxicity of EGBE in rabbits was investigated by the application of 1 ml of 5, 25, 50 or 100% aqueous solutions under occluded conditions, the exposure schedule being as in the inhalation studies. Haemoglobinuria was found in many rabbits treated with the undiluted and 50% solutions but not with the lower concentrations. A reduction in leucocyte count was reported in the male rabbits exposed to the undiluted material although the author expressed some reservations on its relevance to treatment. Reductions in erythrocyte count, haemoglobin concentration and mean corpuscular haemoglobin were observed in female rabbits receiving the undiluted material.

The results of a 90-day inhalation study in rats reported in the same paper showed significant decreases in erythrocyte count, haemoglobin concentration and mean corpuscular haemoglobin in animals exposed to 77 ppm by inhalation for 6 hrs/day, 5 days/wk for 13 weeks. No changes were seen at the lower levels, ie. 5 or 25 ppm, and no histological changes occurred in the testes or bone marrow at any levels.

Results of a short-term study of the inhalation toxicity of EGME and PGME (Miller et al.,1981) substantiated the previous reports of haematological and testicular effects of EGME. In these experiments male and female Fischer 344 rats and B6C7F1 mice were exposed to 0, 100, 300 and 1000 ppm of EGME or 0, 300, 1000 or 3000 ppm of PGME for 6 hours/day for 9 days during an 11 day period. At the 1000 ppm level of EGME there was a reduction in red and white blood cell counts and haemoglobin concentration, a depletion of both myeloid and erythroid cells from bone marrow, and lymphoid atrophy. There was also a statistically-significant reduction in leucocyte count in the 100 ppm group which , although small in relation to historical control values, seems likely to be related to treatment in view of the marked effects seen at the higher dose levels.There was a loss of germinal epithelium, and giant cells were formed in the testes of all animals exposed to 1000 ppm EGME, although sperm was still present in the epididymides. Similar but less marked effects were reported at the 300 ppm level.In contrast there were no gross or histopathological changes that could be ascribed to PGME even at the 3000 ppm exposure level.

Studies (Dow Chemical Company,1982) in which rats and rabbits were exposed to 0, 30, 100 or 300 ppm of EGME for 6 hours/day, 5 days per week for 13 weeks have similarly shown leukocytopenia, severe bilateral

testicular atrophy and atrophy of thymic and intestinal lymphoid tissues in both species at 300 ppm.Infertility was reported in male rats exposed at the 300 ppm level but not in those exposed at 30 or 100 ppm. Although there were no testicular effects in rats exposed to 100 ppm, 3 of 5 male rabbits were reported to have moderate to severe degenerative changes in the testes and, at 30 ppm, 1 of 5 rabbits showed slight testicular changes.

McGregor et al.(1981) reported the results of a dominant lethal study in which male mice were exposed to EGME at 25 and 500 ppm in air, 7 hrs/day for 5 days. The number of pregnancies in the females mated with the control and 25 ppm groups were similar. There was,however,a marked reduction in pregnancies in the females mated with males exposed to 500 ppm between 4 and 8 weeks after the end of treatment.

1.3. Conclusions

The studies described above show that glycol ethers may produce haemolytic anaemia and depression of bone marrow;extramedullary haemapoetic tissue; and in some instances lymphoid organs. The haemolytic effects appear more pronounced in mice, rats and rabbits than in dogs and men, and increase with the size of the alkyl moiety, being minimal with the methyl and ethyl, and greater with the propyl and butyl ethers. Depression of the bone marrow, on the other hand, appears to be most marked with the methyl and ethyl ethers and less marked or absent with higher homologues.

Effects on the germinal epithelium of the testis appear to parallel the bone marrow depression, being greater with the methyl and ethyl than with the butyl and phenyl ethers. This suggests that the mechanism of action may be similar on both organs. Inhibition of cell division provides a plausible mechanism for the bone marrow depression as well as the testicular effects of these materials.
In appendix 3 all the available data are summarised in tabular form. The conclusions specific to each of the glycol ethers considered are summarised below.

EGME. Bone marrow depression, leading to anaemia and leukopoenia has been found in a range of animal species exposed to atmospheric concentrations as low as 100 ppm, and also in man. Degenerative changes in the testis have also been identified in a range of animal species.In

rabbits this was clearly demonstrated following exposure to atmospheric concentrations of 100 ppm. Although early studies suggested some haemolytic activity this does not appear to be marked.

EGEE. This possesses the same spectrum of activity as EGME, although it appears to be less potent. There is no reliable information on the inhalation exposure levels producing these effects in animals or man.

EGnPE. Early studies suggested that both bone marrow hypoplasia and haemolytic effects occur in rats, but there are no reliable studies to corroborate these findings. There are no reliable studies in which testicular effects have been investigated.

EGiPE. As with EGnPE, early studies provided evidence of both bone marrow depression and haemolytic effects although no testicular effects have been reported. Again, there are no recent studies to corroborate these findings.

EGBE. Although early studies suggested that EGBE causes bone marrow depression, more recent studies have failed to substantiate this. The predominant effect appears to be haemolytic and has been observed both *in vitro* and *in vivo*. Recent animal studies have shown haemolytic effects at inhalation exposure levels down to 77 ppm. There is equivocal evidence of testicular injury at high exposure levels.

EGPhE. There is little information on this material. It has not been found to affect the blood. The evidence for testicular injury is equivocal.

PGME. No haematological and testicular changes could be attributed to PGME after exposure of experimental animals to atmospheric concentrations up to 3000 ppm for 2 weeks.

2. Renal Toxicity

Kidney damage was said to occur in a variety of species following exposure to EGME, EGEE, EGnPE or EGBE (Gross,1943). The significance of these observations is uncertain since control data and experimental details were deficient.

Kidney enlargement was reported by Carpenter et al.(1956) following repeated exposure of rats and guinea pigs to EGBE by inhalation. The lowest exposure levels at which this enlargement was found were 107 and 203 ppm (30 x 7hr exposures) respectively.

"Altered" kidney weight and "microscopical lesions"(nature unspecified) were also noted in rats given 0.74 g/kgbw EGEE in the diet for 30 days (Smyth et al.,1953). Kidney enlargement was reported in rabbits treated topically with 0.08 to 0.25 ml/kgbw EGBE (Duprat & Gradski, 1979) and in pregnant rats exposed to atmospheres containing 765 ppm EGEE throughout gestation (Hardin et al.,1981).

Although kidney enlargement has been variously reported for some glycol ethers there do not appear to be any consistent histological changes. Following single exposure of rats to atmospheres containing 432 ppm EGBE, Carpenter et al.(1956) found cloudy swelling in the tubular cells of the kidney and in vivo haemolysis after 2 hours. Haemoglobinuria was found after 3 hours and haemin crystals after 4 hours. After 8 hours, marked cloudy swelling of the convoluted tubules and loops of Henle were reported. The diagnosis of cloudy swelling has been a matter of some controversy, since this condition, particularly in the kidney, may be mimicked by post mortem changes. The significance of these changes should therefore be viewed with some circumspection. Stenger et al.(1971) reported the presence of albumin and erythrocytes in the urine of rats injected subcutaneously with approximately 400 or 800 µl/kgbw/day EGEE for 4 weeks. The histological changes described were congestion of the tubular epithelial cells and constriction of the lumen. Slight changes in the lumen of the convoluted tubules were also reported in 3 of 6 dogs given approximately 200 mg/kgbw/day of EGEE for 13 weeks.

2.1. Conclusion

There are no clear or consistent pathological changes in the kidneys of animals exposed to glycol ethers. Although kidney enlargement appears to occur in animals exposed to either EGBE or EGEE there is no indication of any functional impairment.

3. Teratological, Embryotoxic and Foetotoxic Effects.

The data available on ethylene glycol and propylene glycol monoalkyl ethers are summarised below.

3.1. EGME

Nagano et al.(1981) administered EGME in deionised water, to pregnant mice, by gastric intubation on days 7 to 14 of gestation at levels of 0, 31.2, 62.5, 125, 250, 500 and 1000 mg/kgbw. On day 18 of gestation the mice were killed and examined. Maternal bodyweight gain was depressed in the 250, 500 and 1000 mg/kgbw groups and a significant decrease in the leucocyte count was observed in the 1000 mg/kgbw group. There was an increase in the incidence of dead foetuses in the 250 mg/kgbw group. Only one foetus survived in the 500 mg/kgbw group and showed exencephaly and abnormal digits. All the foetuses were dead in the 1000 mg/kgbw group. Reduction of foetal weight was noted in the 125 and 250 mg/kgbw groups. A total of 57 abnormal foetuses was found among 130 live foetuses in the 250 mg/kgbw group : 24 had exencephaly, 3 umbilical hernia, 29 abnormal digits and 1 both exencephaly and abnormal digits. In appendix 4 is given the lowest dose at which there were significant additional observations. There was a dose-dependent increase in skeletal abnormalities at doses of EGME which caused no maternal toxicity. Although soft tissues were not examined in the study, the results clearly demonstrate that EGME is teratogenic to mice.

A recent study of EGME inhalation with pregnant rats confirmed it to be foetotoxic (Doe et al.,1981). The rats were exposed to atmospheric concentrations of 100 and 300 ppm for 6 hours a day on days 6 to 17 of gestation. A modified Chernoff test was used in which the dams were allowed to litter and the pups observed and weighed over two days. No litters were produced by the rats exposed to 300 ppm and only nine out of the 20 dams exposed to 100 ppm littered. The number, weight and viability of the pups were reduced in these litters, but the pups appeared externally normal.

Preliminary results of the CMA teratogenicity study on EGME, released by the Dow Chemical Company (1982), indicate that exposure to air containing 50 ppm of EGME caused teratogenic effects in rabbits, and produced some evidence of foetotoxicity in mice. At an exposure level of 10 ppm, EGME was not considered teratogenic or foetotoxic on the basis of external and soft tissue examination in rabbits and mice. Exposure of rats to levels up to 50 ppm produced no evidence of teratogenicity or foetotoxicity. Skeletal examination of the foetuses has

not been completed and the final conclusions cannot yet be drawn regarding the no-effect level of EGME by inhalation.

3.2. EGEE. Stenger et al.(1971) dosed rats with EGEE, orally or subcutaneously, at 0, 12.5, 25, 100, 200 and 400 µl/kgbw/day throughout gestation. Skeletal abnormalities were increased eight-fold at 100 µl/kgbw and thirty-fold at 200 µl/kgbw. There was foetal mortality at 400 µl/kgbw, but no apparent maternal toxicity at the levels studied.

The teratogenicity of EGEE by inhalation has been examined in two studies. Nelson et al.(1980) examined the effect of exposing pregnant female rats to EGEE on days 7 to 13 or days 14 to 20 of pregnancy at 0, 100, 200 and 900 ppm for four hours a day. At 900 ppm no foetuses survived either exposure regime, and at 200 ppm there were 25% neonatal deaths following both treatments. There were several behavioural abnormalities in the offspring of the dams exposed to 100 ppm. Exposure from day 7 to day 13 of gestation caused impaired performance in the rota-rod test, and exposure from day 14 to day 20 of gestation caused a lowering of activity in the running wheel test. There were also some alterations in the neurochemistry of the cerebrum, the cerebellum, the brain stem and the mid-brain of the 21-day-old offspring from dams exposed to either regime. This experiment gave definite evidence of embryolethality caused by EGEE inhalation, but the significance of the behavioural tests is not clear.

Andrew et al.(1981) assessed the teratological effects in rats and rabbits exposed to EGEE by inhalation for 20 days prior to conception, or on days 1 to 19 of gestation , or for both periods. Exposure prior to conception had no effect, neither did it modify the effect of subsequent exposure during gestation in either species. The rats were exposed at two atmospheric concentrations, 200 and 770 ppm . No foetus survived to the day-21 sacrifice following exposure to 770 ppm, at which concentration there was evidence of maternal toxicity manifest as a reduction in bodyweight gain and reduced liver weight. At 200 ppm there was no evidence of maternal toxicity.There was an increase in both the number of resorptions and the number of resorptions per litter, and the foetal bodyweight and crown-to-rump length were reduced. There were significantly more cardiovascular defects, mainly transposed and retrotracheal pulmonary artery, and minor skeletal

defects and variants.The rabbits were exposed to 160 and 620 ppm. Again, no foetuses survived to the maternal sacrifice (on day 30) following exposure of the does to the higher concentration. There was some maternal toxicity: bodyweight gain was reduced and the liver and kidney weights were increased. There was an increase in the number of resorptions in the does exposed to 160 ppm, but the surviving foetuses were indistinguishable from the controls in respect of length and body weight. There was a significant increase in the incidence of major malformations : ventral wall defects, fusion of the aorta with the pulmonary artery, and minor anomalies in the kidneys. There were also some common skeletal variants. There was some evidence of maternal toxicity, ie. slightly increased liver and kidney weights. This study confirmed the embryolethality noted by Nelson et al.(1980), and gave evidence of teratogenicity in both species at levels in the range of 150 to 200 ppm.

Further work is necessary to find no-effect-levels. This is currently being sponsored by the Chemical Manufacturers Association (cf.Appendix 5).

Syrovadko and Malysheva (1977) reported an increased incidence of menstrual disorders attributed to hormonal disturbances in women engaged in enameled-wire production and an increased incidence of congenital defects (cardiovascular defects and talipes) in their offspring. The women were exposed to four materials : EGEE (although the translation mentioned "ethyl ethoxyethanol" it is presumed that EGEE is the compound referred to), chlorobenzene, tricresol and solvent naphtha. It is reported that there were significant amounts of chlorobenzene and tricresol in the atmosphere, but only "small amounts" of EGEE. Since low concentrations of EGEE would seem unlikely in a process which involves total loss of solvent composed of equal volumes of EGEE and chlorobenzene, it is possible that the analysis for EGEE was inadequate. Tricresol has been said to cause alteration in the oestrous cycle in rats (Pashkova,1973) and chlorobenzene to affect gonadal function in dogs and cats (Monsanto,1978). It is therefore possible that the above menstrual effects were due to tricresol and chlorobenzene. Teratogenic effects would not be expected for any of the solvents except EGEE. Although there is enough circumstantial evidence in Syrovadko and Malysheva's study to prevent their findings from being dismissed, additional evidence would be required from human studies to

establish EGEE as a human teratogen since the methodology (particularly with reference to the selection of control groups) and data are reported in insufficient detail.

3.3. EGBE

There are currently no data available. The teratogenic effect of EGBE in rabbits is to be investigated as part of the Chemical Manufacturers Association programme (cf.Appendix 5).

3.4. EGiPE, EGnPE, EGPhE

No data available.

3.5. PGME

Stenger et al.(1972) investigated the teratogenic effect of PGME in mice, rats and rabbits by administration by gavage or subcutaneous injection from day 0 to 18 of pregnancy in mice and rats, or from day 0 to 21 in rabbits. A range of doses from 36 to 1800 mg/kgbw was used. The only effect seen was retarded ossification of the skull in rats administered 720 mg/kgbw. The authors attributed this to a foetotoxic effect rather than a teratogenic effect. It is possible to conclude, therefore,that PGME is not teratogenic following oral or subcutaneous administration. The same is apparently true for PGME given by inhalation. Pregnant rats were exposed to atmospheric concentrations of 200 and 600 ppm for 6 hours a day on days 6 to 17 of gestation in a modified Chernoff test (Doe et al.,1982). The rats were allowed to litter and there were no effects on litter numbers, size, weight or viability. It appears, therefore, that PGME does not have the severe effects on the foetus produced by EGME and EGEE at equivalent doses.

3.6. PGEE

No data available.

3.7. Conclusions

In Appendix 4 all the available data are summarised in tabular form. The absence of data on EGiPE, EGnPE, EGBE and EGPhE makes it impossible to identify a structure-activity relationship. In laboratory animals, EGME and EGEE are embryotoxic and they appear to be teratogenic at low doses. PGME, however, does not share this activity at equivalent doses. The lowest doses causing effects are as follows :

EGME	- teratogenicity	- 31.2	mg/kgbw (orally)
		- 50	ppm (inhalation)
	- foetotoxicity	- 50	ppm (inhalation)
EGEE	- teratogenicity	- 160 to 200	ppm (inhalation)
	- foetotoxicity	- 400	µl/kgbw (orally)

The studies described here do not allow the no-effect levels to be derived for either EGME or EGEE. Work has been sponsored by the Chemical Manufacturers Association in the USA to determine such levels. (cf. Appendix 5).

4. Neurotoxicological and Behavioural Effects

Exposure to EGME has been reported to cause intellectual, psychological and neurological disorders in man, collectively described as "toxic encephalopathia" (Greenburg,1938; Parsons et al.,1938; Donley, 1936; Zavon, 1962; Groetschel and Schürmann, 1959; Ohi and Wegman,1978). These effects slowly disappeared when exposure ceased.

A time and dose-dependent specific inhibition of the secondary conditioned-avoidance response has been demonstrated in rats following exposure to EGME at concentrations down to 125 ppm (Goldberg et al.,1962). Changes in the activity of "glial cell marker enzymes" that were found in rats exposed to 50 ppm (Savolainen,1980) are at present difficult to relate to the effects that have been observed in humans and in the "conditioned" rat.

EGEE, EGBE and PGME in contrast to EGME were found not to cause a specific inhibition of the avoidance-escape reactions (Goldberg et al.,1969). These results suggest that the CNS effects of EGME may be different from those of other glycol ethers.

5. Metabolism

Information on the metabolism of ethylene glycol monoalkyl ethers is scant. Early work by Shaffer et al.(1950) suggested that the glycol ethers of low molecular weight,undergo limited metabolic change, and are cleared from the plasma at the same rate as creatinine.

5.1. EGME

Zavon (1963) suggested that oxidation plays a major role in the metabolism of EGME and that methoxyacetic acid may be the major metabolite. This has recently been confirmed by Dow Chemical who found that methoxyacetic acid produced the same spectrum of toxicological effects as does EGME (Cornelius, 1982). Nitter-Hauge (1970) suggested the operation of pathways leading to the formation of methanol and ethylene glycol which would be further metabolised to glycine, formic acid and carbon dioxide (Gessner et al.,1961). The pathway from ethylene glycol to oxalic acid does not appear to be operative at non-saturating doses, as shown by the failure to detect increased urinary excretion of oxalic acid in rabbits and dogs (Wiley et al.,1933). However, in cases of human oral over-exposure an increase in the urinary excretion of oxalic acid has been reported (Nitter-Hauge, 1970). Following an intake of approximately 100 ml of EGME, levels of oxalic acid in the range 105 to 1000 mg/24 hrs were reported, the normal range being 13 to 49 mg/24hrs.

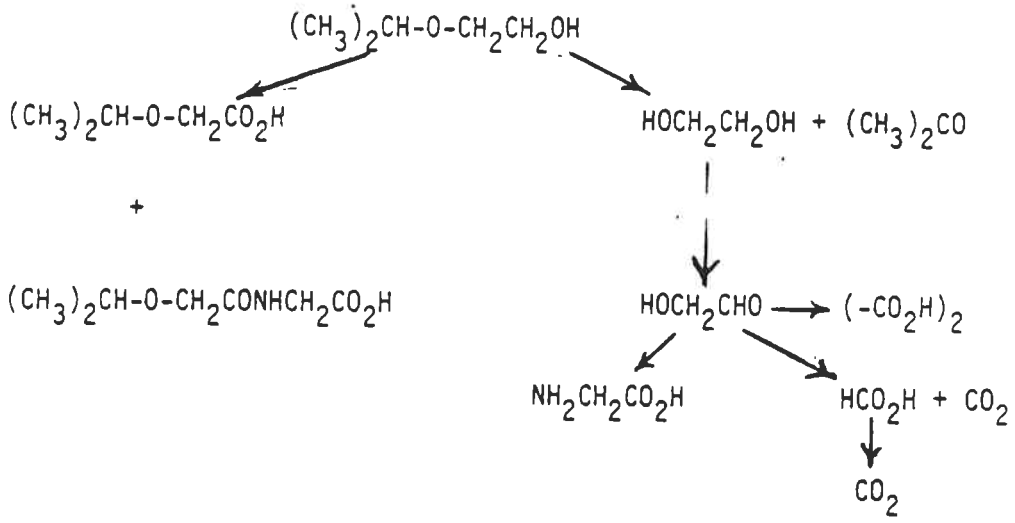
5.2. EGEE

No information is available on the metabolic fate of EGEE. By analogy with other ethylene glycol monoalkyl ethers one would predict that ethoxyacetic acid is the major urinary metabolite.

5.3. EGiPE

EGiPE is the only glycol ether whose metabolism has been studied by modern techniques. Hutson and Pickering (1971) showed it to be rapidly removed from the body in both rats and dogs. Following an intraperitoneal injection of (C^{14})-labelled EGiPE, 87% of the administered radioactivity was excreted within the first 2 hours. The major routes of excretion were the urine (73%) and exhaled air (14%).Two major urinary metabolites were identified: isopropoxyacetic acid and its glycine conjugate. Carbon dioxide was the only metabolite excreted in the respired air. The presence of acetone and ethylene glycol in the urine indicated cleavage of the ether linkage. The metabolic pathway of EGiPE is shown in Fig.1.

Fig.1. Metabolism of EGiPE



5.4. EGBE

Carpenter et al.(1958) isolated butoxyacetic acid as the major urinary metabolite of EGBE in the rat, rabbit, guinea-pig, dog, rhesus monkey and man. Attempts have been made to utilize excretion of butoxyacetic acid as a monitor of EGBE exposure. Considerable individual variation in excretion rates has been demonstrated, making this method unsuitable for human monitoring.

5.5. Monoalkyl Ethers of Propylene Glycol

No information is available on the metabolic fate of the monoalkyl ethers of propylene glycol. However, by analogy with ethylene glycol ethers, and despite the complication that two isomers of propylene glycol exist, two routes of metabolism can be predicted. Oxidation of the glycol moiety would lead to the formation of the corresponding alkoxypropionic acid or ketone derivative. The other route would involve cleavage of the ether linkage, the product depending on the isomer. 1,2-Propylene glycol would be transformed by sequential oxidation via lactaldehyde, methyl glyoxal,lactate and pyruvate. Metabolism of 1,3-propylene glycol, on the other hand, would be routed via malonic acid which could be excreted directly or metabolised via fatty acid pathways.

5.6. Conclusions

The current evidence suggests that the ethylene glycol monoalkyl ethers are metabolised via two discrete pathways, one leading via cleavage of the ether linkage to ethylene glycol and the other giving rise, by oxidation, to the corresponding alkoxyacetic acid.

6. Mutagenicity and Cytotoxicity

6.1. EGME

McGregor et al.(1981) studied the mutagenicity of EGME. Out of 4 Salmonella microsome assays there were slight elevations in the numbers of revertant colonies with strain TA98 in 2 experiments. However, there was no clear dose-response relationship over the range 33.3 to 333mg EGME per plate, and cytotoxicity (manifested as a reduced background lawn) was reported only at 193 mg per plate. These data indicate that EGME does not induce point mutations in bacteria.

No increase in unscheduled DNA synthesis (UDS) was observed in human cell lines at concentrations of up to 10mg/ml. However, a depression of the normal background level of UDS was observed at the highest dose in the presence of S-9 mix. The explanation of this effect may be complex and involve a number of factors, e.g. non-specific toxic effects, perturbations in the nucleotide pools, or specific inhibition of the enzyme systems involved. Analysis of bone marrow metaphase cells failed to reveal any significant increases in chromosome aberration frequencies following exposure of male and female rats to atmospheres of EGME of up to 500 ppm, 7 hrs/day, for 5 days.

A dominant lethal study in which male rats were exposed to atmospheres containing 0, 25 and 500 ppm of EGME, for 7hrs per day on 5 consecutive days, was performed by McGregor (1981). Pregnancy frequencies and total implantations per female in the high dose groups (500 ppm) were not different from those of the controls at weeks 1 and 2, but were greatly reduced at weeks 3 and 4,and totally absent at week 5. At the lower dose (25 ppm) no reduction in these parameters was observed. Because of the profound effect of EGME on male fertility it was not possible to detect an increase in early foetal deaths indicative of a true dominant lethal effect. Abbondandolo et al.(1980) examined the effects of EGME on Schizosaccharomyces pombe and chinese hamster V79 cells, showing it to be weakly cytotoxic to both cell types (media

concentrations of 10% v/v for S.pombe and 0.5 to 2.0% v/v for V79). No forward mutations were induced in S.pombe.

6.2. EGEE

The mutagenic activity of EGEE has been studied in Salmonella typhimurium strain TA 1538 (Kawalek and Andrews,1980) and in Escherichia coli scl-4-73 (Szybalski,1958). It failed to induce mutations in either species of bacteria.

6.3. EGBE

EGBE was evaluated (Tyler, 1981) for potential mutagenic activity via three in vitro tests: chinese hamster ovary (CHO), sister chromatid exchange (SCE) and unscheduled DNA synthesis (UDS). The compound was non-toxic to cells at up to 1% v/v. No mutagenic activity was detected in the CHO assay. A single positive response was obtained in the SCE assay in the presence of S-9, but there was no dose-response relationship . An increase in UDS was observed at the lower dose levels.

6.4. EGiPE

No data are available on the mutagenic effects of EGiPE. However, it was shown to be highly cytotoxic for Ames-strain Salmonella at 25 µg per plate (Maron et al.,1981), and its suggested use as an antiseptic and preservative is well-documented (Gough et al.,1944; Florey et al.,1947; Boehm, 1968; and Parker,1972).

6.5. Conclusions

The current evidence suggests that the glycol ethers are not mutagenic in bacterial or mammalian cell culture systems, and that the effects on bone marrow, testes and the developing embryo are unlikely to be due to an interaction with DNA.

7. Skin and Eye Irritation

EGME and EGEE in repeated and prolonged contact with skin were found not to lead to appreciable irritation (Draize,1944). When these solvents were introduced into the eyes, immediate painful irritation was reported, followed by corneal clouding said to clear within 24 hours (Dow, 1962).

EGnPE and EGiPE have been reported to be more irritating than EGME and EGEE when applied to the skin for prolonged periods, occasionally producing

chemical burns (Dow, 1962). When applied to the eye, reddening and swelling of the conjunctiva and the lids, corneal damage, and sometimes also iritis occurred (Dow,1962; Gross,1938). These effects on the skin and eye were said to be reversible within 7 days.

EGBE caused eye irritation similar to that of EGnPE and EGiPE, but minimal dermal irritation (Gross 1938; Dow,1962). Nasal and eye irritation in humans, under certain working conditions, have been reported (Carpenter,1956).

EGPhE was reported not to irritate the intact skin, but severely damaged the eyes, of rabbits (Dow, 1962).

8. Dermal Absorption of Glycol Ethers

Human and animal data have shown that glycol ethers are readily absorbed through the skin. Ohi and Wegman (1978) described two cases of poisoning (signs of anaemia) by EGME, attributed to skin contamination (cf.B-1.1.1.). Carpenter et al.(1956) gave evidence of rapid absorption of EGBE through the skin of the rabbit. Erythrocyte fragility was observed one hour after a single 3-minute contact with 0.56 ml/kgbw on 4.5 per cent of the total skin surface area. These findings were confirmed by the recent Union Carbide studies (Tyler,1981).
Dugard (1982) tried to obtain more quantitative data on the importance of dermal absorption for four glycol ethers, and found that EGME, EGEE, EGBE and PGME all diffused readily across an *in vitro* preparation of human epidermis, confirming the *in vivo* observations. The skin should therefore be considered as a significant route of exposure for glycol ethers.

C. HUMAN EXPOSURE

1. Number of People Exposed

Exposure to glycol ethers occurs primarily by inhalation or skin contact (Procter and Hughes, 1978).The exact number of people occupationally exposed in manufacture and industrial applications is not accurately known but because of the wide use of these chemicals (cf. Appendix 1) the numbers will be large. Domestic consumers can also be exposed to glycol ethers through their presence in a variety of household products. Although it is impossible in practice to obtain factual information on the number of people exposed, on the basis of the range of products containing glycol ethers it is expected that the number must be large.

2. Exposure Conditions

Data on actual workplace concentrations in Europe are scarce, but some exposure levels are given in the literature describing the effects on humans. Zavon (1963) reported EGME concentrations ranging from 61 to 3960 ppm in a printing department.Greenburg et al.(1938) reported EGME concentrations of 25 ppm in a collar-fusing plant with open windows, and 76 ppm with closed windows. There are doubts about the accuracy of these exposure levels and their relevance to present working conditions.

In 1981 NIOSH issued a health hazard evaluation which included exposure measurements, and medical interviews with approximately 20 workers, at a printing company. The evaluation was requested after liver abnormalities in two employees were found. Workplace sampling indicated that EGEE concentrations were below the OSHA standard of 200 ppm. Other organic solvents were also below OSHA levels. Although inadequate air flow in several areas of the workplace resulted in worker complaints of skin dryness and minor irritations, it was concluded that the two hepatic abnormalities were probably unrelated to the work environment (Burroughs,1981).

No data are available on exposure levels during the use of domestic products containing glycol ethers and more information on industrial and consumer exposure is needed to permit estimations of actual risk.

3. Workplace Monitoring

Various methods have been developed to measure the concentration of methyl, ethyl and butyl glycol ethers and their acetates in the atmosphere. Details are given in Appendix 6.

4. Epidemiological Studies

As glycol ethers are used in many applications and numerous consumer products it is difficult to identify suitable cohorts representative of different types and extents of exposure. High exposures are not expected at production sites but small groups or even single people are exposed under different, and sometimes uncontrolled, conditions at user sites. A number of case reports of EGME exposure are available and are cited and discussed elsewhere in this report. In general, the observations in humans are supported by the results of animal experiments.

A general mortality study of production workers in the paint and coatings manufacturing industry has been conducted by Morgan et al.(1981). According to this, the paint and coatings industry is characterised by a large number of fairly small plants where, because of the small number of cases at any one site, it is possible that health hazards may remain undetected.
This study, sponsored by the US National Paint and Coatings Association and performed by the Stanford Research Institute on the basis of a former pilot study, covered 32 plants. The authors concluded that no relationship could be derived between the exposure to a distinct agent and the incidence of a specific disease. Consequently it was not possible to deduce that there was any effect of glycol ethers *per se*. Further epidemiological studies with more detailed information on human exposure are desirable, although it is acknowledged that they may be difficult to perform. At present the principle basis for an evaluation of the effects of glycol ethers in man is extrapolation from the results of animal experiments.

D. GENERAL CONCLUSIONS

The monoalkyl ethylene glycol ethers have been shown to possess a wide spectrum of biological activity, with some variation in the range of effects and potency among the individual compounds. Although each of the effects has been described separately in the main body of this report, it would be incorrect to consider them in isolation when assessing the safety in use of these materials.

1. Spectrum of Activity and Structure-Activity Relationship in Laboratory Animals

The relationships of biological activities to structure have not been clearly defined. It appears that the testicular and bone marrow effects decrease with increasing size of the alkoxy group, i.e. are maximal with EGME and less marked or absent with the higher homologues.The haemolytic effects, on the other hand, appear to increase with the size of the alkoxy group, i.e. are minimal with EGME and more pronounced with EGBE. There is little species variation in these effects. Testicular atrophy has been observed with EGME in mice, rats, rabbits and dogs and haematological effects in mice, rats, rabbits, cats, dogs and man.

There is insufficient information at present to identify any relationship between foetotoxicity, teratogenicity and the chemical structure. Foetotoxicity and teratogenicity have been established only for EGME and EGEE. The effects of other ethylene glycol ethers on the developing embryo remain to be determined. In contrast, PGME has been found not to produce any adverse effects on either the bone marrow or reproductive systems at doses at which EGME produces severe effects.

Experimental data suggest that EGME is the only member of the series shown to have behavioural effects in rats. From the available evidence, the ethylene glycol monoalkyl ethers do not appear to constitute a genotoxic risk to humans. All available data are summarised in Appendix 7.

2. Possible Mode of Action

The testis, bone marrow and embryo all contain large numbers of rapidly-dividing and differentiating cells and it is possible that the action of glycol ethers arises from an adverse effect on one or more of the processes of cell division. The fact that the compounds show the same order of activity in each of the three tissues supports the idea of a common mechanism of action, although there is no direct evidence for this.

Although the available results suggest that the activity of the glycol ether molecule depends on the number of carbon atoms in the alkyl and glycol moieties, it is not known whether this determines the ability of the chemical to reach the site of action or its intrinsic activity. There are no marked differences in the physico-chemical properties of the ethylene and

propylene glycol ethers and it is possible that the differences in metabolism of the two series are responsible for their differences in biological activities. The available evidence suggests that the ethylene glycol ethers are all metabolised via the alkoxyacetaldehyde to the respective alkoxyacetic acid, whereas the 1-2 propylene series could be metabolised to an alkoxyketone. This has been shown for both EGME and EGBE where the respective alkoxyacid, capable of reproducing the effects of the parent compound, has been found as a urinary metabolite.

3. Extrapolation to Humans

There is a remarkable consistency in the available laboratory animal data, with little or no qualitative or quantitative differences between species.Where human data exist they parellel closely those found in animal studies.These facts suggest that the experimental information provides a reliable basis for extrapolating to humans and it would be unreasonable to disregard the evidence provided by the animal data. It is prudent to assume, in the absence of evidence to the contrary, that in addition to the adverse effects on the haemapoietic systems of man the effects on the testes and the developing embryo would also occur in similarly-exposed humans.

4. Data Gaps

Further information on the toxicology of some glycol ethers is required (cf.Appendix 7). The no-effect levels for EGEE and EGME are not yet known. The Chemical Manufacturers Association in the USA is currently sponsoring a large programme of work, detailed in Appendix 5, and by the end of 1982 the sub-chronic toxicity and teratogenicity of EGME, EGEE and EGBE should have been fully evaluated. It is unlikely that these studies will alter the overall perception of the toxicology of the glycol ethers, but it is hoped that they will define the lower levels at which the effects occur.

5. Ethylene Glycol Methyl and Ethyl Ethers

The Working Group was asked to consider the toxicology of EGME and EGEE in particular as they are the most widely used, the most volatile, and are likely to be the compounds to which the greatest number of people are exposed.

5.1. EGME

This has been shown to produce bone marrow depression, testicular atrophy and teratogenicity . One or more of these effects have been seen in mice, rats, rabbits, dogs, and also humans, with little inter-species variability. It is prudent to assume, in the absence of human data to the contrary, that testicular atrophy and infertility will also result from the equivalent exposure of men to EGME, and that embryo-toxicity or teratogenicity effects could occur in pregnant women exposed to EGME at appropriate doses. The no-effect levels for the testicular* or teratogenic effects have not been defined. Moreover, the levels at which these effects have been found in animals suggest that the present occupational exposure control limits may not afford an adequate safety margin to man. EGME is absorbed through the skin, and this route of exposure should be considered when reviewing its use.

5.2. EGEE

This has been shown to have a spectrum of activity in laboratory animals similar to that of EGME, although it appears to be less potent by a factor of 2 or 3. There are no substantiated reports of effects in man, possibly because of its lower potency. As with EGME, it would be prudent to assume that testicular atrophy and infertility in men could result from exposure to EGEE and that embryotoxic or teratogenic effects could occur in pregnant women exposed to appropriate doses. The no-effect levels for the testicular or teratogenic effects of EGEE have, again, not been defined. The levels at which these effects have been found in animals suggest that the present recommended exposure levels may not afford an adequate safety margin for man. As EGEE is absorbed through the skin, this route of exposure should be considered when the use of EGEE is reviewed.

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* Very recent work (as yet unpublished) on rabbits may indicate a no-effect level for this .

E. RECOMMENDATIONS

When drafting these recommendations, which refer to ethylene glycol ethers, the Working Group took account of current and proposed studies as tabled in Appendix 5 of this report, and was of the opinion that :

1) Continued effort should be made to determine the present extent and pattern of exposure in the manufacture and use of glycol ethers and glycol ether-containing products where data are insufficient.

2) The similarity in mode of action of the ethylene glycol ethers indicates that the ACGIH method of adding fractions of the TLV's might be of use in calculating the TLV where more than one of them is in use.

3) Further epidemiological studies are desirable, although it is acknowledged that they may not be feasible in practice.The need to monitor the health of those exposed should be considered.

4) More studies are required to clarify the absorption, distribution, excretion and mode of action.

5) More information is desirable on the toxicological effects of ethylene glycol n-propyl, iso-propyl and phenyl ethers.

6) This report, and its conclusions, should be reviewed when the results of current and proposed toxicological studies are available.

7) The present occupational exposure limits (TLV's, MAK values etc.) should be reconsidered.

F. APPENDICES

APPENDIX 1

PRODUCTION, PROPERTIES AND USES OF GLYCOL ETHERS

1. Production

Glycol ethers are produced by the reaction of alkylene oxides with alcohols or phenols, or of glycols with alkylating agents. The common ethers are derived from ethylene, diethylene, propylene and dipropylene glycols.
The ethylene glycol methyl, ethyl and butyl ethers are the most widely used. In 1980, 260,000 tons of these ethers were produced in Western Europe and 529,000 tons (all types of glycol ethers) in Japan.

2. Chemical and Physical Properties

Glycol ethers are colourless liquids with mild, pleasant odours. They combine the solubility characteristics of alcohols and ethers. They are completely soluble in acetone, benzene, carbon tetrachloride, diethyl ether, and methanol. The glycol ethers of lower molecular weight are completely soluble in water, and those of higher molecular weight are partially miscible. With the exception of EGME and EGEE, they are completely miscible with n-hexane.They have a wide range of boiling points.

Glycol ethers are strictly speaking hybrids, and are commonly referred to as "two-type" solvents. The glycol ether molecules include an alcohol (-OH) group as well as the ether linkage (-O-). They exhibit the highly polar behaviour of the alcohols and the relatively non-polar character of the ethers, being miscible with both water and hydrocarbons and having valuable solvent properties for both hydrophobic and hydrophilic substances. In table 4 are summarised some of the most important physical and chemical properties of the most common ethers of ethylene and propylene glycol.

TABLE 4

Physico-ChemicalProperties of Glycol Ethers

	Monoethylene glycol					Propylene Glycol
Property	Methyl Ether	Ethyl Ether	n-Propyl Ether	Isopropyl Ether,	Butyl Ether	Methyl Ether
CAS - No.	109-86-4	110-80-5	2807-30-9	109-59-1	111-76-2	107-98-2
Mol.formula	$C_3H_8O_2$	$C_4H_{10}O_2$	$C_5H_{12}O_2$	$C_5H_{12}O_2$	$C_6H_{14}O_2$	$C_4H_{10}O_2$
Mol.wt.	76.1	90.1	104.1	104.1	118.2	90.1
Density (25°/25°C)	0.963	0.928	0.909	0.900	0.900	0.919
B.P.(760 mm.Hg)	124.2	134.7	150-152	140-143	170.6	120.1
Vapour pressure, mm.Hg (25°C)	9.7	5.3	2.9	5.2	0.88	10.9
Refractive index (25°C)	1.400	1.406	1.412	1.407	1.417	
Flash point,°C	39 (IP-170,Abel closed cup)	43 (IP-170,Abel closed cup)	- -	42 (IP-170,Abel closed cup)	67 (Pensky-Martin closed cup)	38 (open cup)
Vapour density (air = 1)	2.6 (approx.)	3.0			4.0 (approx.)	
Per cent in satd.air(25°C)	1.28	0.7	0.38	0.68	0.11	
1 ppm=mg.m^{-3} at 25°C,760 mm Hg	3.11	3.68	4.29	4.29	4.84	3.69
Abbreviation	EGME	EGEE	EGnPE	EGiPE	EGBE	PGME

3. Uses and Applications

The glycol ethers are marketed under the well known tradenames of "Cellosolve", "Dowanol", "Poly-Solv", "Emkanol", "Oxitol", "Jaysolve", "Jeffersol"," Gafcol","Ethoxol", and also under their chemical names.

Glycol ethers find extremely wide applications : as resin solvents in surface coatings and inks; dye solvents in textile and leather applications; as coupling solvents in a variety of special preparations; and as intermediates in the production of plasticizers of improved solubility characteristics.Further solvent uses are : in nitrocellulose and synthetic resins, water-miscible coating materials, printing inks, writing inks, spirit duplicating fluids, and in dye solutions. They improve penetration qualities in rust removers, detergent compositions, carbon removers and slushing compounds. They are emulsion conditioners in soluble oils used in textile, leather and metal fabricating industries. They also find use in degreasing agents, dry cleaning soaps, spotting fluids, nonaqueous wood stains, spinning baths, and mercerizing baths.

APPENDIX 2 : EXPOSURE LIMITS IN THE WORKPLACE ENVIRONMENT FOR GLYCOL ETHERS

		EGME		EGEE		EGiPE		EGBE		PGME*	
		ppm	mg/m³	ppm	mg/m³	ppm	mg/m³	ppm	mg/m³	ppm	mg/m³
EUROPE											
BELGIUM	TLV(1978)	25	80	50 (1981)	185 (1981)	25 (1981)	105 (1981)	25 (1981)	120 (1981)	100	360
BRD (Germany)	MAX(1981)(skin)	25	80	200 (50)+	740 (185)+	-	-	50	240	-	-
DENMARK	HGV(1981)	25	80	100 (50)+	370 (185)+	-	-	50	240	-	-
FINLAND	TLV(1972)	25	80	100	370	-	-	50	240	100	360
FRANCE	TLV(1981)	25	80	50 (1981)	185 (1981)	25 (1981)	105 (1981)	25 (1981)	120 (1981)	100	360
HOLLAND	MAK(1981)	25	80	100	370	-	-	50	240	100	360
ITALY	TLV(1978)	-	-	-	-	-	-	-	-	-	-
NORWAY	TLV(1980)(skin)	25	80	50 (1981)	185 (1981)	-	-	25 (1981)	120 (1981)	100	360
SWEDEN	TLV(1978)(skin)	25	80	100	370	-	-	50	240	-	-
SWITZERLAND	MAK(1980)(skin)	25	80	100	370	-	-	-	-	100	360
UNITED KINDGOM	TWA(1979)(skin)	25	80	100(50)+	370(185)+	-(25)+	-(105)+	50(25)+	240(120)+	100	360
	STEL(1979)(skin)	35	120	150(100)+	560(370)+	-(75)+	-(320)+	150(75)+	720(360)+	150	540
OUTSIDE EUROPE											
JAPAN	TLV(1980)	-	-	-	-	-	-	-	-	-	-
USA											
ACGIH	TLV-TWA(1980)(skin)	25	80	50 (1981)	185 (1981)	25 (1981)	105 (1981)	25 (1981)	120 (1981)	100	36
	TLV-STEL(1980)(skin)	35	120	100(1981)	370 (1981)	75 (1981)	320 (1981)	75 (1981)	360 (1981)	150	54
OSHA	PEL (1980)			200	740						

PEL : Permissible Exposure Limit
STEL : Short Term Exposure Limit
+ Intended changes
- no value

*1 Methoxy-2-propanol

APPENDIX 3 : HAEMATOLOGICAL AND TESTICULAR EFFECTS OF GLYCOL ETHERS

COMPOUND	SPECIES	ROUTE	EXPOSURE DOSE	TIME	RESPONSE	REFERENCE
EGME	Rat	Inhalation	310 ppm	7 hrs/day 5 days/wk 5 wks	-increase in juvenile granulocytes, bone marrow hypoplasia, haemosiderosis	WERNER et al., 1943
	Rabbit	Injected	?	?	-testicular atrophy	WILEY et al., 1938
	Mice	Oral	2000 mg/kgbw 1000 500 250 125 62.5	5/wk 5 wks	-testicular atrophy, reduced WBC,ABC and Hb -testicular atrophy, reduced WBC,ABC and Hb -testicular atrophy, reduced WBC, -testicular atrophy, -no effects observed -no effects observed	NAGANO et al., 1979
	Rat	Inhalation	1000 ppm 300 100	6hrs/day 9 days	)reductions in WBC, RBC, Hb, bone marrow)hypoplasia, lymphoid atrophy, testicular)atrophy	MILLER et al., 1981
	Rat	Inhalation	2000 ppm	single 4 hr.	-slight reduction in WBC only -increased RBC fragility	CARPENTER et al., 1956
	Mice	Inhalation	500 ppm	7hrs/day 5 days	-infertility	McGREGOR et al., 1980

APPENDIX 3(2) HAEMATOLOGICAL AND TESTICULAR EFFECTS OF GLYCOL ETHERS

COMPOUND	SPECIES	ROUTE	EXPOSURE DOSE	TIME	RESPONSE	REFERENCE
EGEE	Rat	Inhalation	370 ppm	7 hrs/day 5 days/wk 5 wks	-increase in juvenile granulocytes, bone marrow hypoplasia, haemosiderosis, decrease in EMH in the spleen	WERNER et al., 1943
	Rat	Sub-cutaneous	200 µg/kgbw 400 µg/kgbw	daily for 4 wks	-testicular interstitial oedema, reduced Hb and PCV	STENGER et al., 1971
	Dog	Oral	50-200 µg/kgbw	daily 13 wk	-testicular interstitial oedema, reduced Hb and PCV.	
	Mice	Oral	4000 mg/kgbw 2000 " 1000 " 500 "	5/wk 5 wks	-testicular atrophy, reduced WBC, RBC, PCV, Hb -testicular atrophy, reduced WBC, RBC, PCV, Hb -testicular atrophy -no effects observed	NAGANO et al., 1979
EGMEAc*	Mice	Oral	2000 mg/kgbw 1000 500 250 125 62.5	5/wk 5 wks	-testicular atrophy, decrease in WBC and Hb -testicular atrophy, decrease in WBC -testicular atrophy -no effects observed -no effects observed -no effects observed	NAGANO et al., 1979
EGEEAc	Mice	Oral	4000 mg/kgbw 2000 1000 500	5/wk 5 wks	-testicular atrophy, decrease WBC, PCV -testicular atrophy, decrease WBC, PVC -testicular atrophy -no effects observed	NAGANO et al., 1979

*Ac = Acetate

APPENDIX 3(3) : HAEMATOLOGICAL AND TESTICULAR EFFECTS OF GLYCOL ETHERS

COMPOUND	SPECIES	ROUTE	EXPOSURE DOSE	TIME	RESPONSE	REFERENCE
EGPE	Rat	Inhalation	315 ppm	7 hrs/day 5 days/wk 5 wks	-decreased RBC and Hb, increase in reticulocytes and juvenile granulocytes, bone marrow hypoplasia	WERNER et al.,1943
EGiPE	Rat	Inhalation	390 ppm	7 hrs/day 5 days/wk 5 wks	-decreased RBC and Hb, increase in reticulocytes and juvenile granulocytes,bone marrow hypoplasia, haemosiderosis	WERNER et al.,1943
EGBE	Rat	Inhalation	432 ppm	2 hrs	-"in vivo" haemolysis hemin crystals in urine severe "in vivo" haemolysis	CARPENTER et al., 1956
	Rat	Inhalation	200 ppm	7 hrs/day 9 days	-increase in RBC fragility, decrease in RBC, Hb	
	Rat	Feeding	2.0 % 1.54 mg/kgbw 0.5 % 0.31 " " 0.125% 0.076 " " 0.03 % 0.018 " "	daily intake " " "	-) -)No haematological or testicular effects -)reported -)	
	Rabbit	Topical	undiluted		-haemaglobinuria	
	Rat	Inhalation	432 ppm 314 ppm 203 ppm 107 ppm 54 ppm	7 hrs/day 5 days/wk 30 days	-increase in RBC fragility, haemoglobinuria -increase in RBC fragility, haemoglobinuria -increase in RBC fragility, haemoglobinuria -increase in RBC fragility -increase in RBC fragility	

APPENDIX 3(4) : HAEMATOLOGICAL AND TESTICULAR EFFECTS OF GLYCOL ETHERS

COMPOUND	SPECIES	ROUTE	EXPOSURE DOSE	TIME	RESPONSE	REFERENCE
EGBE	Guinea Pig	Inhalation	494 ppm 376 ppm 203 ppm 107 ppm 51 ppm	7 hrs/day 5 days/wk 30 days	-) -)No haematological or testicular -)effects reported -) -)	CARPENTER et al.,1956
	Mice	Inhalation	400 ppm 200 ppm 100 ppm	7 hrs/day 30-90 days	-increase in RBC fragility, haemoglobinuria -increase in RBC fragility, haemoglobinuria -increase in RBC fragility	
	Dog	Inhalation	385 ppm 200 ppm 100 ppm	-25 exposures -31 days -90 days	-increase in WBC and RBC fragility -increase in WBC and RBC,slight decrease in RBC -transitory increase in WBC,decrease in WBC	
	Monkey	Inhalation	100 ppm	90 days	-transitory increase in RBC fragility, and decrease in RBC.	
	Monkey	Inhalation	210 ppm	30 days	-increased RBC fragility,decrease in RBC and Hb	
	Rabbit	Topical occluded	100% 1ml 50% 25% 5%	4 hrs/day 9 days	-haemaglobinuria,decrease in WBC, RBC,Hb and MCH -haemaglobinuria,decrease in WBC, RBC,Hb and MCH -no effects observed -no effects observed	CARPENTER et al.,1956
	Rat	Inhalation	77 ppm 25 ppm 5 ppm	6 hrs/day 5 day/wk 13 wks	-decrease in RBC, Hb and MCH -no effects observed -no effects observed	
	Rat	Feeding	1.25% 0.25% 0.05% 0.01%	90 days	-testicular atrophy -testicular atrophy -no effects observed -no effects observed	TYLER,1981

APPENDIX 3(5) : HAEMATOLOGICAL AND TESTICULAR EFFECTS OF GLYCOL ETHERS

COMPOUND	SPECIES	ROUTE	EXPOSURE DOSE	TIME	RESPONSE	REFERENCE
EGBE	Mice	Oral	2000 mg/kgbw 1000 " " 500 " "	5/wk 5 wks	-all animals died -decrease in RBC,testicular atrophy ? -no effects observed	NAGANO et al., 1979
EGPhE	Mice	Oral	2000 mg/kgbw 1000 " " 500 " "	5/wk 5 wks	-all animals died -testicular atrophy ? -no effects observed	NAGANO et al., 1979
EGME	Dog	Oral	2-3 ml/kgbw	5/wk 14 wks	-"abundance of spermiophages in epididymis"	STENGER et al., 1972
	Rats	Oral	4 ml/kgbw 2 " " 1 " " 0,5 " "	7/wk 4 wks	))no effects observed))	STENGER et al., 1972
	Mice	Oral	6 ml/kgbw 4 " " 2 " " 1 " "	7/wk 2 wks	))Heinz bodies))	STENGER et al.,1972
	Rats	Inhalation	3000 ppm 1000 " 300 "	6 hrs/d 9 days	))no effects observed	MILLER et al., 1981

APPENDIX 4 : FOETOTOXIC AND TERATOGENIC EFFECTS OF GLYCOL ETHERS IN ANIMALS

COMPOUND	SPECIES	ROUTE	EXPOSURE DOSE	TIME	RESPONSE	REFERENCE
EGME	Mice	Oral	31.2 mg/kgbw	days 7-14 gestation	-Skeletal variations : number of proximal and middle phalanges, cervical vertebrae bifurcated and split	Nagano et al.,1981
			62.5 mg/kgbw		-Asymetrical sternebrae, spina bifida occulta	
			125 mg/kgbw		-Fused and wavy ribs, agenesis of ribs, fused lumbar vertebrae, fused thoracic vertebrae, foetal bodyweight reduced, foetal mortality, abnormal fingers, fused post lumbar vertebrae exencephaly, maternal bodyweight gain reduced	
			500 mg/kgbw		-Only one surviving foetus, maternal bodyweight gain reduced	
			1000 mg/kgbw		-No live foetuses, maternal bodyweight gain reduced, maternal leucopoenia	
	Rats	Inhalation	100 ppm 6 hrs / day	days 6-17 gestation	-Bodyweight gain reduced in dams Only nine litters from 20 dams. Reduced number, viability and weight of pups	Doe et al., 1981
			300 ppm 6 hrs / day	days 6-17 gestation	-Bodyweight gain reduced in dams No litters produced	
	Rats	Inhalation	3,10,50 ppm 6 hrs/ day	days 6-15 gestation	-No foetotoxicity or effects on soft tissue	Dow, 1982
	Mice	Inhalation	3,10 ppm 6 hrs/ day	days 6-15	-No foetotoxicity or effects on soft tissue	Dow,1982
			50 ppm 6 hrs/ day	days 6-15	-Foetotoxicity	

APPENDIX 4(2) : FOETOTOXIC AND TERATOGENIC EFFECTS OF GLYCOL ETHERS IN ANIMALS

COMPOUND	SPECIES	ROUTE	EXPOSURE DOSE	TIME	RESPONSE	REFERENCE
EGME	Rabbits	Inhalation	50 ppm 6 hrs/day 10, 3 ppm 6 hrs/day	days 6-18 gestation days 6-18 gestation	-Cardiovascular abnormalities Skeletal evaluation not yet done in any of these studies -No effect on soft tissue	DOW, 1982
EGEE	Rats	Oral	12.5; 25 µl/kgbw/day 100,200 µl/kgbw/day 400 µl/kgbw/day	through gestation	-no effects observed -skeletal abnormalities -foetal mortality	STENGER ET AL., 1981
	Rats	Inhalation	900 ppm 4hrs/day 200 ppm 4hrs/day 100 ppm 4hrs/day 900 ppm 4hrs/day 200 ppm 4hrs/day 100 ppm 4hrs/day	days 7-13 pregnancy days 14-20 pregnancy	-No foetuses survived -25% foetal mortality Impaired performance on rotorod -No foetuses survived -25% foetal mortality Less activity in running wheel	Nelson et al., 1980
	Rats	Inhalation	770 ppm 7hrs/day 200 ppm 7hrs/day	through gestation	-No foetuses survived, maternal bodyweight gain reduced -Increased number of resorptions, foetal bodyweight reduced. Increased cardio-vascular abnormalities. Minor skeletal abnormalities	Andrew et al., 1981
	Rabbits	Inhalation	620 ppm 7hrs/day 160 ppm 7hrs/day	through gestation	-No foetuses survived, maternal bodyweight reduced -Increased number of resorptions, significant increase in major malformations : ventral wall defects, fusion of pulmonary arteries with aorta.	Andrew et al., 1981

APPENDIX 4(3) : FOETOTOXIC AND TERATOGENIC EFFECTS OF GLYCOL ETHERS IN ANIMALS

COMPOUND	SPECIES	ROUTE	EXPOSURE DOSE	TIME	RESPONSE	REFERENCE
PGME	Mice	Oral	36-1800 mg/kgbw per day	days 0-18 pregnancy	-No effects observed	Stenger et al., 1972
	Rabbits.	Oral	"	days 0-18 pregnancy	-No effects observed	
	Rats	Oral	"	days 0-21 pregnancy	-Retarded ossification of skull at 720 mg/kg	
	Rats	Inhalation	200 ppm 600 ppm 6 hrs/day	days 6-17 of gesta-tion	-No effects observed	Doe et al., 1981

Appendix 5

CURRENT STUDIES ON GLYCOL ETHERS

EGME

1. 90-day sub-chronic inhalation study in rabbits, CMA sponsored. Start June 1981 . Report Spring 1982.

2. Inhalation teratology study, rats, mice and rabbits, CMA sponsored. Report Summer 1982. - Hanley et al Sept 1982?

3. Metabolism Studies in USA (Industrial Laboratory).

EGEE

1. NCI Bioassay, 2-year dietary study, rats and mice. Finish March 1982.

2. Inhalation teratology study, rats and rabbits, CMA sponsored. Start end 1981. Report end 1982.

3. 90-day sub-chronic inhalation study, rats and rabbits, CMA sponsored. Start Summer 1982.

4. Metabolism, NIOSH, in progress.

EGBE

1. 90-day sub-chronic dermal study in rabbits, CMA sponsored. Start end 1981. Report end 1982.

2. Teratology study in rabbits, CMA sponsored. Start Spring 1982.

PGME

1. 90-day sub-chronic inhalation study, rats and rabbits, in USA. Started end 1981. Results may be released end 1982.

2. Inhalation teratology study, rats and rabbits in USA. Start Spring 1982. Results may be released end 1982, beginning 1983.

Appendix 6 : GLYCOL ETHER MONITORING

1. Chemical Industries Association Methods

The CIA (1981) have described two methods which permit the measurement of 8-hour time weighted average (TWA) concentrations of EGME, EGEE,EGBE and their acetates in the atmosphere. The lower level of detection is 0.1 $ml.m^{-3}$.

The upper limit has not been determined but is above 50 $ml.m^{-3}$(Table 5). The methods are suitable for most atmospheres of up to 95% humidity. At present the method is limited to measurements in production areas.

Table 5

Lower and higher detection levels

	Lower det. level	Higher det. level
EGME	0.02 ppm	> 15 ppm
EGEE	0.03 ppm	> 15 ppm
EGBE	0.02 ppm	> 10 ppm

The atmospheric sample is drawn through a sorption trap containing 200 mg of Tenax GC. At the end of the sampling period, normally four to eight hours, the sorption trap is plugged with nylon or PTFE caps. For analysis, the trap is positioned at the inlet of a gas chromatograph (GC) and the sorbed material is thermally displaced at 280°C in a stream of nitrogen. The components are separated by a gas chromatographic column and detected using a flame ionisation detector.

A method is also described for obtaining air with known concentrations of glycol ether for standardisation of the methods.

2. SRI Method for EGEE

SRI (1979) published a report dealing with the development and validation of methods for sampling and analysing 130 substances, including EGEE. Charcoal was used as the collection medium, and a gas chromatograph with a flame ionisation detector was used for detection. The EGEE is desorbed from the charcoal with 5% methanol in methylene chloride. The method has been validated over the range 337 to 1459 $mg.cm^{-3}$ (105-456 ppm).

APPENDIX 7 : BIOLOGICAL EFFECTS OF ETHYLENE GLYCOL MONOALKYL ETHERS

Ether	Haematology		Testicular Atrophy	Teratological Effects	Neurological and Behavioural Effects	Mutagenic Effects	Kidney Effects
	Haemo-lysis	Bone marrow Depression					
EGME	±(H)	+(H)	+	+	+(H)	no effects observed	no effects observed
EGEE	±	+	+	+	no effects observed	no effects observed	±
EGnPE and EGiPE	+	±	no data	no data	no data	no data	+
EGBE	+(H)	±	±	no data	no effects observed	no effects observed	+
EGPhE	no data	no data	±	no data	no data	no data	no data

+ positive effects in animals studies

± questionable effect

(H) effects in humans

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