CHRONIC TOXICITY SUMMARY

ETHYLENE GLYCOL MONOETHYL ETHER

(2-ethoxyethanol; EGEE)

CAS Registry Number: 110-80-5

I. Chronic Toxicity Summary

Inhalation reference exposure level	**70 µg/m^3 (20 ppb)**
Critical effect(s)	Testicular degeneration and decreased hemoglobin in rabbits
Hazard index target(s)	Reproductive system; hematopoietic system

II. Chemical Property Summary (from HSDB, 1996; 1999)

Description	Colorless liquid; sweet, pleasant, ether-like odor
Molecular formula	$C_4H_{10}O_2$
Molecular weight	90.12
Boiling point	135°C
Vapor pressure	3.8 torr @ 20°C; 5.31 torr at 25°C
Solubility	Miscible with water and organic solvents
Conversion factor	3.69 µg/m^3 per ppb at 25ºC

III. Major Uses and Sources

Ethylene glycol monoethyl ether (EGEE) is a widely used solvent for nitrocellulose, dyes, inks, resins, lacquers, paints, and varnishes (HSDB, 1996). It is also a component of many cleaning agents, epoxy coatings, paints, hydraulic fluid, and is an anti-icing fuel additive in aviation. EGEE is also a chemical intermediate in the production of another solvent, ethylene glycol monoethyl ether acetate. The specific annual statewide industrial emissions of EGEE from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 443,748 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 EGEE.)

IV. Effects of Human Exposure

Sperm quality was examined in 37 workers exposed to EGEE by skin contact and/or inhalation in two buildings (Clapp *et al.*, 1987; Ratcliffe *et al.*, 1989). Exposure levels ranged from undetectable to 24 ppm with an average exposure level of 6 ppm in one building and 11 ppm in the other. A statistically significant difference in mean sperm count was observed between the

37 exposed male workers and 39 unexposed male workers. Semen volume and pH, viability, motility, velocity, and morphology were not significantly different between the two groups. The primary metabolite of EGEE, ethoxyacetic acid, was identified in the urine of exposed but not control workers. Both exposed and control subjects had significantly lower sperm counts than historical controls. Furthermore, members of both groups may have been exposed to other compounds including metals, solvents, heat, and vibration.

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/m^3 with a mean of 9.9 mg/m^3. TWA exposures to EGME ranged from 0 to 17.7 mg/m^3 (mean = 2.6 mg/m^3). 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 make 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.

V. Effects of Animal Exposure

Sprague-Dawley rats (15/sex/group) and New Zealand white rabbits (10/sex/group) were exposed to 0, 25, 103, or 403 ppm EGEE by inhalation for 6 hours/days, 5 days/week, for 13 weeks (Barbee *et al.*, 1984). Animals were physically examined weekly and, at the end of the study, hematology, clinical chemistry, and histopathological examination were performed. No histopathological changes in the respiratory tract were found. Among rabbits, body weight was reduced in the high-dose group males and females. In the 25 ppm dose group, adrenal weight was reduced significantly among males, although this effect was not found to be dose-related. Among males in the high-dose group, testes weights were significantly reduced with a corresponding degenerative change to the seminiferous tubule epithelium. No effect on spermatogenic activity was found, however. Significant hematological effects observed at the high-dose included decreased hemoglobin, hematocrit, and erythrocyte count.

Teratologic effects in pregnant rats from the inhalation of EGEE were reported (Tinston *et al.*, 1983a). The results of this study were presented in summary form (Doe, 1984). Wistar rats (24/group) were exposed to target concentrations of 0, 10, 50, or 250 ppm EGEE for 6 hours/day during gestational days 6-15 and the animals were sacrificed on day 21. Maternal toxicity was observed in the high-dose group with decreased hemoglobin, hematocrit, and mean corpuscular volume. Significant increases in preimplantation loss occurred in the 10 and 50 ppm dose groups, however the absence of this effect at 250 ppm indicated a poor dose-response, and because implantation occurred on the first day of exposure, the relatedness of the effect to exposure is in question. Post-implantation loss was also increased in the mid-dose group, however, no corresponding decrease in intrauterine death was observed in this group. Minor skeletal defects, particularly delayed ossification, were widely observed in the fetuses of mothers exposed to 250 ppm EGEE. Delayed ossification of the cervical vertebrae and sternebrae and the presence of extra ribs was significantly increased in both the 50 and 250 ppm dose groups.

Teratologic effects on pregnant rabbits from inhalation exposure to EGEE were also reported (Tinston *et al.*, 1983b; also summarized by Doe, 1984). Dutch rabbits (24/group) were exposed to 0, 10, 50, or 175 ppm EGEE for 6 hours/day during gestational days 6-18, with sacrifice occurring on gestational day 29. There were no indications of maternal toxicity or litter effects. A statistically significant increase in minor defects and skeletal variants was found in fetuses in the 175 ppm dose group. Other slightly increased incidences of defects in the lower dose groups alone, including extra ribs and partial ossification of the vertebrae, were not considered treatment-related.

Behavioral teratogenic effects were examined in pregnant Sprague-Dawley rats (14 or 15/dose group) exposed to 0 or 100 ppm EGEE for 7 hours/day through gestational days 7-13 (early) or days 14-20 (late) (Nelson *et al.*, 1981). No maternal toxicity was observed and fetal weights were unchanged, although mean gestational length was increased in rats exposed on gestational days 14-20. Six tests (ascent, rotorod, open field, activity wheel, avoidance conditioning, and operant conditioning) were selected to measure motor, sensory, and cognitive function at several stages of development. The offspring of the rats exposed during days 7-13 exhibited impaired performance on the rotorod test (a test of neuromuscular ability) and increased latency in an open field test (a test of exploratory activity) as compared to controls. The offspring of rats exposed during days 14-20 of gestation exhibited decreased activity on an activity wheel (a test of circadian activity). Also, avoidance conditioning revealed that these pups received shocks of a greater number and duration than controls. Neurochemical differences between the prenatally exposed and control pups were measured in newborns and in pups 21 days of age. In newborns from both EGEE-exposed groups, total brain norepinephrine was decreased. In 21-day old pups of both groups, norepinephrine and dopamine levels in the cerebrum were increased. Serotonin level was increased in the cerebrum of the late exposure group only. The authors concluded that there were behavioral and neurochemical alterations in offspring of rats following prenatal exposure to 100 ppm EGEE, however the study design was inadequate to detect gross teratologic anomalies. In a dose range-finding study, two sets of pregnant rats (3-4/group) were exposed during the gestational days 7-13 or 14-20 to 0, 200 (late group only), 300, 600, 900, or 1200 ppm EGEE for 7 hours/day. Increased fetal and pup mortality was observed in all groups exposed to EGEE.

Behavioral and neurochemical effects on the offspring of pregnant S-D rats exposed to 0 or 200 ppm EGEE on gestational days 7-13 were reported (Nelson *et al.*, 1982a; Nelson *et al.*, 1982b). Pregnancy duration was significantly increased in exposed dams. Significantly increased levels of norepinephrine and dopamine were observed in the 21-day old offspring of EGEE-exposed animals. Behavioral changes in pups of treated dams included decreased neuromotor ability and decreased activity.

An investigation into teratologic effects of EGEE was conducted by exposing pregnant rats and rabbits to EGEE by inhalation on gestational days 0-19 (Andrew *et al.*, 1981). Rats (37/group) were exposed to 0, 202, or 767 ppm EGEE for 7 hours/day. All fetuses were resorbed and maternal weight gain was reduced in the high-dose group. In the mid-dose group, a decrease in fetal weight and size (crown-rump length) was observed. Minor skeletal defects and variants and cardiovascular defects were increased in the mid-dose group. Rabbits (29/group) were exposed to 0, 16, or 617 ppm EGEE for 4 hours/day. Maternal weight gain and food intake were decreased in exposed animals. The incidence of fetal resorptions was increased in both the mid- and high-dose group animals. Major cardiovascular defects and minor skeletal defects (extra ribs, delayed ossification) were significantly increased in the mid-dose group. Andrew *et al.* (1981) also examined reproductive effects by exposing female Wistar rats (37/group) to 1, 150, or 649 ppm EGEE 7 hours/day, 5 days/week for 3 weeks before mating with untreated males. No significant effects were observed.

VI. Derivation of Reference Exposure Level

Study	Barbee *et al.*, 1984
Study population	Rabbits
Exposure method	Discontinuous inhalation
Critical effects	Testicular degeneration and decreased hemoglobin levels
LOAEL	403 ppm
NOAEL	103 ppm
Exposure continuity	6 hr/day, 5 days/week
Exposure duration	13 weeks
Average experimental exposure	18.4 ppm (68 mg/m^3) for the NOAEL group
Human equivalent concentration	18.4 ppm (68 mg/m^3) for the NOAEL group (gas with systemic effects, based on RGDR = 1.0 using default assumption that lambda (a) = lambda (h))
Subchronic uncertainty factor	10
LOAEL uncertainty factor	1
Interspecies factor	10 (see explanation below)
Intraspecies factor	10
Cumulative uncertainty factor	1000
Inhalation reference exposure level	0.02 ppm (20 ppb, 0.07 mg/m^3 , 70 µg/m^3)

The reproductive effects observed in the subchronic inhalation study of Barbee *et al.* (1984) were determined by the US EPA (U.S. EPA, 1990) to be the most sensitive endpoints due to EGEE exposure and resulted in a reference concentration (RfC) of 0.2 mg/m^3 (0.06 ppm). OEHHA staff concurred regarding the basis of the U.S. EPA RfC but differed in the application of the interspecies uncertainty factor. Reduced testes weight and testicular degeneration were found in rabbits exposed to EGEE at 403 ppm for 13 weeks. Changes in hematological parameters including decreased hemoglobin, hematocrit, and erythrocyte count were also observed at this dose. A gas:extrarespiratory effect ratio of 1.0 was used to calculate a human equivalency concentration (HEC) in the absence of information relating the effect in rabbits relative to humans.

For a comparison with the proposed REL of 60 ppb (200 µg/m^3) based on testicular degeneration, a REL can be calculated from the LOAEL of 202 ppm observed in the teratology study of Andrew *et al*. (1981). The 7 hour exposure to 202 ppm is time-adjusted to a continuous exposure of 59 ppm. Using a RGDR of 1 for a systemic effect, a UF_L of 10, a UF_A of 3 and a UF_H of 10 results in an estimated REL of 200 ppb (700 µg/m^3). Nelson *et al*. (1981) found a LOAEL of 100 ppm for neurobehavioral developmental toxicity in rats exposed 7 hours per day on days 7 to 13 of gestation. The equivalent continuous exposure is 29 ppm. Using an RGDR of 1, a LOAEL UF of 10, an interspecies UF of 3, and an intraspecies UF of 10 results in a REL of 100 ppb (400 µg/m^3).

Although reproductive toxicity has been reported in male workers occupationally exposed to EGEE (Clapp *et al.*, 1987; Ratcliffe *et al.*, 1989), potential confounding factors, particularly

exposure to other compounds, make the study inadequate for the development of the reference exposure level. However, for another comparison with the proposed REL of 60 ppb, if only EGEE caused the adverse reproductive effect, use of a mean concentration between the 2 buildings of 8 ppm for workplace exposure, extrapolation to an equivalent continuous exposure of 3 ppm, and division by 10 for a LOAEL (serious effect) and 10 for intraspecies variability result in a REL of 30 ppb (100 $\mu g/m^3$).

Another comparison with the proposed REL of 60 ppb can be made using the study of Welch *et al*. (1988), who studied shipyard painters exposed to both EGEE and EGME. The authors examined the semen of 73 painters and 40 non-exposed shipyard employees. The men supplied demographic characteristics, medical conditions, personal habits, and reproductive history; underwent a physical examination; and provided a semen sample. An industrial hygiene survey showed that the painters were exposed to EGEE at a time-weighted average (TWA) concentration varying from 0 to 80.5 mg/m^3 (mean = 9.9 mg/m^3, and to EGME at a TWA concentration varying from 0 to 17.7 mg/m^3 (mean = 2.6 mg/m^3). The painters had an increased prevalence of oligospermia and azoospermia and an increased odds ratio for a lower sperm count per ejaculate. (The results were controlled for smoking.) Adding the mean levels together results in a total glycol ether concentration of 12.5 mg/m^3, which is equivalent to a continuous exposure of 4.5 mg/m^3. Division by a UF of 10 for a LOAEL and by another of 10 for intraspecies variability results in a REL of 40 $\mu g/m^3$ (10 ppb). A similar REL would be calculated using the report by Cullen *et a*l. (1992) of depression in red cell pyruvate kinase among anemic and granulocytopenic painters. Since exposure in these studies was to both EGEE and EGME, and exposure assessment was made difficult by frequent job movement and other factors, these studies were not deemed suitable for developing a REL. However, the possibility that humans are more susceptible to EGEE toxicity is raised by the series of studies by Welch *et al*. (1988) and Welch and Cullen (1988) such that we have deviated from the RfC and opted to use an interspecies uncertainty factor of 10 rather than 3 as would usually be the case with an HEC adjustment.

VII. Data Strengths and Limitations for Development of the REL

The strengths of the inhalation REL for EGEE include the availability of subchronic inhalation exposure data from a well-conducted study with histopathological analysis, and the observation of a NOAEL. The observation in several studies noted above of both hematological abnormalities and sperm abnormalities in exposed workers, although difficult to use in a quantitative risk assessment, provide support for the REL developed from animals. In addition, several comparative calculations indicate that RELs based on other studies are generally in agreement with that based on Barbee *et al*. (1984). 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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