



# Ethylene Glycol

## Toxicological Overview

### Key Points

#### Kinetics and metabolism

- readily absorbed following ingestion and subsequently distributed in the body water
- primarily undergoes metabolism in the liver and kidneys
- metabolites are excreted primarily in the urine and small quantities of ethylene glycol may be excreted unchanged

#### Health effects of acute exposure

- ingestion may initially result in CNS depression with features of dizziness, agitation, nystagmus, nausea, tachycardia, elevated blood pressure and vomiting
- cardiopulmonary features develop around 12 hours after ingestion, manifesting as hyperpnoea, hyperventilation, tachycardia, cyanosis and elevated blood pressure
- renal effects may develop after 24 hours, including oliguria, anuria, flank pain, renal angle tenderness, acute tubular necrosis, hypercalcaemia, hyperkalaemia and hypomagnesaemia
- may cause irritation to the eyes and prolonged dermal contact may cause dry skin
- long-term effects noted following severe intoxication include neurological dysfunction

#### Health effects of chronic exposure

- long-term dermal exposure to ethylene glycol may cause dermatitis
- ethylene glycol is considered not to be a mutagen or carcinogen in humans
- ethylene glycol is considered not to be a reproductive toxicant in humans

## Summary of Health Effects

Ethylene glycol may be acutely toxic following ingestion. Due to its low volatility and low dermal absorption rate, acute toxicity is unlikely following exposure to ethylene glycol by the inhalation or dermal routes.

Acute toxicity following ingestion of ethylene glycol manifests in three phases. The first is characterised by central nervous system (CNS) depression much like in ethanol intoxication, with features including dizziness, agitation, nystagmus, nausea, tachycardia, elevated blood pressure and vomiting between 0.5 and 12 hours. The second phase at around 12 hours after ingestion is characterised by cardiorespiratory effects, with the development of hyperpnoea, metabolic acidosis, dyspnoea, hyperventilation, tachycardia, cyanosis and elevated blood pressure. A third phase, involving renal toxicity may present 24–36 hours after ingestion with flank pain, renal angle tenderness, acute tubular necrosis, hypercalcaemia, hyperkalaemia and hypomagnesaemia. Oliguria or anuria may occur. Some investigators report a fourth stage characterised by delayed neurological dysfunction.

Death may occur after substantial exposures due to cardiopulmonary failure or CNS damage in later stages. Severe intoxication, if survived, may lead to neurological effects including facial paralysis, slurred speech, loss of motor skills and impaired vision.

Contact of ethylene glycol with the eyes may result in slight irritation.

There is limited data on the chronic effects of ethylene glycol exposure in humans. Prolonged dermal contact may result in dry skin.

Ethylene glycol has no structural alerts for mutagenicity and in-vitro and animal studies are negative, it does not have any significant mutagenic potential.

Animal studies indicate that ethylene glycol is not a carcinogen in rats or mice. Ethylene glycol is not classified as a carcinogen in humans.

Ethylene glycol is not classified as a human reproductive or developmental toxicant. However, fetal toxicity may arise secondary to maternal toxicity. It is unlikely that exposure to low concentrations of ethylene glycol would result in adverse effects in the fetus, though exposure should be minimised.

## Kinetics and Metabolism

Ingestion and dermal exposure are the major routes of exposure to ethylene glycol, though dermal exposure is unlikely to lead to toxic effects [1]. Following ingestion, ethylene glycol is readily absorbed throughout the gastrointestinal (GI) tract [2].

Distribution is rapid and occurs throughout body water as indicated by a volume of distribution of approximately 0.7–0.8 L/kg [2]. Peak concentrations following ingestion occur within 1–4 hours [2].

In humans and primates much of ethylene glycol's toxicity is mediated by its metabolites and not the parent molecule.

The liver and kidneys are the primary site of metabolism for ethylene glycol, glycolic acid is its primary metabolite [3]. Ethylene glycol is first oxidised by alcohol dehydrogenase to glycoaldehyde, which is then further metabolised to glycolic acid by mitochondrial aldehyde dehydrogenase and cytosolic aldehyde oxidase [1]. Glycolic acid is then metabolised to glyoxylic acid by glycolic acid oxidase or lactate dehydrogenase. Glycolic acid oxidase also catalyses the formation of oxalic acid from glyoxylic acid. Glyoxylic acid may be metabolised to malate, formate or glycine [4]. Lactic acid is also formed in the metabolic processes following ethylene glycol exposure [1]. It is the accumulation of these acid products that accounts for much of the toxicity of ethylene glycol [2]. Chelation of aqueous oxalic acid with calcium ions forms insoluble calcium oxalate, which cannot be further metabolised by humans [1, 5].

The relative affinity of alcohol dehydrogenase for ethanol is much greater than for ethylene glycol. This difference has been exploited therapeutically in cases of poisoning, where alcohol is administered under medical supervision to reduce the formation of ethylene glycol's metabolites. A selective enzyme inhibitor such as Fomepizole may also be used to block the metabolism of ethylene glycol [6].

Excretion of ethylene glycol is primarily in the urine either as the parent molecule, glycolic acid, calcium oxalate or glycine (and its conjugate hippurate) [4]. Oxalic acid is excreted in the urine and may give rise to dihydrate and or monohydrate oxalate crystals which may precipitate in the kidney causing nephrotoxicity. Approximately 20% of a dose of ethylene glycol may be excreted unchanged by the kidneys [7].

The elimination half-life in humans is estimated to be in the range of 2.5–8.4 hours [1].

## Sources and Route of Human Exposure

Ethylene glycol has a number of uses, which include the production of antifreeze, solvents, dyes, engine coolants and inks; it is also used in de-icing aeroplanes and as a synthetic precursor [1, 5].

Ethylene glycol does not persist in the environment, degradation typically occurs within a few weeks [1]. Water and soil are not expected to be major sources of exposure for the general public. The general public are most likely to be exposed to ethylene glycol by dermal contact with antifreeze products containing ethylene glycol [1].

Many cases of paediatric poisonings have occurred on accidental ingestion of ethylene-glycol-containing antifreeze [1]. Intoxication with ethylene glycol has also been reported on consumption of contaminated water systems and illicit alcoholic beverages [5].

Exposure may occur to those individuals in occupations where ethylene glycol is manufactured, used or stored. A workplace exposure limit (WEL) for ethylene glycol has been set in the UK. The long-term exposure limit (LTEL) for vapour is  $52 \text{ mg/m}^3$  and for particulate it is  $10 \text{ mg/m}^3$  (8-hour time weighted exposure (TWA) reference period). The short-term exposure limit (STEL) for vapour is given as  $104 \text{ mg/m}^3$  (15-minute reference period) [8].

## Health Effects of Acute/Single Exposure

### Human data

#### General toxicity

The key effects of ethylene glycol intoxication are an initial CNS depression much like in ethanol poisoning, metabolic acidosis, cardiopulmonary failure, acute renal failure and, potentially, death [2].

#### Inhalation

There is limited data available on the toxicity of ethylene glycol following inhalation. The vapour pressure of ethylene glycol is considered too low to lead to excessive inhalation exposures at room temperature [5]. However, at increased temperatures or where ethylene glycol is aerosolised, significant inhalation exposure is theoretically possible [5].

#### Ingestion

The type and severity of toxicological effects following ingestion are variable and dependent on the amount consumed, whether ethanol has been co-consumed and the interval between ingestion and the initiation of treatment.

Ingestion of ethylene glycol may lead to three stages of toxicity, which are well characterised in the literature [1]. However, the development, timing and severity of these stages varies and there may be considerable overlap between them [2, 5]. The key phases of ethylene glycol toxicity are summarised in table 1.

Some investigators suggest a fourth “late cerebral” phase to ethylene glycol toxicity [1]. This stage is characterised by delayed neurological dysfunction, which may include cranial nerve neuropathy and deficits, gait disturbance, dysmetria, ankle clonus, extensor plantar reflexes and ascending motor/sensory neuropathy up to 6 days after exposure [1, 5, 9].

Ethylene glycol intoxication may be fatal; the lethal dose is estimated to be within and above the range of 1,400–1,600 mg/kg [1]. Severe metabolic acidosis, hyperkalaemia, seizures and coma are associated with a poor prognosis [6].

Oliguria or anuria may take several days to develop following ingestion of as little as 75 mL of ethylene glycol and may persist for over a week [10, 11].

#### Dermal/ocular exposure

Exposure of large surface areas of the body is required to reach toxic doses, as ethylene glycol is poorly absorbed across the skin [2]. Dermal exposure to ethylene glycol may cause dry skin and dermal irritation in individuals with dermal sensitivity including eczema patients and occupationally exposed workers with a history of dermatitis [4, 12].

Contact of ethylene glycol with the eyes may result in slight irritation [2, 4].

**Table 1: Key phases of ethylene glycol intoxication**

Phase	Comments
<b>0.5–12 hours</b> <b>CNS manifestations</b>	Similar to that arising from ethanol ingestion. Features may include dizziness, agitation, nystagmus, ataxia, nausea, tachycardia ophthalmoplegia papilloedema, hypertonia, hyperflexia, myoclonic jerk, tetanic contractions and cranial nerve palsies, and elevated blood pressure. In severe poisoning, coma and convulsions may occur  Other reported effects in this initial phase include gastric irritation, metabolic acidosis and hyperventilation (becoming more pronounced with progression of metabolic acidosis)
<b>12–24 hours</b> <b>Cardiopulmonary</b>	Thought to occur due to cardiopulmonary failure. Features include hyperpnoea, hyperventilation, tachycardia, cyanosis and elevated blood pressure. Pulmonary oedema may develop, especially if oliguria arises at this stage. Chest X-ray typically shows massive bilateral infiltrations. Most deaths occur during this stage
<b>24–72 hours</b> <b>Renal</b>	Flank pain, renal angle tenderness, acute tubular necrosis, hypercalcaemia, hyperkalaemia and hypomagnesaemia may develop. Oliguria develops in severe cases; urine sediment contains various casts and calcium oxalate crystals. Anuria may occur
<b>References</b> [1, 2, 5-7]	

### Delayed effects following acute exposure

Death may occur 24–48 hours after ingestion due to cardiopulmonary failure [2]. Mortality may also occur secondary to pulmonary infections or various degrees of CNS damage in later stages [2, 13]. The prognosis for renal failure is good [2].

Cerebral infarction and other neurological dysfunctions have been reported in individuals who have survived ethylene glycol ingestion, the onset in some cases being over a week following intoxication. A range of effects related to cranial nerve damage have been observed with varying outcome; these include facial diplegia (the most commonly reported), tinnitus, hearing loss, vertigo or dizziness, dysarthria, dysphagia, absent gag reflex, loss of motor skills, facial sensory loss and ocular and vision effects [4, 5, 11, 14].

In two cases, profound palsies of cranial nerve VII and severe dysfunction of cranial nerves IX and X were reported after ingestions of ethylene glycol. In one of the cases, 75 mL was ingested and 14 days after ingestion (7 days after admission) the patient complained of peri-oral numbness and loss of taste sensation and ability to smile. Speech was slurred and he was unable to use a straw. Cranial nerve VII was found to be almost completely dysfunctional, though other cranial nerves were normal and there were no other systemic complaints. Mild neurological deficit persisted at 3 months' follow up including slurred speech and inability to drink through a straw [11].

## Animal and in-vitro data

Ethylene glycol has shown low toxicity in a number of animal studies following oral, inhalation or dermal exposure [4].

### Inhalation

Ethylene glycol has been demonstrated as toxic by inhalation exposure in a number of animal species. In rats and mice a lethal concentration of  $>200 \text{ mg/m}^3$  was observed following exposure for 2 hours [4]. Exposure of rats to  $500 \text{ mg/m}^3$  for 28 hours over 5 days was reported to cause slight narcosis [4].

### Ingestion

Findings following exposure by ingestion suggest similar mechanisms of toxicity as described in humans. Metabolic acidosis, degeneration in the renal tubules, focal necrosis in the liver and calcium oxalate crystal in the urine have been observed in domestic cats and dogs following accidental ingestion of antifreeze products containing ethylene glycol [4]. Findings at histology include lesions in the kidney including mild tubular nephrosis and the deposition of oxalate crystals in the cortex or medulla [4].

Oral administration of  $2,000 \text{ mg/kg bw/day}$  ethylene glycol to rats for 4 weeks resulted in renal toxicity including tubulopathy and crystalline deposits, changes in urinary parameters and increased kidney weights [4].

### Dermal/ocular exposure

Ethylene glycol induces mild dermal irritation in rabbits and guinea pigs [4].

## Health Effects of Chronic/Repeated Exposure

### Human data

#### Inhalation

There is limited data available on the toxicity of ethylene glycol following chronic inhalation exposure.

In one volunteer study, exposure to up to 67 mg/m<sup>3</sup> was generally well tolerated for up to 30 days, with no significant adverse effects reported, although some individuals experienced throat irritation, headache and back pain. Nasal or throat irritation was noted in all test subjects at 140 mg/m<sup>3</sup>; concentrations above 200 mg/m<sup>3</sup> produced severe irritation and could not be tolerated [4].

#### Dermal/ocular exposure

Long-term or repeated dermal exposures to ethylene glycol may cause dermatitis [12].

#### Genotoxicity

There are no studies in the literature that describe mutagenic or chromosomal effects of ethylene glycol in humans.

There are no structural alerts for ethylene glycol and in-vitro studies are negative, which indicate that ethylene glycol is unlikely to be a human mutagen [4].

#### Carcinogenicity

There is no data from published epidemiology studies to be able to make an assessment of the carcinogenicity of ethylene glycol in humans. Based on animal data, the lack of structural alerts and the lack of genotoxicity, ethylene glycol is not considered to be a carcinogen.

#### Reproductive and developmental toxicity

There is insufficient human data upon which to evaluate the developmental toxicity of ethylene glycol [2, 15]. Ethylene glycol is unlikely to be associated with an increased risk of fetal harm following occupational or environmental exposure. Following an acute exposure to ethylene glycol the risk to the fetus is likely to be determined by maternal toxicity [15].

## Animal and in-vitro data

### Inhalation

There is limited data on the inhalation toxicity of ethylene glycol following chronic inhalation exposure.

In a series of experiments of 6 weeks' duration, no treatment-related effects on survival, haematology or clinical chemistry or histology of liver, lungs and kidneys were noted in rats, guinea pigs, dogs or monkeys exposed to 10 or 57 mg/m<sup>3</sup> ethylene glycol vapour [4].

### Ingestion

The principal target organ following oral exposure to ethylene glycol is the kidney [4].

In a study on rats, significant effects were observed following dosing at 1,300 mg/kg for 13 weeks including increased kidney weights and renal histology findings of necrosis, fibrosis and crystal deposition in renal tubules. At 2,600 mg/kg, mortality was increased in males and in females, a range of microscopic changes were increased including vacuolation and infiltration of inflammatory cells [4]. A no-observed adverse effect level (NOAEL) of 71 mg/kg in rats has been reported [4].

A primate study used three animals dosed with 0.2 or 0.5% ethylene glycol in the diet for a 3-year period. At the termination of the study, one animal had a few glomeruli with thickened Bowman's capsules that were sclerotic and had many tubules containing granular eosinophilic materials. There were also a few scattered interstitial collections of mononuclear cells, with all other tissues examined unremarkable. There were no discernible changes in the other animals. The investigators concluded that exposure at these levels did not produce any toxic effects [16].

### Genotoxicity

Ethylene glycol does not have any structural alerts for DNA mutagenicity and there is no evidence from in-vitro or in-vivo data to suggest it is a mutagen.

Ethylene glycol gave negative results for mutagenicity in a series of the Ames test in *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 [17].

In an in-vivo study, rats dosed 1,000 mg/kg bw/day for 155 days were negative for dominant lethal mutations. Results were also negative for chromosomal aberrations in bone marrow cells of mice following intraperitoneal administration of 638 mg/kg for 2 days [4].

### Carcinogenicity

There is no evidence from animal studies to suggest that ethylene glycol is a carcinogen.

Ethylene glycol was not found to be carcinogenic in a 2-year bioassay of mice dosed at up to 12,000 mg/kg for 103 weeks in the diet [4]. A further bioassay in mice dosed at up to 1,000 mg/kg in the diet for 2 years was also negative, although histological reporting was incomplete [4].

### Reproductive and developmental toxicity

A number of studies have been carried out to investigate the developmental toxicity of ethylene glycol [4, 18]. There is evidence that high oral doses of ethylene glycol may cause developmental toxicity in mice and rats (>500 mg/kg and >1,000 mg/kg, respectively) [18]. However, the high dose levels used in these studies must be considered when relating these findings to possible human exposures. Findings included axial skeletal malformations, reduced body weights, external malformations and increased post-implantation loss [4, 18].

Maternal, but not developmental, toxicity was observed in pregnant rabbits administered up to 2000 mg/kg bw/day ethylene glycol by gavage on gestational days 6–19 [15, 18].

A dermal exposure study in mice on gestational days 6–15 showed no evidence of malformations or increased prenatal death at doses of up to 3,549 mg/kg [18].

There is sufficient evidence that ethylene glycol does not cause reproductive toxicity in multigenerational studies in mice and rats following oral exposure to very high levels in drinking water (>2,826 mg/kg in drinking water and >1,000 mg/kg in the diet, respectively) [18].

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