ETHYLENE GLYCOL

International Programme on Chemical Safety

Poisons Information Monograph 227

Chemical

1. NAME

1.1 Substance

Ethylene Glycol

1.2 Group

Polyalcohols - Glycol

1.3 Synonyms

1,2-dihydroxyethane

1,2-ethane diol

2-hydroxyethanol

ethane-1,2-diol

ethylene alcohol

ethylene dihydrate

1.4 Identification numbers

1.4.1 CAS number

107-21-1

1.4.2 Other numbers

No data available.

1.5 Brand names, trade names

1.6 Manufacturers, importers

2. Summary

2.1 Main risks and target organs

The main risk is severe metabolic acidosis with CNS depression, cardio-pulmonary failure and acute renal failure. Lethal dose as little as 1 mL/kg.

2.2 Summary of clinical effects

Within 4 to 12 hours CNS-depression (like ethanol) and increasing metabolic acidosis. Later stages (>12 hours) severe metabolic acidosis with electrolyte disturbances, elevated blood pressure, cardiopulmonary failure. Decreasing diuresis (>24 hours) with development of acute oliguric renal failure.

2.3 Diagnosis

The diagnosis is based on history of exposure, clinical features and laboratory findings.

Drowsiness, coma, elevated blood pressure, tachycardia and hyperventilation are the typical clinical features of ethylene glycol poisoning.

Severe metabolic acidosis with elevated anion and osmolal gap is typical. The degree of metabolic acidosis is related to the severity of poisoning. Urine microscopy may reveal presence of needle or envelope shaped calcium oxalate crystals (oxalate is one of the metabolites from ethylene glycol metabolism).

Concentrations of both ethylene glycol and the major acidic metabolite, glycolate, are best determined by gas-chromatography or HPLC (Jacobsen & McMartin, 1997).

2.4 First-aid measures and management principles

Standard first aid and symptomatic treatment.

Gastric decontamination

Correction of metabolic acidosis with bicarbonate

Inhibition of ethylene glycol metabolism by giving ethanol or fomepizole as antidotes

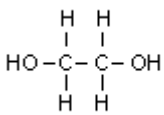
Hemodialysis to remove ethylene glycol and its major toxic metabolite glycolic acid.

3. PHYSICO-CHEMICAL PROPERTIES

3.1 Origin of the substance

Manufactured by oxidation of ethylene in the presence of acetic acid followe by hydrolysis of the ethylene diacetate thus formed.

3.2 Chemical structure



Molecular weight = 62,07

3.3 Physical properties

Boiling point:	198°C
Melting point:	-13°C
Flash point:	111°C closed cup 119°C open cup
Explosive limits:	3.2 – 15.3 volume % in air
Autoignition temperature:	398°C
Relative density of vapour/air mixture at 20°C (air = 1):	1.00
Conversion factors:	1 mg/m^3 = 0.37 ppm (Atm 25°C)
	1 ppm = 2.54 mg/m^3 (Atm 25°C)
Solubility:	Soluble in water, ethanol, acetone, acetic acid, glycerine, pyridine, aldehydes;
	Little soluble in ether;
	Insoluble in oil, fat, hydrocarbures halogènes.

3.4 Other characteristics

Odourless, colourless, viscous, hygroscopic liquid.

4. USES/CIRCUMSTANCES OF POISONING

4.1 Uses

- Antifreeze and engine-cooling liquids (1/4 of the production)
- Hydraulic, brake, thermal exchange fluids.
- Humidifying and plasticising agent.
- Dehydrating agent.
- Softener for textiles.
- Solvent (dyes, inks, dissolvants ...)
- Synthetic intermediate in chemical production.
- Explosives manufacture.
- Electrolytic condenser production.

N.B. Domestic antifreeze is responsible for most cases of poisoning.

4.2 High risk circumstances of poisoning

- Accidental ingestion due to confusion with a soft drink: children, adults (often chronic alcoholics), pets.
- Voluntary ingestion of car radiator water during water shortage (travellers in desert areas) (Bunuan, 1978; Gaultier, 1976).
- Ingestion of water from central heating or water-heater system (no anti-return valve) (Zech, 1974).
- Suicide attempts.
- Food poisoning

4.3 Occupationally exposed populations

Due to its low volatility, ethylene glycol is not an occupational hazard.

5. ROUTES OF ENTRY

5.1 Oral

The usual route of exposure, readily absorbed.

5.2 Inhalation

Well absorbed, but little risk because of low volatility. Inhalation may occur as aerosol, from hot products containing ethylene glycol.

5.3 Dermal

Low absorption requiring application to large surface areas to reach toxic dose.

5.4 Eye

Local irritation.

5.5 Parenteral

Possible but no reports. Risk of hemolysis.

5.6 Others

No data available.

6. TOXICOKINETICS

6.1 Absorption by route of exposure

Rapid absorption from the whole gastrointestinal tract (Gordon, 1982).

6.2 Distribution by route of exposure

Rapidly distributed in total body water with a volume of distribution of 0.7 to 0.8 L/kg (Peterson, 1981; Jacobsen, 1982).

6.3 Biological half-life by route of exposure

The calculated half-life in poisoned patients is 3 to 6 hours(Jacobsen & McMartin, 1997; Peterson, 1982; Winek, 1977).

- During ethanol therapy: t 1/2 = 17 hours(Peterson, 1981)

- During 4-methylpyrazole treatment: t 1/2 = 11.5 to 15 hours (Baud, 1986-1987; Brent et al, 1999).

6.4 Metabolism

Ethylene glycol undergoes enzymatic metabolism, principally in the liver and kidneys. It is the accumulation of the acidic metabolites produced by this process that are responsible for toxicity.

The initial step in metabolism is the conversion of ethylene glycol to glycoaldehyde mediated by alcohol dehydrogenase. Glycoaldehyde is subsequently metabolised to glycolate by the action of aldehyde dehydrogenase. Glycolate undergoes further metabolism to form glycoxylate and oxalate.

6.5 Elimination

Only very small amounts of ethylene glycol and its principal metabolites are excreted in the urine. Oxalic acid excreted in the urine can give rise to dihydrate or monohydrate oxalate crystals.

7. TOXICOLOGY

7.1 Mode of action

Except for the initial CNS-depression caused by ethylene glycol itself, the toxicity is entirely due to its metabolites (see paragraph 6.4).

7.2 Toxicity

7.2.1 Human data

7.2.1.1 Adults

Toxic dose > 0.5 mL/kg (approx. 0.5 g/kg)

Lethal dose = 1.4 mL/kg (approx. 1.5 g/kg), or 100 mL for adults (70 kg).

With early diagnosis and correct treatment even patients who have ingested more than 500 mL of ethylene glycol have survived (Gabow, 1986; Turk, 1986; Vites, 1984; Peterson, 1981).

7.2.1.2 Children

7.2.2 Relevant animal data

(i) Acute toxicity

DL50 mg/kg orally:	mouse =	8,000 to 15,000
	rabbit =	5,000
	rat =	6,000 to 13,000
	guinea pig =	8,000 to 11,000
	dog =	8,000 some survive up to 14,7008,000 some survive up to 14,700

7.2.3 Relevant in vitro data

7.2.4 Workplace standards

OSHA PEL ceiling 50 ppm

7.2.5 Acceptable daily intake (ADI) and other guideline levels

7.3 Carcinogenicity

Not classifiable as a human carcinogen

7.4 Teratogenicity

No data available.

7.5 Mutagenicity

Negative

7.6 Interactions

The major metabolic interaction occurs with ethanol and is described in section 10.6.

8. TOXICOLOGICAL ANALYSES AND BIOMEDICAL INVESTIGATIONS

8.1 Material sampling plan

8.1.1 Sampling and specimen collection

8.1.1.1 Toxicological analyses

8.1.1.2 Biomedical analyses

8.1.1.3 Arterial blood gas analysis

8.1.1.4 Haematological analyses

8.1.1.5 Other (unspecified) analyses

8.1.2 Storage of laboratory samples & specimens

8.1.2.1 Toxicological analyses

8.1.2.2 Biomedical analyses

8.1.2.3 Arterial blood gas analysis

8.1.2.4 Haematological analyses

8.1.2.5 Other (unspecified) analyses

8.1.3 Transport of laboratory samples &specimens

8.1.3.1 Toxicological analyses

8.1.3.2 Biomedical analyses

8.1.3.3 Arterial blood gas analysis

8.1.3.4 Haematological analyses

8.1.3.5 Other (unspecified) analyses

8.2 Toxicological Analyses and Their Interpretation

8.2.1 Tests on toxic ingredient(s) of material

8.2.1.1 Simple Qualitative Test(s)

8.2.1.2 Advanced Qualitative Confirmation Test(s)

After a latent period of 1 to 4 hours clinical features develop. Many authors present the clinical syndrome in stages: a CNS depression, then a cardiopulmonary and finally a renal phase. However in many cases, there is considerable overlap among these stages (Jacobsen & McMartin, 1997).

A. The initial CNS depression is much like that of ethanol with dizziness, agitation, nystagmus, nausea, tachycardia, elevated blood pressure and vomiting. In severe poisoning coma and convulsions occur. Hyperventilation increases as the metabolic acidosis becomes more and more pronounced.

B. Cardio-pulmonary phase:

This phase develops about 24 hours after the ingestion and is thought to be due to cardio-pulmonary failure. Dyspnea, hyperventilation, tachycardia, cyanosis, elevated blood pressure are typical clinical features at this stage and the patient may suffer pulmonary edema, especially if oliguria develops at this stage. Chest X-ray typically shows massive bilateral infiltrations. The patient may die at this stage (Gironimi, 1966; Jacobsen & McMartin, 1997).

C. Renal phase:

About 24 to 36 hours following ingestion oliguria gradually develops in severe cases not given correct treatment. The urine sediment contains various casts and in most patients also calcium oxalate crystals (needle or envelope shaped). The acute oliguric renal failure may be reversed upon correct treatment, but many patients must be treated with temporary dialysis for 2 to 3 weeks. The prognosis for the renal failure per se is good, but some patients may require dialysis for a longer period (Collins, 1970; Jacobsen & McMartin, 1997).

9.1.2 Inhalation

No data available.

9.1.3 Skin exposure

No data available.

9.1.4 Eye contact

No data available.

9.1.5 Parenteral exposure

No data available.

9.1.6 Other

No data available.

9.2. Chronic poisoning

9.2.1 Ingestion

No data available.

9.2.2 Inhalation

Due to its low volatility, inhalation of ethylene glycol vapours is not problematic.

9.2.3 Skin exposure

No data available.

9.2.4 Eye contact

No data available.

9.2.5 Parenteral exposure

No data available.

9.2.6 Other

No data available.

9.3 Course, prognosis, cause of death

This is a potentially lethal poisoning if diagnosis and treatment are delayed. With early diagnosis and treatment can be prevented, even if large doses are ingested (Turk, 1986; Stokes, 1980; Jacobsen & McMartin, 1999).

Death may occur due to aspiration of gastric contents during convulsions or due to cardiopulmonary failure 24 to 48 hours (or later) after ingestion (O'Donoghue, 1985; Ahmed, 197l, Berger, 198l, Gosselin, 1976).

In later stages mortality may be due to secondary (pulmonary) infections or various degree of brain damage (Maier, 1983; Jacobsen et al., 1982a).

The prognosis for the renal failure per se is usually good.

9.4 Systematic description of clinical effects.

9.4.1 Cardiovascular

- Tachycardia and elevated blood pressure.
- Severe metabolic acidosis decreases cardiac contractility and may progress to cardiogenic shock.

9.4.2 Respiratory

- Hyperventilation in response to metabolic acidosis becomes severe and the patient tries to compensate.

- Risk of acute pulmonary oedema and ARDS (see 9.4.1).

9.4.3 Neurological

9.4.3.1 Central nervous system

- Early inebriation and coma like in ethanol poisoning. Generalised convulsions may occur later.
- Cerebral oedema

9.4.3.2 Peripheral nervous system

- In rare cases cranial nerves (I-V-VII-XII) may be affected.

9.4.3.3 Autonomic nervous system

9.4.3.4 Skeletal and smooth muscle

- Rhabdomyolysis may develop secondary to convulsions.

9.4.4 Gastrointestinal

9.4.5 Hepatic

No direct toxicity reported.

9.4.6 Urinary

9.4.6.1 Renal

Acute oliguric renal failure is typically seen if correct treatment is not initiated early. The mechanism behind the acute tubular necrosis is not completely understood but relates to metabolic injury and deposition of calcium oxalate crystals.

9.4.6.2 Others

The presence of calcium oxalate crystals in the urine may be of diagnostic importance (microscopy).

9.4.7 Endocrine and reproductive system

No data available.

9.4.8 Dermatological

Non irritant.

9.4.9 Eye, ears, nose, throat: local effects

Slightly irritating.

9.4.10 Hematological

No data available.

9.4.11 Immunological

No data available.

9.4.12 Metabolic

9.4.12.1 Acid-base disturbances

The underlying disorder in ethylene glycol poisoning is gradual development of severe metabolic acidosis with increased anion gap, mainly caused by accumulation of the metabolite glycolic acid.

9.4.12.2 Fluid and electrolyte disturbances

Hyperkalemia is seen if severe metabolic acidosis or rhabdomyolysis occur.

Hypercalcaemia may occur but is rarely life-threatening.

Overhydration and pulmonary edema may be seen if acute oliguric renal failure develops.

9.4.12.3 Others

9.4.13 Allergic reactions

No data available.

9.4.14 Other clinical effects

No data available.

9.4.15 Special risks

No data available.

9.5 Others

No data available.

10. TREATMENT

10.1 General principles

Treatment consists of:

- emptying the stomach (if indicated);

- correction of acidosis;
- ethanol or fomepizole administration to inhibit the formation of toxic metabolites;
- rapid reduction of the body burden of methanol and formate by haemodialysis;
- intensive supportive care for multiple organ/system failures.

10.2 Relevant laboratory analyses and other investigations

10.2.1 Sample collection

For ethylene glycol and glycolate determination and biomedical analyses, blood and urine should be collected.

10.2.2 Biomedical analyses

Arterial blood gases, serum electrolytes, osmolality, BUN, creatinine and blood glucose. Urine microscopy to search for calcium oxalate crystals if diagnosis is uncertain.

10.2.3 Toxicological analyses

- Determine concentrations of ethylene glycol, methanol and ethanol in blood and urine, and in ingested substance if available.
- In late stages (severe metabolic acidosis), all the ingested ethylene glycol may be metabolized and it cannot therefore be detected in serum (Jacobsen, 1984).

10.3 Life supportive procedures and symptomatic treatment

Intensive supportive care for multiple organ/system failure is frequently necessary.

Since severe, recurrent metabolic acidosis is the underlying feature of ethylene poisoning, the correction of acidosis by administration of sodium bicarbonate is imperative, possibly life-saving. The degree of acidosis has been found to correspond closely to the severity of poisoning (Jacobsen et al., 1983). Repeated and frequent assessment of the acid/base status is necessary.

Correction of acidosis may require as much as 400 to 600 mmol of bicarbonate during the first few hours (Jacobsen & McMartin, 1986).

Fluids must be given orally or intravenously to maintain adequate urine output.

Hyperkalemia is usually corrected by bicarbonate administration (see also treatment guide: hyperkalaemia).

Convulsions should be controlled (see treatment guide: convulsions).

Correct hypocalcaemia if severe (see treatment guide: hypocalcaemia).

10.4 Decontamination

The usual decontamination procedures are required in cases of percutaneous exposure, or exposure to vapours: removal from the exposure, removal of clothes, adequate prolonged washing of skin and eyes.

Consider emptying the stomach by gastric lavage only following recent ingestion (< 1 hour) of a large amount.

10.5 Elimination

Hemodialysis (or peritoneal dialysis) removes ethylene glycol and its toxic metabolite glycolate (Jacobsen & McMartin, 1997). It is not possible to set up strict indications for dialysis as it depends also on which antidote is used, the degree of metabolic acidosis and whether renal failure is present or not. If the patient is seen early before severe metabolic acidosis develops, and fomepizole (4-methylpyrazole) is the antidote used, hemodialysis is usually not necessary. However, if the patient is admitted in later stages with severe metabolic acidosis, hemodialysis should always be performed (Jacobsen & McMartin1997; Brent et al, 1999).

Hemoperfusion is not effective in removing ethylene glycol (Sangster, 1980).

10.6 Antidote treatment

10.6.1 Adults

There are two alternative antidotes, both of which act by blocking the alcohol dehydrogenase-mediated metabolism of ethylene glycol: ethanol, fomepizole.

(i) Ethanol

Effective because it has a much greater affinity for alcohol dehydrogenase than ethylene glycol. A blood ethanol concentration of 100 mg/dL (22 mmol/L) will almost completely block ethylene glycol metabolism (Jacobsen & McMartin, 1986). However, ethanol is sometimes technically difficult to administer because of its rapid and unpredicatable rate of methabolism (Jacobsen & McMartin, 1986). A loading dose followed by titrated maintenance therapy is necessary.

Suggested dosing regime:

	Oral	Intravenous
Loading dose	1 mL/kg of 95% ethanol, diluted	10 mL/kg of 10% ethanol in 5% dextrose over 30 minutes
Maintenance dose	0.1 – 0.2 mL/kg/hour of 95% ethanol, diluted	1-2 mL/kg of 10% ethanol in 5% dextrose over 30 minutes

Notes:

In an emergency, an equivalent amount of any alcoholic drink may be administered orally.

The maintenance dosing needs to be adjusted according blood ethanol concentration, ideally measured hourly, to maintain the concentration >100 mg/dL.

Prolonged ethanol administration may cause hypoglycaemia, especially in children, and frequent blood glucose determinations are mandatory (Bayer et al., 1984). If haemodialysis is started, the ethanol infusion should be increased as detailed in Section 10.5.

(ii) Fomepizole is easily administrated intravenously as a loading dose of 15 mg/kg, followed by bolus doses of 10 mg/kg every 12 hours. After 48 hours, the bolus doses should be increased to 15 mg/kg every 12 hours because of induced metabolism over time. The same dose may be administered orally. No side effects have been reported with this dosage regimen and effectiveness is clearly demonstrated (Brent et al., 2001). If dialysis is performed, the dose of fomepizole must be increased as fomepizole is eliminated at the same rate as urea.

10.6.2 Children

Although there have been fewer reports of ethanol therapy in children, comparable doses may be used. Ethanol is more likely to cause hypoglycaemia in children (Bayer et al., 1984).

10.7 Management Discussion

11. ILLUSTRATIVE CASES

11.1 Cases from the literature

11.2 Internally extracted data on cases

12. ADDITIONAL INFORMATION

12.1 Availability of antidotes

12.2 Specific preventive measures

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See Also:
Toxicological Abbreviations
Ethylene glycol (ICSC)
Ethylene glycol (PIM 227F, French)

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