

Ethylene Glycol Monomethyl Ether (EGME) and Propylene Glycol Monomethyl Ether (PGME): Inhalation Fertility and Teratogenicity Studies in Rats, Mice and Rabbits

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A combined dominant lethal-fertility study was conducted in which male and female Sprague-Dawley (CD) rats were exposed to 0, 30, 100 or 300 ppm of ethylene glycol monomethyl ether (EGME) vapor for 6 hr/day, 5 days/week for 13 weeks and then mated to untreated counterparts. Among males, fertility was completely suppressed after exposure to 300 ppm. A partial restoration of reproductive function was evident following 13 weeks of recovery. No treatment-related reproductive effects were observed among males exposed subchronically to 100 ppm, or among females exposed to 300 ppm or below of EGME.

Studies to assess the effects of inhaled EGME on embryonal and fetal development were also conducted in Fischer 344 rats, CF-1 mice, and New Zealand White rabbits. Rats and rabbits were exposed to concentrations of 0, 3, 10 or 50 ppm for 6 hr/day on days 6-15 or 6-18 of gestation, respectively. Exposure of rabbits to 50 ppm resulted in significant teratologic effects, an increased resorption rate, and decreased fetal body weight. Slight fetotoxicity in the form of skeletal variations were observed among rats exposed to 50 ppm. Exposure of pregnant mice to 0, 10, or 50 ppm for 6 hr/day on days 6-15 of gestation resulted in slight fetotoxicity at 50 ppm. No significant treatment-related effects were observed at 10 ppm of EGME or below in any of the species tested.

Separate groups of pregnant rats and rabbits were exposed to 0, 500, 1500 or 3000 ppm of propylene glycol monomethyl ether (PGME) during organogenesis. Mild CNS depression was observed among rats and rabbits exposed to 3000 ppm of PGME. Fetal examination revealed no embryotoxic or teratogenic effects among either species. Delayed sternebral ossification observed among rats exposed to 3000 ppm of PGME was considered indicative of only slight fetotoxicity. Thus, it was concluded that PGME was not teratogenic at exposure levels up to 3000 ppm.

Introduction

The glycol ethers represent a diverse series of compounds with properties which make them ideally suited for a variety of solvent applications. The widespread use of these compounds and the concern for those potentially exposed are witnessed by our presence here and the extensive testing undergone by various glycol ethers.

The toxicologic literature pertaining to ethylene glycol monomethyl ether (EGME) and propylene glycol monomethyl ether (PGME) is substantial and has been reviewed recently (1). Despite the similarities in chemi-

cal structures, there appears to be a substantial difference in the toxicologic properties of EGME and PGME. Rapidly dividing cell systems, specifically the bone marrow, spleen, thymus and testicular germinal epithelium, appear to be the primary target organs following exposure to EGME (2-9). In contrast, exposure to high concentrations (3000 ppm) of PGME produced none of the effects seen with EGME, but resulted only in slight CNS depression and increased liver weights with no accompanying histopathologic changes (7,8).

One area of major concern is the potential effects exposure to the various glycol ethers may have on reproductive capabilities. The data presented herein are a summarization of the results of a fertility study with EGME and teratology studies conducted with EGME

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and PGME. Specific details of these studies have previously been reported (10-12).

Materials and Methods

Test Materials

The samples of EGME and PGME used in these studies were obtained from The Dow Chemical Company, Midland, MI. Identification and purity analyses conducted using gas chromatography and gas chromatography/mass spectrometry indicated purities of >99.7% for EGME and >98.6% for PGME.

EGME Fertility Study

Adult male and female Sprague-Dawley rats were exposed to vapor concentrations of 0, 30, 100 or 300 ppm of EGME for 6 hr/day, 5 days/week for 13 weeks. Following exposure, treated animals were then mated to unexposed counterparts. Exposed females were mated to unexposed males for 10 days, housed singly in nesting cages containing ground corn cob and allowed to deliver. Exposed males were mated to two separate groups of two females for consecutive 7-day periods. One female, selected from the first mating, was allowed to deliver. Litters that were delivered were evaluated for growth and survival through weaning. The remaining females mated to exposed males were sacrificed at mid-to-late gestation and evaluated for evidence of dominant lethal effects. Additional breedings of control and 300 ppm males were conducted at 13 and 19 weeks post-exposure in order to evaluate recovery of reproductive function. At the termination of the post-exposure periods, all rats were submitted for necropsy examination and representative sections of selected organs were examined histologically as described previously (9).

Teratology Studies

Generally, groups of 29 to 32 timed-pregnant Fischer 344 rats, CF-1 mice and New Zealand White rabbits were exposed to EGME or PGME for 6 hr/day. Rats, mice and rabbits were exposed to vapor concentrations of 0, 3 (rats and rabbits only), 10 or 50 ppm of EGME on days 6-15 (rats and mice) or 6-18 (rabbits) of gestation. Separate groups of rats and rabbits were exposed to 0, 500, 1500, or 3000 ppm of PGME during gestation. Maternal body weights were recorded at regular intervals during gestation, and food and water consumption were measured for rats and mice at 3-day intervals beginning on day 6 of gestation (day 0 denotes day of breeding). All animals were sacrificed by CO₂ asphyxiation on day 18 (mice), 21 (rats), or 29 (rabbits) of gestation, maternal organ weights were recorded, blood from animals exposed to EGME was drawn by cardiac puncture, and fetal examinations were conducted as described previously (11,12). Visceral examinations were conducted by using the Staples method (13).

Table 1. Observations on the parameters evaluated in a fertility study of EGME: comparison with controls.^a

Parameters	Exposure concentration, ppm		
	30	100	300
Body weight			
Male	—	—	Dec
Female	—	—	Dec
Reproductive effects			
Females	—	—	—
Males (fertility phase)			
— fertility index	—	—	Dec
— pup weight	—	—	— ^b
— survival	—	—	— ^b
Males (dominant lethal phase)			
— implantations/litter	—	—	— ^c
— resorption rate	—	—	— ^c
Males (recovery phase)			
— fertility index	NA	NA	Dec
— resorption rate	NA	NA	—

^aCodes (—) comparable to control data; (Dec) indicates a decrease relative to control; (NA) not applicable.

^bNo pups delivered to females mated to exposed males at this level.

^cInfertility at this level precluded evaluation of dominant lethal effects.

Results

Fertility Study

These results are summarized in Table 1 on the basis of comparison with control data. Adult males and females exposed to 300 ppm of EGME had significantly depressed body weights during the course of exposure. There were no treatment-related effects on reproductive function among females at any exposure level. However, among males exposed to 300 ppm of EGME, there was substantial evidence of reproductive toxicity. Among untreated females allowed to deliver litters, there were no pups delivered to those mated to males exposed to 300 ppm. At 30 and 100 ppm, litter size, growth and survival were comparable to controls. Similar results were obtained in the dominant lethal evaluation, where there were no pregnant females from the first week of breeding, and only two females with any indication of conception following the second week of breeding to males exposed to 300 ppm.

As a result of these effects, males from the control and the 300 ppm groups were mated to untreated females following 13 and 19 weeks of recovery to evaluate the reversibility of these reproductive effects. Though fertility among males exposed to 300 ppm remained decreased, approximately 50% of the males showed a reversal of the infertility seen immediately following exposure. Evaluation of the females mated to these males indicated that among those females which were pregnant, normal litter sizes and resorption rates were observed indicating recovery of reproduction function.

Necropsy examination of exposed males revealed testicular changes at 300 ppm similar to those reported elsewhere (6,7,9,14). Testicular weights were depressed

and the testes were flacid. Histologic examination revealed bilateral testicular changes characterized by variable numbers of atrophic seminiferous tubules lined only by Sertoli cells.

Teratology Studies

EGME. The effects of EGME on pregnant rats are summarized in Table 2. At 50 ppm, there was a transient decrease in weight gain during the initial phase of exposure. There were no differences in any of the reproductive indices such as litter size, resorption rate, or fetal weights or lengths. The incidence of malformations observed among exposed rats were not significantly different from the controls, and were all within the historical control incidence of spontaneous malformations. At 50 ppm, significant increases in two minor skeletal variations (lumbar spurs and delayed ossification of the vertebral centra) were considered evidence of only slight fetotoxicity. There were no fetal effects observed among rats at 3 or 10 ppm.

Table 2. Summary of rat teratology study with EGME: comparison with controls.^a

Parameters	Exposure concentration, ppm		
	3	10	50
Maternal parameters			
Body weight gain	—	—	Dec (transient)
Food and water consumption	—	—	—
Organ weights	—	—	—
Hematology	Dec*	Dec*	Dec*
Reproductive indices	—	—	—
Fetal parameters			
Body weight	—	—	—
Crown-rump length	—	—	—
Morphologic examination	—	—	Fetotoxicity (lumbar rib spurs; delayed ossification; vertebral centra)

^aCodes: (—) comparable to control data; (Dec) indicates parameter decreased relative to control data; (*) considered of questionable toxicologic significance.

Table 3. Summary of mouse teratology study with EGME: comparison with controls.^a

Parameter	Exposure concentration, ppm	
	10	50
Maternal parameters		
Body weight gain	—	Dec (transient)
Food and water consumption	—	—
Organ weights	—	—
Hematology	—	—
Reproductive indices	—	—
Fetal parameters		
Body weight	—	—
Crown-rump length	—	—
Morphological examination	—	Fetotoxicity (unilateral testicular hypoplasia; extra lumbar ribs)

^aCodes: (—) comparable to control data; (Dec) indicates a decrease relative to controls.

Evaluation of the hematologic parameters among rats showed slight, but statistically significant, decreases in erythrocytic parameters among all exposure levels. These decreases in RBC, HGB and PCV were very slight, ranging from approximately 3 to 6%, but appeared to be dose-related. Regardless of these slight changes, there were no apparent effects on fetal development at 3 or 10 ppm of EGME.

A similar pattern of response was observed among mice exposed to EGME (Table 3). Minimal maternal effects, consisting of only a slight transient decrease in weight gain during exposure, were seen in mice exposed to 50 ppm. There were no other maternal effects nor were any changes in the hematologic parameters observed. Similar to the pattern seen in rats, there were also no treatment-related effects on reproductive parameters. Fetal effects observed in mice were similar to those seen in rats. Slight fetotoxicity was observed at 50 ppm. Significant increases in the incidences of extra lumbar ribs and unilateral testicular hypoplasia were the only effects observed among exposed mice. As was seen in rats, there were no adverse effects seen at 10 ppm.

Substantially more pronounced effects were observed among rabbits exposed to EGME than among either rats or mice. Maternal weight gain among rabbits exposed to 50 ppm was decreased during exposure, and liver weights, though not considered a primary target organ, were significantly elevated at sacrifice (Table 4). However, there were no changes in the spleen or thymus weights nor any changes in hematologic parameters at any exposure level. Evaluation of the reproductive indices indicated a significant increase in the resorption rate among rabbits exposed to 50 ppm, and fetal body weights at this level were significantly lower than among controls. A statistically significant increase in the resorption rate at 10 ppm was also observed; however, historical control data from 27 studies involving 487 litters revealed a control resorption rate of $9\% \pm 4\%$, with group values ranging as high as 18% of the fetuses. In light of these data, the resorption rate

Table 4. Summary of rabbit teratology study with EGME: comparison with controls.^a

Parameter	Exposure concentration, ppm		
	3	10	50
Maternal parameters			
Body weight gain	—	—	Dec
Organ weights	—	—	Dec (liver)
Hematology	—	—	—
Reproductive indices			
Litter size	—	—	—
Resorption rate	—	Inc*	Inc
Fetal parameters			
Body weight	—	—	Dec
Crown-rump length	—	—	—

^aCodes: (—) comparable to control value; (Inc) or (Dec) indicates an increase or decrease relative to concurrent controls; (*) statistical increase not considered associated with treatment.

Table 5. EGME rabbit teratology: incidence of fetal malformations.

	No. fetuses (no. litters)			
	0	3 ppm	10 ppm	50 ppm
External and skeletal examination	173(23)	172(23)	187(24)	145(22)
Soft tissue examination	95(23)	93(23)	101(24)	80(22)
Total malformations ^a	6(6)	4(4)	3(3)	91(20)*
External malformations				
Limb defects	0	1(1)	1(1)	55(16)*
Digit defects	0	0	0	17(8)*
Ventral wall defects	0	0	0	11(4)*
Soft tissue malformations				
Ventricular septal defects	0	0	0	34(15)*
Aortic coarctation	0	0	0	13(6)*
Renal defects	0	2(2)	1(1)	29(14)*
Skeletal malformations				
Missing bones-extremities	0	0	0	11(5)*
Rib defects	4(4)	1(1)	1(1)	8(5)*

^aTotal number of fetuses (litters) exhibiting at least one malformation.

*Significantly different from the control value, $\alpha = 0.05$.

observed among rabbits at 10 ppm was not considered treatment-related.

Fetal examination of rabbits revealed a substantially different picture than was observed among rats or mice. The data presented in Table 5 represent a portion of the results obtained in rabbits and were condensed for the sake of convenience. Malformations were observed in essentially all organ systems among fetal rabbits exposed to 50 ppm of EGME, with a total of 63% of the fetuses exhibiting at least one malformation. In the majority of affected fetuses, multiple malformations involving different organ systems were observed. Externally, arthrogryposis, digit and ventral wall defects were the most predominant malformations. Viscerally, ventricular septal defects, frequently accompanied by aortic coarctation (segmental constriction) were observed in approximately 42% of the fetuses. Renal defects, consisting primarily of severely dilated renal pelvises, were also frequently observed. Skeletal defects were observed less frequently, with missing bones of the extremities being the predominant finding.

A similar pattern was observed in minor fetal variations among exposed rabbits. Significant increases in numerous indicators of delayed development were observed among fetal rabbits exposed to 50 ppm (data not shown). In contrast to the effects observed at 50 ppm, the incidence of malformations and fetal variations observed among rabbits exposed to 3 or 10 ppm were comparable to the controls.

In summary, substantial evidence of fetotoxicity, embryoletality, and teratogenicity was observed among rabbits exposed to 50 ppm and slight fetotoxicity was observed among rats and mice at this level. There were no treatment-related effects on fetal development at 10 ppm or below in any of the species tested (11).

PGME. The results obtained following exposure to PGME are in sharp contrast with the results following EGME exposure (12). Among rats exposed to 3000 ppm of PGME, evidence of maternal effects were

Table 6. Summary of rat teratology with PGME: comparison with controls.^a

Parameters	Exposure concentration, ppm		
	500	1500	3000
Maternal parameters			
Clinical observations	—	—	CNS depression (transient)
Body weight gain	—	—	Dec
Food consumption	—	—	Dec
Organ weight	—	—	—
Reproductive indices	—	—	—
Fetal parameters			
Body weight	—	—	—
Crown-rump length	—	—	—
Morphologic examination	—	—	Slight fetotoxicity (delayed ossification-sternabrae)

^aCodes: (—) comparable to control value; (Dec) indicates decrease relative to control value.

observed during the first 4 to 5 days of exposure (Table 6). Rats at this level showed mild transient ataxia and lethargy, a small decrease in weight gain, slightly decreased food consumption, and slight-to-moderate chromodacryorrhea (pigmentation around the eyes). At 500 and 1500 ppm, there were no effects observed. Despite the obvious maternal effects, there were no effects on any of the reproductive parameters among any of the exposure groups. Fetal examination revealed a number of malformations scattered among control and treated groups and many of the fetuses which were malformed had multiple malformations. The number of fetuses with malformations at 3000 ppm (seven fetuses in five litters) was higher than the control incidence (one fetus and one malformed late resorption); however, the type and incidences of malformations observed were consistent with historical control incidences. In addition, the lack of any significant effects on parameters such as resorption rate and fetal body weights which are usually altered at or below teratogenic levels

Table 7. Summary of rabbit teratology study with PGME: comparison with controls.^a

Parameters	Exposure concentration, ppm		
	500	1500	3000
Maternal parameters			
Clinical observation	—	—	CNS depression (transient)
Body weight gain	—	—	Dec
Organ weight	—	—	—
Reproductive indices	—	—	—
Fetal parameters			
Body weight	—	—	—
Crown-rump length	—	—	—
Morphologic examination	—	—	—

^aCode: (—) comparable to control value; (Dec) indicates decrease relative to control value.

(15,16) suggested these alterations were not related to PGME exposure.

The only statistical difference among fetal measurements observed in rats exposed to PGME was an increase in the incidence of delayed sternebral ossification. Thus, PGME was not considered teratogenic in rats, though possible slight fetotoxicity was observed at 3000 ppm, a concentration which also produced obvious maternal effects. No adverse effects were observed at 1500 or 500 ppm.

The effects observed among maternal rabbits exposed to PGME were less pronounced than effects among rats, and are presented in Table 7. Mild, transient CNS depression immediately followed exposure among maternal rabbits exposed to 3000 ppm, which resulted in a significant reduction in weight gain during the exposure period (days 6–18 of gestation). As was seen in rats, there were no effects on reproductive parameters among any of the exposure groups. Fetal examination of rabbits revealed only scattered incidences of malformations and minor variations, while there were no patterns of effects which would indicate any fetotoxic or teratogenic effects among rabbits exposed to up to 3000 ppm of PGME.

Discussion

These data indicate substantial differences in the toxicologic properties of EGME and PGME. Exposure to EGME was shown to produce essentially complete infertility among males at 300 ppm, with degenerative changes in the germinal epithelium of the testes consistent with a decreased reproductive capability (10). Inhalation exposure of pregnant rabbits to 50 ppm produced substantial teratogenicity, embryoletality and fetotoxicity, with slight fetotoxicity observed among rats and mice at that level (11). These results are consistent with the results observed in mice following oral administration of EGME (17) in which teratogenic effects were seen at dose levels of 62.5 mg/kg/day and above, and fetotoxicity was seen at the lowest dose

tested (31.25 mg/kg/day). Recent data (18) have also indicated dose-related teratogenic effects among rats exposed to 50 or 100 ppm of EGME for a slightly longer exposure period (7 hr/day). Complete embryoletality in rats reported at 200 ppm (18) was also observed in preliminary studies conducted in this laboratory using 200 ppm of EGME (unpublished data, The Dow Chemical Company).

The direct comparison of the three species under identical exposure conditions in the present studies indicated that the rabbit is the most sensitive of the species to EGME, a finding consistent with other toxicologic effects following subchronic exposure (9). One important aspect to be considered is the establishment of no observed effect levels in all three species. Previous teratologic studies conducted at higher levels (17,18) produced adverse fetal effects even at the lowest levels tested. The establishment of a no-effect level at an exposure concentration only 5-fold below the concentration at which substantial teratogenicity was observed in the most sensitive species also points out the steep dose-effect relationship which exists for EGME.

In contrast to the effects observed with EGME, PGME produced indications of, at most, slight fetotoxicity among rats exposed to extreme vapor concentrations (3000 ppm), a level which produced obvious maternal CNS depression. There were no indications of any effects on fetal development among rabbits at 3000 ppm, and no effects were observed at 1500 ppm of PGME or below (12). These results are consistent with the effects previously reported following oral administration of PGME (19). While fertility testing has not been conducted using PGME, the results of subchronic inhalation exposure to up to 3000 ppm of PGME have not indicated any adverse effects on the testes of exposed males (8).

A recent study (20) of the effects of EGME and PGME exposure on fetal development and survival utilizing an adaption of the rapid assessment method described by Chernoff and Kavlock (21) substantiates the differences in reproductive toxicity reported herein. Exposure of pregnant rats for 6 hr/day on days 6–17 of gestation resulted in no viable litters among females exposed to 300 ppm of EGME, with decreased litter size, pup weights and viability among litters from females exposed to 100 ppm of EGME. In contrast, exposure of pregnant females to 200 or 600 ppm of PGME for this same period had no adverse effects (20). These differences in the toxicologic properties of EGME and PGME are thought to be the result of differences in metabolism observed with these two compounds (22).

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