Appendix B
Section H

ETHYLENE GLYCOL
HEALTH-BASED MAXIMUM CONTAMINANT LEVEL
SUPPORT DOCUMENT

Office of Science and Research

New Jersey Department of Environmental Protection

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EXECUTIVE SUMMARY

Ethylene glycol is commonly used in both industrial and consumer applications. Man appears to be more sensitive than experimental animals to the acute effects of ethylene glycol on the kidney, nervous system, and other organs. Chronic exposure of animals to ethylene glycol results in renal toxicity. Recently, ethylene glycol was found to be teratogenic in rats and mice. The no-observed-adverse-effect level (NOAEL) for this effect has not been determined. A maximum contaminant level (MCL) of 290 ug/L in drinking water was derived for ethylene glycol to protect against renal damage.

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BACKGROUND INFORMATION AND PROPERTIES

Chemical Properties (Rowe and Wolf, 1981)

Chemical name	Ethylene glycol
Synonym	1,2-Ethanediol
CAS number	107-21-1
Chemical Formula	$C_2H_6O_2$
Chemical structure	$HO-CH_2-CH_2-OH$
Molecular weight	62.07
Physical state	slightly viscous liquid
Melting point	-13 ^{o}C
Boiling point	198 ^{o}C
Vapor pressure	0.06 mm Hg at 20 ^{o}C
Specific gravity/density	1.11 at 4 ^{o}C and 20 ^{o}C
Odor threshold (air)	25 ppm (Verschueren, 1983)
Solubility	miscible with water
Conversion factor	1 ppm = 2.54 mg/m^3

Production and Use

Major methods of production of ethylene glycol are hydration of ethylene oxide and oxidation of ethylene with acetic acid followed by hydrolysis (Rowe and Wolf, 1981). In 1983, 4.5 billion pounds of ethylene glycol were produced (U.S. ITC, 1984).

Ethylene glycol is used as antifreeze, as a chemical intermediate as a solvent, as an industrial humectant, as a heat exchanger, and in other ways (Merck Index, 1976; Rowe and Wolf, 1981).

Guidelines, Regulations, and Standards

The ceiling limit threshold limit value determined by American Conference of Governmental Industrial Hygienists (ACGIH) is 50 ppm. Use of ethylene glycol as an indirect food additive is permitted under the Food Additive Regulations of the Federal Food, Drug and Cosmetic Act (HSDB, 1986).

The U.S.EPA (1985) has suggested one-day and longer-term Health Advisories of 19.0 mg/L and 5.5 mg/L, respectively, for a 10 kg child and a longer term Health Advisory of 19.25 mg/L for a 70 kg adult.

ENVIRONMENTAL EXPOSURE

Fate and Transport

Ethylene glycol can be released into water or onto land during production, use, or improper disposal. Adsorption on soil is expected to be low. Ground water contamination has resulted from releases onto land (HSDB, 1986).

Ethylene glycol's low vapor pressure limits its entry into the atmosphere (U.S. EPA, 1985). Atmospheric ethylene glycol would return to earth in rain, and is expected to photo-oxidize rapidly, as do other alcohols (HSDB, 1986).

Ethylene glycol is readily biodegradable in water under aerobic and anaerobic conditions with a half-life of several days. Because of the compound's low octanol/water partition coefficient, bioconcentration in aquatic organisms is not expected (HSDB, 1986).

Ambient Levels

No information is available about environmental concentrations of ethylene glycol. The compound is not currently being monitored under the A-280 testing program.

METABOLISM AND PHARMACOKINETICS

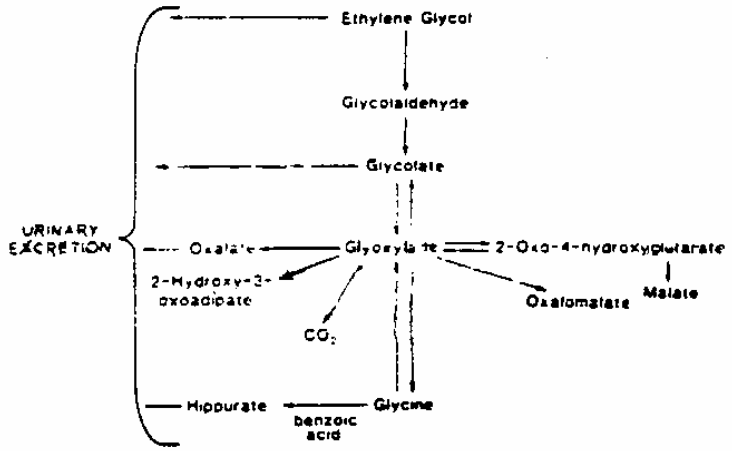
Absorption, Distribution, and Excretion

Ethylene glycol is rapidly absorbed after oral administration (Reif, 1950). Absorption by inhalation (Marshall and Cheng, 1983) and through the skin (Hanzlik et al., 1947) can also occur. The compound is rapidly distributed throughout the body water.

The major routes of elimination are urinary excretion of the parent compound and metabolites, and pulmonary expiration of CO_2 derived from ethylene glycol degradation. Fecal elimination is limited (2% or less) (Marshall, 1982). Values for plasma half-life following a large oral dose in man range from 2 to 6 hours (Reif, 1950; Winek, 1975; Peterson et al., 1981).

Metabolism

The major pathways in the metabolism of ethylene glycol are shown below (Marshall, 1982). Metabolism occurs primarily in the liver and kidney.



The conversion of ethylene glycol to glycoaldehyde by alcohol dehydrogenase and the conversion of glycolate to glyoxylate by glycolic acid oxidase are rate-limiting steps, accounting for the presence of ethylene glycol and glycolate in urine. In contrast, glycoaldehyde and glyoxylate are quickly metabolized and do not accumulate in blood or urine (Chou and Richardson, 1978).

Oxalates are formed by oxidation of glyoxylate. Urinary oxalate levels vary between species; in man, 2.3% of the ingested dose was excreted as urinary oxalates (Reif, 1950).

The toxicity of ethylene glycol has traditionally been attributed to oxalates, which precipitate readily as calcium oxalate. However, more recent evidence suggests that other metabolites are primarily responsible for toxicity, with oxalates making only a minor contribution. Glyoxylate and glycolate have renal and central nervous system (CNS) effects similar to those produced by ethylene glycol, and ethylene glycol toxicity in the absence of oxalate crystallization has occurred (Parry and Wallach, 1974).

Several workers have suggested that glycolate is the intermediate responsible for ethylene glycol toxicity (Clay and Murphy, 1977; Chou and Richardson, 1978; Marshall, 1982). In studies involving administration of pyrazole, an inhibitor of alcohol dehydrogenase, a direct correlation was observed between mortality and urinary glycolate concentrations in ethylene glycol treated rats (Chou and Richardson, 1978).

The disposition of ethylene glycol varies with the dose given (Marshall, 1982). As the dose increases, a greater percentage of it is excreted as glycolate and the percentage expired as CO_2 decreases. This is due to the body's limited capacity for glycolate metabolism. In this regard, Marshall (1982) has suggested that caution be used in extrapolating the health effects due to long-term, low-level exposure from toxicity observed at high doses.

Human Exposure and Body Burden

Human exposure results primarily from contact with antifreeze solutions and with water into which ethylene glycol has been spilled (USEPA, 1985). Few reports of effects due to occupational exposure exist (Rowe and Wolf, 1981). Inhalation exposure becomes important only when the compound is heated or under pressure; such a situation is possible when ethylene glycol is used as a heat-transfer fluid in solar heaters, a relatively new application (Marshall and Cheng, 1983).

HEALTH EFFECTS

Overview

Acute exposure to ethylene glycol causes severe neurological effects, cardiopulmonary failure, oxalate deposition in kidneys and CNS, and renal failure in humans and animals. Humans appear to be more sensitive than experimental animals are to these acute effects. Chronic exposure has been associated with oxalate deposition in the kidney and the brain and with renal and hepatic damage. Reproductive and developmental toxicity from ethylene glycol has recently been demonstrated in rats and mice.

Human

Almost all occurrences of human ethylene glycol toxicity result from intentional or accidental ingestion (Rowe and Wolfe, 1981). Humans are much more susceptible to the acute effects of ethylene glycol than are laboratory animals. The human oral lethal dose is about 1.4 g/kg (Merck Index, 1976) while oral LD_{50} values for laboratory animals range from 5 to 15 g/kg (Rowe and Wolf, 1981).

Human toxicity has been well reviewed by Parry and Wallach (1974). CNS effects (intoxication, neurological abnormalities such as loss of reflexes and seizures, ophthalmic manifestations) are evident shortly after ingestion, and edema and hyperemia of the brain are seen at autopsy. Metabolic acidosis, hypocalcemia, and oxalate crystalluria also occur

rapidly. Within 12 to 18 hours, cardiopulmonary failure associated with pulmonary edema and cardiac dilation and degeneration is seen. Renal failure accompanied by tubular degeneration becomes evident at 36 to 48 hours.

Animal

Acute. The reported LD_{50} values for ethylene glycol administered orally to laboratory animals have been summarized by Rowe and Wolf (1981). These are for the mouse, 8-15 g/kg; for the rat, 5-13 g/kg; for the guinea pig, 7-11 g/kg; for the rabbit, 5 g/kg.

Chronic. Several investigations of the chronic effects of ethylene glycol have been undertaken.

Blood et al. (1962) administered ethylene glycol to two male rhesus monkeys and one female rhesus monkey in their diet for three years. The two males were of different weights and received 0.2% of the compound in their diet:25 to 32 mg/kg per day and 55 to 69 mg/kg per day. The female's diet contained 0.5% ethylene glycol, resulting in a dose of 135 to 170 mg/kg per day. No significant gross or microscopic changes were observed at autopsy.

Morris et al. (1942) observed increased mortality, calcium oxalate bladder stones, kidney injury, and centrilobular hepatic degeneration in male and female albino rats given 1% and 2% ethylene glycol in their diet for two years.

Blood gave Sprague-Dawley rats (16 per group per sex) diets containing 0.1%, 0.2%, 0.5%, 1%, and 4% ethylene glycol for two years. Increased mortality was observed in males given 1% and 4% and in females given 4%. Decreased kidney, liver, and lung weights at autopsy were seen in males given 0.1% and above; these changes were not statistically significant, probably due to the small number of animals surviving until termination at two years. A dose-dependent increase in the number of animals with renal oxalate deposition occurred at 0.5% and above in males and 1% and above in females. Degeneration of the renal tubular epithelium was observed in treated, but not control, rats. However, the ethylene glycol levels which caused these changes were not reported. The authors concluded that the no effect level of ethylene glycol in the diet is 0.2% or less (Blood, 1965).

In a recent subchronic study (Melnick, 1984), ethylene glycol was administered to Fischer 344/N rats and $B6C3F_1$ mice for 13 weeks (10 per sex per dose per species) as 0.32%, 0.63%, 1.25%, 2.5% and 5.0% of their diet. No treatment-related effects occurred at 1.25% or below. Male rats given 2.5% and 5% showed increases in kidney/body weight ratio, blood urea nitrogen, and blood creatinine, as well as nephrotic changes and renal oxalate deposition; the 5% group had oxalate crystal deposition in the brain. Nephrotic changes occurred in female rats given 5%. No effects were seen in female mice, while male mice given 2.5% and 5% exhibited nephrotic changes and centrilobular liver degeneration.

Reproductive, Embryotoxic, and Teratogenic

Recent studies have demonstrated that ethylene glycol causes adverse reproductive effects, is embryotoxic, and teratogenic. Lamb et al. (1985) utilized a continuous breeding protocol to evaluate the effects of 0.25%, 0.5%, and 1% ethylene glycol in drinking water on CD-1 mice. During a 14-week cohabitation period, mice given 1% ethylene glycol exhibited a slight but significant decreases in the number of litters per pair, the number of live pups per litter, and the mean live-pup weight; no significant effects were seen in the 0.25% or 0.05% groups. Exposure to water containing 0% or 1% ethylene glycol was continued only in the F_1 offspring from the control and in the 1% F_0 groups. Unusual facial features and multiple skeletal defects were observed in the treated (1%), but not in the control F_1 animals. The reproductive performance of the control and 1% F_1 mice was evaluated. Fertility, number of live pups per litter, and live-pup weight were reduced in the treated group, but none of these effects was statistically significant.

Price et al. (1985) conducted a teratogenicity study in CD rats and CD-1 mice (20 or more per dose). Rats were given 1250, 2500, or 5000 mg/kg and mice were given 750, 1500, or 3000 mg/kg ethylene glycol by gavage on days 6 through 15 of gestation. The incidence of malformations significantly increased at all dose levels in both rats and mice. The number of malformations was dose-dependent with over 95% of the litters affected at the highest dose. A variety of malformations occurred, with craniofacial, neural tube, and skeletal defects most common. Fetal body weight was significantly reduced in all groups except in mice given 750 mg/kg. Increased post-implanatation losses were seen in rats dosed with 5000 mg/kg. The only observed maternal effect was a slight decrease in weight gain.

Maronpot et al. (1983) detected only an increased incidence of poorly ossified and unossified vertebrae in Fischer 344 rats given 1000 mg/kg ethylene glycol on days 6 through 15 of gestation. No effects were seen in rats given 200 mg/kg and 40 mg/kg.

Genetic

Ethylene glycol has been found to be nonmutagenic in the Ames test, both with and without microsomal activation, in a number of S. tymphimurium strains (McCann et al., 1975; Clark et al., 1979).

Carcinogenicity

No treatment-related tumors were observed when Fischer 344 rats were injected subcutaneously with doses up to 1000 mg/kg twice weekly for one year and then held for six months prior to sacrifice (Mason et al., 1971). Additionally, no treatment-related tumors were seen in the chronic studies by (Blood et al., 1962; Blood, 1965; Morris et al., 1942).

QUANTITATIVE RISK ASSESSMENT

Studies Useful for Risk Assessment

Three studies were considered for use in quantitative risk assessment. For each of these, the daily dose in mg/kg was calculated.

Lamb et al. (1985), using a continuous breeding protocol, detected reproductive effects in mice given 1% ethylene glycol in drinking water; no effects were seen at 0.5%. The no-observed-adverse-effect-level (NOAEL) can be estimated as follows:

Weight of animals at conclusion of 14 week cohabitation: 40 g
Water consumption per day (average for 0.5% group): 6.3 g

$$\frac{6.3 \text{ g/day} \times 5 \text{ mg/g}}{0.04 \text{ kg}} = 787 \text{ mg/kg/day}$$

In the teratogenicity study conducted in rats and mice by Price et al. (1985), a dose-dependent increase in the number of malformations occurred in both species, with significant increases observed at the lowest dose tested in each species (750 mg/kg in mice and 1250 mg/kg in rats). Therefore, the NOAEL cannot be determined. When only a lowest-observed adverse-effect-level (LOAEL) is available, a factor of 10 is used to estimate a NOAEL. Therefore, the LOAEL of 750 mg/kg would convert to a NOAEL of 75 mg/kg.

In the chronic study conducted by Blood (1965), male and female rats were fed varying concentrations of ethylene glycol in their diet for two years. Oxalate crystal deposition was observed in males given 0.5% and above and in females given 1% and above. No deposition occurred at 0.2% or below. The NOAEL for ethylene glycol in the male rats can be estimated as follows:

Maximum weight of animals during study (Blood, 1965): 575 g (maximum used for conservatism).

Daily food consumption of adult male rats (Purina Mills, Inc): 12-15 g (minimum [12 g] used for conservatism).

$$\frac{12 \text{ g/day} \times 2 \text{ mg/g}}{0.575 \text{ kg}} = 42 \text{ mg/kg/day}$$

The study conducted by Blood (1965) was chosen for risk assessment because no other study reported adverse effects at doses lower than the NOAEL reported in this study. The NOAEL for oxalate deposition of 42 mg/kg was used to calculate the maximum contaminant level (MCL).

Calculation of the Health-Based Maximum Contaminant Level

$$\text{Acceptable Daily Intake (ADI)} = \frac{42 \text{ mg/kg/day}}{100 \times 10} = 0.042 \text{ mg/kg/day}$$

where:

42 mg/kg/day = NOAEL

100 = Uncertainty factor appropriate for use with a NOAEL from a chronic animal study.

10 = Additional uncertainty factor used because of the quality of the data (see below)

$$\text{MCL} = \frac{(0.042 \text{ mg/kg/day})\ (0.2)\ (70 \text{ kg})}{2 \text{ L/day}} = 0.029 \text{ mg/L} = 290 \text{ ug/L}$$

where:

0.042 mg/kg/day = ADI

70 kg = assumed weight of human adult

0.2 = contribution from drinking water alone

2 L/day = assumed daily drinking water consumption

Assumptions and Uncertainties

Several uncertainties exist with regard to the study by Blood (1965) used to calculate the MCL. These uncertainties necessitate the use of an additional safety factor of 10.

1. Decreased kidney, liver, and lung weights were observed in males at all doses, including 0.1%, the lowest level tested. These changes were not statistically significant, probably because of the small number of animals per group, and therefore could not be used for MCL calculations.

2. It is stated in the paper that degeneration of the renal tubular epithelium was consistently seen in treated, but not in control animals. The dose levels at which these effects occurred are not reported; therefore it is not known if such changes were observed at levels below those causing oxalate deposition. More recent research suggests that renal toxicity can occur without oxalate

deposition and that glycolate may be responsible (Clay and Murphy, 1977; Chou and Richardson, 1978; Marshall, 1982).

The NOAEL for fetal malformations has not been determined. At the lowest dose tested, 750 mg/kg in mice, 10% of the fetuses and 67% of the litters were affected, as compared to 0.25% of fetuses and 4% of litters in controls. Future evaluation of teratogenicity at lower doses is required.

It is assumed that a 70 kg adult consumes 2 liters of drinking water consumed per day and 20% of the exposure to ethylene glycol is through drinking water.

Conclusions

A health-based maximum contaminant level for ethylene glycol in drinking water of 290 ug/L has been derived, based on renal toxicity in chronically exposed rats.

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