Ethylene glycol

CAS: 107-21-1
MF: C_2-H_6-O_2
MW: 62.07
log Kow= -1.36
pKa = 15.1
Solubility: Miscible with water, lower aliphatic alcohols, glycerol, acetic acid, acetone and similar ketones, aldehydes, pyridine; slightly soluble in ether (1:200); practically insoluble in benzene, chlorinated hydrocarbons, petroleum ether, and oils [1].

Major uses
Ethylene glycol is used as antifreeze in cooling and heating systems; in hydraulic brake fluids and deicing solutions. It is also an ingredient of electrolytic condensers (where it serves as solvent for boric acid and borates) and used as solvent in the paint and plastics industries. It is also used in the formulation of printers' inks, stamp pad inks, and ball-point pen inks, as softening agent for cellophane and as stabilizer for soybean foam used to extinguish oil and gasoline fires. Furthermore, it is used in the synthesis of safety explosives, glyoxal, unsaturated ester type alkyd resins, plasticizers, elastomers, synthetic fibers and synthetic waxes and to create artificial smoke and mist for theatrical uses [1].

Human toxicity
Most ethylene glycol (EG) exposures occur from the ingestion of antifreeze. EG is rapidly absorbed from the gastrointestinal tract. Toxicity can be divided into three stages:
Stage 1: NEUROLOGICAL (0.5 to 12 hours post-ingestion)
A transient inebriation and euphoria, similar to ethanol intoxication, occurs within the first hours. Nausea and vomiting result from direct gastric irritation. EG is metabolized, and metabolic acidosis and CNS depression is developed. Symptoms due to toxic metabolites occur 4 to 12 hours post-ingestion. Serious intoxications may progress to coma associated with hypotonia, hyporeflexia, and less commonly, seizures and meningismus.
Stage 2: CARDIOPULMONARY (12 to 24 hours post-ingestion)
Frequently, tachycardia and hypertension may occur. Severe metabolic acidosis with compensatory hyperventilation can develop with multiple organ failure in significant poisonings. Hypoxia, congestive heart failure, and adult respiratory distress syndrome (ARDS) have been reported. Most deaths are reported during stage 2.
Stage 3: RENAL (24 to 72 hours post-ingestion)
Oliguria, acute tubular necrosis, renal failure, and occasionally bone marrow suppression occur during stage 3. Renal failure may appear early in severe poisonings and progress to anuria. Calcium oxalate crystals may be detected in the urine of some patients with EG poisoning but the absence of calcium oxalate crystals does not rule out the diagnosis. Hematuria and proteinuria are common. In surviving cases, renal function usually returns to normal, but in some cases permanent renal damage has occurred. Serious hepatic injury is uncommon [2].

Lethal symptoms [3]:
1-12 hours: CNS excitation/depression
12-24 hours: heart failure
24-72 hours: kidney failure

Mean time to death: 17 hours [3].

The lethal oral dose is also estimated to be 1.4 ml/kg or 1.56 g/kg. The lowest published oral lethal dose for a human is 398 mg/kg. The minimum lethal dose is on the order of 100 ml in adults, although individuals reportedly have survived much higher doses. Death has been reported after ingestion of as little as 30 or 60 ml, although ingestion of more than 3,000 ml has been survived [2].

Following the ingestion of 3,000 ml of ethylene glycol (EG) antifreeze in a suicide attempt, a patient with an EG blood concentration of 18,890 mg/l was immediately started on hemodialysis and ethanol infusions. This concentration was higher than any level previously documented in the medical literature. The patient survived, in spite of complications of pulmonary edema and acute renal failure [2].

Blood concentrations greater than 300 to 500 mg/l shortly after ingestion of ethylene glycol are frequently associated with severe intoxication. Mean clinically measured lethal blood concentration was reported to be 3,600 mg/l, and mean post-mortem acute lethal blood concentration was reported to 2,600 mg/l [3].

Working place standards:
TLV-Ceiling: 100 mg/m^3 [2].

Kinetic data
Absorption of EG is assumed to be rapid. Signs and symptoms of the central nervous system (CNS) abnormalities occur as early as 30 min post-ingestion [2].

Volume of distribution: 0.5 to 0.8 l/kg [2].

Distribution: EG accumulates in the liver and kidney [3].

The plasma half-life: 3 to 8.6 h [2].

Time to peak: 1-4 h [3].

Protein binding: None [3].

Passage of blood-brain barrier: free [3].

Metabolism and excretion
Metabolism of EG occurs primarily in the liver and results in the formation of toxic acidic metabolites [2].
The metabolites include [2]:
1. Glycoaldehyde
2. Glycolic acid (34 to 44% of the dose)
3. Glyoxylic acid
4. Oxalic acid (up to 2.3% of the dose)
5. Glyoxal
6. Formic acid
7. Glycine

8. Oxalomalate
9. 2-Hydroxy-3-oxoadipate
10. 2-Oxo-4-hydroxygluconate
11. Malate
12. Benzoic acid
13. Hippuric acid

Metabolites more toxic than ethylene glycol: glyoxylic acid, glycolic acid, and oxalic acid [3].

Excretion: About 22 percent of a 1 ml/kg dose, given to monkeys, was excreted in the urine as unchanged ethylene glycol whereas only 0.3 percent was excreted as oxalic acid. Clearance has been reported to be 3.2 ml/kg/min or 0.75 to 27.5 ml/min [2].

Toxicological mechanisms
Neurological – Altered mental stage; such as ataxia, slurred speech, and somnolence are commonly reported after ingestion of ethylene glycol and may be due to unchanged ethylene glycol rather than to oxalic acid. However, the aldehyde metabolite concentration (glyceraldehyde) is at its highest level about 6 to 12 hours post-ingestion, the time the CNS symptoms are most severe and are probably contributory.
Coma - is thought to be due to the effect of unmetabolized ethylene glycol and aldehyde metabolites on the CNS.
Metabolic - Ethylene glycol is metabolized by alcohol dehydrogenase to several toxic organic acids including oxalic acid. The etiology and pathophysiology of the CNS, metabolic, cardiopulmonary, and renal toxicity are primarily due to the formation and accumulation of toxic intermediary metabolites, especially glycolic acid (produces profound acidemia, oxalosis, and renal interstitial edema) and to a lesser but histologically important extent, oxalate production and excretion. Unchanged ethylene glycol is thought to be responsible for the initial signs and symptoms resembling ethanol inebriation [2].

Target organs*:* CNS, heart and kidney [3].

References

1. HSDB, TOXNET (2005).
2. Poisindex, Thomson Micromedex (2005).
3. Ekwall, B., Clemedson, C., Crafoord, B., Ekwall, B., Hallander, S., Walum, E. & Bondesson, I. (1998) MEIC Evaluation of Acute Systemic Toxicity: Part V. Rodent and Human Toxicity Data for the 50 Reference Chemicals, ATLA 26, 571-616.

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