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ETHYLENE GLYCOL

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

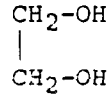
Health Advisories are developed for One-day, Ten-day, Longer-term (approximately 7 years, or 10% of an individual's lifetime) and Lifetime exposures based on data describing noncarcinogenic end points of toxicity. Health Advisories do not quantitatively incorporate any potential carcinogenic risk from such exposure. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

This Health Advisory is based upon information presented in the Office of Drinking Water's Health Advisory Document for Ethylene Glycol (U.S. EPA, 1981). The 1981 Health Advisory is available for review at each EPA Regional Office of Drinking Water counterpart (e.g., Water Supply Branch or Drinking Water Branch).

II. GENERAL INFORMATION AND PROPERTIES

CAS No. 107-21-1

Structural Formula



Synonyms

1,2-ethanediol

Uses

- Antifreeze in cooling and heating systems, industrial humectant, ingredient of electrolytic condensers, solvent in paint and plastic industries and in the formulation of ink.

Properties (Verschueren, 1977; Windholz, 1983)

Chemical Formula	$C_2H_6O_2$
Molecular Weight	62.1
Physical State	colorless liquid
Boiling Point	197.6°C
Melting Point	-12.6°C
Density	--
Vapor Pressure	0.05 mm (20°C)
Specific Gravity	1.113 (20°C)
Water Solubility	completely miscible
Log Octanol/Water Partition Coefficient	--
Taste Threshold	--
Odor Threshold	--
Conversion Factor	

Occurrence

- In 1983, 4.5 billion pounds of ethylene glycol were produced (U.S. ITC, 1984). The majority of ethylene glycol is used consumptively (CEH, 1983).

- Releases of ethylene glycol to the environment can occur during production, use and release. The major source of release is from the disposal of used antifreeze. Releases of ethylene glycol occur

largely to water and land during disposal; releases to the atmosphere are limited by ethlyene glycol's low vapor pressure. Releases of ethylene glycol to the environment are dispersed widely.

° Ethylene glycol in the environment rapidly partitions to water due to its solubility and low vapor pressure. Releases to surface water are biodegraded rapidly. Releases of ethylene glycol to land have resulted in the contamination of ground water (U.S. EPA, 1980). Based upon its physical properties, ethylene glycol is not expected to bioaccumulate.

° There is little information on the presence of ethylene glycol in water, food and air. Because of its rapid degradation in the environment, ethylene glycol is not expected to be a common contaminant in air, food or surface water; however, contamination of ground water is possible. A more likely source of ethylene glycol exposure is the inadvertant contamination of drinking water from the misuse of antifreeze.

III. PHARMACOKINETICS

Absorption

° Ethylene glycol is absorbed rapidly after ingestion. Reif (1950), on three separate occasions, drank pure ethylene glycol in 100 ml of water. Amounts consumed were 5.5, 11.0 and 13.2 g, which would correspond to 78.5, 157 and 188.6 mg/kg, respectively, assuming a body weight of 70 kg for an adult. Ethylene glycol was recovered in the urine at 24 to 31% of the administered dose within 24 to 48 hours. Oxalic acid concentrations in the urine were higher than normal with a peak on the fourth day.

Metabolism

° Gessner et al. (1961) studied the fate of ethylene glycol in Chinchilla rabbits, albino rats, guinea pigs and cats. Doses up to 10.0 g/kg of ethylene glycol ($^{14}C_2$) were given orally or subcutaneously, but most of the data were derived from animals receiving 0.1 to 2.0 g/kg (100 to 2000 mg/kg). At low doses (0.124 g/kg), rabbits exhaled about 60% of the dose as CO_2 and excreted 20% of it in the urine in a time period of 80 to 100 hours; 50% of the dose was exhaled as CO_2 in the first 18 hours after dosing. In one set of experiments with rabbits, urine contained ethylene glycol (10.3%), oxalic acid (0.01%) and urea (0.65%). Nearly one-half of the radioactivity was eliminated in the urine when the dose was increased to 2.5 to 5.0 g/kg. The increase in the radioactivity in the urine was attributed by the authors to unmetabolized ethylene glycol.

° In an *in vitro* experiment utilizing rat liver slices, Gessner et al. (1961) identified the intermediate metabolites of ethylene glycol (^{14}C) as glycoaldehyde and glyoxylic acid.

IV. HEALTH EFFECTS

Humans

- A controlled study of human exposure to ethylene glycol was reported by Reif (1950). The investigator drank 5.5, 11.0 and 13.2 g of ethylene glycol with 100 ml of water on separate occasions and collected his urine for about 14 days after each trial to quantify ethylene glycol and oxalic acid levels. Assuming a body weight of 70 kg, doses consumed would be 78.5, 157.0 and 188.6 mg/kg. Reif found that 24 to 31% of the ethylene glycol was excreted in the urine in an unchanged form within 24 to 36 hours, while urinary oxalic acid levels were elevated for 8 to 12 days. No oxalate crystals were found in the urine, and he reported no impairment of health from these doses.

- Ethylene glycol ingestion by humans results in a variety of CNS/behavioral effects including numbness, visual disturbances, lightheadedness, headache and lethargy (Berman et al., 1957), with doses estimated at 1,000 mg/kg. After ingesting a dose of approximately 3,000 mg/kg, patients exhibited ataxia, somnolence and slurred speech, followed by disorientation with a mental status alternating between stupor and agitation (Parry and Wallach, 1974). At doses which were eventually fatal, coma developed after a period of restlessness, delerium, convulsive seizures and a loss of reflexes (Pons and Custer, 1946). These same symptoms of ataxia, incoordination, somnolence, coma and eventual death have been reported in dogs (Nunamaker et al., 1971).

Animals

Short-term Exposure

- An extensive series of dose-mortality trials were conducted by Laug et al. (1939) for several species of laboratory animals. Mice, rats and guinea pigs were tested by administering single doses of ethylene glycol by stomach tubes. Calculated LD_{50} values were: mice, 13.1 ml/kg (14,253 mg/kg); rats, 5.5 ml/kg (5,984 mg/kg); guinea pigs, 7.35 ml/kg (7,997 mg/kg). It was noted that the animals showed signs of weakness and lack of motor coordination shortly after receiving doses of ethylene glycol. Prostration and coma were later symptoms, followed by death in 18 hours to 6 days. Congestion of the lungs, bladders filled with protein rich urine, hydropic degeneration of the cells lining the cortical convoluted tubules, and focal necrosis of the liver were nearly always found.

- NIOSH (1983-84) lists the following oral LD_{50} data for ethylene glycol: rat (4,700 mg/kg), mouse (7,500 mg/kg), guinea pig (6,610 mg/kg).

Long-term Exposure

- In a study by Blood et al. (1962) ethylene glycol was fed to two male rhesus monkeys and one female Rhesus monkey for three years. Ethylene

glycol was incorporated in the monkey chow and made available to the animals on an ad lib basis. The animals consumed 200 to 250 g of chow/day. From the given body weights of 15.45 and 7.25 kg for the males and 7.4 kg for the female, the amount of ethylene glycol consumed would range from approximately 25 to 69 mg/kg/day for males and 135 to 170 mg/kg/day for females. Prior to the start of the experiment, and at quarterly intervals, the animals were x-rayed to detect the possible appearance of calcification of the urinary tract. At the time of sacrifice all abdominal and endocrine organs, as well as a bone marrow sample, were examined histopathologically. No abnormal calcium deposits were demonstrated by x-ray; microscopic examinations of tissues were unremarkable. The authors concluded that this species was capable of handling the administered ethylene glycol without any discernible toxic effects.

- In a study by Blood (1965), ethylene glycol was fed to groups of 16 male and 16 female Sprague-Dawley rats for 2 years at concentrations of 0.0, 0.1, 0.2, 0.5, 1 or 4% by weight in the diet (corresponds to approximately 0, 50, 100, 250, 500 or 2,000 mg/kg/day (Lehman, 1959)). Increased mortality appeared in males receiving the 1 and 4% diets. Calcification of the kidneys and oxalate-containing calculi were observed in males at doses of 0.5% and greater. Females were similarly affected at the 1% level and greater for calcification and at the 4% level for calculi. Increased water consumption and protein in the urine was evident in males at both 1 and 4% and in females at 4% diet levels. A probable NOAEL of 0.2% was determined (approximately 100 mg/kg/day) and a LOAEL of 0.5% (approximately 250 mg/kg/day).

- A recently completed toxicity study in groups of 130 Fischer 344 rats per sex per level fed ethylene glycol at dosages of approximately 1.0, 0.2, 0.04 or 0.0 g/kg/day for up to 2 years (DePass et al., 1986a) identified a NOAEL of 0.04 g/kg/day (40 mg/kg/day). The mortality rate was increased in the high-dosed males with all dead by 475 days into the study. Oxalate nephrosis was the primary cause of death. Other effects noted in the high-dosed males only included: reduced body weight gain, increased water intake, increased BUN and creatinine, reduced RBCs, hematocrit and hemoglobin, increased neutrophil count, increased urine volume and reduced urinary specific gravity and pH. Additionally, all high-dosed rats had increased kidney weights and urinary calcium oxalate crystals. High-dosed females also showed the presence of uric acid crystals in the urine. Histopathological changes in the high-dosed males included tubular cell hyperplasia, tubular dilation and peritubular nephritis. At the next lower dose, 0.2 g/kg/day, an increase in incidence and amount of calcium oxalate crystals was evident in both sexes. It is apparent in this study that the male rat is more sensitive to the effects of ethylene glycol.

- These same authors treated 80 CD-1 mice per sex per level to the same concentrations of ethylene glycol in the diet and found no clinical or histopathological evidence of toxicity attributable to its intake.

Reproductive Effects

° Timed-pregnant CD rats were dosed by gavage on days 6 through 15 of gestation with ethylene glycol at 0, 1,250, 2,500 or 5,000 mg/kg/day (Price et al., 1985). No maternal deaths or distinctive clinical signs were noted. Significant decreases in maternal weight were dose-related in rats at all levels. Other significant changes included reduced gravid uterus weight, corrected gestational weight gain and reduced fetal body weight per litter at the mid and high doses and increases in post-implantation losses per litter, significant only at the high dose. This study established a LOAEL of 1,250 mg/kg/day for maternal effects and a NOAEL of 1,250 mg/kg/day for fetal effects.

° Timed-pregnant CD-1 mice were dosed by gavage on days 6 through 15 of gestation with ethylene glycol at 0, 750, 1,500 or 3,000 mg/kg/day (Price et al., 1985). No maternal deaths or distinctive clinical signs were noted. Significant decreases in maternal weight, gravid uterus weight and corrected gestational weight gain were evident at the mid and high doses. Fetal body weight per litter was also significantly reduced at all doses. This study established a NOAEL of 750 mg/kg/day for maternal effects and a LOAEL of 750 mg/kg/day for fetal effects.

° In a continuous breeding study, Lamb et al. (1985) dosed CD-1 mice with ethylene glycol by continuous administration in drinking water at 0.0, 0.25, 0.5 or 1%. Slight but statistically significant decreases were found in the numbers of litters per fertile pair ($p < 0.01$), live pups per litter ($p < 0.05$) and mean live pup weight ($p < 0.01$) at the 1% level when compared to F_0 controls. No clinical signs of toxicity or significant adverse effects on body weight or water consumption were seen in this study but two deaths at the 0.5% level may have been related to oxalate crystal deposition. This study established a NOAEL for reproductive effects of 0.5% (w/v) in drinking water. (Between days 98 and 105 on the study, this level corresponded to an average daily intake of 0.84 g/kg.)

° In a three-generation reproduction study, DePass et al. (1986b) fed ethylene glycol to Fischer 344 rats at levels of approximately 1.0, 0.2, 0.04 or 0.0 g/kg/day. No evidence of reduced fertility or increased fetal death was observed in any groups receiving the test diet. This study established a NOAEL for maternal and fetal effects at 1,000 mg/kg/day (highest dose tested).

Developmental Effects

° Lamb et al. (1985), in a continuous breeding study using CD-1 mice, administered ethylene glycol on a continuous basis for 126 days at levels of 0.0, 0.25, 0.5 or 1% in drinking water. The final offspring of these continuously bred mice were examined and the authors noted facial anomalies in a number of the offspring of the high-dosed mice. Examination for skeletal defects demonstrated a pattern including reduction in size of the bones in the skull, fused ribs and abnormally

shaped sternabrae and vertebrae. No similar findings were noted at the two lower dose levels. This study established a NOAEL of 0.5% (w/v) in drinking water for developmental effects in mice. (Between days 98 and 105, the average daily intake corresponded to approximately 840 mg/kg for the parental generation.)

° Administration of ethylene glycol by gavage on days 6 through 15 of gestation at levels of 0, 1,250, 2,500 or 5,000 mg/kg/day in rats and 0, 750, 1,500 or 3,000 mg/kg/day in mice resulted in significant increases in the percentage of malformed live fetuses per litter and/or the percent of litters with malformed fetuses at all dose levels with >95% of the litters affected at the high dose for both species. The most common malformations included craniofacial and neural tube closure defects and axial skeletal hyperplasia in both species (Price et al., 1985). This study established a LOAEL of approximately 1,250 mg/kg/day in rats and 750 mg/kg/day in mice (the lowest levels fed).

Mutagenicity

° In a dominant lethal mutagenesis study in rats, DePass et al. (1986b) bred at weekly intervals the F_2 males (fed ethylene glycol in the diet at 1.0, 0.2, 0.4 or 0.0 g/kg/day) from a three-generation reproduction study to 3 consecutive lots of untreated females. No evidence of reduced fertility or increased fetal death was observed in any of the groups receiving ethylene glycol. This study established a NOAEL for mutagenic effects at 1,000 mg/kg/day (highest dose tested).

° Ethylene glycol demonstrated no significant mutagenic activity in the Salmonella mutagenicity (Ames) test with or without microsomal activation (Clark et al., 1979).

Carcinogenicity

° No evidence of an oncogenic effect of ethylene glycol in 80 CD-1 mice per sex per level or 130 Fischer 344 rats per sex per level was seen when fed in the diet at approximately 1.0, 0.2, 0.04 or 0.0 g/kg/day for 24 months. Mortality of the high-dosed male rats in this study was 100% after 475 days of feeding. Death was attributed to oxalate nephrosis (DePass et al., 1986a).

° In studies designed to determine the toxic and carcinogenic potential of several biological preservatives, ethylene glycol was administered subcutaneously at 5 dose levels to groups of 20 weanling Fischer 344 rats (Mason et al., 1971). The LD_{50} for a single injection was 5,300 mg/kg. When given subcutaneously, twice weekly for four weeks, the maximum tolerated daily dose was found to be lower than 1,700 mg/kg (total dose of 13,600 mg/kg). In a long-term study, 4 groups of 80, 60, 40 and 20 rats were injected subcutaneously twice weekly for 52 weeks with 1,000, 300, 100 and 30 mg/kg, respectively. Animals were observed for an additional six months following treatment. In these animals, there was no evidence of ethylene glycol toxicity based on survival time, weight gain and drug related organ pathology.

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for One-day, Ten-day, Longer-term (approximately 7 years) and Lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(NOAEL \text{ or } LOAEL) \times (BW)}{(UF) \times (\_\_\_ \text{ L/day})} = \_\_\_ \text{ mg/L } (\_\_\_ \text{ ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect-Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100 or 1,000), in accordance with NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

Data from the study of Reif (1950) were used to identify an oral NOAEL in humans. This investigator drank a 188.6 mg/kg dose of ethylene glycol with no discernable effects. Thus, a One-day HA for children exposed to ethylene glycol in drinking water may be calculated as follows:

For a child:

$$\text{One-day HA} = \frac{(188.6 \text{ mg/kg/day})(10 \text{ kg})}{(100)\ (1 \text{ L/day})} = 18.86 \text{ mg/L } (19{,}000 \text{ ug/L})$$

where:

188.6 mg/kg/day = NOAEL in humans consuming up to this dose in water.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from a human study. An additional factor of 10 has been added for a study with only one subject.

1 L/day = assumed daily water consumption of a child.

Ten-day Health Advisory

There are not sufficient data to calculate a Ten-day Health Advisory. The Longer-term HA of 5.5 mg/L for the 10 kg child can serve as a conservative

estimate of an exposure which would be considered adequately protective over a ten-day exposure period.

Longer-term Health Advisory

Exposure of male and female Rhesus monkeys to 55 to 170 mg/kg/day ethylene glycol in the diet for three years caused no adverse response (Blood et al., 1962). A Longer-term HA based on these data is calculated as follows:

For a 10-kg child:

$$\text{Longer-term HA} = \frac{(55 \text{ mg/kg/day}) (10 \text{ kg})}{(100) (1 \text{ L/day})} = 5.5 \text{ mg/L } (5'500 \text{ ug/L})$$

where:

55 mg/kg/day = NOAEL, based on absence of toxic signs in the monkey.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

For a 70-kg adult:

$$\text{Longer-term HA} = \frac{(55 \text{ mg/kg/day}) (70 \text{ kg})}{(100) (2 \text{ L/day})} = 19.25 \text{ mg/L } (19,250 \text{ ug/L})$$

where:

55 mg/kg/day = NOAEL, based on absence of toxic signs in the monkey.

70 kg = assumed body weight of an adult.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

2 L/day = assumed daily water consumption of an adult.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking

water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed for synthetic organic chemicals and a value of 10% is assumed for inorganic chemicals. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

The study of Blood (1965) is considered most appropriate for calculating a Lifetime Health Advisory. In this study rats were fed ethylene glycol in the diet at concentrations of 0.0, 0.1, 0.2, 0.5, 1, or 4% (approximately 0, 50, 100, 250, 500 or 2,000 mg/kg/day according to Lehman, 1959) for up to two years. This study identified a NOAEL of 0.2% (100 mg/kg/day) primarily for kidney effects in rats. Using this NOAEL, the Lifetime HA is calculated as follows:

Step 1: Determination of the Reference Dose (RfD)

$$RfD = \frac{(100\ mg/kg/day)}{(100)} = 1\ mg/kg/day$$

where:

100 mg/kg/day = NOAEL for kidney effects in rats.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$DWEL = \frac{(1\ mg/kg/day)\ (70\ kg)}{(2\ L/day)} = 35\ mg/L\ (35{,}000\ ug/L)$$

where:

1 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

Lifetime HA = (35 mg/L) (20%) = 7 mg/L (7,000 ug/L)

where:

35 mg/L = DWEL.

20% = assumed relative source contribution from water.

Evaluation of Carcinogenic Potential

° Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986), ethylene glycol may be classified in Group D: Not classified. This category is for agents with inadequate animal evidence of carcinogenicity. The study by DePass et al. (1986a) was not a definitive indicator for carcinogenicity. The study indicated a difference in time to detection of lymphocarcinomas in the female rat. The incidence of this tumor type was not significantly different.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

° ACGIH (1984) has proposed a ceiling limit of 50 ppm (125 mg/m^3) for vapor and mist to minimize irritation of respiratory passages.

VII. ANALYTICAL METHODS

° There is no standardized method for the determination of ethylene glycol in drinking water samples. A procedure has been developed (Hartman and Bowman, 1977) to determine the presence of ethylene glycol in drugs and pharmaceutical formulations at concentration levels of 5-200 mg/L. This procedure is based on direct aqueous injection-gas chromatography of samples. It is probable that this procedure also applies to drinking water samples at concentration levels of at least 5 mg/L.

VIII. TREATMENT TECHNOLOGIES

° Ethylene glycol is completely miscible with water (Windholz, 1983) and has a low vapor pressure of 1 mmHg at 53°C (CRC Handbook of Chemistry and Physics, 1982). These two factors make it impractical to consider aeration as a form of removal. Treatment with activated carbon does not remove much of this compound from solution either. The adsorbability of ethylene glycol is only 0.0136 mg/g carbon with only 6.8% ethylene glycol retention (Veschueren, 1977). No information was found on the removal of this compound from drinking water using other techniques.

° Ethylene glycol may contaminate drinking water due to misapplication of the chemical as an antifreeze in potable water systems or through crossconnections with non-potable fire protection or heating/cooling systems. In these cases vigorous flushing of the contaminated components of the distribution system should be sufficient.

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