Agency for Toxic Substances and Disease Registry
Case Studies in Environmental Medicine (CSEM)
Ethylene Glycol and Propylene Glycol Toxicity

Course: **WB 1103**
Original Date: **October 3, 2007**
Expiration Date: **October 3, 2010**

Table of Contents

Key Concepts	• Ethylene glycol ingestion first affects the central nervous system (CNS). After a characteristic latent period, signs of inebriation may be followed by serious illness and even death, caused by toxic metabolites. • Propylene glycol, which is much less toxic than ethylene glycol, is metabolized to compounds that are normal constituents of the citric acid cycle. • No health effects have been reported in persons chronically exposed to ethylene glycol or propylene glycol at levels found in the environment.
About This and Other Case Studies in Environmental Medicine	This educational case study document is one in a series of self-instructional publications designed to increase the primary care provider's knowledge of hazardous substances in the environment and to promote the adoption of medical practices that aid in the evaluation and care of potentially exposed patients. The complete series of Case Studies in Environmental Medicine is located on the ATSDR Web site at http://www.atsdr.cdc.gov/csem/. In addition, the downloadable PDF version of this educational series and other environmental medicine materials provides content in an electronic, printable format, especially for those who may lack adequate Internet service.
How to Apply for and Receive Continuing Education Credit	See Internet address www2.cdc.gov/atsdrce/ for more information about continuing medical education credits, continuing nursing education credits, and other continuing education units.

Acknowledgments

We gratefully acknowledge the work that the medical writers, editors, and reviewers have provided to produce this educational resource. Listed below are those who have contributed to development of this version of the *Case Study in Environmental Medicine*.

Please Note: Each content expert for this case study has indicated that there is no conflict of interest to disclose that would bias the case study content.

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How to Use This Course

Introduction	The goal of *Case Studies in Environmental Medicine* (CSEM) is to increase the primary care provider's knowledge of hazardous substances in the environment and to help in evaluation and treating of potentially exposed patients. This CSEM focuses on ethylene glycol and propylene glycol toxicity**.**
Available Versions	Two versions of the Ethylene Glycol and Propylene Glycol Toxicity. CSEM are available • the HTML version http://www.atsdr.cdc.gov/csem/egpg/ provides content through the Internet; • the downloadable PDF version provides content in an electronic, printable format, especially for those who may lack adequate Internet service. The HTML version offers interactive exercises and prescriptive feedback to the user.
Instructions	To make the most effective use of this course, we recommend that you • take the Initial Check to assess your current knowledge about ethylene glycol and propylene glycol toxicity • read the title, learning objectives, text, and key points in each section • complete the progress check exercises at the end of each section and check your answers • complete and submit your assessment and posttest response online if you wish to obtain continuing education credit. Continuing education certificates can be printed immediately upon completion.
Instructional Format	This course is designed to help you learn efficiently. Topics are clearly labeled so that you can skip sections or quickly scan sections you are already familiar with. This labeling will also allow you to use this training material as a handy reference. To help you identify and absorb important content quickly, each section is structured as follows:

Section Element	Purpose
Title	Serves as a "focus question" that you should be able to answer after completing the section
Learning Objectives	Describes specific content addressed in each section and focuses your attention on important points
Text	Provides the information you need to answer the focus question (s) and achieve the learning objectives
Key Points	Highlights important issues and helps you review
Progress Check exercises	Enables you to test yourself to determine whether you have mastered the learning objectives
Progress Check answers	Provides feedback to ensure you understand the content and can locate information in the text

Learning Objectives	Upon completion of the Ethylene Glycol and Propylene Glycol Toxicity CSEM, you will be able to

Topic	Objectives
What is ethylene glycol?	• Describe the properties of ethylene glycol
Where is ethylene glycol found?	• Identify sources of ethylene glycol exposure
How are people exposed to ethylene glycol?	• Identify the primary route of exposure to ethylene glycol
What are U.S. standards for ethylene glycol exposure levels?	• Identify the American Conference of Governmental Industrial Hygienists (ACGIH) ceiling exposure limit for ethylene glycol • Identify the U.S. Environmental Protection Agency's (EPA) guidelines for ethylene glycol in drinking water
What is the Biological Fate of ethylene glycol?	• Describe why individuals with impaired liver function are more likely to suffer less toxicity but greater intensity of the initial central nervous system (CNS) effects caused by ethylene glycol exposure
What are the stages of ethylene glycol intoxication?	• Explain the mechanism of ethylene glycol toxicity • Describe the three stages of ethylene glycol toxicity
What are the physiologic effects of ethylene glycol poisoning?	• Describe the physiologic effects of ethylene glycol poisoning
How should patients exposed to ethylene glycol be evaluated?	• Describe the primary focus of the exposure history • Describe how the actual clinical presentation changes over time as intoxication evolves
What laboratory tests can help in evaluating patients exposed to ethylene glycol?	• Identify the abnormal laboratory findings associated with ethylene glycol poisoning. • List three measurements that can assist with diagnosis of ethylene glycol poisoning
How should patients exposed to ethylene glycol be treated?	• Identify the primary treatment strategy for managing ethylene glycol poisoning case
What is propylene glycol?	• Describe the properties and uses of propylene glycol
What instructions should be given to patients?	• Explain advice on self care and follow-up care to patients who are exposed to ethylene glycol or propylene glycol

Initial Check

Instructions	This Initial Check will help you assess your current knowledge about ethylene glycol toxicity. To take the Initial Check, read the case below and then answer the questions that follow.
Case Study, First Patient	***Disorientation, Ataxia, and Abdominal Symptoms in Visitors to a Municipal Airport***

A 67-year-old man is brought to the Emergency Department (ED) of a small community hospital where you are the family physician on call. The patient is experiencing ataxia, dizziness, and vomiting. He is hyperventilating. On physical examination, the patient appears well nourished, but agitated and disoriented. There is no odor of ethanol on his breath.

Vital Signs

The patient's vital signs are

- blood pressure (BP): 120/80 mm Hg
- temperature: 98.5° F
- pulse: 80 beats/minute
- respirations: 40 breaths/minute

Neurologic examination is otherwise normal with no crucial findings. There is no nystagmus. Abdominal and cardiorespiratory examinations are also normal.

Additional Information

The patient's friend brought him to the ED. The friend said the patient complained of dizziness and had begun to vomit late last night. This morning the patient was hyperventilating and continued to vomit. Both men are retired pilots who teach at the local airport's ground school. Because two other people had collapsed at the airport that morning and were taken by ambulance to another hospital, the friend wonders if the food at the airport cafeteria is responsible. Both he and the patient had hot dogs and coleslaw, but the friend states that he feels fine.

Results of Lab Tests

- blood ethanol and drug screen are negative
- arterial blood gases **(**ABG) results: pH 7.10; $PaCO_2$=20 mm Hg; PaO_2 =95 mm Hg; and Bicarbonate, =8 mEq/L
- sodium: 145 mmol/L (normal 135-145 mmol/L (Jacobs DS 1996))
- potassium: 3.8 mmol/L (normal 3.1-5.3 mmol/L)
- chloride: 105 mEq/L (normal 98-109 mEq/L)
- BUN: 20 mg/dL (normal 8-18 mg/dL)
- creatinine: 1.0 mg/dl (normal 0.6-1.2 mg/dL)
- glucose: 80 mg/dl (normal 65-110 mg/dL)
- calculated anion gap: 32 (normal 12 to 16)

Normal values may vary from lab to lab and depend upon the elevation above sea level.

Arterial blood gases (at sea level and breathing room air)	
Partial pressure of oxygen (PaO_2)	70–100 millimeters of mercury (mm Hg)
Partial pressure of carbon dioxide ($PaCO_2$)	35–45 mm Hg
pH	7.35–7.44
Bicarbonate (HCO^-_3)	21–28 milliequivalents per liter (mEq/L)
Oxygen content (O_2CT)	15%–23% (15–23 milliliters [mL] per 100 mL of blood)
Oxygen saturation (O_2Sat)	95%–100%

Case Study, Second Patient

Less than 30 minutes later, a 4-year-old boy is brought to the ED. On examination you find a sleepy but arousable child. There is no evidence of trauma or focal neurologic signs. Abdominal and cardiorespiratory examinations are normal.

Vital Signs

The patient's vital signs are

- BP, 94/76 mm Hg
- rectal temperature: 98.5° F
- respirations: 12 breaths/minute
- pulse: 78 beats/minute

Additional Information

The parents tell you they were attending a local fliers' club luncheon at the airport. When they found the child staggering and incoherent, they rushed him to the emergency room. On the way, he vomited in the car.

Results of Lab Tests

You order the same laboratory tests for the child that you ordered for the 67-year-old patient. The tests reveal that the child is

- hypoglycemic
- has slight acidosis
- an anion gap of 13

Additional Information

You contact the local health department. You are told they are investigating the earlier incidents at the airport. They suspect the airport's water supply is contaminated, but they have not identified the contaminant.

Initial Check Questions

1. What would you include in the list of problems for each patient? What is the differential diagnosis for an anion gap metabolic acidosis?
2. What additional tests, if any, will you order for these patients?
3. How will you initially treat these patients?
4. What questions would health department investigators ask airport visitors and employees to establish the exposure source?
5. The health department identifies the water contaminant as ethylene glycol. When construction crews at the airport were repairing the water supply system, they inadvertently connected the water from the heating system to the drinking water system. The concentration of ethylene glycol measured at the cafeteria's water source was 9% (90,000 ppm). The US Environmental Protection Agency (EPA) has an ethylene glycol drinking water quality guideline of 7 ppm (FSTRAC 1990). The lethal dose of 95% ethylene glycol is about 100 ml for an adult or 1.4 ml/kg.

   Who in the case study may be at risk of adverse health effects?

   Explain.

6. A week after the water contamination incident, a patient comes to your office. He de-ices airplanes at the airport and was drenched with de-icing fluid in a major spill yesterday. He knows that de-icing agents contain large amounts of ethylene glycol. He immediately showered and changed clothes after the incident, but he is worried about possible adverse health effects; for example, he wonders if cancer could develop. What will you tell him?
7. A pregnant worker at the airport consults you because she drank tea brewed with the contaminated water. Although she consumed only a small amount of tea and had no ill effects, she is worried that her fetus will be adversely affected. How will you counsel her?
8. It was later determined that during dinner at the cafeteria, the 67-year-old man had consumed several cups of coffee, while his friend, who did not become ill, drank only soda from a can. The serum ethylene glycol level for the 67-year-old patient is 55 mg/dl; the anion gap is 35. How will you treat the 67-year-old patient?
9. The child's ethanol level is 85 mg/dl. You repeat the ethanol test, and again the result is high. The parents are incredulous but admit that the child was not supervised closely during the luncheon, where wine and cocktails were served. Potential ethylene glycol exposure sources for the child could not be identified. How will you treat the child?

Initial Check Answers

1. The man's medical problems include

   - ataxia
   - vomiting
   - agitation
   - disorientation
   - hyperventilation
   - elevated anion-gap metabolic acidosis

   The child's medical problems include

   - somnolence
   - ataxia
   - mental status changes
   - vomiting
   - hypoglycemia
   - low body temperature
   - slight anion-gap metabolic acidosis

   (Common toxic agents associated with an elevated anion gap are shown in **Table 2**.)

2. Additional testing of these patients should include:

   - urinalysis
   - complete blood count
   - serum osmolality measured by the freezing-point–depression technique
   - ethylene glycol and methanol levels,
   - ammonia, acetaminophen, and aspirin levels, and
   - liver function tests.

   More information for this answer can be found in the section "What laboratory tests can help in evaluating patients exposed to ethylene glycol?"

3. Several hours have passed since the ingestion, and emesis or gastric lavage will be of little value. Activated charcoal is likely to be ineffective unless there is a question of a possible overdose. It is important to act promptly to correct the metabolic acidosis and to prevent further conversion of the remaining ethylene glycol into its toxic metabolites. The acidosis can be corrected with sodium bicarbonate therapy. Intravenous administration of ethanol or fomepizole (as described in the Treatment and Management section) will inhibit further metabolism of ethylene glycol. At serum ethylene glycol levels of 50 mg/dl or greater, hemodialysis should be started to remove ethylene glycol and its metabolites from the blood. Pyroxidine and thiamine may also be administered.

The child may be intoxicated with only ethanol or with ethanol and ethylene glycol. If intoxication is due to ethanol alone, carefully monitor blood glucose and ethanol levels until the intoxication resolves. However, you must consider that ethylene glycol poisoning may be a complication. Because ethanol competitively inhibits ethylene glycol metabolism, you may choose to let the ethanol level decrease naturally to 70 mg/dl, then administer ethanol intravenously to maintain that level. If laboratory results indicate that ingestion of ethylene glycol occurred, immediately transfer the child to a pediatric unit to undergo hemodialysis.

More information for this answer can be found in the section "How should patients exposed to ethylene glycol be treated?"

4. The most common sources of epidemic poisonings include contaminated food, beverages, and water supplies. The investigators would ask about types of food and drink available at the airport. They would take a detailed history of food and beverage intake from the patients and all others at the airport. They would attempt to find a common factor that would include those who were ill and exclude those who did not become ill. By gathering such data from a large number of people and statistically analyzing the data, the exposure source can usually be identified or possibilities restricted.

   More information for this answer can be found in the section "Where is ethylene glycol found?"

5. The lethal dose of antifreeze (95% ethylene glycol) is about 100 ml or 1.4 ml/kg, although there is wide variation among reported cases. A cup (240 ml) of the contaminated water would contain about 22 ml of ethylene glycol. This dose could cause significant toxicity. Even mild symptoms of ethylene glycol poisoning would be a concern for air traffic controllers and other airport personnel responsible for judgments affecting many lives. All employees and visitors who consumed beverages or food that was prepared using water at the airport should be examined.
   More information for this answer can be found in the section "How are people exposed to ethylene glycol?"

6. Absorption of ethylene glycol is minimal through intact skin and is not likely to lead to toxic effects. Because the patient showered and changed clothes immediately, it is unlikely that he will experience toxic effects from the spill. In the case of chronic exposure during the de-icing process, few particles from a spraying device are likely to be respirable, so inhalation of ethylene glycol would be minimal. Contact during the de-icing process would not contribute substantially to toxicity, especially if protective clothing and respiratory protection were used. There is no evidence that ethylene glycol causes cancer in humans.

   More information for this answer can be found in the section "What are the physiologic effects of ethylene glycol?"

7. You can inform the patient that studies in experimental animals indicate that ethylene glycol at the high, prolonged levels can cause developmental effects although no studies in humans specifically assess the effects of ethylene glycol on fetal development.

   More information for this answer can be found in the section "What are the physiologic effects of ethylene glycol?"

8. Several hours have passed since the ingestion, and emesis or gastric lavage will be of little value. Activated charcoal is likely to be ineffective. However, it is important to act promptly to correct the metabolic acidosis and to prevent further conversion of the remaining ethylene glycol into its toxic metabolites. The acidosis can be corrected with sodium bicarbonate therapy. Intravenous administration of ethanol or fomepizole (as described in the Treatment and Management section) will inhibit further metabolism of ethylene glycol. At serum ethylene glycol levels of 50 mg/dl or greater, hemodialysis may be instituted to remove ethylene glycol and its metabolites from the blood. Pyroxidine and thiamine may also be administered. Recent studies show that even when ethylene glycol levels exceed 50 mg/dL, hemodialysis can be avoided and patients can be treated solely with fomepizole. However if the level exceeds 50 mg/dL and is accompanied by renal failure and severe metabolic acidosis, then hemodialysis is indicated. The bottom line is that levels of ethylene glycol per se should not determine the indication for dialysis, but should be considered along with the clinical presentation.

   More information for this answer can be found in the section "How should patients exposed to ethylene glycol be treated?"

9. The child could be intoxicated with ethanol alone or with ethanol and ethylene glycol. If intoxication is due only to ethanol, carefully monitor blood glucose and ethanol until the intoxication resolves. However, you must consider that ethylene glycol poisoning may be a complication. Because ethanol competitively inhibits ethylene glycol metabolism, you may choose to let the ethanol level decrease naturally to 70 mg/dl, then administer ethanol intravenously to maintain that level. If laboratory results indicate that ingestion of ethylene glycol occurred, immediately transfer the child to a pediatric unit to undergo hemodialysis.

   More information for this answer can be found in the section "How should patients exposed to ethylene glycol be treated?"

What Is Ethylene Glycol?

Learning Objectives

Upon completion of this section, you should be able to

- describe the properties of ethylene glycol.

Definition

Ethylene glycol is a clear, colorless, odorless, sweet-tasting liquid. It has low vapor pressures at room temperature and, therefore, low potential for significant inhalation exposure.

Ethylene glycol and propylene glycol have similar physical properties and uses. Their chemical structures differ by only one methyl group (ethylene glycol, $HOCH_2CH_2OH$; propylene glycol, $CH_3CH[OH]CH_2OH$).

Synonyms

Ethylene glycol is also known as

- ethylene alcohol
- glycol alcohol
- glycol
- 1,2-dihydroxyethane
- 1,2-ethanediol

Toxicity

Route	Effect
Ingestion	Ethylene glycol causes acute toxicity in humans if ingested
Dermal	Ethylene glycol is poorly absorbed by skin
Inhalation	Ethylene glycol's low vapor pressure limits inhalation exposure.

Properties

Ethylene glycol

- dissolves in water and alcohol
- can hold large amounts of heat before boiling
- lowers the freezing point of water
- absorbs twice its weight in water

Uses

Ethylene glycol is used as

- a drying agent,
- a component of automotive fluids such as antifreeze, coolants, and hydraulic fluids,
- de-icing agents,
- a chemical intermediate,
- a solvent in inks, stains, pesticides, fire extinguishers, foams, polishes, and adhesives, and
- a heat-transfer fluid in air conditioning units and solar energy systems.

It is also used in producing polyester fibers, films, resin products, cosmetics, and fat extractants.

Environmental Fate	Air: Ethylene glycol does not persist in large amounts in ambient air because breakdown is rapid (half-life in air is 8-84 hours). In environmental exposure situations, its low vapor pressure precludes substantial inhalation exposure at ambient temperatures, and its poor skin absorption prevents significant absorption after dermal contact. Water: Ethylene glycol is miscible with water and will leach through soil to groundwater. It biodegrades rapidly in soil (half-life, 2-12 days). The half-life ranges from 2-12 days in surface water and 4- 24 days in ground water. Because it is not fat soluble and biodegrades rapidly, bioconcentration and bioaccumulation are insignificant (Agency for Toxic Substances and Disease Registry 1997).
Key Points	• Because of ethylene glycol's low vapor pressure and poor skin absorption, poisonings normally occur by ingestion. • Ethylene glycol degrades rapidly in the environment.
Progress Check	1. Which of the following statements is correct? A. Ethylene glycol is a colorless, odorless, and sweet-tasting liquid. B. Ethylene glycol dissolves in water and alcohol. C. Ethylene glycol can hold large amount of heat before boiling. D. all of the above. *To review relevant content, see "Definition" and "Properties" in this section.*

Where Is Ethylene Glycol Found?

Learning Objective	Upon completion of this section, you should be able to • identify sources of ethylene glycol exposure.
Introduction	The most common source of ethylene glycol exposure is antifreeze, which can contain up to 95% ethylene glycol. Antifreeze is readily available at hardware and automotive stores. Waste streams produced from the manufacture or use of ethylene glycol account for the most significant releases of this compound into the environment.
Commercial Products	Commercial products* containing high concentrations of ethylene glycol include • Dowtherm SR1 • Lutrol-9 • Norkool • Tescol • UCAR-17 * *Use of trade names is for identification only and does not imply endorsement by the Public Health Service or the U.S. Department of Health and Human Services.*
Environmental Exposures	Waste streams produced when ethylene glycol is manufactured or used account for the most significant releases of this compound into environment. In military and commercial aviation, large amounts of ethylene glycol are used for de-icing. It is sprayed as an aerosol or mist onto airplane wings to prevent ice buildup. Used in this manner, ethylene glycol may contaminate groundwater near airports through runoff and may expose workers to air levels ranging from (mg/m^3) to 10.4 mg/m^3 (*i.e.*, <0.02 parts per million [ppm] to 4.2 ppm)
Occupational Exposure	People who work in industries that use ethylene glycol may be exposed by touching these products or inhaling mists from spraying them. According to the guidelines set by the American Conference of Governmental Industrial Hygienists (ACGIH), the ceiling limit of ethylene glycol in workplace air is 39.4 ppm. (American Conference of Governmental Industrial Hygienists. 2003) Except for operations where ethylene glycol has been sprayed or made into a mist or vapor, exposure to it in the air is unlikely (Agency for Toxic Substances and Disease Registry 1997). Ethylene glycol is used in spacecraft coolant loops and in aviator protective clothing. Both applications present potential for exposure if leaks occur.
Key Points	• Antifreeze, which typically consists of 95% ethylene glycol, accounts for about 40% of the ethylene glycol produced and is easily accessible to the general public.

Progress Check

2. The most common source of ethylene glycol exposure is

   A. polyester fibers
   B. antifreeze
   C. cosmetics
   D. resin products

To review relevant content, see the "Introduction" in this section.

How Are People Exposed to Ethylene Glycol?

Learning Objective	Upon completion of this section, you should be able to • identify the primary route of exposure to ethylene glycol.
Introduction	The primary route of ethylene glycol entry into the body is through accidental or intentional ingestion. Workers in industries producing or using products containing ethylene glycol are at greatest risk of exposure.
Dermal Exposure	Skin contact is the most likely route of occupational exposure, but dermal exposure is not likely to lead to toxic effects. Skin contact while handling automotive antifreezes, coolants, and brake fluids is not likely to cause adverse health effects under normal conditions.
Inhalation Exposure	Ethylene glycol vapor and mist can be inhaled, particularly when the chemical is heated, agitated, or sprayed. A 1981-1983 National Institute for Occupational Safety and Health (NIOSH) survey found that an estimated 1,133,792 workers were potentially exposed to ethylene glycol (NIOSH 1990). In one study, prison volunteers were exposed to aerosolized ethylene glycol concentrations of 3-67 mg/m^3 (1.4-27 ppm) for 20-22 hours a day for 1 month. The resulting body fluid levels were 1.6-8.4 mg% for urine and 8-21.2 mg% for serum. The participants showed no serious signs of ethylene glycol intoxication, but they did experience nose and throat irritation (Wills, Coulston *et al.* 1974). No reports of adverse health effects from chronic ethylene glycol environmental exposures were found.
Ingestion	In the general population, ethylene glycol exposure occurs most commonly through ingestion of antifreeze. In the United States, the Toxic Exposure Surveillance System (TESS) prepared by the American Association of Poison Control Centers documented 4,829 cases of ethylene glycol poisonings, 31% experienced toxicity and needed treatment, and 9 cases were fatal in 1996 (Litovitz TL 1997), 2,174 cases treated in health care facilities in 1998 (Litovitz TL 1999), 6,281 ethylene exposures and 23 deaths in 1999 (Litovitz TL 2000), 5562 exposures; 2109 treated; 23 deaths in 2004 (Watson WA 2004).
Who Is at Risk of Exposure?	Workers at greatest risk of exposure are in industries that manufacture or use products containing ethylene glycol, particularly operations involving • automobile maintenance • aircraft de-icing
Exposure at Home	In the general population, ethylene glycol exposure occurs most commonly through ingestion of antifreeze. Ethylene glycol exposure in the general population may also result from skin contact while handling • automotive antifreezes • coolants • brake fluids Such exposures, however, are not likely to cause adverse health effects under normal conditions.

Key Points	• Workers in industries producing or using products containing ethylene glycol are at greatest risk of exposure. • General population exposures occur most commonly through accidental or intentional ingestion.
Progress Check	3. High doses that could produce harmful effects usually result from which of the following route of exposure to ethylene glycol A. inhalation B. ingestion C. dermal contact D. All are equally important *To review relevant content, see "Ingestion" in this section.*

What Are the U.S. Standards for Ethylene Glycol Exposure Levels?

Learning Objectives	After completing this section, you will be able to • identify the ACGIH ceiling exposure limit for ethylene glycol, and • identify the EPA guidelines for ethylene glycol in drinking water.
Introduction	The government has developed regulations and guidelines for ethylene glycol. These are designed to protect the public from potential adverse health effects.
Workplace Standards	The Occupational Safety and Health Administration (OSHA) has not set a permissible exposure limit (PEL) for ethylene glycol [2] , OSHA did enact a ceiling limit of 125 mg/m^3 (50 ppm) in 1989, but that level, along with 375 others, was vacated for procedural reasons by the 11th Circuit Federal Court in 1993. ACGIH (American Conference of Governmental Industrial Hygienists. 2003) recommends a ceiling exposure limit of 100 mg/m^3 (39.4 ppm).
Environmental Standards	***Water*** EPA recommends that children be exposed to no more than 20 mg/L (20 ppm) ethylene glycol in drinking water for 1 day, or 6 mg/L (6 ppm) per day over 10 days. They also recommend that adults be exposed to no more than a daily total of 7 mg/L (7 ppm) for a lifetime (FSTRAC 1990). ***Food*** The Food and Drug Administration (FDA) has approved ethylene glycol as an indirect food additive, for use only as a component of adhesives used in packaging.
Key Points	• ACGIH recommends a ceiling exposure limit of 100 mg/m^3 (39.4 ppm). • EPA recommends that children be exposed to no more than 20 mg/L (20 ppm) ethylene glycol in drinking water for 1 day, or 6 mg/L (6 ppm) per day over 10 days. They also recommend that adults be exposed to no more than a daily total of 7 mg/L (7 ppm) for a lifetime.

Progress Check

4. ACGIH recommends a ceiling exposure limit for ethylene glycol of

   A. 50 mg/m^3
   B. 100 mg/m^3
   C. 200 mg/m^3
   D. none of the above.

   To review relevant content, see "Key Points" in this section.

5. EPA recommends that, for a life-time ethylene glycol exposure of an adult, the limit should be no more than a daily total of

   A. 20 mg/L (20 ppm)
   B. 6 mg/L (6 ppm)
   C. 7 mg/L (7 ppm)
   D. none of the above

   To review relevant content, see "Environment" in this section.

What Is the Biological Fate of Ethylene Glycol?

Learning Objectives

Upon completion of this section, you should be able to

- describe why individuals with impaired liver function are more likely to suffer less toxicity, but greater intensity of the initial CNS effects caused by ethylene glycol exposure.

Introduction

Ethylene glycol is rapidly absorbed from the gastrointestinal tract and slowly absorbed through the skin or lungs. The toxicity of ethylene glycol results from its metabolism to more toxic metabolites. Like ethanol, ethylene glycol is rapidly absorbed in the GI tract, with peak absorption in 30-60 minutes.

Rapid Transformation

Because it is highly water-soluble, ethylene glycol is distributed throughout total body water. Peak tissue levels occur several hours after ingestion. Approximately 24 to 48 hours later, it is difficult to detect ethylene glycol in urine or tissues, thus indicating rapid biotransformation.

The normal serum half-life of ethylene glycol has been estimated to be about 2.5 hours in children and 3-8 hours in untreated adults.

Metabolism in the Liver

Other than its inebriating effects, ethylene glycol has relatively low toxicity. However, ethylene glycol is metabolized in the liver by successive oxidations to a variety of compounds that include

- glycoaldehyde
- glycolic acid
- glyoxylic acid
- oxalic acid

These compounds are more toxic than ethylene glycol itself (**Figure 1**) (Jacobsen and McMartin 1986; Hall AH 1992; Goldfrank LR 1998).

Some of these compounds have elimination half-lives of up to 12 hours.

The Role of Alcohol Dehydrogenase

The rate-limiting step in this metabolic process is the conversion of ethylene glycol to glycoaldehyde, a process that is catalyzed by alcohol dehydrogenase (ADH).

Several factors may influence susceptibility to ethylene glycol-induced toxicity, including

- individual differences in levels of liver ADH activity, and
- nutritional deficiencies, notably lack of thiamine or pyridoxine (two vitamins that mediate the metabolic detoxification of ethylene glycol).

Concomitant or recent ethanol exposure can *decrease or prevent* toxicity by preferentially competing for ADH, thereby inhibiting transformation of ethylene glycol to glycoaldehyde. Coadministration of ethanol increases the percentage of ethylene glycol excreted unchanged in the urine. Under normal conditions only a small fraction of ethylene glycol (less than 20% after low-dose ingestion) is excreted unchanged.

Fomepizole	A new medication, fomepizole or 4-methylpyrazole, targets the ADH enzyme as well (Baud, Galliot *et al.* 1988; Brent, McMartin *et al.* 1999; Jones and Volans 1999). Both ethanol and fomepizole are used therapeutically to treat ethylene glycol intoxication. Ethanol increases the half-life of ethylene glycol in the body to 17-18 hours; fomepizole increases the half-life to 11-14.75 hours.

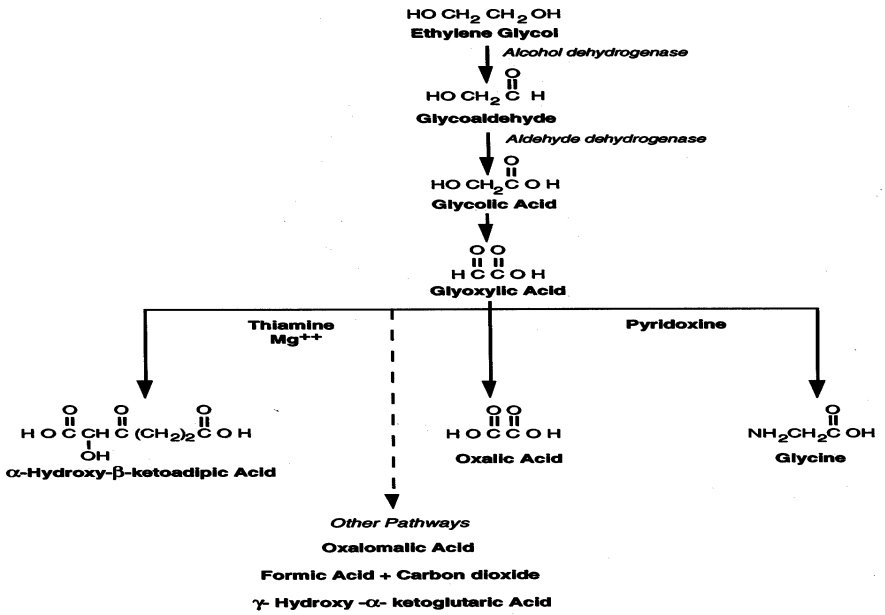

Figure 1. Metabolism of ethylene glycol. Adapted from Hall 1992.

Key Points	• Ethylene glycol is rapidly absorbed by the gastrointestinal tract. Dermal absorption is slow. Inhalation is generally not associated with toxicity. • Ethylene glycol is metabolized in the liver to a variety of compounds of increasing toxicity, such as glycoaldehyde, glycolic acid, and glyoxylic acid. • Under normal conditions, only a small fraction of absorbed ethylene glycol is unchanged when excreted in the urine.

Progress Check

6. Persons with reduced ability to metabolize ethylene glycol are

   A. more likely to suffer the severe toxicity, less likely to experience greater intensity of the initial CNS effects
   B. less likely to suffer the severe toxicity, more likely to experience greater intensity of the initial CNS effects
   C. more likely to suffer the severe toxicity and experience greater intensity of the initial CNS effects
   D. less likely to suffer the severe toxicity or experience greater intensity of the initial CNS effects.

   To review relevant content, see "Metabolism in the Liver" in this section.

What Are the Stages of Ethylene Glycol Intoxication?

Learning Objectives	Upon completion of this section, you should be able to • explain the mechanism of ethylene glycol toxicity and • describe the three stages of ethylene glycol toxicity.
Introduction	Ethylene glycol itself is toxic, but its harmful effects mainly result from the accumulation of its more toxic metabolites. Ethylene glycol is a central nervous system (CNS) depressant that can produce acute effects similar to those of ethanol. These CNS effects predominate during the first hours after exposure.
Mechanism of Toxicity	The main toxicity results from hepatic metabolism of ethylene glycol to glycoaldehyde, glycolate, glyoxylate, and oxalate. These metabolites inhibit • oxidative phosphorylation and cellular respiration • glucose and serotonin metabolism • protein synthesis • DNA replication • ribosomal RNA formation The accumulation of organic acid metabolites, especially glycolic acid, results in anion gap metabolic acidosis which affects many cellular functions.
Stages of Ethylene Glycol Intoxication	Severe ethylene glycol poisoning may go through three stages: CNS depression, cardiopulmonary toxicity, and renal toxicity **(Table 1)** (Friedman, Greenberg *et al.* 1962). However, signs and symptoms in an individual patient might not be separated so cleanly and could have much overlap. ***Stage 1 (CNS depression phase)*** CNS depression begins soon after exposure, lasting for up to 12 hours after ingestion. This depression appears similar to ethanol intoxication, but without the characteristic odor of alcohol. Initially, the inebriation, euphoria, slurred speech, sleepiness, and so forth are due to the unmetabolized ethylene glycol. After the glycoaldehyde forms (at 4-12 hours) and metabolic acidosis begins, CNS depression—if it is a serious intoxication—can lead to the following effects: • seizures • coma • cerebral edema (in some cases) • gastrointestinal irritation (nausea and vomiting) An osmolal gap, without metabolic acidosis, or an anion gap may be seen before significant metabolism of ethylene glycol occurs. As ethylene glycol is metabolized, the osmolal gap, if present, will decrease and an anion gap metabolic acidosis evolves. Patients who present late may have renal failure with normal osmolal and anion gaps and no acidosis or measurable ethylene glycol levels (Ford M 1991). Signs of metabolic acidosis due to the metabolites may become apparent late in stage 1.

Stage 2 (Cardiopulmonary toxicity phase)

The following cardiorespiratory symptoms may appear 12-24 hours after ingestion

- tachycardia,
- tachypnea, and
- hypertension or hypotension.

The following conditions may develop in this stage

- pulmonary edema,
- pneumonitis,
- congestive cardiac failure, and
- shock.

Formation of oxalic acid may lead to deposition of calcium oxalate crystals in

- the meninges,
- blood vessel walls,
- lung, and
- myocardium.

These deposits can cause tissue injury. They also may lead to hypocalcemia secondary to calcium oxalate precipitation. Most deaths from ethylene glycol poisoning occur during stage 2.

Stage 3 (Renal toxicity phase)

Kidney damage usually develops 24-72 hours after exposure. Acidosis and acute renal failure may result from deposition of calcium oxalate crystals in the kidneys.

The following conditions characterize the third phase

- flank pain,
- costovertebral angle tenderness, and
- oliguric renal failure.

Prolonged, rarely permanent, kidney failure is distinguished by

- proteinuria,
- hematuria,
- crystalluria, and
- increased serum BUN and creatinine.

Calcium oxalate crystals may appear in the urine as early as stage 1, but absence of these crystals does not rule out the diagnosis of ethylene glycol poisoning.

Table 1. Clinical course in acute ethylene glycol intoxication.

Stage	Onset after ingestion	Primary systems affected	Signs and symptoms
1	30 minutes to 12 hours	Central nervous system	Inebriation, euphoria, ataxia, slurred speech, drowsiness, irritation, restlessness, and disorientation
		Gastrointestinal	Nausea and vomiting
		Metabolic	Elevated osmolal gap
2	12 to 24 hours	Cardiovascular	Mild hypertension, tachycardia, and shock
		Pulmonary	Tachypnea, adult respiratory distress syndrome, pulmonary edema, and pneumonitis
		Metabolic	Metabolic acidosis with elevated anion gap and decreased osmolal gap, possible tetany from hypocalcemia, and hyperventilation
3	24 to 72 hours	Renal	Flank pain, costovertebral angle tenderness, oliguric renal failure, hyperkalemia, and hypocalcemia
		Metabolic	May have normal anion and osmolal gaps.

Key Points

- Unmetabolized ethylene glycol contributes to CNS depression.
- Delayed clinical toxicity results from conversion of ethylene glycol to metabolites of greater toxicity.

Progress Check

7. Which of the following cellular biochemical reactions can be inhibited by acid and aldehyde metabolites of ethylene glycol?

   A. oxidative phosphorylation and cellular respiration
   B. protein synthesis
   C. DNA replication
   D. all of the above

   To review relevant content, see "Mechanism of Toxicity" in this section.

8. Tachypnea generally appears in which of the following stages:

   A. Stage 1 (0.5 – 12 hr)
   B. Stage 2 (12 – 24 hr)
   C. Stage 3 (24 – 72 hr)
   D. Stage 2 and 3 (12 – 72 hr)

   To review relevant content, see "Table 1" in this section.

What Are the Physiological Effects of Ethylene Glycol Poisoning?

Learning Objectives	Upon completion of this section, you should be able to • describe the physiologic effects of ethylene glycol poisoning.
Introduction	Ingestion of ethylene glycol has significant toxicological implications if undetected or left untreated. The preceding section described the clinical features of ethylene glycol poisoning in three stages that are based on the time after ingestion. This section depicts the systemic effects associated with significant ethylene glycol exposure.
Neurologic Effects	The initial phase of ethylene glycol poisoning is characterized by inebriation caused by unmetabolized ethylene glycol. In acute poisoning cases, the following symptoms are common (Parry and Wallach 1974; Buell, Sterling *et al.* 1998) • ataxia • slurred speech • drowsiness • irritation • restlessness • disorientation
Possible Sequelae	Possible sequelae of severe poisonings (Walder and Tyler 1994; Hantson, Vanbinst *et al.* 2002) include • myoclonic jerks • convulsions • coma • death Cerebral edema and deposition of calcium oxalate crystals in the walls of small blood vessels in the brain contribute to this CNS toxicity (Jobard, Harry *et al.* 1996; Bey, Walter *et al.* 2002; Tobe, Braam *et al.* 2002). Some studies also documented brain dysfunction with corresponding cranial computed tomography findings after ethylene glycol ingestion (Chung and Tuso 1989; Zeiss, Velasco *et al.* 1989; Morgan, Ford *et al.* 2000).
Cranial Nerve Damage	Recovery in survivors is usually rapid and complete. However, the following cranial nerve palsies have been reported one or more weeks after acute exposure • facial palsy • hearing loss • dysphagia • opthalmoplegia • visual disturbances Such adverse effects are not seen often, but delayed treatment may contribute to their development. Such adverse effects are not seen often, but delayed treatment may contribute to their development (Momont and Dahlberg 1989; Broadley, Ferguson *et al.* 1997; Lewis, Smith *et al.* 1997; Tobe, Braam *et al.* 2002).

Respiratory Effects

Inhaled ethylene glycol can irritate the respiratory tract.

- Throat and upper respiratory irritation were the most common complaints following prolonged experimental exposures in humans (4 weeks at concentrations of 1-25 ppm).
- Exposure to 60 ppm aerosolized ethylene glycol caused very noticeable irritation.
- Exposure to 80 ppm aerosolized ethylene glycol was judged "intolerable" because respiratory discomfort developed rapidly (Wills, Coulston *et al.* 1974).

Pulmonary effects typically occur 12 to 72 hours after ingestion of ethylene glycol. Pulmonary edema and adult respiratory distress syndrome (ARDS) have been reported in ethylene glycol victims (Haupt, Zull *et al.* 1988; Piagnerelli, Carlier *et al.* 1999).

The following respiratory effects often occur 12 hours or more after exposure in victims of severe ethylene glycol poisoning.

- tachypnea,
- hyperventilation,
- Kussmaul respirations.

Such effects most often reflect physiological compensation for severe metabolic acidosis rather than primary lung disease (Friedman, Greenberg *et al.* 1962; Parry and Wallach 1974; Godolphin, Meagher *et al.* 1980). Autopsies of ethylene glycol victims revealed the following

- pulmonary edema with diffuse hemorrhagic exudates,
- bronchopneumonia (probably caused by aspiration), and
- deposits of calcium oxalate crystals in lung parenchyma (Vale 1979).

Cardiovascular Effects

The following severe cardiovascular effects have been reported in ingestion victims, during stage 2 (Friedman, Greenberg *et al.* 1962; Parry and Wallach 1974; Vale 1979):

- Congestive heart failure with cardiogenic pulmonary edema
- Circulatory collapse

Severe metabolic and fluid electrolyte abnormalities (Friedman, Greenberg *et al.* 1962; Parry and Wallach 1974) may cause

- cardiac dysrhythmias
- cardiac arrest

Ingestion of antifreeze (Walder and Tyler 1994)' (Jobard, Harry *et al.* 1996; Rasic, Cengic *et al.* 1999) may affect blood pressure, causing either

- hypertension or
- hypotension, which may progress to cardiogenic shock.

Metabolic Effects

Severe ethylene glycol poisoning is characterized by metabolic acidosis.

- Onset occurs within 24 hours after ingestion.
- Acidosis is caused primarily by the accumulation of glycolic and glyoxylic acid. Oxalic and excess lactic acid also contribute.

The metabolic acidosis of ethylene glycol poisoning is characterized as normochloremic (Berman, Schreiner *et al.* 1957; Curtin, Kraner *et al.* 1992; Hantson, Hassoun *et al.* 1998; Bey, Walter *et al.* 2002)with

- low serum bicarbonate level and pH
- elevated acidemia and anion gap

Ethylene glycol is a small, osmotically active molecule that

- markedly increases plasma osmolality
- causes a large osmolal gap

Osmolality reflects the number of solute particles in a solution. Numerical measures of osmolality express the number of particles present in a given weight of solvent.

Tetany can sometimes occur due to hypocalcemia that results from precipitation of calcium by the oxalate formed during ethylene glycol metabolism (Parry and Wallach 1974).

Renal Effects

Kidney damage typically occurs during stage 3 of ethylene glycol intoxication.

- Kidney damage manifests as acute oliguric renal failure.
- Costovertebral angle tenderness is the most common physical finding (Friedman, Greenberg *et al.* 1962).
- The most characteristic abnormality is the presence of large numbers of "tent-shaped" (octahedral) or needle-shaped oxalate crystals in the urine (Olivero 1993; Huhn and Rosenberg 1995).
- Absence of oxalate crystals does not rule out the diagnosis of ethylene glycol poisoning (Haupt, Zull *et al.* 1988; Curtin, Kraner *et al.* 1992; Baum, Langman *et al.* 2000; Boyer, Mejia *et al.* 2001; Hantson, Vanbinst *et al.* 2002).

Other typical urinalysis abnormalities are

- low specific gravity
- proteinuria
- microhematuria
- pyuria
- elevated serum BUN and creatinine

Disturbed renal function may be mild and short-lived or severe and persistent for several months. Permanent renal insufficiency is uncommon but does occur (Berman, Schreiner *et al.* 1957; Friedman, Greenberg *et al.* 1962; Parry and Wallach 1974; Buell, Sterling *et al.* 1998; Hantson, Hassoun *et al.* 1998).

	The toxicity of ethylene glycol is linked with two metabolites.
	
	• Glycolic acid, which causes the acidosis.
	
	• Oxalic acid.
	  o Oxalic acid is poorly soluble in the presence of calcium.
	  o Calcium oxalate crystals in the urine are diagnostic.
	  o The precipitation of oxalate crystals in the tubular lumen leads to luminal blockage and compression-induced loss of glomerular filtration (renal failure).
	
	In transformed kidney cells, the oxalate ion induces cytotoxic damage (McMartin and Cenac 2000). Another study, however, stated that glycoaldehyde and glyoxylate are the principal metabolites responsible for ethylene glycol nephrotoxicity (Poldelski, Johnson *et al.* 2001).

Carcinogenicity and Teratogenicity	Data are insufficient to determine whether ethylene glycol causes cancer or developmental defects. • Human studies have shown no link between ethylene glycol exposure and cancer or reproductive or developmental hazards. • Animal studies have not found an association between ethylene glycol exposure and cancer. • Ethylene glycol exposure was teratogenic to mice and rats, resulting in craniofacial and neural tube closure defects and skeletal dysplasia (Lamb, Maronpot *et al.* 1985; Price, Kimmel *et al.* 1985; Marr, Price *et al.* 1992; Tyl, Ballantyne *et al.* 1995). Ethylene glycol itself is used to cryopreserve embryos of many mammals and is thus an unlikely cause of these abnormalities.
Other Effects	Nausea, vomiting (with or without blood), and abdominal pain are frequent early findings following ethylene glycol ingestion (Meditext 2004). Ethylene glycol is only a minor skin and mucous membrane irritant, although a few cases of allergic contact dermatitis have been documented (Clayton GD & Clayton FE 1994). Reported effects on the blood have included leukocytosis, occasional methemoglobinemia, and bone marrow arrest (Verrilli, Deyling *et al.* 1987; Hantson, Hassoun *et al.* 1998; Rasic, Cengic *et al.* 1999). Reported musculoskeletal effects have included muscle tenderness and elevation of creatine kinase (Friedman, Greenberg *et al.* 1962; Parry and Wallach 1974; Verrilli, Deyling *et al.* 1987).
Key Points	• Signs of inebriation are among the first symptoms to appear after ethylene glycol ingestion. • Delays in initiating treatment can result in more severe adverse effects. • The most common cause of tachypnea is uncompensated metabolic acidosis. • Ethylene glycol poisoning through ingestion can cause noncardiogenic pulmonary edema and ARDS. • Ethylene glycol poisoning can cause dysrhythmias and heart failure. • Ethylene glycol exposure is characterized by an osmolal gap and a metabolic acidosis with an elevated anion gap. • Nephrotoxicity is the dominant effect of significant ethylene glycol

poisoning.

- Human studies have shown no link between ethylene glycol exposure and cancer or reproductive or developmental hazards.

Progress Check

9. Signs of inebriation are among the first symptoms to appear after ethylene glycol ingestion. Inebriation is caused by

   A. ethanol
   B. unmetabolized ethylene glycol
   C. metabolites of ethylene glycol
   D. none of the above.

   To review relevant content, see "Neurologic Effects" in this section.

10. The respiratory effects such as tachypnea and hyperventilation often occur 12 hours or more after exposure in victims of severe ethylene glycol poisoning. Such effects most often reflect

    A. physiological compensation for severe metabolic acidosis
    B. primary lung disease
    C. adult respiratory distress syndrome (ARDS)
    D. all of the above

    To review relevant content, see "Respiratory Effects" in this section.

11. The metabolic acidosis of ethylene glycol poisoning is characterized as

    A. normochloremic
    B. low bicarbonate level and pH
    C. elevated acidemia and anion gap
    D. all of the above

    To review relevant content, see "Metabolic Effects" in this section.

12. Which of the following statements about nephrotoxicity resulting from significant ethylene glycol poisoning is correct?

    A. Kidney damage manifests as acute oliguric renal failure.
    B. Urine contains many oxalate crystals.
    C. Absence of oxalate crystals in the urine does not rule out a diagnosis of ethylene glycol poisoning.
    D. all of the above.

    To review relevant content, see "Renal Effects" in this section.

How Should Patients Exposed to Ethylene Glycol Be Evaluated?

Learning Objective

Upon completion of this section, you should be able to describe

- the primary focuses of the exposure history and
- how the actual clinical presentation changes over time as intoxication evolves.

Introduction

Ethylene glycol ingestion is a medical emergency requiring prompt recognition and aggressive treatment.

- The actual clinical presentation changes over time as intoxication evolves.
- Signs and symptoms depend on the amount ingested and concurrent use of alcohol.

Therefore, making a correct diagnosis requires a reliable history of the time, route, and magnitude of exposure. In some cases, however, a detailed history can be difficult to obtain because of the patient's altered mental state. If ethylene glycol poisoning is strongly suspected, begin appropriate treatment while waiting for confirmation by laboratory results (Stokes and Aueron 1980; Johnson, Meggs *et al.* 1999).

Patients who have been exposed to ethylene glycol should undergo a thorough medical evaluation. Early and accurate diagnosis is important in deciding appropriate care strategies. In cases of ethylene glycol exposure, medical evaluation should include

- an exposure history,
- a physical examination,
- an assessment of clinical presentation, and
- laboratory tests

This section focuses on the first three items, which are typically conducted during the patient's visit to your office. Recommended tests are discussed in the next section.

Exposure History

Although environmental exposures to ethylene glycol are a concern, nearly all cases of ethylene glycol poisoning are due to ingestions (Agency for Toxic Substances and Disease Registry 1997).

- A careful history of possible substance abuse and a meticulous search in the home for ethylene glycol-containing compounds should be made in all suspected poisonings.
- A history of ethanol abuse may suggest ingestion of ethylene glycol as an ethanol substitute. Teens may experiment with this compound.
- Regional poison control centers can often assist in identifying the contents of bottles and packages if product labels do not list the chemical ingredients.
- Inquiring about similar symptoms in family members, friends, and coworkers may be helpful in identifying a common source of exposure.

Physical Examination

The patient's vital signs should be monitored. Although not specific for ethylene glycol intoxication, the following symptoms have been associated with moderate or severe poisoning (Friedman, Greenberg *et al.* 1962; Parry and Wallach 1974):

- tachypnea,
- tachycardia,
- mild hypertension, and
- low-grade fever

A complete neurologic examination should be performed. Pay special attention to

- mental status,
- gait, and
- balance.

Clinical Presentation

Patients who have ingested ethylene glycol often progress through three clinical stages (Friedman, Greenberg *et al.* 1962) (described earlier, *Stages of ethylene glycol intoxication*) that represent a continuum. Individual patients may develop any combination of organ or systemic effects (**Table 1**). The time course for each stage, as well as the severity of illness, depends on the amount of ethylene glycol ingested and whether ethanol was ingested concurrently.

Stage 1

During the first 12 hours after ingestion, the following CNS effects predominate

- headache,
- slurred speech,
- confusion,
- tremor, and
- nystagmus.

Stage 2

Stage 2 begins 12-24 hours after ingestion and is caused by the products of ethylene glycol metabolism. The primary manifestations are cardiopulmonary

- tachypnea,
- tachycardia, and
- hypertension.

You may also see

- hypotension,
- dysrhythmias,
- respiratory distress syndrome,
- pulmonary edema, and
- profound metabolic acidosis.

Stage 3

Stage 3 occurs 24-72 hours after ingestion, if the condition is not treated. Acute renal dysfunction may occur, ranging from mild elevations in BUN and serum creatinine to oliguric renal failure.

- Renal dysfunction usually resolves, but may be irreversible.
- Myopathy and bone marrow suppression have also been reported.

In some cases, cranial nerve abnormalities may develop several days after exposure. These neurologic sequelae are usually found when treatment is delayed or inadequate.

Key Points

- A detailed history is important in diagnosing ethylene glycol poisoning.
- Prompt recognition and early therapeutic intervention are essential to preventing latent effects and potential sequelae of ethylene glycol poisoning.
- Patients poisoned with ethylene glycol may initially appear inebriated and may lack other signs and symptoms of severe toxic exposure.
- After a characteristic latent period, metabolites of ethylene glycol can cause potentially life-threatening illness.

Progress Check

13. Why is a detailed history important in diagnosing ethylene glycol poisoning?

    A. Making a correct diagnosis requires a reliable history of the time, route, and magnitude of exposure.
    B. A history of ethanol abuse may suggest ingestion of ethylene glycol as an ethanol substitute.
    C. A careful history about similar symptoms in family members, friends, and coworkers may be helpful in identifying a common source of exposure.
    D. all of the above.

    To review relevant content, see "Exposure History" in this section.

14. Prompt recognition and early therapeutic intervention are essential in clinical management of ethylene glycol poisoning. Why?

    A. After a characteristic latent period, metabolites of ethylene glycol can cause potentially life-threatening illness.
    B. Prompt recognition and aggressive treatment may prevent latent effects and potential sequelae of ethylene glycol poisoning.
    C. Time is of the essence in the case of serious ethylene glycol poisoning because the renal failure may occur just a matter of days if no appropriate treatment is instituted.
    D. all of the above.

    To review relevant content, see "Clinical Presentation" in this section.

What Laboratory Tests Can Help In Evaluating Patients Exposed to Ethylene Glycol?

Learning Objectives

Upon completion of this section, you should be able to

- identify the abnormal laboratory findings associated with ethylene glycol poisoning and
- list three measurements that can assist with diagnosis of ethylene glycol poisoning.

Introduction

All patients with known or suspected ethylene glycol ingestion require the following tests

- arterial blood gases
- blood glucose
- serum electrolytes
- blood ethanol

Other helpful laboratory tests may include

- serum BUN and creatinine
- calcium and magnesium levels
- acetaminophen and aspirin levels
- liver function tests
- urinalysis (with special attention to crystalluria)

A measured osmolality by the freezing point depression method is needed to detect an osmolal gap. Results of these laboratory tests will confirm the presence and degree of metabolic acidosis and allow calculation of the anion and osmolal gaps (Figure 2).

Ethanol, Methanol, Ketoacidosis

A blood ethanol level will establish whether initial CNS symptoms may be due to ethanol. The presence of ethanol will also have a substantial impact on metabolism and therapy. Patients who have both anion and osmolal gap should also have blood methanol tests. Serum lactate and β-hydroxybutyrate levels may be indicated for an alcoholic patient, if alcoholic ketoacidosis is suspected (Meditext 2004).

Urinary Crystals

The presence of calcium oxalate or hippurate crystals in the urine, together with an elevated anion gap or osmolal gap, strongly suggests ethylene glycol poisoning (Albertson 1999). Urinary crystals result from

- the precipitation of calcium by the oxalic acid metabolite of ethylene glycol
- the reaction of the glycine metabolite with benzoic acid, which forms hippuric acid

Urinary crystals can take many forms

- dumbbells
- envelopes
- needles (most commonly) (Jacobsen, Hewlett *et al.* 1988)

	Absence of urinary crystals, however, does not rule out poisoning. Numerous studies have documented that renal damage occurs after ethylene glycol ingestion without deposition of calcium oxalate crystals in the kidney (Vale 1979; Hall AH 1992).
Urine Fluorescence	Because some antifreeze products contain fluorescein, the urine may fluoresce under a Wood's lamp (Winter, Ellis *et al.* 1990). However, recent studies argued if Wood's lamp determination of urine fluorescence could be a reliable diagnostic test (Casavant, Shah *et al.* 2001; Wallace, Suchard *et al.* 2001; Sharma, O'Shaughnessy *et al.* 2002).
Serum Analysis	An elevated serum level of ethylene glycol confirms ethylene glycol poisoning. Significant toxicity is often associated with levels greater than 25 milligrams per deciliter (mg/dL) (Hall AH 1992; Goldfrank LR 1998).
False Positives	Communication with the laboratory is critical in poisoning cases for several reasons. • 2,3-butanediol, often found in the plasma of alcoholics, can be mistakenly identified as ethylene glycol when the analysis is performed by gas chromatography (Jones, Nilsson *et al.* 1991). • Propylene glycol can also interfere with some ethylene glycol assays (Robinson, Scott *et al.* 1983; Apple, Googins *et al.* 1993; Hilliard, Robinson *et al.* 2004). • An inherited metabolic disorder can present as ethylene glycol intoxication from laboratory results (Pien, van Vlem *et al.* 2002).
Glycolic Acid Analysis	Recent studies have demonstrated usefulness of glycolic acid analysis in ethylene glycol poisoning cases (Fraser 1998; Porter, Rutter *et al.* 2001; Fraser 2002). Most laboratories routinely screen for unchanged ethylene glycol in suspected poisonings. They estimate the amount of ethylene glycol present in positive cases even though toxicity from ethylene glycol exposure is primarily caused by one metabolite—glycolic acid. Measuring glycolic acid in ethylene glycol poisonings has certain advantages • findings correlate better with ethylene glycol toxicity than ethylene glycol levels • findings determine how much ethylene glycol has metabolized to glycolic acid • the presence of glycolic acid objectively indicates toxicity • the test confirms that the metabolic acidosis was due to ethylene glycol poisoning rather than another cause (Fraser 2002) Yao and Porter (1996) were the first to develop a procedure for simultaneously determining ethylene glycol and its major toxic metabolite, glycolic acid. Porter and colleagues published a modification of the method a few years later (Yao and Porter 1996; Porter, Rutter *et al.* 1999).
Anion and Osmolal Gaps	The presence of metabolic acidosis with both anion and osmolal gaps is an important clue to the diagnosis (Friedman, Greenberg *et al.* 1962; Parry and Wallach 1974; Szerlip 1999). Numerous toxic substances are associated with an elevated anion gap (**Table 2**) (Goldfrank LR 1990). An elevated osmolal gap suggests the presence of a low-molecular weight substance.

Only four significant conditions will cause metabolic acidosis and elevate both the anion and osmolal gaps

1. methanol poisoning
2. ethylene glycol poisoning
3. alcoholic ketoacidosis
4. diabetic ketoacidosis

Acetone causes an osmolal gap. Lactic acidosis or propylene glycol intoxication also is capable of causing metabolic acidosis with osmolal gap.

However, when large quantities of ethanol and ethylene glycol are ingested concurrently, metabolic acidosis may be inhibited or delayed. In such cases, the patient may initially develop an osmolal gap but will not immediately develop acidosis or an anion gap.

Although an osmolal gap is often cited as indirect evidence of the presence of an exogenous alcohol or glycol, other substances or conditions may be causative. Conversely, failure to find an osmolal gap may lead to the erroneous assumption that no exogenous substances are present. A small osmolal gap may, however, represent a significant alcohol level.

Caution must be used when interpreting the osmolal gap. Recent reviews argued that the use of the osmolal gap as a screening tool for ethylene glycol has significant limitations and remains hypothetical (Glaser 1996; a, Purssell *et al.* 2004; Purssell, Lynd *et al.* 2004).

Table 2. Common toxic agents associated with an elevated anion gap.

Substance	CNS Depression	Metabolic Acidosis	Ketosis	Increased Osmolality	Characteristic Findings
Methanol	+	++	–	+	Blindness and pink edematous optic disk
Ethanol	+	+	+	+	Alcoholic ketoacidosis
Ethylene glycol	+	++	–	+	Renal failure, calcium oxalate and hippurate crystals, CNS depression, tachycardia, and tachypnea
Isopropanol	+	–	++	+	Hemorrhagic tracheobronchitis and gastritis
Salicylates	+	+	+	–	Vomiting, tinnitus, and hyperthermia

Adapted from Goldfrank LR 1990.

An ethylene glycol level (in mg/dL) may be estimated from the osmolal gap (OG) if it is the only osmotically active poison present and levels are taken early in the course. This is most accurate if the ethylene glycol level is between 50 to 100 mg/dL:

Estimated ethylene glycol level = OG × 6.2.

The serum anion gap (AG) is determined from serum electrolytes measured in mEq/L and may be defined by the formula:

$$AG = (Na^+ + K^+) - (Cl^- + HCO_3^-)$$

(Normal anion gap: 12 to 16)

The serum osmolal gap (OG) is most commonly approximated by the formula:

OG = osmolality (measured)* – $2Na^+$ + [BUN divided by 2.8]

+ [glucose divided by 18]

+ [BAT (ethanol) divided by 4.6 (if present)]

(Normal osmolal gap: < 10)

*In this formula, osmolality (measured) is obtained by the freezing-point–depression method and expressed in milliosmoles per liter (mOsm/L); Na^+ in mEq/L; BUN and glucose in mg/dL; blood alcohol test (BAT) in mg/dL.

Figure 2. Formulas for calculating anion and osmolal gaps. (Goldfrank LR 1990; Hall AH 1992)

Key Points

- Ethylene glycol poisoning is strongly suggested by
  - an elevated anion-gap metabolic acidosis
  - an elevated osmolal gap
  - urinary crystals
- Measurement of serum ethylene glycol levels can confirm poisoning.

Progress Check

15. Which of the following is the most reliable diagnostic index for suspected ethylene glycol ingestion?

    A. an elevated anion gap and an increased osmolal gap
    B. normochloremic metabolic acidosis
    C. calcium oxalate or hippurate crystalluria
    D. elevated serum ethylene glycol level

    To review relevant content, see "Introduction" in this section.

16. Glycolic acid analysis has all of the following advantages except

    A. Findings correlate better with ethylene glycol toxicity than ethylene glycol levels.
    B. Findings determine how much ethylene glycol has metabolized to glycol acid.
    C. The test confirms that the metabolic acidosis was due to ethylene glycol poisoning rather than another cause.
    D. Glycolic acid analysis is routinely performed in most laboratories.

To review relevant content, see Glycolic Acid Analysis in this section.

How Should Patients Exposed to Ethylene Glycol Be Treated?

Learning Objectives

Upon completion of this section, you should be able to

- identify the primary treatment strategy for managing ethylene glycol poisoning cases.

Introduction

Treatment should not be delayed pending results of ethylene glycol serum levels if the patient's condition or history suggests such poisoning. Treatment advice can be obtained from a regional poison control center or medical toxicologist.

First Steps

Initial management of suspected poisoning

- includes basic life support
- may require intubation and mechanical ventilation

Prevent Absorption

When the ingestion is recent, take steps to prevent ethylene glycol absorption.

- Induced emesis or gastric lavage may be useful if
  - ingestion occurred within 2 hours
  - the patient has a normal level of consciousness
- Activated charcoal adsorbs ethylene glycol poorly and is probably not effective in this setting (Goldfrank LR 1998).

Specific Treatment

Specific treatment for ethylene glycol poisoning includes

- sodium bicarbonate to correct the metabolic acidosis as indicated,
- ethanol or fomepizole (Antizol) to competitively inhibit metabolism of ethylene glycol to its more toxic metabolites, and
- hemodialysis, if indicated, to remove ethylene glycol and glycolic acid. (Stokes and Aueron 1980; Gabow, Clay *et al.* 1986; Cheng, Beysolow *et al.* 1987; Malmlund, Berg *et al.* 1991; Jacobsen and McMartin 1997; Moreau, Kerns *et al.* 1998; Bey, Walter *et al.* 2002)

This treatment strategy is effective in most cases, but renal failure and death can occur if treatment is delayed.

Table 3. Intravenous administration of ethanol in ethylene glycol and methanol poisoning.[*]

Dose	Level[†]	Milliliters (mL) of 10% Ethanol[‡]
Loading	600 to 800 mg/kg	7.6 to 10/kg
Maintenance		
Chronic alcoholic	154 mg/kg/hr	1.95 kg/hr
Social drinker	110 mg/kg/hr	1.39 kg/hr
Nondrinker	66 mg/kg/hr	0.83 kg/hr
During hemodialysis[§]		
Chronic alcoholic	304 mg/kg/hr	3.95 kg/hr
Social drinker	256 mg/kg/hr	3.29 kg/hr
Nondrinker	216 mg/kg/hr	2.70 kg/hr

[*]The goal of ethanol therapy is to maintain the blood ethanol level between 100 and 150 mg/dL.

[†]mg/kg: milligrams per kilogram; mg/kg/hr: milligrams per kilogram per hour.

[‡]In 5% dextrose in distilled water (D_5W) per kilogram body weight.

[§]Assuming no ethanol is added to dialysis bath.

Adapted from Hall AH 1992.

Monitor the Patient	Prolonged administration of ethanol can cause hypoglycemia, particularly in children; therefore, blood glucose should be monitored closely throughout treatment. The hypoglycemia that develops in adults is often overlooked because the impairment of mental status is attributed to the ethanol.
Calculate the Dose	• Infuse the loading dose and the maintenance dose over the first hour of therapy. Begin the lower maintenance dose during the second hour. • The patient's actual drinking habits determine the appropriate dose. If those drinking habits cannot be determined, it is best to use the doses for the category of "social drinker." • Adjust doses to achieve a blood ethanol level between 100 and 150 mg/dl, although levels as low as 70 mg/dL have almost completely inhibited ethylene glycol metabolism in some patients (Jacobsen, Ostby *et al.* 1982). To prepare 1 L of 10% ethanol in 5% dextrose in distilled water (D5W) for intravenous infusion, perform either of the following steps • Remove 100 ml of fluid from 1 L of D5W and replace with 100 ml of absolute ethanol, or • Remove 50 ml of fluid from 1 L of commercially available 5% ethanol in D5W solution and replace with 50 ml of absolute ethanol.

Monitor the Dose	Monitor blood ethanol and serum glucose levels at the end of the loading dose and hourly until the maintenance dose is adjusted. Both should then be monitored 2-3 times daily, along with blood glucose. More frequent monitoring is required during dialysis. Most ethylene glycol (93.75%) is eliminated over 4 half-lives (prolonged to 17 hours with therapy). Therefore, most ethylene glycol should be out of the body within 68 hours (2.83 days). Ethanol therapy should be continued for 3 days if ethylene glycol levels are not available, or until the following conditions are met (Burkhart and Kulig 1990): • ethylene glycol level <20 mg/dL • resolution of the acidosis (normal ABGs, pH) • resolved clinical findings (CNS)
Fomepizole Treatment Guidelines	Fomepizole (Antizol) was approved by the FDA in December 1997 for use as an ADH antagonist in treatment of ethylene glycol poisoning. The following criteria (Barceloux, Krenzelok *et al.* 1999) were developed by the American Academy of Clinical Toxicology for using fomepizole rather than ethanol: • ingestion of multiple substances, resulting in depressed level of consciousness • altered consciousness • lack of adequate intensive care staffing or laboratory support to monitor ethanol administration • relative contraindications to ethanol • critically ill patient with an anion-gap metabolic acidosis of unknown origin and potential exposure to ethylene glycol • patients with active hepatic disease The manufacturer recommends a loading dose of 15 mg/kg infused intravenously over 30 minutes, followed by doses of 10 mg /kg every 12 hours for 4 doses, then 15 mg/kg every 12 hours until ethylene glycol levels are below 20 mg/dl (Meditext 2004). The dosage must be adjusted during dialysis.
Advantages of Fomepizole Therapy	This therapy may obviate the need for hemodialysis in the absence of both renal insufficiency and significant metabolic acidosis (Harry, Turcant *et al.* 1994; Harry, Jobard *et al.* 1998; Borron, Megarbane *et al.* 1999; Watson 2000; Brent 2001; Battistella 2002; Druteika, Zed *et al.* 2002). In addition, in comparison with ethanol, fomepizole • is easier to use clinically and requires less monitoring • has a slower rate of elimination • has a longer duration of action • has a reasonable dosing schedule • has less potential for adverse effects • is easier to administer • results in shorter hospital stays, • has more predictable and prolonged results • does not cause CNS depression or hypoglycemia

Disadvantages of Ethanol Therapy

The disadvantages of ethanol are that it

- requires continuous administration and frequent monitoring of serum ethanol and glucose levels
- can cause CNS depression and hypoglycemia
- poses problems in patient care, such as drunkenness

Although ethanol costs much less, the savings may be offset by additional costs for

- monitoring the patient
- lab tests
- hemodialysis for some patients

Hemodialysis

Hemodialysis should be considered under these conditions (Ford M 1991; Hall AH 1992):

- serum ethylene glycol levels exceed 30 mg/dL
- severe upset in blood pH (pH <7.25) or fluid/electrolyte disturbances persist despite decontamination and ethanol or fomepizole therapy
- vital signs continue to deteriorate despite intensive supportive treatment, or
- renal failure develops

However, the decision to add hemodialysis in the treatment of ethylene glycol poisoning on the basis of plasma ethylene glycol concentrations is still debatable (Battistella 2002). A recent study suggested glycolic acid >8 mmol/L as a criterion for the initiation of hemodialysis in ethylene glycol ingestion (Porter, Rutter *et al.* 2001). Hemodialysis should be continued until

- acidosis is controlled
- serum ethylene glycol level falls below 20 mg/dL

At that level, ethanol or fomepizole therapy can also be discontinued. In contrast, a recent report described successful clinical management of pediatric ethylene glycol poisoning cases without hemodialysis (Caravati, Heileson *et al.* 2004).

Vitamin Therapy

Thiamine and pyridoxine are two water-soluble B-complex vitamins that act as metabolic cofactors in the metabolism of ethylene glycol. They

- promote the transformation of glyoxylic acid to nontoxic metabolites and
- may decrease the formation of oxalate

Both should be administered intravenously [in dosages of 100 mg daily until intoxication is resolved (Davis, Bramwell *et al.* 1997; Jacobsen and McMartin 1997)] to patients who have ethylene glycol toxicity. Alcoholics who are nutritionally deprived may need more thiamine. If the vitamins are administered before dialysis, the dose should be repeated after dialysis because they are highly water-soluble and are likely to be removed by the procedure.

Magnesium may help prevent deposition of calcium oxalate in the urine (Meditext 2004).

Key Points

- Correction of metabolic acidosis is an important part of treatment in ethylene glycol poisoning.
- Specific treatments for ethylene glycol poisoning are ethanol or fomepizole therapy and hemodialysis.

Progress Check

17. The primary strategy for managing ethylene glycol poisoning patients includes which of the following?

    A. sodium bicarbonate to correct the metabolic acidosis as indicated
    B. ethanol or fomepizole (Antizol) to competitively inhibit metabolism of ethylene glycol to its more toxic metabolites
    C. hemodialysis, if indicated, to remove ethylene glycol and glycolic acid
    D. all of the above.

    To review relevant content, see "Specific Treatment" in this section.

18. Which of the following conditions in ethylene glycol poisoning is not an indication for hemodialysis treatment?

    A. Severe blood pH imbalance (pH<7.25) or fluid/electrolyte disturbances persist despite decontamination and ethanol or fomepizole therapy.
    B. Vital signs continue to deteriorate despite intensive supportive treatment.
    C. Renal failure develops.
    D. The serum ethylene glycol level is up to the 10-15 mg/dL range.

    To review relevant content, see "Hemodialysis" in this section.

What is Propylene Glycol?

Learning Objective	Upon completion of this section, you should be able to • describe the properties and uses of propylene glycol
Introduction	In contrast to ethylene glycol, a potent cause of acute toxicity in humans, propylene glycol is a "generally recognized as safe" (GRAS) additive for foods and medications. Propylene glycol rarely causes toxic effects, and then only under very unusual circumstances.
Uses	Propylene glycol is a Generally Recognized as Safe (GRAS) food additive that is widely used in • food and tobacco products, • pharmaceuticals, and • cosmetics. In certain medicines, cosmetics, and food products, propylene glycol acts as • an emulsifying agent, • industrial drying agent, • surfactant, and • solvent.
Concentrations in Food	Concentrations in foods range from <0.001% in eggs and soups to about 15% in some seasonings and flavorings. Propylene glycol is an FDA-approved additive for military dietary rations (Agency for Toxic Substances and Disease Registry 1997).
Use in Textiles	The largest amounts of propylene glycol are used in the textile industry, where it is an intermediate in polyester fiber production.
Synonyms	Synonyms for propylene glycol include • 1,2-propanediol, • 1,2-dihydroxypropane, • methyl glycol, and • trimethyl glycol (Agency for Toxic Substances and Disease Registry 1997).
Special Uses	Aerosolized propylene glycol can provide dense "smoke" without flames. It is used • by the military as a smoke screen to conceal the movement of troops on the battlefield and • as a smoke simulator in various types of fire-training procedures and theatrical productions
De-Icing	Propylene glycol is sometimes used as a de-icing agent; however, ethylene glycol is used more often because it costs less.

Sources of Exposure

In the general population, propylene glycol exposure occurs primarily through ingestion of food and medications and through dermal contact with cosmetics or topical medications. Propylene glycol is used as a solvent in cosmetics and pharmaceuticals, in various format

- oral
- injectable
- topical

For example, it makes up 40% of intravenous phenytoin (Dilantin) and other injectable medications (Meditext 2004).

No adverse health effects are likely to occur from normal use of these products. However, heavy use of injectable medications with propylene glycol (Louis, Kutt *et al.* 1967; Seay, Graves *et al.* 1997; Yorgin, Theodorou *et al.* 1997; Wilson, Reardon *et al.* 2000), or prolonged and extensive topical application on compromised skin, such as burns (Peleg, Bar-Oz *et al.* 1998), has caused excess levels of propylene glycol in the body.

Who is at Risk

Propylene glycol toxicity has been reported only rarely and in unusual circumstances. For example, toxicity may result from

- excessively large or rapidly infused intravenous injections of propylene glycol-containing medications, excessively large or rapidly infused intravenous injections of propylene glycol-containing medications (Louis, Kutt *et al.* 1967; Seay, Graves *et al.* 1997; Yorgin, Theodorou *et al.* 1997; Wilson, Reardon *et al.* 2000)
- prolonged dermal contact during treatment of burns

Those at special risk include

- neonates
- infants
- the elderly the elderly the elderly the elderly the elderly (Martin and Finberg 1970; MacDonald, Getson *et al.* 1987; Glover and Reed 1996; Peleg, Bar-Oz *et al.* 1998).

Increased sensitivity (Reprotext 2004) may be seen in people with pre-existing

- skin conditions
- eye conditions
- (possibly) allergic conditions

Biological Fate	Absorption of propylene glycol from the gastrointestinal tract is rapid: maximal plasma concentrations in humans occur within 1 hour after ingestion. ***Metabolites*** Propylene glycol is metabolized in the liver by alcohol dehydrogenase to • lactic acid, and then • pyruvic acid Both of these metabolites are normal constituents of the citric acid cycle and are further metabolized to • carbon dioxide and • water About 45% of an absorbed propylene glycol dose is excreted by the kidneys unchanged or as the glucuronide conjugate. ***Half-Life*** The elimination half-life of propylene glycol is about 4 hours.
Physiological Effects	Topical application to injured skin (as a component of burn creams) or intravenous administration (as an excipient in certain anticonvulsant, antianginal, antibiotic, or other medications) has sometimes been associated with • Hyperosmolality, • lactic acidosis, • intravascular hemolysis, • complications of CNS depression, • seizures, • coma, • hypoglycemia, and • renal failure
Central Nervous System Effects	CNS depression is the primary manifestation of acute propylene glycol poisoning.
Metabolic Effects	***Metabolic acidosis*** Metabolic conversion of propylene glycol to lactic and pyruvic acids can contribute to metabolic acidosis and an abnormal anion gap. ***Hyperosmolality*** Unchanged propylene glycol circulating in the body causes hyperosmolality.

Examples of Propylene Glycol Poisoning	Although propylene glycol is nontoxic under normal conditions, it can cause poisoning in rare and unusual circumstances. In one case, an 8-month-old infant with large surface area second-degree and third-degree burns was treated for many days with topical silver sulfadiazine containing a large amount of propylene glycol. The infant developed acute metabolic acidosis and cardiorespiratory arrest. The daily dose of propylene glycol was 9,000 mg/kg. Serum propylene glycol levels were highest on day 14 (1,059 mg/dL) when the osmolal gap was 75 mOsm/L (normal: <10 mOsm/L) (Fligner, Jack *et al.* 1985).
Phenytoin and Propylene Glycol	Propylene glycol is a common diluent for injectable medications. It constitutes 40% of the intravenous form of phenytoin. This high concentration is necessary to • maintain the phenytoin crystals in a stable preparation and • prevent their precipitation In some patients given intravenous phenytoin, propylene glycol was reported to cause • hypotension, • cardiac conduction disturbances, and • cardiac dysrhythmias Fatal cardiac and respiratory arrests have also been reported, but these effects may have been due to the cardioactive phenytoin. (Donovan and Cline 1991).
Lack of Renal Effects	Propylene glycol has not been associated with nephrotoxicity caused by calcium oxalate in humans. Unlike ethylene glycol, propylene glycol is not metabolized to oxalic acid, so calcium oxalate is not deposited in the kidneys (Agency for Toxic Substances and Disease Registry 1997).
Contact Dermatitis	Propylene glycol can be a skin sensitizer, resulting in allergic contact dermatitis in some individuals (Reprotext 2004).
Comparison with Ethylene Glycol	In comparing the toxicity of ethylene glycol with that of propylene glycol, LaKind *et al.* (1999) stated that "From the standpoint of lethality, acute effects, and reproductive, developmental, and kidney toxicity, the toxicity of ethylene glycol exceeds that of propylene glycol (LaKind, McKenna *et al.* 1999). Further, localized dermal effects from ethylene glycol and propylene glycol are both mild, with data suggesting that propylene glycol may have a skin contact sensitization potential. Finally, propylene glycol exposure in laboratory animals has been associated with reversible hematological changes; no data were located for ethylene glycol from which to draw a toxicological comparison."
Clinical Presentation	Although the toxicity of propylene glycol is low, if excessively large amounts are absorbed, the following health effects may be seen • an elevated osmolal gap, • severe metabolic acidosis (caused by the metabolism of propylene glycol to lactic acid), and • coma, seizures, and hypoglycemia (rarely, among patients who ingested large amounts of propylene glycol over several days).

Treatment	Metabolic acidosis caused by large amounts of propylene glycol in injected medications should be treated with sodium bicarbonate. In severe cases, hemodialysis is effective in correcting hyperosmolality by removing propylene glycol from the blood (Demey, Daelemans *et al.* 1988; Parker, Fraser *et al.* 2002). Ethanol therapy, as described for ethylene glycol-poisoned patients, is unnecessary for patients having propylene glycol poisoning.
Standards and Regulations	There is no workplace or environmental standard for propylene glycol. FDA considers an average daily dietary intake of 23 mg/kg of body weight to be safe for persons 2-65 years of age (Agency for Toxic Substances and Disease Registry 1997).
Key Points	• Propylene glycol is used in various foods, cosmetics, and pharmaceutical products. • Propylene glycol toxicity is not expected in normal environmental or occupational exposures. • Propylene glycol toxicity is metabolized to compounds that are normal constituents of the citric acid cycle. • Large doses and unusual circumstances are necessary for the development of propylene glycol toxicity. • Propylene glycol poisoning is marked initially by CNS depression and an elevated osmolal gap and, later, by an increased anion gap. • Unlike ethylene glycol, propylene glycol does not produce nephrotoxicity in humans. • Treatment for propylene glycol poisoning is supportive. It may involve correction of metabolic acidosis using sodium bicarbonate therapy and, for severe cases, hemodialysis.
Progress Check	19. Propylene glycol is used as which of the following in food products, cosmetics, and pharmaceutical products? A. An emulsifying agent. B. An industrial drying agent. C. A surfactant or solvent. D. All of the above. *To review relevant content, see "Uses" in this section.* 20. In contrast to ethylene glycol, propylene glycol rarely causes toxic effects. This is mainly because A. Absorption of propylene glycol from the gastrointestinal tract is slow. B. Propylene glycol is metabolized to more toxic compounds. C. Ethylene glycol is metabolized in the liver to less toxic metabolites. D. Propylene glycol is metabolized to compounds that are normal constituents of the citric acid cycle. *To review relevant content, see "Biological Fate" in this section.*

21. Unlike ethylene glycol, propylene glycol has not been associated with renal toxicity. For what reason?

    A. Propylene glycol is not metabolized in kidneys.
    B. Propylene glycol is not metabolized to more toxic metabolites to the kidneys.
    C. Propylene glycol is not metabolized to oxalic acid, so calcium oxalate is not deposited in the kidneys.
    D. none of the above.

    To review relevant content, see "Biological Fate" in this section.

22. Ethanol therapy is unnecessary for patients having propylene glycol poisoning for which of the following reasons?

    A. Ethanol is used to saturate the alcohol dehydrogenase enzyme (ADH) so that propylene glycol will be excreted unchanged in the urine.
    B. Ethanol is used to saturate the alcohol dehydrogenase enzyme (ADH) so that propylene glycol will cause less toxic effects since the metabolism in the liver is competitively inhibited.
    C. Propylene glycol is metabolized in the liver by alcohol dehydrogenase (ADH) to the normal constitutes of the citric acid cycle. It's unnecessary to use ethanol to exhaust ADH which in fact detoxifies propylene glycol to nontoxic constitutes.
    D. Ethanol therapy does not help.

    To review relevant content, see "Biological Fate" in this section.

What Instructions Should Be Given to Patients?

Learning Objectives

Upon completion of this section, you should be able to

- explain advice on self care and follow-up to patients who are exposed to ethylene glycol or propylene glycol.

Introduction

All patients with ethylene glycol poisoning should be evaluated and treated without delay. Even patients with no symptoms or mild symptoms should undergo appropriate blood and urine tests if they have a history of significant ingestion. Patients who have no history suggestive of significant exposure and who have no symptoms or laboratory findings of ethylene glycol poisoning may be discharged with instructions to seek medical care promptly if symptoms develop.

All patients exposed to ethylene glycol or propylene glycol need some basic guidance on

- self care, so they can minimize further risks and avoid complications to the extent possible
- clinical follow up, so they understand when and why to return for further medical attention

ATSDR has developed a patient education sheet on ethylene glycol and propylene glycol that you might find useful. It can be found at

http://www.atsdr.cdc.gov/csem/egpg/pated_sheet.html

Self Care

Patients should be advised to avoid exposures and conditions that might further increase their risk of disease or worsen their existing condition. You may offer the following advice to your patient:

- Do not keep antifreeze stored in your home.
- If you have any around, keep it safely and securely stored away from children.
- Be sure that leaking air conditioning units are repaired.
- If you suspect that someone has ingested antifreeze, be sure that they are seen immediately by a doctor.

Clinical Follow Up

Patients should be advised to consult their physician if they develop

- any sign or symptom of central nervous system
- signs or symptoms of other health changes (especially those possibly related to heart and kidney problems)

ATSDR's patient education sheet on ethylene glycol and propylene glycol includes a more detailed checklist that you can use to indicate which types of follow up are relevant for a given patient.

Key Points	• Patients should be advised to avoid exposures and conditions that might further increase their risk of disease or worsen their existing condition. • Patients should contact their physician if they develop neurological problems or other health changes. • A patient education sheet and prescribed follow-up check list on ethylene glycol and propylene glycol is available at http://www.atsdr.cdc.gov/csem/egpg/pated_sheet.html
Progress Check	23. Patients who have been exposed to ethylene glycol should A. seek clinical evaluation and treatment without delay B. learn how to avoid further exposure C. know when to call their doctor D. all of the above. *To review relevant content, see "Self Care" and "Clinical Follow-Up" in this section.*

Where Can I Find More Information?

For more Information

Please refer to the following Web resources for more information on

- adverse effects of ethylene glycol and propylene glycol
- treatment of ethylene and propylene glycol poisoning
- management of persons exposed to ethylene and propylene glycol

You may also contact ATSDR (see URLs provided below), your state and local health departments, and university medical centers.

Association of Occupational and Environmental Clinics:

http://www.aoec.org

American College of Occupational and Environmental Medicine:

http://www.acoem.org

American College of Medical Toxicologists:

http://www.acmt.net

American College of Preventive Medicine:

http://www.acpm.org

ATSDR Information Center:

http://www.atsdr.cdc.gov/icbkmark.html

Other CSEMs

Case Studies in Environmental Medicine: Ethylene Glycol and Propylene Glycol Toxicity is one monograph in a series. To view the *Taking an Exposure History* CSEM and other publications in this series, please go to

http://www.atsdr.cdc.gov/csem/

Posttest Instructions

Introduction	ATSDR seeks feedback on this course so we can asses its usefulness and effectiveness. We ask you to complete the assessment questionnaire online for this purpose. In addition, if you complete the assessment and posttest online, you can receive continuing education credits as follows.

Accrediting Organization	Credits Offered
Accreditation Council for Continuing Medical Education (ACCME)	The Centers for Disease Control and Prevention (CDC) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. CDC designates this educational activity for a maximum of **1.75** *AMA PRA Category 1 Credit(s)*™. Physicians should only claim credit commensurate with the extent of their participation in the activity.
American Nurses Credentialing Center (ANCC), Commission on Accreditation	This activity for **1.75** contact hours is provided by the Centers for Disease Control and Prevention, which is accredited as a provider of continuing education in nursing by the American Nurses Credentialing Center's Commission on Accreditation.
National Commission for Health Education Credentialing, Inc. (NCHEC)	CDC is a designated provider of continuing education contact hours (CECH) in health education by the National Commission for Health Education Credentialing, Inc. The Centers for Disease Control and Prevention is a designated provider of continuing education contact hours (CECH) in health education by the National Commission for Health Education Credentialing, Inc. This program is a designated event for the Certified Health Education Specialist (CHES) to receive **1.5** Category I contact hours in health education, CDC provider number GA0082.
International Association for Continuing Education and Training (IACET)	The Centers for Disease Control and Prevention (CDC) has been reviewed and approved as an Authorized Provider by the International Association for Continuing Education and Training (IACET), Suite 800, McLean, VA 22102. CDC will award **0.15** of CEU's to participants who successfully complete this program.

Disclaimer	In compliance with continuing education requirements, all presenters must disclose any financial or other relationships with the manufacturers of commercial products, suppliers of commercial services, or commercial supporters as well as any use of unlabeled product(s) or product(s) under investigational use. CDC/ATSDR, our planners, and the presenters for this seminar do not have financial or other relationships with the manufacturers of commercial products, suppliers of commercial services or commercial supporters. This presentation does not involve the unlabeled use of a product or product under investigational use.
Instructions	To complete the assessment and posttest, go to www.cdc.gov/atsdrce/ and follow the instructions on that page. You can immediately print your continuing education certificate from your personal transcript online. No fees are charged.

Posttest

Please select the best correct answer.

1. What is ethylene glycol?

   A. It is a clear, colorless, odorless, sweet-tasting liquid.
   B. It causes acute toxicity in humans if ingested.
   C. It is poorly absorbed by skin and has low potential for significant inhalation exposure.
   D. All of the above.

2. Which of the following products may contain ethylene glycol?

   A. Pesticides.
   B. Antifreeze.
   C. Cosmetics.
   D. All of the above.

3. Which of the following statements about ethylene glycol are true?

   A. Inhalation is a common route of exposure because of the high vapor pressure.
   B. Accidental or intentional ingestion accounts for most poisonings.
   C. It is absorbed readily through intact skin.
   D. All of the above.

4. The Food and Drug Administration (FDA) has approved ethylene glycol as

   A. A direct food additive.
   B. An indirect food additive.
   C. A direct pharmaceutical additive.
   D. None of the above.

5. After ingestion, ethylene glycol is

   A. Slowly absorbed by the gastrointestinal tract.
   B. Stored and persists in fatty tissue.
   C. Reaching peak tissue levels after 24 hours.
   D. Metabolized in the liver to a variety of compounds of increased toxicity.

6. The first stage of ethylene glycol poisoning generally includes

   A. A characteristic odor of ethanol on the breath.
   B. Symptoms similar to those of ethanol intoxication.
   C. Cardiopulmonary symptoms such as tachypnea and pulmonary edema.
   D. Oliguric renal failure.

7. Acute ethylene glycol exposure can adversely affect all of the following except

   A. Lungs.
   B. Heart.
   C. Pancreas.
   D. Kidneys.

8. Nephrotoxicity is the dominant effect of serious ethylene glycol poisoning. Which of the following statements is not true?

   A. Kidney damage manifests as acute oliguric renal failure.
   B. Costovertebral angle tenderness is the most common physical finding.
   C. Absence of oxalate crystals will rule out the diagnosis of ethylene glycol poisoning.
   D. Urinalysis shows proteinuria.

9. As part of exposure history, you should explore

   A. A history of ethanol abuse.
   B. A history of possible substance abuse.
   C. Similar symptoms in family members, friends, and coworkers.
   D. All of the above.

10. Useful laboratory tests for diagnosing ethylene glycol poisoning include which of the following?

    A. Arterial blood gases (ABG).
    B. Blood glucose.
    C. Blood ethanol.
    D. All of the above.

11. Which of the following is not a disadvantage of ethanol therapy?

    A. It requires continuous administration and frequent monitoring of serum ethanol and glucose levels.
    B. It can cause CNS depression and hypoglycemia.
    C. It has unpredictable results.
    D. It poses problems in patient care, such as drunkenness.

12. Treatment for acute propylene glycol poisoning might include determinations of which of the following?

    A. Sodium bicarbonate therapy.
    B. Administration of calcium gluconate.
    C. Ethanol administration.
    D. Hyperbaric oxygen.

13. Which of the following statements comparing ethylene glycol and propylene glycol are true?

    A. Propylene glycol is most commonly found in foods and medicines, and ethylene glycol is found in antifreeze and other commercial products.
    B. Both glycols are used for aircraft de-icing.
    C. Neither compound is likely to persist for long periods in the environment.
    D. All of the above.

Relevant Content To review content relevant to the posttest questions, see

Question	Location of Relevant Content
1	What Is Ethylene Glycol?
2	Where Is Ethylene Glycol Found?
3	How Are People Exposed to Ethylene Glycol?
4	What Are U.S. the Standards for Ethylene Glycol Exposure Levels?
5	What Is the Biological Fate of Ethylene Glycol?
6	What Are the Stages of Ethylene Glycol Intoxication
7	What Are the Physiologic Effects of Ethylene Glycol Ingestion Poisoning
8	What Are the Physiologic Effects of Ethylene Glycol Ingestion Poisoning
9	How Should Patients Exposed to Ethylene Glycol Be Evaluated
10	What Laboratory Tests Can Assist in the Evaluation of Patients Exposed to Ethylene Glycol
11	How Should Patients Exposed to Ethylene Glycol Be Treated
12	What Is Propylene Glycol
13	What Is Propylene Glycol

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Answers to Progress Check Questions

1. The best choice is D. Ethylene glycol is a manufactured chemical. It is a clear, colorless, odorless, sweet-tasting liquid. It has low vapor pressures at room temperature and, therefore, low potential for significant inhalation exposure. It dissolves in water and alcohol, can hold large amounts of heat before boiling, and lowers the freezing point of water.
2. The best choice is B. Ethylene glycol is used extensively in automotive fluids such as antifreeze, coolants, and hydraulic fluids. Antifreeze, which typically consists of 95% ethylene glycol, accounts for about 40% of the ethylene glycol produced. It is found in many hardware and automotive stores, and is easily accessible to the general public.
3. The best choice is B. In the general population, ethylene glycol severe exposure occurs most commonly through accidental or intentional ingestion of antifreeze. Skin contact is the most likely route of occupational exposure, but dermal exposure rarely leads to toxic effects.
4. The best choice is B. ACGIH recommends ceiling exposure limit of 100 mg/m^3 (39.4 ppm).
5. The best choice is C. EPA recommends that adults be exposed to no more than a daily total of 7 mg/L (7 ppm) ethylene glycol for a lifetime.
6. The best choice is B. Persons with reduced ability to metabolize ethylene glycol are less likely to suffer the severe toxicity associated with its metabolites. However, they are more likely to experience greater intensity of the initial central nervous system (CNS) effects caused by ethylene glycol. Such individuals include those with impaired liver or kidney function, and children who may have immature hepatic detoxification systems.
7. The best choice is D. Acid and aldehyde metabolites of ethylene glycol inhibit many cellular biochemical reactions including oxidative phosphorylation and cellular respiration, glucose and serotonin metabolism, protein synthesis, DNA replication, and the formation of ribosomal RNA.
8. The best choice is B. Stage 2 involves cardiorespiratory symptoms appearing 12-24 hours after ingestion of ethylene glycol, with tachycardia, tachypnea, and hypertension as the most frequent symptoms. The body attempts to compensate for severe metabolic acidosis by hyperventilation (tachypnea).
9. The best choice is B. The initial phase of ethylene glycol poisoning is characterized by inebriation caused by unmetabolized ethylene glycol.
10. The best choice is A. The most common cause of tachypnea is uncompensated metabolic acidosis.
11. The best choice is D. The metabolic acidosis of ethylene glycol poisoning is characterized as normochloremic, with low bicarbonate level and pH, and elevated acidemia and anion gap.
12. The best choice is D. Kidney damage, which typically occurs during stage 3 of ethylene glycol intoxication, manifests as acute oliguric renal failure. The most characteristic abnormality is the presence of large numbers of oxalate crystals, either tent-shaped or needle shaped, in the urine. However, absence of these crystals does not rule out the diagnosis of ethylene glycol poisoning.
13. The best choice is D. The actual clinical presentation of ethylene glycol poisoning changes over time as intoxication evolves. Signs and symptoms depend on the amount ingested and concurrent use of alcohol. Therefore, making a correct diagnosis requires a

reliable history of the time, route, and magnitude of exposure. A history of ethanol abuse may suggest ingestion of ethylene glycol as an ethanol substitute. Inquiring about similar symptoms in family members, friends, and coworkers may help identify a common source of exposure.

14. The best choice is D. Ethylene glycol ingestion is a medical emergency requiring prompt recognition and aggressive treatment to prevent from life-threatening illness such as renal failure caused by toxic metabolites produced in latent period of course of ethylene glycol poisoning.

15. The best choice is D. The presence of metabolic acidosis (answer B) with both anion and osmolal gaps (answer A) is an important clue to the diagnosis. However, numerous toxic substances are associated with an elevated anion gap (Table 2). Numerous studies have documented that renal damage occurs after ethylene glycol ingestion without deposition of calcium oxalate crystals (answer C) in the kidney. Although answers A, B, and C together strongly suggest ethylene glycol poisoning, elevated serum ethylene glycol level is the most reliable index for diagnosis. All, some, or none of these findings may be present at the time of testing in ethylene glycol poisoning.

16. The best choice is D. Most laboratories routinely screen for unchanged ethylene glycol in suspected poisonings. They estimate the amount of ethylene glycol present in positive cases even though toxicity from ethylene glycol exposure is primarily caused by one metabolite – glycolic acid.

17. The best choice is D. Specific treatment for ethylene glycol poisoning includes

    - sodium bicarbonate to correct the metabolic acidosis as indicated
    - ethanol or fomepizole (Antizol) to competitively inhibit metabolism of ethylene glycol to its more toxic metabolites
    - hemodialysis, if indicated, to remove ethylene glycol and glycolic acid

    This treatment strategy is effective in most cases, but renal failure and death can occur if treatment is delayed.

18. The best choice is D. The decision to add hemodialysis in the treatment of ethylene glycol poisoning on the basis of plasma ethylene glycol concentrations is still debatable. Some studies suggest hemodialysis when the serum ethylene glycol levels exceed 30-50 mg/dL. Other studies recommend glycolic acid >8 mmol/L as a criterion for the initiation of hemodialysis in ethylene glycol ingestion.

19. The best choice is D. In certain medicines, cosmetics, and food products, propylene glycol acts as

    - an emulsifying agent
    - an industrial drying agent
    - a surfactant
    - a solvent

20. The best choice is D. Unlike the more toxic metabolites from ethylene glycol metabolism, propylene glycol is metabolized in the liver by alcohol dehydrogenase to lactic acid, then to pyruvic acid. Both of these metabolites are normal constitutes of the citric acid cycle and are further metabolized to carbon dioxide and water.

21. The best choice is C. Propylene glycol is not metabolized to oxalic acid, so calcium oxalate is not deposited in the kidneys. Therefore, propylene glycol does not produce nephrotoxicity in humans.

22. The best choice is C. Propylene glycol is metabolized in the liver by alcohol dehydrogenase (ADH) to the normal constitutes of the citric acid cycle. It is unnecessary to use ethanol to exhaust ADH, which in fact detoxifies propylene glycol to nontoxic constitutes.

23. The best choice is D. Medical tests and treatment are available for ethylene glycol poisoning, and treatment should begin as soon as possible. The treating physician should find out whether the patient has any materials at home or work that contain ethylene glycol. Patients should be advised to avoid exposures and conditions that might further increase their risk of disease or worsen their existing condition. In addition, patients should contact their physician if they develop neurological problems or other health changes.