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Reproductive toxicity of ethylene glycol monomethyl ether, ethylene glycol monoethyl ether and their acetates

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Ethylene glycol monomethyl ether (EGME), ethylene glycol monoethyl ether (EGEE), and their acetates, ethylene glycol monomethyl ether acetate (EGMEA) and ethylene glycol monoethyl ether acetate (EGEEA), belong to a family of ethylene glycol monoalkyl ethers. They are widely distributed in industry and are used in jet fuel deicers, inks and coatings, photography, dyeing, and the manufacture of printed circuit boards and plasticizers.

Until 10 years ago, the most commonly recognized targets of toxicity for these glycol ethers were the central nervous and hematopoietic systems, blood, liver, and kidneys. Severe central nervous system disorders and hematologic disturbances had been reported following occupational exposure to EGME. In one of the reports, exposure was almost exclusively by dermal contact, indicating that these glycol ethers readily penetrate the skin in toxic amounts (1). In recent years, attention has focused on the effects of these chemicals on reproduction and fetal development. Research in these areas was stimulated by an announcement at a US-Finnish joint conference in October 1980 (Cincinnati, Ohio) that teratogenicity had been demonstrated in the offspring of rats and rabbits exposed to EGEE vapor (2). Until then, an earlier report of testicular atrophy in mice had gone virtually unnoticed (3). This overview presents evidence from studies on animals that EGME, EGEE, and their acetates are reproductive and developmental hazards.

Reproductive and developmental effects

EGME, EGEE, and their acetates have caused adverse effects on the male reproductive system in multiple species. These effects include microscopic testicular lesions, testicular atrophy, reduced numbers of late-maturation-stage cells, and infertility (3—7). Investigators have correlated the impairment of testicular function with changes in testicular histology and abnormal sperm morphology. On a molar basis, the methyl derivatives were more toxic than the ethyl derivatives, and the acetates were equivalent in toxicity to the parent alcohol.

Treating pregnant females of various animal species with EGME, EGEE, or EGEEA has caused decreased body weight and body weight gain (2, 8—10), prolonged gestation (11, 12), a significantly increased mean number and percentage of resorptions (13), and infertility (7).

Adverse fetal effects include death, decreased fetal weights and litter sizes (2, 8), skeletal defects (2, 13), digit anomalies (10, 14), cardiovascular defects (2, 8, 9), visceral malformations (10, 13), and renal and ventral body wall defects (2). In addition, EGME and EGEE have adversely affected various central nervous system functions in the offspring of exposed pregnant animals (11, 15).

Only limited evidence indicates that EGME, EGEE, or their acetates cause adverse effects on the male reproductive system in humans. Investigators have determined that EGME and EGEE caused functional impairment (lowered sperm counts) in male workers preparing ceramic shells used to cast metal parts and in a group of shipyard painters (1).

No reports describe the effects of these glycol ethers on the female reproductive system in humans, and only one report describes the possible effect of EGMEA on the embryo (16). In this report, the occurrence of hypospadias in two boys at birth was attributed to their mother's exposure to EGMEA during her pregnancies, when she used a cleaning solution containing EGMEA (usually without gloves).

Despite the lack of evidence from humans, studies on animals clearly indicate that these glycol ethers adversely affect reproduction (table 1). In humans and animals, methoxyacetic acid (MAA) has been identified as the major metabolite of EGME, and ethoxyacetic acid (EAA) has been identified as the major metabolite of EGEE and EGEEA. Although no metabolism studies have been reported using EGMEA, it is expected to act similarly to EGEEA and to be metabolized to MAA, the metabolite of EGME (1). MAA and EAA have been shown to cause testicular damage comparable with that caused by their parent compounds. They have also caused adverse effects on fetal development, and MAA has produced digit anomalies comparable with those produced by EGME

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Table 1. Summary of adverse reproductive and developmental effects[a] (EGME = ethylene glycol monomethyl ether, EGMEA = ethylene glycol monomethyl ether acetate, EGEE = ethylene glycol monoethyl ether, EGEEA = ethylene glycol monoethyl ether acetate, + = effect observed in this species)

Observed effects	Species				
	Mouse	Rat	Rabbit	Dog	Monkey
Testicular atrophy					
EGME	+	+	+	·	·
EGMEA	+	·	·	·	·
EGEE	+	+	·	+	·
EGEEA	+	·	·	·	·
Microscopic testicular lesions					
EGME	·	+	+	·	·
EGEE	·	+	+	+	·
Abnormal sperm morphology					
EGME	·	+	·	·	·
EGEE	·	+	·	·	·
Infertility					
EGME	·	+	·	·	·
EGEE	+	·	·	·	·
Reduced maternal body weight					
EGME	·	+	·	·	·
EGEE	·	+	·	·	·
Extended gestation time					
EGME	·	+	·	·	·
EGEE	·	+	·	·	·
Postimplantation loss					
EGEE	·	+	·	·	·
Skeletal defects					
EGME	+	+	+	·	·
EGEE	+	+	+	·	·
EGEEA	·	+	+	·	·
Cardiovascular defects					
EGME	·	+	·	·	·
EGEE	·	+	+	·	·
EGEEA	·	+	+	·	·
Renal defects					
EGEE	·	+	+	·	·
Visceral malformations					
EGME	+	+	+	·	·
EGEE	·	+	·	·	·
EGEEA	·	+	+	·	·
Digit anomalies					
EGME	+	+	+	·	+
Adverse neurobehavioral effects					
EGME	·	+	·	·	·
EGEE	·	+	·	·	·

[a] Source: reference 1.

(1). The animal data are therefore considered to be highly predictive of the hazard for humans.

Discussion

The consistent occurrence of adverse reproductive and developmental effects in laboratory animals makes it clear that human exposure to EGME, EGEE, and their acetates should be minimized (table 1).

Production volumes of EGME and EGEE have decreased in the past decade, possibly because of concern for human exposure to these chemicals. Furthermore, in 1980—1984, the use of EGME and EGEE in protective coatings declined by more than 80 and 50%, respectively, and reformulation has virtually eliminated EGME, EGEE, and their acetates from consumer paints and inks.

The manufacture of propylene glycol ethers has increased since 1985, probably because they have been commonly used as substitutes for the ethylene glycol ethers. Because of health concerns, the Interagency Testing Committee has recommended to the United States (US) Environmental Protection Agency that several propylene glycol ethers be tested for reproductive effects.

After reviewing the available health data on EGME and EGEE in 1983, the National Institute for Occupational Safety and Health (NIOSH) recommended that exposure to these glycol ethers be minimized in the workplace. NIOSH was concerned by the results of animal studies showing that airborne concentrations of EGME or EGEE at or below the current permissible exposure limits of the Occupational Safety and Health Administration (OSHA) caused testicular atrophy, infertility, and teratogenic effects. In April 1987, OSHA announced a notice of intended change for EGME, EGEE, and their acetates, and the agency is currently engaged in rule making for these chemicals.

After reviewing and critically evaluating the available data on the toxicity and health effects of EGME, EGEE, and their acetates, NIOSH recommended an occupational standard in 1991 that included the following recommended exposure limits for these glycol ethers: 0.1 part EGME or EGMEA per million parts of air (0.1 ppm) as a time-weighted average for up to a 10-h day during a 40-h workweek (10-h TWA), and 0.5 ppm EGEE or EGEEA as a 10-h TWA. NIOSH also recommended that dermal contact be prohibited for all four of these glycol ethers.

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