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The Toxicology of Glycol Ethers and its Relevance to Man: An Up-dating of ECETOC Technical Report No 4

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THE TOXICOLOGY OF GLYCOL ETHERS

AND ITS RELEVANCE TO MAN :

AN UP-DATING OF ECETOC TECHNICAL REPORT N° 4

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CONTENTS

A. SUMMARY

(See pages 5-7 for the abbreviations used for the glycol ethers and their derivatives in this report).

1. Since the previous ECETOC review, which concentrated on the toxicology of the ethylene glycol mono-alkyl ethers, additional information on these and other glycol ethers has become available. The new data, and data on industrially-important derivatives of glycol ethers have been critically reviewed and their relevance to humans assessed.

2. It has been confirmed in animal experiments that the short-chain ethylene glycol ethers (EGME, EGEE) and their acetates cause testicular atrophy, teratogenicity/foetotoxicity and pancytopenia, whereas the longer-chain ethylene glycol ethers, (EGnPE, EGiPE and EGBE) do not cause these effects but do cause haemolysis. There is evidence that the diethylene glycol monoethers do not cause adverse effects on reproduction, but diethylene glycol dimethylether appears to affect the testes.

3. Evidence suggests that the acetates derived from the glycol ethers have the same toxicological activity as their parent glycol ether.

4. The toxic effects seen with the ethylene glycol methyl and ethyl ethers are not observed with 2PG1ME or with the isomeric dipropylene glycol monomethyl ethers. 1PG2MEA does not cause testicular atrophy or bone-marrow toxicity but preliminary data suggest that it has teratogenic potential in rabbits.

5. Samples of the different types of glycol ethers have been assessed for mutagenicity. Evidence from the large number of compounds tested suggests that this class of chemicals does not pose a genotoxic risk to man.

6. Studies on EGME and EGEE provide reliable data for consideration of their subchronic toxicity and teratogenicity/foetotoxicity. The consistent nature of the results between studies and between species indicates that they form a reliable basis, in conjunction with the metabolic and human data, for extrapolation to man.

7. No new findings on EGBE have emerged to suggest that a significant reappraisal of its toxicology is necessary. EGBE does not produce adverse effects on the testes, the developing foetus or the blood-forming elements. Its most significant effect in laboratory animals is lysis of the red blood cells, which occurs at much lower concentrations in rodents than in humans. Haemolysis does not therefore provide a relevant basis for quantitative extrapolation to humans.

8. The data on 2PG1ME form a reliable basis for the evaluation of its subchronic toxicity and teratogenicity. The consistent nature of the results between species and between studies, in conjunction with the metabolic data, indicates that the findings constitute a good basis for extrapolation to man.

9. In the previous ECETOC report reasons were given as to why it would be prudent to assume that adverse effects on the testes and developing embryos of animals would also occur in humans exposed to appropriate concentrations of EGME or EGEE. No evidence has emerged to challenge this assumption. However, it is also justified to assume that glycol ethers which do not produce testicular toxicity or teratogenicity in laboratory animals would not cause these effects in humans.

B. INTRODUCTION

In 1982 ECETOC reviewed, and published its comments on, the available toxicological information on ethylene glycol monoalkyl ethers and assessed its relevance for health effects in man (ECETOC, 1982). In that report (Appendix 5) a number of recommendations for further studies were formulated, and a list of studies in hand at the time was given. A number of new results, some of which were presented at a NIOSH Symposium on "Toxic Effects of Glycol Ethers" (19 to 21 September, 1983, Cincinnati, USA) have now been disclosed and published. The information obtained at the Symposium, other results published in the literature, and data from other sources have been taken into account in this document.

In the first ECETOC report only monoethylene glycol alkyl ethers were considered. The present report up-dates the previous one and includes information which has become available on other types of glycol ethers and their

acetates. In Table 1 are listed the glycol ethers and their derivatives considered in this report, and the abbreviations used are also given.

TABLE 1

Names	Structure IUPAC name	Abbreviations	CAS-No.
ethylene glycol monomethyl ether	$HO\text{-}CH_2CH_2\text{-}OCH_3$ 2-methoxyethanol	EGME	109-86-4
methoxy acetic acid	$CH_3O\text{-}CH_2\text{-}COOH$ 2-methoxyacetic acid	MAA	625-45-6
ethylene glycol monomethyl-ether acetate	$CH_3COOCH_2CH_2\text{-}OCH_3$ 2-methoxyethanol acetate	EGMEA	110-49-6
ethylene glycol monoethyl ether	$HO\text{-}CH_2CH_2\text{-}OCH_2CH_3$ 2-ethoxyethanol	EGEE	110-80-5
ethylene glycol monoethyl-ether acetate	$CH_3COO\text{-}CH_2CH_2\text{-}OCH_2CH_3$ 2-ethoxyethanol acetate	EGEEA	111-15-9
ethylene glycol-mono-n-propyl ether	$HO\text{-}CH_2CH_2\text{-}O\text{-}CH_2CH_2CH_3$ 2-n-propoxyethanol	EGnPE	2807-30-9
ethylene glycol mono-isopropyl ether	$HO\text{-}CH_2CH_2\text{-}O\text{-}CH(CH_3)_2$ 2-(1-methylethoxy)ethanol	EGiPE	109-59-1
ethylene glycol mono-n-propyl ether acetate	$CH_3COO\text{-}CH_2CH_2\text{-}OCH_2CH_2CH_3$ 2-n-propoxyethanol acetate	EGnPEA	20706-25-6
ethylene glycol mono-n-butyl ether	$HO\text{-}CH_2CH_2\text{-}OCH_2CH_2CH_2CH_3$ 2-n-butoxyethanol	EGBE	111-76-2
ethylene glycol mono-n-butyl ether acetate	$CH_3COO\text{-}CH_2CH_2\text{-}OCH_2CH_2CH_2CH_3$ 2-n-butoxyethanol acetate	EGBEA	112-07-2
ethylene glycol dimethyl ether	$CH_3O\text{-}CH_2\text{-}CH_2\text{-}OCH_3$ 1,2-dimethoxy ethane	EGDME	25154-53-4
ethylene glycol diethyl ether	$CH_3CH_2O\text{-}CH_2CH_2\text{-}OCH_2CH_3$ 1,2-diethoxy ethane	EGDEE	629-14-1

TABLE 1 (continued-2)

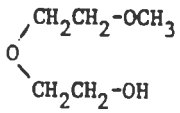
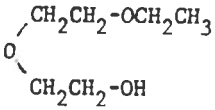
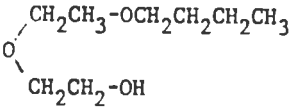
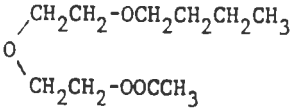
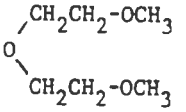
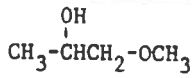
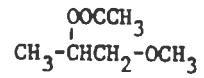
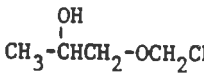
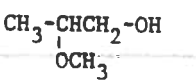
diethylene glycol mono-methyl ether	 2-(2-methoxyethoxy)ethanol	DEGME	111-77-3
diethylene glycol mono-ethyl ether	 2-(2-ethoxyethoxy)ethanol	DEGEE	111-90-0
diethylene glycol mono-n-butyl ether	 2-(2-n-butoxyethoxy)ethanol	DEGBE	112-34-5
diethylene glycol mono-n-butyl ether acetate	 2-(2-n-butoxyethoxy)ethanol acetate	DEGBEA	124-17-4
diethylene glycol dimethyl ether	 1,1'-oxybis(2-methoxyethane)	DEGDME	111-96-6
triethyleneglycol mono-methylether	$HO-CH_2CH_2O-CH_2CH_2-O-CH_2CH_2-OCH_3$ 2-(2-(2-methoxyethoxy)-ethoxy)ethanol	TEGME	112-35-6
triethyleneglycol dimethylether	$CH_3O-CH_2CH_2-O-CH_2-CH_2-O-CH_2CH_2-OCH_3$ 2,5,8,11-tetra-oxadodecane	TEGDME	112-49-2
2-propylene glycol 1-methyl ether	 1-methoxy-2-propanol	2PG1ME	107-98-2
2-propylene glycol 1-methyl ether acetate	 1-methoxy-2-propanol acetate	2PG1MEA	108-65-6
2-propylene glycol 1-ethyl ether	 1-ethoxy-2-propanol	2PG1EE	1569-02-4
1-propylene glycol 2-methyl ether	 2-methoxy-1-propanol	1PG2ME	1589-47-5

TABLE 1 (continued-3)

1-propylene glycol 2-methyl ether acetate	$CH_3-CH(OCH_3)CH_2-OOCCH_3$ 2-methoxy-1-propanol acetate	1PG2MEA	70657-70-4
dipropylene glycol monomethyl ether	$O(C_3H_6-OCH_3)(C_3H_6-OH)$ (4 isomers)	DPGME	
tripropylene glycol monomethyl ether	$HO-CH(CH_3)CH_2-O-CH(CH_3)CH_2-O-CH(CH_3)CH_2-OCH_3$ 1-(2-(2-methoxy-1-methylethoxy)-1-methylethoxy)-2-propanol	TPGME	20324-33-8

C. TOXICOLOGICAL DATA

1. Haematological, Testicular and Other Systemic Toxic Effects

The details of the principal studies are summarised in tabular form in Appendix 1.

1.1. EGME and EGMEA

Vapour inhalation studies, considered in the previous report, in which male and female rats and rabbits were exposed to concentrations of 0, 30, 100 or 300 ppm of EGME, 6 h/d, 5 d/wk for 13 weeks have now been published (Miller et al.,1983-a). A reduction in body weight, testicular and thymic atrophy, haematological changes (pancytopenia) and decreased amounts of abdominal fat were reported in both species exposed to 300 ppm. The pancytopenia was no more severe at 13 weeks than after 4 weeks exposure and no microscopic changes were observed in the sections or smears of bone marrow prepared from the rats. A decrease in mean liver weight was also found in male and female rats in the 300 ppm group which, although considered to reflect the reduced body weight of these animals, was also accompanied by a significant reduction in serum levels of total protein, albumin and globulin. No liver-weight changes were reported in rabbits similarly exposed although there was some evidence of glycogen depletion. Degenerative changes in the testes were also found in 3 of 5 rabbits exposed to 100 ppm, and in 1 of 5 rabbits at 30 ppm. The lesion found at 30 ppm is of doubtful significance since lesions of this type occur in untreated rabbits and testicular effects were

not found at this exposure level in a subsequent study (Miller et al.,1982-a).

A concurrent evaluation (Rao et al., 1983) of reproductive capability and dominant lethal effects in rats, following an exposure regime similar to that described above, showed complete arrest of fertility in males exposed to 300 ppm of EGME. There was marked testicular atrophy at this dose level in the previous study. Fertility was partially restored 13 weeks after exposure. Although infertility prevented an evaluation of dominant lethal effects at 300 ppm there was no evidence of an increased incidence of resorptions when animals that had recovered were mated. No dominant lethal effects or impaired fertility were found in animals exposed to 30 or 100 ppm of EGME.

Rats exposed for a single 4 hour period to atmospheres containing 625, 2500 or 5000 ppm of EGME were found to have testicular atrophy when killed 14 days after exposure (Doe, 1984-a). There was also evidence of damage to maturing spermatids in the testes of animals exposed to 625 ppm. In a subsequent study, groups of rats were exposed for 4 hours to either 1000 or 2500 ppm of EGME and killed 1-19 days after exposure. Damage to the germinal epithelium was evident at 24 hours and at all subsequent observation times up to 19 days, the primary spermatocytes being the cell type initially affected. Electron-microscopic examination of the testes at 4 days also revealed swollen mitochondria and retraction of the Sertoli cell cytoplasm.

An effect of EGME on primary spermatocytes was reported by Chapin and Lamb (1984). Foster et al.(1984) reported degeneration of pachytene spermatocytes 24 hours after the administration of single oral doses of 100, 250 and 500 mg/kgbw. Continued dosing for 2, 4, 7 or 11 days resulted in progressive depletion of maturation, and degenerative changes in the secondary spermatocytes and most stages of meiotic division of the primary spermatocytes. This resulted in tubules possessing only spermatogonia, Sertoli cells, and primary spermatocytes arrested at the zygotene stage. Electron-microscopy showed evidence of disrupted mitochondria and cytoplasmic vacuolation in the spermatocytes. Partial to complete restoration of spermatogenesis was reported 7 to 8 weeks (one complete cycle) after cessation of treatment.

Creasy and Foster (1984) described a variation in the susceptibility of spermatocytes to damage by EGME depending on the stage of meiosis. The order of sensitivity was reported as: dividing spermatocytes > early-pachytene > late pachytene > mid pachytene > leptotene/zygotene.

A dose equivalence between the effects of EGME and its major metabolite, methoxyacetic acid, was demonstrated by Miller et al.(1982-b). Atrophic changes in the testes, thymus and bone marrow and reductions in red blood cell count, haemoglobin concentration, packed cell volume and white blood cell count were found in rats given eight daily doses of 300 mg/kgbw of methoxyacetic acid by gavage. Similar but less severe changes were seen in animals administered 100 mg/kgbw.

Equimolar doses of methoxyacetic acid produced testicular damage of similar severity to that produced by 500 mg/kgbw of EGME over a four-day period (Foster et al.,1984).

No data additional to those discussed in the first ECETOC report (1982) are available on EGMEA.

1.2. EGEE and EGEEA

Groups of 15 male and female rats and 10 rabbits were exposed 6h/d, 5d/wk for 13 wks to atmospheres containing 0, 25, 100 or 400 ppm of EGEE (Terril and Daly,1983). The occurrence of a limited number of unexpected pregnancies (in the 100 ppm groups for both rats and rabbits) during the course of these studies was not considered to have affected their integrity. Lachrymation was reported at all dose levels in both species throughout most of the study. At the end of the rat study, a decreased absolute spleen weight was found in all female groups treated with EGEE, and a decreased relative spleen weight occurred in the groups exposed to 25 and 400 ppm of EGEE. Decreases in absolute and relative pituitary weight were found in male rats exposed to 400 ppm of EGEE. There were no histopathological changes in these or any other tissues, and the toxicological significance of the organ weight changes is unclear. There were no haematological changes that could be related to treatment. Although no effects were found on the testes in the rat study, a decrease in the absolute and relative weights of the testes was found in rabbits exposed to 400 ppm of EGEE. On microscopic examination of the testes, degeneration of

the seminiferous epithelium was found in three of the 10 animals. Reductions in red blood cell counts, haemoglobin and haematocrit concentration were also found in this group.

Testicular atrophy was also found in rats 15 days after a single 3-hour exposure to an atmosphere containing nominally 4500 ppm of EGEE (estimated by weight loss), and haematuria was observed during exposure (Doe, 1984-a).

In a comparative study of the toxicology of EGEEA and EGBEA in rats and rabbits (Truhaut et al.,1979), kidney damage was the predominant effect of both compounds. Haematuria was also consistently found following single oral, dermal or inhalation exposure. After single oral and dermal administration of EGEEA to rats, ketone bodies were found in the urine. Post mortem examination revealed kidney damage in animals exposed to either EGEEA or EGBEA. Reductions in erythrocyte count and haemoglobin concentration of the blood also occurred following dermal exposure, the effects being more pronounced with EGBEA than with EGEEA. A considerable decrease in the white blood cell count was also found with EGEEA. The range of dose levels at which these effects occurred was not stated. Rats and rabbits survived a single 4-hour exposure to atmospheres containing either 2000 ppm of EGEEA or 400 ppm of EGBEA - haematuria was transient and no pathological lesions were noted at post mortem. "Discrete renal lesions" were reported in male rats exposed 4 h/d, 5 d/wk for 10 months to atmospheres containing either 200 ppm of EGEEA or 100 ppm of EGBEA, similar lesions being reported among controls. No testicular effects were reported in any of these studies. Although histological examination of a number of tissues, including the testes, was undertaken, the studies in which these examinations took place were not specified.

As with methoxyacetic acid and EGME there appeared to be a close similarity between the testicular effects of ethoxyacetic acid and EGEE (Foster et al., 1984).

1.3. EGnPE and EGnPEA

Studies of the comparative toxicity of EGnPE and EGnPEA following repeated oral administration or inhalation exposure have been reported (Katz et al.,1984). Groups of ten male rats were dosed with 1.88, 3.75, 7.5 or 15 mmole of EGnPE/kgbw (equivalent to 195, 390, 780 or 1560 mg/kgbw) or 7.5,

15 or 30 mmole of EGnPEA/kgbw (equivalent to 1097, 2193 or 4386 mg/kgbw) by gavage, 5 d/wk for 6 wks. Deaths occurred immediately following dosing at 390, 780 or 1560 mg/kgbw (1/10, 3/10 and 2/10 animals respectively). Two of the deaths at 780 mg/kgbw and the single death at 390 mg/kgbw were ascribed to aspiration of the test material into the lung. In contrast, 8 of 10 animals administered 4386 mg of EGnPEA/kgbw died (the majority after 2 or 3 doses) and two were killed in extremis. Haemoglobinuria was reported at all doses with both compounds early in the experiment, the frequency of the observation declining as the study progressed. At the end of the study, reductions in red blood cell count and/or haemoglobin and haematocrit concentration occurred at all dose levels, and enlargement of the spleen at all but the 195 mg EGnPE/kgbw dose level. Post mortem examination and microscopic examination of tissues revealed gastric haemorrhage and degenerative changes in the thymus, liver, kidney, spleen and testes of the animals that died or were killed after dosing with 4386 mg of EGnPEA/kgbw. In the group of animals administered 2193 mg of EGnPEA/kgbw, atrophy of the seminiferous epithelium occurred in one animal, and cytoplasmic vacuolation in the seminiferous tubules with degenerate sperm in the epididymis in another. Congestion of the spleen and brown pigment in the kidney were reported in the majority of animals treated with either 1097 or 2193 mg of EGnPEA/kgbw. Histological changes in the liver, kidney or spleen consistent with a haemolytic process were seen at all dose levels of EGnPE.

In the study with repeated inhalation exposure (6h/d, 5d/wk and 11 exposures), haemoglobinuria was observed in rats exposed to 400 or 800 ppm of EGnPE and to 200, 400 and 800 ppm of EGnPEA only after the first or second, but not subsequent, exposure. At the end of the study, haematological changes similar to those in the oral study were found in animals exposed to either EGnPE or EGnPEA at 400 or 800 ppm. Histological evidence of a haemolytic process were found in the spleen in the groups exposed to 400 or 800 ppm of EGnPE, and in the spleen, liver and kidneys in the groups exposed to 800 ppm of EGnPEA. The majority of the haematological and histopathological changes found in both studies indicated an increased rate of red blood cell destruction. The aetiology of the testicular lesions reported in the oral study on EGnPEA is uncertain in view of the absence of similar lesions in animals treated orally with equimolar doses of EGnPE, and by inhalation with both the ether and acetate, but they were probably related to the general toxicity caused by the high dose of EGnPEA. The

no-observed-effect level in the inhalation studies was 200 ppm for EGnPE and 100 ppm for EGnPEA.

1.4. EGiPE

Transient haematuria was observed in 5 rats given a single 4 hour exposure to an atmosphere estimated by weight loss to contain approximately 3500 ppm of EGiPE. No effect on testis weight was apparent when the animals were killed 15 days later (Doe,1984-a).

In an additional study, groups of 10 male rats were exposed 6 h/d for 9d to atmospheres containing either 300 or 1000 ppm of EGiPE (Doe, 1984-a). A reduction in body weight, red blood cell count and haemoglobin concentration, and transient haematuria, occurred only in the animals exposed to 1000 ppm of EGiPE. A marginal increase in mean corpuscular volume was the only effect noted at 300 ppm. There was no evidence of testicular atrophy at either level.

1.5. EGBE and EGBEA

Rats were exposed for 90 days to atmospheres containing 0, 5, 25 or 77 ppm of EGBE, 6 h/d, 5 d/wk (Dodd et al.,1983). Blood samples collected after 31 exposures showed reductions in mean red blood cell count and mean corpuscular volume in female rats exposed to 77 ppm of EGBE. At the end of the study the magnitude of these effects had declined although in the male rats there was a 5% decrease in mean red cell count. No other treatment-related effects occurred in these animals and no treatment-related effects occurred in animals exposed to 5 or 25 ppm of EGBE.

The CMA (1983) has reported a study of the percutaneous toxicity of aqueous solutions of EGBE. Rabbits were treated topically with doses of 10, 50 or 150 mg EGBE/kgbw, under occlusion for 6h/d, 5 d/wk for 90 days. No treatment-related changes could be found at any dose level for any of the measurements or observations made during the study, which included comprehensive haematology and histopathology, and an assessment of red cell fragility.

Haematuria was observed in a group of 5 rats given a single 3 h exposure to an atmosphere containing nominally 800 ppm of EGBE, as estimated by weight loss (Doe, 1984-a).

No effects on the testis weight were noted in any of the above studies.

The studies on EGBEA performed by Truhaut et al.(1979) are discussed in section 1.2, above.

1.6. DEGME

Smyth and Carpenter (1948) administered DEGME in drinking water to rats for 30 days. The maximum dose having no detectable effect was stated to be less than 190 mg/kgbw. This "no-effect" level was based upon "microscopic examination of tissues" although the findings were not disclosed.

The results of a 13 wk vapour inhalation study with DEGME in rats have been reported by Miller et al.(1984-d). Groups of 10 male and 10 female Fischer 344 rats were exposed to 0, 30, 100 or 216 ppm of DEGME 6h/d, 5d/wk for 13 wks. The highest concentration tested was approximately 65% of the theoretical maximum vapour concentration at room temperature and pressure and was stated to be the "maximum practically attainable". The growth rate and behaviour of the animals was unaffected. At the end of the study there were no treatment-related changes in organ weights, haematology and serum chemistry or the incidence of histopathological abnormalities.

Although relatively low exposure levels were used in this study, the data do provide reasonable reassurance that DEGME in the vapour phase is free of the characteristic systemic toxicity of EGME and EGEE.

1.7. DEGEE

Morris et al.(1942) studied the chronic toxicity of a number of glycols and glycol ethers including DEGEE. Groups of 12 male and 8 female rats were fed diets containing either 1.45% of EGEE or 2.16% of DEGEE, for 2 years. A limited histopathological examination was conducted on tissues taken from "essentially those animals surviving to 24 months" and from 10 of 40 controls. Two-thirds of the animals dosed with EGEE were reported to exhibit testicular enlargement, oedema and tubular atrophy. The animals fed a diet containing DEGEE were reported to have a "few" such lesions, and

similar lesions were described as occurring "occasionally" in the other experimental groups and controls. Chronic liver damage, consisting of diffuse centrilobular atrophy, bile duct proliferation and fatty change, was described as "slight" in the animals administered DEGEE; no kidney effects were reported in these animals.

Groups of 10 male and 5 female rats, and groups of 10 male and 10 female mice, were given specially purified DEGEE containing only trace amounts of ethylene glycol, at levels of 1% in the water and 5% in the diet (Hanzlik et al.,1947). No effects were found on the body weight gain of the young animals or on the mortality rate, compared with controls. Kidney damage was found in 1 of the 4 rats surviving past 16 months. No effects were reported on either the testes or liver.

In a 2yr study of DEGEE (Smyth et al.,1964), two grades of "carbitol" containing either 0.2 or 29.5% of ethylene glycol were given to groups of 8 rats of each sex in the drinking water at concentrations providing daily intakes of 0.01, 0.04, 0.2 or 0.95 g/kgbw. The study was continued through 3 generations and terminated at 718 days from the start. Severe kidney damage or bladder concretions were reported in animals receiving 0.95 g/kgbw of either grade of material and in animals receiving 0.2 g/kgbw of the high EG grade. Serious or fatal injury was also characterised by cloudy swelling in the livers, phagocytosed pigment in the spleen and degeneration of intestinal villi. An early cessation of breeding also occurred in these animals probably due to the severe systemic toxicity rather than a specific effect on the reproductive system. There were no effects on the testes, which were said to have been examined in some cases. Haematological examinations, carried out on 2 male and 2 female rats 4 times a year showed no outstanding effects.

Hall et al.(1966) reported the results of a feeding study in which groups of 12 male and 12 female rats were fed diets containing 0, 0.25, 1.0 or 5.0% of DEGEE containing 0.6% of ethylene glycol, for 90 days. The growth rate of the animals at the 5% dietary level was reduced, and post mortem examination revealed increases in relative kidney and testis weight in these animals. Histological examination showed hydropic degeneration of the kidneys of two males and one female. The increased relative testis weight

was ascribed to testicular oedema. No effects were observed in the animals fed the diet containing 0.25 or 1.0% of DEGEE.

DEGEE containing less than 0.4% of ethylene glycol was administered to groups of 20 male and 20 female mice at dietary levels of 0, 0.2, 0.6, 1.8 or 5.4%, to groups of rats (15 male and 15 female) at dietary levels of 0, 0.5 or 5%, and to pigs (3 male and 3 female) at daily oral doses of 0, 167, 500 or 1500 mg/kgbw for 90 days (Gaunt et al.,1968). Three pigs given 1500 mg/kgbw/d died after 14-21 days and the dose administered to the remaining animals was reduced to 1000 mg/kgbw. A number of mice fed with 5.4% of DEGEE also died. Increased mean relative kidney weight and hydropic degeneration of the proximal tubular cells were found in all three species at the highest dietary level or dose. Oxalate crystals were found in the urine of the rats and mice but not of the pigs. Hydropic degeneration of the liver was found in the pigs given doses of 500 mg/kgbw/d and above, and cell enlargement was found in the livers of mice given 1.8 and 5.0% of DEGEE. There were small but significant reductions in mean RBC and/or haemoglobin concentrations in all three species at the highest treatment level. The erythrocytes of the male pigs that died following doses of 1500 mg/kgbw/d were reported to be severely crenated. In all three species no effects were reported on the testes, and the no-observable-effect levels in these studies were 0.5% (approximately 250 mg/kgbw/d) for rats, 0.6% (850-1000 mg/kgbw/d) for mice and 167 mg/kgbw/d for pigs.

Groups of two or three ferrets were administered 0.5, 1.0, 2.0 or 3.0 ml of DEGEE/kgbw/d in the diet, for 9 months (Butterworth et al.,1976). No adverse effects were reported in any of the organs examined, including the blood, kidneys, liver and reproductive system.

The above data on DEGEE have provided evidence of degenerative changes in both the kidneys and, to a lesser extent, the livers of a number of species. They have not, however, revealed any clear or consistent effects on the testes, haematopoietic system or blood. Early reports of testicular oedema and tubular atrophy have not been confirmed in later studies. Although testicular oedema was reported by Hall et al.(1966), the mean absolute testes weights of these animals were indistinguishable from control values, the increased relative weight being a reflection of significantly-reduced body weight. Testicular oedema was not reported in

later studies in rats, mice, pigs and ferrets, and no degenerative changes have been reported in any of the more recent studies.

1.8. DEGBE

Groups of 5 rats were administered DEGBE in the drinking water, at doses of approximately 51 to 1830 mg/kgbw/d for 30 days (Smyth and Carpenter, 1948). The maximum dose having no effect was 51 mg/kgbw and the lowest dose producing (unspecified) histopathological changes in either the liver, kidney, spleen or testis was 650 mg/kgbw. Doses down to 94 mg/kgbw were reported to reduce the growth rate.

The 28-day percutaneous toxicity of DEGBE has been investigated in rabbits (Procter and Gamble, 1982). Groups of 3 male and 3 female rabbits were treated topically (abraded skin) with 2 ml/kgbw of a 1.5% aqueous solution of DEGBE (=30 mg/kgbw), 5 days/wk for 4 wks. A number of statistically significant alterations in serum constituents, haematological parameters and organ weights were found in treated animals compared with controls. Since all of the changes were small, were found only in animals of one sex, and/or were within the range of historical control values, it is likely that they were chance variations unrelated to treatment. There were no histopathological findings that could be related to treatment.

Groups of 25 male rats were administered 0, 250, 500 or 1000 mg of DEGBE/kgbw by gavage for 60 days before mating with untreated females (cf 2.8). There was no evidence of reduced fertility at any dose level (Procter and Gamble, 1984).

1.9. DEGDME

Dominant lethal studies and sperm-head abnormality assessments were carried out as part of an evaluation of the comparative mutagenic potential of EGME and DEGDME (McGregor et al.,1983). Rats and mice were exposed to atmospheres containing 250 or 1000 ppm of DEGDME, 7 h/d for 1 or 5 days. Both species were reported to be subdued and unresponsive to auditory stimuli following exposure to atmospheres containing 1000 ppm, the male mice becoming ataxic and having a reduced bodyweight gain compared with control animals. Four of the ten mice died after the 4th exposure, but the cause of death was not investigated. In the dominant lethal study in rats a large reduction in the number of pregnancies was reported in female rats

mated with males exposed to 1000 ppm of DEGDME. This occurred between the 4th to 9th week after dosing and was particularly marked in weeks 5-7 following exposure. Large increases in all categories of sperm abnormalities were found in mice exposed to 1000 ppm of DEGDME. No effects were found in either species at 250 ppm.

Similar results were obtained with EGME, although at a lower exposure level (500 ppm). The results of these studies suggest that DEGDME damages the developing germ cells, and the period of infertility indicates that it is probably the primary spermatocytes which are affected. There was no histological examination of the testes of these animals.

1.10 2PG1ME and 2PG1MEA

In a comparative 9-day inhalation study of 2PG1ME (300, 1000 and 3000 ppm, 6h/d) and EGME (Miller et al., 1984-a), CNS depression, increased liver weight, and lower specific gravity and slightly elevated pH of the urine were the only effects reported in rats and/or mice exposed 6 h/d for 9 days to 3000 ppm of 2PG1ME. There was no evidence of any effects on those tissues which in the same study were conspicuously affected by exposure to EGME, namely the bone marrow, testes and lymphoid tissue. No effects were found in animals exposed to 300 or 1000 ppm.

These findings were substantiated in a study in which rats and rabbits were exposed 6 h/d, 5 d/wk for 13 weeks to atmospheres containing 0, 300, 1000 or 3000 ppm of 2PG1ME (Landry et al.,1983). CNS depression was observed in both species in the first few days of exposure to 3000 ppm, the effect disappearing after 1-2 weeks of exposure. At the end of the study an increased relative liver weight was found only in the rats. In the livers of the female rats there was evidence of centrilobular-midzonal hepatocellular hypertrophy. In view of the absence of any microscopic damage in these livers, the increased weight and cellular hypertrophy were considered to represent a process of physiological adaptation. This interpretation is consistent with the observed tolerance to the CNS effects of 2PG1ME acquired after repeated exposure. Small increases in the activities of serum glutamic pyruvic transaminase (in female rats) and alkaline phosphatase (in male and female rabbits) were also noted, although the values were stated as "not greater" than those found in recent historical controls. An increase in urinary pH was reported in male rats

after 4 weeks exposure to 3000 ppm. This was not found at 13 weeks and there were no histopathological findings in the kidneys. No treatment-related haematological or testicular effects were found in either species, and no treatment-related effects in any animals exposed to 300 or 1000 ppm of 2PG1ME.

Rats and mice were exposed to 0, 300, 1000 or 3000 ppm of 2PG1MEA for 6 hours per day for a total of 9 exposures in 11 days (Miller et al.,1984-a). Exposure to 3000 ppm, may have had some slight effect on the liver of male rats as indicated by increased relative liver weight. However, there were no treatment-related histopathological changes in the livers of rats and mice. Although red blood cell counts and packed cell volumes of female mice in the 1000 and 3000 ppm groups were slightly higher than for controls, they were within the range of normal values. The kidneys of all male rats at 3000 ppm, and 1 of 5 male rats in the 1000 ppm group, had increased eosinophilic granularity of the cytoplasm of the proximal tubular cells. These findings were consistent with the reticulated appearance of the kidneys at post mortem. Since prominent granularity is commonly found in the proximal tubular cells of Fischer 344 male rats, the toxicological significance of these findings is uncertain. Degenerative changes were also observed in the olfactory portions of the nasal mucosa of three of five male and one of five female rats in the 3000 ppm group, and in a dose related manner in the mice at all three dose levels. In addition, most of the mice at the two higher dose levels and one female mouse at 300 ppm had focal areas of respiratory metaplasia whereby olfactory epithelium is replaced by respiratory epithelium of normal appearance. No exposure-related gross or histopathological effects were identified in either male or female rats in the 300 ppm group or in females in the 1000 ppm group.

1.11 1PG2MEA

Groups of 5 male and 5 female rats were exposed to 110, 560 or 2800 ppm of 1PG2MEA 6 h/d for 28 days (Klimisch et al.,1984). At the end of the study the animals were subjected to a post mortem examination in which the liver, kidneys, testes, lung, thymus and adrenals were weighed. Samples of these tissues and of heart, spleen, nasal passages and lachrymal gland were preserved and examined microscopically in the control and highest exposure

groups. The thymus, nasal passage and lacrymal glands were also examined in the intermediate groups.

Animals exposed to 2800 ppm exhibited irregular breathing, hunched posture, pallor of the skin and signs of local irritation of the eyes and nose, but after cessation of exposure they recovered rapidly. Similar, but less marked, effects were seen in animals exposed to 560 ppm, but no effects were seen in animals exposed to 110 ppm. At the end of the study there was a slight reduction in the mean liver weight of both male and female rats exposed to 2800 ppm of 1PG2MEA. Relative to bodyweight, the values were indistinguishable from the controls. There was also a marked reduction in thymus weight and a slight increase in adrenal weight in these groups. Examination of the serum from these animals revealed a number of statistically significant findings. In the male animals there was a reduction in mean glucose concentration and increases in mean albumin concentration and thromboplastin time. In the female rats there were decreases in mean urea concentration and total protein concentration, and an increase in alkaline phosphatase activity. Apart from a small increase in segmented neutrophils in female rats, there were no haematological changes. In the other exposure groups there was a small increase in cholesterol concentration in the male rats exposed to 560 ppm and increased mean glucose in the female rats exposed to 110 ppm. The only remarkable histopathological finding was thymic atrophy in 8 of the 10 rats exposed to 2800 ppm.

Degenerative changes in the testes, or haematological changes indicative of either bone marrow suppression or haemolysis, were clearly absent in this study. The thymic atrophy was considered to have resulted from stress probably induced by exposure to irritant concentrations of 1PG2MEA. The alterations in the concentrations of some serum constituents are of doubtful toxicological significance since they appeared to be unrelated to any pathological findings and were not observed in both sexes.

1.12 DPGME

An inhalation study with a mixture of DPGME isomers (see Table 2) was conducted in rats and mice at exposure levels of 50, 140 or 330 ppm (Landry and Yano, 1984). The exposure was for 6h/d for 9 days. No treatment-related effects were observed with respect to post-exposure clinical observations,

body weight, urinalysis, gross pathology or histopathology. There were statistically significant increases in mean relative liver weights of male rats at all exposure concentrations and an increase in mean absolute weight of livers in the male rats exposed to 330 ppm. These relative increases were small (7% at 50 and 140 ppm, 16% at 330 ppm). The relative liver weights of female mice exposed to 330 ppm were also statistically-significantly greater than the controls. In the absence of histopathological changes suggesting hepatotoxicity it is probable that these minor liver weight changes indicate an adaptive response.

TABLE 2

Approximate Composition of DPGME (Landry and Yano, 1984)

DPGME ISOMER	%
$CH_3O-CH_2-CH(CH_3)-O-CH_2-CH(CH_3)-OH$	82
$CH_3O-CH_2-CH(CH_3)-O-CH(CH_3)-CH_2-OH$	2-3
$CH_3O-CH(CH_3)-CH_2-O-CH(CH_3)-CH_2-OH$	2-3
$CH_3O-CH(CH_3)-CH_2-O-CH_2-CH(CH_3)-OH$	13
$-O-CH_2-CH=CH_2$ (presumed allyl impurity)	0.5

When rats and rabbits were exposed to 0, 15, 50, or 200 ppm of DPGME for 6h/d, 5d/wk for 13 weeks (Landry and Yano, 1984), no effects attributable to exposure were found in either species at any concentration.

2. Teratological, Embryotoxic and Foetotoxic Effects

In Appendix 2 the principal data are summarised in tabular form.

2.1. EGME

The effect of EGME on the developing foetus has been studied in three species : the rat, the mouse and the rabbit (Hanley et al.,1984-a). Mice were exposed, on the 6th to 15th days of gestation inclusive, to 0, 3, 10 or 50 ppm of EGME for 6h/d. The dams were killed on day 18 and the uterine contents examined. There were no effects on the dams. There was a low incidence of malformations throughout the groups, including the controls, but no evidence of teratogenicity. Slight foetotoxicity was seen at 50 ppm

(unilateral testicular hypoplasia and extra lumbar ribs). There were no treatment-related effects at 10 ppm.

Pregnant Fischer 344 rats were exposed to 0, 3, 10 or 50 ppm of EGME on gestation days 6 to 15 inclusive, for 6h/d (Hanley et al.,1982-b). There were no signs of maternal toxicity, but there were minor skeletal variations at 50 ppm of EGME. There were no effects at 3 or 10 ppm of EGME and no evidence of teratogenicity.

Pregnant New Zealand white rabbits were exposed to 0, 3, 10 or 50 ppm of EGME on gestation days 6 to 18 inclusive, for 6h/d (Hanley et al.,1982-b). At 50 ppm there was a transient loss of body weight which may have been indicative of maternal toxicity. Major malformations increased significantly in foetuses from the 50 ppm group (63% of foetuses examined), indicating teratogenicity. At 10 ppm there was a statistically significant increase in resorption rate and a reduction in foetal body weight. These values were within the range of historical controls and it is questionable whether they indicate foetotoxicity. There were no treatment-related effects at 3 ppm.

In order to provide rapid assessments of the teratogenic and embryotoxic potential of glycol ethers, Doe et al. (1983) assessed the effects of exposure to 100 - 300 ppm of EGME and compared them with those of exposure to 200 and 600 ppm of 2PG1ME. The duration of exposure was 6 h/d from gestation days 6 to 17. After the last exposure period the rats were housed singly until they delivered their litters, which were observed for 3 days post partum. The number of live and dead pups in each litter and the weight of each litter were determined on days 1 and 3 post partum. Animals which did not bear litters by day 24 of gestation were sacrificed and examined for resorptions and status of pregnancy. At 300 ppm of EGME there was a significant maternal body weight reduction and no litters were produced at all. At 100 ppm only 9/20 rats produced litters. The mean gestation time was prolonged from 22 to 23.6 days. The number of live pups and of pups surviving for 3 days was significantly reduced, and the weight of the survivors on day 3 was lower than that of the controls. All pups seemed to be externally normal and were not further investigated.

Doe (1984-b) demonstrated that 100-250 mg/kgbw of EGME administered by the oral, intraperitoneal and subcutaneous (s.c.) routes caused complete litter resorption in rats. Exposure to 300 ppm by inhalation, which corresponds to a daily dose of approximately 350 mg/kgbw assuming 100% retention, led to the same effect. Application of 40 mg/kgbw s.c. and exposure to 100 ppm by inhalation caused a loss of approximately half the litters, and a reduced litter size and pup survival. 40 mg/kgbw administered dermally, however, had no effect on the developing foetuses.

2.2. EGEE and EGEAA

The effect of EGEE on the developing foetus has been examined in the rat and rabbit (Doe, 1984-b). The purpose of these studies was to establish "no-effect" levels for the teratogenic and foetotoxic effects previously described by Andrew et al.(1981). Pregnant female rats were exposed to 0, 10, 50 or 250 ppm of EGEE for 6h/d on gestation days 6 to 15 (Tinston et al.,1983-a). There were reductions in haemoglobin concentration, mean cell volume and packed cell volume in the dams exposed to 250 ppm of EGEE, but no other signs of maternal toxicity. There was no evidence of teratogenicity at any dose level, but reduced foetal weight and an increase in minor skeletal defects indicated foetotoxicity at 250 ppm. There was a low incidence of similar defects at 50 ppm, which may indicate minimal foetotoxicity.

Pregnant rabbits were exposed to 10, 50 or 175 ppm of EGEE on gestation days 6 to 18 (Tinston et al.1983-b). There were no indications of maternal toxicity at any dose, but the absence of a right subclavian artery in one foetus and the occurrence of an abdominal wall defect in another were thought by the authors to indicate a marginal teratogenic effect at 175 ppm of EGEE, bearing in mind other data on EGEE. Minor skeletal defects and partial ossification constituted evidence of foetotoxicity at 175 ppm. There were some isolated instances of minor skeletal variants at 50 and 10 ppm but they were probably not treatment related.

The effects of EGEEA have been investigated in pregnant rabbits exposed by inhalation to 0, 25, 100 or 400 ppm (Tinston et al.,1983-c; Doe, 1984-b). At 400 ppm of EGEEA there were haematological effects and a decrease in body weight gain and food consumption in the dams. In the 400 ppm group there was evidence of teratogenicity in the foetuses comprising dilatation

of the brain ventricles, forelimb mal-rotation and severe defects of the vertebral column. There was also foetotoxicity at 400 ppm, shown by reduced foetal weights and increased incidences of minor visceral and skeletal abnormalities. An increased incidence of retarded ossification occurred at 100 ppm, indicating foetotoxicity. There were no effects at 25 ppm.

These results are in agreement with the results of a rat inhalation study (Nelson et al.,1984-a) at exposure levels of 130, 390 or 600 ppm of EGEEA on days 7 to 15 of gestation. All litters were resorbed at 600 ppm, and there was an increase in the number of resorptions at 390 ppm. There were also teratogenic and foetotoxic effects at 390 ppm and foetotoxicity at 130 ppm. Overall, the effects of EGEEA are similar to those of the parent ether.

In teratology studies in rats, dermally applied EGEE and EGEEA caused visceral and skeletal malformations (Hardin et al.,1984). The undiluted materials (the control was water) were applied with an automatic pipette to the shaved interscapular skin, 4 times daily on gestation days 7 - 16. Volumes per treatment were 0.25 ml for EGEE and 0.35 ml for EGEEA (2.6 mmol each). In the dams there was a decrease in body weight associated with litter resorption. At days 17 and 21 the body weight gain in the EGEEA group was significantly lower than in the EGEE group and the number of dead implants per litter was significantly higher in the former. Significant increases of visceral malformations (cardiovascular, renal and CNS) occurred with EGEE. In the EGEEA group only few foetuses were available for evaluation, but a significant incidence of similar cardiovascular malformations was, however, observed. Vertebral malformations and rib variations in EGEE- and EGEEA-treated litters were of borderline significance. Three EGEE-treated foetuses had acaudia and imperforate anus.

Goad and Cranmer (1984) demonstrated that short periods of oral exposure of EGEE at dose levels of 200 mg/kgbw per day, predominantly from gestation days 10 - 12 or 7 - 9, produced teratogenic effects in rats such as were seen in longer periods of exposure. In the groups exposed from gestation days 7 - 9 or 10 - 12, cardiovascular and skeletal abnormalities were detected with incidences of 5 and 11% of foetuses respectively, with none in the control group. If the animals were exposed from day 7 - 15, 24% of the foetuses were malformed and prenatal mortality increased.

2.3. EGnPE and EGnPEA

Groups of 30 pregnant rats were exposed to EGnPE vapour at atmospheric concentrations of 0, 100, 200, 300 or 400 ppm for 6h/d on days 6 to 15 of gestation (Krasavage and Katz, 1984-a). Haemoglobinuria occurred among the animals exposed to 200, 300 or 400 ppm of EGnPE after the first or second exposures but not after subsequent exposures. Haematological examination of these animals on day 20 showed a reduction in red blood cell count and increases in mean corpuscular volume and haemoglobin concentration compared to control values. These findings were statistically-significant. The absolute and relative spleen weights increased and microscopic examination of the spleen showed increased haemosiderin deposition and extramedullary haemapoesis. Reticulocytosis and polychromasia occurred at all exposure levels. The number of corpora lutea, implantation sites, viable foetuses and resorptions, and the foetal body weights and sex ratio, were unaffected by treatment with EGnPE. The incidences of all external or internal defects in the EGnPE groups, whether taken individually or collectively, were not statistically different from control values. The distribution of major external and soft tissue abnormalities in both control and treatment groups suggests that EGnPE is not teratogenic. The increased incidence of some common skeletal variants at 200, 300 and 400 ppm of EGnPE suggests a degree of foetotoxicity, albeit minor, although this was probably a reflection of maternal toxicity which was evident at these exposure levels.

Krasavage and Katz (1984-b) performed an inhalation teratogenicity study with rats at exposure levels of 0, 100, 200, 400 and 800 ppm of EGnPEA, for 6 h/d during day 6 to 15 of gestation. At 400 and 800 ppm, but not at 100 or 200 ppm, there were signs of maternal toxicity (decreased food consumption and weight gain and, in a few cases, haemoglobinuria after the first exposure). At these concentrations there was also a decrease in the number of red blood cells, an increase in mean cell volume, and, later, an increase in mean corpuscular haemoglobin concentration. Mean cell volume also increased marginally at 200 ppm. There was an increase of resorptions per litter and a reduction of foetal weights at 800 ppm. Retarded ossification of skull bones occurred at 400 ppm and (marginally) at 200 ppm, indicating some embryo- and foeto-toxicity. Two foetuses from the 800 ppm group and one from the control group had a cardiovascular defect consisting of a right-sided aortic arch. The only skeletal abnormalities were minor rib anomalies the incidence of which increased slightly in the

two higher dose groups. At 200 ppm a marginal increase of common skeletal variants was observed. There were no effects at 100 ppm of EGnPEA. It is concluded that EGnPEA is not a teratogen and is only foetotoxic/embryotoxic at those concentrations (>200 ppm) which also produce maternal toxic effects.

2.4. EGBE

The teratogenicity of EGBE has been examined in three inhalation studies in the rat and one in the rabbit. In the first rat study (Nelson et al., 1984-a), atmospheric concentrations of 150 and 200 ppm of EGBE were used at days of gestation 7-15, and there was no evidence of foetotoxicity at either level, although at 200 ppm haematuria was observed. There was no evidence of teratogenicity from this study.

A study in which rats were exposed to atmospheric concentrations of 100, 200 and 300 ppm (days of gestation 6-15) of EGBE was carried out by Tyl et al.(1984). Significant evidence of a toxic effect on the dams was noted at all three exposure levels. In the foetuses there was an increased mortality rate and some cardiovascular abnormalities were present which, although not seen in controls, did not occur in a dose-related manner. Most of the abnormalities (shortened or absent inominate arteries) have not previously been described as occurring with glycol ethers, but they have been observed in other studies and have been attributed to poor nutritional status.

A subsequent rat and rabbit study (Tyl et al.,1984) carried out with EGBE at the same laboratory to clarify the questions raised by the initial study failed to reproduce these results. The rats and rabbits were exposed to 25, 50, 100 or 200 ppm of EGBE at days of gestation 6 to 15 and 6 to 18, respectively. Exposure to 200 ppm caused significant maternal toxicity in rats, attributable to the haemolytic activity of EGBE, and increased embryolethality and foetotoxicity. Exposure to 100 ppm of EGBE caused some maternal haemolysis and a few minor changes attributed by the authors to foetotoxicity. The fact that the increase over background was marginal, and the small number of changes present in the foetuses at 100 ppm, make this interpretation open to question. In any case, the foetotoxicity, if present, is consistent with the maternal toxicity. There were no effects at either 25 ppm or 50 ppm in either the dams or the offspring, and no evidence of teratogenicity at any concentration. In the rabbit there was

some embryotoxicity and maternal toxicity at 200 ppm, with a clear no-effect level at 100 ppm. At 50 ppm there was clear no-effect level for effects on both the foetus and the dam, with a marginal effect level of 100 ppm for both maternal and foetotoxicity.

After dermal application (0.12 ml, 0.9 mmole) 4 times per day during gestation days 7 to 16, no malformations, foetal resorptions or embryotoxic effects were observed in rats (Hardin et al.,1984). This contrasts with EGEE and EGEEA.

The balance of evidence from the available studies indicates that EGBE is not teratogenic.

2.5. EGDME

Uemura (1980) reported teratogenic effects in mice after administration of doses of 250, 350 and 490 mg/kgbw by gavage on days of gestation 7 to 14. The investigation was limited to skeletal and gross abnormalities. Many foetuses showed exencephalies. A no-effect level was not established.

2.6. DEGME

After subcutaneous injection of 250, 500 or 1000 mg/kgbw of DEGME in pregnant albino rats from gestation day 6 to 20, the highest dose level resulted in a slight but not statistically significant decrease of the 4-day survival rate among new-born litters, but no effects were observed on their numbers or weights (Doe, 1984-a). Rats treated with 250 mg/kgbw of EGME served as a positive control group in which no viable foetus was seen. The results of the study demonstrated that DEGME is far less foetotoxic than is EGME and is unlikely to present a teratogenic risk.

In a probe dermal teratogenicity study in rabbits by John et al.(1983), undiluted DEGME was applied daily to the backs of groups of 10 pregnant New Zealand white rabbits at dose levels of 100, 300 and 1000 mg/kgbw/d, from days 6 to 18, inclusive, of gestation. The animals were killed on day 19. The highest dose level was found to be toxic; 3 of 10 animals died, and the surviving animals lost weight. The number of resorptions increased significantly (46% versus 4% in controls). No indications of maternal- or embryo-toxicity were seen at the two lower dose levels.

Diethylene glycol monomethyl ether (DEGME) was applied to the shaved skin of pregnant rabbits on days 6 through 18 of gestation in order to assess the foetotoxic and teratogenic potential by the dermal route (John et al.,1983,1984). Groups of 25 rabbits were treated with 0, 50, 250 or 750 mg/kgbw/d of DEGME, and the 29-day foetuses were examined for external, soft tissue and skeletal alterations. Topical application of the highest dose produced slight embryotoxicity, foetotoxicity and toxicity in the maternal animal, characterised by decreased weight gain and a concurrent decrease in RBC and PCV values. In addition, a slight increase in embryonic resorptions was observed. The foetal alterations observed at 750 mg/kgbw/d, i.e. mild forelimb flexure, slight-to-moderate dilation of the renal pelvis, retrocaval ureter, cervical spurs and delayed ossification of the skull and sternebral bones, are considered to indicate foetotoxicity but not teratogenicity. Slight foetotoxicity in the form of delayed ossification of the skull and cervical spurs was seen in the 250 mg/kgbw/d dose group. No adverse maternal, embryonic or foetal effects were observed at 50 mg/kgbw/d.

2.7. DEGEE

A multi-generation study on groups of 8 rats of each sex has been undertaken (Smyth et al., 1964) on DEGEE containing 0.2% EG.The dose levels were 0.01, 0.04, 0.2 and 1% in the drinking water, corresponding to 0.01, 0.04, 0.2 and 0.95 g/kgbw. The F_1 and F_2 generations received the same dose levels. All survivors were killed 718 days from the start of the study. There was no overt teratogenicity and no change in fertility was observed.

Hardin et al.(1984) have also investigated DEGEE in a dermal teratogenicity study in rats. The doses administered (0.35 ml per animal, 4 times a day) were equimolar to those of EGEE and EGEEA in the same study. No embryotoxic, foetotoxic or teratogenic effects were detected among the litters.

2.8. DEGBE

Benedict et al.(1983) carried out a dermal teratology study in rabbits (20 pregnant animals per treatment group) at dose levels of 100, 300 and 1000 mg/kgbw/d for 4h/d under non-occlusive conditions. DEGBE was administered as an aqueous solution of constant volume (3 ml/kgbw) in the dorsal region,

from day 7-18 of gestation. No embryotoxicity and no teratogenicity were detected.

In a study of fertility and reproductive performance, groups of 25 male and 25 female rats were administered DEGBE at oral doses of 0, 250, 500 or 1000 mg/kgbw/d for 60 days (males) or 14 days (females) days before mating with untreated animals (Procter and Gamble, 1984). No effects on male fertility were found. Uterine examination was carried out on approximately half the mated females on day 13 of pregnancy and on the remaining females at weaning. In untreated females mated with treated males there was a slight increase in post-implantation loss at examination on day 13, and a decrease in the mean number of implantation sites and live pups at weaning compared with control data. All values were, however, within the range of historical control values, and were not statistically significant. In view of this, and the lack of concordance between the findings at 13 days and at weaning, it is unlikely that these effects were treatment related. Among female rats treated with 1000 mg/kgbw and mated with untreated males there was a slightly lower number of mean implantation sites and mean number of live pups per dam at the weaning examination. These values were within the range of historical control values and similar changes were not evident at the 13-day uterine examination. The only effect considered to be related to treatment during this study was a reduction in the mean body weight of pups from females dosed at 1000 mg/kgbw of DEGBE, which occurred only during the later stages of lactation.

2.9. 2PG1ME

In an inhalation study reported by Hanley et al.(1984-b), rats and rabbits were exposed to atmospheric concentrations of 500, 1500 and 3000 ppm of 2PG1ME. Signs of mild CNS depression were observed immediately after exposure to 3000 ppm, although a tolerance to this effect gradually developed. Body weight gain decreased in the dams. The total number of major malformations per group in the rats increased with increasing exposure concentration, but none of the increases was statistically significantly different from controls. This, coupled with the variable nature of the malformations, indicates that this observation is unlikely to be biologically significant. At 3000 ppm there was an increased incidence of delayed sternebral ossification as evidence of slight foetotoxicity. No

treatment-related effects occurred at 500 or 1500 ppm in either the dams or foetuses.

Rabbit dams were mildly lethargic immediately following exposure to 3000 ppm on the first two days of exposure but there were no other signs of maternal toxicity. No treatment-related adverse effects on the rabbit foetuses were found at any exposure level.

The above evidence that 2PG1ME is not teratogenic is consistent with the results of Stenger et al.(1972) who investigated this ether in mice, rats and rabbits (see previous ECETOC, 1982, report), and with the lack of adverse effects in pregnant rats exposed to 2PG1ME at concentrations of 200 and 600 ppm (Doe et al.,1983).

2.10 1PG2MEA

The effect of 1PG2MEA on the developing foetus has been investigated in the rat (Merkle et al.,1984). Pregnant female rats were exposed to 0, 110, 560 or 2800 ppm of 1PG2MEA on gestation days 6-15 for 6h/d. The rats exposed to 560 or 2800 ppm gained weight less rapidly than did the controls and there were clinical signs related to exposure consistent with irritation of the respiratory tract. In the foetuses from the group exposed to 2800 ppm there was some foetotoxicity, manifested as reduced foetal weight and some retarded ossification. In addition, the incidence of minor vertebral anomalies increased in this group (dumb-bell-shaped bones and notched cartilage), and were probably associated with the foetotoxicity seen at 2800 ppm of 1PG2MEA. 1PG2MEA does not exert the severe toxicity to the developing rat foetus which is shown by EGME or EGEE *.

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* Preliminary information received shortly before this report was published (BASF, 1985), but not evaluated by the Task Force, suggests that 1PG2MEA had teratogenic effects in the rabbit when administered by inhalation at 545 ppm, but not at 36 or 145 ppm. There was no evidence of teratogenicity when rabbits were treated by occlusive dermal application of 1000 or 2000 mg of 1PG2MEA/kgbw/d on gestation days 6 to 18.

2.11 Pilot studies

Schuler et al.(1984) examined 15 mono-, di- and triethylene glycol ethers for toxic effects on reproduction using a mouse in vivo screening test based on the method of Chernoff and Kavlock (1980). Doses of the test material ranging from approximately the LD_5 to the LD_{20} were administered to groups of pregnant mice, daily from day 7 to 14 of gestation. Litter size, peri- and post-natal survival and pup weight gain were measured as criteria of reproductive performance. The animals administered EGME, EGEE, EGDME, DEGDME and TEGDME did not produce viable litters. There were statistically significant reductions in the number of viable litters from the animals given EG, EGBE, EGDEE or DEGME. The other test materials had no effect on the number of viable litters produced. Based on the effects observed in relation to the dose administered, the materials were placed in an order of priority for further testing. TEGDME was given the highest priority since at a dose producing 4% maternal mortality there were no viable litters. The other materials were placed in the following order:

High Priority	: EG, EGME, EGEE, EGDEE and DEGME;
Middle to High Priority	: EGDME, DEGDME;
Middle Priority	: EGBE, DEG, DEGDEE and TEG;
Low Priority	: DEGEE, DEGDEE.

Although these data indicate the urgency with which further testing should be carried out on some of these materials they cannot be taken as a reliable index of toxic effects on reproduction in view of the maternally toxic doses employed.

3. Neurological and Behavioural Effects

These have been extensively discussed in the previous report (ECETOC, 1982) and no new data indicating direct neurological effects of glycol ethers have become available.

Nelson et al.(1981; 1982a-b; 1984-b) studied the behavioural effects of EGME (25 ppm) and EGEE (100 ppm) on the offspring of pregnant rats exposed by inhalation. A variety of behavioural anomalies as measured by the rota-rod, open field, ascent on a wire mesh, activity wheel, operant conditioning and avoidance conditioning were observed. In addition, changes were found in

neurotransmitter levels (acetyl choline, dopamine, noradrenaline, 5-hydroxytryptamine) in various regions of the brain. Although the significance of these changes is far from clear, the author concluded that exposure to low levels of EGME and EGEE could produce behavioural changes and that neurochemical assays might be sensitive indicators of prenatal toxicity.

In a recent inhalation study, Nelson et al.(1984-b) exposed male rats, by inhalation, to 25 ppm of EGME, 7h/d, 7d/wk for 6 weeks, and investigated the inpact of this exposure on the behavioural performance of their offspring. The offspring were tested for neuromotor functions, activity and learning ability during the 10-90 days post partum. There were no behavioural deviations from the control group in these tests, but some neurochemical alterations in the cerebrum and brainstem were observed. Since EGME is not mutagenic, these results raise some questions of interpretation. When pregnant rats were exposed for 7h/d during gestation days 7-13 there was a significant impairment of avoidance conditioning among their offspring. Given the current status of this developing field of toxicology it is impossible to determine the significance of this work.

4. Genetic Toxicity

The available data on the genotoxicity of glycol ethers and some of their acetates are summarised in Appendix 3.

The genetic toxicology of the glycol ethers has been reviewed by McGregor (1984). EGME and DEGDME have been more extensively studied than have the other members of the series, and results are available from bacterial mutation assays, mammalian in vitro unscheduled DNA synthesis, drosophila, and sex-linked recessive lethal assay. The results from this battery of tests do not suggest a significant genotoxic activity. The in vitro results must however be qualified by reservations about the metabolising systems employed, since, e.g. the microsomal mixed-function oxidase systems do not permit alcohol oxidation by dehydrogenase enzymes. Foster et al.(1984) have shown that EGME is inactive in an in vitro culture of testes cells, but that the metabolite, methoxyacetic acid, is active. In an attempt to overcome this problem, McGregor (1984) exposed S. typhimurium strains to EGME in the presence of β-NAD^+ and alcohol dehydrogenase. The results of these experiments were inconclusive because of the cytotoxicity of the system.

There can be no such reservations about the in vivo studies in which metabolism of the compounds can take place. EGME and DEGDME caused both a marked reduction of fertility in rats and abnormal sperm head morphology in mice (McGregor et al., 1983). However, there were indications of only weak dominant lethal mutations with EGME and DEGDME, and it is probable that the effects reflect testicular toxicity rather than genotoxicity. Neither EGME nor DEGDME caused chromosome aberrations in rat bone marrow.

In summary, effects have been seen only at very high doses or they can be attributed to a non-genetic mechanism, and it is concluded that the glycol ethers do not have a significant genotoxic action.

5. Carcinogenicity

EGEE is currently the subject of a lifetime study in rats and mice (Melnick, 1984) with administration by gavage. Final results are not yet available.

6. Dermal Absorption

As part of the evaluation of the hazards of undiluted glycol ethers, their absorption across isolated human abdominal epidermis has been measured (Dugard et al., 1984). The compounds can be listed in order of decreasing steady-state absorption rate as follows : EGME> PGME> EGEE = EGEEA> DEGME> EGBE> DEGEE> DEGBE. The ability of EGME readily to penetrate human skin is confirmed by the study of Nakaaki et al. (1980) who found high blood levels of EGME following dermal exposure to 15 ml of undiluted EGME for 2 hours. The dermal absorption rates and subsequent fate of EGEEA and EGnPEA have been studied in beagle dogs by Guest et al.(1984) who concluded that these materials were absorbed in a similar way to that of other lipid-soluble compounds. Dermal absorption is therefore considered to be a significant route of exposure for the glycol ethers.

7. Metabolism and its Effect on Toxicity

7.1. Metabolic studies

7.1.1. EGME. Two studies in which male rats were orally dosed with ^{14}C-labelled EGME gave very similar results (Miller et al., 1983-b,1984-c; Foster et al., 1984). Within 48 hours of dosing, 50 to 70% of the radiolabel was excreted in the urine, mostly in the form of methoxyacetic acid; 1 to 3% was excreted in the faeces as parent compound and 12 to 18% remained in the carcass. A major difference between the two studies was in the

radiolabel found in the expired air. Miller found 12%, as CO_2, whereas Foster found only 3%, as EGME. The difference is almost certainly due to a difference in the position of the label (see below) and supports the previous indications that the ether linkage is relatively stable in mammalian metabolism.

$CH_3O-CH_2-CH_2-OH$ (a) Miller study (* *)

$CH_3O-CH_2-CH_2-OH$ (b) Foster study (*)

7.1.2. EGEE and EGEEA. Johnsson et al.(1982) and Cheever et al.(1984) showed that in rats orally dosed with EGEE the major urinary metabolite was ethoxyacetic acid and its glycine conjugate. When the radiolabel was in the ethanol part of the molecule, analogous to (a) above, 5% appeared as exhaled CO_2 in the first 10 hours, whereas when the label was in the ethoxy group, analogous to (b) above, 12% appeared as CO_2. Ten minor unidentified urinary metabolites represented 3-5% of the dose.

Guest et al.(1984) showed that in beagle dogs EGEEA was rapidly absorbed through the lungs. At equilibrium (ca. 3 h) approximately 70% of the inhaled vapour was retained. The rapid decline in the post-exposure breath concentrations indicated rapid removal of the compound from the blood. There was no indication of metabolites in the exhaled air. Dogs exposed percutaneously to ^{14}C-EGEEA rapidly excreted ^{14}C in the urine, there being no difference in the rate of excretion following 30 or 60 minute exposure. Following intravenous administration of ^{14}C-EGEEA, the half-life for the elimination of ^{14}C from the blood was 7.9 h.

Pederson et al.(1980) reported that although EGEE has a higher affinity than has ethanol for alcohol dehydrogenase in vitro, simultaneous administration of EGEE (316 ppm by inhalation for 5.5h period) and ethanol (a single oral dose of 104 g) to a human volunteer did not affect the rate of elimination of ethanol. This is not surprising as ethanol is normally excreted largely unchanged.

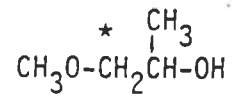
7.1.3. EGiPE. The metabolism of this compound has been extensively reviewed in the previous report (ECETOC, 1982). No new data are available.

7.1.4. EGnPEA. In a study parallel to their study on EGEEA, Guest et al.(1984) showed that EGnPEA was rapidly absorbed through the lungs. At equilibrium (ca. 3 h) about 75% of the inhaled vapour was retained by the dogs. As indicated by the rapid decline in post-exposure breath concentrations, EGnPEA is rapidly removed from the blood. After intravenous administration of ^{14}C-EGnPEA, the half-life of elimination of ^{14}C from the blood was 1.6 h. The rate of urinary excretion of ^{14}C following percutaneous absorption of ^{14}C-EGnPEA was greater than that observed with ^{14}C-EGEEA although the total amounts of each compound absorbed were similar.

7.1.5. DEGEE. DEGEE was subcutaneously administered to rabbits in doses of 3 and 5 ml/kgbw, and in doses of 4 ml/kgbw by gavage. The total percentage increase in glucuronic acid excretion was 78 to 87.5% (Fellows et al.,1947). This considerable increase suggests that DEGEE is excreted in a conjugate form as a glucuronide. Even on the assumption that one molecule of the compound combines with one molecule of glucuronic acid, the amount excreted in this way represents only a very small percentage (0.8 to 2.3%) of the total amount administered. Presumably, the greater part of the DEGEE is oxidized in the body.

2-Ethoxyethoxyacetic acid has been detected in urine samples from humans with suspected in-born errors of metabolism and was assumed to be formed endogenously from an exogenous precursor, probably DEGEE (Kamerling et al.,1977). Oral administration of 1503 mg (11.2 mmole) of DEGEE in a normal adult resulted in the excretion of 1140 mg (7.7 mmole) of 2-ethoxyethoxy acetic acid (69% of the dose) in 12 hours.

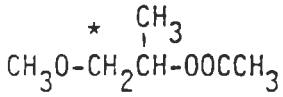
7.1.6. 2PG1ME and 2PG1MEA. 2PG1ME, labelled as below,



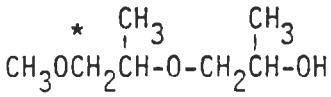
was administered by gavage to young male rats (Miller et al.,1983-b). Within 48 hours 10-20% of the radioactivity appeared in the urine, and 50-60% as CO_2 in expired air (33% in the first 4 hours).. Three to 7% of the label appearing in the expired air was absorbed on charcoal (probably parent compound) and approximately 1% of the label was found in the faeces. The compounds identified in the urine were propylene glycol and the sulphate and glucuronide conjugates of 2PG1ME. The highest

concentration of ^{14}C found in the carcass was in the liver and there was no obvious accumulation in other organs. Increasing the dose from 1 to 8.7 mmole/kgbw resulted in a lower percentage of the radioactivity appearing in the expired air and more in the urine. The results indicate a qualitative difference in metabolism between 2PG1ME and the monoethylene glycol ethers. In the former, rupture of the ether linkage is a rapid and major route whereas in the latter it is not.

An essentially similar metabolic pattern was obtained when rats were exposed to 2PG1MEA, labelled as below, either by oral dosing or by inhalation (Miller et al.,1984-a).



7.1.7. DPGME. In rats dosed orally with ^{14}C-labelled D2PG1ME (see below) approximately 60% of the label was excreted in the urine and 27% as CO_2, within 48 hours. Less than 3% was excreted in the faeces (Miller et al.,1984-b).

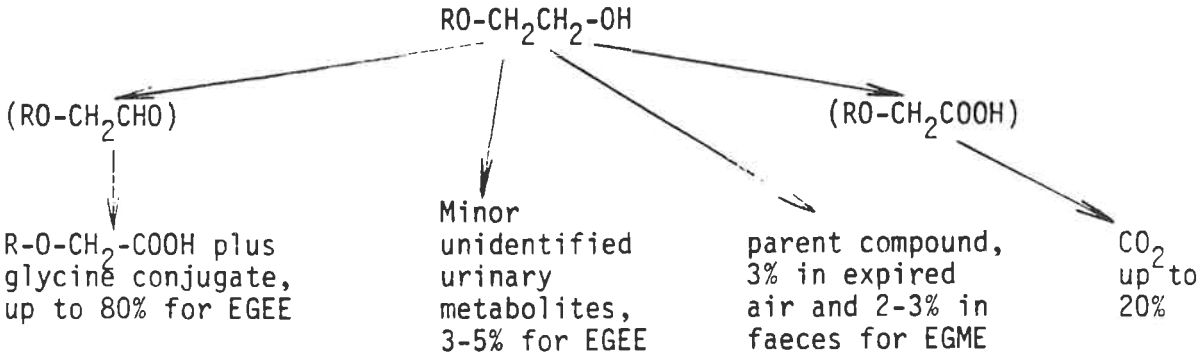


DPGME, PGME, dipropylene glycol, propylene glycol, and the sulphate and glucuronide conjugates of DPGME were identified in the urine. The highest concentrations of ^{14}C in the carcass were found in the liver and skin (approximately twice the blood concentration) but there was no obvious organ accumulation.

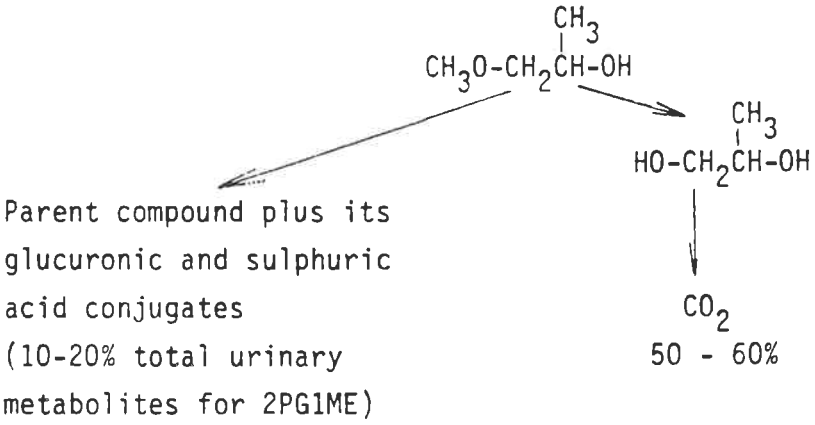
7.2. Qualitative patterns of metabolism

The following patterns of metabolism have been deduced from the work described above.

7.2.1. Ethylene glycol ethers



7.2.2. Propylene glycol ethers



7.2.3. Glycol ether acetates. In the only study on glycol ether acetate metabolism (Miller, 1984-a) it was shown that glycol ether acetates are metabolised to the parent glycol ethers. Recent in vitro experiments with ethylene glycol ether acetates demonstrated that they are readily hydrolysed by plasma esterases. The half-lives of the acetates in rat plasma were determined by gas liquid chromatography, and the following values were found: ca. 12 min. for EGMEA, ca. 10 min. for EGEEA and ca. 1 min. for EGBEA (Hoffman, 1984). These data are consistent with the fact that the toxicological effects of the glycol ether acetates are similar to those of their respective parent glycol ethers.

7.3. Effect of metabolism on the toxicity of glycol ethers

A number of studies have indicated the involvement of metabolite(s) of the ethylene glycol monoalkyl ethers in the generation of their toxic effects. Foster et al.(1984) investigated the way in which the metabolism of EGME influences its testicular toxicity. Methoxyacetic acid and an equimolar

dose of EGME produced essentially similar testicular effects in orally-dosed rats. Mixed Sertoli cell and germ cell cultures from young male rats showed dose-related degeneration of the spermatocytes, but not the Sertoli cells, when treated with methoxyacetic acid. On the other hand, EGME produced no adverse effects on these cultures at ten times the lowest concentration at which effects were produced with methoxyacetic acid.

In a parallel in vivo experiment (Foster et al.,1984), rats pre-treated with pyrazole to inhibit alcohol dehydrogenase were completely protected from the testicular toxicity of a subsequent dose of EGME, whereas pretreatment with disulfiram to inhibit aldehyde dehydrogenase gave no protection. Similarly, pretreatment with disulfiram and pargyline (another aldehyde dehydrogenase inhibitor) did not protect from methoxyacetic acid testicular toxicity. Thus there are indications that the agents responsible for the testicular toxicity of the ethylene glycol monoalkyl ethers are either the corresponding alkoxyacetic acid, alkoxyacetaldehyde or some further metabolite. In addition, the only metabolite found in the testes of EGEE-exposed rats was ethoxyacetic acid (Cheever et al.,1984).

Cleavage of the ether linkage is a minor metabolic route for the ethylene glycol ethers. By contrast, 2PG1ME is metabolised mainly to propylene glycol which is subsequently oxidised to carbon dioxide. Small quantities are excreted in the urine as the parent compound, its conjugates and propylene glycol. None of these metabolites has been shown to cause the toxic effects characteristic of EGME, EGEE or their metabolites.

From an in vitro study with Chinese hamster ovary (CHO-K1) cells, Jaeckh (1984) assessed the ability of EGME, EGEE and EGBE to reduce the cloning efficiency as a measure of their cytotoxicity. As the chain length increased so did the cytotoxicity, in the order EGME < EGEE < EGBE. A study with the corresponding alkoxyacetic acids showed a much higher cytotoxicity, but no trend with increasing chain length. This indicates that cytotoxicity itself is not the mechanism of teratogenicity, testicular toxicity or myelotoxicity. There was no apparent difference between the cytotoxic effects of 1PG2ME and 2PG1ME, but 2-methoxypropionic acid (a postulated metabolite of 1PG2ME) was less cytotoxic than were the alkoxyacetic acids tested.

Adverse effects of methoxyacetic acid (MAA) on a rat embryo culture system have been reported by Yonamoto et al.(1984). The incorporation of 1 - 5 mmole of MAA into the culture medium produced a series of effects characterised as reduction in yolk-sac diameter, somite number, crown-rump length and other morphological scores. The predominant abnormality was irregular fusion of the neural tube and at high concentrations (3 and 5 mmole) exposure led to open neural tubes and stunted telecephalic hemispheres. EGME itself had no effects in this system. MAA however has been shown by Brown et al.(1984) to be teratogenic in vivo in rats.

An investigation into the effects of EGBE and its prime metabolite, butoxyacetic acid, on the erythrocyte membrane has been reported by Hext (1984). Erythrocytes from the rat, rabbit, dog and man were treated with 0.05 - 0.5% of EGBE or BAA and then suspended in 0.68% sodium chloride at 37°C. Rat erythrocytes were very susceptible to the membrane damage caused by BAA (98.8% lysis following treatment with 0.5% BAA). Human, dog and rabbit erythrocytes were resistant to such effects over a wide range of concentration (0 - 1.1% lysis following treatment with 0.5% BAA). In dog erythrocytes there was a slight haemolysis at one of the lower concentrations (0.02% BAA). When the erythrocytes were exposed to EGBE a different pattern was observed: rat, human and rabbit erythrocytes were lysed at similar concentrations (0.2 and 0.5% EGBE) whereas at all concentrations (0.05 - 0.5%) a high percentage of dog erythrocytes was lysed.

D. HUMAN EXPOSURE

1. Exposure Limits

As new experimental and human toxicological data became available, the ACGIH (1984) lowered the Threshold Limit Values for EGME and EGEE and their acetates, from 25 ppm (skin) and 50 ppm (skin), respectively, to 5 ppm. The German MAK commission (DFG, 1984) also lowered the MAK values of EGME and EGMEA to 5 ppm, and of EGEE and EGEEA to 10 ppm. The hygiene standard of EGBE and EGBEA has been adjusted to 20 ppm. The Dutch MAC Commission was advised by its Working Group of Experts to reduce the MAC values for EGME and EGEE and their acetates from, respectively, 25 and 100 ppm, to 5 ppm. A

revised list of exposure limits is added in Appendix 4. No exposure limits are available for the glycol ethers not mentioned in the Appendix.

2. Workplace Monitoring

2.1. Physical monitoring. A new method based on a diffusive monitor has been developed to determine personal inhalation exposure to glycol ethers. The main advantage of this method is its ability to cope with a large number of samples, but lightness and acceptability to workers are also important (Hamlin et al., 1982). Data on actual workplace concentrations remain scarce but some were, however, obtained from certain European industries and are summarised in Table 3 (personal communication).

Hamlin et al.(1982) published the results of monitoring exercises carried out in 1982 in a variety of industries where glycol ethers are used. Diffusive monitors were used for both personal and area monitoring. Measurements were carried out by area monitoring in large printing works (2 sites), in large car refinishing shops (3 sites), in film coating plants, at seven printing ink manufacturers and in the laboratories of lithographic plate development. The exposure levels for EGME, EGEE and their acetates were generally below 4 ppm. Levels of between 13 and 20 ppm of EGEE and between 31 and 47 ppm of EGME were found, respectively, in an unventilated solvent storeroom and a poorly-ventilated automatic lithographic-plate developing room.

In 1981 and 1982 NIOSH conducted several surveys which included preliminary measurements of personal and area exposure levels in a variety of industries including painting trades, coal mining, production blending and distribution facilities, aircraft fuelling, and communications equipment repair facilities. Most personal and area exposure data for EGME, EGEE, EGEEA and EGBE were well below 1 ppm. The EGME values appeared to be highest, eg. 2.8 ppm (personal sampling) in a drumming area. The collection of these data revealed several problems in sampling low concentrations reliably. It became apparent from the data and from observations of work practices that air monitoring alone provided an inadequate measure of exposure to glycol ethers (Clapp et al.,1984).

Between 1979 and 1982, OSHA collected monitoring data from over 51 different plants at which glycol ethers were being used. The average 8h

TWAs for worker exposure to EGME, EGMEA, EGEE and EGEEA were 9.3, 0.9, 4.3 and 2.7 ppm, respectively. Peak exposure levels could, however, have been greater than 6.1, 8.4, 85.3 and 50.4 ppm, respectively.

No surveys are available of the exposure levels arising from the use of consumer products. However, even low concentrations of these glycol ethers and their acetates in specific consumer products are considered by the EPA(1984) to produce exposure levels of concern.

TABLE 3

Exposure Levels of Glycol Ethers in European Plants

EGME			
SITE 1	Manufacturing	PAS* TWA	0.12 - 0.5 ppm
SITE 1	Drum-filling	PAS TWA	0.9 - 6.4 ppm
SITE 2	Manufacturing	PAS TWA	0.6 - 1 ppm
		AREA TWA	0.6 - 1 ppm
SITE 2	Drum filling	PAS TWA	0.2 - 4 ppm
SITE 3	Laboratory (Karl Fischer reagent)	PAS TWA	<1.2 ppm
EGEE			
SITE 1	Drum filling	PAS TWA	0.9 - 6.5 ppm
SITE 1	Blending, static		0.01 - 6.2 ppm
SITE 2	Manufacturing	PAS TWA	0.08 - 0.2 ppm
		AREA TWA	0 - 4.2 ppm
SITE 2	Roadcar filling	PAS AREA	0.05 - 2.3 ppm
SITE 3	Blending	PAS TWA	0.1 - 0.7 ppm
EGiPE			
SITE 1	Manufacturing	PAS TWA	0.02 - 0.2 ppm
SITE 1	Drum filling	PAS TWA	0.2 ppm
EGBE			
SITE 1	Manufacturing	PAS TWA	0.01 - 0.4 ppm
SITE 1	Blending	PAS TWA	0.5 - 2.7 ppm
SITE 2	Manufacturing	PAS TWA	0.1 - 0.4 ppm
		AREA TWA	0.03 - 5.3 ppm
SITE 2	Drum filling	PAS TWA	0.03 - 0.3 ppm
SITE 2	Roadcar filling	PAS TWA	<1.6 ppm

* PAS : personal air sampling.
TWA : time-weighted average.
AREA : area exposure levels.

No information is available concerning the possible exposure to glycol ethers via the dermal route. The information reported in chapter C, section

6, justifies the conclusion that dermal absorption should be considered as a important route of exposure.

2.2. Biological monitoring.

As humans may be exposed to glycol ethers by different routes (inhalation, dermal), the measurement of personal exposure by biological means would be the ideal. Blood from humans exposed to EGME has been shown to contain this glycol ether and thus may be a suitable medium for biological monitoring. The chromatographic detection limits for EGEE and EGBE are 5.0 and 4.0 µg/g blood, while EGME has a slightly higher detection limit of 8.8 µg/g because of its close proximity to the methylene chloride solvent front. The average recovery of glycol ethers added to blood was approximately 78% for EGME and 89% for EGEE over a wide concentration range (Smallwood et al.,1984).

Nakaaki et al.(1980) exposed 12.5 cm^2 of the forearm of two human volunteers to liquid EGME. A rapid rise in blood levels was reported after 2 hours, and concentrations of EGME of between 106 and 493 µg/ml were recorded. The analytical method was not given in detail, but a recovery of 66% was reported.

NIOSH conducted a survey in a company in Atlanta where 300 workers occasionally used EGEE for cleaning. Since air sampling revealed extremely low breathing-zone concentrations, biological sampling was attempted. Analyses of blood samples gave results below the limit of detection, which was 5µg/ml (Clapp et al., 1984).

Tentative procedures have also been developed to measure the metabolites, methoxyacetic acid and ethoxyacetic acid, in urine as possible indices of exposure. Detection limits for methoxyacetic and ethoxyacetic acid are 11.4 and 5.0 µg/ml, respectively. Recoveries determined over a concentration range of approximately 10 to 1000 µg/ml ranged from 78 to 91% for the two metabolites, respectively (Smallwood et al.,1984). These authors suggested that the biological monitoring procedures based on blood and urine are ready to be validated in workers exposed to EGME, EGEE and EGBE.

3. Evidence of Effects on Humans

Since publication of the first ECETOC (1982) report, few new data have become available.

In a cross-sectional epidemiological study conducted among white male employees at a Dow Chemical plant (Cook et al.,1982), 40 workers exposed to EGME and 25 controls drawn from the alkanolamine and salicylic acid plants were studied. Personal monitoring in the production area in January 1976 revealed an 8h TWA of 0.42 ppm or less of EGME; wearing of gloves was recommended to avoid skin contact. In 1980, personal monitoring in the packaging and distribution building revealed 2h TWAs of 5.4 to 8.5 ppm, and area monitoring showed that atmospheric levels were between 4 and 20 ppm. Blood samples on all 65 subjects and on 9 controls, and semen samples from 6 workers exposed to EGME, were analysed. There were no differences of clinical significance between exposed and unexposed subjects in a variety of haematological and fertility indices studied. A possible diminution in testicular size in the exposed workers may have been due to errors in measurement and, in any case, was not consistent with the results of the semen analyses.

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 6 of 7 subjects examined, bone marrow hypoplasia was seen in 6 subjects, and an increase in Periodic acid Schiff(PAS)-positive stromal material was seen in 3. Although the myeloid/erythroid ratio in these subjects was lower than in the normal population, the other bone marrow changes described, such as reduced cellularity, the presence of ringed sideroblasts and PAS-positive material, are 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 the study about the possible association between bone marrow changes and exposure to glycol ether.

E. DISCUSSION

In the previous ECETOC (1982) report, EGME and EGEE were reported to cause toxic effects on reproduction, but clear no-effect exposure levels had not been established for either material. The data available at that time on other glycol ethers were not extensive, but were sufficient for some tentative conclusions regarding structure-activity relationships to be drawn. Since that time a great deal of experimental work, which has confirmed the effects of EGME and EGEE and extended the number of compounds for which acceptable data are available, has been completed. These studies, described in this report, have allowed the development of a more complete picture of the toxicology of the glycol ethers and related compounds as a class, and have often yielded clear no-effect levels.

1. Structure-Activity Relationships

No new major biological effects attributable to the glycol ethers have emerged, the four major effects being testicular atrophy, teratogenesis/foetotoxicity, depression of bone marrow (producing pancytopenia), and haemolysis.

EGME and EGEE have been shown to cause pancytopenia, testicular atrophy and teratogenicity, EGME being more potent than EGEE. EGDME also produces these three effects. EGnPE, EGiPE and EGBE have no effect on either the testes or the bone marrow and are not teratogenic. Thus ethylene glycol ethers with an alkyl-moiety chain-length of greater than 2 carbon atoms do not cause these three types of toxic effect. However, these latter compounds do cause haemolysis, an effect observed to a lesser extent with EGEE.

The available evidence for the diethylene glycol series is less complete but suggests that the monoethers do not give rise to testicular atrophy or foetotoxicity/teratogenicity. However, DEGDME, a diethylene glycol diether, appears to have an effect on the testes although the dose-response relationship of this effect has not been explored.

2PG1ME, a member of the propylene glycol mono-ether series, does not induce any of the four effects seen with the ethylene glycol monoether family.

On the basis of the available data on DPGME, it is unlikely that the dipropylene monoether series cause any of the major effects seen with the ethylene glycol monoethers.

The acetates derived from the glycol ethers appear to have the same activity as their parent ethers e.g. EGMEA causes testicular atrophy at equimolar concentrations to EGME. Recent studies have demonstrated that the acetates hydrolyse rapidly to the parent ether.

These data have therefore confirmed the structure-activity relationships which were suggested in the original report.

2. Relevance to Man

In the previous ECETOC (1982) report, reasons were given why it is prudent to assume that the adverse effects of EGME or EGEE on the testes and the developing embryo observed in experimental animals would also occur in humans exposed to appropriate concentrations. No evidence has emerged to challenge this assumption. The assumption that those glycol ethers which do not produce testicular toxicity or foetotoxicity/teratogenicity in laboratory animals (even when exposed to high concentrations) would not cause these effects in humans is equally valid.

Even though EGME has been shown to produce adverse effects on the haemopoietic system in humans, the significance of the haemolytic effects of EGEE, EGPE and EGBE requires further consideration. Comparative studies have shown large differences in the susceptibility of the erythrocytes from different species to the effects of EGBE. Rats, mice and rabbits have been found to be more susceptible than the guinea pig, monkey, dog and man. This has been demonstrated for rats and man in both in vivo and in vitro studies. The erythrocytes of human volunteers were unaffected after exposure to 100 or 200 ppm of EGBE, whereas the exposed rats had increased erythrocyte fragility. Butoxyacetic acid, the major metabolite of EGBE, has been shown to cause almost complete lysis of rat erythrocytes at concentrations causing no lysis in human cells. These data suggest that the rat erythrocyte is particularly sensitive to the haemolytic effect of EGBE such that it would be inappropriate to extrapolate the findings directly to man.

F. GENERAL CONCLUSIONS

The studies considered in this report have enabled conclusions to be drawn concerning the sub-chronic and testicular toxicology, mutagenicity and teratogenicity/ foetotoxicity of each of the major compounds studied. These are presented below for EGME, EGEE, EGEEA, EGnPE, EGnPEA, EGBE, PGME, PGMEA, the diethylene glycol ethers and the dipropylene glycol ethers. Representative samples of the different types of glycol ethers have been assessed for mutagenicity. The evidence from the large number of compounds tested suggests that this class of chemicals does not pose a genotoxic risk to man.

1. EGME

Effects on the testes have been examined in 13-week inhalation studies in which rats and rabbits were exposed to EGME at concentrations up to and including 300 ppm. In rats exposed to 300 ppm the principal effects observed were testicular atrophy and infertility. There were no effects in rats at 100 ppm and below. In rabbits, testicular atrophy was observed at 300 and 100 ppm. There were no reproducible effects on the testes at 30 ppm of EGME, which can be considered a marginal effect level for such effects.

In inhalation teratology studies on rats, rabbits and mice, 50 ppm of EGME produced teratogenicity, foetotoxicity and maternal toxicity in rabbits, foetotoxicity in mice, and no effects in rats. Ten and 3 ppm of EGME were without toxicologically-significant effect in all three species, and 10 ppm can be considered to be a no-effect level for the foetus.

The consistent nature of the results between studies and between species indicates that they form a reliable basis, in conjunction with the metabolic and human data,for assessing the toxicity of EGME and for extrapolation to man.

2. EGEE and EGEEA

In 13-week inhalation toxicity studies of EGEE in rats and rabbits there was evidence of testicular atrophy in rabbits at 400 ppm, but no effects in either species at 100 ppm (a clear no-effect level) or 25 ppm.

The teratogenicity of EGEE has been explored in inhalation toxicity studies on rats and rabbits. Rats were exposed to 10, 50 or 250 ppm. No evidence of

teratogenicity was seen at any level, but there was evidence of foetotoxicity at 250, and possibly at 50 ppm. There was considered to be a marginal effect level at 175 ppm for teratogenicity in rabbits and there was evidence of foetoxicity at this level. There were no effects at 50 or 10 ppm in the rabbit. A clear no-effect level for the effects of EGEE on the foetus is 10 ppm, with only a slight foetotoxic effect in one species (the rat) at 50 ppm.

There has been no further information on the subchronic effects of EGEEA, but inhalation teratology studies in rats and rabbits have demonstrated that it possesses the teratogenicity and foetotoxicity of the parent ether. When rats were exposed to EGEEA, all implants were completely resorbed at 600 ppm. At 390 ppm foetotoxicity occurred in the form of delayed ossification, and a cardiac abnormality gave evidence of teratogenicity. At 130 ppm there was a major abnormality and evidence of foetotoxicity. When rabbits were exposed to EGEEA there was evidence of teratogenicity (major malformations of the vertebral column) at 400 ppm, but none at either 100 or 25 ppm. Some delayed ossification indicated foetotoxicity at 100 ppm of EGEEA, but 25 ppm was a clear no-effect level. The two studies together show that at 390 and 400 ppm EGEEA is teratogenic, at 100 and 130 ppm it is foetotoxic, and that 25 ppm is a no-effect level.

These studies provide a reliable basis for consideration of the toxicity of EGEE and EGEEA. The consistent nature of the results between studies and between species indicates that they form a sound basis, in conjunction with the metabolic data, for extrapolation to man.

3. EGnPE and EGnPEA

Both EGnPE and EGnPEA have been studied in two-week inhalation studies at 100, 300, 400 and 800 ppm. Neither compound caused testicular atrophy or bone marrow effects, but at 800 and 400 ppm produced the haematuria and decreased red blood cell counts expected of erythrocytolytic compounds. No-effect levels were 200 ppm for EGnPE and 100 ppm for EGnPEA.

The inhalation teratology of EGnPE and EGnPEA has been studied in rats. Pregnant rats were exposed to 0, 100, 200, 300 or 400 ppm EGnPE. Maternal toxicity attributable to haemolysis was seen at 200, 300 and 400 ppm of EGnPE, and was accompanied by slight foetotoxicity. There was no evidence of teratogenicity and 100 ppm was a no-effect level. For EGnPEA there was

evidence of maternal toxicity at 400 and 800 ppm and foetotoxicity at 200 and 400 ppm. There was no evidence of teratogenicity and the no-effect level for EGnPEA was 100 ppm.

It is likely that the same reservations concerning the relevance of the haemolytic effect to humans apply as for EGBE (cf. 4 below).

4. EGBE

Both the inhalation and dermal toxicity of EGBE have been studied. A 90 day inhalation study was carried out in rats at concentrations of 5, 25 and 77 ppm. An effect on erythrocytes was noted after 6 weeks in the females exposed to 77 ppm, but after 12 weeks no effects were seen. There were no other effects in any other rats in the study. EGBE has been shown not to affect the testes of mice, rats and rabbits when given by the inhalation, oral or dermal routes.

The effect of EGBE in pregnant laboratory animals has been studied. There was maternal toxicity in rats at 200 and 100 ppm, accompanied by slight foetotoxicity. In rabbits there was some embryotoxicity and maternal toxicity at 200 ppm, 100 ppm being a clear no-effect level. Overall, there was no evidence of teratogenicity from either study and it can be concluded that EGBE is not teratogenic. A clear no-effect level for the rat foetus and mother was established at 50 ppm, while at 100 ppm there was minor maternal toxicity and possibly foetotoxicity.

No new findings have emerged from the recent work on EGBE which would alter the previous appraisal of its toxicology. It does not share the effect on the testes, the blood-forming elements and the developing foetus possessed by EGME and EGEE. EGBE's most significant effect in laboratory animals is lysis of the red blood cells which occurs at much lower concentrations than in humans. Its relevance for predicting adverse effects in humans is extremely doubtful.

5. PGME and PGMEA

There are two isomeric forms of PGME : 2PG1ME and 1PG2ME. A mixture of approximately 95% 2PG1ME and 5% 1PG2ME has been most fully evaluated. A 13-week inhalation study in rats and rabbits revealed minor CNS depression and liver weight increase in the rats exposed to 3000 ppm. There were no

effects in the rabbits at any concentration and no effects in the rats at either 300 or 1000 ppm. Inhalation teratology studies with this material in rats and rabbits revealed only minor effects, i.e. slight maternal toxicity and slight foetotoxicity in rats at 3000 ppm. At 3000 ppm in rabbits and 500 and 1500 ppm in rats there were neither maternal nor foetal effects. Metabolic studies have revealed than an alkoxyacid metabolite is not formed, which may explain the marked lack of toxicity when compared with EGME. The consistent nature of the results with this mixture of isomers between species and between studies indicates that they form a sound basis, in conjunction with the metabolic data, for extrapolation to man.

1PG2MEA has been examined in a subchronic 28-day study and a teratology study in the rat. Apart from minor non-specific effects and some irritation to the respiratory tract, there were no other effects at 2800 ppm. In pregnant rats, 560 and 2800 ppm caused body weight reductions and irritation of the respiratory tract. There was some foetotoxicity at 2800 ppm, but no effects on the foetus at 560 ppm. For preliminary information on the possible teratogenic potential of 1PG2MEA see footnote on p.29 .

6. Diethylene Glycol Ethers

The diethylene glycol mono-alkoxy ethers appear not to have the same spectrum of activity as the monoethylene glycol mono-alkyl ethers. Available data indicate that DEGME, DEGEE and DEGBE do not cause toxic effects on reproduction. In contrast, diethylene glycol dimethyl ether (DEGDME) appears to share the effect of EGME and EGDME on the testis and it would be prudent, in the absence of any other evidence, to consider that this chemical would have adverse effects on reproduction in man.

7. Dipropylene Glycol Ethers

Data are available only for a commercial mixture of dipropylene glycol monomethyl ethers (DPGME) as described above. No effects were found in rats and rabbits following 13 weeks exposure by inhalation at 15, 50 or 200 ppm. As the methyl ethers are generally the most active members of each series, this study indicates that the dipropylene monoalkyl ethers probably have no toxic effects on reproduction.

F. APPENDICES

Appendix 1 : Haematological Testicular and Other Systemic Toxic Effects

COMPOUND	SPECIES	ROUTE	ANIMALS PER DOSE LEVEL	EXPOSURE CONC. or DOSE	TIME	RESPONSE	REFERENCE
EGME	Rats	Inhalation	10 M* 10 F*	30 ppm 100 ppm 300 ppm	6h/d, 5d/wk, 13 wks	- No effects - No effects - Testicular and thymic atrophy; pancytopenia; decreased abdominal fat	Miller et al. (1983-a)
	Rabbits	Inhalation	5 M 5 F	30 ppm 100 ppm 300 ppm	6h/d, 5d/wk, 13 wks	- Testicular atrophy ? - Testicular atrophy; 2F died - Testicular and thymic atrophy; pancytopenia; decreased abdominal fat; 2M, 2F died	Miller et al. (1983-a)
	Rat	Inhalation	20-30 M	30 ppm 100 ppm 300 ppm	6h/d, 5d/wk, 13 wks	- No effects - No effects - Complete infertility	Rao et al. (1983)
	Rat	Inhalation	20 M	150 ppm 300 ppm 625 ppm 1,250 ppm 2,500 ppm 5,000 ppm	Single 4 h exposure	- No effects - No effects - Damage to maturing spermatids - Testicular atrophy - Testicular atrophy - Testicular atrophy	Doe (1984-a)
	Rat	Inhalation	10 M	1,000 ppm 2,500 ppm	Single 4 h exposure	) Damage to germinal epithelium) after 24 h. Mitochondrial swelling after) 4 d	Doe (1984-a)
EGEE	Rat	Inhalation	15 M 15 F	25 ppm 100 ppm 400 ppm	6h/d, 5d/wk, 13 wks	- F-decrease in spleen and relative spleen weights - F-decrease in spleen weights - F-decrease in spleen and relative spleen weights M-decrease in pituitary and relative pituitary weights	Terril and Daly (1983)
	Rabbit	Inhalation	10 M 10 F	25 ppm 100 ppm 400 ppm	6h/d, 5d/wk, 13 wks	- No effects - No effects - Testicular atrophy, reductions in RBC, Hb and HCT	
	Rat	Inhalation	5 M	4,500 ppm	Single 3h exposure	- Testicular atrophy, haematuria	Doe (1984-a)

* F - female
M - male

Appendix 1 (2)

COMPOUND	SPECIES	ROUTE	ANIMALS PER DOSE LEVEL	EXPOSURE CONC. or DOSE	TIME	RESPONSE	REFERENCE
EGnPE	Rat	Oral	10 M	195 mg/kgbw	5d/wk, 6wks	- Haemoglobinuria; reduction in RBC* and/or Hb* and HCT*	Katz et al.(1984)
				390 mg/kgbw		- Deaths, haemoglobinuria; reductions in " " ") enlargement	
				780 mg/kgbw		- Deaths, haemoglobinuria; reductions in " " ") of the spleen	
				1,560 mg/kgbw		- Deaths, haemoglobinuria; reductions in " " ")	
	Rat	Inhalation	5 M	100 ppm	6/d, 5d/wk,	- No effects	Katz et al.(1984)
			5 F	200 ppm	11 exposures	- No effects	
				400 ppm		- Haemoglobinuria; increases in MCV*; histological changes in the spleen	
				800 ppm		- Haemoglobinuria; decrease in RBC; increases in MCV; histological changes in the spleen	
EGnPEA	Rat	Oral	10 M	1,097 mg/kgbw	5d/wk, 6wks	- haemoglobinuria) reductions	Katz et al.(1984)
				2,193 mg/kgbw		- haemoglobinuria) in RBC, Hb & HCT;	
				4,386 mg/kgbw		- 100% mortality; haemoglobinuria) enlargement of the) spleen	
	Rat	Inhalation	5 M	100 ppm	6h/d, 5d/wk,	- No effects	Katz et al.(1984)
			5 F	200 ppm	11 exposures	- Haemoglobinuria	
				400 ppm		- Haemoglobinuria; reductions in RBC, Hb and HCT; increases in MCV	
				800 ppm		- Haemoglobinuria; reductions in RBC, Hb and HCT; increases in MCV; histological changes in the spleen, liver and kidneys	
EGiPE	Rat	Inhalation	5 M	3,500 ppm	Single 4h exposure	- Transient haematuria	Doe (1984-a)
	Rat	Inhalation	10 M	300 ppm	6h/d, 9 d	- Small increase in MCV	Doe (1984-a)
				1,000 ppm		- Transient haematuria; reduction in body weight, RBC and Hb	
EGBE	Rat	Inhalation	16 M	5 ppm	5d/wk, 90 d	- No effects	Dodd et al. (1983)
			16 F	25 ppm		- No effects	
				77 ppm		- Reduction in RBC, Hb; MCH at 6wk	
	Rabbit	Percutaneous	10 M	10 mg/kgbw	5d/wk, 90 d	- No effects	CMA (1983)
			10 F	50 mg/kgbw		- No effects	
				150 mg/kgbw		- No effects	

* RBC : red blood cells
* Hb : haemoglobin
* HCT : haemotocrit
* MCV : mean corpuscular volume
* MCH : mean cell haemoglobin

Appendix 1 (3)

COMPOUND	SPECIES	ROUTE	ANIMALS PER DOSE LEVEL	EXPOSURE CONC. or DOSE	TIME	RESPONSE	REFERENCE
EGBE	Rat	Inhalation	5 M	800 ppm	Single 3 h exposure	- Haematuria	Doe (1984-a)
DEGME	Rat	Inhalation	10 M 10 F	30 ppm 100 ppm 216 ppm	6 h/d, 5d/wk, 13 wks	- No effects - No effects - No effects	Miller et al.(1984-d)
DEGEE	Rat	Dietary	12 M 12 F	0.25% (*) 1.0% (*) 5% (*)	90 d	- No effects - No effects - Reduced growth rate; hydropic degeneration of kidney; fatty change in liver; testicular oedema ?	Hall et al.(1966)
	Mouse	Dietary	20 M 20 F	0.2% 0.6% 1.8% 5.4%	90 d	- No effects - No effects - Liver cell enlargement - Deaths; hydropic degeneration of kidney; liver cell enlargement; reduction in RBC	Gaunt et al. (1968)
	Rat	Dietary	15 M 15 F	0.5% 5%	90 d	- No effects - Hydropic degeneration of kidney; reduction in Hb, RBC	Gaunt et al. (1968)
	Pig	Oral	3 M 3 F	167 mg/kgbw 500 mg/kgbw 1,500 mg/kgbw	90 d	- No effects - Hydropic degeneration of liver - Deaths; hydropic degeneration of kidney; reduction in Hb, RBC	Gaunt et al. (1968)
	Ferret	Dietary	2 M 3 F	0.5 ml/kgbw 1.0 ml/kgbw 2.0 ml/kgbw 3.0 ml/kgbw	9 m	- No effects - No effects - No effects - No effects	Butterworth et al., (1976)
DEGBE	Rabbit	Percutaneous	3 M 3 F	2 ml/kgbw 1.5% aqueous solution	5d/wk, 4 wks	- No effects	Procter and Gamble (1984)
	Rat	Oral	25 M 25 F	250 mg/kgbw 500 mg/kgbw 1,000 mg/kgbw	60d(M),14d (F) prior to mating	- No effects on male fertility - No effects on male fertility - No effects on male fertility; small increase in post-implantation loss; small decrease in implantation sites and delivered pups - not statistically significant; reduction in mean body weight of pups.	Procter and Gamble (1984)

* containing 0.6% ethylene glycol

Appendix 1 (4)

COMPOUND	SPECIES	ROUTE	ANIMALS PER DOSE LEVEL	EXPOSURE CONC. or DOSE	TIME	RESPONSE	REFERENCE
DEGDME	Rat	Inhalation	10 M	250 ppm 1,000 ppm	7h/d, 1-5d	- No effects on fertility - Reduced fertility	McGregor et al.(1983)
	Mouse	Inhalation	10 M	250 ppm 1,000 ppm	7h/d, 1-5d	- No effects - Deaths; ataxia; reduced body weight gain; sperm abnormalities	McGregor et al.(1983)
2PG1ME	Rat	Inhalation	10 M 10 F	300 ppm 1,000 ppm 3,000 ppm	6h/d, 5d/wk, 13 wks	- No effects - No effects - CNS depression; increase in liver weight; hepatocellular hypertrophy	Landry and Yano (1984)
	Rabbit	Inhalation	7 M 7 F	300 ppm 1,000 ppm 3,000 ppm	6h/d, 5d/wk, 13 wks	- No effects - No effects - CNS depression	Landry and Yano (1984)
2PG1MEA	Rat	Inhalation	5 M 5 F	300 ppm 1000 ppm 3000 ppm	6h/d, 9 exp./11d	- No effects - M increased granularity of kidney tubular cells - M increased relative liver weight, increased granularity of kidney tubular cells; degenerative changes in olfactory mucosa.	Miller et al.(1984-a)
	Mice	Inhalation	5 M 5 F	300 ppm 1000 ppm 3000 ppm	6h/d, 9 exp./11d	- 1 F, olfactory mucosa replaced by respiratory mucosa in nose - all M-F, olfactory mucosa replaced by respiratory mucosa in nose - all M-F olfactory mucosa replaced by respiratory mucosa in nose	
1PG2MEA	Rat	Inhalation	5 M 5 F	110 ppm 560 ppm 2,800 ppm	6h/d, 28 days	- No effects - No effects - Slight reduction in liver and thymus weight; increase of adrenal weight; reduction in blood glucose conc.(M); increase in albumin conc. and thromboplastin time (M); decrease in urea conc.(F); increase in AP act.(F).	Klimisch et al. (1984)
DPGME	Rat Mouse	Inhalation	5 M 5 F	50ppm 140 ppm 330 ppm	6h/d, 9 days	- Small increases in liver weight (rat) - Small increases in liver weight (rat) - Increase of liver weight	Landry and Yano (1984)
	Rat	Inhalation	10 M 10 F	15ppm 50ppm 200 ppm	6h/d, 5d/wk, 13 wks	- No effects - No effects - No effects	Landry and Yano (1984)

Appendix 2 : Foetotoxic and Teratogenic Effects

COMPOUND	SPECIES	ROUTE	ANIMALS PER DOSE LEVEL	EXPOSURE CONC. or DOSE	TIME	RESPONSE	REFERENCE
EGME	Mouse	Inhalation	29-32 F**	10 ppm 50 ppm	d.g.* 6-15	No effects Decrease in weight gain; slightly foetotoxic	Hanley et al.(1982-a)
	Rat	Inhalation	29-32 F	3 ppm 10 ppm 50 ppm	d.g. 6-15	No effects No effects Two minor skeletal variations	Hanley et al.(1982-b)
	Rabbit	Inhalation	29-32 F	3 ppm 10 ppm 50 ppm	d.g. 6-18	No effects Higher resorption rate Major malformations	Hanley et al.(1982-c)
EGEE	Rat	Inhalation	24 F	10 ppm 50 ppm 250 ppm	d.g. 6-15	No effects Minor foetotoxicity Post-implantation loss; foetal weight reduction	Tinston et al.(1983-a)
	Rabbit	Inhalation	24 F	10 ppm 50 ppm 175 ppm	d.g. 6-18	No effects No effects Marginal teratogenic effect,foetotoxicity	Tinston et al.(1983-b)
	Rat	Dermal	18 F	0.25 ml	4/d, d.g. 7-16	Increase of visceral malformations	Hardin et al.(1984)
	Rat	Oral	16-21 F	200 mg/kgbw/d	d.g. 7-9 or 10-12	Teratogenic effects	Goad and Cranmer (1984)
EGEEA	Rabbit	Inhalation	24 F	25 ppm 100 ppm 400 ppm	d.g. 6-18	No effects Reduction of mean foetal weight; foetotoxicity Embryotoxic/teratogenic effects	Tinston et al.(1983-c)
		Dermal	18 F	0.35 ml	4/d, d.g. 7-16	Increase of visceral malformations	Hardin et al.(1984)
	Rat	Inhalation	15 F 15 F 9 F	130 ppm 390 ppm 600 ppm	d.g. 7-15	Foetotoxicity Foetotoxicity; teratogenicity; increase of number of resorptions All litters resorbed	Nelson et al.(1984-a)

* d.g. : days of gestation
** M : males, F : females

Appendix 2 (2)

COMPOUND	SPECIES	ROUTE	ANIMALS PER DOSE LEVEL	EXPOSURE CONC. or DOSE	TIME	RESPONSE	REFERENCE
EGnPE	Rat	Inhalation	24 F	100 ppm	d.g. 6-15	No effects	Krasavage and Katz, (1984-a)
				200 ppm		Maternal- and slight foeto-toxicity	
				300 ppm		Maternal- and slight foeto-toxicity	
				400 ppm		Maternal- and slight foeto-toxicity	
EGnPEA	Rat	Inhalation	24 F	100 ppm	d.g. 6-15	No effects	Krasavage and Katz (1984-b)
				200 ppm		Minor maternal toxicity; Minor foetotoxicity	
				400 ppm		Maternal- and foeto-toxicity	
				800 ppm		Maternal- and foeto-toxicity	
EGBE	Rat	Inhalation	15-16 F	150 ppm	d.g. 7-15	No effects	Nelson et al.(1984-a)
				200 ppm		Haematuria	
	Rat	Inhalation	36 F	25 ppm	d.g. 6-15	No effects	Tyl et al.(1984)
				50 ppm		No effects	
				100 ppm		Maternal-, embryo- and foeto-toxicity	
				200 ppm		Maternal toxicity, embryolethality and foetotoxicity	
	Rabbit	Inhalation	24 F	25 ppm	d.g. 6-18	No effects	Tyl et al.(1984)
				50 ppm		No effects	
				100 ppm		No effects	
				200 ppm		Maternal- and embryo-toxicity	
	Rat	Dermal	9 F	0.12 ml	4/d, d.g. 7-16	No effects	Hardin et al.(1984)
EGDME	Mouse	Oral (gavage)	23-28 F	250 mg/kgbw	d.g. 7-10	)	Uemura (1980)
				350 mg/kgbw		) Teratogenic effects	
				490 mg/kgbw		)	
DEGME	Rat	Injection s.c.	15 F	250 mg/kgbw	d.g. 6-20	No effects	Doe (1984-a)
				500 mg/kgbw		No effects	
				1,000 mg/kgbw		No effects	
	Rabbit	Dermal	25 F	50 mg/kgbw	d.g. 6-18	No effects	John et al.(1984)
				250 mg/kgbw		Slight foetotoxicity	
				750 mg/kgbw		Maternal-, embryo- and foeto-toxicity	
DEGEE	Rat	Dermal	13 F	0.35 ml	4/d, d.g. 7-16	No effects	Hardin et al. (1984)

* M : males
F : females

COMPOUND	SPECIES	ROUTE	ANIMALS PER DOSE LEVEL	EXPOSURE CONC. or DOSE	TIME	RESPONSE	REFERENCE
DEGBE	Rabbit	Dermal	20 F	100 mg/kgbw 300 mg/kgbw 1,000 mg/kgbw	d.g. 7-18	No effects No effects No effects	Benedict et al.(1983)
2PG1ME	Rat	Inhalation	29-32 F	500 ppm 1,500 ppm 3,000 ppm	d.g. 6-15	No effects No effects Foetotoxicity	Hanley et al.(1984-b)
	Rabbit	Inhalation	29-32 F	500 ppm 1,500 ppm 3,000 ppm	d.g. 6-18	No effects No effects Mild lethargy in dams on the first two days of exposure	Hanley et al.(1984-b)
1PG2MEA	Rat	Inhalation	25 F	110 ppm 560 ppm 2,800 ppm	d.g. 6-15	No effects Maternal toxic effects Maternal toxic effects; increase of minor vertebral variations; foetotoxicity	Merkle et al.(1984)

Appendix 3 : Mutagenicity Tests

Type of Test	Compound	Test Species/Exposure details	Results (see footnote for symbols)	Reference
Bacterial, mutation	EGME	S. typhimurium TA1535, TA100, TA1537, TA1538, TA98 with and without S9 mix and with alcohol dehydrogenase	-	McGregor et al.(1983)
	EGME	S. typhimurium TA102 with and without S9 mix and with alcohol dehydrogenase	-	McGregor (1983), unpublished
	EGEE	S. typhimurium TA1535, TA100, TA1537, TA1538, TA98, without S9 mix, and with rat S9 mix and hamster S9 mix	-	NTP unpublished results
	EGEE	S. typhimurium TA1538	-	Kowalek and Andrews (1980)
	EGEE	E. coli scl-4-73	-	Szybalski (1958)
	Methoxyacetic acid	S. typhimurium TA1535, TA100, TA1537, TA1538, TA98, no activation	-	McGregor et al.(1983)
	DEGBE	S. typhimurium TA1535, TA1537, TA1538, TA98, TA100 with and without S9 mix	-	Thompson et al.(1984)
	DEGDME	S. typhimurium TA1535, TA100, TA1537, TA158, TA98 with or without rat S9 mix	-	McGregor et al.(1983)
	2PGME 2PG1MEA	S. typhimurium TA1535, TA1537, TA 1538, TA98, T100 with and without S9 mix	- -	Kirkland and Varley (1983-a), Mendrala (1983-c)
	2PG1EE	S. typhimurium TA1535, TA100, TA1537	-	Dow Chemical Company (1982)
	DPGME	S. typhimurium TA1535, TA1537, TA1538, TA98, TA100, with and without S9 mix	-	Mendrala (1983-b), Kirkland and Varley (1983-b)
	DPGMEA	S. typhimurium TA1535, TA1537, TA1538, TA98, TA100, with and without S9 mix	-	Mendrala (1983-c)
	TPGME	S. typhimurium TA1535, TA1537, TA1538, TA98, TA100	-	Mendrala (1982)

Appendix 3 (2)

Type of Test	Compound	Test Species	Results (see footnote for symbols)	Reference
Yeast, mutation	EGME	Schizosaccharomyces pombe	-	Abbandandolo et al.(1980).
Mammalian, in vitro, unscheduled DNA synthesis	EGME	Fibroblasts, grain counts, with and without rat S9 mix	-	McGregor et al.(1983).
	EGBE	Primary hepatocyte, scintillation	?	Tyler (1982).
	DEGBE	Primary hepatocyte, grain counts	-	Thompson et al.(1984)
	DEGDME	Primary hepatocyte, grain counts	-	McGregor et al.(1983)
	2PG1ME	Primary hepatocyte, grain counts	-	Mendrala (1983-a)
	2PG1MEA	Primary hepatocyte, grain counts	-	Mendrala (1983-d)
	DPGME	Primary hepatocyte, grain counts	-	Mendrala (1983-b)
Mammalian in vitro, sister chromatid exchange	EGEE	CHO cells with and without rat S9 mix	+ (weaker with rat S9 mix)	NTP, unpublished results.
	EGBE	CHO cells with and without rat S9 mix	-	Tyler (1982).
Mammalian, in vitro, chromosomal aberrations	EGEE	CHO cells with and without rat S9 mix	+ (weaker with rat S9 mix)	NTP, unpublished results.
	DEGBE	CHO cells	-	Thompson et al.(1984)
	2PG1ME	CHO cells	-	Kirkland (1983-a)
	DPGME	CHO cells	-	Kirkland (1983-b)
Mammalian, in vitro, point mutations	EGME	L5178Y mouse lymphoma TK+/-cells with rat S9 mix	-	McGregor (1984)
	EGBE	CHO cells, HGPRT locus, with and without rat S9 mix	-	Tyler (1982).
	DEGBE	Mouse lymphoma L5178Y	±	Thompson et al.(1984)

Appendix 3 (3)

Type of Test	Compound	Test Species	Results (see footnote for symbols)	Reference
Drosophila, sex-linked recessive lethal	EGME	3 d old male OrK stock, dynamic atmosphere of 25 ppm for 1 h or 500 ppm for 15 min	?	McGregor et al.(1983).
	EGEE	3 d old males, feeding and injection	-	NTP, unpublished results.
	DEGDME	3 d old male OrK stock, dynamic atmosphere of 250 ppm for 2.75 h	?	McGregor, unpublished results.
	DEGBE	3 d old males, feeding and injection	-	Thompson et al.(1984)
Rat bone marrow cytogenetics	EGME	Dynamic atmospheres of 25 or 500 ppm, 7 h/d, for either 5 d with sampling 6 h later, or 1 d with sampling 6 h, 24 h or 48 h later	-	McGregor et al.(1983).
	DEGDME	Dynamic atmospheres of 250 ppm or 1000 ppm, 7h/d for either 5 d with sampling 6 h later, or 1 d with sampling 6 h, 24 h or 48 h later	-	McGregor et al.(1983).
	Isobutyl ether of a mixture of propylene glycols (Dowanol PIB-T)	Dynamic atmospheres of 200 ppm, 7h/d for 4 weeks	-	Dow Chemical Company (1982)
Mouse sperm abnormality test	EGME	Dynamic atmospheres of 25 or 500 ppm, 7 h/d for 5 d, with sampling 35 d later	+	McGregor et al.(1983).
	DEGDME	Dynamic atmospheres of 250 ppm for 7h/d for 5 d, or 1000 ppm for 7h/d for 4 d, with sampling 35 d later	+	McGregor et al.(1983).

Appendix 3 (4)

Type of Test	Compound	Test Species	Results (see footnote for symbols)	Reference
Male rat dominant lethal test	EGME	Dynamic atmospheres of 30, 100 or 300 ppm for 6h/d, 5d/wk for 13 wks	Male sterility at 300 ppm, reversible	Rao et al.(1983).
	EGME	Dynamic atmospheres of 25 or 500 ppm for 7 h/d for 5 d, followed by 10 successive weekly matings	± High dose, male sterility at wk 5, reversible	McGregor et al.(1983).
	DEGDME	Dynamic atmospheres of 250 or 1000 ppm for 7h/d for 5 d, followed by 10 successive weekly matings	± High dose, low male fertility at wks 5 - 7, reversible	Mc Gregor et al.(1983).

\- no significant response

\+ significant response

± significant response, but weak

? unclear or not reproducible, further testing needed.

Appendix 4 : Exposure Limits In The Workplace Environment For Glycol Ethers and their Acetates

		EGME		EGMEA		EGEE		EGEEA	
		ppm	mg/m³	ppm	mg/m³	ppm	mg/m³	ppm	mg/m³
BELGIUM		25	80	-	-	50	185	25	135
BRD (Germany)	MAK (skin)	5	15	5	25	20	75	20	110
DENMARK		25	80	25	120	100	370	50	270
						(50)+	(185)+	50	270
FINLAND		25	80	25	120	100	370	25	135
FRANCE		5	16	5	24	5	19	5	27
HOLLAND	MAC	5+	15+	-	-	5+	19+	-	-
ITALY		-	-	-	-	-	-	-	-
NORWAY	(skin)	25	80	-	-	50	185	-	-
SWEDEN	(skin)	10	30	10	50	20	70	20	110
SWITZERLAND	MAK (skin)	5+	15+	-	-	20+	75+	100	540
UNITED KINGDOM	TWA (skin)	25(5)+	80(15)+	25(5)+	120(25)+	100(10)+	370(37)+	(10)+	(55)+
	STEL(skin)	35(15)+	120(45)+	35(15)+	170(75)+	150(30)+	560(115)+	(30)+	(175)+
JAPAN		25	80	25	120	100	370		
USA								100	540
ACGIH	TLV®-TWA (skin)	5	16	5	24	5	19	5	27
	TLV®-STEL (skin)	-	-	-	-	-	-	-	-
OSHA	PEL (skin)	25	80	25	120	200	740	100	540

PEL : Permissible Exposure Limit

STEL : Short Term Exposure Limit

\+ : Intended changes

\- : No value

Appendix 4 (continued)

		EG1PE		EGBE		EGBEA		2PG1ME		DPGME	
		ppm	mg/m³	ppm	mg/m³	ppm	mg/m³	ppm	mg/m³	ppm	mg/m³
BELGIUM		25	105	100	480	-	-	-	-	-	-
BRD (GERMANY)	MAK(skin)	20	100	20	100	20	135	100	375	100	600
DENMARK	HGV	25	105	25	120	-	-	100	360	-	-
FINLAND		50	210	25	120	-	-	100	360	-	-
FRANCE		25	105	25	120	-	-	-	-	-	-
HOLLAND	MAK	50+	210+	100+	480+	-	-	100+	360+	-	-
ITALY		-	-	-	-	-	-	-	-	-	-
NORWAY	(skin)	25	105	100	480	-	-	-	-	-	-
SWEDEN	(skin)	50	210	20	100	-	-	-	-	-	-
SWITZERLAND	MAK(skin)	-	-	100	480	-	-	100	360	-	-
UNITED KINGDOM	TWA(skin)	50(25)+	210(105)+	(25)+	(120)+	-	-	100	360	-	-
	STEL(skin)	150(75)+	640(320)+	(75)+	(360)+	-	-	150	540	-	-
JAPAN	TLV	-	-	50	240	-	-	-	-	-	-
USA											
ACGIH	TLV-®TWA(skin)	25	105	25	120	-	-	100	360	100	600
	TLV-®STEL(skin)	75	320	75	360	-	-	150	540	150	900
OSHA	PEL (skin)			50	240	-	-			100	600

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