

Casarett & Doull's Essentials of Toxicology, 2e >

Chapter 24. Toxic Effects of Solvents and Vapors

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Key Points

- The term *solvent* refers to a class of liquid organic chemicals of variable lipophilicity and volatility, small molecular size, and lack of charge.
- Absorption of inhaled volatile organic compounds occurs in the alveoli, with almost instantaneous equilibration with blood in the pulmonary capillaries.
- Solvents are readily absorbed from the gastrointestinal tract and across the skin.
- Most solvents produce some degree of CNS depression.

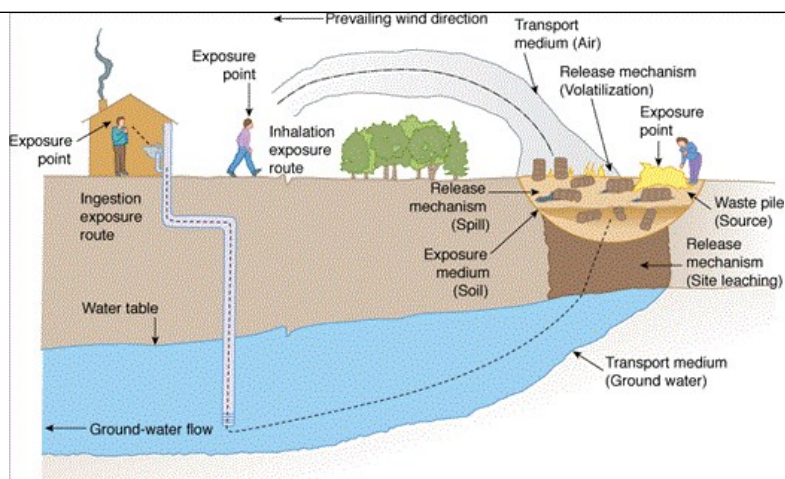
Toxic Effects of Solvents and Vapors: Introduction

The term *solvent* refers to a class of liquid organic chemicals of variable lipophilicity and volatility, small molecular size, and lack of charge. Solvents undergo ready absorption across the lung, skin, and gastrointestinal (GI) tract. In general, the lipophilicity of solvents increases with increasing molecular weight, while volatility decreases. Solvents are frequently used to dissolve, dilute, or disperse materials that are insoluble in water. Most solvents are refined from petroleum. Many, such as naphthas and gasoline, are complex mixtures consisting of hundreds of compounds.

Solvents are classified largely according to molecular structure or functional group. Classes of solvents include aliphatic hydrocarbons, many of which are chlorinated (i.e., halocarbons), aromatic hydrocarbons, alcohols, ethers, esters/acetates, amides/amines, aldehydes, ketones, and complex mixtures that defy classification. The main determinants of a solvent's inherent toxicity are: (1) its number of carbon atoms; (2) whether it is saturated or has double or triple bonds between adjacent carbon atoms; (3) its configuration (i.e., straight chain, branched chain, or cyclic); and (4) the presence of functional groups. Subtle differences in chemical structure can translate into dramatic differences in solvent toxicity.

Nearly everyone is exposed to solvents during normal daily activities. Environmental exposures to solvents in air and groundwater use multiple exposure pathways (Figure 24–1). Though not reflected in Figure 24–1, household use of solvent-contaminated water may result in solvent intake from inhalation, and dermal and oral absorption. In many cases, environmental risk assessment requires that risks be determined for physiologically diverse individuals who are exposed to several solvents by multiple exposure pathways.

Figure 24–1



Source: Klassen CD, Watkins JB: Casarett & Doull's Essentials of Toxicology, 2nd Edition. <http://www.accesspharmacy.com>. Copyright © The McGraw-Hill Companies, Inc. All rights reserved.

Solvent exposure pathways and media. (From EPA: *Risk Assessment Guidance for Superfund. Human Health Evaluation Manual Part A, Interim Final*. Washington, DC: Office of Emergency and Remedial Response, 1989.)

The Occupational Safety and Health Administration (OSHA) has established legally enforceable Permissible Exposure Limits (PELs) for over 100 solvents. The majority of existing PELs were adopted from the list of Threshold Limit Values (TLVs) published by the American Conference of Governmental Industrial Hygienists (ACGIH). Whereas the ACGIH's TLVs for an 8-h work day, 40-h work week are designed to be protective for a working lifetime, its Short-term Exposure Limits (STELs) and ceiling values are designed to protect against the acute effects of high-level, short-term solvent exposures. If warranted, the ACGIH will assign a skin notation to a solvent, indicating that significant dermal exposure is possible.

Most solvent exposures involve a mixture of chemicals, rather than a single compound. Whereas the assumption is frequently made that the toxic effects of multiple solvents are additive, solvents may also interact synergistically or antagonistically.

Although some solvents are less hazardous than others, all solvents can cause toxic effects. Most have the potential to induce narcosis and cause respiratory and mucous membrane irritation. Numerous solvents are animal carcinogens, but only a few are classified as known human carcinogens.

Is There a Solvent-Induced Chronic Encephalopathy?

Considerable debate has examined whether chronic, low-level exposure to virtually any solvent or solvent mixture can produce a pattern of neurologic dysfunction referred to as *painter's syndrome*, *organic solvent syndrome*, *psychoorganic syndrome*, and *chronic solvent encephalopathy* (CSE). CSE is characterized by nonspecific symptoms (e.g., headache, fatigue, and sleep disorders) with or without changes in neuropsychological function. A reversible form of CSE, the *neuroasthenic syndrome*, consists of symptoms only. The "mild" and "severe" forms are accompanied by objective signs of neuropsychological dysfunction that may or may not be fully reversible. Well-designed and controlled clinical epidemiologic studies are needed to resolve this controversy of CSE.

Solvent Abuse

Many solvents are intentionally inhaled in order to achieve a state of intoxication, with euphoria, delusions, and sedation as well as visual and auditory hallucinations. Solvent abuse is a unique exposure situation, in that participants repeatedly subject themselves to vapor concentrations high enough to produce effects as extreme as unconsciousness. These can be breathed in through the nose or the mouth by "sniffing" or "snorting" vapors from containers, spraying aerosols directly into the nose or mouth, "bagging" by inhaling vapors from substances inside plastic or paper bags, or "huffing" from a solvent-soaked rag stuffed into the mouth. Solvents can be addictive and are often abused in combination with other drugs. Solvents present in relatively inexpensive household and commercial products are readily available to children and adolescents.

Environmental Contamination

Most solvents enter the environment through evaporation (Figure 24-1). The majority of the more volatile organic compounds (VOCs) volatilize when

products containing them (e.g., aerosol propellants, paint thinners, cleaners, and soil fumigants) are used as intended. Solvent loss into the atmosphere also occurs during production, processing, storage, and transport activities. Winds dilute and disperse solvent vapors across the world. Atmospheric concentrations of most VOCs are usually extremely low, though higher concentrations have been measured in urban areas, around petrochemical plants, and in the immediate vicinity of hazardous waste sites.

Solvent contamination of drinking water supplies is a major health concern. Solvents spilled onto the ground may permeate the soil and migrate until reaching groundwater or impermeable material. All solvents are soluble in water to some extent. Concentrations diminish rapidly after VOCs enter bodies of water, due primarily to dilution and evaporation. VOCs in surface waters rise to the surface or sink to the bottom, according to their density. VOCs on the surface will largely evaporate. VOCs on the bottom depend on solubilization in the water or on mixing by current or wave action to reach the surface. VOCs in groundwater tend to remain trapped until the water reaches the surface.

Toxicokinetics

Toxicokinetic (TK) studies delineate the uptake and disposition of chemicals in the body. Toxicity is a dynamic process, in which the degree and duration of injury of a target tissue depend on the net effect of toxicodynamic (TD) and TK processes, interaction with cellular components, and tissue repair.

Volatility and lipophilicity are two important properties of solvents that govern their absorption and deposition in the body. Lipophilicity also can vary from quite water soluble (e.g., glycols and alcohols) to quite lipid soluble (e.g., halocarbons and aromatic hydrocarbons). Many solvents have a relatively low molecular weight and are uncharged, enabling passive diffusion through membranes from areas of high to low concentration.

Absorption

Most systemic absorption of inhaled VOCs occurs in the alveoli, with some absorption occurring in the upper respiratory tract. Gases in the alveoli equilibrate almost instantaneously with blood in the pulmonary capillaries. Blood:air partition coefficients (PCs) of VOCs may be defined as the ratio of concentration of VOC achieved between two different media at equilibrium. More hydrophilic solvents have relatively high blood:air PCs, which favor extensive uptake. Because VOCs diffuse from areas of high to low concentration, increases in respiration (to maintain a high alveolar concentration) and in cardiac output/pulmonary blood flow (to maintain a large concentration gradient by removing capillary blood containing the VOC) enhance pulmonary absorption.

Solvents are well absorbed from the GI tract. Peak blood levels are observed within minutes of dosing, although the presence of food in the GI tract can delay absorption. It is usually assumed that 100 percent of an oral dose of most solvents is absorbed systemically. The vehicle or diluent in which a solvent is ingested can affect the absorption and TK of the compound.

Absorption of solvents through the skin can result in both local and systemic effects. Solvents penetrate the stratum corneum by passive diffusion. Determinants of the rate of dermal absorption of solvents include the chemical concentration, surface area exposed, exposure duration, integrity and thickness of the stratum corneum, and lipophilicity and molecular weight of the solvent.

Transport and Distribution

Solvents absorbed into portal venous blood from the GI tract are subject to uptake/elimination by the liver and exhalation by the lungs during their first pass along this absorption pathway. Those solvents that are well metabolized and quite volatile are most efficiently eliminated before they enter the arterial blood. Hepatic first-pass elimination depends on the chemical and the rate at which it arrives in the liver. Pulmonary first-pass elimination, in contrast, is believed to be a first-order process irrespective of the chemical concentration in the blood.

Solvents transported by the arterial blood are taken up according to rate of tissue blood flow and the tissue:blood PC of the solvent. Relatively hydrophilic solvents solubilize to different extents in plasma. Lipophilic solvents do not bind to plasma proteins or hemoglobin, but partition into hydrophobic sites in the molecules. They partition into phospholipids, lipoproteins, and cholesterol that are present in the blood.

Blood levels of solvents drop rapidly during the initial elimination phase. This redistribution phase is characterized by rapid diffusion of solvent from the blood into most tissues. Equilibration of adipose tissue is prolonged due to the small fraction of cardiac output (~3 percent) supplying fat depots.

Body fat increases the volume of distribution and total body burden of lipophilic solvents.

Metabolism

Biotransformation can modulate the toxicities of solvents. Many solvents are poorly soluble in water and must be converted to relatively water-soluble derivatives, which may be more readily eliminated in the largely aqueous urine and/or bile. Some solvents can undergo bioactivation to produce reactive metabolites that are cytotoxic and/or mutagenic.

Physiologic Modeling

Physiologically based toxicokinetic (PBTK) models are used to relate the administered dose to the tissue dose of a bioactive moiety or moieties. With knowledge of the physiology of the test animal and tissue, physiologically based toxicodynamic (PBD) models can be developed. PBTK/PBD models are well suited for species-to-species extrapolations, because human physiologic and metabolic parameter values can be entered and simulations of target tissue doses and effects in humans generated. Thus, solvent exposures necessary to produce the same target organ dose in humans as that found experimentally to cause an unacceptable cancer or noncancer incidence in test animals can be determined in some cases with reasonable certainty. In the limited number of cases where there may be species differences in tissue sensitivity, PBD models can be used to forecast toxicologically effective target organ doses.

Potentially Sensitive Subpopulations

Endogenous Factors

Children

Limited information is available on the toxic potential of solvents in children. Most age-dependent differences are less than an order of magnitude, usually varying no more than two- to threefold. The younger and more immature the subject, the more different is his or her response from that of adults.

GI absorption of solvents varies little with age, because most solvents are absorbed by passive diffusion. Systemic absorption of inhaled VOCs may be greater in infants and children than in adults owing to the relatively high cardiac output and respiratory rates despite their lower alveolar surface area. Extracellular water, expressed as percentage of body weight, is highest in newborns and gradually diminishes through childhood. Body fat content is high from ~1/2 to 3 years of age, and then steadily decreases until adolescence, when it increases again in females. Lipophilic solvents accumulate in adipose tissue, so more body fat would result in greater body burdens and slower clearance of the chemicals.

Changes in xenobiotic metabolism during maturation may impact susceptibility to solvent toxicity. P450 isoforms develop asynchronously. Increased rates of metabolism, urinary excretion, and exhalation by children should hasten elimination and reduce body burdens of solvents. However, the net effect of immaturity on solvent disposition and toxicity is difficult to predict.

Elderly

Age influences the distribution of xenobiotics in the body as well as their metabolism and elimination. With aging, body fat usually increases substantially at the expense of lean mass and body water. Thus, relatively polar solvents tend to reach higher blood levels during exposures. Relatively lipid-soluble solvents accumulate in adipose tissue and are released slowly. Cardiac output and renal and hepatic blood flows are diminished in the elderly.

The elderly, like infants and children, may be more or less sensitive to the toxicity of solvents than young adults. Greater organ system toxicity could be due to increased inflammatory damage or to age-related dysregulation of cytokines. Other major sources of variability and complexity in geriatric populations include inadequate nutrition, the prevalence of disease states, and the concurrent use of multiple medications.

Gender

Physiologic and biochemical differences between men and women have the potential to alter tissue dosimetry and health effects of certain solvents. Whereas most predictive models suggest effects of toxicants are independent of sex, physical differences, such as the tendency of men to have more lean body mass and a larger body size, could potentially cause physiologic differences.

Genetics

Genetic polymorphisms for biotransformation occur at different frequencies in different ethnic groups. Polymorphisms for xenobiotic-metabolizing enzymes may affect the quantity and quality of enzymes and the outcomes of exposures to solvents in different racial groups. Disentangling the influences of genetic traits from those of socioeconomic status, lifestyles, and geographic setting is difficult.

Exogenous Factors

P450 Inducers and Inhibitors

Preexposure to chemicals that induce or inhibit biotransformation enzymes can potentiate or reduce the toxicity of high doses of solvents that undergo metabolism. Inhibitors would generally be anticipated to enhance the toxicity of solvents that are metabolically inactivated and protect from solvents that undergo metabolic activation.

Physical Activity

Exercise increases alveolar ventilation and cardiac output/pulmonary blood flow. Polar solvents with relatively high blood:air PCs (e.g., acetone, ethanol, and ethylene glycol [EG]) are very rapidly absorbed into the pulmonary circulation. Alveolar ventilation is rate-limiting for these chemicals. In contrast, pulmonary blood flow and metabolism are rate-limiting for uptake of more lipophilic solvents. Heavy exercise can increase pulmonary uptake of relatively polar solvents as much as fivefold in human subjects. Light exercise doubles uptake of relatively lipid-soluble solvents, but no further increase occurs at higher workloads. Blood flow to the liver and kidneys diminishes with exercise, which may diminish biotransformation of metabolized solvents and urinary elimination.

Diet

The mere bulk of food in the stomach and intestines can inhibit systemic absorption of ingested chemicals by preventing contact of the chemical with the GI epithelium. VOCs in the GI tract partition into dietary lipids, largely remaining there until the lipids are emulsified and digested. Food intake results in increased splanchnic blood flow, which favors GI absorption, hepatic blood flow, and biotransformation. Foods may contain certain natural constituents, pesticides, and other chemicals that may enhance or reduce solvent metabolism.

Chlorinated Hydrocarbons

Trichloroethylene

1,1,2-Trichloroethylene (TCE) is a widely used solvent for metal degreasing. Although present data support weak associations between TCE exposure and multiple myeloma, Hodgkin's disease, and cancers of the prostate, skin, cervix, and kidney, this is a topic of much debate.

Metabolism and Modes of Action

Toxicities associated with TCE are predominantly mediated by metabolites rather than by the parent compound. Even the CNS-depressant effects of TCE are due in part to the sedative properties of the metabolites trichloroethanol (TCOH) and chloroform. After either oral or inhalational absorption, most of the TCE undergoes oxidation via cytochrome P450s, with a small proportion being conjugated with glutathione. Both of the following metabolic pathways are implicated in the carcinogenicity of TCE: reactive metabolite(s) of the GSH pathway in kidney tumors in rats and oxidative metabolites in liver and lung tumors in mice.

Liver Cancer

TCE induces liver cancer in B6C3F1 mice but not in rats. This differential susceptibility is due to the greater capacity of mice to metabolize TCE to an oxidative metabolite that stimulates peroxisome proliferation. Propagation results in an increased potential for oxidative DNA damage and decreased gap-junctional intercellular communication, both of which have been implicated in neoplastic transformation.

Kidney Cancer

TCE exposure by inhalation or the oral route results in kidney tumors in male but not female rats. The susceptibility of the male rat can be explained by its greater capacity for TCE metabolism via the GSH pathway. TCE-induced kidney tumors are believed to result from reactive metabolite(s) of this pathway alkylating cellular nucleophiles, including DNA. The resulting DNA mutations lead to alterations in gene expression, which in turn lead to neoplastic transformation and tumorigenesis via a genotoxic pathway.

Alternatively, proximal tubular cell cytotoxicity and subsequent tumor formation via a nongenotoxic mode of action could be induced by reactive metabolites that cause oxidative stress, alkylation of cytosolic and mitochondrial proteins, marked ATP depletion, and perturbations in Ca^{2+} homeostasis. Tubular necrosis ensues, with subsequent reparative proliferation that can alter gene expression and, in turn, alter the regulation of cell growth and differentiation. In fact, somatic mutations in the von Hippel-Lindau (VHL) tumor suppressor gene might be a specific and susceptible target of TCE.

Chronic tubular damage may be a prerequisite to TCE-induced renal cell cancer. Reactive metabolite(s) of the GSH pathway may have a genotoxic effect on the proximal tubule of the human kidney, but full development of a malignant tumor requires a promotional effect such as cell proliferation in response to tubular damage.

Lung Cancer

Inhaled TCE is carcinogenic to the mouse lung but not to that of the rat. Oral TCE is not carcinogenic to the lung, probably due to hepatic metabolism that limits the amount of TCE reaching the organ. The primary target of TCE within the mouse lung is the nonciliated Clara cell. Cytotoxicity to these cells is characterized by vacuolization and increases in cell replication in the bronchiolar epithelium. Clara cells of the mouse efficiently metabolize TCE to toxic metabolites. In mouse lung, Clara cells are more numerous and have a much higher concentration of metabolizing enzymes than rat lung.

Tetrachloroethylene

Tetrachloroethylene (perchloroethylene, PERC) is commonly used as a dry cleaner, fabric finisher, degreaser, rug and upholstery cleaner, paint and stain remover, solvent, and chemical intermediate. The highest exposures usually occur in occupational settings via inhalation. PERC is the third most frequently found chemical contaminant in groundwater at hazardous waste sites in the United States.

The systemic disposition and metabolism of PERC and TCE are quite similar. Both chemicals are well absorbed from the lungs and GI tract, distributed to tissues according to their lipid content, partially exhaled unchanged, and metabolized by P450s. PERC is oxidized by hepatic P450s to a much lesser degree than TCE, though trichloroacetic acid is a common major metabolite. GSH conjugation is a minor metabolic pathway, quantitatively, for TCE and PERC.

PERC's potential for causing cancer in humans is controversial. The many epidemiologic studies of cancer incidence and mortality in groups of persons occupationally exposed to PERC are equivocal and do not support a cause-and-effect relationship between either PERC or TCE and cancer. Cigarette smoking and alcohol consumption are important confounders for esophageal cancer. Kidney cancer incidences did not appear to be elevated.

Methylene Chloride

Methylene chloride (dichloromethane, MC) enjoys widespread use as a solvent in industrial processes, food preparation, degreasing agents, aerosol propellants, and agriculture. The primary route of exposure to this very volatile solvent is inhalation.

MC has limited systemic toxicity potential. High, repeated inhalation exposures produce slight, reversible changes in the livers of rodents. Persons subjected to high vapor levels manifest kidney injury occasionally. Carbon monoxide that is formed from MC binds to hemoglobin to produce dose-dependent increases in carboxyhemoglobin. Residual neurologic dysfunction in MC-exposed workers has been reported.

Occupational and environmental MC exposures are of concern primarily because of MC's carcinogenicity in rodents and its potential as a human carcinogen. Epidemiologic studies of employees exposed to MC have revealed that cancer risks from occupational exposure to MC, if any, are quite small.

Carbon Tetrachloride

Carbon tetrachloride (CCl₄) is a classic hepatotoxin, but kidney injury is often more severe in humans. There does not appear to be a good animal model for kidney toxicity.

Early signs of hepatocellular injury in rats include dissociation of polysomes and ribosomes from rough endoplasmic reticulum, disarray of smooth endoplasmic reticulum, inhibition of protein synthesis, and triglyceride accumulation. CCl₄ undergoes metabolic activation, producing lipid peroxidation, covalent binding, and inhibition of microsomal ATPase activity. Single cell necrosis, evident 5 to 6 h postdosing, progresses to maximal centrilobular necrosis within 24 to 48 h. Cellular regeneration is maximal 36 to 48 h postdosing. The rate and extent of tissue repair are important determinants of the ultimate outcome of liver injury.

Perturbation of intracellular calcium (Ca²⁺) homeostasis appears to be part of CCl₄ cytotoxicity. Increased cytosolic Ca²⁺ levels may result from influx of extracellular Ca²⁺ due to plasma membrane damage and from decreased intracellular Ca²⁺ sequestration. Elevation of intracellular Ca²⁺ in hepatocytes can activate phospholipase A₂ and exacerbate membrane damage. Elevated Ca²⁺ may also be involved in alterations in calmodulin and phosphorylase activity as well as changes in nuclear protein kinase C activity. High intracellular Ca²⁺ levels activate a number of catabolic enzymes including proteases, endonucleases, and phospholipases, which kill cells via apoptosis or necrosis. Increased Ca²⁺ may stimulate the release of cytokines and eicosanoids from Kupffer cells, inducing neutrophil infiltration and hepatocellular injury. CCl₄ hepatotoxicity is obviously a complex, multifactorial process.

Chloroform

Chloroform (CHCl₃, trichloromethane) is used primarily in the production of the refrigerant chlorodifluoromethane (Freon 22). Measurable concentrations of CHCl₃ are found in municipal drinking water supplies. CHCl₃ is hepatotoxic and nephrotoxic. It can invoke CNS symptoms at subanesthetic concentrations similar to those of [alcohol](#) intoxication. Extremely high CHCl₃ exposures can sensitize the myocardium to catecholamines.

The metabolite phosgene covalently binds hepatic and renal proteins and lipids, which damages membranes and other intracellular structures, leading to necrosis and subsequent reparative cellular proliferation that promotes tumor formation in rodents by irreversibly “fixing” spontaneously altered DNA and clonally expanding initiated cells. The expression of certain genes, including *myc* and *fos*, is altered during regenerative cell proliferation in response to CHCl₃-induced cytotoxicity.

Although a rodent carcinogen, ingestion of CHCl₃ in small increments, similar to drinking water patterns of humans, fails to produce sufficient cytotoxic metabolite(s) per unit time to overwhelm detoxification mechanisms. Currently, CHCl₃ is classified as a probable human carcinogen (group B2).

Aromatic Hydrocarbons

Benzene

Benzene is derived primarily from petroleum and is used in the synthesis of other chemicals and as an antiknock agent in unleaded gasoline. Inhalation is the primary route of exposure in industrial and in everyday settings. Cigarette smoke is the major source of benzene in the home. Smokers have benzene body burdens which are 6 to 10 times greater than those of nonsmokers. Passive smoke can be a significant source of benzene exposure to nonsmokers. Gasoline vapor emissions and auto exhaust are the other key contributors to exposures of the general populace.

The hematopoietic toxicity of chronic exposure to benzene may manifest initially as anemia, leukopenia, thrombocytopenia, or a combination of these. Bone marrow depression appears to be dose-dependent in both laboratory animals and humans. Continued exposure may result in marrow aplasia and pancytopenia, an often fatal outcome. Survivors of aplastic anemia frequently exhibit a preneoplastic state, termed *myelodysplasia*, which may progress to myelogenous leukemia.

There is strong evidence from epidemiologic studies that high-level benzene exposures result in an increased risk of acute myelogenous leukemia (AML) in humans. Evidence of increased risks of other cancers in such populations is less compelling.

Various potential mechanisms require the complementary actions of benzene and several of its metabolites for toxicity. (1) A number of benzene metabolites bind covalently to GSH, proteins, DNA, and RNA. This can result in disruption of the functional hematopoietic microenvironment by inhibition of enzymes, destruction of certain cell populations, and alteration of the growth of other cell types. Covalent binding of hydroquinones to spindle-fiber proteins will inhibit cell replication. (2) Oxidative stress contributes to benzene toxicity. As the bone marrow is rich in peroxidase activity, phenolic metabolites of benzene can be activated there to reactive quinone derivatives, which can cause DNA damage, leading to cell mutation or apoptosis. Modulation of apoptosis may lead to aberrant hematopoiesis and neoplastic progression.

Toluene

Toluene is present in paints, lacquers, thinners, cleaning agents, glues, and many other products. It is also used in the production of other chemicals. Gasoline, which contains 5 to 7 percent toluene (w/w), is the largest source of atmospheric emissions and exposure of the general populace. Inhalation is the primary route of exposure, though skin contact occurs frequently. Toluene is a favorite of solvent abusers, who intentionally inhale high concentrations of the VOC.

Toluene is well absorbed from the lungs and GI tract. It rapidly accumulates in the brain, and subsequently, is deposited in other tissues according to their lipid content, with adipose tissue attaining the highest levels. Toluene is well metabolized, but a portion is exhaled unchanged.

The CNS is the primary target organ of toluene and other alkylbenzenes. Manifestations of exposure range from slight dizziness and headache to unconsciousness, respiratory depression, and death. Occupational inhalation exposure guidelines are established to prevent significant decrements in psychomotor functions. Acute encephalopathic effects are rapidly reversible on cessation of exposure. Subtle neurologic effects have been reported in some groups of occupationally exposed individuals. Severe neurotoxicity is sometimes diagnosed in persons who have abused toluene for a prolonged period. Clinical signs include abnormal electroencephalographic (EEG) activity, tremors, nystagmus, and cerebral atrophy as well as impaired hearing, vision, and speech. Magnetic resonance imaging has revealed permanent changes in brain structure, which correspond to the degree of brain dysfunction. These changes include ventricular enlargement, cerebral atrophy, and white matter hyperintensity, a characteristic profile termed *toluene leukoencephalopathy*.

Xylenes and Ethylbenzene

Large numbers of people are exposed to xylenes and ethylbenzene occupationally and environmentally. Xylenes and ethylbenzene, like benzene and toluene, are major components of gasoline and fuel oil. The primary uses of xylenes industrially are as solvents and synthetic intermediates. Most of the aromatics released into the environment evaporate into the atmosphere.

Similar to toluene, xylenes and other aromatic solvents are well absorbed from the lungs and GI tract, distributed to tissues according to tissue blood flow and lipid content, exhaled to some extent, well metabolized by hepatic P450s, and largely excreted as urinary metabolites. Acute lethality of hydrocarbons (i.e., CNS depression) varies directly with lipophilicity. There is limited evidence that chronic occupational exposure to xylenes is associated with residual neurologic effects.

Xylenes and ethylbenzene have limited capacity to adversely affect organs other than the CNS. Mild, transient liver and/or kidney toxicity have been reported occasionally in humans exposed to high vapor concentrations of xylenes. The majority of alkylbenzenes do not appear to be genotoxic or carcinogenic. Ethylbenzene and styrene are known animal carcinogens, but there are limited human data.

Alcohols

Ethanol

Many humans experience greater exposure to ethanol (ethyl **alcohol** and **alcohol**) than to any other solvent. Ethyl **alcohol** is used as an additive in gasoline, as a solvent in industry, in many household products and pharmaceuticals, and in intoxicating beverages. Frank toxic effects are less important occupationally than injuries resulting from psychomotor impairment. Driving under the influence of **alcohol** is the major cause of fatal auto accidents. Blood **alcohol** level and the time necessary to achieve it are controlled largely by the rapidity and extent of ethanol consumption. Ethanol is distributed in body water and to some degree in adipose tissue. The **alcohol** is eliminated by urinary excretion, exhalation, and metabolism. The blood level in an average adult decreases by ~15 to 20 mg/dL per hour. Thus, a person with a blood **alcohol** level of 120 mg/dL would require 6 to 8 h to reach negligible levels.

Ethanol is metabolized to acetaldehyde by three enzymes: (1) **alcohol** dehydrogenase (ADH) catalyzes oxidation of most of the ethanol to acetaldehyde, which is rapidly oxidized by acetaldehyde dehydrogenase (ALDH) to acetate; (2) catalase, utilizing H_2O_2 supplied by the actions of NADPH oxidase and xanthine oxidase, will normally account for more than 10 percent of ethanol metabolism; (3) CYP2E1 of the hepatic microsomal ethanol oxidizing system (MEOS) will metabolize only a few percent.

ALDH activity is usually sufficiently high to metabolize large amounts of acetaldehyde to acetate. Caucasians, blacks, and Asians have varying percentages of different ALDH isozymes, which impact the efficiency of acetaldehyde metabolism. Some 50 percent of Asians have inactive ALDH, and these persons may experience flushing, headache, nausea, vomiting, tachycardia, and hyperventilation on ingestion of ethanol. Whereas this syndrome offers protection against developing alcoholism, it increases the risk of acetaldehyde-related cancers of the esophagus, stomach, colon, lung, head, and neck.

Gender differences in responses to ethanol are well recognized. Females exhibit slightly higher blood ethanol levels than men following ingestion of equivalent doses. This phenomenon is due in part to more extensive ADH-catalyzed metabolism of ethanol by the gastric mucosa of males and to the smaller volume of distribution in women for relatively polar solvents such as alcohols. Also, women are more susceptible to alcohol-induced hepatitis and cirrhosis.

Fetal **alcohol** syndrome (FAS) is the most common preventable cause of mental retardation. Diagnostic criteria for FAS include (1) heavy maternal **alcohol** consumption during gestation; (2) pre- and postnatal growth retardation; (3) craniofacial malformations including microcephaly; and (4) mental retardation. Less complete manifestations of gestational ethanol exposure are referred to as fetal **alcohol** effects or alcohol-related neurodevelopmental disorder. Overconsumption during all three trimesters of pregnancy can result in particular manifestations depending on the period of gestation during which insult occurs.

Human CYP2E1 is effective in production of reactive **oxygen** intermediates from ethanol that cause lipid peroxidation. Also, ethanol induces the release of endotoxin from gram-negative bacteria in the gut. The endotoxin is taken up by Kupffer cells, causing the release of inflammatory mediators, which are cytotoxic to hepatocytes.

Alcohol-induced tissue damage results from both nutritional disturbances and direct toxic effects. Malabsorption of **thiamine**, diminished enterohepatic circulation of folate, degradation of pyridoxal phosphate, and disturbances in the metabolism of **vitamins** A and D can occur. Prostaglandins released from endotoxin-activated Kupffer cells may be responsible for a hypermetabolic state in the liver. With the increase in **oxygen** demand, the viability of centrilobular hepatocytes would be most compromised due to their relatively poor **oxygen** supply. Metabolism of ethanol via ADH and ALDH results in a shift in the redox state of the cell. The resulting hyperlacticacidemia, hyperlipidemia, hyperuricemia, and hyperglycemia lead to increased steatosis and **collagen** synthesis.

Alcoholism can result in damage of extrahepatic tissues. Alcoholic cardiomyopathy is a complex process that may result from decreased synthesis of cardiac contractile proteins, attack of **oxygen** radicals, increases in endoplasmic reticulum Ca^{2+} -ATPase, and antibody response to acetaldehyde-protein adducts. Heavy drinking appears to deplete antioxidants and increases the risk of both hemorrhagic and ischemic strokes. The brain and pancreas may be adversely affected in alcoholics.

The associations between **alcohol** and cancers came primarily from epidemiologic case-control and cohort studies. Ethanol and smoking act synergistically to cause oral, pharyngeal, and laryngeal cancers. It is generally believed that **alcohol** induces liver cancer by causing cirrhosis or other liver damage and/or by enhancing the bioactivation of carcinogens.

Chronic ethanol consumption may promote carcinogenesis by: (1) production of acetaldehyde, a weak mutagen and carcinogen; (2) induction of CYP2E1 with conversion of procarcinogens to carcinogens; (3) depletion of SAM and, consequently, global DNA hypomethylation; (4) increased production of inhibitory guanine nucleotide regulatory proteins and components of extracellular signal-regulated kinase-mitogen-activated protein kinase signaling; (5) accumulation of iron and associated oxidative stress; (6) inactivation of the tumor suppressor gene *BRCA1* and increased estrogen responsiveness (primarily in the breast); and (7) impairment of retinoic acid metabolism.

Methanol

Methanol (methyl alcohol and wood alcohol) is found in a host of consumer products including windshield washer fluid, and is used in the manufacture of formaldehyde and methyl *tert*-butyl ether. Methanol can produce reversible sensory irritation and narcosis at airborne concentrations below those producing organ system pathology. Serious methanol toxicity is most commonly associated with ingestion. Acute methanol poisoning in humans is characterized by an asymptomatic period of 12 to 24 h followed by formic acidemia, ocular toxicity, coma, and in extreme cases death. Visual disturbances develop between 18 and 48 h after ingestion and range from mild photophobia and blurred vision to markedly reduced visual acuity and complete blindness.

The target of methanol within the eye is the retina, specifically the optic disk and optic nerve. Müller cells and rod and cone cells are altered functionally and structurally, because cytochrome *c* oxidase activity in mitochondria is inhibited, resulting in a reduction in ATP.

Though metabolized in liver, intraretinal conversion of methanol to formaldehyde and formate is critical. Metabolism of formate to CO₂ then occurs via a two-step, tetrahydrofolate (THF)-dependent pathway. Susceptibility to methanol toxicity is dependent on the relative rate of formate clearance. Conversion of formate to CO₂ is slower in primates than in rodents. In fact, formate acts as a direct ocular toxin and the acidotic state potentiates formate toxicity because the inhibition of cytochrome oxidase increases as pH decreases.

Glycols

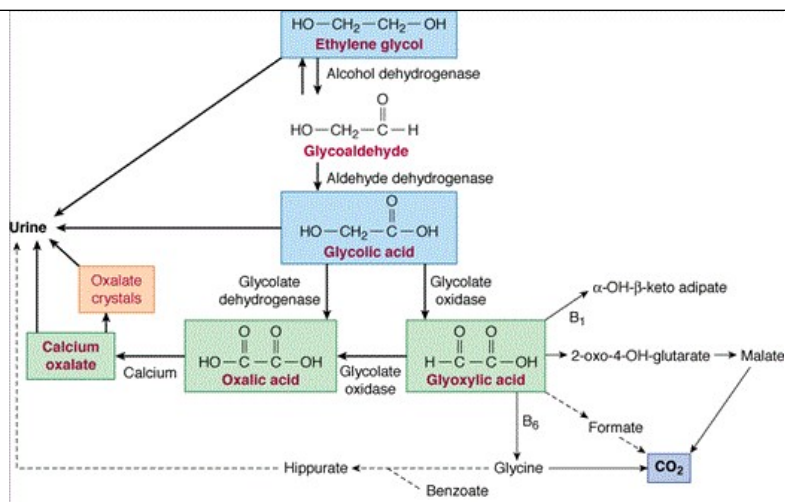
Ethylene Glycol

EG is a major constituent of antifreeze, deicers, hydraulic fluids, drying agents, and inks, and is used to make plastics and polyester fibers. The most important routes of exposure are dermal and accidental or intentional ingestion. EG is rapidly degraded in environmental media.

Acutely toxic to humans, EG is believed to cause over 100 deaths annually in the United States. Three clinical stages of acute poisoning entail: (1) a period of inebriation, the duration and degree depending on dose; (2) the cardiopulmonary stage 12 to 24 h after exposure, characterized by tachycardia and tachypnea, which may progress to cardiac failure and pulmonary edema; and (3) the renal toxicity stage 24 to 72 h postexposure. Metabolic acidosis can progress in severity during stages 2 and 3.

Absorption from the GI tract of rodents is very rapid and virtually complete. Dermal absorption in humans appears to be less extensive. EG is distributed throughout the body extracellular fluid. As illustrated in [Figure 24-2](#), EG is metabolized by NAD⁺-dependent ADH to glycolaldehyde and on to glycolic acid. Glycolic acid is oxidized to glyoxylic acid by glycolic acid oxidase and lactic dehydrogenase. Glyoxylic acid may be converted to formate and CO₂, or oxidized by glyoxylic acid oxidase to oxalic acid. Metabolic acidosis in humans appears to be due to accumulation of glycolic acid. Hypocalcemia can result from calcium chelation by oxalic acid to form calcium oxalate crystals. Deposition of these crystals in tubules of the kidney and small blood vessels in the brain is associated with damage of these organs. Additionally, hippuric acid crystals and direct cytotoxicity by other metabolites may act as damaging agents to the kidney in EG exposure. EG appears to have limited chronic toxicity potential, exhibits no evidence of carcinogenicity, and does not appear to be a reproductive toxicant.

Figure 24-2



Source: Klassen CD, Watkins JB: Casarett & Doull's Essentials of Toxicology, 2nd Edition. <http://www.accesspharmacy.com>
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Metabolic scheme for ethylene glycol in animals. Key metabolites that have been observed in vivo are highlighted in boxes. Dashed lines are theoretical pathways that have not been verified in vivo or in vitro. (Used with permission from Corley RA, Bartels MJ, Carney EW, et al: Development of a physiologically based pharmacokinetic model for ethylene glycol and its metabolite, glycolic acid, in rats and humans. *Toxicol Sci* 85:476–490, 2005.)

Propylene Glycol

Propylene glycol (PG) is used as an intermediate in the synthesis of polyester fibers and resins, as a component of automotive antifreeze/coolants, and as a deicing fluid for aircraft. As PG is “generally recognized as safe” by the FDA, it is a constituent of many cosmetics and processed foods. Furthermore, it serves as a solvent/diluent for a substantial number of oral, dermal, and intravenous drug preparations. The most important routes of exposure are ingesting and dermal contact. PG is readily metabolized by ADH to lactaldehyde, which is then oxidized by aldehyde dehydrogenase to lactate. Excessive lactate is primarily responsible for the acidosis. PG has a very low order of acute and chronic toxicity.

Glycol Ethers

The glycol ethers include EG monomethyl ether, also called 2-methoxyethanol (2-ME; $\text{CH}_3-\text{O}-\text{CH}_2-\text{CH}_2-\text{OH}$), EG dimethyl ether ($\text{CH}_3-\text{O}-\text{CH}_2-\text{CH}_2-\text{O}-\text{CH}_3$), 2-butoxyethanol (2-BE; $\text{CH}_3-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{O}-\text{CH}_2-\text{CH}_2-\text{OH}$), and 2-ME acetate ($\text{CH}_3-\text{CO}-\text{O}-\text{CH}_2-\text{CH}_2-\text{O}-\text{CH}_3$). These solvents undergo rapid ester hydrolysis in vivo, and exhibit the same toxicity profile as unesterified glycols. The glycol ethers are metabolized to alkoxyacetic acids, which are regarded as the ultimate toxicants. Their acetaldehyde precursors have also been implicated.

Like glycol ether metabolism, glycol ether toxicity varies with chemical structure. With increasing alkyl chain length, reproductive and developmental toxicity decrease, whereas hematotoxicity increases.

Reproductive Toxicity

Epidemiologic studies have reported associations between glycol ether exposure and increased risk for spontaneous abortion, menstrual disturbances, and subfertility among women employed in the semiconductor industry. Reversible spermatotoxicity in males has been described for those exposed to glycol ethers. Typical responses include testicular and seminiferous tubule atrophy, abnormal sperm head morphology, necrotic spermatocytes, decreased sperm motility and count, and infertility.

Developmental Toxicity

Developmental toxicity in rodents includes a variety of minor skeletal variations, hydrocephalus, exencephaly, cardiovascular malformations, dilatation of the renal pelvis, craniofacial malformations, and digit malformations. There are significant associations for glycol ether exposure inducing cleft lip and neural tube defects such as spina bifida.

Hematotoxicity

Some glycol ethers are hemolytic to red blood cells. Typically, the osmotic balance of the cells is disrupted, they imbibe water and swell, their ATP concentration decreases, and hemolysis occurs. Humans are less susceptible than rodents to glycol ether-induced erythrocyte deformity and hemolysis.

Automotive Gasoline and Additives

Gasoline is a mixture of hundreds of hydrocarbons predominantly in the range of C₄ to C₁₂. Because its composition varies with the crude oil from which it is refined, the refining process, and the use of specific additives, generalizations regarding the toxicity of gasoline must be made carefully. Experiments conducted with fully vaporized gasoline may not be predictive of actual risk, because humans are exposed primarily to the more volatile components in the range of C₄ to C₅, which are generally less toxic than higher molecular-weight fractions.

The most extreme exposures occur to those intentionally sniffing gasoline for its euphoric effects. This dangerous habit can cause acute and chronic encephalopathies that are expressed as both motor and cognitive impairment. Ingestion of gasoline during siphoning events is typically followed by a burning sensation in the mouth and pharynx, as well as nausea, vomiting, and diarrhea resulting from GI irritation. Gasoline aspirated into the lungs may produce pulmonary epithelial damage, edema, and pneumonitis.

Oxygenated gasoline contains additives that boost its octane quality, enhance combustion, and reduce exhaust emissions. Benzene and 1,3-butadiene are classified as known or probable human carcinogens. The co-exposure of ethanol and gasoline shows additive and possibly synergistic toxic effects on growth, neurochemistry, and histopathology of the adrenal gland and respiratory tract. No significant epidemiologic association exists between methyl *tertiary*-butyl ether (MTBE) exposure and the acute symptoms commonly attributed to MTBE, including headache; eye, nose, and throat irritation; cough; nausea; dizziness; and disorientation. Because three MTBE animal cancer bioassays indicate kidney and testicular tumors in male rats and liver adenomas, leukemia, and lymphoma in female rats, MTBE is classified as a possible human carcinogen (group C).

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