

Acute and Subchronic Toxicity of Ethylene Glycol Monobutyl Ether

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The available information on the acute and subchronic toxicity of ethylene glycol monobutyl ether is reviewed. Data from animal studies have been examined from the standpoint of dose-response relationships and the sensitivity of various animal species, including man, to the effects of this chemical. In view of recent findings with other chemically related glycol ethers, particular attention has been given to possible adverse effects on blood and testicular tissue. In evaluating the hazard that this chemical may pose to man, consideration has been given to likely routes of exposure and its irritant properties. It is concluded that the available information continues to support the current ACGIH TWA₈-TLV of 25 ppm with a STEL of 75 ppm.

Introduction

Ethylene glycol monobutyl ether (EGBE) has been studied extensively with respect to establishing exposure conditions at which adverse health effects are unlikely to occur in humans. Information obtained in these studies has defined the major organs and tissues affected by EGBE, established differential response of various laboratory animal species, and provides a clear picture of dose-response relationships by various routes of exposure. In this paper, the acute toxicity of EGBE and the effects of repeated exposure by oral administration, inhalation of vapor and application to the skin are reviewed. Recent interest in the toxicity of monoalkyl glycol ethers has centered around effects on blood forming tissues and the testes. Therefore, observations in some of the previous studies have been reevaluated, paying particular attention to detecting effects on these possible target tissues.

In attempting to assess the potential hazards of EGBE to humans, the available toxicology information clearly needs to be evaluated in terms of probable routes of exposure. Therefore, emphasis has been placed on studies conducted in laboratory animals by dermal application and vapor inhalation. Although the vapor pressure of EGBE (0.6 mm Hg) is lower relative to that of ethylene glycol monomethyl (EGME) or monoethyl (EGEE) ether (6 and 4 mm Hg, respectively), inhalation remains one of the predominant routes of exposure due to some of the major end uses, i.e.,

coatings applications. Skin is also a potential significant route of human exposure, through contact with various cleaning solutions formulated with EGBE. Ingestion, on the other hand, is an unlikely primary route of entry for humans; exceptions include instances of accidental poisoning or attempts at suicide. However, there appear to be no reports of human ingestion of EGBE.

Acute Toxicity

The acute (single dose) lethal toxicity of EGBE has been determined in a number of laboratory animal species (Table 1). Rabbits appear to be the most susceptible to the acute induced effects of this material followed by mice, guinea pigs and rats (1). Carpenter et al. (1) suggested that the wide intraspecies variation reported for LD₅₀ values in rats correlates with the apparently greater susceptibility of older animals as compared to younger animals, which are four to five times more resistant to the effects of single oral EGBE administration.

EGBE is readily absorbed across the skin as indicated by its lethal toxicity in dermal application studies. Again, rabbits appear to be more susceptible to the toxic effects of this chemical at a lower dosage level than rats, when applied to the skin. Although quantitative data are not available, it is relevant that Saparamedov (5) submerged the tails of mice (up to two-thirds of their lengths) into undiluted EGBE for 2-hr periods. No death, adverse systemic effects or skin irritation was reported.

The effects of a single inhalation exposure to EGBE to different animal species are shown in Table 2. Again,

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Table 1. Acute toxicity and primary irritancy of EGBE.

Species		Reference
Single oral LD ₅₀ , mg/kg		
Rat	530 to 3000	(1)
	1480	(2)
	620	(3)
	2680	(4)
Rabbit	320 to 370	(1)
Mouse	1230	(1)
	1170 to 1700	(3)
	1000 to 1600	(5)
Guinea pig	1200	(1)
Single percutaneous LD ₅₀ , mL/kg		
Rat	2.52 (4 hr)	(7)
Rabbit	0.45 to 2.00 (24 hr)	(1)
	0.63 (24 hr)	(4)
	0.11 (8 hr)	(6)
Primary irritation, skin		
Rabbit	Mild irritation	(3)
	Mild irritation (grade 2 of 10)	(4)
Mice	Mild irritation	(5)
Primary irritation, eye		
Rabbit	Severe (grade 8 of 10)	(4)
	Moderate (grade 4 of 10)	(8)

there is variability in the data, particularly with respect to the response of rats. Substantially saturated vapor, which approaches a concentration of 1300 ppm (5), killed only one of six rats after an 8-hr exposure, while a single exposure to a concentration of 375 ppm produced complete mortality in a group of older animals. Again, this variability has been attributed to the greater susceptibility of older animals.

A consideration of the data from these studies indicates that EGBE presents a slight to moderate acute hazard to man by single skin contact or by swallowing. Results of acute inhalation studies indicate EGBE to be of moderate toxicity. However, its relatively low vapor pressure and good warning properties, discussed by Carpenter et al. (1), diminish the inhalation hazard when handled under most foreseeable situations.

Primary Irritation

EGBE is only mildly irritating to rabbit skin when applied and left uncovered for a 4-hr period. However, more prolonged exposure to the undiluted chemical, as encountered in 24-hr percutaneous toxicity studies, can lead to moderate irritation characterized by erythema, edema and necrosis (4).

There is conflict with regard to reports on the effects of EGBE on the eye. Early work by Carpenter and Smyth (8) indicated that the chemical produced only moderate irritation when 0.02 mL was instilled into the conjunctival sac; the response was graded 4 out of a possible maximum of 10. In a more recent study (4), instillation of 0.005 mL into rabbit eyes produced severe corneal injury with iritis. Moderate corneal injury was observed when 0.5 mL of a 15% aqueous dilution was

Table 2. Effects of single vapor exposure of EGBE to laboratory animals.

Exposure level, ppm	Response	Reference
2400	8 hr: killed 8 of 8 rats	(9)
Substantially saturated vapor (≈1300)	Rats: LT ₅₀ = 9 hr	(1)
	Guinea pigs: LT ₅₀ = 7 hr	(10)
800	8 hr: killed 3 of 6 rats	(1)
	4 hr: killed 0 of 6 rats	
700	7 hr: LC ₅₀ for mice	(11)
500	8 hr: killed 0 of 6 rats	(1)
	4 hr: killed 1 of 6 rats	
375	7 hr: killed 11 of 13 and 23 of 23 older rats	(1)

instilled into the eye, and no injury was noted from a 5% aqueous dilution. Based on these observations, the material was graded 8 on the 10-point scale.

Repeated Oral Administration

Results of three studies in which EGBE was administered repeatedly by mouth to rats or mice are given in Table 3. In an early rat study conducted by Carpenter and Pozzani (12), decreased weight gain was noted at dosage levels of 1500 or 300 mg/kg administered in feed for 90 days. An increase in the relative liver and kidney weight was reported at 1500 mg/kg, and in relative liver weight at 300 mg/kg. The value of this study is limited by a high mortality in all treatment and control groups, probably caused by a high incidence of pneumonia. It is of interest to note that when pooled urine from rats fed EGBE at 1500 or 300 mg/kg for 3 or 6 days was analyzed by a benzidine test, no hemoglobin was detected.

In a second study (13) decreased weight gain and increased relative liver and kidney weights were reported at 950 mg/kg. In addition, testicular atrophy was reported at 950 and 200 mg/kg. The sections of testes from this study have been recently reviewed and confirm a treatment-related degeneration and atrophy of the seminiferous tubules. The lesion was present at 950 and 200 mg/kg, but not in those animals receiving EGBE at 40 or 8 mg/kg. The EGBE used in this study was manufactured using boron trifluoride (BF₃) as a catalyst, a process which has not been used for the past 15 years. EGBE so produced is known to contain a number of impurities not found in current production material (16); these include crown ethers, which have been shown to produce testicular atrophy with degeneration of the germinal epithelium (17), and fluoroethanol.

More recently, mice were given EGBE by gavage over a 5-week period at dosages of 2000, 1000 and 500 mg/kg (14,15). At 2000 mg/kg all the animals died. This finding is consistent with the acute toxicity data presented in Table 1, which indicates that the acute oral LD₅₀ in mice lies between 1000 and 1700 mg/kg. In the mice receiving the test chemical at 1000 and 500 mg/kg, erythrocyte counts were statistically significantly decreased, but

Table 3. Effects of repeated peroral administration of EGBE in rats and mice.

Species	Experimental design	Dosage concentration, mg/kg	Significant effects	Reference
Rats	5/sex/dosage group EGBE in feed daily for 90 days	1500	Decreased body weight gain; increased relative liver and kidney weights	(12)
		300	Increased relative liver weight	
		80	No observable effects	
		20	No observable effects	
Rats	10/sex/dosage group EGBE in feed daily for 91 to 93 days	950	Decreased body weight gain; increased relative liver and kidney weights; seminiferous tubule degeneration	(13)
		200	Decreased weight gain in males, seminiferous tubule degeneration	
		40	No observable effects	
		8	No observable effects	
Mice	5 males/dosage group administered by gavage 5 days/week for 5 weeks	2000	Complete mortality	(14,15)
		1000	1 of 5 with testicular atrophy, depressed erythrocyte count	
		500	Depressed erythrocyte count	

there was no statistically significant effect on white blood cell counts, or on body, testicular, liver or kidney weights. In the 1000 mg/kg group one of five mice demonstrated seminiferous tubular atrophy.

The data taken from these studies indicate that repeated oral administration of EGBE will produce adverse effects on the liver, kidney and erythrocytes. It is not clear whether the chemical which is available by current production processes is capable of producing damage to testicular tissues when administered orally. The available data concerning this effect is equivocal with respect to sample purity and a lack of response by other routes of administration. The lowest dosage at which any adverse effect was noted was 200 mg/kg in the rat (testicular effects) and 500 mg/kg in the mouse (decreased RBC). The no-observable effect level in rats was 80 mg/kg.

Repeated Inhalation Exposure

Results of repeated inhalation exposures conducted in various laboratory animal species, along with observations from brief human exposures, are given in Table 4. The predominant effects observed in rats include reduced body weight gain, hematological changes and increased absolute and relative kidney and liver weights. In some of the earliest work with this chemical, Werner and co-workers identified the red blood cell as one of the more sensitive indicators of toxicity (20). Using *in vitro* methodology, these workers demonstrated that erythrocytes became extremely susceptible to osmotic hemolysis in the presence of low concentrations of the chemical. This observation was confirmed by extensive *in vivo* studies conducted by Carpenter and his co-workers (1), who demonstrated erythrocyte fragility in the rat, mouse and rabbit after exposure to EGBE, but could not demonstrate the effect in the monkey, dog, guinea

pig or human. The lowest exposure level at which erythrocyte fragility was detected in rats was 62 ppm, while no effect was noted at 32 ppm. Erythrocyte fragility, at least in mice, appeared to be transient with the effect being noted immediately after a 7-hr exposure, but with recovery during the 17-hr period between exposures. Mice did not develop a tolerance, since the effect of EGBE on the erythrocyte was as great after the 89th exposure as it was after the first exposure.

The hemolytic effect of EGBE appears to be responsible for the transient hemoglobinuria, or red discolored urine, noted during the first few days of several of the animal studies. In all studies where hemoglobinuria has been noted, it seldom persisted beyond 3 to 5 days of exposure. Increased liver and kidney weights have also been noted at higher exposure levels. This effect appears to be reversible with absolute or relative organ weights returning to values similar to those in control animals after a recovery period as short as 1 week. In no case did exposure to EGBE vapor produce decreased testicular weight. Histological examination was conducted on testes of rats exposed to concentrations as high as 250 ppm for 30 exposures (12) and more recently to 77 ppm for 90 days (19), and on the testes from guinea pigs exposed at a concentration of 500 ppm for 30 days (1), a dog exposed to 385 ppm and a monkey exposed to 100 ppm (21). In no case was there any evidence of treatment-related testicular pathology.

In rats, the lowest exposure concentration of EGBE which produced any adverse effect was 62 ppm, where erythrocyte fragility was increased. Exposure to 77 ppm produced transient decreases in weight gain and erythrocyte count with complete recovery by the completion of the 90-day exposure period. The no observable effect level in rats was 32 ppm. No effects were observed in guinea pigs exposed to 125 ppm, but increased erythrocyte fragility was detected in mice

Table 4. Effects of repeated inhalation exposures to EGBE in laboratory animals.

Species	Experimental design	Dosage concentration, mg/kg	Significant effects	Reference
Rats	23/exposure concentrations for 5 hr/day, 5 days/week; groups killed at 1, 3, or 5 weeks of exposure and at 1 week post-exposure	320	Decreased erythrocyte count and Hb concentration; increased reticulocytes; Recovery during post-exposure period	(18)
		135	Decreased erythrocyte count and Hb concentration; increased reticulocytes; recovery during week 3-5 of exposure	
Rats	15/sex/exposure concentration for 7 hr/day for 5 days/week for 30 exposures	250	Hemoglobinuria in both sexes after first 3 exposures; increased relative liver and kidney weight	(12)
		125	Increased relative liver and kidney weights	
		62	No observable effects	
Rats	4/sex/exposure concentration for 6 hr/day for 15 exposures	100	Increased erythrocyte fragility	(9)
		50	No observable effects	
		20	No observable effects	
Rats	7 to 8/sex exposure concentration for 6 hr/day, 5 days/week for 9 exposures over 11 days with one of two groups exposed to 245 ppm killed at 14 days post-exposure	245	Decreased weight gain; hemoglobinuria; decreased erythrocyte count and Hb concentration; increased reticulocytes and nucleated RBC; increased liver weight; substantial recovery of erythroid values during 14 day recovery; complete recovery of liver weight	(19)
		86	Decreased body weight gain in females; decreased erythrocyte count and Hb concentration; increased reticulocytes and nucleated erythrocyte count	
		20	No observable effects	
Rats	16/sex/exposure concentration for 6 hr/day, 5 days/week with groups killed at 5 and 13 weeks of exposure	77	Transient decrease in weight gain of females; decrease in erythrocyte count in females at 6 weeks but not at 13 weeks of exposure	(19)
		25	No observable effects	
		5	No observable effects	
Guinea pigs	10 males/exposure concentration for 7 hr/day, 5 days/week for 6 weeks	250	Increased kidney weight	(12)
		125	No observable effects	
		62	No observable effects	
Guinea pigs	10 males/exposure concentration for 7 hr/day, 5 days/week for 6 weeks	500	Increased mortality; decreased body weight	(1)
		375	Increased mortality; decreased body weight gain; increased kidney weight	
Mice	70 males/exposure concentration for 7 hr/day, for 5 days/week, with groups killed at 6, 12, and 18 weeks of exposure and at 6 weeks post-exposure	400	Increased erythrocyte fragility; hemoglobinuria during first 3 exposures; increased liver weight with recovery during post-exposure	(1)
		200	Increased erythrocyte fragility; hemoglobinuria during first 3 exposures; increased liver weight after 6 weeks of exposure with recovery during post-exposure	
		100	Increased erythrocyte fragility	
Dogs	2 exposed 5 hr/day for 5 days/week for 12 weeks and killed 5 weeks post-exposure	415	Signs of respiratory and eye irritation; decreased erythrocyte count and Hb concentration; increased blood urea	(20)
Humans	3 to 4 subjects exposed for two 4-hr periods with 30 min rest period between exposures	200	Nose, throat and eye irritation with taste disturbances; headache	(1)
		100	Nose, throat and eye irritation with taste disturbances; nausea	

exposed to 100 ppm. Humans found both 200 ppm and 100 ppm intolerable due to irritancy.

Repeated Dermal Exposure

The results from two repeated skin application studies conducted with New Zealand rabbits are summa-

rized in Table 5. In a 9-day study, EGBE was applied to the clipped skin of the animals under an occlusive dressing (22). Different doses were achieved by applying a constant volume of varying concentrations of aqueous dilutions of the test material. Applications were made for 5 consecutive days followed by a 2-day recovery period and then four additional applications

were made. The animals were killed 14 days after the ninth application.

Significant findings included decreased rate of body weight gain in the female rabbits dosed with undiluted material. These animals also exhibited a decreased erythrocyte count, hemoglobin (Hb) concentration, mean corpuscular Hb concentration and an increase in the mean corpuscular Hb. Hemoglobinuria was noted in male and female rabbits treated with undiluted EGBE and in females treated with 50% aqueous dilution. Erythema and edema were noted at the site of application of the test material in all animals dosed with the undiluted chemical. Necrosis also developed in these animals by the sixth study day. In those receiving the 50% aqueous dilution, erythema and edema were also present with necrosis developing in one of five males and four of five females. Only mild indications of skin irritation were reported in the lower two dosage level groups in which 25%, or 5% aqueous dilutions of EGBE were applied. There were no differences in the weight gain of male animals at any dosage level. In addition, there were no differences in the absolute or relative weights of organs between the treated male or female rabbits at any dosage level and the controls. Of note was one female rabbit treated with undiluted EGBE killed *in extremis* on the fifth treatment day. The moribund condition of this animal could not be attributed to EGBE application.

Based on the results of the 9-day study, a 13-week (subchronic) study was conducted under sponsorship of the Chemical Manufacturers Association. Dosage levels were 150, 50 and 10 mg/kg body weight (23). In order to ensure a relatively constant surface area coverage of test material, aqueous dilutions were prepared which would allow approximately 1 mL of solution to supply the appropriate quantity of EGBE, i.e., 42.8% 14.3% or 2.8%. The diluted test material was applied under a poly (vinylidene chloride) wrap to the clipped skin of 10 rabbits of each sex for each dosage group. Applica-

tions were made 6 hr/day for 5 days/week. The animals remained unrestrained both during and after exposure.

No EGBE-induced changes were noted with respect to clinical observations, skin irritation, body weight, body weight changes, food consumption, hematology values, red blood cell fragility, differential white blood cell counts, serum chemistry, organ weights, final body weights or relative organ weights. The only microscopic pathological changes noted in animals of all groups, including the control, were related to subclinical parasitic or bacterial infections. Four animals were either found dead or killed *in extremis* during the study for causes unrelated to treatment. These included: one male from the high dose group found dead on study day 92 from encephalitozoonosis; one female in this group killed on study day 32 after suffering a broken back; a male rabbit in the 50 mg/kg group found dead on study day 15, attributed to a gastric ulcer; and finally, a female in the 10 mg/kg dosage group found dead due to pasteurellosis on study day 96.

In summary, the two studies show that adverse systemic effects from dermal application of EGBE to rabbits would appear to be dependent both on the concentration applied and the dosage level employed. The lowest level at which effects were noted was 180 mg/kg applied as a 50% aqueous dilution, where hemoglobinuria was noted in female rabbits. The highest no-observable level for systemic effects was 150 mg/kg applied as a 43% solution. Indeed, at this dosage level no increased incidence of skin irritation was noted.

Discussion

Over a number of years, extensive animal testing of EGBE has provided information which may be used to evaluate the potential for adverse effects in exposed humans. The most sensitive index of toxicity is the effect on the red blood cell, although liver and kidney are also implicated as target organs. EGBE would

Table 5. Effects of repeated application of EGBE to the skin of rabbits.

Experimental design	Dosage concentration, mg/kg	Significant effects	Reference
5/sex/dosage concentration treated with 1 mL of 100%, 50% 25% or 5% solutions of EGBE under an occlusive dressing 5 days/week for 6 hr/day for 9 applications over 11 days; 14 day observation period after final application	360 (undiluted)	Decreased body weight gain and erythropoietic values in females; hemoglobinuria in males and females; erythema, edema and necrosis at site of application; recovery at end of 14-day observation period	(22)
	180 (50%)	Hemoglobinuria in females; erythema, edema and necrosis at site of application	
	90 (25%)	Mild skin irritation	
	18 (5%)	Mild skin irritation	
10/sex/dosage level treated with 1 mL of 43%, 14% or 3% solutions of EGBE under an occlusive dressing; 5 days/week, 6 hr/day for 13 weeks	150 (43%)	No observable systemic effects	(23)
	50 (14%)	No observable effects	
	10 (3%)	No observable effects	

appear to have a specific effect on the erythrocyte membrane, causing the cell to become more fragile and have an increased susceptibility to osmotic hemolysis. It is likely that in exposed animals this increased cellular fragility leads to intravascular hemolysis which is responsible for the hemaglobinuria noted in several animal studies. Urine discoloration noted in these studies was transient in nature. Carpenter et al. (1) suggested that it was only the older erythrocytes which were susceptible to the effects of EGBE, and that after a loss of these cells due to lysis during initial exposures, a younger and less susceptible cell population would be established. It is possible that the early hemoglobinuria may have played a role in the pathogenesis of the kidney damage reported in some EGBE animal toxicity studies (24).

Increased liver and kidney weight, particularly when expressed as a percentage of body weight, has been the only other organ finding in laboratory animals exposed to EGBE.

Although there has been one report of testicular damage arising from ingestion of EGBE (12), this result is considered suspect for several reasons. First, the test chemical may have contained impurities known to produce testicular damage. Second, in a further and more detailed gavage study no statistically significant decrease in testicular weight or increased incidence of germinal epithelial cell damage was obtained (15). Third, testicular effects have not been seen in laboratory animals administered EGBE by other routes i.e., inhalation or dermal exposure. Although there is no analytical data on the test material, it is likely that the effects produced in testes were the result of impurities found in EGBE manufactured by a process which is no longer in use.

The acute percutaneous toxicity of EGBE indicates that it is readily absorbed across the skin. The dosage levels at which adverse effects are observed, however, appear to be influenced by the concentration of the chemical in the aqueous dilutions employed in the tests. This suggests that water may influence the ability of the chemical to pass through the skin barrier. However, it has been noted that no discernible liquid remains on the skin at the end of a 6 hr exposure. Therefore, additional studies may be required to clarify the effect of aqueous dilution on the skin permeability of EGBE and other glycol ethers.

Conclusions

EGBE has been tested for its potential to produce adverse effects in laboratory animals by ingestion, vapor inhalation and skin penetration. The lowest dosage level at which effects were noted by ingestion was 200 mg/kg for 90 days, which produced testicular effects in rats, and 500 mg/kg for 5 weeks in mice where a decrease in erythrocyte count was noted. The significance of the testicular effect is uncertain because of the possibility that impurities were present in the

test sample which are known to produce germinal epithelial cell damage. A no-observable effect level of 80 mg/kg was obtained in rats which received the EGBE in feed for 90 days. The lowest vapor exposure concentration at which effects were noted was 62 ppm (RBC fragility). Female rats exposed to 77 ppm for 13 weeks exhibited transient decreased weight gain and a transient decrease in erythrocyte count. An exposure concentration of 100 ppm produced increased erythrocyte fragility in mice. The no-observable effect level in rats exposed for 13 weeks was 25 ppm and in guinea pigs exposed for 6 weeks was 125 ppm. A dosage concentration of 180 mg/kg applied as a 50% aqueous dilution to the skin of female rabbits for nine applications produced hemoglobinuria. No observable systemic effects were noted when 150 mg/kg was applied to the skin of rabbits for 13 weeks.

Although the rabbit appears to be the most sensitive species with regard to the acutely induced effects of EGBE, the rat is more susceptible to repeated exposures and to effects on the erythrocyte. The dog, guinea pig, monkey and man are resistant to the effects of this chemical on the erythrocyte. Vapor concentrations of 200 and 100 ppm produce nasal, respiratory and eye irritations of approximately the same degree. It is unlikely that humans would tolerate exposure levels of 100 ppm for prolonged periods of time.

The available information on the acute and repeated exposure toxicity of EGBE to laboratory animals and man accords with the current ACGIH Threshold Limit Value (TWA₈) of 25 ppm and a short-term exposure limit of 75 ppm.

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