Technical Report

No 17

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

April 1985

ISSN-0773-8072-17

ECETOC

Brussels, 19 April 1985.

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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)

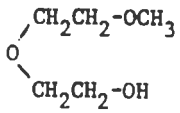
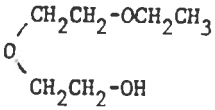
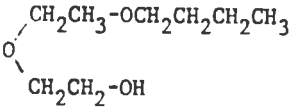
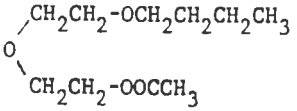
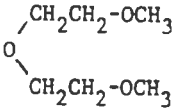
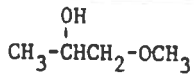
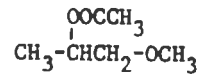
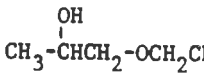
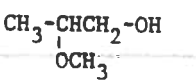
diethylene glycol mono-methyl ether	 2-(2-methoxyethoxy)ethanol	DEGME	111-77-3
diethylene glycol mono-ethyl ether	 2-(2-ethoxyethoxy)ethanol	DEGEE	111-90-0
diethylene glycol mono-n-butyl ether	 2-(2-n-butoxyethoxy)ethanol	DEGBE	112-34-5
diethylene glycol mono-n-butyl ether acetate	 2-(2-n-butoxyethoxy)ethanol 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