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Review paper

REPRODUCTIVE TOXICITY OF THE GLYCOL ETHERS

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SUMMARY

The glycol ethers are an important and widely used class of solvents. Recent studies have demonstrated that ethylene glycol monomethyl ether (EGME), ethylene glycol dimethyl ether (EGdiME), ethylene glycol monoethyl ether (EGEE), and ethylene glycol monoethyl ether acetate (EGEEA) are teratogenic. Other studies have demonstrated that testicular atrophy or infertility follow treatment of males with EGME, ethylene glycol monomethyl ether acetate (EGMEA), EGEE, EGEEA, diethylene glycol dimethyl ether (diEGdiME), and diethylene glycol monoethyl ether (diEGEE). Experimental data are reviewed and structure-activity relationships are speculated upon.

Key words: Infertility; Solvents; Teratogenicity; Testis; Embryotoxicity

INTRODUCTION

The alkyl ether derivatives of ethylene, diethylene, and triethylene glycol

Abbreviations: diEG, diethylene glycol; diEGdiME, diethylene glycol dimethyl ether; diEGEE, diethylene glycol monoethyl ether; EG, ethylene glycol; EGA, ethylene glycol monoacetate; EGME, ethylene glycol monomethyl ether; EGMEA, ethylene glycol monomethyl ether acetate; EGdiME, ethylene glycol dimethyl ether; EGEE, ethylene glycol monoethyl ether; EGEEA, ethylene glycol monoethyl ether acetate; EGBE, ethylene glycol monobutyl ether; EGBEA, ethylene glycol monobutyl ether acetate; EGPE, ethylene glycol monoisopropyl ether; EGPhE, ethylene glycol monophenyl ether; triEG, triethylene glycol.

are an important class of solvents with numerous industrial and comsumer applications. These ethers and ether acetates are used in surface coatings (paints, lacquers, varnishes, etc.), fingernail polishes and polish removers, liquid cleaning products, degreasing agents and spotting fluids, hydraulic brake fluids, printing and writing inks, and textile and leather dyeing solutions. The toxicologic properties of ethylene glycol (EG) and its derivatives have been thoroughly reviewed elsewhere [1,2] and will only be summarized here. Based on data contained in the NIOSH Registry of Toxic Effects of Chemical Substances [3], toxicity decreases in the order EG, diethylene glycol (diEG), triethylene glycol (triEG). Substitution of an alkyl group to form a monoalkyl ether increases acute toxicity on a molar basis. In general, the longer straight-chain alkyl groups enhance toxicity more than the shorter alkyl groups except methyl. The toxicity of the ether acetates is comparable to the parent glycol ether, as the ester linkage apparently is readily hydrolized.

The most prominent and well-recognized targets of glycol and glycol ether toxicity are the central nervous, renal, and hematopoeitic systems [1,2]. Fatty degeneration of the liver and pulmonary edema have also been reported. High doses may cause death either by respiratory arrest or renal failure. Severe hematological and central nervous system disturbances have been reported following occupational exposure to ethylene glycol monomethyl ether (EGME) [4—8]. In one of these reports [7] exposure was almost exclusively cutaneous, vividly demonstrating that these compounds readily penetrate the skin in toxic amounts.

Potential reproductive toxicity of chemicals is a matter of growing public concern. Recently, four glycol ethers have been found to be teratogenic in experimental animals. Although not widely recognized, adverse effects on the male reproductive system were first observed over 40 years ago. The purpose of this paper is to summarize and call attention to the available evidence of reproductive toxicity by the glycol ethers.

MALE REPRODUCTIVE EFFECTS

Apparently the first report of adverse effects on the male reproductive system is that of Wiley et al. in 1936 [9]. Mice and rats were exposed to EG by inhalation at 350—400 mg/m^3 (140—160 ppm) for 8 h/day, 5 day/week, for 16 weeks. Histopathologic examination of testes revealed degenerative changes in the germinal epithelium, but the changes were not believed to be compound related. Two years later, using only 2 animals per chemical, the same group reported [10] degeneration of the germinal epithelium in the testes of rabbits injected with EG, ethylene glycol monoacetate (EGA), diEG, and EGME. In contrast to the 1936 report, these testicular effects were judged to be chemically induced. Later studies of EG [11,12], EGA [13], ethylene glycol monobutyl ether acetate (EGBEA) [13], and diEG [11] were contradictory. The investigations by Truhaut et al. [13] were conducted in rats and rabbits and included acute (oral, inhalation, and cutaneous) and 1- and 10-month inhalation exposures. In none of these later

studies [11—13] were testicular effects reported. The inconsistency of these investigations might be attributable, in part, to impurities in the solvents used in older studies. However, as described in detail below, marked testicular effects with a number of other glycol ethers have recently been observed and confirmed. Non-contradictory evidence of testicular toxicity is available for at least 6 EG derivatives: EGME [12,14,15], ethylene glycol monomethyl ether acetate (EGMEA) [12], ethylene glycol monoethyl ether (EGEE) [11,12,16], ethylene glycol monoethyl ether acetate (EGEEA) [12] diethylene glycol monoethyl ether (diEGEE) [11], and diethylene glycol dimethyl ether (diEGdiME) [17].

In 2-year feeding studies with rats, Morris et al. [11] administered EG or diEG in the diet at levels up to 2% or 3.42%, respectively, without testicular effects. However, in the same study, EGEE in the diet at 1.45% induced marked testicular enlargement, edema, and tubular atrophy. Similar but less severe changes were seen in the testes of rats receiving 2.16% diEGEE, Stenger et al. [16] reported histopathological testicular changes in rats and dogs dosed with EGEE for varying times and by various routes. Changes included interstitial edema and reduced numbers of late maturation stages, culminating in testicular atrophy with the germinal epithelium consisting of a single layer of cells composed of Sertoli cells and primary spermatogonia.

Using 3—6 dose levels per compound, Nagano et al. [12] orally dosed groups of male mice once daily, 5 days/week for 5 weeks with EG, EGME, EGMEA, EGEE, EGEEA, ethylene glycol monobutyl ether (EGBE), or ethylene glycol monophenyl ether (EGPhE). Testicular atrophy was assessed in terms of testicular weight, both absolute and relative to body weight. Significant reductions in testicular weight were recorded in mice treated with EGME, EGMEA, EGEE, and EGEEA. On a molar basis, the methyl derivatives were more toxic than the ethyl derivatives. When testis to body weight ratios were graphed as a function of dose expressed in mmole/kg body weight, the EGME and EGMEA curves were essentially identical, as were the EGEE and EGEEA curves. Histopathologic examination of testes revealed dose-related tubular atrophy in the EGME, EGMEA, EGEE and EGEEA groups. A single instance of tubular atrophy was also seen in both the EGBE and EGPhE groups at the highest dose level with survivors at the time of necropsy. A statistically significant, dose-related leukopenia was also observed in the EGME, EGMEA, EGEE, and EGEEA groups.

Miller et al. [14] reported results of a study in which mice and rats were exposed to EGME (0, 100, 300, or 1000 ppm) or 1-methoxy-2-propanol (propylene glycol monomethyl ether) (0, 300, 1000, or 3000 ppm) for 9 days in an 11-day interval. Only minor effects of exposure to 1-methoxy-2-propanol at 3000 ppm were noted. Hematological, testicular, and lymphoid effects were found in both rats and mice exposed to EGME. The most severe hematologic effect of EGME was a concentration-related reduction in white blood cell counts. White counts were statistically significantly reduced in male rats at the lowest exposure level (100 ppm). Thymus weights were significantly reduced at 300 and 1000 ppm EGME. Histopathologic changes,

occurring in a concentration-related pattern, included decreased bone marrow cellularity, degeneration of the testicular germinal epithelium, and partial depletion of lymphoid elements in the thymus, spleen, and lymph nodes. Microscopic examination of the intestinal epithelium and ovarian follicular cells, tissues with high mitotic rates, did not reveal treatment-related effects. This suggests that factors other than high rates of cell division are involved in EGME toxicity.

Two glycol ethers, EGME [15] and diEGdiME [17], were included in a series of compounds tested in 6 mutagenesis assays. Neither compound was active when administered in DMSO in the Ames and unscheduled DNA synthesis tests. Both compounds were also tested as vapors in the *Drosophila* sex-linked recessive lethal, mouse sperm head morphology, rat dominant lethal, and rat bone marrow cytogenetics tests at exposure concentrations of 25 and 500 ppm (EGME), and 250 and 1000 ppm (diEGdiME). With both glycol ethers, there was some suggestion of mutagenic activity in the sex-linked recessive lethal test, but results were inconclusive in both cases. Neither glycol ether induced an increased frequency of chromosomal aberrations in the bone marrow cytogenetic assay. However, the higher, but not the lower, concentration of both ethers induced an increased incidence of abnormal sperm head morphology in the fifth post-exposure week, and the fertility of male rats was dramatically reduced in weeks 3—8 post-exposure. Recovery of fertility was complete by week 10. No dominant lethal effects were detected in any of the fertile matings in these studies.

FEMALE REPRODUCTIVE EFFECTS

Stenger et al. [16] treated pregnant rats with EGEE either orally or subcutaneously on days 1—21 of gestation. Pregnant mice and rabbits were dosed subcutaneously on days 1—18 and 7—16 of gestation, respectively. No adverse effects were seen in mice and rabbits at the highest doses used (100 and 25 μl/kg/day, respectively). In orally dosed rats, there was a significant increase in embryonic and fetal death at doses of 50 μl/kg/day and higher, and the incidence of skeletal aberrations increased in a dose-related pattern at oral doses of 100—400 μl/kg/day. No statistically significant effects were reported for rats treated subcutaneously with a maximum of 100 μl/kg/day. Nagano et al. [18] treated pregnant mice with EGME by gavage on days 7—14 of gestation. They observed significant dose-related increases in the incidence of intrauterine fetal death at doses of 250 mg/kg/day and higher, and skeletal defects or variations at all lower doses, the lowest of which was 31.25 mg/kg/day. Two externally visible malformations (exencephaly and digital defects) appeared with significantly increased frequency among treated litters. Mice were orally dosed with 0, 250, 350, or 490 mg/kg ethylene glycol dimethyl ether (EGdiME) by Uemura [19] on days 7—10 of gestation. Dose-related increases in the incidence of intrauterine death were observed which were statistically significant at 490 mg/kg. Similarly increased were externally visible malformatons, primarily exencephaly, and

various skeletal defects. Fetuses apparently were not examined for visceral defects in any of these 3 studies [16,18,19].

In an inhalation teratology study, Andrew et al. [20,21] exposed pregnant New Zealand rabbits for 7 h/day on days 1—18 of gestation to filtered air or to EGEE at 160 or 615 ppm. At the higher EGEE concentration, maternal toxicity was severe and 5 of 29 rabbits died. All litters of surviving rabbits were totally resorbed. At the lower exposure level, maternal toxicity was mild but fetuses exhibited significant increases in cardiovascular, renal, and ventral body wall defects, and minor skeletal changes in ribs, sternebrae, and vertebrae. Resorptions per litter were significantly increased and the number of live fetuses per litter was corespondingly reduced. Andrew et al. [20,21] also exposed pregnant Wistar rats to filtered air or to EGEE at 0, 150, or 650 ppm for 7 h/day, 5 day/week for 3 weeks before breeding, and then for 7 h/day on days 1—19 of gestation at 0, 200, or 765 ppm. There was no effect of EGEE on mating success or on establishment of pregnancy. Maternal toxicity at 765 ppm was mild, but all litters were totally resorbed following exposure at the higher (765 ppm) concentration during gestation. At the lower (200 ppm) gestational exposure level, there was a significant increase in the incidence of cardiovascular defects and wavy ribs. Fetal body weight and crown-rump length were significantly reduced. There was some evidence (increased organ weights) of slight maternal toxicity at the 200 ppm concentration.

In a behavioral teratology study, Nelson et al. [22] exposed pregnant Sprague—Dawley rats to filtered air or EGEE at 100 ppm for 7 h/day on days 7—13 or 14—20 of gestation. Six behavioral tests were selected to assess various central nervous system functions: neuromuscular ability (ascent and rotorod tests), exploratory activity (open field test), circadian activity (activity wheel test), aversive learning (avoidance conditioning test), and appetitive learning (operant conditioning test). Behavioral testing of offspring from dams exposed to EGEE on gestation days 7—13 revealed impaired performance on the rotorod test and prolonged latency of leaving the start area of an open field when compared with controls. Offspring from dams exposed to EGEE on gestation days 14—20 were less active than controls in the activity wheel test, and received an increased number and duration of shocks in the avoidance conditioning test begun at 60 days of age. Neurochemicals were evaluated in brains of newborn and 21-day-old rats, and significant changes were detected, relative to control levels. In a subsequent study, Nelson et al. [23,24] investigated the possibility of interactions between EGEE and ethanol. Using a similar exposure regimen and testing protocol, some pregnant rats were exposed to EGEE, others received 10% ethanol in their drinking water, and still others received both ethanol and EGEE exposure. These investigators concluded that ethanol early in gestation (days 7—13) reduced the effects of EGEE exposure while ethanol later in gestation (days 14—20) enhanced the effects.

In another series of experiments, Nelson et al. [25] exposed pregnant rats on days 7—15 of gestation to one of 3 different glycol ethers: EGME,

EGEEA, or EGBE. The lower vapor pressure of EGBE limited, to a degree, the magnitude of vapor concentrations. At the highest concentration employed, 200 ppm, EGBE was not teratogenic or embryotoxic, although it was slightly maternally toxic. Both EGME and EGEEA, on the other hand, were embryotoxic and teratogenic. Complete resorption of all litters occurred at the highest concentrations of these glycol ethers: 200 ppm EGME and 600 ppm EGEEA. A statistically significant increase of cardiovascular defects was seen at intermediate EGME and EGEEA exposures: 100 and 390 ppm, respectively. Skeletal defects and variations were statistically significant at both intermediate and low exposure levels: 100 and 50 ppm for EGME; 390 and 130 ppm for EGEEA.

The effects of EGEE applied to the skin of pregnant rats have also been investigated [26]. The interscapular region of Sprague–Dawley rats was shaved and 0.25 ml or 0.50 ml of undiluted EGEE was applied 4 times daily on days 7–16 of gestation. Control rats were similarly treated with distilled water. All rats were singly housed in a ventilated cage rack, and charcoal tube samples collected inside cages indicated average vapor concentrations of 48 ppm. There was no evidence of maternal toxicity except slight ataxia following treatment with 0.50 ml. All litters were completely resorbed in the 0.50-ml group, and the incidence of resorptions was significantly increased in the 0.25-ml group. Both cardiovascular malformations and skeletal variations were significantly increased in the litters treated with 0.25 ml EGEE.

Another effect of at least some glycol ethers appears to be prolongation of gestation in exposed animals. Nelson et al. [22] observed a slight (0.7-day) but statistically significant lengthening of gestation in rats exposed to EGEE at 100 ppm on days 14–20 of gestation, and a 12–48-h delayed delivery of litters in other rats exposed to EGEE at concentrations of 200–1200 ppm [22,23]. Similar effects were seen following exposure of pregnant rats on days 14–20 of gestation to EGME at 100 ppm or EGEEA at 600 ppm (B.K. Nelson, pers. commun). In mice orally dosed with EGME at 125 or 250 mg/kg/day on days 6–15 of gestation, there was a pronounced delay in delivery of litters (Fig. 1) (B.D. Hardin, unpublished). Despite the fact that the final dose was delivered on day 15 of gestation, the median length of gestation was approximately 18.5, 19.0, and 20.0 days for the control, 125, and 250 mg/kg groups, respectively. The mechanism of action underlying this effect is unknown, but may involve impaired uterine smooth muscle contractility. In 1931 von Oettingen and Jirouch [27] reported that, in an in vitro preparation, rabbit intestinal smooth muscle was "depressed" by EG, diEG, EGEE, diEGEE, EGEEA, and EGBE (listed in order from least to most inhibitory). Perfused frog hearts also were inhibited by glycol ethers, and intravenous injection into rabbits caused a reduction in blood pressure. Andrew et al. [20], conducting necropsies of rabbits that died during exposure to 615 ppm EGEE, noted that the intestines were almost empty while the stomachs contained atypical hair balls and recycled fecal material. They speculated that EGEE exposure had reduced appetite and gastrointestinal function.

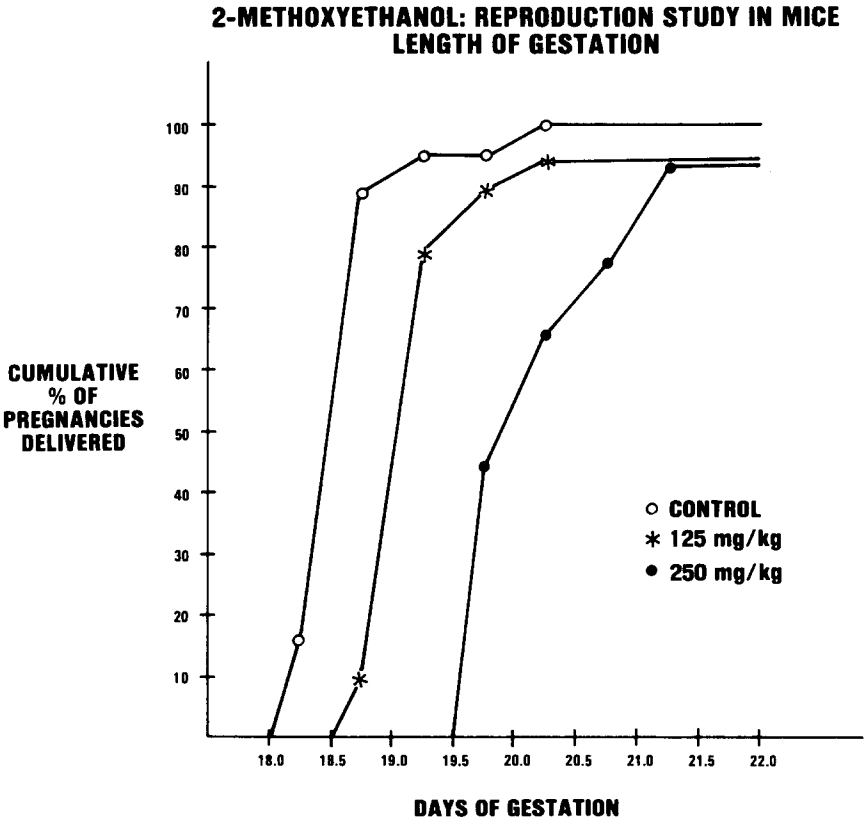

Fig. 1. Pregnant CD-1 mice were orally dosed on days 6—15 of gestation (plug = day 0) with EGME at 0, 125, or 250 mg/kg/day. Following final treatments, females were singly housed in polycarbonate cages and observed twice daily for signs of parturition.

There apparently is only one published investigation of reproductive performance in a human population having glycol ether exposure. The following discussion of that report is included primarily for the sake of completeness. The contribution, if any, of environmental factors to the effects reported is unknown. Syrovadko and Malsheva [28] examined female enamelers in a plant producing insulated wire. Two insulating varnishes were used, the solvents for which were chlorobenzene and EGEE (1:1 mixture) and tricresol and solvent naphtha (1:4). Concentrations of solvents in air were reported as 11—429 mg/m^3 for chlorobenzene (72.3 mg/m^3 average) and 0.8—18.7 mg/m^3 (4.3 mg/m^3 average) for tricresol. Concentrations of EGEE and solvent naphtha were not reported but were said to be low. There was no difference in the overall incidence of gynecological disorders among 311 female enamelers and 120 female administrative workers, but the incidences for both groups were said to be 2.6—9.4 times higher than found in female silica plant workers or at a regional hospital.

Former enamelers were said to be included in the control (administrative) group, which also was reported to be subject to a less rigorous pre-employment screening procedure. Syrovadko and Malsheva [28] also reported that among enamelers the incidence of gynecological disorders was directly related to the concentration of solvent vapors. The most important disorders were inflammatory processes, benign neoplasms, cervical erosions and menstrual disorders. Time lost due to gynecological problems was higher for enamelers than for administrative workers. Pregnancy outcome was evaluated for 190 enamelers and 150 controls. Congenital anomalies were significantly increased among enamelers (10.0% vs. 3.9% in controls), with congenital heart defects and talipes (clubfoot) being the predominant defects.

SUMMARY

Table I summarizes published reports of reproductive toxicity attributed to various glycol ethers. Data are negative or contradictory for EG, EGA, EGBE, EGBEA, and diEG. However, adverse effects on the male reproductive system have been demonstrated in 4 mammalian species (mouse [12,14,15,17], rat [11,14–17], dog [16], and rabbit [10]) following treatment with 6 glycol ethers (EGME [10,12,14,15], EGMEA [12], EGEE [11,12,16], EGEEA [12], diEGEE [11], and diEGdiME [17]). Observations in various studies include testicular atrophy [12,14], degeneration of the germinal epithelium [10–12,14,16], infertility [15,17], and abnormal sperm head morphology [15,17]. Embryotoxicity and teratogenicity have been demonstrated in 3 mammalian species (mouse [18,19], rat [16,20,22, 25,26], and rabbit [20]) following treatment with 4 glycol ethers (EGME [18,25], EGdiME [19], EGEE [16,20,22,26], and EGEEA [25]). In those species that have been examined for visceral defects following treatment with glycol ethers, cardiovascular malformations were significant observations [20,25,26]. Some of these reproductive effects have been noted at vapor concentrations slightly above [25] or below [20,22] the current federal occupational exposure limit. All routes of exposure appear to be effective, including oral [11,12,16,18,19], cutaneous [26], subcutaneous [16], and inhalation [14,15,17,20,22,25,26].

All of the glycol ethers exhibiting clear reproductive toxicity have been, thus far, methyl and ethyl derivatives of EG (Table I). EGBE and EGPhE failed to cause testicular atrophy in mice [12], and EGBE was not embryotoxic or teratogenic in rats exposed by inhalation [25]. Thus, excessively long or bulky terminal substituents appear to inhibit biologic activity. Such considerations may explain the relatively minor effects reported [14] for 1-methoxy-2-propanol. Although it is untested, 3-methoxy-1-propanol, a linear molecule with a primary alcohol group, might be less sterically inhibited and therefore a more active reproductive toxin if the alcohol group is the active site or the site of metabolism to an active form. Three glycol ethers are reported to be metabolized by rats to the acetic acid derivative:

TABLE I

PUBLISHED REPORTS OF REPRODUCTIVE EFFECTS OF GLYCOL ETHERS

Chemical	Species	Response	Reference
Ethyl glycol (EG)	Mouse	Testicular atrophy	9
		No testicular effects	12
	Rat	Testicular atrophy	9
		No testicular effects	11
	Rabbit	Testicular atrophy	10
Ethylene glycol acetate (EGA)	Rat	No testicular effects	13
	Rabbit	Testicular atrophy	10
		No testicular effects	13
Ethylene glycol monomethyl ether (EGME)	Mouse	Testicular atrophy	12,14
		Abnormal sperm morphology	15
		Tetratogenicity-Embryotoxicity	18
	Rat	Testicular atrophy	14
		Male infertility	15
		Teratogenicity-Embryotoxicity	25
	Rabbit	Testicular atrophy	10
Ethylene glycol monomethyl ether acetate (EGMEA)	Mouse	Testicular atrophy	12
Ethylene glycol dimethyl ether (EGdiME)	Mouse	Teratogenicity-Embryotoxicity	19
Ethylene glycol monoethyl ether (EGEE)	Mouse	Testicular atrophy	12
	Rat	Testicular atrophy	11,16
		Teratogenicity-Embryotoxicity	16,20,22,26
	Dog	Testicular atrophy	16
	Rabbit	Teratogenicity-Embryotoxicity	20
Ethylene glycol monoethyl ethyl acetate (EGEEA)	Mouse	Testicular atrophy	12
	Rat	Teratogenicity-embryotoxicity	25
Ethyl glycol monobutyl ether (EGBE)	Mouse	Slight testicular effect	12
	Rat	No embryotoxic or teratogenic effect	25
Ethylene glycol monobutyl ether acetate (EGBEA)	Rat	No testicular effects	13
	Rabbit	No testicular effects	13
Ethylene glycol monophenyl ether (EGPhE)	Mouse	Slight testicular effect	12
Diethylene glycol (diEG)	Rat	No testicular effects	11
	Rabbit	Testicular atrophy	10
Diethylene glycol dimethyl ether (diEGdiME)	Mouse	Abnormal sperm morphology	17
	Rat	Male infertility	17
Diethylene glycol monoethyl ether (diEGEE)	Rat	Testicular atrophy	11

EGEE to ethoxyacetic acid [29], ethylene glycol monoisopropyl ether (EGPE) to isopropoxyacetic acid [30], and EGBE to butoxyacetic acid [31]. Human urine contained (2-ethoxyethoxy)acetic acid following oral administration of diEGEE [32]. Other glycol ethers presumably would be metabolized to a corresponding alkyloxyacetic acid.

In addition to 1-methoxy-2-propanol and 3-methoxy-1-propanol, 3 other isomers are possible with the same molecular formula, $C_4H_{10}O_2$. Both of the straight-chain isomers EGEE and EGdiME are teratogenic. EGEE also causes testicular atrophy, but EGdiME is untested in males. The final isomer is the untested branched-chain 2-methoxy-1-propanol. The methoxypropanol series, tested under comparable conditions, would make an interesting test of the importance of primary versus secondary alcohol and of straight- versus branched-chain structure in the toxicity of these solvents.

Not unexpectedly, metabolic conversion of doubly substituted EG derivatives apparently occurs readily in the case of the acetates. In one study [12] EGMEA and EGEEA produced testicular changes equivalent on a molar basis to the corresponding alcohols. On the other hand, the diether derivatives appear to have reduced biological activity, although those tested to date remain active and produce responses qualitatively like the corresponding monoethers. For example, EGME [18] and EGdiME [19] produced similar spectra of embryotoxic and teratogenic effects. EGME [15] and diEGdiME [17] produced remarkably similar effects in males following 5 days of inhalation exposure. These observations suggest that the mono- and diether derivatives are metabolized in vivo to a common active form, involving cleavage of an ether linkage in the case of the diethers. Ether cleavage has been reported [30] in rats and dogs for EGPE.

Based in part on these data as well as on unpublished results of ongoing research programs, several manufacturers of glycol ethers have reduced their own internal exposure guidelines to 5 ppm or less, and have suggested that the users of their products do the same. The American Conference of Governmental Industrial Hygienists has published notice of an intended change of their Threshold Limit Values to 5 ppm for EGME and EGMEA (presently 25 ppm) and for EGEE and EGEEA (presently 50 ppm) [33]. No data are available to permit an evaluation of the impact of glycol ethers on human fertility or reproductive outcome. There is one Soviet report [28] of gynecological difficulties among women occupationally exposed to solvents, one of which was EGEE. The incidence of cardiovascular defects and talipes in the children of these women were also reported to be increased, but the description of conditions in which these women worked is inadequate to judge what occupational factors, if any, contributed to the observations.

The existing experimental data clearly indicate that alkyl ether derivatives of EG and diEG must be treated as potential reproductive toxins. Both sexes are potentially at risk, and exposure by any route, including inhalation and cutaneous, may be hazardous. No reproductive or developmental toxicity has been demonstrated in humans, but there have been no adequate studies, so the question of human sensitivity remains unaddressed. However, the

consistency of the effects in laboratory animals makes it clear that human exposure should be minimized. Because glycol ethers are used extensively in consumer products as well as in numerous industrial settings, the potential implications for human health are serious. Epidemiologic surveys are urgently needed to explore the fertility and reproductive outcome in populations exposed to glycol ethers, and NIOSH is currently attempting to identify a suitable industrial population.

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