

CHRONIC TOXICITY SUMMARY

ETHYLENE GLYCOL MONOMETHYL ETHER

(EGME; 2-methoxyethanol; 1-hydroxy-2-methoxyethane; methyl cellosolve)

CAS Registry Number: 109-86-4

I. Chronic Toxicity Summary

<i>Inhalation reference exposure level</i>	60 µg/m³ (20 ppb)
<i>Critical effect(s)</i>	Testicular toxicity in rabbits
<i>Hazard index target(s)</i>	Reproductive system

II. Physical and Chemical Properties (HSDB, 1995)

<i>Description</i>	Colorless liquid
<i>Molecular formula</i>	C ₃ H ₈ O ₂
<i>Molecular weight</i>	76.09
<i>Density</i>	0.965 g/cm ³ @ 20° C
<i>Boiling point</i>	125°C
<i>Melting point</i>	-85.1°C
<i>Vapor pressure</i>	6.2 torr @ 20°C
<i>Solubility</i>	Miscible with water, alcohol, benzene, ether, acetone
<i>Conversion factor</i>	1 ppm = 3.1 mg/m ³ @ 25°C

III. Major Uses and Sources

Ethylene glycol monomethyl ether (EGME) is used as a solvent for cellulose acetate and resins (HSDB, 1995) as well as a solvent in the semiconductor industry. It is also used in dyeing leather and in the manufacture of photographic film. EGME is used as an anti-freeze in jet fuels. Quick drying varnishes, enamels, nail polishes, and wood stains may also contain EGME. The specific annual statewide industrial emissions of EGME from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 7398 pounds (CARB, 1999). (Many industries did not report emissions of specific glycol ethers. Thus there were also emitted 2,922,744 pounds of the general category glycol ethers, which can include EGME.)

IV. Effects of Human Exposure

Human exposures to ethylene glycol monomethyl ether have been associated with hematological and neurological abnormalities. To determine whether employees potentially exposed to ethylene glycol monomethyl ether during manufacturing and packaging had a higher prevalence

of anemia, leukopenia, or sterility than an in-plant comparison group, a cross-sectional study was conducted. Blood samples on 65 of 97 potentially exposed and control white males, and semen samples from a subset of 15 were analyzed. No gross abnormalities or clinically meaningful differences in hematological or fertility indices were noted. Decreased testicular size was reported in workers (who were exposed to an 8-hour TWA concentration of 0.42 ppm EGME or less) but it was not statistically significant (Cook *et al.*, 1982).

Cullen *et al.* (1983) studied possible bone marrow toxicity of workplace substances including dipropylene glycol monomethyl ether, EGME, and various aliphatic, aromatic and halogenated hydrocarbons used for offset and ultraviolet cured multicolor printing. Evaluation of seven co-workers of a printer with aplastic anemia indicated normal peripheral blood, but bone marrow specimens demonstrated clear patterns of injury in three while the others had nonspecific signs of marrow effect. The authors could not assign the changes to known risk factors and concluded that further evaluation of possible bone marrow toxicity resulting from exposure to glycol ethers and ultraviolet curing printing processes was warranted. This was done to some extent in their studies on shipyard painters below.

Welch and Cullen (1988) evaluated shipyard painters exposed to ethylene glycol ethers (EGEE and EGME). Air concentrations at the workplace were estimated based on 102 samples over six shifts in Sparer *et al.* (1988). Time-weighted average (TWA) exposures to EGEE ranged from 0 to 80.5 mg/m³ with a mean of 9.9 mg/m³. TWA exposures to EGME ranged from 0 to 17.7 mg/m³ (mean = 2.6 mg/m³). The authors note that during the time period of measurement, painting activities were unusually low and previous NIOSH analyses indicated considerably higher exposures. Ninety-four painters and 55 controls answered a medical and environmental exposure questionnaire including work history and provided blood, urine, and in some cases semen samples. Mean hemoglobin levels, total cell counts and differential counts did not differ between exposed and control. However, the authors found that the lowest quartile of hemoglobin was mostly painters and the lowest polymorphonuclear leukocyte counts were in painters. Nine painters were considered anemic and five were considered granulocytopenic. The authors note that the absence of a significant difference in the group as a whole and the inability to detect a dose-response pattern in the exposed group makes a strong conclusion unwarranted.

Welch *et al.* (1988) evaluated the semen samples from the workers in the cohort from Welch and Cullen (1988). Sperm concentration, velocity, motility, morphology, morphometry, and viability were measured. Although not statistically significant, the measures of sperm count tended to be lower in the painters with a $p = 0.10$ for density and $p = 0.11$ for count. When nonsmokers were analyzed separately from smokers, the number of oligospermic painters was larger than that in controls at $p = 0.05$. There was no difference between controls and exposed men who were smokers. The authors state that although mean values of sperm count did not differ significantly between controls and exposed groups, biologically important differences were seen when the proportion of men with oligospermia was examined. The proportion of painters with azoospermia was 5% with only 1% expected based on other population surveys. The authors note that to create a dose-response model for an effect of glycol ethers on semen parameters would require description of the exposure of each individual 3 to 6 months prior to sampling.

The painters moved frequently from one exposure area to the next, making exposure assessment particularly difficult in this cohort.

Cullen *et al.* (1992) conducted a histopathologic analysis of the bone marrow and circulating blood cells in the workers previously examined in Welch *et al.* (1988). The objects of the study included : 1) to exclude other causes for granulocytopenia and depressed hemoglobin levels noted in some painters exposed to ethylene glycol ethers, 2) to determine if subclinical evidence of hematologic damage is present in healthy coworkers, and 3) to identify host or exogenous factors which may increase the risk of hematologic damage in glycol ether exposed painters. Workers were grouped as follows: Group I consisted of those painters that had anemia or granulocytopenia in the Welch and Cullen (1988) study; Group II consisted of exposed painters with normal hematology; Group III consisted of unexposed controls. A battery of hematologic and biochemical parameters were measured and a questionnaire was completed to determine occupational exposure status, health status and drug and alcohol consumption. All hematologic parameters were normal in all groups. Tests of liver, renal, and thyroid function were normal in all groups. Bone marrow histology showed no differences between groups. One biochemical parameter, pyruvate kinase activity, was lower in Group I than Groups II and III ($p = 0.05$). Depression of red cell pyruvate kinase did not vary by race and was lower in every subject in Group I by more than one standard deviation. Low pyruvate kinase is the most consistent red cell enzyme defect noted in acquired hematologic disorders.

Reversible neurological symptoms (apathy, fatigue, decreased appetite) and macrocytic anemia were observed in a worker following occupational dermal and inhalation exposure to an average concentration of 35 ppm EGME for 1-1.5 years (Cohen, 1984). The worker was also exposed to methyl ethyl ketone and propylene glycol monomethyl ether at concentrations of 1-5 ppm and 4.2-12.8 ppm, respectively.

Hematologic effects were also reported in three women employed in a factory working with glue consisting of 70% acetone and 30% EGME (Larese *et al.*, 1992). The women exhibited abnormally low white blood cell counts, relative lymphocytosis and macrocytosis. These hematological parameters returned to normal following cessation of exposure.

Older case reports support findings of neurological and hematological toxicity following occupational exposure to EGME (Greenburg *et al.*, 1938; Zavan, 1963; Parsons and Parsons, 1938).

V. Effects of Animal Exposure

A concentration dependent decrease in testes weight was observed in male rabbits exposed to 30, 100, or 300 ppm EGME 6 hours per day, 5 days per week for 13 weeks (Miller *et al.*, 1983). Degenerative changes in the germinal epithelium were observed in male rabbits of all exposed groups, but were not statistically significant at 30 ppm. Two of five male rabbits exposed to 300 ppm EGME died during the course of the study. Female rabbits were also exposed; two of five female rabbits exposed to 100 or 300 ppm EGME died during the course of the study. The animals died at different times of different causes and thus the authors were uncertain if the

deaths were treatment related. Reduced body weight gain, pancytopenia (abnormal depression of all the cellular elements of the blood), and thymic atrophy were observed in rabbits of both sexes exposed to 300 ppm EGME. No effects on the reproductive organs of the female rabbits were observed.

In the same study (Miller *et al.*, 1983) male and female rats were exposed to 30, 100, or 300 ppm EGME 6 hours per day, 5 days per week for 13 weeks. Moderate to severe degeneration of the germinal epithelium and seminiferous tubules was observed in male rats exposed to 300 ppm EGME. A significant decrease in body weight was observed in male rats exposed to 300 ppm and in female rats exposed to concentrations of EGME of 100 ppm or greater. Pancytopenia, lymphoid tissue atrophy, and decreased liver weights were observed in animals of both sexes exposed to the highest concentration. Also in the highest exposure group, mean values for total serum protein, albumin and globulins were lower than control values.

Doe *et al.* (1983) designed a two-part study to provide a rapid assessment of the effect of glycol ethers on some aspects of reproduction in the rat. Exposure to EGME was by inhalation at 100 and 300 ppm for 6 hr/day. First, pregnant females were exposed on Days 6 to 17 of gestation. Body weight gain was reduced in both groups. No litters were delivered in the 300-ppm group and only 9/20 rats in the 100-ppm group produced litters; the number, weight, and viability of the pups were reduced, but the pups appeared normal externally. Second, male rats were exposed for 10 days. There was a reduction in testicular weight accompanied by seminiferous tubular atrophy in the 300-ppm group. There were no effects at 100 ppm. Exposure at 300 ppm EGME caused significant reductions in white blood cell count, red blood cell count, hemoglobin concentration, hematocrit, and mean cell hemoglobin.

More recent data point to the immune system as a key endpoint of EGME toxicity. A statistically significant dose-related decrease in thymus weight was observed both in male rats administered drinking water containing 2000 and 6000 ppm EGME (161 or 486 mg/kg/day) and in female rats administered drinking water containing 1600 and 4800 ppm EGME (200 or 531 mg/kg/day) for 21 days (Exon *et al.*, 1991). Histopathological examination revealed thymic atrophy and loss of demarcation between the cortex and medulla. Decreased spleen cell numbers were observed in female rats at both dose levels and male rats at the high dose level. Male rats in the high dose group exhibited a statistically significant decrease in body weight gain. Testicular effects were also observed in exposed male rats.

Pregnant mice were exposed to 100, 150, or 200 mg/kg/day EGME on days 10-17 of gestation (Holladay *et al.*, 1994). Thymic atrophy and inhibition of fetal thymocyte maturation were observed in EGME-treated offspring examined on day 18 of gestation. Also, the ability of the EGME-treated fetal mouse liver cells to repopulate the spleen of irradiated mice was significantly impaired as compared to that of control fetal mouse liver cells.

VI. Derivation of Reference Exposure Level

<i>Study</i>	Miller <i>et al.</i> , 1983; U.S. EPA, 1995
<i>Study population</i>	Rats and rabbits
<i>Exposure method</i>	Inhalation (0, 30, 100, or 300 ppm)
<i>Critical effects</i>	Decreased testes weight and degenerative changes in the testicular germinal epithelium.
<i>LOAEL</i>	100 ppm
<i>NOAEL</i>	30 ppm
<i>Exposure continuity</i>	6 hours/day, 5 days/week
<i>Average experimental exposure</i>	5.4 ppm for NOAEL group
<i>Human equivalent concentration</i>	5.4 ppm for NOAEL group (gas with systemic effects, based on RGDR = 1.0 using default assumption that $\lambda(a) = \lambda(b)$)
<i>Exposure duration</i>	13 weeks
<i>LOAEL uncertainty factor</i>	1
<i>Subchronic uncertainty factor</i>	10
<i>Interspecies uncertainty factor</i>	3
<i>Intraspecies uncertainty factor</i>	10
<i>Cumulative uncertainty factors</i>	300
<i>Inhalation reference exposure level</i>	0.02 ppm (20 ppb; 0.06 mg/m ³ ; 60µg/m ³)

The REL is based on the same study on which U.S. EPA based its RfC. However, OEHHA declined to use a modifying factor because the criteria for use of such factors are not well described by U.S. EPA. However, since rabbits were the more sensitive species and live 6 years (312 weeks), a 13 week study in rabbits merits a subchronic UF of 10.

A comparison with the proposed REL for EGME of 20 ppb (60 µg/m³) can be made using the occupational study of Welch *et al.* (1988) of the semen of shipyard painters exposed to both EGEE and EGME. The men supplied demographic characteristics, medical conditions, personal habits, and reproductive history; underwent a physical examination; and provided a semen sample. The painters were exposed to EGEE at a TWA concentration of 0 to 80.5 mg/m³ (mean = 9.9 mg/m³, and to EGME at a TWA concentration of 0 to 17.7 mg/m³ (mean = 2.6 mg/m³). The painters had an increased prevalence of oligospermia and azoospermia and an increased odds ratio for a lower sperm count per ejaculate compared to shipyard employees who were not painters. (The results were controlled for smoking.) Adding the mean exposure levels together results in a total glycol ether concentration (EGME + EGEE) of 12.5 mg/m³, equivalent to a continuous exposure of 4.5 mg/m³. Division by a UF of 10 for a LOAEL and by another of 10 for human intraspecies variability results in a REL of 40 µg/m³ (10 ppb), similar to the REL based on rabbits. Since exposure was primarily to EGEE with co-exposure to EGME, and exposure assessment was difficult to quantify, this study was not deemed suitable for developing a REL. Nonetheless, the REL developed using this study is close in value to the proposed REL of 20 ppb.

VII. Data Strengths and Limitations for Development of the REL

The strengths of the inhalation REL for EGME include the availability of subchronic inhalation exposure data from a well-conducted study with histopathological analysis and the observation of a NOAEL. In addition, there are a number of human studies showing similar toxicological endpoints to those demonstrated in animal studies. Major areas of uncertainty are the lack of adequate human exposure data, and the lack of chronic inhalation exposure studies.

VIII. References

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