Agency for Toxic Substances and Disease Registry

Case Studies in Environmental Medicine (CSEM)

Ethylene Glycol and Propylene Glycol Toxicity

Course: WB 4342

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Key Concepts	• Ethylene glycol ingestion first affects the central nervous system (CNS). After a characteristic latent period, toxic metabolites might produce signs of inebriation followed by serious illness and even death. • No studies were located regarding a link between ethylene glycol exposure and cancer or reproductive or developmental hazards in humans. • Propylene glycol is much less toxic than ethylene glycol.
About This and Other Case Studies in Environmental Medicine	This educational case study is one in a series of self-instructional modules designed to increase the primary care provider's knowledge of hazardous substances in the environment. The modules also promote adoption of medical practices that aid in the evaluation and care of potentially exposed patients. You can access the complete series of Case Studies in Environmental Medicine on the Agency for Toxic Substances and Disease Registry (ATSDR) website at URL: https://www.atsdr.cdc.gov/emes/health_professionals/index.html. A downloadable PDF version of this educational series and other environmental medicine materials provides content in an electronic, printable format, especially for those who might lack adequate Internet service.

Acknowledgments	**We gratefully acknowledge the work of the medical writers, editors, and reviewers in producing this educational resource. Listed below are the contributors to this version of the Case Study in Environmental Medicine.** **Please Note: Each content expert for this case study has indicated that he or she has no conflict of interest to disclose that would bias the case study content.** **ATSDR Authors:** Dianyi Yu, MD **ATSDR Planners:** Charlton Coles, PhD; Sharon L. Hall, PhD; Delene Roberts MSMHC; Julia Smith, MPH, CHES; Germania Pinheiro MD, MSc, PhD; Dianyi Yu, MD **Peer Reviewers:** Obaid Faroon, DVM, PhD, and Ki Moon Bang, PhD, MPH **ATSDR Commenters:** Alaina Steck, MD
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How to Use This Course

Introduction	Case Studies in Environmental Medicine's goal 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 case study focuses on ethylene glycol and propylene glycol toxicity.
Availability	Two versions of the Ethylene Glycol/Propylene Glycol Toxicity CSEM are available. • The HTML version (*To be added after clearance during Web production*) provides content through the Internet. • The downloadable PDF version (*To be added after clearance during web production*) provides content in an electronic, printable format, especially for those who might lack adequate Internet service. • The HTML version offers interactive exercises and prescriptive feedback to the user.
Instructions	Follow these steps to make the most effective use of this course: • 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 want continuing education credit. You can print continuing education certificates immediately after course completion.

Instructional Format	This course is designed to help you learn efficiently. Topics are clearly labeled; you can skip sections or quickly scan sections with which you are already familiar. This labeling also allows you to use this training material as a handy reference. To help you identify and absorb important content quickly, we've structured each section as follows:
Section Element	**Purpose**
Title	Serves as a "focus question" 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	After completing the Ethylene Glycol and Propylene Glycol CSEM, you will be able to accomplish the following:
Content Area	**Learning Objectives**
What Is Ethylene Glycol?	• Describe the properties of ethylene glycol
Where Is Ethylene Glycol Found?	• Identify sources of ethylene glycol exposure

What Are Routes of Exposure to Ethylene Glycol?	• Identify the most common route of exposure to ethylene glycol that results in toxicity in the general U.S. population
Who Is at Risk of Exposure to Ethylene Glycol?	• Identify who is at risk of exposure to ethylene glycol
What Are U.S. Regulations and Guidelines for Ethylene Glycol Exposure?	• Describe current U.S. regulations and guidelines for ethylene glycol exposure
What Is the Biologic Fate of Ethylene Glycol?	• Explain the major pathway of ethylene glycol metabolism in the body
What Are the Toxicological Effects of Ethylene Glycol Poisoning?	• Describe the toxicological effects of ethylene glycol poisoning.
Clinical Assessment – History and Physical Exam	• Describe what is included in the initial history and physical examination of patients potentially exposed to ethylene glycol • Describe how the clinical presentation changes over time
Clinical Assessment - Laboratory Tests	• 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 and Managed?	• Describe treatment strategies for managing ethylene glycol poisoning cases
What Is Propylene Glycol?	• Describe the uses of propylene glycol • Explain the potential risk of propylene glycol

	toxicity
What Instructions Should You Give to Patients Regarding Ethylene Glycol/Propylene Glycol Exposure?	• Describe self-care and clinical follow-up instructions for patients 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 arrives at 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. He has no odor of ethanol on his breath. **Vital Signs** The patient's vital signs are as follows: • 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 focal findings, particularly no nystagmus. Abdominal examination is normal. **Additional Information** The patient's friend brought him to the ED. The friend said that late the previous night the patient complained of dizziness and had begun to vomit. The patient was hyperventilating in the morning and continued to vomit. Both men are retired pilots who teach at the local airport's ground school. The friend wonders whether the food at the airport cafeteria was responsible because two other people collapsed at the airport that morning

	and were taken by ambulance to another hospital. Both the friend and the patient ate hot dogs and coleslaw from the cafeteria, but the friend states that he feels fine. **Results of Laboratory Tests** • Blood ethanol and routine urine 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). • 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 12–16). Note that results might vary from laboratory to laboratory and depend on the elevation above sea level (see Table 1).

Table 1. Arterial blood gases – Ranges Considered Within Normal Limits 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	Fewer than 30 minutes later, a 4-year-old boy arrives at the ED. On examination, you find a sleepy but responsive child who shows no evidence of trauma or focal neurologic signs. Abdominal examinations are normal. **Vital Signs** The patient's vital signs are as follows: 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 noticed the child staggering and incoherent, they rushed him to the ED. On the way, he vomited in the car. **Results of Laboratory 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, and • has an anion gap of 13. **Additional Information** You contact the local health department. They tell you they are investigating the earlier incidents at the airport. They have not identified the contaminant, but they suspect the airport's water supply is contaminated.

Initial Check Questions	1. What would you include in the problem list 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. While repairing the water supply system, construction crews at the airport inadvertently connected the heating system water supply to the drinking water system. The concentration of ethylene glycol measured at the cafeteria's water source was 9% (90,000 parts per million [ppm]). The U.S. 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 might be at risk of adverse health effects? Explain. 6. An airport employee comes to your office a week after the water contamination incident. One of his jobs is to de-ice aircraft. A major spill occurred on the previous day, drenching him with de-icing fluid. He knows that de-icing agents contain large amounts of ethylene glycol. Immediately after the spill, he showered and changed clothes. He is worried about possible adverse health effects, such as cancer. What will you tell him? 7. A pregnant airport worker consults you because she drank tea brewed with the contaminated water at the airport. Although she drank only a small amount of tea and had no ill effects, she is worried that even that small amount of contaminant will adversely affect her fetus. How will you counsel her?

	8. You later learn that during dinner at the cafeteria, the 67-year-old man drank several cups of coffee, while his friend, who did not become ill, drank only canned soda. 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. They state the luncheon did include wine and cocktails, but they did not supervise the child closely. Potential ethylene glycol exposure sources for the child were not immediately identifiable. How will you treat the child?
Initial Check Answers	1. The man's medical problems include the following: • Ataxia • Vomiting • Agitation • Disorientation • Hyperventilation • Elevated anion-gap metabolic acidosis The child's medical problems include the following: • Somnolence • Ataxia • Mental status changes • Vomiting • Hypoglycemia • Low body temperature • Slight anion-gap metabolic acidosis Differential diagnoses include toxic alcohol ingestion and diabetic or starvation ketoacidosis. (Table 3 shows common toxic agents associated with an elevated anion gap.)

	2. Additional testing of these patients should include the following: • Urinalysis • Complete blood count • Serum osmolality measured by the freezing-point–depression technique • Ethylene glycol and methanol levels • Ammonia, acetaminophen, and aspirin levels • Liver function Find more information for this answer in the "Clinical Assessment – Laboratory Tests" section. 3. Because the critical ingestion occurred several hours ago, emesis or gastric lavage will be of little value, and activated charcoal will 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. Intravenous administration of the antidote, fomepizole, will inhibit further ethylene glycol metabolism. In the absence of both renal insufficiency and significant metabolic acidosis, fomepizole may be used without hemodialysis. Start hemodialysis if severe metabolic acidosis or renal failure develops. Find more information for this answer in the "How should patients exposed to ethylene glycol be treated and managed?" section. 4. The most common sources of epidemic poisonings include • contaminated food, • beverages, and • water supplies. Incident investigators would ask about types of food and drink available at the airport. They would take a detailed history of food and beverage intake

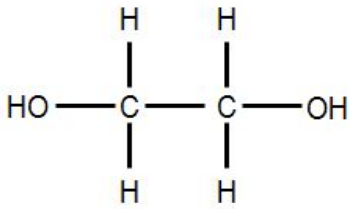
	from the patients and all others at the airport. They would attempt to find a common factor that would include those who were ill and exclude those who did not become ill. Investigators can usually identify the exposure source or restrict the exposure source possibilities by gathering and statistically analyzing data from a large group of people. Find more information for this answer in the "Where is ethylene glycol found?" section. 5. The lethal dose of antifreeze (95% ethylene glycol) is about 100 mL or 1.4 mL/kg, although amounts in the reported cases vary widely. 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. Healthcare providers should examine every employee and visitor who consumed beverages or food prepared with water at the airport. Find more information for this answer in the "Where is ethylene glycol found?" section. 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 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 inhaled, so inhalation of ethylene glycol would be minimal. Contact during the de-icing process would not contribute substantially to toxicity, especially if the exposed person wore protective clothing and respiratory protection. No studies were located regarding carcinogenicity in humans after exposure to ethylene glycol.

	Find more information for this answer in the Sections of "Where is ethylene glycol found?", "What Are Routes of Exposure to Ethylene Glycol?", and "What Are the Toxicological Effects of Ethylene Glycol Poisoning?". 7. You can inform the pregnant patient that experimental animal studies indicate that ethylene glycol at high, prolonged levels can cause developmental effects. However, no human studies specifically assess the effects of ethylene glycol on fetal development. Find more information for this answer in the "What are the toxicological effects of ethylene glycol poisoning?" section. 8. The initial treatment is described in answer 3. Traditionally, an ethylene glycol level of 50 mg/dL was an indication for hemodialysis. However, some patients with normal renal function and no evidence of metabolic acidosis have been treated effectively with fomepizole, despite having ethylene glycol levels of 50 mg/dL. In the absence of both renal insufficiency and significant metabolic acidosis, fomepizole may be used without hemodialysis. Hemodialysis should be started if metabolic acidosis develops. Find more information for this answer in the "How should patients exposed to ethylene glycol be treated and managed?" section. 9. The child could be intoxicated with ethanol alone or with ethanol and ethylene glycol. If intoxication is from ethanol only, carefully monitor blood glucose and ethanol until the intoxication resolves. If laboratory results indicate that ingestion of ethylene glycol occurred, the patient can be treated with fomepizole. The limited data available suggest that fomepizole, at the same dosage used for adults, is effective and well tolerated in pediatric patients. For many pediatric patients treated with fomepizole for ethylene glycol poisoning, hemodialysis might not be

	needed, despite high ethylene glycol concentrations and the presence of metabolic acidosis. Find more information for this answer in the “How should patients exposed to ethylene glycol be treated and managed?” section.

What Is Ethylene Glycol?

Learning Objectives	After completing this section, you will be able to describe the properties of ethylene glycol.

Definition	Ethylene glycol is a liquid that is • clear, • colorless, • odorless, and • sweet tasting. Ethylene glycol has low vapor pressures at room temperature and, therefore, low potential for significant inhalation exposure. Its chemical structure is $HOCH_2CH_2OH$. 
Synonyms	Common synonyms for ethylene glycol include • ethylene alcohol, • glycol alcohol, • glycol, • 1,2-dihydroxyethane, and • 1,2-ethanediol.
Properties	Ethylene glycol • dissolves in water and alcohol, • can hold large amounts of heat before boiling, • lowers the freezing point of water, and • absorbs twice its weight in water.

Uses	Ethylene glycol is widely used as antifreeze (concentration range: 80%–99%) or de-icing solutions (concentration range: 3%–40%) for cars, boats, and aircraft. It is also used in the chemical synthesis of plastics, films, and solvents. It can be found in many consumer products, including solvents, paints, and coolants (concentration range: 20%–95%) (Caravati et al. 2005).
Toxicity	Ethylene glycol poisoning is a relatively common occurrence worldwide. Thousands of cases of poisoning and some fatal cases occur annually in the United States alone (AAPCC 2016). Systemic ethylene glycol toxicity can occur following ingestion. The toxic metabolic by-products of ethylene glycol metabolism cause a buildup of acids in the blood (metabolic acidosis). These toxic substances first affect the central nervous system, then the cardiopulmonary system, and finally can cause renal failure. Untreated ethylene glycol poisoning can be fatal (NIOSH 2014). The lethal oral dose in humans is approximately 1.4 mL/kg of pure ethylene glycol (Brent 2001).
Key Points 1.	• Ethylene glycol is widely used in antifreeze and in de-icing solutions for cars, boats, and aircraft. • Untreated ethylene glycol poisoning can be fatal.
Progress Check	Which of the following statements is NOT true? A. Ethylene glycol is a colorless, odorless, and sweet-tasting liquid. B. Ethylene glycol can lower the freezing point of water. C. Ethylene glycol can hold large amounts of heat before boiling. D. Ethylene glycol poisoning is rare.

Answers 1.	The false statement is D. Ethylene glycol poisoning is, in fact, a relatively common occurrence worldwide. More than 5,000 cases of poisoning occur in the United States each year. Untreated ethylene glycol poisoning can be fatal; such deaths have occurred annually in the United States. Additionally, ethylene glycol is a colorless, odorless, and sweet-tasting liquid that can lower the freezing point of water and hold large amounts of heat before boiling. Feedback for A. (Web only): The false statement is D. In fact, ethylene glycol poisoning is a relatively common occurrence worldwide. Additionally, ethylene glycol is a colorless, odorless, and sweet-tasting liquid. It can lower the freezing point of water and hold large amounts of heat before boiling. Feedback for B. (Web only): The false statement is D. In fact, ethylene glycol poisoning is a relatively common occurrence worldwide. Ethylene glycol also can lower the freezing point of water. It is a colorless, odorless, and sweet-tasting liquid that holds large amounts of heat before boiling. Feedback for C. (Web only): The false statement is D. In fact, ethylene glycol poisoning is a relatively common occurrence worldwide. Ethylene glycol also can hold a large amount of heat before boiling. It can lower the freezing point of water and is a colorless, odorless, and sweet-tasting liquid. Feedback for D. (Web only): Correct. The false statement is D. In fact, ethylene glycol poisoning is a relatively common occurrence worldwide. More than 5,000 cases of poisoning occur in the United States each year. Untreated ethylene glycol poisoning can be fatal; such deaths have occurred annually in the United States. Additionally, ethylene glycol is a colorless, odorless, and sweet-tasting liquid. It can lower the freezing point of water and hold large amounts of heat before boiling.

	To review relevant content, see "Definition", "Properties", and "Toxicity" in this section.

Where Is Ethylene Glycol Found?

Learning Objective	After completing this section, you will be able to identify sources of ethylene glycol exposure.
Introduction	The most common source of ethylene glycol exposure is antifreeze. Antifreeze, which is readily available at hardware and automotive stores, can contain up to 95% ethylene glycol. The primary sources of ethylene glycol in the environment are disposal of used antifreeze and use of de-icing solutions at airports (ATSDR 2010; EPA 2000).
Environmental Sources	The primary sources of ethylene glycol in the environment are from disposal of used antifreeze and use of de-icing solutions at airports. **Air** Ethylene glycol does not persist in large amounts in ambient air. This is because breakdown is rapid (half-life in air is 8–84 hours).

	Water Ethylene glycol is miscible with water. Its half-life ranges from 2 to 12 days in surface water and 4 to 24 days in groundwater. Bioconcentration and bioaccumulation are insignificant because ethylene glycol is not fat-soluble and biodegrades rapidly [Howard 1991]. **Soil** Ethylene glycol will leach through soil to groundwater. It biodegrades rapidly in soil (ATSDR 2010).
Occupational Sources	Workers in industries producing or using products containing ethylene glycol might be exposed to ethylene glycol.
Sources from consumer products	A number of household products contain ethylene glycol as an ingredient [(NLM 2016)]. Those containing high concentrations of ethylene glycol include antifreeze products.
Key Points 2.	• The primary sources of ethylene glycol in the environment are disposal of used antifreeze and use of de-icing solutions at airports. • Most antifreeze products contain high concentrations of ethylene glycol.
Progress Check 2.	The most common source of ethylene glycol exposure that leads to poisoning in the general U.S. population is which of the following? A. Polyester fibers B. Antifreeze C. Cosmetics D. Resin products
Answer	The best choice is B. Ethylene glycol is a significant ingredient of 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 sold in many hardware and automotive stores and therefore easily accessible to the public. Feedback for A. (Web only): The best choice B. The industrial uses of ethylene glycol include production of polyester fibers, films, resin products, cosmetics, and fat extractants. Antifreeze, however, which typically consists of 95% ethylene glycol and accounts for about 40% of ethylene glycol produced, is the most common source of ethylene glycol exposure in the general population. Feedback for B. (Web only): Correct. The best choice is B. Ethylene glycol is a significant ingredient of 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 sold in many hardware and automotive stores and therefore easily accessible to the public. Feedback for C. (Web only): The best choice is B. The industrial uses of ethylene glycol include production of polyester fibers, films, resin products, cosmetics, and fat extractants. Antifreeze, however, which typically consists of 95% ethylene glycol and accounts for about 40% of ethylene glycol produced, is the most common source of ethylene glycol exposure in the general population. Feedback for D. (Web only): The best choice is B. The industrial uses of ethylene glycol include production of polyester fibers, films, resin products, cosmetics, and fat extractants. Antifreeze, however, which typically consists of 95% ethylene glycol and accounts for about 40% of ethylene glycol produced, is the most common source of ethylene glycol exposure in the general population. *To review relevant content, see the "Introduction" in this section.*

	To review relevant content, see “Ingestion” in this section.

Who is at Risk of Exposure to Ethylene Glycol?

Learning Objectives	After completing this section, you will be able to identify who is at risk of exposure to ethylene glycol.
Introduction	For the general population, the primary risk of exposure to ethylene glycol is through contact with automobile antifreezes and coolants. People potentially at greater risk for ethylene glycol exposure include those who live near ● airports where large amounts of ethylene glycol are used for aircraft de-icing or ● hazardous waste sites contaminated with ethylene glycol. Workers in industries producing or using products that contain ethylene glycol are at greatest risk for exposure.
General U.S. Population	In the general U.S. population, exposure leading to ethylene glycol toxicity occurs most commonly through accidental or intentional ingestion of antifreeze. The 2015 annual report of the American Association of Poison Control Centers documented 6,895 ethylene glycol exposures and 22 deaths. The general U.S. population also can be exposed to ethylene glycol by skin contact while handling automotive antifreezes, coolants, and brake fluids. However, such exposure is generally not likely to cause adverse health effects.

Special Populations – Environmental Exposures	Persons living near airports where large amounts of ethylene glycol are used for aircraft de-icing or persons who live near hazardous waste sites contaminated with ethylene glycol are potentially at greater risk for ethylene glycol exposure, particularly if they consume contaminated groundwater. Large amounts of ethylene glycol are sprayed onto airplane wings as an aerosol or mist to prevent ice buildup. Used in this manner, ethylene glycol might contaminate groundwater near airports through runoff. The spray also might expose workers to air levels ranging from .05- 22 milligrams per cubic meter (mg/m^3) [(ATSDR 2010). Ethylene glycol rapidly degrades in air, water, and soil. Available monitoring data indicate that it is only found near areas of release. Ethylene glycol is not expected to be found in the environment away from areas where it is released. Because of that, the general U.S. population is not expected to be exposed to significant environmental background levels of this substance (ATSDR 2010).
Workers - Occupational Exposure	Products containing high concentrations of ethylene glycol include antifreeze, coolants, de-icing fluids, brake fluids, solvents, and latex paints. Workers in industries producing or using those products potentially are at high risk for exposure. Although skin contact is the main route of occupational exposure, vapors or mists can be inhaled when the chemical is heated, agitated, or sprayed.

What Are U.S. Regulations and Guidelines for Ethylene Glycol Exposure?

Learning Objectives	After completing this section, you will be able to describe current U.S. regulations and guidelines for ethylene glycol exposure.
Introduction	The U.S. government has developed ethylene glycol regulations and guidelines intended to protect the public and workers from potential adverse health effects should exposure occur.
Workplace Standards	The Occupational Safety and Health Administration (OSHA) has not established a permissible exposure limit (PEL). The National Institute for Occupational Safety and Health (NIOSH) has provided a recommended ethylene glycol exposure limit (REL) of 50 ppm (ceiling limit) (NIOSH 2005). The American Conference of Governmental Industrial Hygienists (ACGIH) has established threshold limit values (TLVs) for workplace exposure [(ACGIH 2017)].
Environmental Standards	**Air** The Environmental Protection Agency (EPA) has designated ethylene glycol as a hazardous air pollutant under the Clean Air Act (EPA 2007). **Water** EPA recommends that children not be exposed to 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. EPA also recommends that adults not be exposed to more than a daily total of 7 mg/L (7 ppm) for a lifetime [FSTRAC 1990].

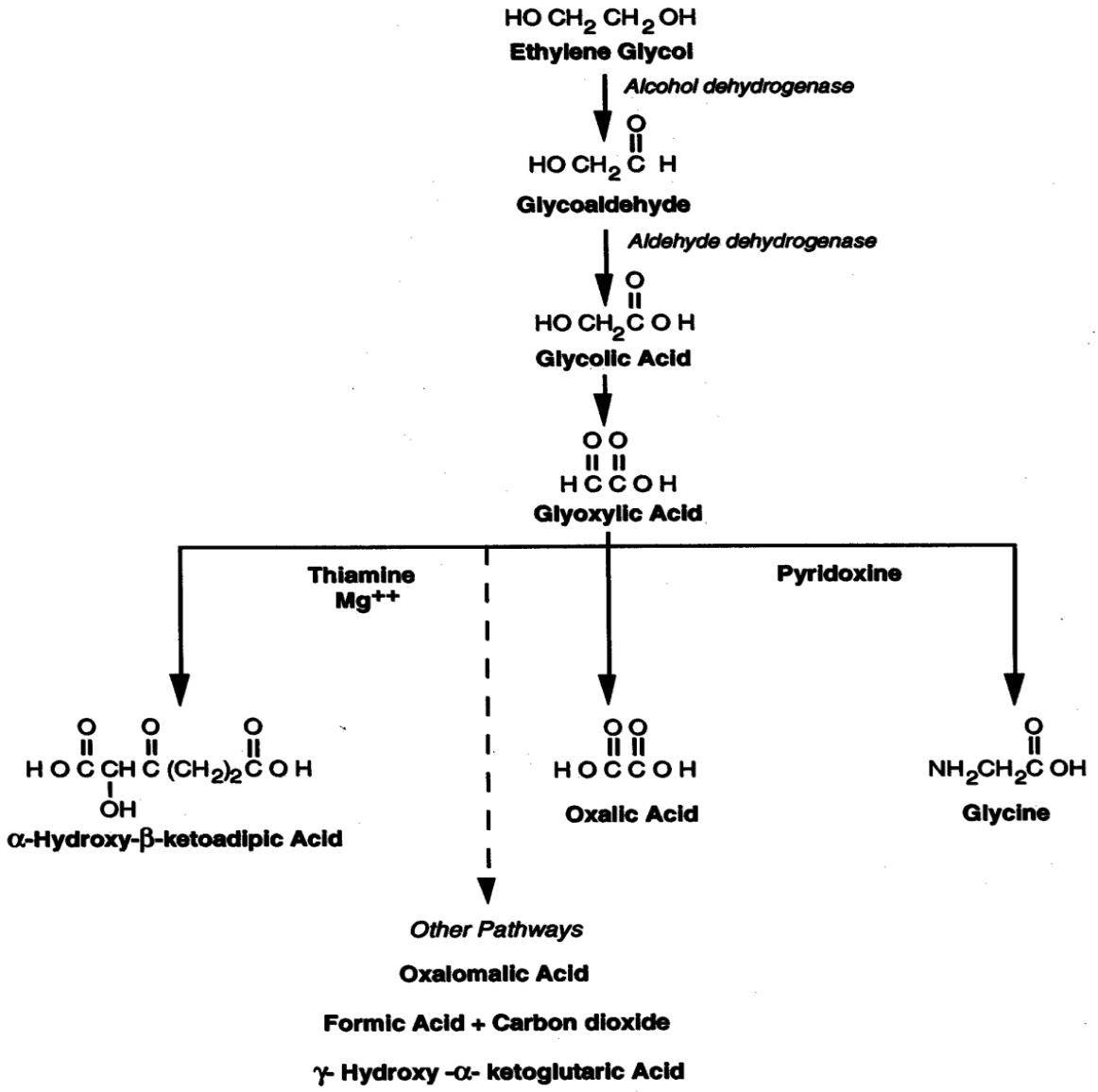


Figure 1. Metabolism of ethylene glycol. Adapted from (Hall AH 1992).

	glycol is metabolized in the liver. Only a small portion (less than 20%) of absorbed ethylene glycol is eliminated unchanged by the kidney. Feedback for C. (Web only): Correct. About 80% of an absorbed dose of ethylene glycol is metabolized in the liver. Feedback for D. (Web only): The correct answer is C. About 80% of an absorbed dose of ethylene glycol is metabolized in the liver. The breakdown of metabolites of ethylene glycol can generate CO_2, which is one of the elimination pathways of ethylene glycol through the lungs. To review relevant content, see “Metabolic Pathway” and “Elimination” in this section.

What Are the Toxicological Effects of Ethylene Glycol Poisoning?

Learning Objectives	After completing this section, you will be able to describe the toxicological effects of ethylene glycol poisoning.
Introduction	Ethylene glycol’s toxicity mainly results from the accumulation of its toxic metabolites. Ethylene glycol is a central nervous system (CNS) depressant that produces acute effects similar to those of ethanol. These CNS effects predominate during the first hours after exposure. If undetected or untreated, ethylene glycol ingestion can cause serious or fatal toxicity. This section describes the systemic effects associated with significant ethylene glycol exposure.

	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 et al. 1962; Godolphin et al. 1980; Parry and Wallach 1974). Autopsies [(Vale 1979) of ethylene glycol victims revealed the following: • Pulmonary edema with diffuse hemorrhagic exudates • Bronchopneumonia (probably caused by aspiration) • Deposits of calcium oxalate crystals in lung parenchyma
Cardiovascular Effects	The following severe cardiovascular effects have been reported in persons 12-24 hours (stage 2) after ingesting ethylene glycol (Friedman et al. 1962; Gordon and Hunter 1982; Parry and Wallach 1974; Vale 1979): • Hypertension or hypotension • Dysrhythmias (from electrolyte abnormalities) • Congestive heart failure with cardiogenic pulmonary edema • Circulatory collapse • Cardiac arrest • Death

Metabolic Effects	Ethylene glycol exposure is characterized by an elevated osmolal gap and metabolic acidosis with an elevated anion gap. • Onset occurs within 24 hours after ingestion. • Acidosis is caused primarily by the accumulation of glycolic and glyoxylic acids. Oxalic acid and lactic acid also contribute. Ethylene glycol is a small, osmotically active molecule that • increases plasma osmolality, and • can cause a large osmolal gap. Tetany, including muscle twitches, cramps, and contractions, can sometimes result from hypocalcemia, which results from calcium precipitation by the oxalate formed during ethylene glycol metabolism (Parry and Wallach 1974).
Renal Effects	Adverse renal effects after ethylene glycol ingestion typically occur during the third stage of ethylene glycol toxicity, 24–72 hours after acute exposure (Davis et al. 1997; Hess et al. 2004). • Kidney damage manifests as acute oliguric renal failure. • The most common physical finding is costovertebral angle tenderness (Friedman 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 (Froberg et al. 2006; Hantson et al. 2002; Huhn and Rosenberg 1995; Leth and Gregersen 2005; McMartin K 2009; Olivero 1993; Takayesu et al. 2006). • Absence of oxalate crystals does not rule out an ethylene glycol poisoning diagnosis (Baum et al. 2000; Boyer et al. 2001; Curtin et al. 1992; Hantson et al. 2002; Haupt et al. 1988).

	Other typical urinalysis abnormalities include the following: • Low specific gravity • Proteinuria • Microhematuria • Pyuria Renal dysfunction might be mild and short-lived or severe and persistent. Although uncommon, permanent renal insufficiency does occur (Berman et al. 1957; Buell et al. 1998; Friedman et al. 1962; Hantson et al. 1998; Parry and Wallach 1974; Takayesu et al. 2006). The toxicity of ethylene glycol is linked with all four metabolites. • Glycolic acid contributes to the metabolic acidosis. • Oxalic acid is poorly soluble in the presence of calcium. o Calcium oxalate crystals in the urine are supportive of the diagnosis. o The precipitation of oxalate crystals in the tubular lumen leads to luminal blockage and compression-induced loss of glomerular filtration (renal failure). o In transformed kidney cells, the oxalate ion induces cytotoxic damage (McMartin KE and Cenac 2000). • Glycoaldehyde and glyoxylate might be responsible for ethylene glycol nephrotoxicity (Poldelski et al. 2001).
Carcinogenicity	Studies in humans and animals have not shown any associations between ethylene glycol exposure and the incidence of any cancer (ATSDR 2014).
Developmental and Reproductive Effects	No known human studies have evaluated a link between ethylene glycol exposure and reproductive or developmental hazards in humans (ATSDR 2014).

	• Ethylene glycol exposure was teratogenic to mice and rats, resulting in craniofacial and neural tube closure defects and skeletal dysplasia [Lamb et al. 1985; Marr et al. 1992; Price et al. 1985; Tyl et al. 1995]. • Large oral doses of ethylene glycol (>500 mg kg-1 in mice and >1,000 mg kg-1 in rats) might cause developmental toxicity in those animals, including o axial skeletal malformations, o reduced body weights, o external malformations, and o increased post-implantation loss [IPCS 2002; NTP-CERHR 2004].
Other Effects	Nausea, vomiting (with or without blood), and abdominal pain often occur soon after ethylene glycol ingestion (Davis et al. 1997; Johnson et al. 1999; Moossavi et al. 2003; Singh et al. 2001; Verrilli et al. 1987). Ethylene glycol is only a minor skin and mucous membrane irritant, although a few patients have had allergic contact dermatitis (Clayton GD & Clayton FE 1994). Reported effects on the blood have included (Hantson et al. 1998; Rasic et al. 1999; Verrilli et al. 1987) • leukocytosis, • methemoglobinemia (rare), and • bone marrow arrest. Reported musculoskeletal effects have included • muscle tenderness and • elevation of creatine kinase (Friedman et al. 1962; Parry and Wallach 1974; Verrilli et al. 1987).
Key Points	• After ethylene glycol ingestion, signs of inebriation are among the first manifestations. • Unmetabolized ethylene glycol causes CNS depression. Delays in initiating treatment can result in more severe adverse effects. • The most common cause of tachypnea is uncompensated metabolic acidosis.

	15. The best choice is D. The presence of metabolic acidosis (answer B) with anion and osmolal gaps (answer A) are important clues to the diagnosis. However, numerous toxic substances are associated with an elevated anion gap (Table 3). Numerous studies have documented that renal damage occurs after ethylene glycol ingestion, even without deposition in the kidney of calcium oxalate crystals (answer C). Although answers A, B, and C together strongly suggest ethylene glycol poisoning, elevated serum ethylene glycol level remains the most reliable diagnostic index. At the time of testing for ethylene glycol poisoning, all, some, or none of the findings in answers A, B, or C might be present. Feedback for A. (Web only): The best choice is D. The presence of anion and osmolal gaps are important clues to the diagnosis. However, numerous toxic substances are associated with an elevated anion gap (Table 3). Although an elevated anion gap and an increased osmolal gap strongly suggest ethylene glycol poisoning, an elevated serum ethylene glycol level is the most reliable diagnostic index. Feedback for B. (Web only): The best choice is D. The presence of normochloremic metabolic acidosis is an important clue to the diagnosis. However, numerous toxic substances are associated with metabolic acidosis (Table 3). Thus, an elevated serum ethylene glycol level is the most reliable diagnostic index. Feedback for C. (Web only): The best choice is D. Numerous studies have documented that renal damage occurs after ethylene glycol ingestion, even without deposition of calcium oxalate crystals in the kidney. Although calcium oxalate or hippurate crystalluria strongly suggests ethylene glycol poisoning, an elevated serum ethylene glycol level is the most reliable diagnostic index. Feedback for D. (Web only): Correct. The presence of metabolic acidosis (answer B) with anion and osmolal gaps (answer A) are important clues to the diagnosis. However, numerous toxic substances are associated

	with an elevated anion gap (Table 3). Numerous studies have documented that renal damage occurs after ethylene glycol ingestion, even without deposition in the kidney of calcium oxalate crystals (answer C). Although answers A, B, and C together strongly suggest ethylene glycol poisoning, an elevated serum ethylene glycol level remains the most reliable diagnostic index. At the time of testing for ethylene glycol poisoning, all, some, or none of the findings in answers A, B, or C might be present. *To review relevant content, see "Serum Analysis" in this section.*

How Should Patients Exposed to Ethylene Glycol Be Treated and Managed?

Learning Objectives	After completing this section, you will be able to describe treatment strategies 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 specialists such as the following with expertise and experience treating patients exposed to ethylene glycol: • Board-certified occupational and environmental medicine physicians • Board-certified pediatric environmental health specialists • Board-certified medical toxicologists
Supportive Care	For initial patient stabilization, the clinician should first assess and secure the patient's airway, breathing, and circulation.
Gastrointestinal Decontamination	Gastrointestinal decontamination measures, such as activated charcoal, gastric lavage, and gastric aspiration, provide little benefit in ethylene glycol poisoning because ethylene glycol is rapidly absorbed (Sivilotti 2018).
Specific Treatment	Specific treatment for ethylene glycol poisoning may include the following: • Sodium bicarbonate to temporarily correct the metabolic acidosis, as indicated • Fomepizole or ethanol to competitively inhibit metabolism of ethylene glycol to its more toxic metabolites (Baud et al. 1988; Brent et al. 1999; Jones AL and Volans 1999; Sivilotti 2018) • If indicated, hemodialysis to remove ethylene glycol and glycolic acid (Bey et al. 2002; Cheng et al.

	1987; Gabow et al. 1986; Jacobsen and McMartin 1997; Malmlund et al. 1991; Moreau et al. 1998; Sivilotti 2018; Stokes and Aueron 1980). The above treatment strategies are effective in most cases, but if treatment is delayed, renal failure and death can occur (Leth and Gregersen 2005; Pellegrino et al. 2006).
Fomepizole Therapy	Fomepizole, an alcohol dehydrogenase enzyme (ADH) antagonist, is the preferred therapy for ethylene glycol poisoning. The American Academy of Clinical Toxicology developed the following criteria for using fomepizole rather than ethanol (Barceloux et al. 1999): • 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
Advantages of Fomepizole Therapy	Fomepizole therapy might obviate the need for hemodialysis in the absence of renal insufficiency and significant metabolic acidosis (Battistella 2002; Borron et al. 1999; Brent 2001; Bronstein et al. 2009; Druteika et al. 2002; Harry et al. 1998; Harry et al. 1994; Watson 2000). In comparison with ethanol (Lepik et al. 2009), 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, and • does not cause central nervous system (CNS) depression or hypoglycemia.
Ethanol Therapy	If fomepizole is unavailable or the patient has a known allergy, alcohol dehydrogenase can be blocked with 10 mL/kg of a 10% ethanol solution, followed by 1 mL/kg of 10% ethanol solution infused per hour. Titrate to a serum ethanol concentration of 100 mg/dL (Sivilotti 2018). 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, and • poses problems in patient care, such as drunkenness. Although ethanol costs much less, the savings might be offset by additional costs for • monitoring the patient, • laboratory tests, and • hemodialysis for some patients.

Hemodialysis	Hemodialysis can rapidly remove toxic acid metabolites and parent alcohols. Several studies (Barceloux et al. 1999; Brent et al. 1999; Jammalamadaka and Raissi 2010; Sivilotti 2018) suggest considering hemodialysis when • serum ethylene glycol levels exceed 50 mg/dL (8.1 mmol/L), • severe acidemia (pH <7.25) or fluid/electrolyte disturbances persist despite ethanol or fomepizole therapy, • vital signs continue to deteriorate despite intensive supportive treatment, or • renal failure develops. Continue hemodialysis until • acidosis is controlled, and • serum ethylene glycol level falls below 20 mg/dL. When renal function is preserved, patients often can be treated without hemodialysis. This outcome underscores the effectiveness of supportive care and the use of fomepizole in the treatment of ethylene glycol poisoning, even at levels that have traditionally required hemodialysis (Buchanan et al. 2010; Levine et al. 2012; Velez L. I. et al. 2007).
Vitamin Treatment	Thiamine and pyridoxine are two water-soluble B-complex vitamins that act as metabolic cofactors in the metabolism of ethylene glycol. The benefits of giving supplemental thiamine (100 mg IV) or pyridoxine (50 mg IV) to patients poisoned with ethylene glycol are unknown. However, both are routinely administered, particularly if the patient's nutritional status is suspect (Sivilotti 2018).
Pediatric Cases	For those pediatric patients who do show signs of ethylene glycol poisoning, the diagnostic and treatment considerations described above for adults largely apply. The limited published experience with fomepizole

	supports its safe and effective use in children at the same dosing protocol given above (Brent 2010; Caravati et al. 2004; Schwerk et al. 2007; Sivilotti 2018).
Key Points	• Supportive care is the cornerstone of treatment of the poisoned patient. • Because ethylene glycol is rapidly absorbed, gastrointestinal decontamination has little role in treatment. • Fomepizole therapy might obviate the need for hemodialysis in the absence of renal insufficiency and significant metabolic acidosis. • A regional poison control center or medical specialists with expertise and experience treating patients exposed to ethylene glycol can provide treatment advice.
Progress Check 16. 17.	Which of the following best describes the treatment strategy for managing patients with ethylene glycol poisoning? A. Sodium bicarbonate to correct the metabolic acidosis as indicated. B. Ethanol or fomepizole 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. Which of the following IS NOT considered a current indication for hemodialysis after ethylene glycol ingestion? A. Severe acidemia (pH <7.25) or fluid/electrolyte disturbances that persist despite fomepizole therapy. B. Vital signs continue to deteriorate despite intensive supportive treatment. C. Renal failure develops. D. A serum ethylene glycol level of 10–15 mg/dL.

Answers	16. The best choice is D. All of the above. A treatment strategy to best manage patients with ethylene glycol poisoning includes, when indicated, ● use of sodium bicarbonate to correct metabolic acidosis, ● use of ethanol or fomepizole (antizol) to competitively inhibit the metabolism of ethylene glycol to its more toxic metabolites, and ● hemodialysis to remove ethylene glycol and glycolic acid. This treatment strategy is effective in most cases, but if treatment is delayed, renal failure and death can occur. Feedback for A. (Web only): The best choice is D. All of the above. A treatment strategy to best manage patients with ethylene glycol poisoning includes, when indicated, use of bicarbonate to correct metabolic acidosis. It also might include use of ethanol or fomepizole to competitively inhibit metabolism of ethylene glycol to its more toxic metabolites. Hemodialysis might be needed to remove ethylene glycol and glycolic acid. Feedback for B. (Web only): The best choice is D. All of the above. A treatment strategy to best manage patients with ethylene glycol poisoning includes, when indicated, use of ethanol or fomepizole to competitively inhibit metabolism of ethylene glycol to its more toxic metabolites. It also might include use of bicarbonate to correct metabolic acidosis and hemodialysis to remove ethylene glycol and glycolic acid. Feedback for C. (Web only): The best choice is D. All of the above. A treatment strategy to best manage patients with ethylene glycol poisoning includes, when indicated, hemodialysis to remove ethylene glycol and glycolic acid. It also might include use of bicarbonate to correct metabolic acidosis, and use of ethanol or fomepizole to competitively inhibit metabolism of ethylene glycol to its more toxic metabolites.

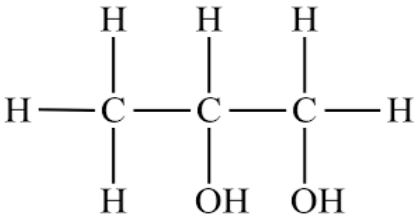
	Feedback for D. (Web only): Correct. All of the above. A treatment strategy to best manage patients with ethylene glycol poisoning includes, when indicated, ● use of sodium bicarbonate to correct metabolic acidosis, ● use of ethanol or fomepizole (antizol) to competitively inhibit the metabolism of ethylene glycol to its more toxic metabolites, and ● hemodialysis to remove ethylene glycol and glycolic acid. This treatment strategy is effective in most cases, but if treatment is delayed, renal failure and death can occur. *To review relevant content, see "Specific Treatment" in this section.* 17. The best choice is D. Indications for hemodialysis treatment after ethylene glycol ingestion include ● severe acidemia (pH <7.25) or fluid/electrolyte disturbances that persist despite fomepizole therapy, ● vital signs that continue to deteriorate despite intensive supportive treatment, and ● development of renal failure. Although a serum ethylene glycol level of ≥50 mg/dL was considered an indication for hemodialysis, there are reports of patients with levels of ≥50 mg/dL being successfully treated with fomepizole, with or without bicarbonate, and without hemodialysis. Feedback for A. (Web only): The best choice is D. An indication for hemodialysis treatment after ethylene glycol ingestion is severe acidemia (pH <7.25) or fluid/electrolyte disturbances that persist despite fomepizole therapy. Indications also include vital signs that continue to deteriorate despite intensive supportive treatment, and development of renal failure. Although a serum ethylene glycol level of ≥50 mg/dL was considered an indication for hemodialysis, there are reports of patients with levels of ≥50 mg/dL being successfully

	treated with fomepizole, with or without bicarbonate, and without hemodialysis. Feedback for B. (Web only): The best choice is D. An indication for hemodialysis treatment after ethylene glycol ingestion is vital signs that continue to deteriorate despite intensive supportive treatment. Indications also include severe acidemia (pH <7.25) or fluid/electrolyte disturbances that persist despite fomepizole therapy, and development of renal failure. Although a serum ethylene glycol level of ≥50 mg/dL was considered an indication for hemodialysis, there are reports of patients with levels of ≥50 mg/dL being successfully treated with fomepizole, with or without bicarbonate, and without hemodialysis. Feedback for C. (Web only): The best choice is D. An indication for hemodialysis treatment after ethylene glycol ingestion is development of renal failure. Indications also include severe acidemia (pH <7.25) or fluid/electrolyte disturbances that persist despite fomepizole therapy, and vital signs that continue to deteriorate despite intensive supportive treatment. Although a serum ethylene glycol level of ≥50 mg/dL was considered an indication for hemodialysis, there are reports of patients with levels of ≥50 mg/dL being successfully treated with fomepizole, with or without bicarbonate, and without hemodialysis. Feedback for D. (Web only): Correct. Indications for hemodialysis treatment after ethylene glycol ingestion include ● severe acidemia (pH <7.25) or fluid/electrolyte disturbances that persist despite fomepizole therapy, ● vital signs that continue to deteriorate despite intensive supportive treatment, and ● development of renal failure. Although a serum ethylene glycol level of ≥50 mg/dL was considered an indication for hemodialysis, there are reports of patients with levels of ≥50 mg/dL (ethylene glycol ≥7.5 mmol/L) being successfully treated with fomepizole, with or without bicarbonate, and without hemodialysis.

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

What Is Propylene Glycol?

Learning Objective	After completing this section, you will be able to • describe the uses of propylene glycol, and • explain the potential risk for propylene glycol toxicity.

Definition	Propylene glycol is a • clear, • colorless, • viscous liquid with a faintly sweet taste. Its chemical structure is $CH_3CH[OH]CH_3OH$.  Propylene glycol and ethylene glycol have similar physical properties and uses. Their chemical structures differ by only one methyl group (ethylene glycol = $HOCH_2CH_2OH$; propylene glycol = $CH_3CH[OH]CH_2OH$). Ethylene glycol is a potent cause of acute toxicity in humans. In contrast, propylene glycol is a "generally recognized as safe" additive for foods and medications. Most reported cases of propylene glycol toxicity have resulted from propylene glycol used as a diluent for intravenous administration of benzodiazepines (Kraut and Kurtz 2008).
Synonyms	Synonyms for propylene glycol (ATSDR 1997) include • 1,2-propanediol, • 1,2-dihydroxypropane, • methyl glycol, and • trimethyl glycol.

Uses	Propylene glycol is generally recognized as safe by the Food and Drug Administration (FDA) (FDA 2017) for uses in • food and tobacco products, • pharmaceuticals, and • cosmetics. It has a wide range of other practical applications (ATSDR 2008), including use in • deicers, • coolants, • antifreeze, • heat transfer and hydraulic fluids, • plasticizers, and • other applications (smoke screen, smoke simulator, etc.).
Sources of Exposure	In the general population, propylene glycol exposure occurs primarily through ingestion of food and medications and through skin contact with cosmetics or topical medications. Propylene glycol is used as a solvent in cosmetics and pharmaceuticals, in various • oral, • injectable, and • topical formulations. Propylene glycol is a diluent found in many intravenous and oral drugs, including • phenytoin, • diazepam, and • lorazepam. No adverse health effects are likely to occur from normal use of these products. However, heavy use of injectable medications with propylene glycol has caused excess levels of propylene glycol in the body (Horinek et al. 2009; Louis et al. 1967; Neale et al. 2005; Seay et al. 1997; Wilson et al. 2000; Yorgin et al. 1997; Zar et al. 2007; Zosel et al. 2010). Prolonged and extensive

	topical application on compromised skin, such as burns, has also caused excess propylene glycol levels (Peleg et al. 1998).
Who Is at Risk	Patients in intensive care, for example, might experience toxicity from either of the following: • Excessively large or rapidly infused intravenous injections of propylene glycol-containing medications (Horinek et al. 2009; Louis et al. 1967; Neale et al. 2005; Seay et al. 1997; Wilson et al. 2000; Yorgin et al. 1997; Zar et al. 2007; Zosel et al. 2010) • Prolonged dermal contact during treatment of burns (Peleg et al. 1998) Patients at risk for propylene glycol toxicity (Lim et al. 2014) include the following: • Patients with underlying kidney disease • Patients with less effective or impaired alcohol dehydrogenase enzyme systems (e.g., children younger than 4 years, pregnant women, patients with hepatic disease, and patients treated with disulfiram or metronidazole) • Patients with epilepsy • Burn patients who receive extensive dermal applications of propylene glycol

Biological Fate	Absorption of propylene glycol from the gastrointestinal tract is rapid. The 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 unchanged by the kidneys or as the glucuronide conjugate. **Half-life** In adults with normal liver and kidney function, the terminal half-life of propylene glycol ranges from 1.4 hours to 3.3 hours (Speth et al. 1987). In contrast, the mean half-life is significantly longer in infants — 19.3 hours (range: 10.8–30.5 hours) — because of decreased renal elimination (Lim et al. 2014).
Toxicological Effects at a Glance	Although propylene glycol is a commonly used solvent for intravenous medications, it might become toxic when administered in large doses over a short period (Bledsoe and Kramer 2008; Zar et al. 2007). Iatrogenic propylene glycol overdose can cause the following: • Hyperosmolality and an anion gap metabolic acidosis, often accompanied by acute kidney injury, and potential multisystem organ failure (Arroliga et al. 2004; Greller and Gupta 2017; Tietze and Fuchs 2018; Wilson et al. 2000; Wilson et al. 2005; Yahwak et al. 2008; Zar et al. 2007)

	• Refractory hypotension (Wilson et al. 2000) • Arrhythmias (Louis et al. 1967) • Hemolysis (Demey et al. 1988) • Renal dysfunction (e.g., increased serum creatinine concentrations, proximal renal tubular cell injury, etc.) (Yaucher et al. 2003; Yorgin et al. 1997) • Seizure, coma (Greller and Gupta 2017) Pediatric patients also might develop CNS depression and seizures (Lim et al. 2014; O'Donnell et al. 2000).
Clinical Evaluation	Propylene glycol toxicity should be suspected in any patient receiving medication that contains propylene glycol as a diluent or solvent and who has • hyperosmolality, • lactic acidosis, • acute kidney injury, or • a clinical scenario similar to sepsis or systemic inflammatory response syndrome (SIRS) (Zar et al. 2007). The clinical diagnosis of propylene glycol intoxication may be difficult because many hospitals do not measure propylene glycol levels. However, the osmolar gap, anion gap, and lactate are commonly elevated in propylene glycol intoxication (Lim et al. 2014). An osmolar gap at 48 hours after continuous infusion strongly predicts propylene glycol accumulation. An elevated anion gap and lactic acidosis are poor indicators (Arroliga et al. 2004; Barnes et al. 2006; Wilson et al. 2005; Yahwak et al. 2008; Zar et al. 2007). An osmolar gap >10 mmoles/L suggests that the serum propylene glycol concentration is high enough to cause toxicity (Barnes et al. 2006; Tietze and Fuchs 2018; Yahwak et al. 2008).

Treatment	Because this disorder is iatrogenic, prevention by limiting the dosage of propylene glycol given to patients in the intensive care unit might be the best treatment [(Kraut and Kurtz 2008). Healthcare providers should consider a 50% reduction in the maximum daily dose for patients with underlying risk factors (see discussion on "Who's at Risk"). The maximum daily dose of drug for a pediatric patient can be extrapolated from the adult data (based on a 70-kg patient) (Lim et al. 2014). Metabolic acidosis caused by large amounts of propylene glycol in injected medications can be treated by discontinuing the offending medication and providing sodium bicarbonate and fomepizole (Zosel et al. 2010). In severe cases, hemodialysis is effective in correcting hyperosmolality by removing propylene glycol from the blood (Demey et al. 1988; Kraut and Kurtz 2008; Lim et al. 2014; Parker et al. 2002; Wilson et al. 2000).
Standards and Regulations	No workplace or environmental standards govern propylene glycol. Propylene glycol is "generally recognized as safe" by the U.S. Food and Drug Administration (FDA) (FDA 2017). FDA considers an average daily dietary intake of 23 mg/kg of body weight to be safe for persons 2–65 years of age (ATSDR 2008).
Key Points	• Various foods, cosmetics, and pharmaceutical products contain propylene glycol. • Propylene glycol is metabolized to compounds that are normal constituents of the citric acid cycle. • Propylene glycol toxicity generally is not a factor in environmental or occupational exposures. • Iatrogenic propylene glycol overdose is the most common cause of propylene glycol poisoning.

	• The major toxicological effects of propylene glycol poisoning include the following: o Hyperosmolality o Elevated lactate o Refractory hypotension o Arrhythmias o Hemolysis o Renal dysfunction • Because this disorder is iatrogenic, prevention by limiting the dosage of propylene glycol given to patients in the intensive care unit might be the best treatment.
Progress Check 18. 19.	Propylene glycol is used in which of the following products? A. Emulsifying agents. B. Industrial drying agents. C. Surfactants or solvents. D. All of the above. In contrast with ethylene glycol, propylene glycol less commonly causes toxic effects. Why is that? 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. 20. Metabolic acidosis caused by large amounts of propylene glycol in injected medications can be treated with all of the following EXCEPT which? A. Sodium bicarbonate. B. Fomepizole. C. Ethanol.

	D. Hemodialysis.
Answers	18. The best choice is D. All of the above. Propylene glycol is used in certain medicines, cosmetics, and food products as an emulsifying agent, an industrial drying agent, a surfactant or, a solvent. Feedback for A. (Web only): The best choice is D. All of the above. In certain medicines, cosmetics, and food products, propylene glycol is used as an emulsifying agent. It also serves as an industrial drying agent, a surfactant, and a solvent. Feedback for B. (Web only): The best choice is D. All of the above. In certain medicines, cosmetics, and food products, propylene glycol is used as an industrial drying agent. It also serves as an emulsifying agent, a surfactant, and a solvent. Feedback for C. (Web only): The best choice is D. All of the above. In certain medicines, cosmetics, and food products, propylene glycol is used as a surfactant or solvent. It also serves as an emulsifying agent and an industrial drying agent. Feedback for D. (Web only): Correct. Propylene glycol is used in certain medicines, cosmetics, and food products as an emulsifying agent, an industrial drying agent, a surfactant or a solvent. *To review relevant content, see "Uses" in this section.* 19. 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 constituents of the citric acid cycle and are further metabolized to carbon dioxide and water. Feedback for A. (Web only): The best choice is D. Absorption of propylene glycol from the gastrointestinal

	tract is rapid. 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. Feedback for B. (Web only): The best choice is D. 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. Feedback for C. (Web only): The best choice is D. Ethylene glycol is metabolized in the liver to more toxic 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. Feedback for D. (Web only): Correct. 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 constituents of the citric acid cycle and are further metabolized to carbon dioxide and water. *To review relevant content, see "Biological Fate" in this section.* 20. The correct choice is C. Metabolic acidosis caused by large amounts of propylene glycol in injected medications can be treated with sodium bicarbonate and fomepizole. In severe cases, hemodialysis is effective in correcting hyperosmolality by removing propylene glycol from the blood. Propylene glycol is metabolized in the liver by alcohol dehydrogenase (ADH) to the normal constituents of the citric acid cycle. Ethanol is not needed to exhaust ADH because ADH metabolizes propylene glycol to nontoxic constituents.

	Feedback for A. (Web only): The correct choice is C. Metabolic acidosis caused by large amounts of propylene glycol in injected medications can be treated with sodium bicarbonate and fomepizole. In severe cases, hemodialysis is effective in correcting hyperosmolality by removing propylene glycol from the blood. Ethanol is not needed to exhaust ADH because ADH metabolizes propylene glycol to nontoxic constituents. Feedback for B. (Web only): The best choice is C. Metabolic acidosis caused by large amounts of propylene glycol in injected medications can be treated with sodium bicarbonate and fomepizole. In severe cases, hemodialysis is effective in correcting hyperosmolality by removing propylene glycol from the blood. Ethanol is not needed to exhaust ADH because ADH metabolizes propylene glycol to nontoxic constituents. Feedback for C. (Web only): Correct. Propylene glycol is metabolized in the liver by alcohol dehydrogenase (ADH) to the normal constituents of the citric acid cycle. In severe cases, hemodialysis is effective in correcting hyperosmolality by removing propylene glycol from the blood. Ethanol is not needed to exhaust ADH because ADH metabolizes propylene glycol to nontoxic constituents. Feedback for D. (Web only): The correct choice is C. Metabolic acidosis caused by large amounts of propylene glycol in injected medications can be treated with sodium bicarbonate and fomepizole. In severe cases, hemodialysis is effective in correcting hyperosmolality by removing propylene glycol from the blood. Ethanol is not needed to exhaust ADH because ADH metabolizes propylene glycol to nontoxic constituents. *To review relevant content, see "Biological Fate" in this section.*

What Instructions Should You Give to Patients Regarding Ethylene Glycol/Propylene Glycol Exposure?

Learning Objectives	After completing this section, you will be able to describe self-care and clinical follow-up instructions for patients exposed to ethylene glycol or propylene glycol.
Introduction	• All patients with ethylene glycol poisoning should be evaluated and treated immediately. • All patients exposed to ethylene glycol or propylene glycol need basic guidance on o self-care, so they can minimize further risks and avoid complications to the extent possible, and o 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 is available at http://www.atsdr.cdc.gov/csem/egpg/pated_sheet.html.
Self-Care	Advise patients to avoid exposures and conditions that might further increase their risk for disease or worsen their existing health condition(s). You might offer the following advice to your patient: • If you have any antifreeze in your home, keep it in original, labeled containers and securely stored and out of children's reach. • If you suspect that someone has ingested antifreeze, be sure he or she sees a healthcare provider immediately.
Clinical Follow Up	Patients should be advised to consult their healthcare provider if they develop • any sign or symptom of CNS involvement, or

	• signs or symptoms of other health changes (especially those possibly related to heart and kidney problems). ATSDR's patient education and care instruction sheet on ethylene glycol and propylene glycol is a job aid that provides relevant follow-up instructions for patients possibly exposed to ethylene glycol or propylene glycol including follow-up instructions.
Key Points	• Advise patients to avoid exposures and conditions that might further increase their risk for disease or worsen their existing health condition(s). • Patients should seek immediate evaluation if they develop neurological problems or other health changes after exposure. • A patient education and care instruction sheet for ethylene glycol and propylene glycol is available at: http://www.atsdr.cdc.gov/csem/egpg/pated_sheet.html
Progress Check	21. Patients who have been exposed to ethylene glycol should take what action? A. Seek clinical evaluation and treatment as soon as possible. B. Learn how to avoid further exposure. C. Know when to call their healthcare provider. D. All of the above.
Answers	21. The best choice is D: All of the above. 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 and advise patients to avoid exposures and conditions that might increase their risk for disease or worsen their existing health condition(s). In addition, patients should contact their physician if they develop neurological problems or other health changes.

	Feedback for A. (Web only): The best choice is D. All of the above. All patients with ethylene glycol poisoning should be evaluated and treated as soon as possible. Even patients with no or mild symptoms should undergo appropriate blood and urine tests if they have a history of significant ingestion. Feedback for B. (Web only): The best choice is D. All of the above. Advise patients to avoid exposures and conditions that might increase their risk for disease or worsen their existing health condition(s). Feedback for C. (Web only): The best choice is D. All of the above. Patients should contact their healthcare provider if they develop neurological problems or other health changes. Feedback for D. (Web only): Correct. 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 and advise patients to avoid exposures and conditions that might increase their risk for disease or worsen their existing health condition(s). In addition, patients should contact their healthcare providers if they develop neurological problems or other health changes. *To review relevant content, see "Self Care" and "Clinical Follow-Up" in this section.*

Sources of Additional Information

Ethylene Glycol and Propylene Glycol Specific Information	The following Web resources may provide more information on the adverse effects of ethylene glycol and propylene glycol, treatment of ethylene glycol and propylene glycol associated diseases, and management of persons exposed to ethylene glycol and propylene glycol.

- Agency for Toxic Substances and Disease Registry (ATSDR) http://www.atsdr.cdc.gov

- For chemical, emergency situations

  - CDC Emergency Response: 770-488-7100 and request the ATSDR Duty Officer

- For chemical, non-emergency situations

  - CDC-INFO http://www.cdc.gov/cdc-info/
  - 800-CDC-INFO (800-232-4636) TTY 888-232-6348 - 24 Hours/Day
  - E-mail: cdcinfo@cdc.gov

  Note:

  ATSDR cannot respond to questions about individual medical cases, provide second opinions, or make specific recommendations regarding therapy. Those issues should be addressed directly with your healthcare provider.

- Toxicological profile for ethylene glycol http://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=86&tid=21
- TOXFAQs for ethylene glycol (English) http://www.atsdr.cdc.gov/toxfaqs/TF.asp?id=85&tid=21
- TOXFAQs for ethylene glycol (Spanish) http://www.atsdr.cdc.gov/toxfaqs/TF.asp?id=85&tid=21
- ATSDR medical management guidelines for ethylene glycol http://www.atsdr.cdc.gov/MMG/MMG.asp?id=82&tid=21
- ATSDR minimal response levels http://www.atsdr.cdc.gov/mrls/index.html
- ATSDR ToxFAQs for propylene glycol (English) http://www.atsdr.cdc.gov/toxfaqs/tf.asp?id=1121&tid=240

	o ATSDR ToxFAQs for propylene glycol (Spanish) http://www.atsdr.cdc.gov/es/toxfaqs/es_tfacts189.html • NIOSH pocket guide to chemical hazards – ethylene glycol http://www.cdc.gov/niosh/npg/npgd0272.html • EPA Technology Transfer Network – ethylene glycol http://www.epa.gov/ttn/atw/hlthef/ethy-gly.html • OSHA Safety and Health Topics – ethylene glycol https://www.osha.gov/SLTC/ethyleneoxide/index.html
General Environmental Health Information	The following Web resources provide general information on environmental health. • Agency for Toxic Substances and Disease Registry http://www.atsdr.cdc.gov o Taking an exposure history CSEM http://www.atsdr.cdc.gov/csem/csem.asp?csem=17&po=0 o To view the complete library of CSEMs http://www.atsdr.cdc.gov/csem/csem.html o Exposure history form http://www.atsdr.cdc.gov/csem/csem.asp?csem=17&po=19 **ATSDR Division of Regional Operations** Through the working relationships they have established with EPA, other federal and state agencies, individual citizens, and community groups, ATSDR regional representatives are able to maintain current and historic knowledge of the sites and issues in their regions. Information about ATSDR's regional offices, the states and territories that they cover, and contact information, is available at http://www.atsdr.cdc.gov/DRO/dro_contact.html • ATSDR State Cooperative Agreement Program http://www.atsdr.cdc.gov/states/index.html.

	• The Cooperative Agreement Program provides essential support in communities nationwide to fulfill ATSDR's mission. • The program funds 30 states and one tribal government to develop and strengthen their abilities to evaluate and respond to environmental public health issues. **Centers for Disease Control and Prevention (CDC)** http://www.cdc.gov CDC works to protect public health and the safety of people by providing information to support health decisions. CDC also promotes health through partnerships with state health departments and other organizations. CDC focuses national attention on developing and applying disease prevention and control (especially infectious diseases), environmental health, occupational safety and health, health promotion, prevention, and education activities designed to improve the health of the people of the United States. National Center for Environmental Health (NCEH) http://www.cdc.gov/nceh NCEH works to prevent illness, disability, and death from interactions between people and the environment. It is especially committed to safeguarding the health of populations that are particularly vulnerable to certain environmental hazards — children, the elderly, and people with disabilities. NCEH seeks to achieve its mission through science, service, and leadership. **National Institute of Health (NIH)** http://www.nih.gov

	A part of the U.S. Department of Health and Human Services, NIH is the primary federal agency for conducting and supporting medical research. National Institute for Occupational Safety and Health (NIOSH) http://www.cdc.gov/niosh/ NIOSH is in the U.S. Department of Health and Human Services. NIOSH was established to help assure safe and healthful working conditions for workers by providing research, information, education, and training in the field of occupational safety and health. **American College of Occupational and Environmental Medicine (ACOEM)** http://www.acoem.org/ ACOEM is the nation's largest medical society dedicated to promoting the health of workers through preventive medicine, clinical care, research, and education. ACOEM members include specialists in a variety of medical practices united to develop positions and policies on vital issues relevant to the practice of preventive medicine within and outside of the workplace. **American College of Medical Toxicologists (ACMT)** http://www.acmt.net ACMT is a professional, nonprofit association of physicians with recognized expertise in medical toxicology. ACMT is dedicated to advancing the science and practice of medical toxicology through a variety of activities. **American College of Preventive Medicine (ACPM)** http://www.acpm.org

	ACPM is the national professional society for physicians committed to disease prevention and health promotion. ACPM's 2,000 members are engaged in preventive medicine practice, teaching, and research. **Association of Occupational and Environmental Clinics(AOEC)** http://aoec.org AOEC is a network of more than 60 clinics and more than 250 individuals committed to improving the practice of occupational and environmental medicine through information sharing and collaborative research. **Pediatric Environmental Health Specialty Units (PEHSUs)** http://www.pehsu.net Based at an academic center, each PEHSU is collaboration between the pediatric clinic and the AOEC occupational and environmental clinic at each site. The PEHSUs were developed to provide education and consultation for health professionals, public health professionals, and others, about the topic of children's environmental health. PEHSU staff members are available for consultation about potential pediatric environmental health concerns affecting the child and the family. Healthcare professionals can contact their regional PEHSU site for clinical advice. **Poison Control Center** http://www.aapcc.org The American Association of Poison Control Centers supports the nation’s 55 poison centers in their efforts to prevent and treat poison exposures. Poison centers offer free, confidential medical advice 24 hours a day, seven days a week, through the Poison Help line at 1-800-222-1222. This service is a primary resource for poisoning information and helps reduce costly emergency department visits through in-home treatment.

	AAPCC's mission is to actively advance the health care role and public health mission of our members through information, advocacy, education, and research.

Posttest

Instructions	For each question, select the one best answer.
Posttest	
1.	What are characteristics of 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 might contain ethylene glycol? A. Latex Paints. B. Antifreeze. C. Solvents. 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.	Propylene glycol is generally recognized as safe by the Food and Drug Administration (FDA) for use in which of the following? A. Food and tobacco products. B. Pharmaceuticals. C. Cosmetics. D. All of the above.
5.	After ingestion, what happens to ethylene glycol? A. It is slowly absorbed by the gastrointestinal tract. B. It is stored and persists in fatty tissue.

	C. It reaches peak tissue levels after 24 hours. D. It is metabolized in the liver to a variety of compounds of increased toxicity.
6.	The first signs of ethylene glycol poisoning generally include which of the following? A. A characteristic odor of ethanol on the breath. B. Signs and symptoms similar to those of ethanol intoxication. C. Cardiopulmonary signs such as tachypnea and pulmonary edema. D. Oliguric renal failure.
7.	Acute ethylene glycol exposure can adversely affect all of the following except which? A. Lungs. B. Heart. C. Pancreas. D. Kidneys.
8.	Which of the following statements regarding nephrotoxicity from ethylene glycol poisoning is false? 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.	While determining the patient's exposure history, what additional information should you ask about? A. A history of ethanol abuse. B. A history of possible substance abuse. C. Similar symptoms in family members, friends, pets, 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. Treatment strategies for ethylene glycol poisoning may include which of the following? A. Sodium bicarbonate to correct the metabolic acidosis, as indicated. B. Fomepizole 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. 12. What are the disadvantages 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 poses problems in patient care, such as drunkenness. D. All of the above. 13. Treatment for acute propylene glycol poisoning might include which of the following? A. Sodium bicarbonate therapy. B. Administration of calcium gluconate. C. Ethanol administration. D. Hyperbaric oxygen. 14. 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.

1. 2. 3. 4. 5. 6. 7. 8. 9. 10. 11. 12. 13. 14.	B. Both glycols are used for aircraft de-icing. C. Neither compound is likely to persist for long in the environment. D. All of the above. **EG/PG Post-test Answers:** D D B D D B C C D D D D A D

Relevant Content	You can review content relevant to the posttest questions in the following areas
Question	Location of relevant content
1	What is ethylene glycol? • Describe the properties of ethylene glycol.
2	Where is ethylene glycol found? • Identify sources of ethylene glycol exposure.
3	What are routes of exposure to ethylene glycol?

	• Identify the most common route of exposure to ethylene glycol that results in toxicity in the general U.S. population.
4	What are U.S. regulations and guidelines for ethylene glycol exposure? • Describe current U.S. regulations and guidelines for ethylene glycol exposure.
5	What is the biological fate of ethylene glycol? • Explain the major pathway of ethylene glycol metabolism in the body.
6	Clinical assessment – history and physical examination • Describe how the clinical presentation changes over time.
7	What are the toxicological effects of ethylene glycol poisoning? • Describe the toxicological effects of ethylene glycol poisoning.
8	What are the toxicological effects of ethylene glycol poisoning? • Describe the toxicological effects of ethylene glycol poisoning.
9	Clinical assessment — history and physical examination • Describe what is included in the initial history and physical examination of patients potentially exposed to ethylene glycol.
10	Clinical assessment — laboratory tests • Identify the abnormal laboratory findings associated with ethylene glycol poisoning.
11	How should patients exposed to ethylene glycol be treated and managed? • Describe treatment strategies for managing ethylene glycol poisoning cases.
12	How should patients exposed to ethylene glycol be treated and managed?

	• Describe treatment strategies for managing ethylene glycol poisoning cases.
13	What is propylene glycol? • Describe the uses of propylene glycol.
14	What is propylene glycol? • Describe the uses of propylene glycol.

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