CHAPTER 10

Toxic Elements

10.1 INTRODUCTION

It is somewhat difficult to define what is meant by a toxic element. Some elements, such as white phosphorus, chlorine, and mercury, are quite toxic in the elemental state. Others, such as carbon, nitrogen, and oxygen, are harmless as usually encountered in their normal elemental forms. But, with the exception of those noble gases that do not combine chemically, all elements can form toxic compounds. A prime example is hydrogen cyanide. This extremely toxic compound is formed from three elements that are nontoxic in the uncombined form, and produce compounds that are essential constituents of living matter, but when bonded together in the simple HCN molecule constitute a deadly substance.

The following three categories of elements are considered here:

- Those that are notable for the toxicities of most of their compounds
- Those that form very toxic ions
- Those that are very toxic in their elemental forms

Elements in these three classes are discussed in this chapter as **toxic elements**, with the qualification that this category is somewhat arbitrary. With a few exceptions, elements known to be essential to life processes in humans have not been included as toxic elements.

10.2 TOXIC ELEMENTS AND THE PERIODIC TABLE

It is most convenient to consider elements from the perspective of the periodic table, which is shown in Figure 1.3 and discussed in Section 1.2. Recall that the three main types of elements, based on their chemical and physical properties as determined by the electron configurations of their atoms, are metals, nonmetals, and metalloids. Metalloids (B, Si, Ge, As, Sb, Te, At) show some characteristics of both metals and nonmetals. The nonmetals consist of those few elements in groups 4A to 7A above and to the right of the metalloids. The noble gases, only some of which form a limited number of very unstable chemical compounds of no toxicological significance, are in group 8A. All the remaining elements, including the lanthanide and actinide series, are metals. Elements in the periodic table are broadly distinguished between representative elements in the A groups of the periodic table and transition metals constituting the B groups, the lanthanide series, and the actinide series.

10.3 ESSENTIAL ELEMENTS

Some elements are essential to the composition or function of the body. Since the body is mostly water, hydrogen and oxygen are obviously essential elements. Carbon (C) is a component of all life molecules, including proteins, lipids, and carbohydrates. Nitrogen (N) is in all proteins. The other essential nonmetals are phosphorus (P), sulfur (S), chlorine (Cl), selenium (Se), fluorine (F), and iodine (I). The latter two are among the essential trace elements that are required in only small quantities, particularly as constituents of enzymes or as cofactors (nonprotein species essential for enzyme function). The metals present in macro amounts in the body are sodium (Na), potassium (K), and calcium (Ca). Essential trace elements are chromium (Cr), manganese (Mn), iron (Fe), cobalt (Co), copper (Cu), zinc (Zn), magnesium (Mg), molybdenum (Mo), nickel (Ni), and perhaps more elements that have not yet been established as essential.

10.4 METALS IN AN ORGANISM

Metals are mobilized and distributed through environmental chemical processes that are strongly influenced by human activities. A striking example of this phenomenon is illustrated by the lead content of the Greenland ice pack. Starting at very low levels before significant industrialization had occurred, the lead content of the ice increased in parallel with the industrial revolution, showing a strongly accelerated upward trend beginning in the 1920s, with the introduction of lead into gasoline. With the curtailment of the use of leaded gasoline, some countries are now showing decreased lead levels, a trend that hopefully will extend globally within the next several decades.

Metals in the body are almost always in an oxidized or chemically combined form; mercury is a notable exception in that elemental mercury vapor readily enters the body through the pulmonary route. The simplest form of a chemically bound metal in the body is the hydrated cation, of which $Na(H_2O)_6^+$ is the most abundant example. At pH values ranging upward from somewhat less than seven (neutrality), many metal ions tend to be bound to one or more hydroxide groups; an example is iron(II) in $Fe(OH)(H_2O)_5^+$. Some metal ions have such a strong tendency to lose H^+ that, except at very low pH values, they exist as the insoluble hydroxides. A common example of this phenomenon is iron(III), which is very stable as the insoluble hydrated iron(III) oxide, $Fe_2O_3 \cdot xH_2O$, or hydroxide, $Fe(OH)_3$. Metals can bond to some anions in body fluids. For example, in the strong hydrochloric acid medium of the stomach, some iron(III) may be present as $HFeCl_4$, where the acid in the stomach prevents formation of insoluble $Fe(OH)_3$ and a high concentration of chloride ion is available to bond to iron(III). Ion pairs may exist that consist of positively charged metal cations and negatively charged anions endogenous to body fluids. These do not involve covalent bonding between cations and anions, but rather an electrostatic attraction, such as in the ion pairs $Ca^{2+}HCO_3^-$ or $Ca^{2+}Cl^-$.

10.4.1 Complex Ions and Chelates

With the exception of group lA metals and the somewhat lesser exception of group 2A metals, there is a tendency for metals to form **complexes** with **electron donor** functional groups on **ligands** consisting of anionic or neutral inorganic or organic species. In such cases, covalent bonds are formed between the **central metal ion** and the ligands. Usually the resulting complex has a net charge and is called a complex ion; $FeCl_4^-$ is such an ion. In many cases, an organic ligand has two or more electron donor functional groups that may simultaneously bond to a metal ion to form a complex with one or more rings in its structure. A ligand with this capability is called a **chelating agent**, and the complex is a **metal chelate**. Copper(II) ion forms such a chelate with the anion of the amino acid glycine, as shown in Figure 10.1. This chelate is very stable.

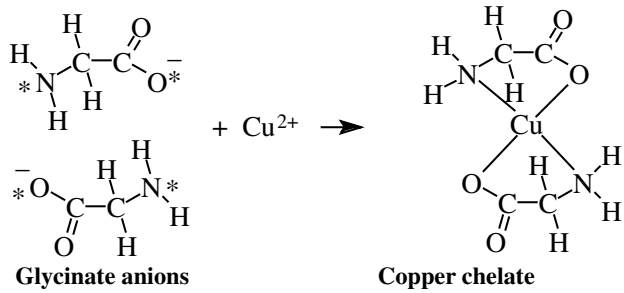


Figure 10.1 Chelation of Cu^{2+} by glycinate anion ligands to form the glycinate chelate. Each electron donor group on the glycinate anion chelating agents is designated with an asterisk. In the chelate, the central copper(II) metal ion is bonded in four places and the chelate has two rings composed of the five-atom sequence Cu–O–C–C–N.

Organometallic compounds constitute a large class of metal-containing species with properties quite different from those of the metal ions. These are compounds in which the metal is covalently bonded to carbon in an organic moiety, such as the methyl group, $–CH_3$. Unlike metal complexes, which can reversibly dissociate to the metal ions and ligands, the organic portions of organometallic compounds are not normally stable by themselves. The chemical and toxicological properties of organometallic compounds are discussed in detail in Chapter 12, so space will not be devoted to them here. However, it should be mentioned that neutral organometallic compounds tend to be lipid soluble, a property that enables their facile movement across biologic membranes. They often remain intact during movement through biological systems and so become distributed in these systems as lipid-soluble compounds.

A phenomenon not confined to metals, **methylation** is the attachment of a methyl group to an element and is a significant natural process responsible for much of the environmental mobility of some of the heavier elements. Among the elements for which methylated forms are found in the environment are cobalt, mercury, silicon, phosphorus, sulfur, the halogens, germanium, arsenic, selenium, tin, antimony, and lead.

10.4.2 Metal Toxicity

Inorganic forms of most metals tend to be strongly bound by protein and other biologic tissue. Such binding increases bioaccumulation and inhibits excretion. There is a significant amount of tissue selectivity in the binding of metals. For example, toxic lead and radioactive radium are accumulated in osseous (bone) tissue, whereas the kidneys accumulate cadmium and mercury. Metal ions most commonly bond with amino acids, which may be contained in proteins (including enzymes) or polypeptides. The electron-donor groups most available for binding to metal ions are amino and carboxyl groups (see Figure 10.2). Binding is especially strong for many metals to thiol (sulfhydryl) groups; this is particularly significant because the –SH groups are common components of the active sites of many crucial enzymes, including those that are involved in cellular energy output and oxygen transport. The amino acid that usually provides –SH groups in enzyme active sites is cysteine, as shown in Figure 10.2. The imidazole group of the amino acid histidine is a common feature of enzyme active sites with strong metal-binding capabilities.

The absorption of metals is to a large extent a function of their chemical form and properties. Pulmonary intake results in the most facile absorption and rapid distribution through the circulatory system. Absorption through this route is often very efficient when the metal is in the form of respirable particles less than 100 μm in size, as volatile organometallic compounds (see Chapter 12) or (in the case of mercury) as the elemental metal vapor. Absorption through the gastrointestinal tract is affected by pH, rate of movement through the tract, and presence of other materials. Particular combinations of these factors can make absorption very high or very low.

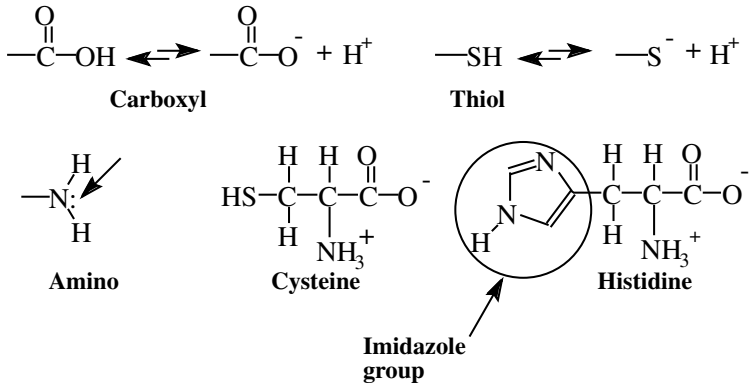


Figure 10.2 Major binding groups for metal ions in biologic tissue (carboxyl, thiol, amino) and amino acids with strong metal-binding groups in enzyme active sites (cysteine, histidine). The arrow pointing to the amino group designates an unshared pair of electrons available for binding metal ions. The thiol group is a weak acid that usually remains unionized until the hydrogen ion is displaced by a metal ion.

Metals tend to accumulate in target organs, and a toxic response is observed when the level of the metal in the organ reaches or exceeds a threshold level. Often the organs most affected are those involved with detoxication or elimination of the metal. Therefore, the liver and kidneys are often affected by metal poisoning. The form of the metal can determine which organ is adversely affected. For example, lipid-soluble elemental or organometallic mercury damages the brain and nervous system, whereas Hg^{2+} ion may attack the kidneys.

Because of the widespread opportunity for exposure, combined with especially high toxicity, some metals are particularly noted for their toxic effects. These are discussed separately in the following sections in the general order of their appearance in groups in the periodic table.

10.4.3 Lithium

Lithium, Li, atomic number 3, is the lightest group 1A metal that should be mentioned as a toxicant because of its widespread use as a therapeutic agent to treat manic-depressive disorders. It is also used in a number of industrial applications, where there is potential for exposure.

The greatest concern with lithium as a toxicant is its toxicity to kidneys, which has been observed in some cases in which lithium was ingested within therapeutic ranges of dose. Common symptoms of lithium toxicity include high levels of albumin and glucose in urine (albuminuria and glycosuria, respectively). Not surprisingly, given its uses to treat manic-depressive disorders, lithium can cause a variety of central nervous system symptoms. One symptom is psychosomatic retardation, that is, retardation of processes involving both mind and body. Slurred speech, blurred vision, and increased thirst may result. In severe cases, blackout spells, coma, epileptic seizures, and writhing, turning, and twisting choreoathetoid movements are observed. Neuromuscular changes may occur as irritable muscles, tremor, and ataxia (loss of coordination). Cardiovascular symptoms of lithium poisoning may include cardiac arrhythmia, hypertension, and, in severe cases, circulatory collapse. Victims of lithium poisoning may also experience an aversion to food (anorexia) accompanied by nausea and vomiting.

Lithium exists in the body as the Li^+ ion. Its toxic effects are likely due to its similarity to physiologically essential Na^+ and K^+ ions. Some effects may be due to the competion of Li^+ ion for receptor sites normally occupied by Na^+ or K^+ ions. Lithium toxicity may be involved in G protein expression and in modulating receptor–G protein coupling.[1]

10.4.4 Beryllium

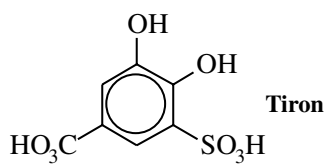
Beryllium (Be) is in group 2A and is the first metal in the periodic table to be notably toxic. When fluorescent lamps and neon lights were first introduced, they contained beryllium phosphor; a number of cases of beryllium poisoning resulted from the manufacture of these light sources and the handling of broken lamps. Modern uses of beryllium in ceramics, electronics, and alloys require special handling procedures to avoid industrial exposure.

Beryllium has a number of toxic effects. Of these, the most common involve the skin. Skin ulceration and granulomas have resulted from exposure to beryllium. Hypersensitization to beryllium can result in skin dermatitis, acute conjunctivitis, and corneal laceration.

Inhalation of beryllium compounds can cause **acute chemical pneumonitis**, a very rapidly progressing condition in which the entire respiratory tract, including nasal passages, pharynx, tracheobronchial airways, and alveoli, develops an inflammatory reaction. Beryllium fluoride is particularly effective in causing this condition, which has proven fatal in some cases.

Chronic berylliosis may occur with a long latent period of 5 to 20 years. The most damaging effect of chronic berylliosis is lung fibrosis and pneumonitis. In addition to coughing and chest pain, the subject suffers from fatigue, weakness, loss of weight, and dyspnea (difficult, painful breathing). The impaired lungs do not transfer oxygen well. Other organs that can be adversely affected are the liver, kidneys, heart, spleen, and striated muscles.

The chemistry of beryllium is atypical compared to that of the other group 1A and group 2A metals. Atoms of Be are the smallest of all metals, having an atomic radius of 111 pm. The beryllium ion, Be^{2+}, has an ionic radius of only 35 pm, which gives it a high polarizing ability, a tendency to form molecular compounds rather than ionic compounds, and a much greater tendency to form complex compounds than other group 1A or 2A ions. The ability of beryllium to form chelates is used to treat beryllium poisoning with ethylenediaminetetraacetic acid (EDTA) and another chelating agent called Tiron[2]:



Tiron

10.4.5 Vanadium

Vanadium (V) is a transition metal that in the combined form exists in the +3, +4, and +5 oxidation states, of which +5 is the most common. Vanadium is of concern as an environmental pollutant because of its high levels in residual fuel oils and subsequent emission as small particulate matter from the combustion of these oils in urban areas. Vanadium occurs as chelates of the porphyrin type in crude oil, and it concentrates in the higher boiling fractions during the refining process. A major industrial use of vanadium is in catalysts, particularly those in which sulfur dioxide is oxidized in the production of sulfuric acid. The other major industrial uses of vanadium are for hardening steel, as a pigment ingredient, in photography, and as an ingredient of some insecticides. In addition to environmental exposure from the combustion of vanadium-containing fuels, there is some potential for industrial exposure.

Probably the vanadium compound to which people are most likely to be exposed is vanadium pentoxide, V_2O_5. Exposure normally occurs via the respiratory route, and the pulmonary system is the most likely to suffer from vanadium toxicity. Bronchitis and bronchial pneumonia are the most common pathological effects of exposure; skin and eye irritation may also occur. Severe exposure can also adversely affect the gastrointestinal tract, kidneys, and nervous system.

Both V(IV) and V(V) have been found to have reproductive and developmental toxic effects in rodents. In addition to decreased fertility, lethal effects to embryos, toxicity to fetuses, and teratogenicity have been observed in mice, rats, and hamsters exposed to vanadium.[3]

It has been observed that vanadium has insulin-like effects on the main organs targeted by insulin — skeletal muscles, adipose, and liver — and vanadium has been shown to reduce blood glucose to normal levels in rats that have diabetic conditions. In considering the potential of vanadium to treat diabetes in humans, the toxicity of vanadium is a definite consideration. Several organically chelated forms of vanadium have been found to be more effective in treating diabetes symptoms and less toxic than inorganic vanadium.[4]

10.4.6 Chromium

Chromium (Cr) is a transition metal. In the chemically combined form, it exists in all oxidation states from +2 to +6, of which +3 and +6 are the more notable.

In strongly acidic aqueous solution, chromium(III) may be present as the hydrated cation $Cr(H_2O)_6^{3+}$. At pH values above approximately 4, this ion has a strong tendency to precipitate from solution the hydroxide:

$$Cr(H_2O)_6^{3+} \rightarrow Cr(OH)_3 + 3H^+ + 3H_2O \tag{10.4.1}$$

The two major forms of chromium(VI) in solution are yellow chromate, CrO_4^{2-}, and orange dichromate, $Cr_2O_7^{2-}$. The latter predominates in acidic solution, as shown by the following reaction, the equilibrium of which is forced to the left by higher levels of H^+:

$$Cr_2O_7^{2-} + H_2O \rightleftharpoons 2HCrO_4^- \rightleftharpoons 2H^+ + 2CrO_4^{2-} \tag{10.4.2}$$

Chromium in the +3 oxidation state is an essential trace element (see Section 10.3) required for glucose and lipid metabolism in mammals, and a deficiency of it gives symptoms of diabetes mellitus. However, chromium must also be discussed as a toxicant because of its toxicity in the +6 oxidation state, commonly called **chromate**. Exposure to chromium(VI) usually involves chromate salts, such as Na_2CrO_4. These salts tend to be water soluble and readily absorbed into the bloodstream through the lungs. The carcinogenicity of chromate has been demonstrated by studies of exposed workers. Exposure to atmospheric chromate may cause bronchogenic carcinoma with a latent period of 10 to 15 years. In the body, chromium(VI) is readily reduced to chromium(III), as shown in Reaction 10.4.3; however, the reverse reaction does not occur in the body.

$$CrO_4^{2-} + 8H^+ + 3e^- \rightarrow Cr^{3+} + 4H_2O \tag{10.4.3}$$

An interesting finding regarding potentially toxic chromium (and cobalt) in the body is elevated blood and urine levels of these metals in patients who have undergone total hip replacement.[5] The conclusion of the study was that devices such as prosthetic hips that involve metal-to-metal contact may result in potentially toxic levels of metals in biological fluids.

10.4.7 Cobalt

Cobalt is an essential element that is part of vitamin B_{12}, or cobalamin, a coenzyme that is essential in the formation of proteins, nucleic acids, and red blood cells. Although cobalt poisoning is not common, excessive levels can be harmful. Most cases of human exposure to toxic levels of cobalt have occurred through inhalation in the workplace. Many exposures have been suffered by workers working with hard metal alloys of cobalt and tungsten carbide, where very fine particles

of the alloy produced from grinding it were inhaled. The adverse effects of cobalt inhalation have been on the lungs, including wheezing and pneumonia as well as allergic asthmatic reactions and skin rashes. Lung fibrosis has resulted from prolonged exposures. Human epidemiology and animal studies suggest an array of systemic toxic effects of cobalt, including, in addition to respiratory effects, cardiovascular, hematological hepatic, renal, ocular, and body weight effects.

Exposure to cobalt is also possible through food and drinking water. An interesting series of cobalt poisonings occurred in the 1960s when cobalt was added to beer at levels of 1 to 1.5 ppm to stabilize foam. Consumers who drank excessive amounts of the beer (4 to 12 liters per day) suffered from nausea and vomiting, and in several cases, heart failure and death resulted.

10.4.8 Nickel

Nickel, atomic number 28, is a transition metal with a variety of essential uses in alloys, catalysts, and other applications. It is strongly suspected of being an essential trace element for human nutrition, although definitive evidence has not yet established its essentiality to humans. A nickel-containing urease metalloenzyme has been found in the jack bean.

Toxicologically, nickel is important because it has been established as a cause of respiratory tract cancer among workers involved with nickel refining. The first definitive evidence of this was an epidemiological study of British nickel refinery workers published in 1958. Compared to the general population, these workers suffered a 150-fold increase in nasal cancers and a 5-fold increase in lung cancer. Other studies from Norway, Canada, and the former Soviet Union have shown similar increased cancer risk from exposure to nickel. Nickel subsulfide, Ni_3S_2, has been shown to cause cancer in rats at sites of injection and in lungs from inhalation of nickel subsulfide.

The other major toxic effect of nickel is nickel dermatitis, an allergic contact dermatitis arising from contact with nickel metal. About 5 to 10% of people are susceptible to this disorder. It almost always occurs as the result of wearing nickel jewelry in contact with skin. Nickel carbonyl, $Ni(CO)_4$, is an extremely toxic nickel compound discussed further in Chapter 12.

10.4.9 Cadmium

Along with mercury and lead, cadmium (Cd) is one of the "big three" heavy metal poisons. Cadmium occurs as a constituent of lead and zinc ores, from which it can be extracted as a by-product. Cadmium is used to electroplate metals to prevent corrosion, as a pigment, as a constituent of alkali storage batteries, and in the manufacture of some plastics.

Cadmium is located at the end of the second row of transition elements. The +2 oxidation state of the element is the only one exhibited in its compounds. In its compounds, cadmium occurs as the Cd^{2+} ion. Cadmium is directly below zinc in the periodic table and behaves much like zinc. This may account in part for cadmium's toxicity; because zinc is an essential trace element, cadmium substituting for zinc could cause metabolic processes to go wrong.

The toxic nature of cadmium was revealed in the early 1900s as a result of workers inhaling cadmium fumes or dusts in ore processing and manufacturing operations. Welding or cutting metals plated with cadmium or containing cadmium in alloys, or the use of cadmium rods or wires for brazing or silver soldering, can be a particularly dangerous route to pulmonary exposure. In general, cadmium is poorly absorbed through the gastrointestinal tract. A mechanism exists for its active absorption in the small intestine through the action of the low-molecular-mass calcium-binding protein CaBP. The production of this protein is stimulated by a calcium-deficient diet, which may aggravate cadmium toxicity. Cadmium is transported in blood bound to red blood cells or to albumin or other high-molecular-mass proteins in blood plasma. Cadmium is excreted from the body in both urine and feces. The mechanisms of cadmium excretion are not well known.

Acute pulmonary symptoms of cadmium exposure are usually caused by the inhalation of cadmium oxide dusts and fumes, which results in cadmium pneumonitis, characterized by edema

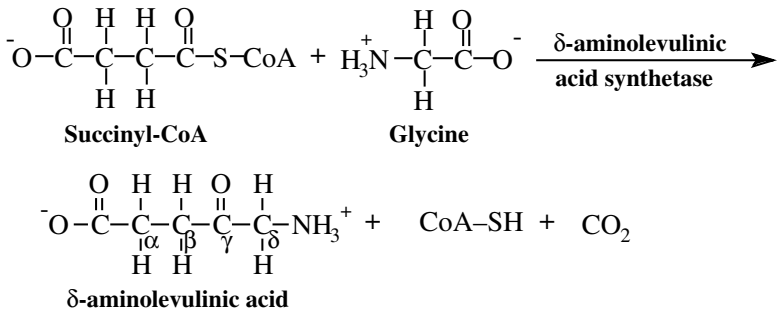


Figure 10.3 Path of synthesis of delta-aminolevulinic acid (coenzyme A abbreviated as CoA). Cadmium tends to inhibit the enzyme responsible for this process.

and pulmonary epithelium necrosis. Chronic exposure sometimes produces emphysema severe enough to be disabling. The kidney is generally regarded as the organ most sensitive to chronic cadmium poisoning. The function of renal tubules is impaired by cadmium, as manifested by excretion of both high-molecular-mass proteins (such as albumin) and low-molecular-mass proteins. Chronic toxic effects of cadmium exposure may also include damage to the skeletal system, hypertension (high blood pressure), and adverse cardiovascular effects. Based largely on studies of workers in the cadmium–nickel battery industry, cadmium is regarded as a human carcinogen, causing lung tumors and possibly cancer of the prostate.

Cadmium is a highly **cumulative** poison with a biologic half-life estimated at about 20 to 30 years in humans. About half of the body burden of cadmium is found in the liver and kidneys. The total body burden reaches a plateau in humans around age 50. Cigarette smoke is a source of cadmium, and the body burden of cadmium is about 1.5 to 2 times greater in smokers than in nonsmokers of the same age.

Cadmium in the body is known to affect several enzymes. It is believed that the renal damage that results in proteinuria is the result of cadmium adversely affecting enzymes responsible for reabsorption of proteins in kidney tubules. Cadmium also reduces the activity of delta-aminolevulinic acid synthetase (Figure 10.3), arylsulfatase, alcohol dehydrogenase, and lipoamide dehydrogenase, whereas it enhances the activity of delta-aminolevulinic acid dehydratase, pyruvate dehydrogenase, and pyruvate decarboxylase.

The most spectacular and publicized occurrence of cadmium poisoning resulted from dietary intake of cadmium by people in the Jintsu River Valley, near Fuchu, Japan. The victims were afflicted by *itai, itai* disease, which means "ouch, ouch" in Japanese. The symptoms are the result of painful osteomalacia (bone disease) combined with kidney malfunction. Cadmium poisoning in the Jintsu River Valley was attributed to irrigated rice contaminated from an upstream mine producing lead, zinc, and cadmium.

10.4.10 Mercury

Mercury is directly below cadmium in the periodic table, but has a considerably more varied and interesting chemistry than cadmium or zinc. Elemental mercury is the only metal that is a liquid at room temperature, and its relatively high vapor pressure contributes to its toxicological hazard. Mercury metal is used in electric discharge tubes (mercury lamps), gauges, pressure-sensing devices, vacuum pumps, valves, and seals. It was formerly widely used as a cathode in the chlor-alkali process for the manufacture of NaOH and Cl_2, a process that has been largely discontinued, in part because of the mercury pollution that resulted from it.

In addition to the uses of mercury metal, mercury compounds have a number of applications. Mercury(II) oxide, HgO, is commonly used as a raw material for the manufacture of other mercury

compounds. Mixed with graphite, it is a constituent of the Ruben–Mallory dry cell, for which the cell reaction is

$$Zn + HgO \rightarrow ZnO + Hg \tag{10.4.4}$$

Mercury(II) acetate, $Hg(C_2H_3O_2)_2$, is made by dissolving HgO in warm 20% acetic acid. This compound is soluble in a number of organic solvents. Mercury(II) chloride is quite toxic. The dangers of exposure to $HgCl_2$ are aggravated by its high water solubility and relatively high vapor pressure, compared to other salts. Mercury(II) fulminate, $Hg(ONC)_2$, has been used as a detonator for explosives. In addition to the +2 oxidation state, mercury can also exist in the +1 oxidation state as the dinuclear Hg_2^{2+} ion. The best-known mercury(I) compound is mercury(I) chloride, Hg_2Cl_2, commonly called calomel. It is a constituent of calomel reference electrodes, such as the well-known saturated calomel electrode (SCE).

A number of organomercury compounds are known. These compounds and their toxicities are discussed further in Chapter 12.

10.4.10.1 Absorption and Transport of Elemental and Inorganic Mercury

Monatomic elemental mercury in the vapor state, $Hg(g)$, is absorbed from inhaled air by the pulmonary route to the extent of about 80%. Inorganic mercury compounds are absorbed through the intestinal tract and in solution through the skin.

Although elemental mercury is rapidly oxidized to mercury(II) in erythrocytes (red blood cells), which have a strong affinity for mercury, a large fraction of elemental mercury absorbed through the pulmonary route reaches the brain prior to oxidation and enters that organ because of the lipid solubility of mercury(0). This mercury is subsequently oxidized in the brain and remains there. Inorganic mercury(II) tends to accumulate in the kidney.

10.4.10.2 Metabolism, Biologic Effects, and Excretion

Like cadmium, mercury(II) has a strong affinity for sulfhydryl groups in proteins, enzymes, hemoglobin, and serum albumin. Because of the abundance of sulfhydryl groups in active sites of many enzymes, it is difficult to establish exactly which enzymes are affected by mercury in biological systems.

The effect on the central nervous system following inhalation of elemental mercury is largely psychopathological. Among the most prominent symptoms are tremor (particularly of the hands) and emotional instability characterized by shyness, insomnia, depression, and irritability. These symptoms are probably the result of damage to the blood–brain barrier, which regulates the transfer of metabolites, such as amino acids, to and from the brain. Brain metabolic processes are probably disrupted by the effects of mercury. Historically, the three symptoms of increased excitability, tremors, and gum inflammation (gingivitis) have been recognized as symptoms of mercury poisoning from exposure to mercury vapor or mercury nitrate in the fur, hat, and felt trades.

The kidney is the primary target organ for Hg^{2+}. Chronic exposure to inorganic mercury(II) compounds causes proteinuria. In cases of mercury poisoning of any type, the kidney is the organ with the highest bioaccumulation of mercury.

Mercury(I) compounds are generally less toxic than mercury(II) compounds because of their lower solubilities. Calomel, a preparation containing Hg_2Cl_2, was once widely used in medicine. Its use as a teething powder for children has been known to cause a hypersensitivity response in children called "pink disease," manifested by a pink rash and swelling of the spleen and lymph nodes.

Excretion of inorganic mercury occurs through the urine and feces. The mechanisms by which excretion occurs are not well understood.

10.4.10.3 Minimata Bay

The most notorious incident of widespread mercury poisoning in modern times occurred in the Minimata Bay region of Japan during the period of 1953 to 1960. Mercury waste from a chemical plant draining into the bay contaminated seafood consumed regularly by people in the area. Overall, 111 cases of poisoning with 43 deaths and 19 congenital birth defects were documented. The seafood was found to contain 5 to 20 ppm of mercury.

10.4.11 Lead

Lead (Pb) ranks fifth behind iron, copper, aluminum, and zinc in industrial production of metals. About half of the lead used in the U.S. goes for the manufacture of lead storage batteries. Other uses include solders, bearings, cable covers, ammunition, plumbing, pigments, and caulking.

Metals commonly alloyed with lead are antimony (in storage batteries), calcium and tin (in maintenance-free storage batteries), silver (for solder and anodes), strontium and tin (as anodes in electrowinning processes), tellurium (pipe and sheet in chemical installations and nuclear shielding), tin (solders), and antimony and tin (sleeve bearings, printing, high-detail castings).

Lead(II) compounds are predominantly ionic (for example, $Pb^{2+}SO_4^{2-}$), whereas lead(IV) compounds tend to be covalent (for example, tetraethyllead, $Pb(C_2H_5)_4$). Some lead(IV) compounds, such as PbO_2, are strong oxidants. Lead forms several basic lead salts, such as $Pb(OH)_2{\cdot}2PbCO_3$, which was once the most widely used white paint pigment and the source of considerable chronic lead poisoning to children who ate peeling white paint. Many compounds of lead in the +2 oxidation state (lead(II)) and a few in the +4 oxidation state (lead(IV)) are useful. The two most common of these are lead dioxide and lead sulfate, which are participants in the following reversible reaction that occurs during the charge and discharge of a lead storage battery:

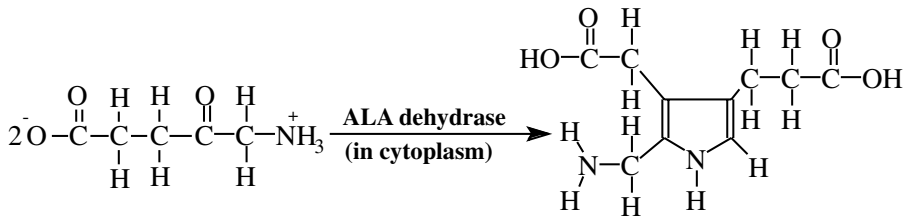
$$Pb + PbO_2 + 2H_2SO_4 \underset{\text{Charge}}{\overset{\text{Discharge}}{\rightleftharpoons}} 2PbSO_4 + 2H_2O \qquad (10.4.5)$$

In addition to the inorganic compounds of lead, there are a number of organolead compounds, such as tetraethyllead. These are discussed in Chapter 12.

10.4.11.1 Exposure and Absorption of Inorganic Lead Compounds

Although industrial lead poisoning used to be very common, it is relatively rare now because of previous experience with the toxic effects of lead and the protective actions that have been taken. Lead is a common atmospheric pollutant (though much less so now than when leaded gasoline was in general use), and absorption through the respiratory tract is the most common route of human exposure. The greatest danger of pulmonary exposure comes from inhalation of very small respirable particles of lead oxide (particularly from lead smelters and storage battery manufacturing) and lead carbonates, halides, phosphates, and sulfates. Lead that reaches the lung alveoli is readily absorbed into blood.

The other major route of lead absorption is the gastrointestinal tract. Dietary intake of lead reached average peak values of almost 0.5 mg per person per day in the U.S. around the 1940s. Much of this lead came from lead solder used in cans employed for canned goods and beverages. Currently, daily intake of dietary lead in the U.S. is probably only around 20 μg per person per



δ-aminolevulinic acid Porphobilinogen

Figure 10.4 Synthesis of porphobilinogen from delta-aminolevulinic acid, a major step in the overall scheme of heme synthesis that is inhibited by lead in the body.

day. Lead(II) may have much the same transport mechanism as calcium in the gastrointestinal tract. It is known that lead absorption decreases with increased levels of calcium in the diet and vice versa.

10.4.11.2 Transport and Metabolism of Lead

A striking aspect of lead in the body is its very rapid transport to bone and storage there. Lead tends to undergo bioaccumulation in bone throughout life, and about 90% of the body burden of lead is in bone after long-term exposure. The half-life of lead in human bones is estimated to be around 20 years. Some workers exposed to lead in an industrial setting have as much as 500 mg of lead in their bones. Of the soft tissues, the liver and kidney tend to have somewhat elevated lead levels.

About 90% of blood lead is associated with red blood cells. Measurement of the concentration of lead in the blood is the standard test for recent or ongoing exposure to lead. This test is used routinely to monitor industrial exposure to lead and in screening children for lead exposure.

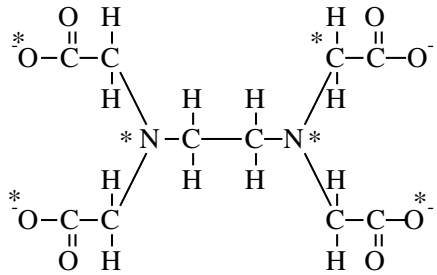
The most common biochemical effect of lead is inhibition of the synthesis of heme, a complex of a substituted porphyrin and Fe^{2+} in hemoglobin and cytochromes. Lead interferes with the conversion of delta-aminolevulinic acid to porphobilinogen, as shown in Figure 10.4, with a resulting accumulation of metabolic products. Hematological damage results. Lead inhibits enzymes that have sulfhydryl groups. However, the affinity of lead for the –SH group is not as great as that of cadmium or mercury.

10.4.11.3 Manifestations of Lead Poisoning

Lead adversely affects a number of systems in the body. The inhibition of the synthesis of hemoglobin by lead has just been noted. This effect, plus a shortening of the life span of erythrocytes, results in anemia, a major manifestation of lead poisoning.

The central nervous system is adversely affected by lead, leading to encephalopathy, including neuron degeneration, cerebral edema, and death of cerebral cortex cells. Lead may interfere with the function of neurotransmitters, including dopamine and γ-butyric acid, and it may slow the rate of neurotransmission. Psychopathological symptoms of restlessness, dullness, irritability, and memory loss, as well as ataxia, headaches, and muscular tremor, may occur with lead poisoning. In extreme cases, convulsions followed by coma and death may occur. Lead affects the peripheral nervous system, causing peripheral neuropathy. Lead palsy used to be a commonly observed symptom in lead industry workers and miners suffering from lead poisoning.

Lead causes reversible damage to the kidney through its adverse effect on proximal tubules. This impairs the processes by which the kidney absorbs glucose, phosphates, and amino acids prior to secretion of urine. A longer-term effect of lead ingestion on the kidney is general degradation of the organ (chronic nephritis), including glomular atrophy, interstitial fibrosis, and sclerosis of vessels.



Anion of ethylenediaminetetraacetic acid, EDTA

Figure 10.5 The ionized form of EDTA. Asterisks denote binding sites.

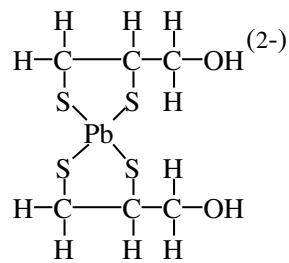


Figure 10.6 Lead chelated by the lead antidote BAL.

10.4.11.4 Reversal of Lead Poisoning and Therapy

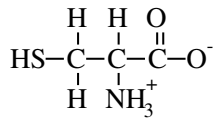
Some effects of lead poisoning, such as those on proximal tubules of the kidney and inhibition of heme synthesis, are reversible upon removal of the source of lead exposure. Lead poisoning can be treated by chelation therapy, in which the lead is solubilized and removed by a chelating agent. One such chelating agent is ethylenediaminetetraacetic acid, which binds strongly to most +2 and +3 cations (Figure 10.5). It is administered for lead poisoning therapy in the form of the calcium chelate. The ionized Y^{4-} form chelates metal ions by bonding at one, two, three, or all four carboxylate groups ($-CO_3^{2-}$) and one or both of the two N atoms (see glycinate-chelated structure in Figure 10.1). EDTA is administered as the calcium chelate for the treatment of lead poisoning to avoid any net loss of calcium by solubilization and excretion.

Another compound used to treat lead poisoning is British anti-Lewisite (BAL), originally developed to treat arsenic-containing poison gas Lewisite. As shown in Figure 10.6, BAL chelates lead through its sulfhydryl groups, and the chelate is excreted through the kidney and bile.

10.4.12 Defenses Against Heavy Metal Poisoning

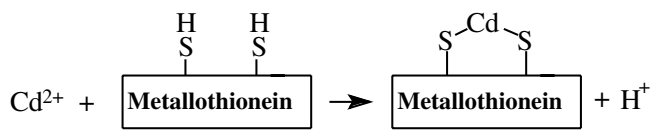
Organisms have some natural defenses against heavy metal poisoning. Several factors are involved in regulating the uptake and physiological concentrations of heavy metals. For example, higher levels of calcium in water tend to lower the bioavailability of metals such as cadmium, copper, lead, mercury, and zinc by fish, and the presence of chelating agents affects the uptake of such metals. Some evidence suggests that mechanisms developed to maintain optimum levels of essential metals, such as zinc and copper, are utilized to minimize the effects of chemically somewhat similar toxic heavy metals, of which cadmium, lead, and mercury are prime examples.

An interesting feature of heavy metal metabolism is the role of intracellular **metallothionein**, which consists of two similar proteins with a low molecular mass of about 6500. As a consequence of a high content of the amino acid cysteine,



Cysteine

metallothionein contains a large number of thiol (sulfhydryl, –SH) groups. These groups bind very strongly to other heavy metals, particularly mercury, silver, zinc, and tin. The metal most investigated for its interaction with metallothionein is cadmium. The general reaction of metallothionein with cadmium ion is the following:



(10.4.6)

By binding with metallothionein, the mobility of metals by diffusion is greatly reduced and the metals are prevented from binding to enzymes or other proteins essential to normal metabolic function.

Metallothionein has been isolated from virtually all of the major mammal organs, including liver, kidney, brain, heart, intestine, lung, skin, and spleen. Nonlethal doses of cadmium, mercury, and lead induce synthesis of metallothionein. In test animals, nonlethal doses of cadmium followed by an increased level of metallothionein in the body have allowed later administration of doses of cadmium at a level fatal to nonacclimated animals, but without fatalities in the test subjects.

Endogenous substances other than metallothionein may be involved in minimizing the effects of heavy metals and excreting them from the body. Hepatic (liver) glutathione, discussed as a phase II conjugating agent in Section 7.4, plays a role in the excretion of several metals in bile. These include the essential metals copper and zinc; toxic cadmium, mercury(II), and lead(II) ions; and organometallic methyl mercury.

Some plants have particularly high tolerances for cadmium and some other heavy metals by virtue of their content of cysteine-rich peptides, known as **phytochelatins**, sulfur-rich peptides that perform in plants much like metallothionein acts in animals. Plants that resist the effects of heavy metals through the action of phytochelatins require a high activity of cysteine synthase enzyme that makes the sulfur-containing cysteine amino acid from hydrogen sulfide and O-acetylserine. Cadmium-resistant transgenic tobacco plants have been bred that have a high activity of cysteine synthase from genes taken from rice.[6]

10.5 METALLOIDS: ARSENIC

10.5.1 Sources and Uses

Arsenopyrite and loellingite are both arsenic minerals that can be smelted to produce elemental arsenic. Both elemental arsenic and arsenic trioxide (As_2O_3) are produced commercially; the latter is the raw material for the production of numerous arsenic compounds. Elemental arsenic is used to make alloys with lead and copper. Arsenic compounds have a number of uses, including

applications in catalysts, bactericides, herbicides, fungicides, animal feed additives, corrosion inhibitors, pharmaceuticals, veterinary medicines, tanning agents, and wood preservatives. Arsenicals were the first drugs to be effective against syphilis, and they are still used to treat amebic dysentery. Arsobal, or Mel B, an organoarsenical, is the most effective drug for the treatment of the neurological stage of African trypanosomiasis, for which the infectious agents are *Trypanosoma gambiense* or *T. rhodesiense*.

10.5.2 Exposure and Absorption of Arsenic

Arsenic can be absorbed through both the gastrointestinal and pulmonary routes. Although the major concern with arsenic is its effect as a systemic poison, arsenic trichloride ($AsCl_3$) and the organic arsenic compound Lewisite (used as a poison gas in World War I) can penetrate skin; both of these compounds are very damaging at the point of exposure and are strong vesicants (causes of blisters). The common arsenic compound As_2O_3 is absorbed through the lungs and intestines. The degree of coarseness of the solid is a major factor in how well it is absorbed. Coarse particles of this compound tend to pass through the gastrointestinal tract and to be eliminated with the feces.

The chemistry of arsenic is so varied that it is difficult to regard as a single element.[7] Arsenic occurs in the +3 and +5 oxidation states; inorganic compounds in the +3 oxidation state (arsenite) are generally more toxic. The conversion to arsenic(V) is normally favored in the environment, which somewhat reduces the overall hazard of this element.

Arsenic is a natural constituent of most soils. It is found in a number of foods, particularly shellfish. The average adult ingests somewhat less than 1 mg of arsenic per day through natural sources. Drinking water is a source of arsenic in some parts of the world. This was tragically illustrated in Bangladesh, where a United Nations program to develop water wells as a source of pathogen-free drinking water later resulted in perhaps millions of cases of arsenic poisoning from arsenic-containing well water. A directive by the U.S. Environmental Protection Agency in 2000 to lower the long-standing (since 1942) arsenic drinking water standard in the U.S. was overturned, pending further review by the newly elected administration in early 2001, causing a great deal of controversy (The new standard has since been reinstated).

10.5.3 Metabolism, Transport, and Toxic Effects of Arsenic

Biochemically, arsenic acts to coagulate proteins, forms complexes with coenzymes, and inhibits the production of adenosine triphosphate (ATP) (see Section 4.3). Like cadmium and mercury, arsenic is a sulfur-seeking element. Arsenic has some chemical similarities to phosphorus, and it substitutes for phosphorus in some biochemical processes, with adverse metabolic effects. Figure 10.7 summarizes one such effect. The top reaction in the figure illustrates the enzyme-catalyzed synthesis of 1,3-diphosphoglycerate from glyceraldehyde 3-phosphate. The product undergoes additional reactions to produce ATP, an essential energy-yielding substance in body metabolism. When arsenite AsO_3^{3-} is present, it bonds to glyceraldehyde 3-phosphate to yield a product that undergoes nonenzymatic spontaneous hydrolysis, thereby preventing ATP formation.

Symptoms of acute arsenic poisoning are many and may be severe — fatal at high doses. Fatal cases of arsenic poisoning have exhibited symptoms of fever, aversion to food, abnormal liver enlargement (hepatomegaly), cardiac arrhythmia, development of dark patches on skin and other tissue (melanosis), peripheral neuropathy, including sensory loss in the peripheral nervous system, gastrointestinal disorders, cardiovascular effects, and adverse effects on red blood cell formation, which can result in anemia. Mucous membranes may be irritated, form blisters, or slough off.

Chronic effects of arsenic poisoning include neurotoxic effects to the central and peripheral nervous systems. Symptoms include sensory changes, muscle sensitivity, prickling and tingling sensations (paresthesia), and muscle weakness. Liver injury is a common symptom of chronic arsenic poisoning. Studies of victims of chronic arsenic poisoning from contaminated drinking

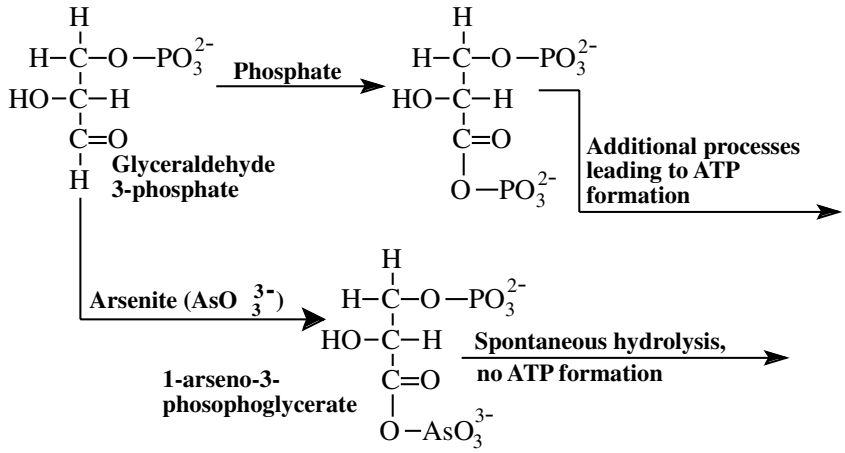


Figure 10.7 Interference of arsenic(III) with ATP production by phosphorylation.

water in Taiwan and Chile have exhibited blueness of the skin in extremities, a condition called acrocyanosis, the result of peripheral vascular disease. In extreme cases, this may progress to gangrene in the lower extremities, a condition called blackfoot disease.

There is now sufficient epidemiological evidence to classify arsenic as a human carcinogen and a cause of skin cancer. In people chronically exposed to toxic doses of arsenic, such cancers may be preceded by discolored skin (hyperpigmentation) and development of horny skin surfaces (hyperkeratosis). These areas may progress to locally invasive basal cell carcinomas or to squamous cell carcinomas capable of metastasis. Unlike skin cancers that develop on skin exposed to ultraviolet solar radiation, arsenic-induced skin cancer frequently develops in areas not commonly exposed to sunlight, such as the palms of hands or soles of feet.

Analysis of hair, fingernails, and toenails can serve as evidence of arsenic ingestion. Such analyses are complicated by the possible presence of arsenic contamination, particularly in a work environment in which the air and surroundings may be contaminated with arsenic. Levels of arsenic may be correlated with the growth of nails and hair so that careful analysis of segments of these materials can indicate time frames of exposure.

Antidotes to arsenic poisoning take advantage of the element's sulfur-seeking tendencies and contain sulfhydryl groups. One such antidote is 2,3-mercaptopropanol (BAL), discussed in the preceding section as an antidote for lead poisoning.

10.6 NONMETALS

10.6.1 Oxygen and Ozone

Molecular oxygen, O_2, is essential for life processes in both humans and other aerobic organisms and is potentially damaging to tissue. Exposure to excessive levels of O_2 can cause toxic responses. This was tragically illustrated by the use of oxygen to assist the respiration of premature infants, a procedure that caused many to become blind. Even at normal levels of oxygen, some toxicants can cause this essential element to cause toxic lesions. To understand why this is so, consider that aerobic organisms, including humans, derive their energy by mediating the oxidation of nutrient molecules such as glucose:

$$C_6H_{12}O_6 + 6O_2 \rightarrow 6CO_2 + 6H_2O + \text{energy} \qquad (10.6.1)$$

In this aerobic respiration process, molecular oxygen is the oxidizing agent or electron receptor and is reduced to the –2 oxidation state in the H_2O product. The process by which elemental oxygen accepts electrons is complex and multistepped. In this process, reactive intermediates are produced that can seriously damage the lipids in cell membranes, DNA in cell nuclei, and proteins. Under normal circumstances, these reactive oxidant species undergo further reactions before they can do much harm, or are scavenged by antioxidant molecules or by the action of enzymes designed to keep them at acceptable levels. However, under conditions of excessive exposure to oxidants and by the action of some kinds of toxicants, harmful levels of reactive intermediate oxidant species can build up to harmful levels.

The metabolic conversion of oxygen(0) in elemental oxygen to bound oxygen in the –2 oxidation state in H_2O can be viewed as the successive addition of electrons (e^-) and H^+ ions to O_2. The first step is addition of an electron to O_2 to produce reactive superoxide ion, $O_2^{\cdot-}$:

$$O_2 + e^- \rightarrow O_2^{\cdot-} \tag{10.6.2}$$

In formulas such as that of superoxide, the dot represents an unpaired electron. Species that have unpaired electrons are very reactive **free radicals**. Addition of H^+ ion to superoxide produces reactive hydroperoxyl radical, HO_2.:

$$O_2^{\cdot-} + H^+ \rightarrow HO_2^{\cdot} \tag{10.6.3}$$

Another electron and H^+ ion may be added to the hydroperoxyl radical, a process equivalent to adding an H atom, to produce hydrogen peroxide:

$$HO_2^{\cdot} + e^- + H^+ \rightarrow H_2O_2 \tag{10.6.4}$$

Hydrogen peroxide may be produced from the superoxide radical anion by the action of superoxide dismutase enzyme. The catalase enzyme may act on hydrogen peroxide to produce O_2 and H_2O. Hydrogen peroxide may also be eliminated by the action of glutathione peroxidase, producing the oxidized form of glutathione (see below). In the presence of appropriate metal ion catalysts, hydrogen peroxide may undergo the Haber–Weiss reaction,

$$O_2^{\cdot-} + H_2O_2 + Fe^{2+} \rightarrow Fe^{3+} + O_2 + OH^- + HO\cdot \tag{10.6.5}$$

and the Fenton reaction,

$$H_2O_2 + Fe^{2+} \rightarrow Fe^{3+} + OH^- + HO\cdot \tag{10.6.6}$$

to produce hydroxyl radical, $HO\cdot$.

Superoxide, hydroperoxyl, and especially reactive hydroxyl radicals along with hydrogen peroxide attack tissue and DNA either directly or through their reaction products. The damage done is sometimes referred to as oxidative lesions. It is now recognized that some toxicants have the ability to promote the formation of reactive oxidizing species to the extent that defensive mechanisms against oxidants are overwhelmed, a condition called **oxidative stress**. Under conditions of oxidative stress, lipids, nucleic acids, and proteins may be damaged by reactive oxidants. Another very damaging effect of oxidant reactive intermediates is **lipid peroxidation**, in which polyunsaturated fatty acids on lipids are attacked and oxidized, as shown in Figure 10.8. This can be especially damaging to lipid-rich cell membranes.

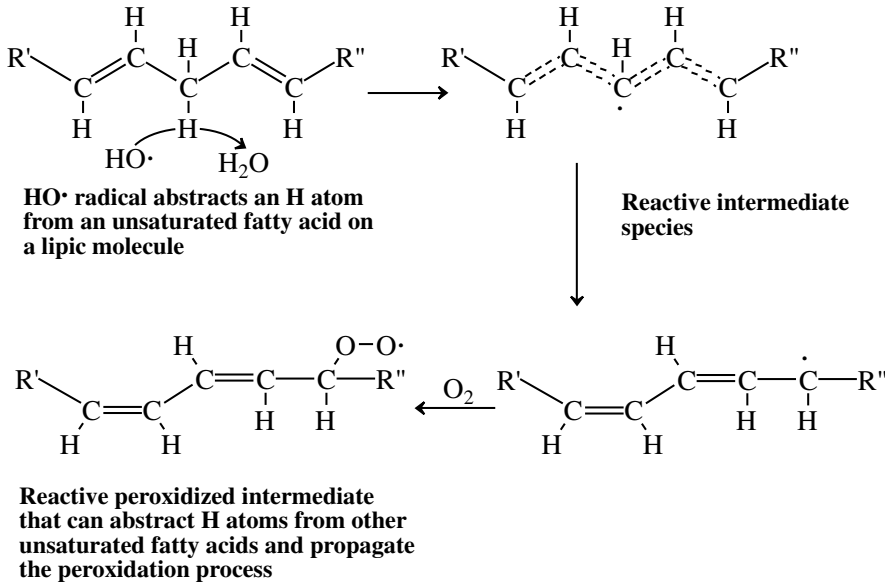
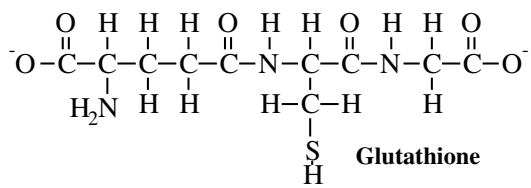


Figure 10.8 Peroxidation of lipid molecules by reactive radical species such as the hydroxyl radical, HO·.

Superoxide radical anion, hydroxyl radical, and hydrogen peroxide are known as prooxidants, whereas substances that neutralize their effects are called antioxidants. Oxidative stress occurs when the prooxidant–antioxidant balance becomes too favorable to the prooxidants. The effects of prooxidants can be neutralized by their direct reaction with small-molecule antioxidants, including glutathione, ascorbate, and tocopherols. In addition, oxidizing radicals are scavenged from a living system by several enzymes, including peroxidase, superoxide dismutase, and catalase. Oxidative lesions on DNA may be repaired by DNA repair enzymes.

Probably the most important antioxidant molecule is glutathione, a tripeptide formed from glutamic acid, cysteine, and glycine amino acids:



This substance reacts with oxidant radicals to produce H_2O and the oxidized form of glutathione, consisting of two of the molecules of this substance joined by an SS bridge.

A potent oxidizing form of elemental oxygen is **ozone**, O_3. This species is arguably the most toxic environmental pollutant to which the general population is exposed because of its presence in polluted atmospheres, especially under conditions where photochemical smog is present. It can be a pollutant of the workplace in locations where electrical discharges or ultraviolet radiation pass through air (from sources such as laser printers). The reactions for the production of ozone, beginning with the splitting of O_2 molecules to produce O atoms, are given in Section 2.8.

A deep lung irritant, ozone causes pulmonary edema, which can be fatal. It is also strongly irritating to the upper respiratory system and eyes and is largely responsible for the unpleasantness

of photochemical smog. A level of 1 ppm of ozone in air has a distinct odor, and inhalation of such air causes severe irritation and headache. The primary toxicological concern with ozone involves the lungs. Exposure to ozone increases the activity of free-radical-scavenging enzymes in the lung, indicative of ozone's ability to generate the reactive oxidant species responsible for oxidative stress. Arterial lesions leading to pulmonary edema have resulted from ozone exposure by inhalation. Animal studies of ozone inhalation have shown injury of epithelial (surface) cells throughout the respiratory tract.

Like nitrogen dioxide and ionizing radiation, ozone in the body produces free radicals that can be involved in destructive oxidation processes, such as lipid peroxidation or reaction with sulfhydryl (–SH) groups. Exposure to ozone can cause chromosomal damage. Ozone also appears to have adverse immunological effects. Radical-scavenging compounds, antioxidants, and compounds containing sulfhydryl groups can protect organisms from the effects of ozone.

Ozone is notable for being **phytotoxic** (toxic to plants). Loss of crop productivity from the phytotoxic action of ozone is a major concern in areas afflicted with photochemical smog, of which ozone is the single most characteristic manifestation.

10.6.2 Phosphorus

The most common elemental form of phosphorus, white phosphorus, is highly toxic. White phosphorus (melting point (mp), 44°C; boiling point (bp), 280°C) is a colorless waxy solid, sometimes with a yellow tint. It ignites spontaneously in air to yield a dense fog of finely divided, highly deliquescent P_4O_{10}:

$$P_4 + 5O_2 \rightarrow P_4O_{10} \tag{10.6.7}$$

White phosphorus can be absorbed into the body, particularly through inhalation, as well as through the oral and dermal routes. It has a number of systemic effects, including anemia, gastrointestinal system dysfunction, and bone brittleness. Acute exposure to relatively high levels results in gastrointestinal disturbances and weakness due to biochemical effects on the liver. Chronic poisoning occurs largely through the inhalation of low concentrations of white phosphorus and through direct contact with this toxicant. Severe eye damage can result from chronic exposure to elemental white phosphorus. A number of cases of white phosphorus poisoning have resulted from exposure in the fireworks industry. At least one case of fatal poisoning has occurred when a child accidentally ate a firecracker containing white phosphorus. White phosphorus used to be a common ingredient of rat poisons, and some suicidal individuals have been fatally poisoned from ingesting rat poison.

The most characteristic toxic effects of white phosphorus are musculoskeletal effects. Victims of phosphorus poisoning tend to develop necrosis of both bone and soft tissue in the oral cavity. As a result, the jawbone may deteriorate and become brittle, a condition called **phossy jaw**. Instances of this malady have been reported among workers handling white phosphorus, and it is believed that direct exposure of the mouth and oral cavity have occurred as the result of poor hygiene practices. Those afflicted with phossy jaw tend to develop abscessed teeth, and the sockets remaining from the extraction of teeth heal poorly. Infections of the jaw around teeth accompanied by severe pain are common symptoms of phossy jaw.

10.6.3 The Halogens

The elemental **halogens** — fluorine, chlorine, bromine, and iodine — are all toxic. Both fluorine and chlorine are highly corrosive gases that are very damaging to exposed tissue. These elements are chemically and toxicologically similar to many of their compounds, such as the interhalogen compounds, discussed in Chapter 11. The toxicities of halogen compounds are discussed in the next two sections.

10.6.3.1 Fluorine

Fluorine, F_2 (mp, –218°C; bp, –187°C), is a pale yellow gas produced from calcium fluoride ore by first liberating hydrogen fluoride with sulfuric acid, then electrolyzing the HF in a 4:1 mixture with potassium fluoride, KF, as shown in the reaction

$$2HF(\textit{molten KF}) \xrightarrow[\text{current}]{\text{Direct}} H_2(\textit{cathode}) + F_2(\textit{anode}) \tag{10.6.8}$$

Of all the elements, fluorine is the most reactive and the most electronegative (a measure of tendency to acquire electrons). In its chemically combined form, it always has an oxidation number of –1. Fluorine has numerous industrial uses, such as the manufacture of UF_6, a gas used to enrich uranium in its fissionable isotope, uranium-235. Fluorine is used to manufacture uranium hexafluoride, SF_6, a dielectric material contained in some electrical and electronic apparatus. A number of organic compounds contain fluorine, particularly the chlorofluorocarbons used as refrigerants and organofluorine polymers, such as DuPont's Teflon.

Given elemental fluorine's extreme chemical reactivity, it is not surprising that F_2 is quite toxic. It is classified as "a most toxic irritant." It strongly attacks skin and the mucous membranes of the nose and eyes.

10.6.3.2 Chlorine

Elemental chlorine, Cl_2 (mp, –101°C; bp, –34.5°C), is a greenish yellow gas that is produced industrially in large quantities for numerous uses, such as the production of organochlorine solvents (see Chapter 11) and water disinfection. Liquified Cl_2 is shipped in large quantities in railway tank cars, and human exposure to chlorine from transportation accidents is not uncommon.

Chlorine was the original poison gas used in World War I. It is a strong oxidant and reacts with water to produce an acidic oxidizing solution by the following reactions:

$$Cl_2 + H_2O \rightleftharpoons HCl + HOCl \tag{10.6.9}$$

$$Cl_2 + H_2O \rightleftharpoons 2HCl + \{O\} \tag{10.6.10}$$

where HOCl is oxidant hypochlorous acid and {O} stands for nascent oxygen (in a chemical sense regarded as freshly generated, highly reactive oxygen atoms). When chlorine reacts in the moist tissue lining the respiratory tract, the effect is quite damaging to the tissue. Levels of 10 to 20 ppm of chlorine gas in air cause immediate irritation to the respiratory tract, and brief exposure to 1000 ppm of Cl_2 can be fatal. Because of its intensely irritating properties, chlorine is not an insidious poison, and exposed individuals will rapidly seek to get away from the source if they are not immediately overcome by the gas.

10.6.3.3 Bromine

Bromine, Br_2 (mp, –7.3°C; bp, 58.7°C), is a dark red liquid prepared commercially from elemental chlorine and bromide ion in bromide brines by the reaction

$$Cl_2 + 2Br^- \rightarrow 2Cl^- + Br_2 \tag{10.6.11}$$

and the elemental bromine product is swept from the reaction mixture with steam. The major use of elemental bromine is for the production of organobromine compounds such as 1,1-dibromoethane,

formerly widely used as a grain and soil fumigant for insect control and as a component of leaded gasoline for scavenging lead from engine cylinders.

Bromine is toxic when inhaled or ingested. Like chlorine and fluorine, it is an irritant to the respiratory tract and eyes because it attacks their mucous membranes. Pulmonary edema may result from severe bromine poisoning. The severely irritating nature of bromine causes a withdrawal response in its presence, thereby limiting exposure.

10.6.3.4 Iodine

Elemental iodine, I_2 (solid, sublimes at 184°C), consists of violet-black rhombic crystals with a lustrous metallic appearance. More irritating to the lungs than bromine or chlorine, its general effects are similar to the effects of these elements. Exposure to iodine is limited by its low vapor pressure, compared to liquid bromine or gaseous chlorine or fluorine.

10.6.4 Radionuclides

10.6.4.1 Radon

In Section 9.3 the toxicological effects of ionizing radiation are mentioned, and radon is cited as a source of such radiation. Radon can pose very distinct health risks.[8] Radon's toxicity is not the result of its chemical properties, because it is a noble gas and does not enter into any normal chemical reactions. However, it is a radioactive element (radionuclide) that emits positively charged alpha particles, the largest and — when emitted inside the body — the most damaging form of radioactivity. Furthermore, the products of the radioactive decay of radon are also alpha emitters. Alpha particles emitted from a radionuclide in the lung cause damage to cells lining the lung bronchi and other tissues, resulting in processes that can cause cancer.

Radon is a decay product of radium, which in turn is produced by the radioactive decay of uranium. During its brief lifetime, radon may diffuse upward through soil and into dwellings through cracks in basement floors. Radioactive decay products of radon become attached to particles in indoor air, are inhaled, and lodge in the lungs until they undergo radioactive decay, damaging lung tissue. Synergistic effects between radon and smoking appear to be responsible for most of the cases of cancer associated with radon exposure.

10.6.4.2 Radium

A second radionuclide to which humans are likely to be exposed is **radium**, Ra. Occupational exposure to radium is known to have caused cancers in humans, most tragically in the cases of a number of young women who were exposed to radium because of their employment in painting luminescent radium-containing paint on the dials of watches, clocks, and instruments.[9] These workers would touch their tongues with the very fine brushes used for the radioactive paint in order to "point" the brushes. Many eventually developed bone cancer and died from this malady.

The most likely route for human exposures to low doses of radium is through drinking water. Areas in the U.S. where significant radium contamination of water has been observed include the uranium-producing regions of the western U.S., Iowa, Illinois, Wisconsin, Missouri, Minnesota, Florida, North Carolina, Virginia, and the New England states.

The maximum contaminant level (MCL) for total radium (^{226}Ra plus ^{228}Ra) in drinking water is specified by the U.S. Environmental Protection Agency as 5 pCi/l, where a picocurie is 0.037 disintegrations per second. Perhaps as many as several hundred municipal water supplies in the U.S. exceed this level and require additional treatment to remove radium. Fortunately, conventional water-softening processes, which are designed to take out excessive levels of calcium, are relatively efficient in removing radium from water.

10.6.4.3 Fission Products

The anthropogenic radionuclides of most concern are those produced as fission products from nuclear weapons and nuclear reactors. The most devastating release from the latter source to date resulted from the April 26, 1986, explosion, partial meltdown of the reactor core, and breach of confinement structures by a power reactor at Chernobyl in the Ukraine. This disaster released 5×10^7 Ci of radionuclides from the site, which contaminated large areas of Soviet Ukraine and Byelorussia, as well as areas of Scandinavia, Italy, France, Poland, Turkey, and Greece. Radioactive fission products that are the same or similar to elements involved in life processes can be particularly hazardous. One of these is radioactive iodine, which tends to accumulate in the thyroid gland, which may develop cancer or otherwise be damaged as a result. Radioactive cesium exists as the Cs^+ ion and is similar to sodium and potassium in its physiological behavior. Radioactive strontium forms the Sr^{2+} ion and substitutes for Ca^{2+}, especially in bone.

REFERENCES

1. Blake, B.L., Lawler, C.P., and Mailman, R.B., Biochemical toxicology of the central nervous system, in *Introduction to Biochemical Toxicology*, 3rd ed., Hodgson, E. and Smart, R.C., Eds., Wiley Interscience, New York, 2001, pp. 453–486.
2. Sharma, P., Johri, S., and Shukla, S., Beryllium-induced toxicity and its prevention by treatment with chelating agents, *J. Appl. Toxicol.*, 20, 313–318, 2000.
3. Domingo, J.L., Vanadium: a review of the reproductive and developmental toxicity, *Reprod. Toxicol.*, 10, 175–182, 1996.
4. Goldwaser, I. et al., Insulin-like effects of vanadium: basic and clinical implications, *J. Inorg. Biochem.*, 80, 21–25, 2000.
5. Schaffer, A.W. et al., Increased blood cobalt and chromium after total hip replacement, *J. Toxicol. Clin. Toxicol.*, 37, 839–844, 1999.
6. Harada, E. et al., Transgenic tobacco plants expressing a rice *cysteine synthase* gene are tolerant to toxic levels of cadmium, *J. Plant Physiol.*, 158, 655–661, 2001.
7. Goyer, R.A. and Clarkson, T.W., Toxic effects of metals, in *Casarett and Doull's Toxicology: The Basic Science of Poisons*, 6th ed., Klaassen, C.D., Ed., McGraw-Hill, New York, 2001, chap. 23, pp. 811–867.
8. Committee on Health Risks of Exposure to Radon, *Health Effects of Exposure to Radon*, National Academy Press, Washington, D.C., 1999.
9. Mullner, R., *Deadly Glow: The Radium Dial Worker Tragedy*, American Public Health Association, Washington, D.C., 1999.

SUPPLEMENTARY REFERENCE

Manahan, S.E., *Environmental Chemistry*, 7th ed., CRC Press/Lewis Publishers, Boca Raton, FL, 2000.

QUESTIONS AND PROBLEMS

1. Why is it difficult to define what is meant by a toxic element? What are the major categories of toxic elements? Give an example of each.
2. Into which four main categories are elements divided in the periodic table? Why does one of these categories consist of elements of no toxicological chemical significance? What might be a toxicity characteristic of these "nontoxic" elements?
3. What has the Greenland ice pack revealed about the environmental chemistry and distribution of a toxicologically significant element?

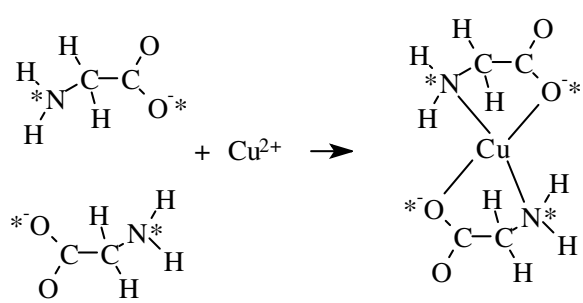
4. List and explain the forms in which metals may occur in the body.
5. What is a metal chelate? How are metal complexes related to chelates? In what sense may water be regarded as a ligand and metal ions dissolved in water regarded as complex ions?
6. What is the distinguishing feature of organometallic compounds as related to metal complexes? How is methylation related to organometallic compounds?
7. Which two kinds of functional molecules in biomolecules are most available for bonding to metal ions by complexation? What other functional group forms especially strong bonds with some important toxic heavy metals? In what common biological compound produced as a defense against heavy metal poisoning is this functional group most abundant?
8. In what form are metals most likely to be taken in by the pulmonary route? What is one very special case of a toxic heavy metal taken in by this route?
9. What are the major toxic effects of beryllium? What may be said about the latent period for beryllium poisoning?
10. Although metal ions are generally not very soluble in hydrocarbons, vanadium occurs at high levels in some crude oil products. What is there about vanadium in crude oil that enables this to occur?
11. What are the most common oxidation states of chromium? Of these, why is chromium in the lower oxidation state generally insignificant in water?
12. In what respect does cadmium's chemical similarity to zinc possibly contribute to the toxicity of cadmium? Which organ in the body is most susceptible to cadmium poisoning?
13. What is a cumulative poison? In what sense is cadmium a cumulative poison? What might be a metabolic explanation for why a poison is cumulative?
14. Match the following:

(a) $PbSO_4$	1. Organometallic compound
(b) $Pb(C_2H_5)_4$	2. In sealed nickel–cadmium batteries
(c) PbO_2	3. Basic salt
(d) $Pb(OH)_2{\cdot}2PbCO_3$	4. Strong oxidant
(e) $Pb(OH)_2$	5. Ionic lead(II) compound

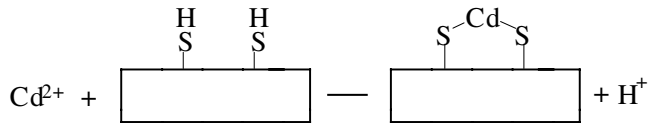
15. Match the following:

(a) Hg metal	1. In Ruben–Mallory dry cell
(b) HgO	2. Very soluble in water
(c) $Hg(C_2H_3O_2)_2$	3. Explosives' detonator
(d) $HgCl_2$	4. Used in gauges
(e) $Hg(ONC)_2$	5. Soluble in a number of organic solvents

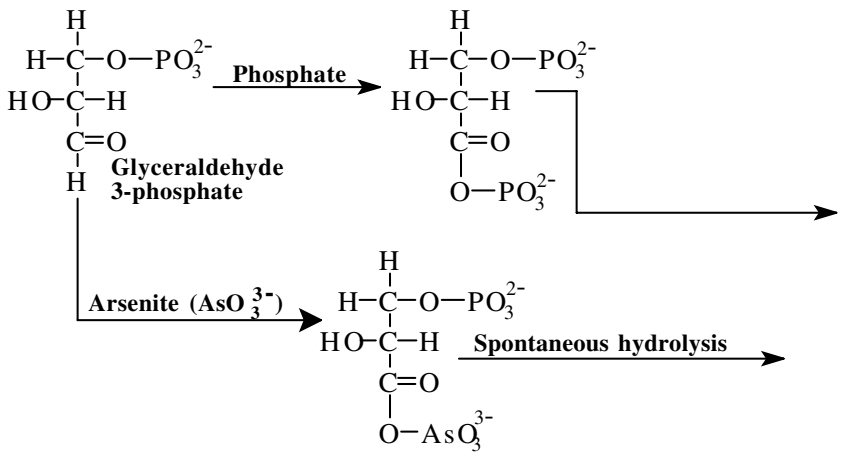
16. What is the predominant function of the blood–brain barrier? How is it affected by mercury?
17. What is the greatest single use for lead? How might this use lead to lead exposure?
18. What is the effect of calcium on the absorption of dietary lead? How might this effect be explained?
19. What is the major biochemical effect of lead, and how is this effect manifested?
20. What are the toxic effects of lead and cadmium on the kidney?
21. What is used as a therapeutic agent for lead poisoning? Why is this antidote always administered with calcium?
22. Explain what is shown by the illustration below:



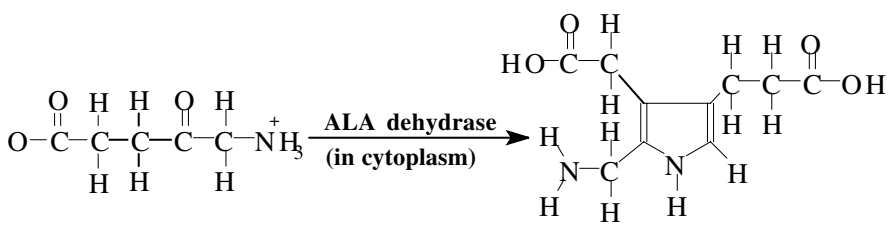
23. What toxicological chemical effect is illustrated by the figure below?



24. What are some of the uses of elemental arsenic and of arsenic compounds? How might these uses lead to human exposure?
25. Which of the oxidation states of arsenic is most likely to be toxic?
26. Explain what is shown by the following figure:



27. List the respects in which arsenic is similar to cadmium and mercury, as well as phosphorus. Why is its chemical similarity to phosphorus especially damaging?
28. In what respects do antidotes to arsenic poisoning take advantage of arsenic's sulfur-seeking tendencies? What is the name and chemical formula of one such antidote?
29. Explain what the following figure shows about toxicological chemistry:



30. Phosphorus and arsenic are chemically similar. Compare the toxic effects of elemental and combined phosphorus and arsenic.
31. Although noble gases are chemically unreactive and cannot be toxic because of any chemical interactions, one such gas is particularly toxic by nonchemical mechanisms. Which noble gas is that, and why is it toxic?
32. Which metallic element, though chemically not similar to radon, operates through a similar mode of toxic action? What is the most likely route of exposure to this element?

33. Designate which of the following is **not** true of the toxicological hazards or effects of lead:
    (a) inhibition of the synthesis of hemoglobin
    (b) particularly hazardous from inhalation of the elemental metal
    (c) psychopathological symptoms, including restlessness, dullness, irritability, and memory loss
    (d) effects on the peripheral nervous system
    (e) reversible damage to the kidney through its adverse effect on proximal tubules
34. Which radicals are produced by oxygen in the body? What are radicals? Why are they toxic?

CHAPTER 11

Toxic Inorganic Compounds

11.1 INTRODUCTION

In Chapter 10 elements were discussed that as a rule tend to be toxic in their various forms. Chapter 11 covers toxic inorganic compounds of elements that are not themselves generally regarded as toxic. These elements include for the most part the lighter nonmetals located in the upper right of the periodic table (Figure 1.3) and exclude the heavy metals. Most of the elements involved in the inorganic compounds discussed in this chapter are those that are essential for life processes. Any division between "toxic" and "nontoxic" elements is by nature artificial in that most of the heavy metals have compounds of relatively low toxicity, and there are deadly compounds that contain elements essential for life.

11.1.1 Chapter Organization

In general, this chapter is organized in the order of increasing atomic number of the elements that are covered. Inorganic compounds of carbon, atomic number 6, are discussed first, followed by toxic inorganic compounds of nitrogen, atomic number 7. The next element, oxygen, occurs in so many different inorganic compounds that it is not discussed in a separate category. The halogens — fluorine, chlorine, bromine, and iodine — are discussed as a group because of their chemical similarities. The other major elements whose toxic inorganic compounds are discussed are silicon, phosphorus, and sulfur.

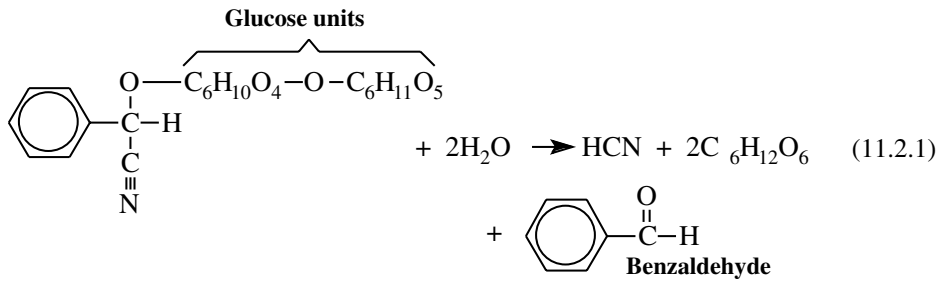
11.2 TOXIC INORGANIC CARBON COMPOUNDS

11.2.1 Cyanide

Cyanide, in the form of either gaseous **hydrogen cyanide** (HCN) or **cyanide ion** (CN^-) (present in cyanide salts such as KCN), is a notably toxic substance. Cyanide is a rapidly acting poison, and the fatal oral dose to humans is believed to be only 60 to 90 mg. Hydrogen cyanide and cyanide salts have numerous uses; examples are as ingredients of pest poisons, fumigants, metal (silver) polishes, and photographic chemical solutions. Therefore, exposure to cyanide is certainly possible. Hydrogen cyanide is used as a fumigant to kill pests such as rodents in warehouses, grain storage bins, greenhouses, and holds of ships, where its high toxicity and ability to penetrate obscure spaces are advantageous. Cyanide salt solutions are used to extract some metals such as gold from ores, in metal refining, in metal plating, and for salvaging silver from exposed photographic and x-ray film. Cyanide is used in various chemical syntheses. Polyacrylic polymers may evolve HCN during

combustion, adding to the toxic gases that are usually responsible for deaths in fires. Sodium nitroprusside, $Na_2Fe(NO)(CN)_5$, used intravenously in humans to control hypertension, can hydrolyze in the body to release cyanide and cause cyanide poisoning.

Some plants contain cyanogenic glycosides, saccharidal substances that contain the –CN group and that may hydrolyze to release cyanide. Such substances, called **cyanogens**, include amygdalin, linamarin, and linseed cyanogens consisting of mixtures of linustatin and neolinustatin.[1] The release of cyanide by the enzymatic or acidic hydrolysis of amygdalin in the digestive tract is shown below:



(11.2.1)

The Romans used cyanide from natural seed sources, such as apple seeds, for executions and suicides. The seeds of apples, apricots, cherries, peaches, plums, and some other fruits contain sources of cyanide. Other natural sources of cyanide include arrowgrass, sorghum, flax, velvet grass, and white clover.

A potential source of cyanide poisoning is cassava, a starch from the root of *Manihot esculenta*, used as food in much of Africa. The root contains cyanogenic linamarin, which is normally removed in processing the root for food. Widespread cases of a spinal cord disorder called konzo and characterized by spastic paralysis have been attributed to ingestion of linamarin from inadequately processed cassava root.

11.2.1.1 Biochemical Action of Cyanide

Cyanide deprives the body of oxygen by acting as a **chemical asphyxiant** (in contrast to simple asphyxiants that simply displace oxygen in respired air). In acting as an asphyxiant, cyanide inhibits an enzyme (see enzyme inhibition, Section 7.6) involved in a key step in the oxidative phosphorylation pathway, by which the body utilizes oxygen in cell mitochondria. The inhibited enzyme is ferricytochrome oxidase (Fe(III)-oxid), an iron-containing metalloprotein that acts as an acceptor of electrons and is converted to ferrouscytochrome oxidase (Fe(II)-oxid) during the oxidation of glucose. The ferrouscytochrome oxidase that is formed transfers the electrons to molecular oxygen and produces energetic adenosine triphosphate (ATP) from adenosine diphosphate (ADP) (see Section 4.3), regenerating Fe(III)-oxid that can repeat the cycle. The overall process is represented as follows:

$$\text{Fe(III)-oxid} + \text{Reducing agent} \rightarrow \text{Fe(II)-oxid} + \text{Oxidized reducing agent} \qquad (11.2.2)$$

$$\text{Fe(II)-oxid} + 2H^+ + \tfrac{1}{2}O_2 \xrightarrow[\text{ADP}]{\text{ATP}} \text{Fe(III)-oxid} + H_2O \qquad (11.2.3)$$

Cyanide bonds to the iron(III) of the ferricytochrome enzyme, preventing its reduction to iron(II) in the first of the two reactions above. The result is that ferrouscytochrome oxidase, which is required to react with O_2, is not formed and utilization of oxygen in cells is prevented, leading to rapid cessation of metabolic processes. The decreased utilization of oxygen in tissue results in a

buildup of oxyhemoglobin in venous blood, which gives the skin and mucous membranes a characteristic red color (flush).

The metabolic pathway for the detoxification of cyanide involves conversion to the less toxic thiocyanate by a reaction requiring thiosulfate or colloidal sulfur as a substrate:

$$CN^- + S_2O_3^{2-} \xrightarrow[\text{Rhodanase}]{} SCN^- + SO_3^{2-} \tag{11.2.4}$$

This reaction is catalyzed by *rhodanase* enzyme, also called *mitochondrial sulfur transferase*. Although not found in the blood, this enzyme does occur abundantly in liver and kidney tissue. Because of this reaction, thiosulfate can be administered as an antidote for cyanide poisoning.

Nitrite, NO_2^-, administered intravenously as sodium nitrite solution or inhaled as amyl nitrite, $C_5H_{11}NO_2$, an ester which hydrolyzes to NO_2^- in the blood, functions as an antidote to cyanide poisoning. This occurs because nitrite oxidizes iron(II) in blood hemoglobin (HbFe(II)) to methemoglobin (HbFe(III)), a brown substance that is ineffective in carrying oxygen to tissues. (This reaction is the mechanism of nitrite toxicity; excessive formation of methemoglobin causes oxygen deprivation that can be fatal.) Methemoblogin in the blood, however, has a high affinity for cyanide and removes it from ferricytochrome oxidase enzyme that has been inhibited by binding of cyanide (Fe(III)-oxid–CN),

$$\text{HbFe(III)} + \text{Fe(III)-oxid–CN} \rightarrow \text{HbFe(III)–CN} + \text{Fe(III)-oxid} \tag{11.2.5}$$

freeing the ferricytochrome oxidase enzyme so that it can participate in its normal metabolic functions. Additional treatment with thiosulfate results in elimination of the cyanide:

$$\text{HbFe(III)–CN} + S_2O_3^{2-} \rightarrow SCN^- + \text{HbFe(III)} + SO_3^{2-} \tag{11.2.6}$$

11.2.2 Carbon Monoxide

Carbon monoxide, CO, is a toxic industrial gas produced by the incomplete combustion of carbonaceous fuels. It is used as a reductant for metal ores, for chemical synthesis, and as a fuel. As an environmental toxicant, it is responsible for a significant number of accidental poisonings annually. Observable acute effects of carbon monoxide exposure in humans cover a wide range of symptoms and severity. These include impairment of judgment and visual perception at CO levels of 10 ppm in air; dizziness, headache, and weariness (100 ppm); loss of consciousness (250 ppm); and rapid death (1000 ppm). Chronic effects of long-term low-level exposure to carbon monoxide include disorders of the respiratory system and the heart. As evidence of the latter, cardiac dysfunctions, including arrhythmia and myocardia ischemia (blood deficiency in the heart muscles), have been reported in victims of carbon monoxide poisoning.[2] Autopsies of such victims have shown scattered hemorrhages throughout the heart.

11.2.3 Biochemical Action of Carbon Monoxide

Carbon monoxide enters the bloodstream through the lungs and reacts with oxyhemoglobin (O_2Hb) to produce carboxyhemoglobin (COHb):

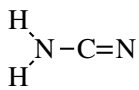
$$O_2Hb + CO \rightarrow COHb + O_2 \tag{11.2.7}$$

Carboxyhemoglobin is several times more stable than oxyhemoglobin and ties up the hemoglobin so that it cannot carry oxygen to body tissues.

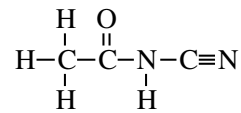
11.2.4 Cyanogen, Cyanamide, and Cyanates

Cyanogen, NCCN, is a colorless, violently flammable gas with a pungent odor. It may cause permanent injury or even death in exposed individuals. Fumes produced by the reaction of cyanogen with water or acids are highly toxic.

Cyanamide, H_2NCN, and calcium cyanamide, CaNCN, are used as fertilizers and raw materials. Calcium cyanamide is employed for the desulfurization and nitridation of steel. Inhalation or oral ingestion of cyanamide causes dizziness, lowers blood pressure, and increases rates of pulse and respiration. Calcium cyanamide acts as a primary irritant to the skin and to nose and throat tissues. The major metabolic product of cyanimide is N-acetylcyanamide, which is found in the urine of subjects exposed to cyanamide.



Cyanamide



N-acetylcyanamide

Cyanic acid, HOCN (boiling point (bp), 23.3°C; melting point (mp), –86°C), is a dangerously explosive liquid with an acrid odor. The acid forms cyanate salts, such as NaOCN and KOCN. During decomposition from heat or contact with strong acid, cyanic acid evolves very toxic fumes.

11.3 TOXIC INORGANIC NITROGEN COMPOUNDS

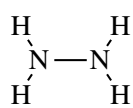
11.3.1 Ammonia

Ammonia, NH_3, is widely used as a gas for chemical synthesis, fertilizer, and other applications. It is also used as a solution of concentrated NH_3 in water as a chemical reagent and as a fertilizer. Tanks of liquified anhydrous ammonia are common targets for the operators of "meth labs" in rural areas, who steal this dangerous chemical to make illicit amphetamines. Undoubtedly, some of the thieves suffer injury in the process, though such injuries are rarely reported.

The evaporation of liquid ammonia in contact with flesh can cause frostbite. Ammonia is a potent skin corrosive and can damage eye tissue. When inhaled, ammonia causes constriction of the bronchioles. Because of its high water solubility, ammonia is absorbed by the moist tissues of the upper respiratory tract. Irritant damage to the lungs from ammonia can cause edema and changes in lung permeability.

11.3.2 Hydrazine

Hydrazine,



Hydrazine

is a common inorganic nitrogen compound. Hydrazine is hepatotoxic, causing accumulation of triglycerides in the liver, a condition commonly called fatty liver. These effects may be related to hydrazine's ability to increase the activity of enzymes required to produce diglycerides, depletion of ATP, or inhibition of protein synthesis. Hydrazine acting in the liver induces hydrolysis of glycogen (animal starch) to release glucose, causing excessive blood glucose levels, a condition

called hyperglycemia. This can result in depletion of glycogen, leading to the opposite effect, hypoglycemia. Hydrazine inhibits some enzymes, including phosphoenol pyruvatecarboxykinase and some transaminases that are involved in intermediary metabolism. Swelling of cell mitochondria has been observed after exposure to hydrazine, and prolonged exposure can result in formation of large megamitochondria.

The most serious toxicologic effect of hydrazine is its ability to indirectly cause methylation of DNA, leading to cancer. Inhalation of hydrazine has been linked to lung cancer.

11.3.3 Nitrogen Oxides

The two most common oxides of nitrogen are **nitric oxide** (NO) and **nitrogen dioxide** (NO_2), designated collectively as NO_x. Nitric oxide is produced in combustion processes from organically bound nitrogen endogenous to fossil fuels (particularly coal, heavy fuel oil, and shale oil) and from atmospheric nitrogen under the conditions that exist in an internal combustion engine, as shown by the two following reactions:

$$2N(\textit{fossil fuel}) + O_2 \rightarrow 2NO \tag{11.3.1}$$

$$N_2 + O_2 \xrightarrow[\textbf{engine}]{\textbf{Internal combustion}} 2NO \tag{11.3.2}$$

Under the conditions of photochemical smog formation, nitric oxide is converted to nitrogen dioxide by the following overall reaction:

$$2NO + O_2 \xrightarrow[\textbf{processes}]{\textbf{Organics, photochemical}} 2NO_2 \tag{11.3.3}$$

This conversion consists of complex chain reactions involving light energy and unstable reactive intermediate species. The conditions required are stagnant air, low humidity, intense sunlight, and the presence of reactive hydrocarbons, particularly those from automobile exhausts. Of the NO_x constituents, NO_2 is generally regarded as the more toxic, although all nitrogen oxides and potential sources thereof (such as nitric acid in the presence of oxidizable organic matter) should be accorded the same respect as nitrogen dioxide.

11.3.4 Effects of NO_2 Poisoning

The toxic effects of NO_2 have been summarized.[3] Inhalation of NO_2 causes severe irritation of the innermost parts of the lungs, resulting in pulmonary edema and fatal bronchiolitis fibrosa obliterans. Inhalation, for even very brief periods, of air containing 200 to 700 ppm of NO_2 can be fatal. The biochemical action of NO_2 includes disruption of some enzyme systems, such as lactic dehydrogenase. Nitrogen dioxide probably acts as an oxidizing agent similar to, though weaker than, ozone, which is discussed in Section 10.6.1. Included is the formation of free radicals, particularly the hydroxyl radical HO·. Like ozone, it is likely that NO_2 causes **lipid peroxidation**. This is a process in which the C=C double bonds in unsaturated lipids are attacked by free radicals and undergo chain reactions in the presence of O_2, resulting in their oxidative destruction.

11.3.5 Nitrous Oxide

Nitrous oxide, once commonly known as laughing gas, is used as an oxidant gas and in dental surgery as a general anesthetic. It is a central nervous system depressant and can act as an asphyxiant.

11.4 HYDROGEN HALIDES

Hydrogen halides are compounds with the general formula HX, where X is F, Cl, Br, or I. They are all gases, and all are relatively toxic. Because of their abundance and industrial uses, HF and HCl have the greatest toxicological significance of these gases.

11.4.1 Hydrogen Fluoride

Hydrogen fluoride, HF (mp, –83.1°C; bp, 19.5°C), may be in the form of either a clear, colorless liquid or gas. It forms corrosive fumes when exposed to the atmosphere. The major commercial application of hydrogen fluoride is as an alkylating catalyst in petroleum refining. Pot room workers in the primary aluminum industry are exposed to levels up to 5 mg/m^3 in the workplace atmosphere and exhibit elevated levels of F^- ion in their blood plasma.[4] Hydrogen fluoride in aqueous solution is called **hydrofluoric acid**, which contains 30 to 60% HF by mass. Hydrofluoric acid must be kept in plastic containers because it vigorously attacks glass and other materials containing silica (SiO_2), producing gaseous silicon tetrafluoride, SiF_4. Hydrofluoric acid is used to etch glass and clean stone.

Both hydrogen fluoride and hydrofluoric acid, referred to collectively as HF, are extreme irritants to any tissue they contact. Exposed areas heal poorly, gangrene may develop, and ulcers can occur in affected areas of the upper respiratory tract.

The toxic nature of fluoride ion, F^-, is not confined to its presence in HF. It is toxic in soluble fluoride salts, such as NaF. At relatively low levels, such as about 1 ppm, used in some drinking water supplies, fluoride prevents tooth decay. At excessive levels, fluoride causes **fluorosis**, a condition characterized by bone abnormalities and mottled, soft teeth. Livestock are especially susceptible to poisoning from fluoride fallout on grazing land as a result of industrial pollution. In severe cases, the animals become lame and even die.

11.4.2 Hydrogen Chloride

Hydrogen chloride, HCl (mp, –114°C; bp, –84.8°C), may be encountered as a gas, pressurized liquid, or aqueous solution called **hydrochloric acid**, commonly denoted simply as HCl. This compound is colorless in the pure state and in aqueous solution. As a saturated solution containing 36% HCl, hydrochloric acid is a major industrial chemical, with U.S. production of about 2.3 million tons per year. It is used for chemical and food manufacture, acid treatment of oil wells to increase crude oil flow, and metal processing.

Hydrogen chloride is not nearly as toxic as HF, although inhalation can cause spasms of the larynx as well as pulmonary edema and even death at high levels. Because of its high affinity for water, HCl vapor tends to dehydrate tissue of the eyes and respiratory tract. Hydrochloric acid is a natural physiological fluid found as a dilute solution in the stomachs of humans and other animals.

11.4.3 Hydrogen Bromide and Hydrogen Iodide

Hydrogen bromide, HBr (mp, –87°C; bp, –66.5°C), and **hydrogen iodide**, HI (mp, –50.8°C; bp, –35.4°C), are both pale yellow or colorless gases, although contamination by their respective elements tends to impart some color to these compounds. Both are very dense gases, 3.5 g/l for HBr and 5.7 g/l for HI at 0°C and atmospheric pressure. These compounds are used much less than HCl. Both are irritants to the skin and eyes and to the oral and respiratory mucous membranes.

11.5 INTERHALOGEN COMPOUNDS AND HALOGEN OXIDES

Halogens form compounds among themselves and with oxygen. Some of these compounds are important in industry and toxicologically. Some of the more important such compounds are discussed below.

Table 11.1 Major Interhalogen Compounds

Compound Name and Formula	Physical Properties
Chlorine monofluoride, ClF	Colorless gas; mp, –154°C; bp, 101°C
Chlorine trifluoride, ClF_3	Colorless gas; mp, –83°C; bp, 12°C
Bromine monofluoride, BrF	Pale brown gas; bp, 20°C
Bromine trifluoride, BrF_3	Colorless liquid; mp, 8.8°C; bp, 127°C
Bromine pentafluoride, BrF_5	Colorless liquid; mp, –61.3°C; bp, 40°C
Bromine monochloride, BrCl	Red or yellow highly unstable liquid and gas
Iodine trifluoride, IF_3	Yellow solid decomposing at 28°C
Iodine pentafluoride, IF_5	Colorless liquid; mp, 9.4°C; bp, 100°C
Iodine heptafluoride, IF_7	Colorless sublimable solid; mp, 5.5°C
Iodine monobromide, IBr	Gray sublimable solid; mp, 42°C
Iodine monochloride, ICl	Red-brown solid alpha form; mp, 27°C; bp, 9°C
Iodine pentabromide, IBr_5	Crystalline solid
Iodine tribromide, IBr_3	Dark brown liquid
Iodine trichloride, ICl_3	Orange-yellow solid subliming at 64°C
Iodine pentachloride, ICl_5	—

Table 11.2 Major Oxides of the Halogens

Compound Name and Formula	Physical Properties
Fluorine monoxide, OF_2	Colorless gas; mp, –224°C; bp, –145°C
Chlorine monoxide, Cl_2O	Orange gas; mp, –20°C; bp, 2.2°C
Chlorine dioxide, ClO_2	Orange gas; mp, –59°C; bp, 9.9°C
Chlorine heptaoxide, Cl_2O_7	Colorless oil; mp, –91.5°C; bp, 82°C
Bromine monoxide, Br_2O	Brown solid; decomp. –18°C
Bromine dioxide, BrO_2	Yellow solid; decomp. 0°C
Iodine dioxide, IO_2	Yellow solid
Iodine pentoxide, I_2O_5	Colorless oil; decomp. 325°C

11.5.1 Interhalogen Compounds

Fluorine is a sufficiently strong oxidant to oxidize chlorine, bromine, and iodine, whereas chlorine can oxidize bromine and iodine. The compounds thus formed are called **interhalogen compounds**. The major interhalogen compounds are listed in Table 11.1.

The liquid interhalogen compounds are usually described as "fuming" liquids. For the most part, interhalogen compounds exhibit extreme reactivity. They react with water or steam to produce hydrohalic acid solutions (HF, HCl) and nascent oxygen {O}. They tend to be potent oxidizing agents for organic matter and oxidizable inorganic compounds. These chemical properties are reflected in the toxicities of the interhalogen compounds. Too reactive to enter biological systems in their original chemical state, they tend to be powerful corrosive irritants that acidify, oxidize, and dehydrate tissue. The skin, eyes, and mucous membranes of the mouth, throat, and pulmonary systems are susceptible to attack by interhalogen compounds. In some respects, the toxicities of the interhalogen compounds resemble the toxic properties of the elemental forms of the elements from which they are composed. The by-products of chemical reactions of the interhalogen compounds — such as HF from fluorine compounds — pose additional toxicological hazards.

11.5.2 Halogen Oxides

The oxides of the halogens tend to be unstable and reactive. Although these compounds are called oxides, it is permissible to call the ones containing fluorine fluorides because fluorine is more electronegative than oxygen. The major halogen oxides are listed in Table 11.2. Commercially, the most important of the halogen oxides is chlorine dioxide, which offers some advantages over

chlorine as a water disinfectant. It is also employed for odor control and bleaching wood pulp. Because of its extreme instability, chlorine dioxide is manufactured on the site where it is used.

Investigations on human blood and on rodents suggest that ClO_2 and its metabolic product ClO_2^- cause formation of methemoglobin, decrease the activities of glucose-6-phosphate dehydrogenase and glutathione peroxidase enzymes, reduce levels of reduced glutathione (a protective agent against oxidative stress), increase levels of hydrogen peroxide, and cause breakdown of red blood cells releasing hemoglobin (hemolysis).[5] These effects would suggest an overall hematotoxicity of chlorine dioxide.

For the most part, the halogen oxides are highly reactive toxic substances. Their toxicity and hazard characteristics are similar to those of the interhalogen compounds, described previously in this section.

11.5.3 Hypochlorous Acid and Hypochlorites

The halogens form several oxyacids and their corresponding salts. Of these, the most important is hypochlorous acid (HOCl), formed by the following reaction:

$$Cl_2 + H_2O \rightleftharpoons HCl + HOCl \tag{11.5.1}$$

Hypochlorous acid and hypochlorites are used for bleaching and disinfection. They produce active (nascent) oxygen, {O}, as shown by the reaction below, and the resulting oxidizing action is largely responsible for the toxicity of hypochlorous acid and hypochlorites as irritants to eye, skin, and mucous membrane tissue.

$$HClO \rightarrow H^+ + Cl^- + \{O\} \tag{11.5.2}$$

11.5.4 Perchlorates

Perchlorates are the most oxidized of the salts of the chlorooxyacids. Although perchlorates are not particularly toxic, ammonium perchlorate (NH_4ClO_4) should be mentioned because it is a powerful oxidizer and reactive chemical produced in large quantities as a fuel oxidizer in solid rocket fuels. Each of the U.S. space shuttle booster rockets contains about 350,000 kg of ammonium perchlorate in its propellant mixture. By 1988, U.S. consumption of ammonium perchlorate for rocket fuel uses was of the order of 24 million kg/year. In May 1988, a series of massive explosions in Henderson, Nevada, demolished one of only two plants producing ammonium perchlorate for the U.S. space shuttle, MX missile, and other applications, so that supplies were severely curtailed. The plant has since been rebuilt.

The toxicological hazard of perchlorate salts may depend on the cation in the compound. In general, the salts should be considered as skin irritants and treated as such. Perchlorate ion, ClO_4^-, may compete physiologically with iodide ion, I^-. This can occur in the uptake of iodide by the thyroid, leading to the biosynthesis of thyroid hormones. As a consequence, perchlorate can cause symptoms of iodine deficiency.

11.6 NITROGEN COMPOUNDS OF THE HALOGENS

11.6.1 Nitrogen Halides

The general formula of the nitrogen halides is N_nX_X, where X is F, Cl, Br, or I. A list of nitrogen halides is presented in Table 11.3. The nitrogen halides are considered to be very toxic, largely as irritants to eyes, skin, and mucous membranes. Direct exposure to nitrogen halide compounds tends

Table 11.3 Nitrogen Halides

Compound Name and Formula	Physical Properties
Nitrogen trifluoride, NF_3	Colorless gas; mp, –209°C; bp, –129°C
Nitrogen trichloride, NCl_3	Volatile yellow oil; melting below –40°C; boiling below 71°C; exploding around 90°C
Nitrogen tribromide, NBr_3	Solid crystals
Nitrogen triiodide, NI_3	Black crystalline explosive substance
Tetrafluorohydrazine, N_2F_4	—

to be limited because of their reactivity, which may destroy the compound before exposure. Nitrogen triiodide is so reactive that even a "puff" of air can detonate it.[6]

11.6.2 Azides

Halogen azides are compounds with the general formula XN_3, where X is one of the halogens. These compounds are extremely reactive and can be spontaneously explosive. Their reactions with water can produce toxic fumes of the elemental halogen, acid (e.g., HCl), and NO_X. The compound vapors are irritants.

11.6.3 Monochloramine and Dichloramine

The substitution of Cl for H on ammonia can be viewed as a means of forming nitrogen trichloride (Table 11.3), monochloramine, and dichloramine. The formation of the last two compounds from ammonium ion in water is shown by the following reactions:

$$NH_4^+ + HOCl \rightarrow H^+ + H_2O + NH_2Cl \quad (11.6.1)$$

Monochloramine

$$NH_2Cl + HOCl \rightarrow H_2O + NHCl_2 \quad (11.6.2)$$

Dichloramine

The chloramines are disinfectants in water and are formed deliberately in the purification of drinking water to provide **combined available chlorine**. Although combined available chlorine is a weaker disinfectant than water, containing Cl_2, HOCl, and OCl^-, it is retained longer in the water distribution system, affording longer-lasting disinfection.

Since they work as disinfectants, the chloramines have to have some toxic effects. They have been shown to inhibit acetylcholinesterase activity.[7]

11.7 INORGANIC COMPOUNDS OF SILICON

Because of its use in semiconductors, silicon has emerged as a key element in modern technology. Concurrent with this phenomenon has been an awareness of the toxicity of silicon compounds, many of which, fortunately, have relatively low toxicities. This section covers the toxicological aspects of inorganic silicon compounds.

11.7.1 Silica

The silicon compound that has probably caused the most illness in humans is **silica**, SiO_2. Silica is a hard mineral substance known as quartz in the pure form and occurring in a variety of minerals,

such as sand, sandstone, and diatomaceous earth. Because of silica's occurrence in a large number of common materials that are widely used in construction, sand blasting, refractories manufacture, and many other industrial applications, human exposure to silica dust is widespread. Such exposure causes a condition called **silicosis**, a type of pulmonary fibrosis, one of the most common disabling conditions that result from industrial exposure to hazardous substances. Silicosis causes fibrosis and nodules in the lung, lowering lung capacity and making the subject more liable to pulmonary diseases, such as pneumonia. A lung condition called silicotuberculosis may develop. Severe cases of silicosis can cause death from insufficient oxygen or from heart failure.

Silica exposure has been associated with increased incidences of **scleroderma**, a condition manifested by hardened, rigid connective tissue. In this respect, it is believed that silica acts by an adjuvant mechanism in which it enhances the autoimmune response caused by other agents, such as silicones or paraffin.[8]

11.7.2 Asbestos

Asbestos describes a group of silicate minerals, such as those of the serpentine group, approximate formula $Mg_3P(Si_2O_5)(OH)_4$, which occur as mineral fibers. Asbestos has many properties, such as insulating abilities and heat resistance, that have given it numerous uses. It has been used in structural materials, brake linings, insulation, and pipe manufacture. Unfortunately, inhalation of asbestos damages the lungs and results in a characteristic type of lung cancer in some exposed subjects. The toxic effects of asbestos are initiated when asbestos fibers in the lung act as local irritants and become phagocytosed by macrophages (large white blood cells). The bodies of phagocytosed asbestos are taken up by cellular lysosomes, which secrete hydrolytic enzymes, digesting the matter surrounding the asbestos particles and releasing them to start the process over. This process causes lymphoid tissue to aggregate in the vicinity of the insult, forming fibrotic lesions from the synthesis of excess collagen.[9]

The three major pathological conditions caused by the inhalation of asbestos are asbestosis (a pneumonia condition), mesothelioma (tumor of the mesothelial tissue lining the chest cavity adjacent to the lungs), and bronchogenic carcinoma (cancer originating with the air passages in the lungs). Because of these health effects, uses of asbestos have been severely curtailed and widespread programs have been undertaken to remove asbestos from buildings.

Lung cancer from asbestos exposure has a strong synergistic relationship with exposure to cigarette smoke.[10] Long-term exposure to asbestos, alone, increases the incidence of lung cancer about 5-fold, cigarette smoking roughly 10-fold, but the two together more than 50-fold.

11.7.3 Silanes

Compounds of silicon with hydrogen are called **silanes**. The simplest of these is silane, SiH_4. Disilane is H_3SiSiH_3. Numerous organic silanes exist in which alkyl moieties are substituted for H.

In addition to SiH_4, the inorganic silanes produced for commercial use are dichloro- and trichlorosilane, SiH_2Cl_2 and $SiHCl_3$, respectively. These compounds are used as intermediates in the synthesis of organosilicon compounds and in the production of high-purity silicon for semiconductors. Several kinds of inorganic compounds derived from silanes have potential uses in the manufacture of photovoltaic devices for the direct conversion of solar energy to electricity. In general, not much is known about the toxicities of silanes. Silane itself burns readily in air. Chlorosilanes are irritants to eye, nasal, and lung tissue. The toxicities of silane, dichlorosilane, and tetraethoxysilane, $Si(OC_2H_5)$, have been reviewed for their relevance in the semiconductor industry.[11] The major effects of silane and tetraethoxysilane appeared to be nephrotoxicity (kidney damage).

11.7.4 Silicon Halides and Halohydrides

Four **silicon tetrahalides**, with the general formula SiX_4, are known to exist. Of these, only silicon tetrachloride, $SiCl_4$, is produced in significant quantities. It is used to manufacture fumed silica (finely divided SiO_2). In addition, numerous **silicon halohydrides**, with the general formula $H_{4-X}SiX_X$, have been synthesized. The commercially important compound of this type is trichlorosilane, $HSiCl_3$, which is used to manufacture organotrichlorosilanes and elemental silicon for semiconductors.

Both silicon tetrachloride and trichlorosilane are fuming liquids with suffocating odors. They both react with water to give off HCl vapor.

11.8 INORGANIC PHOSPHORUS COMPOUNDS

11.8.1 Phosphine

Phosphine, PH_3 (mp, –132°C; bp, –88°C), is a colorless gas that undergoes autoignition at 100°C. It is used for the synthesis of organophosphorus compounds. Its inadvertent production in chemical syntheses involving other phosphorus compounds is a potential hazard in industrial processes and in the laboratory. Phosphine gas is a pulmonary tract irritant and central nervous system depressant that is very toxic when inhaled and can be fatal. Symptoms of acute exposure include headache, dizziness, burning pain below the sternum, nausea, vomiting, difficult, painful breathing, pulmonary irritation and edema, cough with fluorescent green sputum, tremors, and fatigue. Convulsions have appeared in some victims after they have apparently recovered from phosphine poisoning. Workers chronically exposed to phosphine have exhibited inflammation of the nasal cavity and throat, nausea, dizziness, weakness, and adverse gastrointestinal, cardiorespiratory, and central nervous system effects. Chronic effects have also included hepatotoxic symptoms, jaundice, nervous system abnormalities, and increased bone density.

Arsine gas, AsH_3, is mentioned here because of the position of arsenic directly below phosphorus in the periodic table, and hence the similarity between arsine and phosphine. Arsine may be generated by chemically reductive processes in the refining of various metals. It is a highly toxic substance that can cause fatal instances of poisoning. Its major effect is on the blood, and it may cause breakdown of red blood cells with liberation of hemoglobin (hemolysis).[12] Symptomatic of this effect is the presence of hemoglobin in urine (hemoglobinuria). Acute symptoms of arsine poisoning include headache, shortness of breath, nausea, and vomiting. Jaundice and anemia may also accompany arsine poisoning.

11.8.2 Phosphorus Pentoxide

The oxide most commonly formed by the combustion of elemental white phosphorus and many phosphorus compounds is P_4O_{10}. As an item of commerce, this compound is usually misnamed **phosphorus pentoxide**. When produced from the combustion of elemental phosphorus (see Reaction 10.6.7), it is a fluffy white powder that removes water from air to form syrupy orthophosphoric acid:

$$P_4O_{10} + 6H_2O \rightarrow 4H_3PO_4 \tag{11.8.1}$$

Because of its dehydrating action and formation of acid, phosphorus pentoxide is a corrosive irritant to skin, eyes, and mucous membranes.

11.8.3 Phosphorus Halides

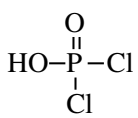
Phosphorus forms halides with the general formulas PX_3 and PX_5. Typical of such compounds are phosphorus trifluoride (PF_3), a colorless gas (mp, –152°C; bp, –102°C), and phosphorus pentabromide (PBr_5), a yellow solid that decomposes at approximately 100°C. Of these compounds, the most important commercially is phosphorus pentachloride, used as a catalyst in organic synthesis, as a chlorinating agent, and as a raw material to make phosphorus oxychloride ($POCl_3$). Phosphorus halides react violently with water to produce the corresponding hydrogen halides and oxophosphorus acids, as shown by the following reaction of phosphorus pentachloride:

$$PCl_5 + 4H_2O \rightarrow H_3PO_4 + 5HCl \qquad (11.8.2)$$

Largely because of their acid-forming tendencies, the phosphorus halides are strong irritants to eyes, skin, and mucous membranes, and should be regarded as very toxic.

11.8.4 Phosphorus Oxyhalides

Phosphorus oxyhalides, with the general formula POX_3, are known for fluoride, chloride, and bromide. Of these, the one with commercial uses is phosphorus oxychloride ($POCl_3$). Its uses are similar to those of phosphorus trichloride, acting in chemical synthesis as a chlorinating agent and for the production of organic chemical intermediates. It is a faintly yellow fuming liquid (mp, 1°C; bp, 105°C). It reacts with water to form hydrochloric acid and phosphonic acid (H_3PO_3). The liquid evolves toxic vapors, and it is a strong irritant to the eyes, skin, and mucous membranes. Phosphorus oxychloride is metabolized to phosphorodichloridic acid,



Phosphorodichloridic acid

a phosphorylating agent that phosphorylates acetylcholinesterase at the active site to form enzymically inactive (O-phosphoserine)acetylcholinesterase.[13]

11.9 INORGANIC COMPOUNDS OF SULFUR

One of the elements essential for life, sulfur is a constituent of several of the more important toxic inorganic compounds. The common elemental form of yellow crystalline or powdered sulfur, S_8, has a low toxicity, although chronic inhalation of it can irritate mucous membranes.

11.9.1 Hydrogen Sulfide

Hydrogen sulfide (H_2S) is a colorless gas (mp, –86°C; bp, –61°C) with a foul, rotten-egg odor. It is produced in large quantities as a by-product of coal coking and petroleum refining, and massive quantities are removed in the cleansing of sour natural gas. Hydrogen sulfide is released in large quantities from volcanoes and hydrothermal vents. Indeed, if Yellowstone National Park in the U.S. were an industrial enterprise, parts of it would be shut down because of release of hydrogen sulfide from geothermal sources. Hydrogen sulfide is a major source of elemental sulfur by a process that involves oxidation of part of the H_2S to SO_2, followed by the Claus reaction:

$$2H_2S(g) + SO_2(g) \rightarrow 2H_2O(l) + 3S(s) \quad (11.9.1)$$

Hydrogen sulfide is a very toxic substance, which in some cases can cause a fatal response more rapidly even than hydrogen cyanide, the toxic effects of which it greatly resembles. Like cyanide, hydrogen sulfide inhibits the cytochrome oxidase system essential for respiration. Hydrogen sulfide affects the central nervous system, causing symptoms that include headache, dizziness, and excitement. Rapid death occurs at exposures to air containing more than about 1000 ppm of H_2S, and somewhat lower exposures for about 30 min can be lethal. Death results from asphyxiation as a consequence of respiratory system paralysis. Sulfide can also cause localized toxic effects at the point of contact, one of which is pulmonary edema. Another localized effect is eye conjunctivitis, a condition called "gas eye," perhaps named after conditions suffered by gas works employees formerly exposed to hydrogen sulfide produced in the gasification of high-sulfur coal in the production of synthetic gas, once widely used for cooking and lighting.

Accidental poisonings by hydrogen sulfide are not uncommon. In the most notorious such case, 22 people (by some accounts many more) were killed in 1950 in Poza Rica, Mexico, when a flare used to "dispose" of hydrogen sulfide from natural gas by burning it to sulfur dioxide became extinguished, releasing large quantities of H_2S and asphyxiating victims as they slept. In 1975, at Denver City, Texas, nine people were killed from hydrogen sulfide blown out of a secondary petroleum recovery well. There are numerous effects of chronic H_2S poisoning, including general debility.

Hydrogen sulfide is acted on in the body by methylation with thiol S-methyl transferase. The initial product is methanethiol, $HSCH_3$, which is also quite toxic. A second methylation produces dimethylsulfide, H_2CSCH_3. (Of some interest is the fact that dimethylsulfide is the major volatile sulfur compound released to the atmosphere from oceans, where it is produced by the action of marine microorganisms.)

Bacteria acting anaerobically in the colon produce large quantities of hydrogen sulfide and methanethiol. There is evidence to suggest that the mucous membranes of the colon have enzymes that convert hydrogen sulfide and methanethiol to nontoxic thiosulfate, $S_2O_3^{2-}$.[14]

The nitrite-induced formation of blood methemoglobin has been used successfully to treat hydrogen sulfide poisoning. Like cyanide, hydrogen sulfide bonds to iron(III) in methemoglobin so that it is not available to inhibit cytochrome oxidase.[15]

11.9.2 Sulfur Dioxide and Sulfites

Sulfur dioxide (SO_2) is an intermediate in the production of sulfuric acid. It is a common air pollutant produced by the combustion of pyrite (FeS_2) in coal and organically bound sulfur in coal and fuel oil, as shown by the two following reactions:

$$4FeS_2 + 11O_2 \rightarrow 2Fe_2O_3 + 8SO_2 \quad (11.9.2)$$

$$S(\textit{organic, in fuel}) + O_2 \rightarrow SO_2 \quad (11.9.3)$$

These sources add millions of tons of sulfur dioxide to the global atmosphere annually and are largely responsible for acid rain.

Sulfur dioxide is an irritant to the eyes, skin, mucous membranes, and respiratory system. As a water-soluble gas, it is largely removed in the upper respiratory tract. Its major effect is as a respiratory tract irritant, where it irritates the upper airways and causes bronchioconstriction, resulting in increased airflow resistance.[16] Subjects who are hyperresponsive to sulfur dioxide are especially at risk from it. Asthmatics may suffer bronchioconstriction after only a few breaths of

sulfur dioxide-contaminated air. The degree of response of asthma sufferers to sulfur dioxide is highly variable.[17]

Dissolved in water, sulfur dioxide produces **sulfurous acid** (H_2SO_3), **hydrogen sulfite ion** (HSO_3^-), and **sulfite ion** (SO_3^{2-}). Sodium sulfite (Na_2SO_3) has been used as a chemical food preservative, although some individuals are hypersensitive to it.

11.9.3 Sulfuric Acid

Sulfuric acid is number one in synthetic chemical production. It is used to produce phosphate fertilizer, high octane gasoline, and a wide variety of inorganic and organic chemicals. Large quantities are consumed to pickle steel (cleaning and removal of surface oxides); disposal of spent pickling liquor can be a problem.

Sulfuric acid is of particular concern as an atmospheric pollutant. In times past, air polluted with unquestionably toxic levels of sulfuric acid aerosols (see Section 2.8.3), such as in the severe air pollution that occurred in London and around various smelters in the 1950s and early 1960s, produced toxic effects and even fatalities. At present, sulfuric acid is a major contributor to acid precipitation (see Section 2.8.1), and it may well be the most intense common irritant occurring in air polluted with acid substances. Most of the pollutant sulfur that becomes atmospheric H_2SO_4 is emitted to the atmosphere as SO_2 from the burning of sulfur-containing fuels (particularly coal). Sulfur dioxide emissions are almost always accompanied by emissions of particulate matter, which often contains metals, such as vanadium, iron, and manganese. These metals can catalyze the oxidation of SO_2 to H_2SO_4, either on particle surfaces or leached into aqueous solution in aerosol droplets:

$$SO_2 + \tfrac{1}{2}O_2 + H_2O \rightarrow H_2SO_4(aq) \tag{11.9.4}$$

The result can be formation of an aerosol mist of droplets containing intensely irritating sulfuric acid.

Sulfuric acid is a severely corrosive poison and dehydrating agent in the concentrated liquid form. It readily penetrates skin to reach subcutaneous tissue and causes tissue necrosis, with effects resembling those of severe thermal burns. Sulfuric acid fumes and mists can act as irritants to eye and respiratory tract tissue. Industrial exposure has caused tooth erosion in workers.

At lower levels, inhalation of sulfuric acid from sources such as atmospheric precipitation is damaging to the pulmonary tract. Compared to sulfur dioxide, sulfuric acid is the much more potent lung tissue irritant. Animal studies and limited data from exposed humans indicate that inhalation of H_2SO_4 aerosol increases airway resistance and inhibits bronchial clearance of inhaled particles. Asthmatic subjects are sensitive to sulfuric acid inhalation, and the effect may be synergistic with sulfur dioxide. Therefore, particularly for sensitive individuals, exposure to air containing sulfuric acid, sulfur dioxide, and particles — all of which tend to occur together when one is present in a polluted atmosphere — may be particularly damaging to the lungs.

11.9.4 Carbon Disulfide

Carbon disulfide, CS_2, is a toxicologically important compound because of its widespread use in making rayon and cellophane from cellulose and its well-established toxic effects. Skin contact with carbon disulfide has caused skin disorders, including blisters in rayon plant workers. Very high levels of atmospheric carbon disulfide vapor in the workplace of the order of 10 ppt can cause life-threatening effects on the central nervous system. Epidemiologic studies of viscose rayon workers exposed to carbon disulfide have shown increased mortalities, including cardiovascular mortality. Vascular atherosclerotic changes have been observed in workers exposed to carbon disulfide for long periods of time.

Table 11.4 Inorganic Sulfur Compounds

Compound Name and Formula	Properties
Sulfur	
Monofluoride, S_2F_2	Colorless gas; mp, –104°C; bp, –99°C; toxicity similar to HF
Tetrafluoride, SF_4	Gas; mp, –124°C; bp, –40°C; powerful irritant
Hexafluoride, SF_6	Colorless gas; mp, –51°C; surprisingly nontoxic when pure, but often contaminated with toxic lower fluorides
Monochloride, S_2Cl_2	Oily; fuming orange liquid; mp, –80°C; bp, 138°C; strong irritant to eyes, skin, and lungs
Tetrachloride, SCl_4	Brownish yellow liquid or gas; mp, –30°C; decomp. below 0°C; irritant
Trioxide, SO_3	Solid anhydride of sulfuric acid (see toxic effects above); reacts with moisture or steam to produce sulfuric acid
Sulfuryl chloride, SO_2Cl_2	Colorless liquid; mp, –54°C; bp, 69°C; used for organic synthesis, corrosive toxic irritant
Thionyl chloride, $SOCl_2$	Colorless-to-orange fuming liquid; mp, –105°C; bp, 79°C; toxic corrosive irritant
Carbon oxysulfide, COS	Volatile liquid by-product of natural gas or petroleum refining; toxic narcotic

The most notable toxicological effects of carbon disulfide are on the nervous system, including damage to the peripheral nervous system.[18] Individuals exposed to carbon disulfide have lost consciousness. Decreased nerve conduction velocities have been observed in workers exposed to 10 to 20 ppm of carbon disulfide in the workplace over periods of 10 to 20 years. Brain abnormalities suggesting toxic encephalopathy have been observed in exposed workers. Some studies have suggested the possibility of mental performance and personality disorders in workers exposed to carbon disulfide, including heightened levels of anxiety, introversion, and depression.

11.9.5 Miscellaneous Inorganic Sulfur Compounds

A large number of inorganic sulfur compounds, including halides and salts, are widely used in industry. The more important of these are listed in Table 11.4.

REFERENCES

1. Lei, V., Amoa-Awua, W.K.A., and Brimer, L., Degradation of cyanogenic glycosides by *Lactobacillus plantarum* strains from spontaneous cassava fermentation and other microorganisms, *Int. J. Food Microbiol.*, 53, 169–184, 1999.
2. Gandini, C. et al., Carbon monoxide cardiotoxicity, *J. Toxicol. Clin. Toxicol.*, 39, 35–44, 2001.
3. Elsayed, N.M., Toxicity of nitrogen dioxide: an introduction, *Toxicology*, 89, 161–174, 1994.
4. Lund, K. et al., Exposure to hydrogen fluoride: an experimental study in humans of concentrations of fluoride in plasma, symptoms, and lung function, *Occup. Environ. Med.*, 54, 32–37, 1997.
5. Ueno, H., Sayato, Y., and Nakamuro, K., Hematological effects of chlorine dioxide on in vitro exposure in mouse, rat, and human blood and on subchronic exposure in mice, *J. Health Sci.*, 46, 110–116, 2000.
6. Sax, N.I., *Dangerous Properties of Industrial Materials*, 5th ed., Van Nostrand Reinhold, New York, 1979.
7. Wang, Z. and Minami, M., Effects of chloramine on neuronal cholinergic factors: further studies of toxicity mechanism suggested by an unusual case record, *Biogenic Amines*, 12, 213–223, 1996.
8. Burns, L.A., Meade, B.J., and Munson, A.E., Toxic responses of the immune system, in *Casarett and Doull's Toxicology: The Basic Science of Poisons*, 5th ed., Klaassen, C.D., Ed., McGraw-Hill, New York, 1996, chap. 12, pp. 355–402.
9. Timbrell, J.A., *Principles of Biochemical Toxicology*, 3rd ed., Taylor and Francis, London, 2000, p. 190.
10. Modifying factors of toxic effects, in *Basic Toxicology*, Lu, F.C., Ed., Hemisphere Publishing Corp., New York, 1991, chap. 5, pp. 61–73.

11. Nakashima, H. et al., Toxicity of silicon compounds in semiconductor industries, *J. Occup. Health*, 40, 270–275, 1998.
12. Goyer, R.A., Toxic effects of metals, in *Casarett and Doull's Toxicology: The Basic Science of Poisons*, 5th ed., Klaassen, C.D., Ed., McGraw-Hill, New York, 1996, chap. 23, pp. 691–736.
13. Quistad, G.B. et al., Toxicity of phosphorus oxychloride to mammals and insects that can be attributed to selective phosphorylation of acetylcholinesterase by phosphorodichloridic acid, *Chem. Res. Toxicol.*, 13, 652–657, 2000.
14. Furne, J. et al., Oxidation of hydrogen sulfide and methanethiol to thiosulfate by rat tissues: a specialized function of the colonic mucosa, *Biochem. Pharmacol.*, 62, 255–259, 2001.
15. Smith, R.P., Toxic responses of the blood, in *Casarett and Doull's Toxicology: The Basic Science of Poisons*, 5th ed., Klaassen, C.D., Ed., McGraw-Hill, New York, 1996, chap. 11, pp. 335–354.
16. Costa, D.L., Air pollution, in *Casarett and Doull's Toxicology: The Basic Science of Poisons*, 5th ed., Klaassen, C.D., Ed., McGraw-Hill, New York, 1996, chap. 28, pp. 857–882.
17. Trenga, C.A., Koenig, J.Q., and Williams, P.V., Sulphur dioxide sensitivity and plasma antioxidants in adult subjects with asthma, *Occup. Environ. Med.*, 56, 544–547, 1999.
18. Newhook, R., Meek, M.E., and Walker, M., Carbon disulfide: hazard characterization and exposure-response analysis, *Environ. Carcinog. Ecotoxicol. Rev.*, C19, 125–160, 2001.

QUESTIONS AND PROBLEMS

1. What are the two main toxic forms of cyanide? Which of these is most dangerous by inhalation? Which by ingestion?
2. What is a common natural source of cyanide? How is this form converted to toxic cyanide ion in the body? How did the Romans use this substance?
3. In what sense does cyanide deprive the body of oxygen? How does this differ from the way in which methane gas or nitrogen gas deprives the body of oxygen, or the way in which carbon monoxide does?
4. What is the biochemical action of carbon monoxide? What is the receptor with which carbon monoxide reacts? In what sense is this reaction reversible?
5. In general, how does NO_X enter the atmosphere? How does the more toxic form of NO_X form in the atmosphere?
6. Which organ is most affected by exposure to NO_2? What are the toxic effects, including bronchiolitis fibrosa obliterans? In general, what is the biochemical action of NO_2, and how does it involve free radical and lipid peroxidation?
7. What is the major toxic effect of nitrous oxide, N_2O? What might lead you to believe that it is much less toxic than NO_2?
8. What are the major toxicological effects of ozone? What kinds of groups does it attack in the body?
9. What is the main kind of reaction of chlorine in water? In what sense is this reaction tied to chlorine toxicity?
10. What may be said about the toxicity of fluorine compared to that of chlorine? Why is toxic exposure to bromine and iodine usually less of a problem than that to fluorine or chlorine?
11. Of the hydrogen halides, which is the most dangerous? How does this substance occur? What does it do to the body?
12. What are the nature and symptoms of fluorosis? How can this condition result from air pollution?
13. What kind of compound is ClF_3? What kind of compound is ClO_2? What are their chemical and toxicological similarities?
14. What kinds of compounds are NF_3 and NCl_3? What may be said about their chemical properties? What is their major toxicological effect?
15. What would lead you to believe that monochloramine and dichloramine are not regarded as very toxic, at least in an unconcentrated form? How are these compounds used? How are they related to combined available chlorine?
16. What is the chemical nature of silica? What is its major toxicological effect? What are the symptoms of this toxic effect?

17. In addition to silica, there is another silicon-containing mineral that is toxic. What is it? What are its toxic effects? How are its toxic effects synergistic with cigarette smoke?
18. What are silanes? How are they used? Is much known about their toxicities? What are the toxic effects of chlorosilanes?
19. What is the most commonly produced silicon tetrahalide? How is it used? Why might its toxicological properties be similar to those of HCl?
20. Why is PH_3 a particular hazard in the laboratory and in industrial chemical synthesis? Is it very toxic? What are its major toxic effects?
21. What role may be played by particulate matter and by metals, such as vanadium, iron, and manganese, in the production of toxic sulfuric acid?
22. What is the chemical nature of P_4O_{10}? What does it form when exposed to atmospheric moisture? What are its major toxicological effects? Suggest a sequence of reactions by which H_3PO_4 might be formed from PH_3.
23. What is PCl_5? How is it used? How does it react with water, and how is this reaction related to its toxic properties? What are some compounds that are related to PCl_5?
24. What is the most commonly used phosphorus oxyhalide, general formula POX_3? What are its industrial uses? How does it react with water, and how is this reaction related to the fact that it is a strong irritant to the eyes, skin, and mucous membranes?
25. In addition to the "miscellaneous" inorganic sulfur compounds listed in Table 11.4, four sulfur compounds were discussed separately for their toxicities. Of these, which is the most toxic? What is its mode of toxicity?
26. Why does exposure to fatal doses of H_2S still occur? What are some specific incidents in which such exposure has occurred?
27. What is SO_2 like chemically? What does it form in water? Why does it contribute to acid precipitation? In what sense is it less effective than H_2SO_4 as a constituent of acid precipitation?
28. Explain how the following reactions may lead to the occurrence of a major toxic air pollutant:

$$4FeS_2 + 11O_2 \rightarrow 2Fe_2O_3 + 8SO_2$$

$$S(\textit{organic, in fuel}) + O_2 \rightarrow SO_2$$

$$SO_2 + \tfrac{1}{2}O_2 + H_2O \rightarrow H_2SO_4(aq)$$

29. What are the major toxic effects of sulfuric acid? How is exposure to sulfuric acid likely to occur?

CHAPTER 12

Organometallics and Organometalloids

12.1 THE NATURE OF ORGANOMETALLIC AND ORGANOMETALLOID COMPOUNDS

An **organometallic compound** is one in which the metal atom is bonded to at least one carbon atom in an organic group. An **organometalloid compound** is a compound in which a metalloid element is bonded to at least one carbon atom in an organic group. The metalloid elements are shown in the periodic table of elements in Figure 1.3 and consist of boron, silicon, germanium, arsenic, antimony, tellurium, and astatine (a very rare radioactive element). In subsequent discussions, *organometallic* will be used as a term to designate both organometallic and organometalloid compounds, and *metal* will refer to both metals and metalloids, unless otherwise indicated. Given the predominance of the metals among the elements, and the ability of most to form organometallic compounds, it is not surprising that there are so many organometallic compounds, and new ones are being synthesized regularly. Fortunately, only a small fraction of these compounds are produced in nature or for commercial use, which greatly simplifies the study of their toxicities.

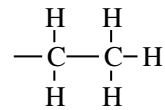
A further clarification of the nature of organometallic compounds is based on the **electronegativities** of the elements involved, i.e., the abilities of covalently bonded atoms to attract electrons to themselves. Electronegativity values of the elements range from 0.86 for cesium to 4.10 for fluorine. The value for carbon is 2.50, and all organometallic compounds involve bonds between carbon and an element with an electronegativity value of less than 2.50. The value of the electronegativity of phosphorus is 2.06, but it is so nonmetallic in its behavior that its organic compounds are not classified as organometallic compounds.

Organometallic compounds are very important in environmental and toxicological chemistry. The formation of organometallic species in the environment, such as occurs with the methylation of mercury by anaerobic bacteria in sediments, is an important mode of mobilizing metals. Toxicologically, organometallic species often behave in an entirely different way from inorganic forms of metals and may be more toxic than the inorganic ions or compounds.

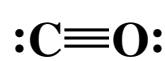
12.2 CLASSIFICATION OF ORGANOMETALLIC COMPOUNDS

The simplest way to classify organometallic compounds for the purpose of discussing their toxicology is the following:[1]

1. Those in which the organic group is an alkyl group, such as ethyl in tetraethyllead, $Pb(C_2H_5)_4$:

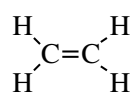


2. Those in which the organic group is carbon monoxide:

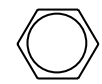


(In the preceding Lewis formula of CO, each dash represents a pair of bonding electrons, and each pair of dots represents an unshared pair of electrons.) Compounds with carbon monoxide bonded to metals, some of which are quite volatile and toxic, are called **carbonyls**.

3. Those in which the organic group is a π electron donor, such as ethylene or benzene:



Ethylene



Benzene

Combinations exist of the three general types of compounds outlined above, the most prominent of which are arene carbonyl species, in which a metal atom is bonded to both an aromatic entity, such as benzene, and several carbon monoxide molecules. A more detailed discussion of the types of compounds and bonding follows.

12.2.1 Ionically Bonded Organic Groups

Negatively charged hydrocarbon groups are called **carbanions**. These can be bonded to group 1A and 2A metal cations, such as Na^+ and Mg^{2+}, by predominantly ionic bonds. In some carbanions the negative charge is localized on a single carbon atom. For species in which conjugated double bonds and aromaticity are possible, the charge may be delocalized over several atoms, thereby increasing the carbanions' stability (see Figure 12.1).

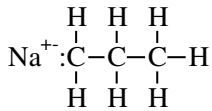
Ionic organic compounds involving carbanions react readily with oxygen. For example, ethylsodium, $C_2H_5^- Na^+$, self-ignites in air. Ionic organometallic compounds are extremely reactive in water, as shown by the following reaction:

$$C_2H_5^- Na^+ \xrightarrow{H_2O} \text{Organic products} + NaOH \qquad (12.2.1)$$

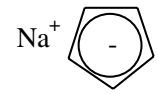
One of the products of such a reaction is a strong base, such as NaOH, which is very corrosive to exposed tissue.

12.2.2 Organic Groups Bonded with Classical Covalent Bonds

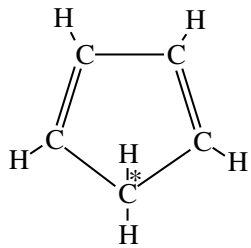
A major group of organometallic compounds has carbon–metal covalent single bonds in which both the C and metal (or metalloid) atoms contribute one electron each to be shared in the bond (in contrast to ionic bonds, in which electrons are transferred between atoms). The bonds produced by this sharing arrangement are sigma-covalent bonds, in which the electron density is concentrated between the two nuclei. Since in all cases the more electronegative atom in this bond is carbon



Negative charge localized on a single carbon atom in propylsodium



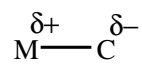
Negative charge delocalized in the 5-carbon ring of cyclopentadiene (see cyclopentadiene below)



Cyclopentadiene. Loss of H^+ from the carbon marked with an asterisk gives the negatively charged cyclopentadienide anion.

Figure 12.1 Carbanions showing localized and delocalized negative charges.

(see Section 12.1), the electrons in the bond tend to be more attracted to the more electronegative atom, and the covalent bond has a **polar** character, as denoted by the following:



When the electronegativity difference is extreme, such as when the metal atom is Na, K, or Ca, an ionic bond is formed. In cases of less extreme differences in electronegativity, the bond may be only partially ionic; i.e., it is intermediate between a covalent and ionic bond. Organometallic compounds with classical covalent bonds are formed with representative elements and with zinc, cadmium, and mercury, which have filled *d* orbitals. In some cases, these bonds are also formed with transition metals. Organometallic compounds with this kind of bonding comprise some of the most important and toxicologically significant organometallic compounds. Examples of such compounds are shown in Figure 12.2.

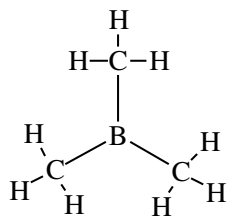
The two most common reactions of sigma-covalently bonded organometallic compounds are oxidation and hydrolysis (see Chapter 1). These compounds have very high heats of combustion because of the stabilities of their oxidation products, which consist of metal oxide, water, and carbon dioxide, as shown by the following reaction for the oxidation of diethyl zinc:

$$Zn(C_2H_5)_2 + 7O_2 \rightarrow ZnO(s) + 5H_2O(g) + 4CO_2(g) \qquad (12.2.2)$$

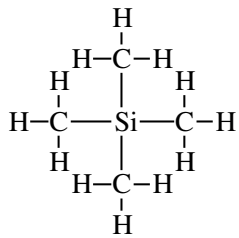
Industrial accidents in which the combustion of organometallic compounds generates respirable, toxic metal oxide fumes can certainly pose a hazard.

The organometallic compounds most likely to undergo hydrolysis are those with ionic bonds, those with relatively polar covalent bonds, and those with vacant atomic orbitals (see Chapter 1) on the metal atom, which can accept more electrons. These provide sites of attack for the water molecules. For example, liquid trimethylaluminum reacts almost explosively with water or water and air:

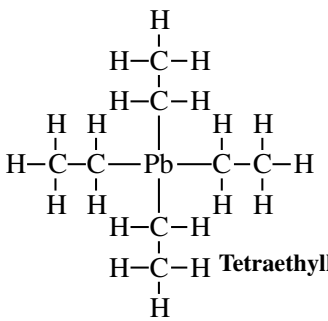
$$Al(CH_3)_3 \xrightarrow[\{O_2\}]{H_2O} Al(OH)_3 + \text{Organic products} \qquad (12.2.3)$$



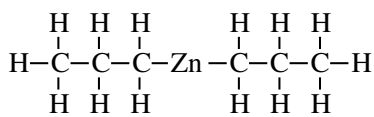
Trimethylboron



Tetramethylsilicon



Tetraethyllead



Di-*n*-propylzinc

Figure 12.2 Some organometallic compounds with sigma-covalent metal–carbon bonds.

In addition to the dangers posed by the vigor of the reaction, it is possible that noxious organic products are evolved. Accidental exposure to air in the presence of moisture can result in the generation of sufficient heat to cause complete combustion of trimethylaluminum to the oxides of aluminum and carbon and to water.

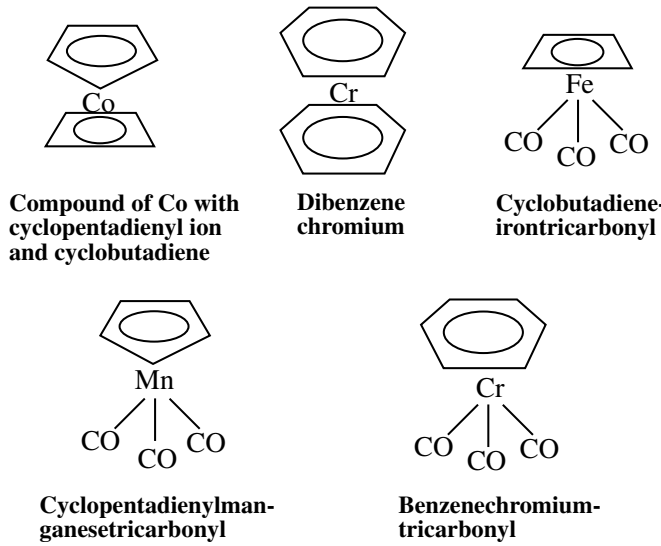
12.2.3 Organometallic Compounds with Dative Covalent Bonds

Dative covalent bonds, or coordinate covalent bonds, are those in which electrons are shared (as in all covalent bonds), but in which both electrons involved in each bond are contributed from the same atom. Such bonds occur in organometallic compounds of transition metals having vacant *d* orbitals. It is beyond the scope of this book to discuss such bonding in detail; the reader needing additional information should refer to works on organometallic compounds.[1,2] The most common organometallic compounds that have dative covalent bonds are **carbonyl compounds**, which are formed from a transition metal and carbon monoxide, where the metal is usually in the –1, 0, or +1 oxidation state. In these compounds the carbon atom on the carbon monoxide acts as an electron-pair donor:

$$\underset{\textbf{Dative bond}}{\mathrm{M} + :\mathrm{CO}: \rightarrow \mathrm{M}:\mathrm{CO}:} \qquad (12.2.4)$$

Most carbonyl compounds have several carbon monoxide molecules bonded to a metal.

Many transition metal carbonyl compounds are known. The one that is the most significant toxicologically, because of its widespread occurrence and extremely poisonous nature, is the nickel carbonyl compound, $Ni(CO)_4$. Perhaps the next most abundant is $Fe(CO)_5$. Other examples are



Compound of Co with cyclopentadienyl ion and cyclobutadiene

Dibenzene chromium

Cyclobutadiene-irontricarbonyl

Cyclopentadienylmanganesetricarbonyl

Benzenechromium-tricarbonyl

Figure 12.3 Compounds of metals with π-electron donor hydrocarbons and with carbon monoxide.

$V(CO)_6$ and $Cr(CO)_6$. In some cases, bonding favors compounds with two metal atoms per molecule, such as $(CO)_5Mn–Mn(CO)_5$ or $(CO)_4Co–Co(CO)_4$.

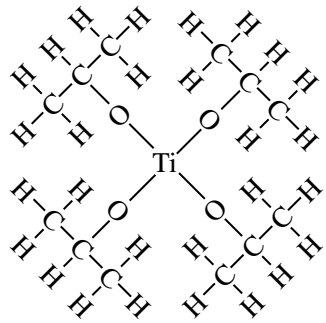
12.2.4 Organometallic Compounds Involving π-Electron Donors

Unsaturated hydrocarbons, such as ethylene, butadiene, cyclopentadiene, and benzene, contain π-electrons that occupy orbitals that are not in a direct line between the two atoms bonded together, but are above and below a plane through that line. These electrons can participate in bonds to metal atoms in organometallic compounds. Furthermore, the metal atoms in a number of organometallic compounds are bonded to both a π-electron donor organic species — most commonly the cyclopentadienyl anion with a –1 charge — and one or more CO molecules. A typical compound of this class is cyclopentadienylcobalt-dicarbonyl, $C_5H_5Co(CO)_2$. Examples of these compounds and of compounds consisting of metals bonded only to organic π-electron donors are shown in Figure 12.3.

12.3 MIXED ORGANOMETALLIC COMPOUNDS

So far in this chapter the discussion has centered on compounds in which all of the metal bonds are with carbon. A large number of compounds exist that have at least one bond between the metal and a C atom on an organic group, as well as other covalent or ionic bonds between the metal and atoms other than carbon. Because they have at least one metal–carbon bond, as well as properties, uses, and toxicological effects typical of organometallic compounds, it is useful to consider such compounds along with organometallic compounds. Examples are monomethylmercury chloride, CH_3HgCl, in which the organometallic CH_3Hg^+ ion is ionically bonded to the chloride anion. Another example is phenyldichloroarsine, $C_6H_5AsCl_2$, in which a phenyl group is covalently bonded to arsenic through an As–C bond and two Cl atoms are also covalently bonded to arsenic.

A number of compounds exist that consist of organic groups bonded to a metal atom through atoms other than carbon. Although they do not meet the strict definition thereof, such compounds can be classified as organometallics for the discussion of their toxicology and aspects of their chemistry. An example of such a compound is isopropyl titanate, $Ti(OC_3H_7)_4$,



Isopropyl titanate

also called titanium isopropylate. This compound is a colorless liquid melting at 14.8°C and boiling at 104°C, low values that reflect the organic nature of the molecule, which is obvious even in the two-dimensional structural representation of the formula above. The behavior of isopropyl titanate is more that of an organometallic compound than that of an inorganic compound, and by virtue of its titanium content, it is not properly classified as an organic compound. The term *organometal* is sometimes applied to such a compound. For toxicological considerations, it may be regarded as an organometallic compound.

Several compounds are discussed in this chapter that have some organometallic character, but which also have formulas, structures, and properties of inorganic or organic compounds. These compounds could be called mixed organometallics. However, so long as the differences are understood, compounds such as isopropyl titanate (see above) that do not meet all the criteria of organometallic compounds can be regarded as such for the discussion of their toxicities.

12.4 ORGANOMETALLIC COMPOUND TOXICITY

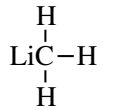
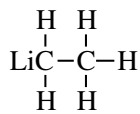
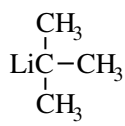
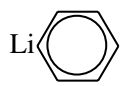
Some organometallic compounds have been known and used for decades, so that their toxicological properties are rather well known. Prominent among these are organoarsenicals used as drugs, organomercury fungicides, and tetramethyl- and tetraethyllead, used as antiknock additives for gasoline. Since about 1950, there has been very substantial growth in chemical research devoted to organometallic compounds, and large numbers and varieties of these compounds have been synthesized. Although the applications of organoarsenicals and organomercury compounds as human drugs and pesticides have been virtually eliminated because of their toxicities, environmental effects, and the development of safer substitutes, a wide variety of new organometallic compounds has come into use for various purposes, such as catalysis and chemical synthesis. The toxicological properties of these compounds are very important, and they should be treated with great caution until proven safe. Many are very reactive chemically, so they are hazardous to directly exposed tissue, even if not toxic systemically.

12.5 COMPOUNDS OF GROUP 1A METALS

12.5.1 Lithium Compounds

Table 12.1 shows some organometallic lithium compounds. It is seen from their formulas that these compounds are ionic. As discussed in Section 12.2, 1A metals have low electronegativities and form ionic compounds with hydrocarbon anions. Of these elements, lithium tends to form metal–carbon bonds with the most covalent character; therefore, lithium compounds are more stable (though generally quite reactive) than other organometallic compounds of group 1A metals, most

Table 12.1 Some Organometallic Compounds of Lithium

Name	Formula	Properties and Uses
Methyllithium		Initiator for solution polymerization of elastomers
Ethyllithium		Transparent crystals melting at 95°C, pyrophoric, [a] decomposes in water
Tert -butyllithium		Colorless crystalline solid subliming at 70-80°C, used as synthesis reagent
Phenyllithium		Colorless pyrophoric solid used in Grignard-type reactions to attach a phenyl group

[a] Pyrophoric means spontaneously flammable in air.

likely to exist as liquids or low-melting-point solids, and generally more soluble in organic solvents.[3] These compounds are moisture sensitive, both in the pure state and in solution, and can undergo spontaneous ignition when exposed to air.

The most widely used organolithium compound is *n*-butyllithium (see formulas of related compounds in Table 12.1), used as an initiator for the production of elastomers by solution polymerization, predominantly of styrene-butadiene.

Lithium forms a very unstable carbonyl, for which the toxicity is suspected of being high. The formula of this compound is LiCOCOLi, written in this manner to show that the two CO molecules form bridges between two Li atoms.

Unless otherwise known, the toxicities of lithium organometallic compounds should be regarded as those of lithium compounds and of organometallic compounds in general. The latter were discussed in Section 12.4. Lithium oxide and hydroxide are caustic bases, and they may be formed by the combustion of lithium organometallic compounds or by their reaction with water.

Lithium ion, Li^+, is a central nervous system toxicant that causes dizziness, prostration, anorexia, apathy, and nausea. It can also cause kidney damage and, in large doses, coma and death.

12.5.2 Compounds of Group 1A Metals Other Than Lithium

As discussed in Section 12.2, group 1A metals form ionic metal–carbon bonds. Organometallic compounds of group 1A metals other than lithium have metal–carbon bonds with less of a covalent character than the corresponding bonds in lithium compounds and tend to be especially reactive. Compounds of rubidium and cesium are rarely encountered outside the laboratory, so their toxicological significance is relatively minor. Therefore, aside from lithium compounds, the toxicology of sodium and potassium compounds is of most concern.

Both sodium and potassium salts are natural constituents of body tissues and fluids as Na^+ and K^+ ions, respectively, and are not themselves toxic at normal physiological levels. The oxides and hydroxides of both these metals are very caustic, corrosive substances that damage exposed tissue. Oxides are formed by the combustion of sodium and potassium organometallics, and hydroxides are produced by the reaction of the oxides with water or by direct reaction of the organometallics with water, as shown below for cyclopentadienylsodium:

$$C_5H_5^- Na^+ + H_2O \rightarrow C_5H_6 + NaOH \quad (12.5.1)$$

Both sodium and potassium form carbonyl compounds, NaCO and KCO, respectively. Both compounds are highly reactive solids prone to explode when exposed to water or air. Decomposition of the carbonyls gives off caustic oxides and hydroxides of Na and K, as well as toxic carbon monoxide.

Sodium and potassium form alkoxide compounds with the general formula $M^{+-}OR$, in which R is a hydrocarbon group. Typically, sodium reacts with methanol:

$$2CH_3OH + 2Na \rightarrow 2Na^{+-}OCH_3 + H_2 \quad (12.5.2)$$

to yield sodium methoxide and hydrogen gas. The alkoxide compounds are highly basic and caustic, reacting with water to form the corresponding hydroxides, as illustrated by the following reaction:

$$K^{+-}OCH_3 + H_2O \rightarrow KOH + CH_3OH \quad (12.5.3)$$

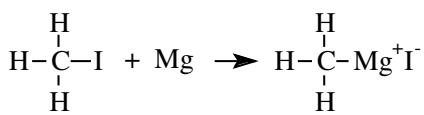
12.6 COMPOUNDS OF GROUP 2A METALS

The organometallic compound chemistry of the 2A metals is similar to that of the 1A metals, and ionically bonded compounds predominate. As is the case with lithium in group 1A, the first 2A element, beryllium, behaves atypically, with a greater covalent character in its metal–carbon bonds.

Beryllium organometallic compounds should be accorded the respect due all beryllium compounds because of beryllium's extreme toxicity (see Section 10.4). Dimethylberyllium, $Be(CH_3)_2$, is a white solid having needle-like crystals. When heated to decomposition, it gives off highly toxic beryllium oxide fumes. Diethylberyllium, $Be(C_2H_5)_2$, with a melting point of 12°C and a boiling point of 110°C, is a colorless liquid at room temperature and is especially dangerous because of its volatility.

12.6.1 Magnesium

The organometallic chemistry of magnesium has been of the utmost importance for many decades because of **Grignard reagents**, the first of which was made by Victor Grignard around 1900 by the reaction



(12.6.1)

Iodomethane **Methylmagnesium iodide**

Grignard reagents are particularly useful in organic chemical synthesis for the attachment of their organic component ($–CH_3$ in the preceding example) to another organic molecule. The development of Grignard reagents was such an advance in organic chemical synthesis that in 1912 Victor Grignard received the Nobel Prize for his work.

Grignard reagents can cause damage to skin or pulmonary tissue in the unlikely event that they are inhaled. These reagents react rapidly with both water and oxygen, releasing a great deal of heat in the process. Ethyl ether solutions of methylmagnesium bromide (CH_3MgBr) are particularly hazardous because of the spontaneous ignition of the reagent and the solvent ether in which it is contained when the mixture contacts water, such as water on a moist laboratory bench top.

The simplest dialkyl magnesium compounds are dimethylmagnesium, $Mg(CH_3)_2$, and diethylmagnesium, $Mg(C_2H_5)_2$. Both are pyrophoric compounds that are violently reactive to water and steam and that self-ignite in air, the latter even in carbon dioxide (like the elemental form, magnesium in an organometallic compound removes O from CO_2 to form MgO and release elemental carbon). Diethylmagnesium has a melting point of 0°C and is a liquid at room temperature. Diphenylmagnesium, $Mg(C_6H_5)_2$, is a feathery solid, somewhat less hazardous than the dimethyl and diethyl compounds. It is violently reactive with water and is spontaneously flammable in humid air, but not dry air.

Unlike the caustic oxides and hydroxides of group 1A metals, magnesium hydroxide, $Mg(OH)_2$, formed by the reaction of air and water with magnesium organometallic compounds, is a relatively benign substance that is used as a food additive and ingredient of milk of magnesia.

12.6.2 Calcium, Strontium, and Barium

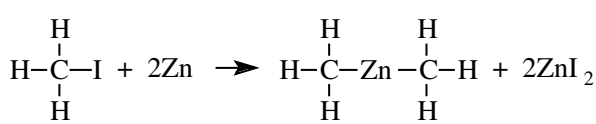
It is much more difficult to make organometallic compounds of Ca, Sr, and Ba than it is to make those of the first two group 2A metals. Whereas organometallic compounds of beryllium and magnesium have metal–carbon bonds with a significant degree of covalent character, the Ca, Sr, and Ba organometallic compounds are much more ionic. These compounds are extremely reactive to water, water vapor, and atmospheric oxygen. There are relatively few organometallic compounds of calcium, strontium, and barium; their industrial uses are few, so their toxicology is of limited concern. Grignard reagents in which the metal is calcium rather than magnesium (general formula RCa^+X^-) have been prepared, but are not as useful for synthesis as the corresponding magnesium compounds.

12.7 COMPOUNDS OF GROUP 2B METALS

It is convenient to consider the organometallic compound chemistry of the group 2B metals immediately following that of the 2A metals because both have two 2*s* electrons and no partially filled *d* orbitals. The group 2B metals — zinc, cadmium, and mercury — form an abundance of organometallic compounds, many of which have significant uses. Furthermore, cadmium and mercury (both discussed in Chapter 10) are notably toxic elements, so the toxicological aspects of their organometallic compounds are of particular concern. Therefore, the organometallic compound chemistry of each of the 2B metals will be discussed separately.

12.7.1 Zinc

Organozinc compounds are widely used as reagents.[4] A typical synthesis of a zinc organometallic compound is given by the reaction below, in which the Grignard-type compound CH_3ZnI is an intermediate:



(12.7.1)

Dimethylzinc has a rather low melting temperature of –40°C, and it boils at 46°C. At room temperature, it is a mobile, volatile liquid that undergoes self-ignition in air and reacts violently with water. The same properties are exhibited by diethylzinc, $(C_2H_5)_2Zn$, which melts at –28°C and boils at 118°C. Both dimethylzinc and diethylzinc are used in organometallic chemical vapor

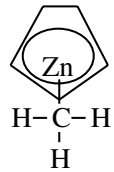


Figure 12.4 Methylcyclopentadienylzinc. The monomer shown exists in the vapor phase. In the solid phase, a polymeric form exists.

deposition of zinc and zinc oxide in fabrication of semiconductors and light-emitting diodes. Diphenylzinc, $(C_6H_5)Zn$, is considerably less reactive than its methyl and ethyl analogs; it is a white crystalline solid melting at 107°C. Zinc organometallics are similar in many respects to their analogous magnesium compounds (see Section 12.6), but do not react with carbon dioxide, as do some of the more reactive magnesium compounds. An example of an organozinc compound involving a π-bonded group is that of methylcyclopentadienylzinc, shown in Figure 12.4.

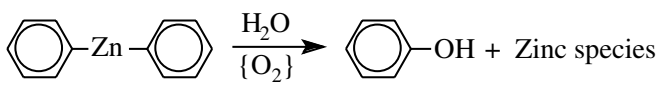
Zinc forms a variety of Grignard-type compounds, such as ethylzinc chloride, ethylzinc bromide, butylzinc chloride, and butylzinc iodide.

Zinc organometallic compounds should be accorded the same caution in respect to toxicology as that given to organometallic compounds in general. The combustion of highly flammable organozinc compounds such as dimethyl and diethyl compounds produces very finely divided particles of zinc oxide fumes, as illustrated by the reaction

$$2(CH_3)_2Zn + 8O_2 \rightarrow 2ZnO + 4CO_2 + 6H_2O \qquad (12.7.2)$$

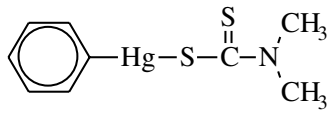
Although zinc oxide is used as a healing agent and food additive, inhalation of zinc oxide fume particles causes zinc **metal fume fever**, characterized by elevated temperature and chills. The toxic effect of zinc fume has been attributed to its flocculation in lung airways, which prevents maximum penetration of air to the alveoli and perhaps activates endogenous pyrogen in blood leukocytes. An interesting aspect of this discomfiting but less-than-deadly affliction is the immunity that exposed individuals develop to it, but which is lost after only a day or two of nonexposure. Thus workers exposed to zinc fume usually suffer most from the metal fume fever at the beginning of the work week, and less with consecutive days of exposure as their systems adapt to the metal fume.

Diphenylzinc illustrates the toxicity hazard that may obtain from the organic part of an organometallic compound upon decomposition. Under some conditions, this compound can react to release toxic phenol (see Chapter 14):

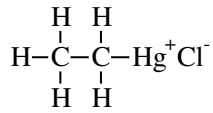


(12.7.3)

A number of zinc compounds with organic constituents (e.g., zinc salts of organic acids) have therapeutic uses. These include antidandruff zinc pyridinethione, antifungal zinc undecylenate used to treat athlete's foot, zinc stearate and palmitate (zinc soap), and antibacterial zinc bacitracin. Zinc naphthenate is used as a low-toxicity wood preservative, and zinc phenolsulfonate has insecticidal properties and was once used as an intestinal antiseptic. The inhalation of zinc soaps by infants has been known to cause acute fatal pneumonitis characterized by lung lesions similar to, but more serious than, those caused by talc. Zinc pyridine thione (zinc 2-pyridinethiol-1-oxide) has been shown to cause retinal detachment and blindness in dogs; this is an apparently species-specific effect because laboratory tests at the same and even much higher dosages in monkeys and rodents do not show the same effect.



Phenylmercurydimethyldithiocarbamate (slimicide for wood pulp and mold retardant for paper)

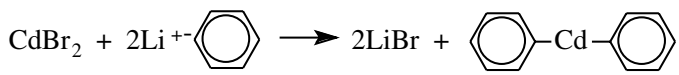


Ethylmercury chloride (seed fungicide)

Figure 12.5 Two organomercury compounds that have been used for fungicidal purposes.

12.7.2 Cadmium

In the absence of water, cadmium halides, CdX_2, react with organolithium compounds, as shown by the following example:



(12.7.4)

Dimethylcadmium, $(CH_3)_2Cd$, is an oily liquid at room temperature and has a very unpleasant odor. The compound melts at –4.5°C and boils at 106°C. It decomposes in contact with water. Diethylcadmium is likewise an oil; it melts at –21°C, boils at 64°C, and reacts explosively with oxygen in air. Dipropylcadmium, $(C_3H_7)_2Cd$, is an oil that melts at –83°C, boils at 84°C, and reacts with water. The dialkyl cadmium compounds are distillable, but decompose above about 150°C, evolving toxic cadmium fume.

The toxicology of cadmium organometallic compounds is of particular concern because of the high toxicity of cadmium. The organometallic compounds of cadmium form vapors that can be inhaled and that can cross membranes because of their lipid solubility. The reaction of cadmium organometallic compounds with water can release highly toxic fumes of cadmium and CdO. Inhalation of these fumes can cause chronic cadmium poisoning and death. The toxicological aspects of cadmium are discussed in Section 10.4.

Evidence has been detected of the biomethylation of cadmium. Studies with differential pulse anodic stripping voltammetry have shown detectable amounts of monomethylcadmium ion, H_3CCd^+, in surface water of the South Atlantic.[5] Examination of water from some Arctic meltwater ponds showed that up to half of the cadmium present in the water was in the monomethylcadmium ion form.

12.7.3 Mercury

In 1853, E. Frankland made the first synthetic organomercury compound by the photochemical reaction below:

$$2Hg + 2CH_3I + h\nu(\text{sunlight}) \rightarrow (CH_3)_2Hg + HgI_2 \qquad (12.7.5)$$

Numerous synthetic routes are available for the preparation of a variety of mercury organometallic compounds.

In the late 1800s and early 1900s, numerous organomercury pharmaceutical compounds were synthesized and used. These have since been replaced by more effective and safe nonmercury substitutes. Organomercury compounds have been widely used as pesticidal fungicides (see Figure 12.5), but these applications have been phased out because of the adverse effects of mercury in the environment. Mercury levels in organs of wildlife, such as white-tailed eagles in Germany and Austria, have decreased significantly with the phaseout of organomercury seed-treating chemicals.[6]

The most notorious mercury compounds in the environment are monomethyl mercury (CH_3Hg^+) salts and dimethylmercury ($(CH_3)_2Hg$). The latter compound is both soluble and volatile, and the salts of the monomethylmercury cation are soluble. These compounds are produced from inorganic mercury in sediments by anaerobic bacteria through the action of methylcobalamin, a vitamin B_{12} analog and intermediate in the synthesis of methane:

$$HgCl_2(s) \xrightarrow{\textbf{Methylcobalamin}} CH_3Hg^+(aq) + 2Cl^- \qquad (12.7.6)$$

The preceding reaction is favored in somewhat acidic water in which anaerobic decay, which often produces CH_4, is occurring. If the water is neutral or slightly alkaline, dimethylmercury formation is favored; this volatile compound may escape to the atmosphere. Discovered around l970, the biosynthesis of the methylmercury species in sediments was an unpleasant surprise, in that it provides a means for otherwise insoluble inorganic mercury compounds to get into natural waters. Furthermore, these species are lipid soluble, so that they undergo bioaccumulation and biomagnification in aquatic organisms. Fish tissue often contains more than 1000 times the concentration of mercury as does the surrounding water.

The toxicity of mercury is discussed in Section 10.4. Some special considerations apply to organomercury compounds, the foremost of which is their lipid solubility and resulting high degree of absorption and facile distribution through biological systems. The lipid solubilities and high vapor pressures of the methylmercuries favor their absorption by the pulmonary route. These compounds also can be absorbed through the skin, and their uptake approaches 100% (compared to less than 10% for inorganic mercury compounds) in the gastrointestinal tract.

With respect to distribution in the body, the methylmercury species behave more like mercury metal, Hg(0), than inorganic mercury(II), Hg^{2+}. Like elemental mercury, methylmercury compounds traverse the blood–brain barrier and affect the central nervous system. However, the psychopathological effects of methylmercury compounds (laughing, crying, impaired intellectual abilities) are different from those of elemental mercury (irritability, shyness).

Both dimethylmercury and salts of monomethylmercury, such as H_3CHgCl, are extraordinarily dangerous. Most of what is known about their toxicities has been learned from exposure to monomethylmercury chloride on treated seed grains consumed by people and by exposure of people in Japan to seafood contaminated with methylmercury compounds. (Early investigators of volatile dimethylmercury, a liquid that readily penetrates skin, died from its toxic effects within months of making the compound.) Fetuses of pregnant women who consumed seafood contaminated with methylmercury have suffered grievous damage. The major effects of exposure of adults to methylmercury compounds are neurotoxic effects on the brain. Victims exhibit a variety of devastating symptoms, the earliest of which are numbnesss and tingling of the mouth, lips, fingers, and toes. Swallowing and word pronunciation become difficult, and the victim staggers while attempting to walk. Symptoms of weakness and extreme fatigue are accompanied by loss of hearing, vision, and ability to concentrate. Ultimately, spasticity, coma, and death occur.

The extreme toxicity of dimethylmercury was demonstrated tragically by the 1997 death of Professor Karen Wetterhahn of Dartmouth College. Dr. Wetterhahn was exposed to dimethylmercury from an accidental spill of about two drops of this liquid onto the latex rubber gloves she was wearing for protection. The lipid-soluble compound permeates latex and skin, and Dr. Wetterhahn died less than a year later from neurotoxic effects to the brain.

12.8 ORGANOTIN AND ORGANOGERMANIUM COMPOUNDS

Global production of organotin compounds has reached levels around 40,000 metric tons per year, consuming about 7 to 8% of the tin used each year. Of all the metals, tin has the greatest

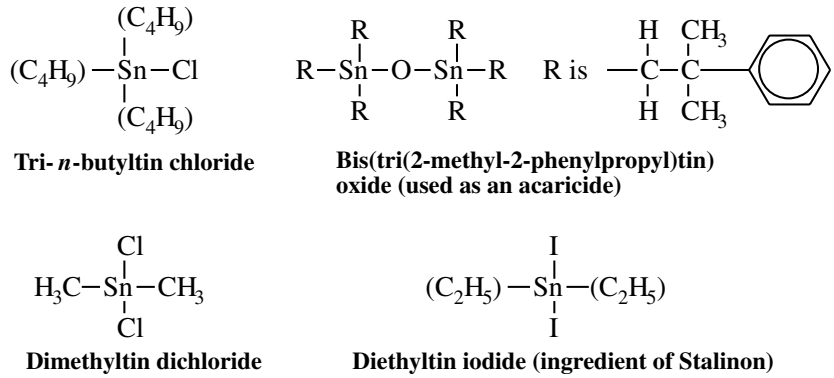


Figure 12.6 Examples of organotin compounds.

number of organometallic compounds in commercial use.[7] Major industrial uses include applications of tin compounds in fungicides, acaricides, disinfectants, antifouling paints, stabilizers to lessen the effects of heat and light in polyvinyl chloride (PVC) plastics, catalysts, and precursors for the formation of films of SnO_2 on glass. Tributyl tin (TBT) chloride and related TBT compounds have bactericidal, fungicidal, and insecticidal properties and are of particular environmental significance because of their once widespread use as industrial biocides. In addition to tributyl tin chloride, other tributyl tin compounds used as biocides include hydroxide, naphthenate, bis(tributyltin) oxide, and tris(tributylstannyl) phosphate. A major use of TBT has been in boat and ship hull coatings to prevent the growth of fouling organisms. Other applications have included preservation of wood, leather, paper, and textiles. Because of their antifungal activity, TBT compounds have been used as slimicides in cooling tower water.

In addition to synthetic organotin compounds, methylated tin species can be produced biologically in the environment. Figure 12.6 gives some examples of the many known organotin compounds.

12.8.1 Toxicology of Organotin Compounds

Many organotin compounds have the general formula R_nSnX_{4-n}, where R is a hydrocarbon group and X is an inorganic entity, such as a chlorine atom, or an organic group bonded to tin through a noncarbon atom (for example, acetate bonded to Sn through an O atom). As a general rule, in a series of these compounds, toxicity is at a maximum value for n = 3. Furthermore, the toxicity is generally more dependent on the nature of the R groups than on X.

Organotin compounds are readily absorbed through the skin, and skin rashes may result. Organotin compounds, especially those of the R_3SnX type, bind to proteins, probably through the sulfur on cysteine and histidine residues. Interference with mitochondrial function by several mechanisms appears to be the mode of biochemical action leading to toxic responses.

Much of what is known of organotin toxicity to humans was learned in the 1950s from exposure of humans in France to Stalinon, used to treat skin disorders, osteomyelitis, and anthrax. The active ingredient of this formulation was diethyltin iodide, although the toxic agent may have been impurity triethyltin iodide. Neural tissue was most susceptible to damage. Victims exhibited swelling of brain tissue, edema of white matter, and cerebral hemorrhages. Tragically, approximately 100 people died from taking Stalinon in France.

Although human exposure to organotin compounds is not believed to cause many cases of poisoning, the ecotoxicological effects of organotins may be quite significant. This is because of exposure to sediment-dwelling organisms to organotins leached from ship and boat hulls treated with biocidal organotins. Increasingly stringent regulation of this application of organotin compounds should continue to reduce the ecotoxicological problems resulting from these compounds.

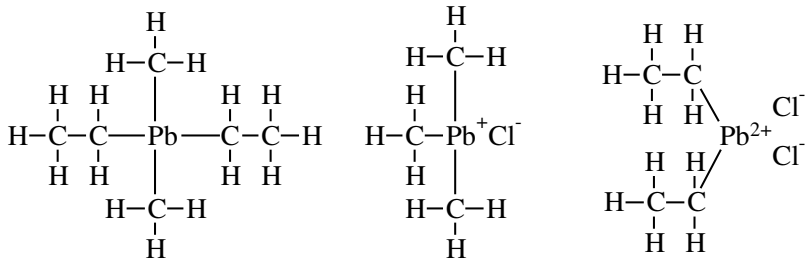
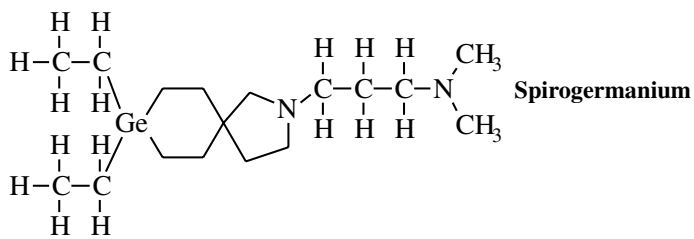


Figure 12.7 Alkyllead compounds and salts.

12.8.2 Organogermanium Compounds

Organogermanium compounds, including tetramethyl- and tetraethylgermanium, are used in the semiconductor industry to prepare deposits of germanium. Spirogermanium,



has been tested for antitumor activity. Not much is known about the toxicities of organogermanium compounds, although spirogermanium was of some interest for chemotherapy because it is reputed to be only moderately toxic.

12.9 ORGANOLEAD COMPOUNDS

The toxicities and environmental effects of organolead compounds are particularly noteworthy because of the former widespread use and distribution of tetraethyllead as a gasoline additive (see structure in Figure 12.2).[8] Although more than 1000 organolead compounds have been synthesized, those of commercial and toxicological importance are largely limited to the alkyl (methyl and ethyl) compounds and their salts, examples of which are shown in Figure 12.7.

In addition to manufactured organolead compounds, the possibility exists of biological methylation of lead, such as occurs with mercury (see Section 12.7). However, there is a great deal of uncertainty regarding biological methylation of lead in the environment.

12.9.1 Toxicology of Organolead Compounds

Because of the large amounts of tetraethyllead used as a gasoline additive, the toxicology of this compound has been investigated much more extensively than that of other organolead compounds and is discussed briefly here. Tetraethyllead is a colorless, oily liquid with a strong affinity for lipids and is considered highly toxic by inhalation, ingestion, and absorption through the skin. Most commonly, exposure is through inhalation, and around 70% of inhaled tetraethyllead is

absorbed. Numerous cases of poisoning have been reported in individuals sniffing leaded gasoline for "recreational" purposes.

In common with other organollead compounds, tetraethyllead has a strong affinity for lipid and nerve tissue and is readily transported to the brain. Symptoms of tetraethyllead poisoning reflect effects on the central nervous system. Among these symptoms are fatigue, weakness, restlessness, ataxia, psychosis, and convulsions. Victims may also experience nausea, vomiting, and diarhhea. In cases of fatal tetraethyllead poisoning, victims may experience convulsions and coma; death has occurred as soon as one or two days after exposure. Almost one third of victims acutely exposed to tetraethyllead die, although fatalities from chronic exposure have been comparatively rare, considering the widespread use of tetraethyllead. Recovery from poisoning by this compound tends to be slow.

The toxicological action of tetraethyllead is different from that of inorganic lead. As one manifestation of this difference, chelation therapy is ineffective for the treatment of tetraethyllead poisoning. The toxic action of tetraethyllead appears to involve its metabolic conversion to the triethyl form.

12.10 ORGANOARSENIC COMPOUNDS

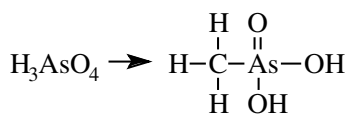
There are two major sources of organoarsenic compounds: those produced for commercial applications and those produced from the biomethylation of inorganic arsenic by microorganisms. Many different organoarsenic compounds have been identified.

12.10.1 Organoarsenic Compounds from Biological Processes

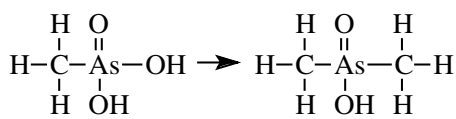
The reactions that follow illustrate the production of organoarsenic compounds by bacteria. In a reducing environment, arsenic(V) is reduced to arsenic(III):

$$H_3AsO_4 + 2H^+ + 2e^- \rightarrow H_3AsO_3 + H_2O \tag{12.10.1}$$

Through the action of methylcobalamin in bacteria, arsenic(III) is methylated to methyl, and then to dimethylarsinic acid:

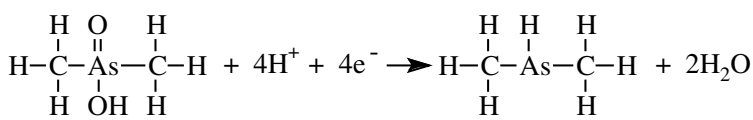


(12.10.2)



(12.10.3)

Dimethylarsinic acid can be reduced to volatile dimethylarsine:



(12.10.4)

Methylarsinic acid and dimethylarsinic acid are the two organoarsenic compounds that are most likely to be encountered in the environment.

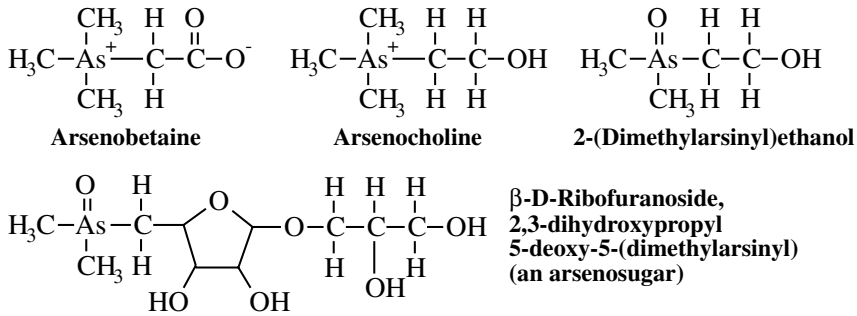


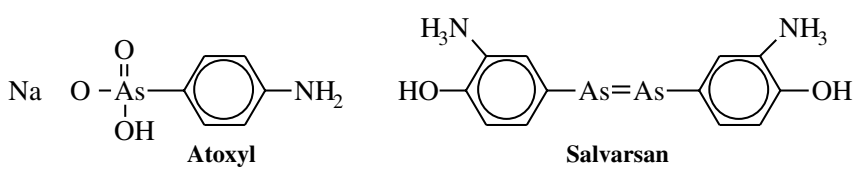
Figure 12.8 Examples of organoarsenic compounds found in seaweed and in sheep feeding on the seaweed.

Biomethylated arsenic was responsible for numerous cases of arsenic poisoning in Europe during the 1800s. Under humid conditions, arsenic in plaster and wallpaper pigments was converted to biomethylated forms, as manifested by the strong garlic odor of the products, and people sleeping and working in the rooms became ill from inhaling the volatile organoarsenic compounds.

Foods from marine sources may have high levels of arsenic. An interesting study of arsenic in sheep that live off seaweed detected 15 different organoarsenic compounds in the seaweed and in the blood, urine, liver, kidney, muscle, and wool of the sheep.[9] The rare breed of North Ronaldsay sheep studied live on the beach of Orkney Island off Northern Scotland, eating up to 3 kg per day of seaweed washed ashore. The seaweed consumed is predominantly brown algae containing 20 to 100 mg of arsenic per milligram dry mass, giving each adult sheep an intake of approximately 50 kg/day of arsenic. The arsenic in the seaweed is present predominantly as four kinds of dimethylarsinoylribosides known as arsenosugars. In addition to the arsenosugars, the organoarsenic species detected in either the seaweed or samples from the sheep include dimethylarsinic acid, monomethyl arsonic acid, trimethylarsine oxide, tetramethylarsonium ion, arsenobetaine, arsenocholine, and dimethylarsinyl ethanol. Examples of these compounds are shown in Figure 12.8. Around 95% of the arsenic excreted from the sheep was in the form of dimethylarsinic acid, shown in reaction 12.10.3. The blood, urine, and tissue arsenic concentrations in these sheep were approximately 100 times those of grass-fed sheep that did not eat the arsenic-laden seaweed. However, the arsenic levels in the meat from the sheep did not exceed U.K. guidelines of a maximum of 1 mg/kg fresh weight. The fact that sheep have been kept on Orkney Island beach and feeding on arsenic-laden seaweed for several centuries suggests that arsenic tolerance has developed in this particular breed of sheep.

12.10.2 Synthetic Organoarsenic Compounds

Although now essentially obsolete for the treatment of human diseases because of their toxicities, organoarsenic compounds were the first synthetic organic pharmaceutical agents and were widely used in the early 1900s. The first pharmaceutical application was that of atoxyl (the sodium salt of 4-aminophenylarsinic acid), which was used to treat sleeping sickness. The synthesis of Salvarsan by Dr. Paul Ehrlich in 1907 was a development that may be considered the beginning of modern **chemotherapy** (chemical treatment of disease). Salvarsan was widely used for the treatment of syphilis. Toxic effects of Salvarsan included jaundice and encephalitis (brain inflammation).



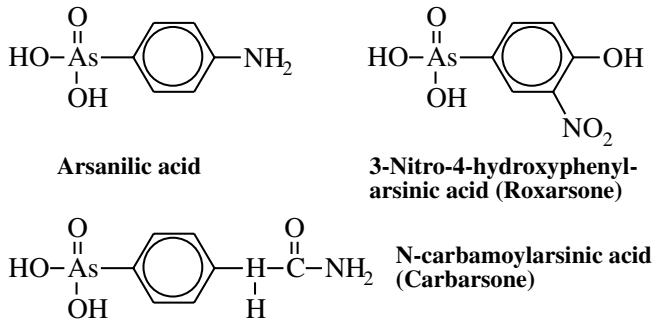
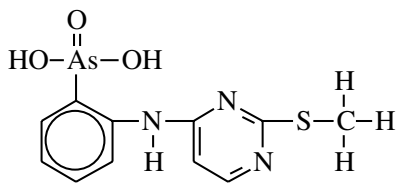


Figure 12.9 Major organoarsenic animal feed additives. Arsanilic acid and Roxarsone are used to control swine dysentery and increase the rate of gain relative to the amount of feed in swine and chickens. Carbarsone and nitarsone (4-nitrophenylarsanilic acid) act as antihistomonads in chickens.

Some organoarsenic compounds that are cytotoxic (toxic to tissue) have been found to have antitumor activity. One of these, which is active against breast cancer and leukemic cells, is 2-methylthio-4-(2'-phenylarsenic acid)-aminopyrimidine:



2-Methylthio-4-(2'-phenylarsenic acid)-aminopyrimidine

Organoarsenic compounds are used as animal feed additives. The major organoarsenic feed additives and their uses are summarized in Figure 12.9.

12.10.3 Toxicities of Organoarsenic Compounds

The toxicities of organoarsenic compounds vary over a wide range. In general, the toxicities are less for those compounds that are not metabolized in the body and that are excreted in an unchanged form. Examples of such compounds are the animal feed additives shown in Figure 12.9. Metabolic breakdown of organoarsenic compounds to inorganic forms is correlated with high toxicity. This is especially true when the product is inorganic arsenic(III), which, for the most part, is more toxic than arsenic(V). The toxicity of arsenic(III) is related to its strong affinity for sulfhydryl (–SH) groups. Detrimental effects are especially likely to occur when sulfhydryl groups are adjacent to each other on the active sites of enzymes, enabling chelation of the arsenic and inhibition of the enzyme.

To a certain extent, toxic effects of dimethylarsinic acid (cacodylic acid) have been observed because of its applications as an herbicide and the former uses of its sodium salt for the treatment of human skin disease and leukemia. It is most toxic via ingestion because the acidic medium in the stomach converts the compound to inorganic arsenic(III). A portion of inorganic arsenic in the body is converted to dimethylarsinic acid, which is excreted in urine, sweat, and exhaled air, accompanied by a strong garlic odor. Roxarsone has a relatively high acute toxicity to rats and dogs. Among the effects observed in these animals are internal hemorrhage, kidney congestion, and gastroenteritis. Rats fed fatal doses of about 400 ppm in the diet exhibited progressive weakness prior to death.

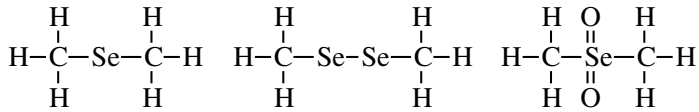


Figure 12.10 Example organoselenium compounds.

12.11 ORGANOSELENIUM AND ORGANOTELLURIUM COMPOUNDS

Organo compounds of the two group 6A elements, selenium and tellurium, are of considerable environmental and toxicological importance. Organoselenium and organotellurium compounds are produced both synthetically and by microorganisms. The selenium compounds are the more significant because of the greater abundance of this element.

12.11.1 Organoselenium Compounds

The structures of three common organoselenium compounds produced by organisms are given in Figure 12.10. Some organisms convert inorganic selenium to dimethylselenide. Several genera of fungi are especially adept at this biomethylation process, and their activities are readily detected from the very strong ultragarlic odor of the product. The bioconversion of inorganic selenium(II) and selenium(VI) to dimethylselenide and dimethyldiselenide, respectively, occurs in animals such as rats, and the volatile compounds are evolved with exhaled air. Another organoselenium compound produced by bacteria is dimethylselenone. Some synthetic organoselenium compounds have selenium as part of a ring, such as is the case with the cyclic ether 1,4-diselenane.

Inorganic selenium compounds are rather toxic, and probably attach to protein sulfhydryl groups, much like inorganic arsenic. In general, organoselenium compounds are regarded as less toxic than inorganic selenium compounds.

12.11.2 Organotellurium Compounds

Inorganic tellurium is used in some specialized alloys, to color glass, and as a pigment in some porcelain products. The breath of workers exposed to inorganic tellurium has a garlic odor, perhaps indicative of bioconversion to organotellurium species. Dimethyltelluride can be produced by fungi from inorganic tellurium compounds. Tellurium is a rather rare element in the geosphere and in water, so that biomethylation of this element is unlikely to be a major environmental problem. In general, the toxicities of tellurium compounds are less than those of their selenium analogs.

REFERENCES

1. Elschenbroich, C. and Salzer, A., *Organometallics: A Concise Introduction*, 2nd ed., Vch Verlagsgesellschaft Mbh, Berlin, 1992.
2. Crabtree, R.H., *The Organometallic Chemistry of the Transition Metals*, 3rd ed., John Wiley & Sons, New York, 2000.
3. Bach, R. et al., Lithium and lithium compounds, in *Kirk–Othmer Concise Encyclopedia of Chemical Technology*, Wiley Interscience, New York, 1985, pp. 706–707.
4. Knochel, P. and Jones, P., Eds., *Organozinc Reagents: A Practical Approach*, Oxford University Press, Oxford, 1999.
5. Pongratz, R. and Heumann, K., Determination of monomethyl cadmium in the environment by differential pulse anodic stripping voltammetry, *Anal. Chem.*, 68, 1262–1266, 1996.

6. Kenntner, N., Tataruch, F., and Krone, O., Heavy metals in soft tissue of white-tailed eagles found dead or moribund in Germany and Austria from 1993 to 2000, *Environ. Toxicol. Chem.*, 20, 1831–1837, 2001.
7. Hoch, M., Organotin compounds in the environment: an overview, *Appl. Geochem.*, 16, 719–743, 2001.
8. Hernberg, S., Lead poisoning in a historical perspective, *Am. J. Industrial Med.*, 38, 244–254, 2000.
9. Feldmann, J. et al., An appetite for arsenic: the seaweed-eating sheep from Orkney, *Spec. Publ. R. Soc. Chem.*, 267, 380–386, 2001.

SUPPLEMENTARY REFERENCES

Bochmann, M., *Organometallics*, Oxford University Press, New York, 1994.
Craig, P.J., Ed., *Organometallic Compounds in the Environment*, John Wiley & Sons, New York, 1986.
Crompton, T.R., *Occurrence and Analysis of Organometallic Compounds in the Environment*, John Wiley & Sons, New York, 1998.
Kirchner, K. and Weissensteiner, W., *Organometallic Chemistry and Catalysis*, Springer, New York, 2001.
Spessard, G.O. and Miessler, G.L., *Organometallic Chemistry*, Prentice Hall, Upper Saddle River, 1997.
Thayer, J.S., *Environmental Chemistry of the Heavy Elements: Hydrido and Organo Compounds*, VCH, New York, 1995.

QUESTIONS AND PROBLEMS

1. How is carbon involved in defining what an organometallic compound is? How is electronegativity involved in this definition? How does an organometalloid differ from an organometallic?
2. What are the three major kinds of organic groups, or ligands, bonded to a metal in an organometallic compound? How might the bonding of an alkyl ligand to an element with a very low electronegativity, such as potassium, differ from the bonding to an element with a higher electronegativity, such as arsenic?
3. What is a carbanion? How are carbanions involved in organometallic compounds? How can neutral cyclopentadiene form a carbanion?
4. Match the following pertaining to bonding in organometallic compounds:

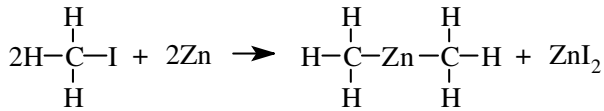
(a) Sigma-covalent	1. Mixed organometallic
(b) Dative covalent	2. Formed by benzene, cyclopentadiene
(c) Bonds with π-electrons	3. Shared electrons all contributed by one atom
(d) CH_3HgCl	4. Electron density is concentrated between the two nuclei

5. What would be the expected reactions of $C_2H_5^- Na^+$ with water? How might this species react with oxygen in air? What toxic effects might result from these kinds of reactions?
6. Discuss the historical aspects of organometallic compound toxicity, including organoarsenicals used as pharmaceutical agents, gasoline antiknock additives, and compounds used in applications such as catalysis and chemical synthesis.
7. Which organometallic compounds of group 1A are more stable than other organometallic compounds of this group, most likely to exist as liquids or low-melting-point solids, and generally more soluble in organic solvents?
8. In general, how should the toxicities of lithium organometallic compounds be regarded? Do they have any unique toxicity characteristics?
9. What are alkoxide compounds? In what sense are they organometallic compounds? In what respects are they not organometallic compounds? What does the reaction

$$K^{+-}OCH_3 + H_2O \rightarrow KOH + CH_3OH$$

show about alkoxides?
10. What are Grignard reagents? In what sense are they mixed organometals?

11. Diethylmagnesium, $Mg(C_2H_5)_2$, is described as a pyrophoric compound that is violently reactive to water and steam and that self-ignites in air, burning even in a carbon dioxide atmosphere. Describe the significance of this description in terms of reactivity, susceptibility to hydrolysis or oxidation, and potential toxic effects.
12. Describe what is shown by the following reaction:



13. Describe a specific toxic reaction that may result from the following combustion reaction:

$$2(CH_3)_2Zn + 8O_2 \rightarrow 2ZnO + 4CO_2 + 6H_2O$$

14. Why is the toxicology of cadmium organometallic compounds of particular concern?
15. Describe one chemical and one biochemical means of synthesis of $(CH_3)_2Hg$. In what sense was the discovery of biosynthesis of methylmercury species an unpleasant surprise in environmental chemistry?
16. List some special considerations that apply to organomercury compounds. How do their properties and pathways in the body compare to Hg(0) and Hg^{2+}?
17. Describe the biocidal properties and uses of tributyl tin chloride and related tributyl tin compounds.
18. What are some of the biocidal uses of tributyl tin compounds?
19. In what sense are the toxicities and environmental effects of organolead compounds particularly noteworthy?
20. What is some of the evidence that the toxicological action of tetraethyllead is different from that of inorganic lead? What are some of the symptoms of tetraethyllead poisoning?
21. What are the two major sources of organoarsenic compounds? Give some examples of organoarsenic compounds produced by these two routes.
22. What may be said about the range of toxicities of organoarsenic compounds? How do these toxicities vary with organoarsenic compounds that are readily metabolized in the body, compared to those that are excreted in an unchanged form?
23. Why are organoselenium compounds of more concern than organotellurium compounds despite the close chemical similarity of selenium and tellurium?

CHAPTER 13

Toxic Organic Compounds and Hydrocarbons

13.1 INTRODUCTION

The fundamentals of organic chemistry are reviewed in Chapter 1. The present chapter is the first of seven that discuss the toxicological chemistry of organic compounds that are largely of synthetic origin. Since the vast majority of the several million known chemical compounds are organic — most of them toxic to a greater or lesser degree — the toxicological chemistry of organic compounds covers an enormous area. Specifically, this chapter discusses hydrocarbons, which are organic compounds composed only of carbon and hydrogen and are in a sense the simplest of the organic compounds. Hydrocarbons occur naturally in petroleum, natural gas, and tar sands, and they can be produced by pyrolysis of coal and oil shale or by chemical synthesis from H_2 and CO.

13.2 CLASSIFICATION OF HYDROCARBONS

For purposes of discussion of hydrocarbon toxicities in this chapter, hydrocarbons will be grouped into the five categories: (1) **alkanes**, (2) **unsaturated nonaromatic** hydrocarbons, (3) **aromatic** hydrocarbons (understood to have only one or two linked aromatic rings in their structures), (4) **polycyclic** aromatic hydrocarbons with multiple rings, and (5) **mixed** hydrocarbons containing combinations of two or more of the preceding types. These classifications are summarized in Figure 13.1.

13.2.1 Alkanes

Alkanes, also called **paraffins** or **aliphatic hydrocarbons**, are hydrocarbons in which the C atoms are joined by single covalent bonds (sigma bonds) consisting of two shared electrons (see Section 1.3). As shown by the examples in Figure 13.1 and Section 1.7, alkanes may exist as straight chains or branched chains. They may also exist as cyclic structures, for example, as in cyclohexane (C_6H_{12}). Each cyclohexane molecule consists of six carbon atoms (each with two H atoms attached) in a ring. The general molecular formula for straight- and branched-chain alkanes is C_nH_{2n+2}, and that of a cyclic alkane is C_nH_{2n}. The names of alkanes having from one to ten carbon atoms per molecule are respectively (1) methane, (2) ethane, (3) propane, (4) butane, (5) pentane, (6) hexane, (7) heptane, (8) octane, (9) nonane, and (10) decane. These names may be prefixed by *n*- to denote a straight-chain alkane. The same base names are used to designate substituent groups on molecules; for example, a straight-chain four-carbon alkane group (derived from butane) attached by an end carbon to a molecule is designated as an *n*-butyl group.

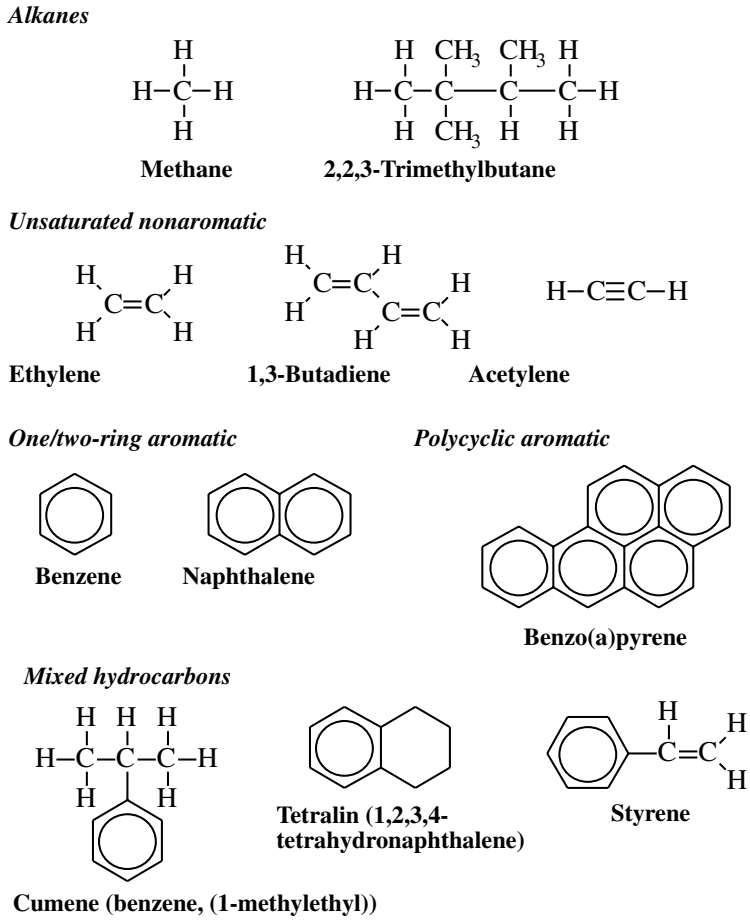


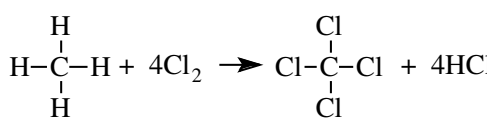
Figure 13.1 Hydrocarbons classified for discussion of their toxicological chemistry.

Alkanes undergo a number of chemical reactions, two classes of which should be mentioned here. The first of these is **oxidation** with molecular oxygen in air, as shown for the following combustion reaction of propane:

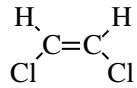
$$C_3H_8 + 5O_2 \rightarrow 3CO_2 + 4H_2O + \text{heat} \qquad (13.2.1)$$

Such reactions can pose flammability and explosion hazards. Another hazard occurs during combustion in an oxygen-deficient atmosphere or in an automobile engine, in which significant quantities of toxic carbon monoxide (CO) are produced.

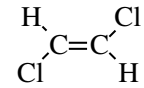
The second major type of alkane reaction that should be considered here consists of **substitution reactions**, in which one or more H atoms on an alkane are replaced by atoms of another element. Most commonly, the H is replaced by a halogen, usually chlorine, to yield **organohalide** compounds; when chlorine is the substituent, the product is called an **organochlorine** compound. An example of this kind of reaction is that of methane with chlorine to give carbon tetrachloride, reaction 13.2.2. Organohalide compounds are of great toxicological significance and are discussed in Chapter 16.



(13.2.2)



Cis **-1,2-dichloroethylene, mp -80.5°C, bp 59°C**



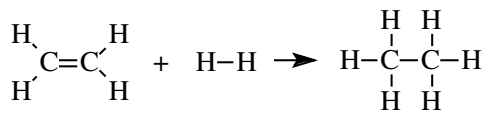
Trans **-1,2-dichloroethylene, mp -50°C, bp 48°C**

Figure 13.2 The two geometrical isomers of 1,2-dichloroethane.

13.2.2 Unsaturated Nonaromatic Hydrocarbons

Unsaturated hydrocarbons are those that have multiple bonds, each involving more than two shared electrons, between carbon atoms. Such compounds are usually **alkenes** or **olefins** that have double bonds consisting of four shared electrons, as shown for ethylene and 1,3-butadiene in Figure 13.1. Triple bonds consisting of six shared electrons are also possible, as illustrated by acetylene in the same figure.

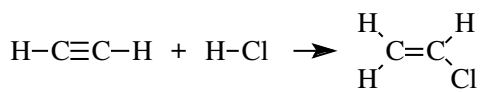
Alkenes may undergo **addition reactions**, in which pairs of atoms are added across unsaturated bonds, as shown in the following reaction of ethylene with hydrogen to give ethane:



(13.2.3)

This kind of reaction, which is not possible with alkanes, adds to the chemical and metabolic, as well as toxicological, versatility of compounds containing unsaturated bonds.

Another example of an addition reaction is that of a molecule of HCl gas to one of acetylene to yield vinyl chloride:



(13.2.4)

The vinyl chloride product is the monomer used to manufacture polyvinylchloride plastic and is a carcinogen known to cause a rare form of liver cancer among exposed workers.

As discussed in Section 1.7, compounds with double bonds can exist as geometrical isomers exemplified by the two isomers of 1,2-dichloroethylene in Figure 13.2. Although both of these compounds have the molecular formula $C_2H_2Cl_2$, the orientations of their H and Cl atoms relative to each other are different, and their properties, such as melting and boiling points, are not the same. Their toxicities are both relatively low, but significantly different. The *cis-* isomer is an irritant and narcotic known to damage the liver and kidneys of experimental animals. The *trans-* isomer causes weakness, tremor, and cramps due to its effects on the central nervous system, as well as nausea and vomiting, resulting from adverse effects on the gastrointestinal tract.

13.2.3 Aromatic Hydrocarbons

Aromatic compounds were discussed briefly in Section 1.7. The characteristics of **aromaticity** of organic compounds are numerous and are discussed at length in works on organic chemistry. These characteristics include a low hydrogen:carbon atomic ratio, C–C bonds that are quite strong and of intermediate length between such bonds in alkanes and those in alkenes, a tendency to

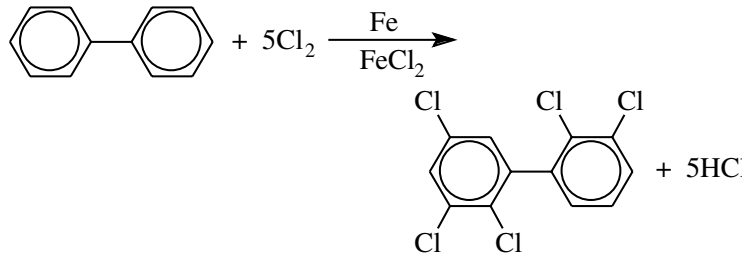


Figure 13.3 An example of a substitution reaction of an aromatic hydrocarbon compound (biphenyl) to produce an organochlorine product (2,3,5,2',3'-pentachlorobiphenyl, a PCB compound). The product is 1 of 210 possible congeners of PCBs, widespread and persistent pollutants found in the fat tissue of most humans and of considerable environmental and toxicological concern.

undergo substitution reactions (see Reaction 13.2.2) rather than the addition reactions characteristic of alkenes, and delocalization of π-electrons over several carbon atoms, resulting in resonance stabilization of the molecule. For more detailed explanations of these concepts, refer to standard textbooks on organic chemistry. For purposes of discussion here, most of the aromatic compounds discussed are those that contain single benzene rings or fused benzene rings, such as those in naphthalene or benzo(a)pyrene, shown in Figure 13.1.

An example reaction of aromatic compounds with considerable environmental and toxicological significance is the chlorination of biphenyl. Biphenyl gets its name from the fact that it consists of two **phenyl** groups (where a phenyl group is a benzene molecule less a hydrogen atom) joined by a single covalent bond. In the presence of an iron(II) chloride catalyst, this compound reacts with chlorine to form a number of different molecules of polychlorinated biphenyls (PCBs), as shown in Figure 13.3. These environmentally persistent compounds are discussed in Chapter 16.

13.3 TOXICOLOGY OF ALKANES

Worker exposure to alkanes, especially the lower-molecular-mass compounds, is most likely to come from inhalation. In an effort to set reasonable values for the exposure by inhalation of vapors of solvents, hydrocarbons, and other volatile organic liquids, the American Conference of Governmental Industrial Hygienists sets **threshold limit values** (TLVs) for airborne toxicants.[1,2] The **time-weighted average exposure** (E) is calculated by the formula

$$E = \frac{C_a T_a + C_b T_b + \cdots + C_n T_n}{8} \qquad (13.3.1)$$

where C is the concentration of the substance in the air for a particular time T (hours), such as a level of 3.1 ppm by volume for 1.25 h. The 8 in the denominator is for an 8-h day. In addition to exposures calculated by this equation, there are short-term exposure limits (STELs) and ceiling (C) recommendations applicable to higher exposure levels for brief periods of time, such as 10 min once each day.

"Safe" levels of air contaminants are difficult to set based on systemic toxicologic effects. Therefore, TLVs often reflect nonsystemic effects of odor, narcosis, eye irritation, and skin irritation. Because of this, comparison of TLVs is often not useful in comparing systemic toxicological effects of chemicals in the workplace.

13.3.1 Methane and Ethane

Methane and ethane are **simple asphyxiants**, which means that air containing high levels of these gases does not contain sufficient oxygen to support respiration. Table 13.1 shows the levels of asphyxiants in air at which various effects are observed in humans. Simple asphyxiant gases are

Table 13.1 Effects of Simple Asphyxiants in Air

Percent Asphyxiant[a]	Percent Oxygen, O_2[a]	Effect on Humans
0–33	21–14	No major adverse symptoms
33–50	14–10.5	Discernible effects beginning with air hunger and progressing to impaired mental alertness and muscular coordination
50–75	10.5–5.3	Fatigue, depression of all sensations, faulty judgment, emotional instability; in later phases, nausea, vomiting, prostration, unconsciousness, convulsions, coma, death
75–100	5.3–0	Death within a few minutes

[a] Percent by volume on a "dry" (water vapor-free) basis.

not known to have major systemic toxicological effects, although subtle effects that are hard to detect should be considered as possibilities.

13.3.2 Propane and Butane

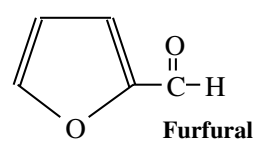
Propane has the formula C_3H_8 and butane C_4H_8. There are two isomers of butane, *n*-butane and isobutane (2-methylpropane). Propane and the butane isomers are gases at room temperature and atmospheric pressure; like methane and ethane, all three are asphyxiants. A high concentration of propane affects the central nervous system. There are essentially no known systemic toxicological effects of the two butane isomers; behavior similar to that of propane might be expected.

13.3.3 Pentane through Octane

The alkanes with five to eight carbon atoms consist of *n*-alkanes, and there is an increasing number of branched-chain isomers with higher numbers of C atoms per molecule. For example, there are nine isomers of heptane C_7H_{16}. These compounds are all volatile liquids under ambient conditions; the boiling points for the straight-chain isomers range from 36.1°C for *n*-pentane to 125.8°C for *n*-octane. In addition to their uses in fuels, such as in gasoline, these compounds are employed as solvents in formulations for a number of commercial products, including varnishes, glues, and inks. They are also used for the extraction of fats.

Once regarded as toxicologically almost harmless, the C_5–C_8 aliphatic hydrocarbons are now recognized as having some significant toxic effects. Exposure to the C_5–C_8 hydrocarbons is primarily via the pulmonary route, and high levels in air have killed experimental animals. Humans inhaling high levels of these hydrocarbons have become dizzy and have lost coordination as a result of central nervous system depression.

Of the C_5–C_8 alkanes, the one most commonly used for nonfuel purposes is *n*-hexane. It acts as a solvent for the extraction of oils from seeds, such as cottonseed and sunflower seed. This alkane serves as a solvent medium for several important polymerization processes and in mixtures with more polar solvents, such as furfural,



Furfural

for the separation of fatty acids. **Polyneuropathy** (multiple disorders of the nervous system) has been reported in several cases of human exposure to *n*-hexane, such as Japanese workers involved in home production of sandals using glue with *n*-hexane solvent. The workers suffered from muscle weakness and impaired sensory function of the hands and feet. Biopsy examination of nerves in

leg muscles of the exposed workers showed loss of myelin (a fatty substance constituting a sheath around certain nerve fibers) and degeneration of axons (part of a nerve cell through which nerve impulses are transferred out of the cell). The symptoms of polyneuropathy were reversible, with recovery taking several years after exposure was ended.

Exposure of the skin to C_5–C_8 liquids causes dermatitis. This is the most common toxicological occupational problem associated with the use of hydrocarbon liquids in the workplace, and is a consequence of the dissolution of the fat portions of the skin. In addition to becoming inflamed, the skin becomes dry and scaly.

13.3.4 Alkanes above Octane

Alkanes higher than C_8 are contained in kerosene, jet fuel, diesel fuel, mineral oil, and fuel oil distilled from crude oil as middle distillate fuels with a boiling range of approximately 175 to 370°C. Kerosene, also called fuel oil no. 1, is a mixture of primarily C_8–C_{16} hydrocarbons, predominantly alkanes. Diesel fuel is called fuel oil no. 2. The heavier fuel oils, no. 3 to 6, are characterized by increasing viscosity, darker color, and higher boiling temperatures with increasing fuel oil number. Mineral oil is a carefully selected fraction of petroleum hydrocarbons with density ranges of 0.83 to 0.86 g/ml for light mineral oil and 0.875 to 0.905 g/ml for heavy mineral oil.

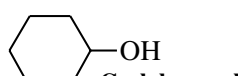
The higher alkanes are not regarded as very toxic, although there are some reservations about their toxicities. Inhalation is the most common route of occupational exposure and can result in dizziness, headache, and stupor. In cases of extreme exposure, coma and death have occurred. Inhalation of mists or aspiration of vomitus containing higher alkane liquids has caused a condition known as aspiration pneumonia. They are not regarded as carcinogenic, although experimental mice have shown weak tumorigenic responses with long latency periods upon prolonged skin exposure to middle distillate fuels. The observed effects have been attrributed to chronic skin irritation, and these substances do not produce tumors in the absence of skin irritation.[3] Middle distillate fuels can be effective carriers of known carcinogens, especially polycyclic aromatic hydrocarbons.

13.3.5 Solid and Semisolid Alkanes

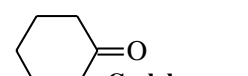
Semisolid petroleum jelly is a highly refined product commonly known as vaseline, a mixture of predominantly C_{16}–C_{19} alkanes. Carefully controlled refining processes are used to remove nitrogen and sulfur compounds, resins, and unsaturated hydrocarbons. Paraffin wax is a similar product, behaving as a solid. Neither petroleum jelly nor paraffin is digested or absorbed by the body.

13.3.6 Cyclohexane

Cyclohexane, the six-carbon ring hydrocarbon with the molecular formula C_6H_{12}, is the most significant of the cyclic alkanes. Under ambient conditions it is a clear, volatile, highly flammable liquid. It is manufactured by the hydrogenation of benzene and is used primarily as a raw material for the synthesis of cyclohexanol and cyclohexanone through a liquid-phase oxidation with air in the presence of a dissolved cobalt catalyst.



Cyclohexanol



Cyclohexanone

Like *n*-hexane, cyclohexane has a toxicity rating of 3, moderately toxic (see Table 6.1 for toxicity ratings). Cyclohexane acts as a weak anesthetic similar to, but more potent than, *n*-hexane. Systemic effects have not been shown in humans.

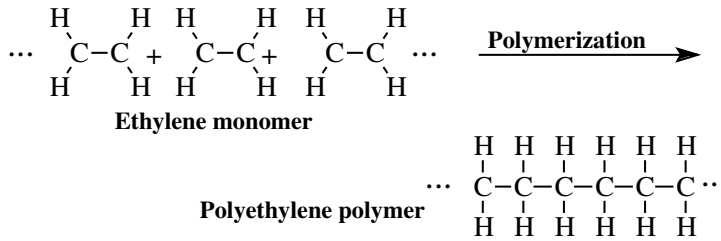
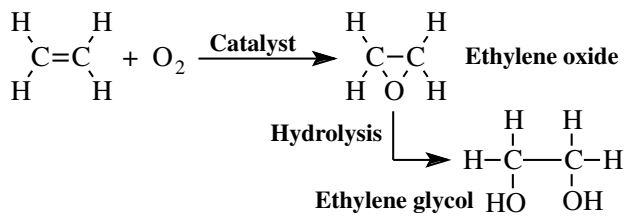


Figure 13.4 Polymerization of ethylene to produce polyethylene.

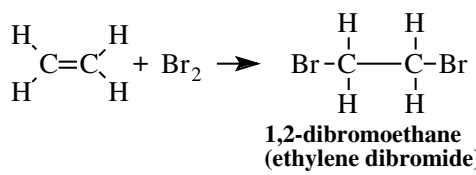
13.4 TOXICOLOGY OF UNSATURATED NONAROMATIC HYDROCARBONS

Ethylene (structure in Figure 13.1) is the most widely used organic chemical. Almost all of it is consumed as a chemical feedstock for the manufacture of other organic chemicals. Polymerization of ethylene to produce polyethylene is illustrated in Figure 13.4. In addition to polyethylene, other polymeric plastics, elastomers, fibers, and resins are manufactured with ethylene as one of the ingredients. Ethylene is also the raw material for the manufacture of ethylene glycol antifreeze, solvents, plasticizers, surfactants, and coatings.

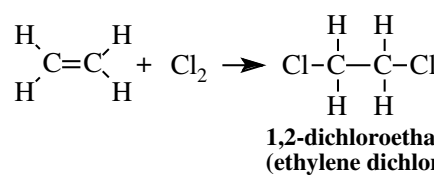
The boiling point (bp) of ethylene is –105°C, and under ambient conditions it is a colorless gas. It has a somewhat sweet odor, is highly flammable, and forms explosive mixtures with air. Because of its double bond (unsaturation), ethylene is much more active than the alkanes. It undergoes addition reactions, as shown in the following examples, to form a number of important products:



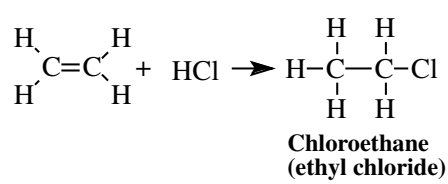
(13.4.1)



(13.4.2)



(13.4.3)



(13.4.4)

The products of the addition reactions shown above are all commercially, toxicologically, and environmentally important. Ethylene oxide is a highly reactive colorless gas used as a sterilizing agent, fumigant, and intermediate in the manufacture of ethylene glycol and surfactants. It is an irritant to eyes and pulmonary tract mucous membrane tissue; inhalation of it can cause pulmonary edema. Ethylene glycol is a colorless, somewhat viscous liquid used in mixtures with water as a high-boiling, low-freezing-temperature liquid (antifreeze and antiboil) in cooling systems. Ingestion of this compound causes central nervous system effects characterized by initial stimulation, followed by depression. Higher doses can cause poisoning due to metabolic oxidation of ethylene glycol to glycolic acid, glyoxylic acid, and oxalic acid. Glycolic acid causes acidosis, and oxalate forms insoluble calcium oxalate, which clogs the kidneys, as discussed in Section 14.2.

Ethylene dibromide has been used as an insecticidal fumigant and additive to scavenge lead from leaded gasoline combustion. During the early 1980s, there was considerable concern about residues of this compound in food products, and it was suspected of being a carcinogen, mutagen, and teratogen. Ethylene dichloride (bp, 83.5°C) is a colorless, volatile liquid with a pleasant odor that is used as a soil and foodstuff fumigant. It has a number of toxicological effects, including adverse effects on the eye, liver, and kidneys, and a narcotic effect on the central nervous system. Ethyl chloride seems to have similar, but much less severe, toxic effects.

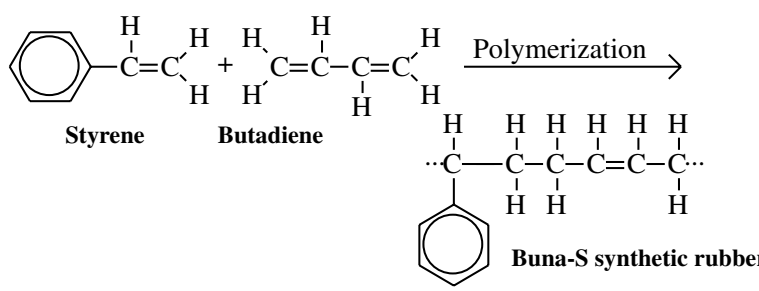
A highly flammable compound, ethylene forms dangerously explosive mixtures with air. It is phytotoxic (toxic to plants). Ethylene, itself, is not very toxic to animals, but it is a simple asphyxiant (see Section 13.3 and Table 13.1). At high concentrations, it acts as an anesthetic to induce unconsciousness. The only significant pathway of human exposure to ethylene is through inhalation. This exposure is limited by the low blood–gas solubility ratio of ethylene, which applies at levels below saturation of blood with the gas. This ratio for ethylene is only 0.14, compared, for example, with the very high value of 15 for chloroform.[4]

13.4.1 Propylene

Propylene (C_3H_6) is a gas with chemical, physical, and toxicological properties very similar to those of ethylene. It, too, is a simple asphyxiant. Its major use is in the manufacture of polypropylene polymer, a hard, strong plastic from which are made injection-molded bottles, as well as pipes, valves, battery cases, automobile body parts, and rot-resistant indoor–outdoor carpet.

13.4.2 1,3-Butadiene

The dialkene 1,3-butadiene is widely used in the manufacture of polymers, particularly synthetic rubber. The first synthetic rubber to be manufactured on a large scale and used as a substitute for unavailable natural rubber during World War II was a styrene–butadiene polymer:



(13.4.5)

Butadiene is a colorless gas under ambient conditions with a mild, somewhat aromatic odor. At lower levels, the vapor is an irritant to eyes and respiratory system mucous membranes, and at

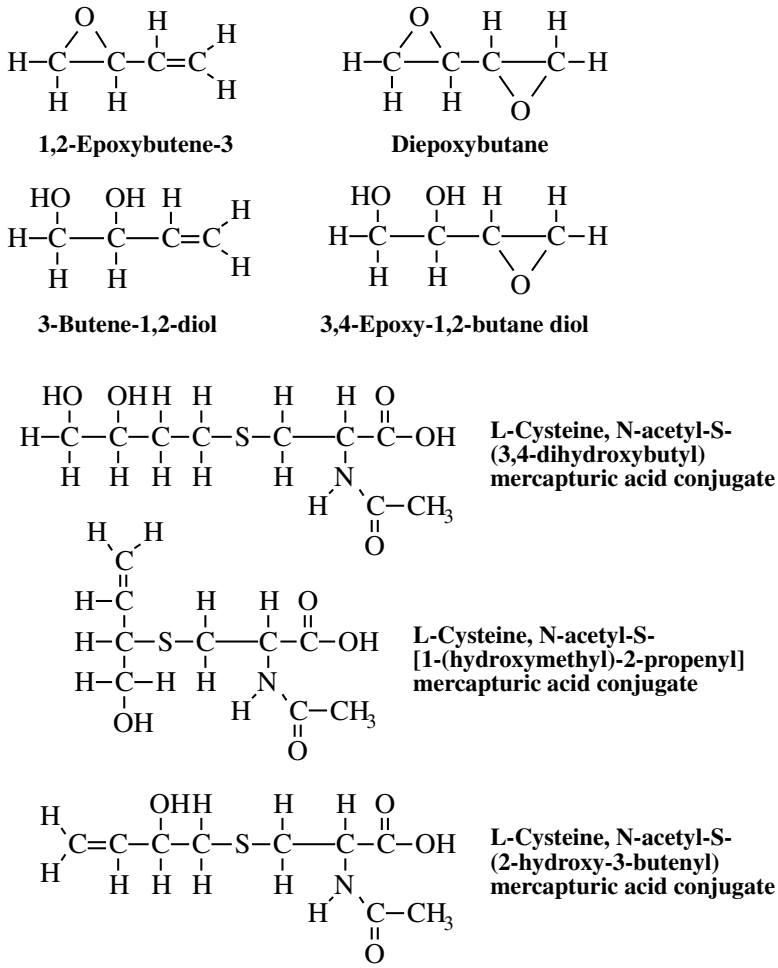
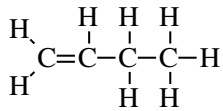


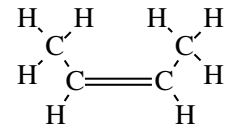
Figure 13.5 Common metabolites of 1,3-butadiene.

higher levels, it can cause unconsciousness and even death. Symptoms of human exposure include, initially, blurred vision, nausea, and paresthesia, accompanied by dryness of the mouth, nose, and throat. In cases of severe exposure, fatigue, headache, vertigo, and decreased pulse rate and blood pressure may be followed by unconsciousness. Fatal exposures have occurred only as the result of catastrophic releases of 1,3-butadiene gas. The compound boils at –4.5°C and is readily stored and handled as a liquid. Release of the liquid can cause frostbite-like burns on exposed flesh.

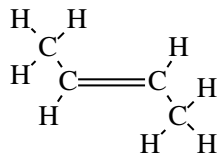
The aspect of 1,3-butadiene of greatest toxicological concern is its potential carcinogenicity. Butadiene is a known carcinogen to rats and mice and is more likely to cause cancer in the latter. Although it is a suspected carcinogen to humans, epidemiological studies of exposed workers in the synthetic rubber and plastics industries suggest that normal worker exposures are insufficient to cause cancer. Butadiene is acted on by P-450 isoenzymes to produce genotoxic metabolites, most prominently epoxybutene and diepoxybutene.[5] In addition, microsomal metabolic processes in rats produce the two possible stereoisomers of diepoxybutane, 3-butene-1,2-diol, and the two stereoisomers of 3,4-epoxy-1,2-butanediol (Figure 13.5). The production of mercapturic acid derivatives of the oxidation products of 1,3-butadiene (see Figure 13.5) results in detoxication of this compound and serves as a biomarker of exposure to it. Other useful biomarkers consist of the hemoglobin adducts 1- and 2-hydroxy-3-butenylvaline.[6]



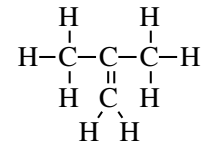
1-Butene



***Cis* -2-butene**



***Trans* -2-butene**



Isobutylene (methylpropene)

Figure 13.6 The four butylene compounds, formula C_4H_8.

13.4.3 Butylenes

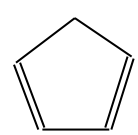
There are four monoalkenes with the formula C_4H_8 (butylenes), as shown in Figure 13.6. All gases under ambient conditions, these compounds have boiling points ranging from –6.9°C for isobutylene to 3.8°C for *cis*-2-butene. The butylenes readily undergo isomerization (change to other isomers). They participate in addition reactions and form polymers. Their major hazard is extreme flammability. Though not regarded as particularly toxic, they are asphyxiants and have a narcotic effect when inhaled.

13.4.4 Alpha-Olefins

Alpha-olefins are linear alkenes with double bonds between carbons 1 and 2 in the general range of carbon chain length C_6 through about C_{18}. They are used for numerous purposes. The C_6–C_8 compounds are used as comonomers to manufacture modified polyethylene polymer, and the C_{12}–C_{18} alpha-olefins are used as raw materials in the manufacture of detergents. The compounds are also used to manufacture lubricants and plasticizers. Worldwide consumption of the alpha-olefins was around 1 million metric tons. With such large quantities involved, due consideration needs to be given to the toxicological and occupational health aspects of these compounds.

13.4.5 Cyclopentadiene and Dicyclopentadiene

The cyclic dialkene cyclopentadiene has the structural formula shown below:



Cyclopentadiene

Two molecules of cyclopentadiene readily and spontaneously join together to produce dicyclopentadiene, widely used to produce polymeric elastomers, polyhalogenated flame retardants, and polychlorinated pesticides. Dicyclopentadiene mp, 32.9°C; bp, 166.6°C) exists as colorless crystals. It is an irritant and has narcotic effects. It is considered to have a high oral toxicity and to be moderately toxic through dermal absorption.

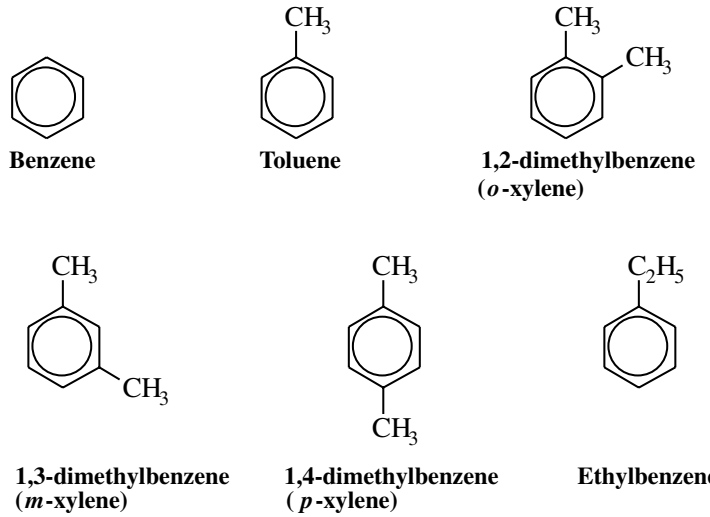


Figure 13.7 Benzene and its most common methyl-substituted hydrocarbon derivatives.

13.4.6 Acetylene

Acetylene (Figure 13.1) is widely used as a chemical raw material and fuel for oxyacetylene torches. It was once the principal raw material for the manufacture of vinyl chloride (see reaction 13.2.4), but other synthetic routes are now used. Acetylene is a colorless gas with an odor resembling garlic. Though not notably toxic, it acts as an asphyxiant and narcotic and has been used for anesthesia. Exposure can cause headache, dizziness, and gastric disturbances. Some adverse effects from exposure to acetylene may be due to the presence of impurities in the commercial product.

13.5 BENZENE AND ITS DERIVATIVES

Figure 13.7 shows the structural formulas of benzene and its major hydrocarbon derivatives. These compounds are very significant in chemical synthesis, as solvents, and in unleaded gasoline formulations.

13.5.1 Benzene

Benzene (C_6H_6) is chemically the single most significant hydrocarbon. It is used as a starting material for the manufacture of numerous products, including phenolic and polyester resins, polystyrene plastics and elastomers (through intermediate styrene, Figure 13.1), alkylbenzene surfactants, chlorobenzene compounds, insecticides, and dyes. Benzene (bp, 80.1°C) is a volatile, colorless, highly flammable liquid with a characteristic odor.

13.5.1.1 Acute Toxic Effects of Benzene

Benzene has been in commercial use for over a century, and toxic effects of it have been suspected since about 1900. Benzene has both acute and chronic toxicological effects.[7] It is usually absorbed as a vapor through the respiratory tract, although absorption of liquid through the skin and intake through the gastrointestinal tract are also possible. Benzene is a skin irritant, and progressively higher local exposures can cause skin redness (erythema), burning sensations, fluid accumulation (edema), and blistering. Inhalation of air containing about 64 g/m^3 of benzene can

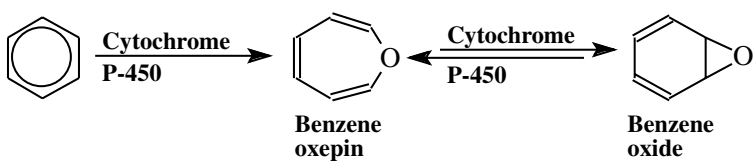
be fatal within a few minutes; about one tenth that level of benzene causes acute poisoning within an hour, including a narcotic effect on the central nervous system manifested progressively by excitation, depression, respiratory system failure, and death.

13.5.1.2 Chronic Toxic Effects of Benzene

Of greater overall concern than the acute effects of benzene exposure are chronic effects, which are still subject to intense study. As with many other toxicants, subjects suffering from chronic benzene exposure suffer nonspecific symptoms, including fatigue, headache, and appetite loss. More specifically, blood abnormalities appear in people suffering chronic benzene poisoning. The most common of these is a lowered white cell count. More detailed examination may show an abnormal increase in blood lymphocytes (colorless corpuscles introduced to the blood from the lymph glands), anemia, and decrease in the number of blood platelets required for clotting (thrombocytopenia). Some of the observed blood abnormalities may result from damage by benzene to bone marrow. Epidemiological studies suggest that benzene may cause acute melogenous (from bone marrow) leukemia. Because of concerns that long-term exposure to benzene may cause preleukemia, leukemia, or cancer, the allowable levels of benzene in the workplace have been greatly reduced, and substitutes such as toluene and xylene are used wherever possible.

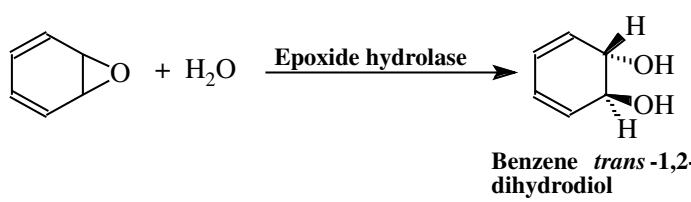
13.5.1.3 Metabolism of Benzene

For a hydrocarbon, the water solubility of benzene is a moderately high 1.80 g/l at 25°C. The vapor is readily absorbed by blood, from which it is strongly taken up by fatty tissues. For nonmetabolized benzene, the process is reversible and benzene is excreted through the lungs. Benzene metabolism occurs largely in the liver. Initially, benzene is oxidized by the action of cytochrome P-450 enzymes to benzene oxepin and benzene oxide, which are interchangeable through the action of cytochrome P-450 enzymes:



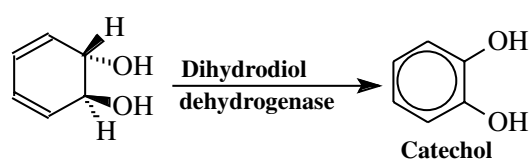
(13.5.1)

Benzene oxide may be hydrated through the action of epoxide hydrolase enzyme,



(13.5.2)

to produce benzene *trans*-1,2-dihydrodiol. This product is acted on by dihydrodiol dehydrogenase enzyme,



(13.5.3)

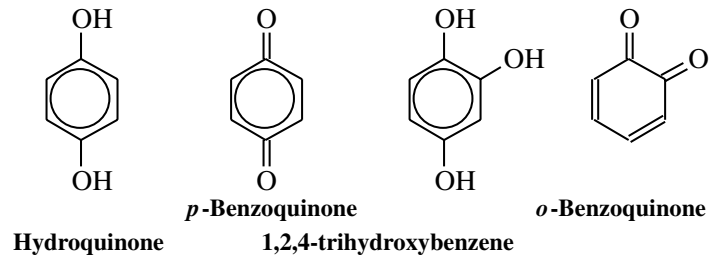
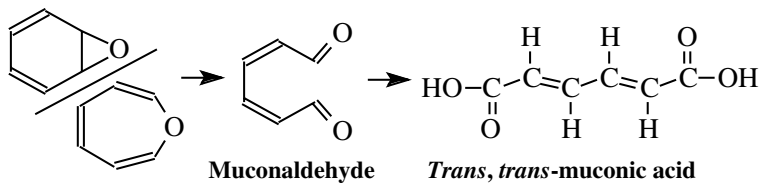


Figure 13.8 Products of phenol and catechol produced by the metabolic oxidation of benzene.

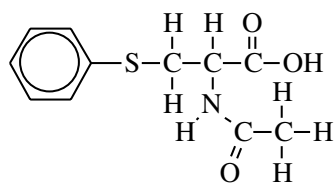
to produce catechol. Benzene oxepin or oxide may also react to produce muconaldehyde and muconic acid:



(13.5.4)

Benzene oxepin or oxide may form a glutathione conjugate or undergo nonenzymatic rearrangement to produce phenol. Phenol and catechol produce several oxyaryl species, shown in Figure 13.8.

Phase 1 oxidation products of benzene, including phenol, hydroquinone, catechol, 1,2,4-trihydroxybenzene, and *trans*,*trans*-muconic acid in urine, are evidence of exposure to benzene. Another substance observed in urine of individuals exposed to benzene is S-phenylmercapturic acid,



S-phenylmercapturic acid
(L-cysteine, N-acetyl-S-phenyl-)

which is formed as a result of the phase 2 conjugation of benzene oxide by glutathione and subsequent reactions. Hemoglobin and albumin adducts of benzene oxide are commonly detected in the blood of workers exposed to benzene.

The oxidized metabolites of benzene, including reactive benzene oxide intermediate, are known to bind with DNA, RNA, and proteins. This can result in cell destruction, alteration of cell growth, and inhibition of enzymes involved in the processes of forming blood cells. This phenomenon is probably responsible for the bone marrow damage, aplastic anemia (lowered production of blood cells due to damage to bone marrow), and, in severe cases, leukemia associated with benzene exposure.

13.5.2 Toluene, Xylenes, and Ethylbenzene

Toluene is a colorless liquid boiling at 101.4°C. Gasoline is 5 to 7% toluene and is the most common source of human exposure to toluene. Toluene is one of the most common solvents inhaled by solvent abusers. It is classified as moderately toxic through inhalation or ingestion and has a low toxicity by dermal exposure. Concentrations in ambient air up to 200 ppm usually do not result

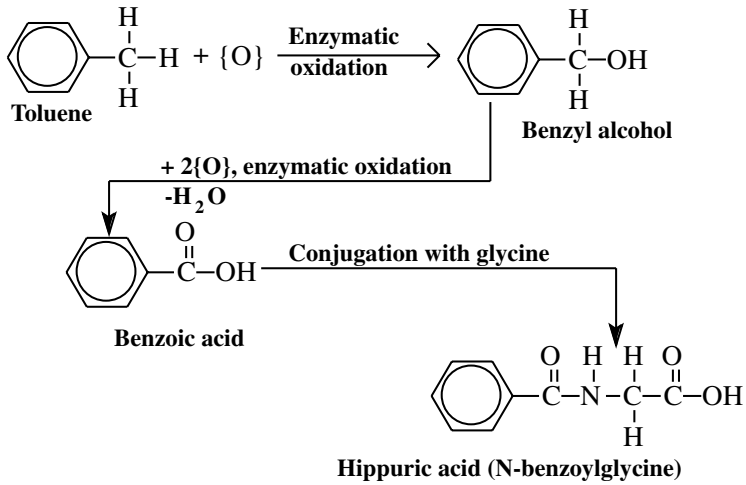


Figure 13.9 Metabolic oxidation of toluene with conjugation to hippuric acid, which is excreted with urine.

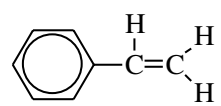
in significant symptoms, but exposure to 500 ppm may cause headache, nausea, lassitude, and impaired coordination without detectable physiological effects. At massive exposure levels, toluene acts as a narcotic, which can lead to coma.

Toluene tends to enter brain tissue, which it affects, and accumulates in adipose tissue. Unlike benzene, toluene possesses an aliphatic side chain that can be oxidized enzymatically, leading to products that are readily excreted from the body. The metabolism of toluene is thought to proceed via oxidation of the methyl group and formation of the conjugate compound hippuric acid, as shown in Figure 13.9.

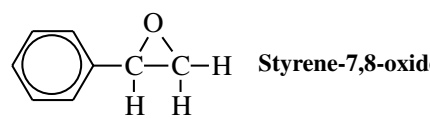
Xylenes and ethylbenzene (Figure 13.7) are common gasoline constituents, industrial solvents, and reagents, so human exposure to these materials is common. The absorption (primarily through inhalation), metabolism, and effects of these solvents are generally similar to those of toluene. Effects are largely on the central nervous system. Effects of xylenes and ethylbenzene on organs other than the central nervous system appear to be limited.

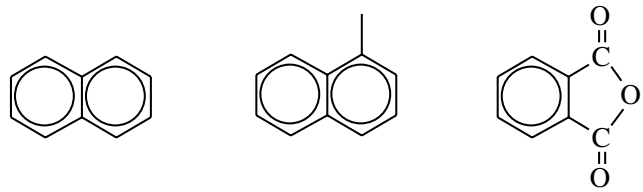
13.5.3 Styrene

Styrene,



is widely used to make various kinds of rubber (see styrene–butadiene polymer in reaction 13.4.5), polystyrene plastics, resins, and insulators. As a consequence, human exposure to this substance in the workplace has been quite high. As with the other volatile aromatic hydrocarbons discussed in this section, styrene is readily absorbed by inhalation, is lipid soluble, and is readily metabolized in the liver. The presence of the C=C group in styrene provides an active site for biochemical attack, and styrene is readily oxidized metabolically to styrene oxide:





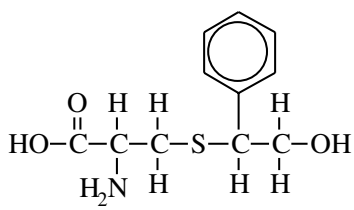
Naphthalene **1-(2-propyl)naphthalene** **Phthalic anhydride**

Figure 13.10 Naphthalene and two of its derivatives.

The major toxicological concern with styrene has to do with its potential role as a procarcinogen in producing carcinogenic styrene oxide, itself an industrial chemical to which workers may be exposed. Styrene oxide that is inhaled directly is distributed in the body by systemic circulation. However, styrene oxide that is produced by the metabolic oxidation of styrene in the liver is rapidly hydrolyzed in the liver by the action of epoxide hydrolase, leading to the formation of mandelic acid and phenylgloxylic acid, probably making the carcinogenicity hazard of styrene much lower than that of styrene oxide:[8]

Mandelic acid **Glyoxylic acid**

The albumin adduct of styrene oxide, S-(2-hydroxyl-1-phenylethyl)cysteine,



S-(2-hydroxy-1-phenylethyl)cysteine

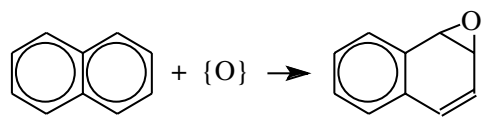
has been monitored in blood as a biomarker of exposure to styrene and styrene oxide.[9] Exposures to styrene oxide gave levels of the adduct approximately 2000 times that of comparable exposure to styrene. Since the production of S-(2-hydroxyl-1-phenylethyl)cysteine is a measure of tendency toward adduct formation, and by inference the formation of nucleic acid adducts leading to cancer, these findings are strong evidence that exposure to styrene poses a much lower risk of carcinogenicity than does direct exposure to styrene oxide.

13.6 NAPHTHALENE

Naphthalene, also known as tar camphor, and its alkyl derivatives, such as 1-(2-propyl)naphthalene (Figure 13.10), are important industrial chemicals. Used to make mothballs, naphthalene is a volatile white crystalline solid with a characteristic odor. Coal tar and petroleum are the major sources of naphthalene. Numerous industrial chemical derivatives are manufactured from it. The most important of these is phthalic anhydride (Figure 13.10), used to make phthalic acid plasticizers, which are discussed in Chapter 14.

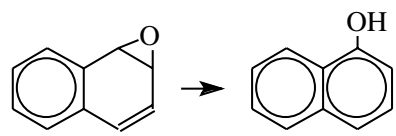
13.6.1 Metabolism of Naphthalene

The metabolism of naphthalene is similar to that of benzene, starting with an enzymatic epoxidation of the aromatic ring:



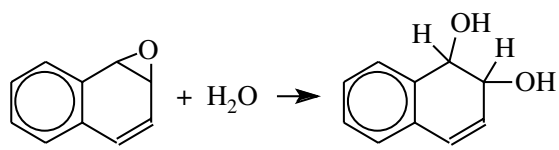
(13.6.1)

followed by a nonenzymatic rearrangement to 1-naphthol:



(13.6.2)

or addition of water to produce naphthalene-1,2-dihydrodiol through the action of epoxide hydrase enzyme:



(13.6.3)

Elimination of the metabolized naphthalene from the body may occur as a mercapturic acid, preceded by the glutathione S-transferase-catalyzed formation of a glutathione conjugate.

13.6.2 Toxic Effects of Naphthalene

Exposure to naphthalene can cause a severe hemolytic crisis in some individuals with a genetically linked metabolic defect associated with insufficient activity of the glucose-6-phosphate dehydrogenase enzyme in red blood cells.[10] Effects include anemia and marked reductions in red cell count, hemoglobin, and hematocrit. Contact of naphthalene with skin can result in skin irritation or severe dermatitis in sensitized individuals. In addition to the hemolytic effects just noted, both inhalation and ingestion of naphthalene can cause headaches, confusion, and vomiting. Kidney failure is usually the ultimate cause of death in cases of fatal poisonings.

Naphthalene may adversely affect the eye, causing cortical cataracts and retinal degeneration.[11] These affects are attributed to the naphthalene dihydrodiol metabolite (see the product of reaction 13.6.3).

13.7 POLYCYCLIC AROMATIC HYDROCARBONS

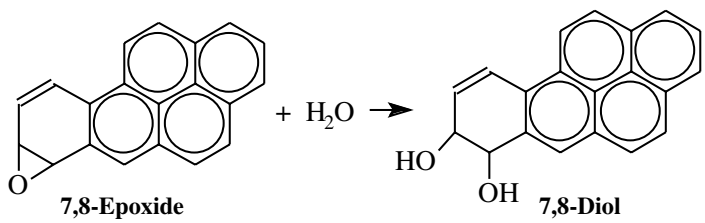
Benzo(a)pyrene (Figure 13.1) is the most studied of the polycyclic aromatic hydrocarbons (PAHs). These compounds are formed by the incomplete combustion of other hydrocarbons so that

hydrogen is consumed in the preferential formation of H_2O. The condensed aromatic ring system of the PAH compounds produced is the thermodynamically favored form of the hydrogen-deficient, carbon-rich residue. To cite an extreme example, the H:C ratio in methane (CH_4) is 4:1, whereas in benzo(a)pyrene ($C_{20}H_{12}$) it is only 3:5.

There are many conditions of partial combustion and pyrolysis that favor production of PAH compounds, and they are encountered abundantly in the atmosphere, soil, and elsewhere in the environment. Sources of PAH compounds include engine exhausts, wood stove smoke, cigarette smoke, and charbroiled food. Coal tars and petroleum residues have high levels of PAHs.

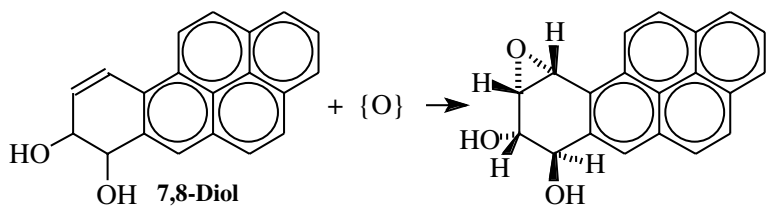
13.7.1 PAH Metabolism

The metabolism of PAH compounds is mentioned here with benzo(a)pyrene as an example. Several steps lead to the formation of the carcinogenic metabolite product of benzo(a)pyrene. After an initial oxidation to form the 7,8-epoxide, the 7,8-diol is produced through the action of epoxide hydrase enzyme, as shown by the following reaction:



7,8-Epoxide **7,8-Diol** (13.7.1)

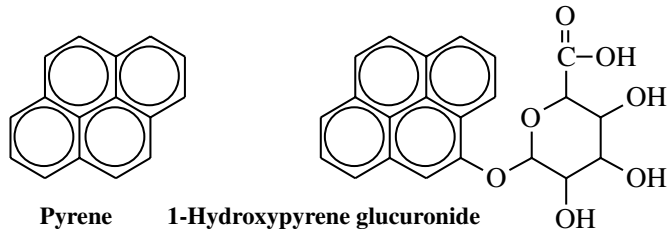
The microsomal mixed-function oxidase enzyme system further oxidizes the diol to the carcinogenic 7,8-diol-9,10-epoxide:



7,8-Diol **7,8-Diol-9,10-epoxide, carcinogenic (+)anti-isomer**

Several isomers of the 7,8-diol-9,10-epoxide are formed, depending on the orientations of the epoxide and OH groups relative to the plane of the molecule. The (+)antiisomer is the one that is regarded as carcinogenic based on its demonstrated mutagenicity, ability to bind with DNA, and extreme pulmonary carcinogenicity to newborn mice.[12]

Because of inhalation of smoke, especially tobacco smoke, the lungs are the most likely sites of cancer from exposure to PAH compounds. However, these compounds are also found in foods cooked under direct exposure to pyrolysis conditions and are suspected of causing cancer in the alimentary canal. Extraordinarily high rates of esophageal cancer have been observed in Linxian, China, and may be attributable to PAHs from unvented cookstoves.[13] In this study, the glucuronide conjugate of 1-hydroxypyrene was monitored as a biomarker of exposure to PAH compounds (Figure 13.11).



Pyrene **1-Hydroxypyrene glucuronide**

Figure 13.11 Pyrene, a common PAH compound, and the 1-hydroxypyrene glucuronide conjugate that may serve as a biomarker of exposure to pyrene.

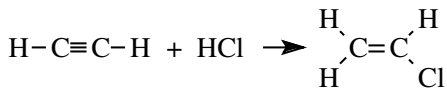
REFERENCES

1. Threshold limit values (TLVs) for chemical substances and physical agents and biological exposure indices (BEIs) 2002, American Conference of Governmental Industrial Hygienists, Cincinnati, OH, 2002.
2. Kennedy, G.L., Setting a threshold limit value (TLV): the process, *Chem. Health Safety*, 8, 13–15, 2001.
3. Nessel, C.S., A comprehensive evaluation of the carcinogenic potential of middle distillate fuels, *Drug Chem. Toxicol.*, 22, 165–180, 1999.
4. Rozman, K.K. and Klaassen, C.D., Adsorption, distribution, and excretion of toxicants, in *Casarett and Doull's Toxicology: The Basic Science of Poisons*, 6th ed., Klaassen, C.D., Ed., McGraw-Hill, New York, 2001, chap. 8, pp. 107–132.
5. Bond, J.A. and Medinsky, M.A., Insights into the toxicokinetics and toxicodynamics of 1,3-butadiene, *Chem. Biol. Interact.*, 135/136, 599–614, 2001.
6. Boogaard, P.J., van Sittert, N.J., and Megens, H.J.J.J., Urinary metabolites and hemoglobin adducts as biomarkers of exposure to 1,3-butadiene: a basis for 1,3-butadiene cancer risk assessment, *Chem. Biol. Interact.*, 135/136, 695–701, 2001.
7. Bruckner, J.V. and Warren, D.A., Toxic effects of solvents and vapors, in *Casarett and Doull's Toxicology: The Basic Science of Poisons*, 6th ed., Klaassen, C.D., Ed., McGraw-Hill, New York, 2001, chap. 24, pp. 869–916.
8. Tornero-Velez, R. and Rappaport, S.M., Physiological modeling of the relative contributions of styrene-7,8-oxide derived from direct inhalation and from styrene metabolism to the systemic dose in humans, *Toxicol. Sci.*, 64, 151–161, 2001.
9. Rappaport, S.M. and Yeowell-O'Connell, K., Protein adducts as dosimeters of human exposure to styrene, styrene-7,8-oxide, and benzene, *Toxicol. Lett.*, 108, 117–126, 1999.
10. Gosselin, R.E., Smith, R.P., and Hodge, H.C., Naphthalene, in *Clinical Toxicology of Commercial Products*, 5th ed., Williams & Wilkins, Baltimore, 1984, pp. III-307–III-311.
11. Fox, D.A. and Boyes, W.K., Toxic responses of the ocular and visual system, in *Casarett and Doull's Toxicology: The Basic Science of Poisons*, 6th ed., Klaassen, C.D., Ed., McGraw-Hill, New York, 2001, chap. 17, pp. 565–595.
12. Rubin, H., Synergistic mechanisms in carcinogenesis by polycyclic aromatic hydrocarbons and by tobacco smoke: a biohistorical perspective with updates, *Carcinogenesis*, 22, 1903–1930, 2001.
13. Roth, M.J. et al., High urine 1-hydroxpyrene glucuronide concentrations in Linxian, China, an area of high risk for squamous esophageal cancer, *Biomarkers*, 6, 381–386, 2001.

QUESTIONS AND PROBLEMS

1. Using compounds other than those shown in Figure 13.1, give examples of each of the following kinds of hydrocarbons: (1) alkanes, (2) unsaturated nonaromatic hydrocarbons, (3) aromatic hydrocarbons, (4) polycyclic aromatic hydrocarbons with multiple rings, and (5) mixed hydrocarbons.
2. What kind of carbon–carbon bond characterizes alkanes? What kind of carbon–carbon bond characterizes other types of hydrocarbons?

3. Give examples of hydrocarbons having the following general formulas: C_nH_{2n+2}, C_nH_{2n}, C_nH_n, and C_nH_x, where x is a number less than n.
4. What are the two most important reactions of alkanes? What kind of additional reaction is possible with alkenes? What may the latter have to do with the toxicological chemistry of alkenes?
5. What kind of reaction is shown below? What is the organic reactant? What is the product? What is the special toxicological significance of the product?

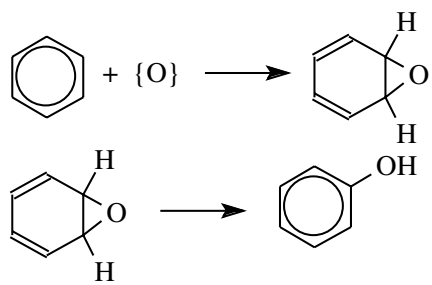


6. What structural phenomenon may be shown by the following formulas? What is its toxicological significance?

7. Describe the special characteristics of aromaticity.
8. Explain the significance of the following formula:

$$E = \frac{C_a T_a + C_b T_b + \cdots + C_n T_n}{8}$$

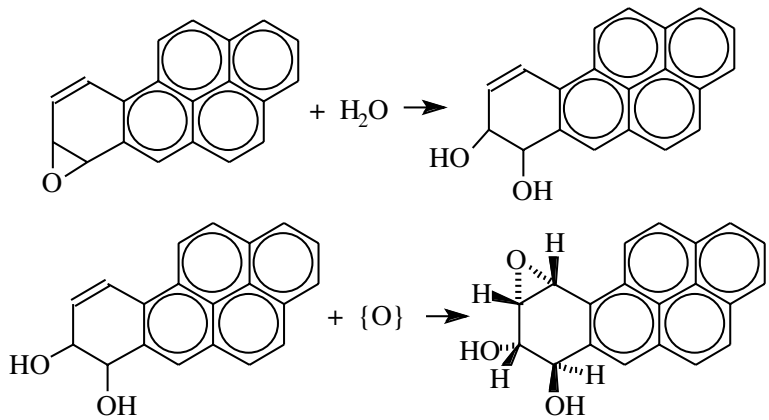
9. What is the main toxicological characteristic of low-molecular-mass alkanes? What condition may be caused by exposure to somewhat higher-molecular-mass alkanes, such as *n*-hexane? How is this condition caused?
10. Consider the following reactions:



Discuss these reactions in terms of their significance for benzene toxicity and toxicological chemistry, phase I reactions, phase II reactions, and other aspects pertinent to benzene's effects on the body.

11. What is the formula of acetylene? What are its main toxicological effects?
12. What are the major acute toxicological effects of benzene? How does benzene exposure usually occur? How does benzene affect the central nervous system? At what levels of exposure are the acute toxicological effects manifested?
13. What are the chronic toxicological effects of benzene? What kinds of blood abnormalities are caused by benzene exposure? How does benzene toxicity affect white cell count? How does it affect bone marrow?
14. What may be said about the vapor pressure and water solubilities of benzene as they influence its toxicity?

15. In what important respects are the toxicological chemistry and toxicity of toluene quite different from those of benzene? How is hippuric acid formed from toluene?
16. What are the major toxicological chemical and toxicological aspects of naphthalene?
17. Discuss what the following shows about the toxicological chemistry and toxicity of some important polycyclic aromatic hydrocarbons:



CHAPTER 14

Organooxygen Compounds

14.1 INTRODUCTION

A very large number of organic compounds and natural products, many of which are toxic, contain oxygen in their structures. This chapter concentrates on organic compounds that have oxygen covalently bonded to carbon. Organic compounds in which oxygen is bonded to nitrogen, sulfur, phosphorus, and the halogens are discussed in Chapters 15 to 18.

14.1.1 Oxygen-Containing Functional Groups

As shown in Table 1.4 and Figure 14.1, there are several kinds of oxygen-containing functional groups in organic compounds. In general, the organooxygen compounds can be classified according to the degree of oxygenation, location of oxygen on the hydrocarbon moiety, presence of unsaturated bonds in the hydrocarbon structure, and presence or absence of aromatic rings. Some of the features of organooxygen compounds listed above can be seen from an examination of some of the oxidation products of propane in Figure 14.1. Some organooxygen compounds discussed in this chapter are made from the bonding together of two of the many molecules shown in Figure 14.1.

14.2 ALCOHOLS

This section discusses the toxicological chemistry of the **alcohols**, oxygenated compounds in which the hydroxyl functional group is attached to an aliphatic or olefinic hydrocarbon skeleton. The phenols, which have –OH bonded to an aromatic ring, are covered in Section 14.3. The three lightest alcohols — methanol, ethanol, and ethylene glycol (shown in Figure 14.2) — are discussed individually in some detail because of their widespread use and human exposure to them. The higher alcohols, defined broadly as those containing three or more carbon atoms per molecule, are discussed as a group.

14.2.1 Methanol

Methanol, also called methyl alcohol and once commonly know as wood alcohol, is a clear, volatile liquid mp, –98°C; bp, 65°C). Until the early 1900s, the major commercial source of methanol was the destructive distillation (pyrolysis) of wood, a process that yields a product contaminated with allyl alcohol, acetone, and acetic acid. Now methanol is synthesized by the following reaction of hydrogen gas and carbon monoxide, both readily obtained from natural gas or coal gasification:

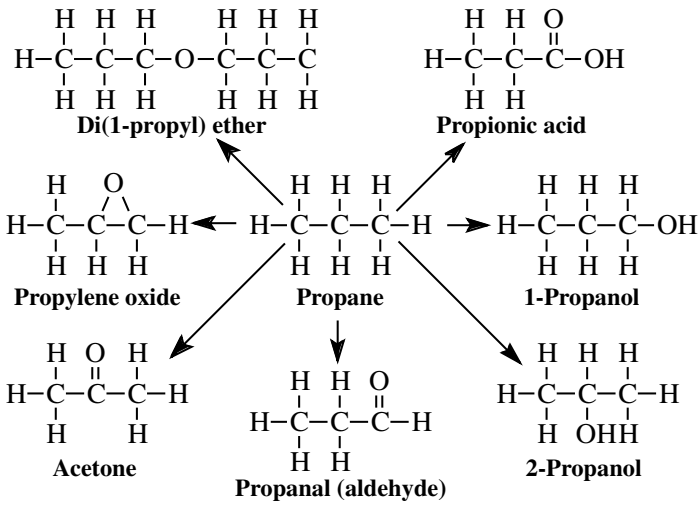


Figure 14.1 Oxygenated derivatives of propane.

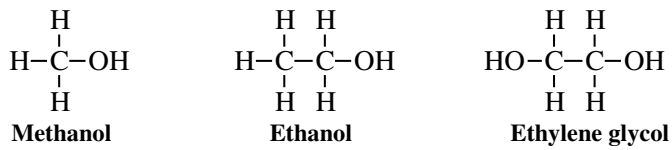
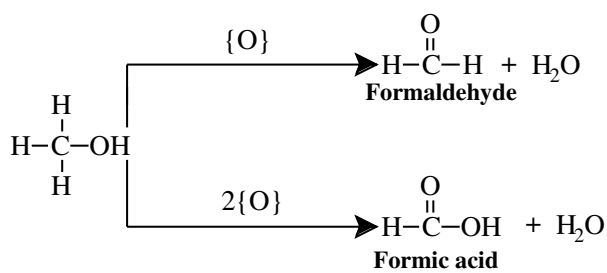


Figure 14.2 Three lighter alcohols with particular toxicological significance.

$$CO + 2H_2 \xrightarrow[\text{catalyst}]{\text{Metal}} CH_3OH \qquad (14.2.1)$$

The greatest use for methanol is in the manufacture of formaldehyde (see Section 14.5). Additional uses include the synthesis of other chemicals, including acetic acid, applications as an organic solvent, and addition to unleaded gasoline for fuel, antifreeze, and antiknock properties.

Methanol has been responsible for the deaths of many humans who ingested it accidentally or as a substitute for beverage ethanol. The fatal human dose is believed to lie between 50 and 250 g. In the body, methanol undergoes metabolic oxidation to formaldehyde and formic acid:[1]



(14.2.2)

The formic acid product of this reaction causes acidosis, with major adverse effects on the central nervous system, retina, and optic nerve.[2] In cases of acute exposure, an initially mild inebriation

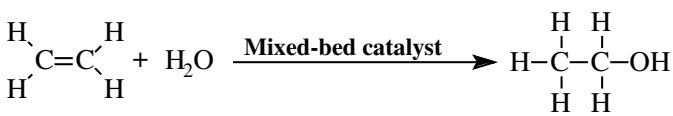
is followed in about 10 to 20 h by unconsciousness and cardiac depression; death may occur. For sublethal doses, initial symptoms of visual dysfunction may clear temporarily, followed by blindness from deterioration of the optic nerve and retinal ganglion cells. Chronic exposures to lower levels of methanol may result from fume inhalation.

Methanol occurs in some foods. Distilled fruit spirits such as those from the fermentation of Bartlett pears contain some methanol. This has led to European standards for methanol limits in distilled fruit spirits. The levels of methanol can be reduced by appropriate adjustment of fermentation conditions and the distillation processes used.[3]

14.2.2 Ethanol

Ethanol, ethyl alcohol (mp, –114°C; bp, 78°C), is a clear, colorless liquid widely used as a beverage ingredient, synthetic chemical, solvent, germicide, antifreeze, and gasoline additive. It is produced by the fermentation of carbohydrates or by the hydration of ethylene, as shown by the following two reactions:

$$C_6H_{12}O_6 \xrightarrow{\text{Yeasts}} 2C_2H_5OH + 2CO_2 \tag{14.2.3}$$



(14.2.4)

Ethanol misused in beverages is responsible for more deaths than any other chemical when account is taken of chronic alcoholism, vehicle fatalities caused by intoxicated drivers, and alcohol-related homicides. Chronic alcoholism is a distinct disease arising from generally long-term systemic effects of the ingestion of alcohol. Often the most damaging manifestation of chronic alcohol toxicity consists of adverse effects on the liver (alcohol-induced hepatotoxicity).[4] Some of these adverse effects are due to oxidative stress and lipid peroxidation. Other effects may result from the formation of protein adducts of acetaldehyde and 1-hydroxyethyl radical, leading to immunogenic processes that damage the liver.

Ethanol has a range of acute effects, normally expressed as a function of percent blood ethanol. In general, these effects are related to central nervous system depression. Mild effects such as decreased inhibitions and slowed reaction times begin to appear at about 0.05% blood ethanol. Most individuals are clinically intoxicated at a level of 0.15 to 0.3% blood ethanol; in the 0.3 to 0.5% range, stupor may be produced; and at 0.5% and above, coma and often death occur.

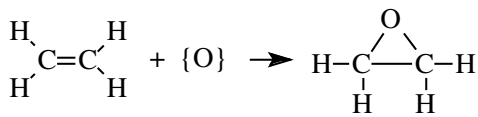
Metabolically, ethanol is oxidized first to acetaldehyde (Section 14.6), then to CO_2. The overall oxidation rate is faster than that for methanol.

In addition to absorption through the gastrointestinal tract, ethanol can be absorbed by the alveoli of the lungs. Symptoms of intoxication can be observed from inhalation of air containing more than 1000 ppm ethanol.

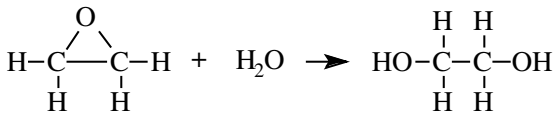
One of the more serious toxic effects of ethanol is its role as a teratogen when ingested during pregnancy, causing **fetal alcohol syndrome**. Fetal alcohol syndrome is manifested by a number of effects, with perhaps more to be discovered. One of the more obvious of these is the occurrence of defects in the head and face structure. Fetal alcohol syndrome is also manifested by central nervous system abnormalities, and it is one of the leading causes of nongenetic mental retardation. It also retards growth, both prenatally and postnatally. Ethanol and its first metabolite, acetaldehyde, rapidly cross the placenta and have adverse effects on its function. Both of these compounds are teratogens, and both are toxic to embryos.

14.2.3 Ethylene Glycol

Although used in cosmetics, chemical synthesis, and other applications, most ethylene glycol is consumed as the major ingredient of antifreeze and antiboil formulations for automobile radiators. Ethylene glycol (mp, –13°C; bp, 198°C) is synthesized by the oxidation of ethylene to ethylene oxide, followed by hydrolysis of the latter compound:

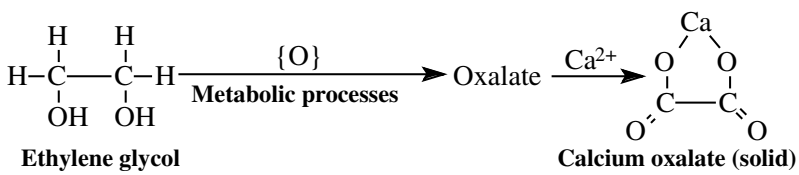


(14.2.5)



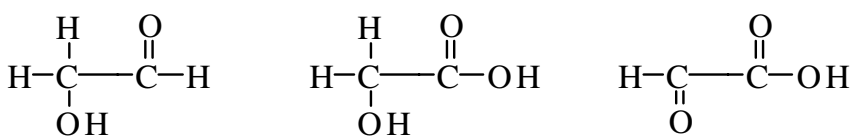
(14.2.6)

Toxic exposures to ethylene glycol are rare because of its low vapor pressure, but inhalation of droplets can be very dangerous. Significant numbers of human fatalities attributable to ethylene glycol poisoning have been documented.[5] From the limited amount of information available, the LD_{50} for humans has been estimated to be about 110 g. Ingested ethylene glycol initially stimulates the central nervous system, and then depresses it. Victims may suffer acidemia from the presence of the intermediate metabolite glycolic acid. Kidney damage occurs later, and it can be fatal. The kidneys are harmed because of the deposition of solid calcium oxalate, resulting from the following overall process:



(14.2.7)

Important intermediates in this process are glycoaldehyde, glycolate, and glyoxalate:



Glycoaldehyde **Glycolic acid** **Glyoxylic acid**

Kidney failure from the metabolic formation of calcium oxalate has been especially common in cat species, which have voracious appetites for ethylene glycol in antifreeze. Deposits of solid calcium oxalate have also been observed in the liver and brain tissues of victims of ethylene glycol poisoning.

14.2.4 The Higher Alcohols

Numerous alcohols containing three or more carbon atoms are used as solvents and chemical intermediates and for other purposes. Exposure to these compounds can occur, and their toxicities are important. Some of the more significant of these alcohols are listed in Table 14.1.

Table 14.1 Some Alcohols with Three or More Carbons

Alcohol Name and Formula	Properties
2-Propanol, $CH_3CHOHCH_3$	Isopropyl alcohol; used as rubbing alcohol and food additive; irritant; narcotic; relatively low toxicity
Allyl alcohol, $CH_2{=}CHCH_2OH$	Olefinic alcohol; pungent odor; strongly irritating to eyes, mouth, lungs
1-Butanol, $CH_3(CH_2)_2CH_2OH$	Butyl alcohol or *n*-butanol; irritant; limited toxicity because of low vapor pressure
1-Pentanol, $CH_3(CH_2)_3CH_2OH$	Amyl alcohol; liquid; bp, 138°C; irritant, causes headache and nausea; low vapor pressure and low water solubility reduce toxicity hazard
1-Decanol, $CH_3(CH_2)_8CH_2OH$	Viscous liquid; bp, 233°C; low acute toxicity
2-Ethylhexanol, $CH_3(CH_2)_3CH{-}(C_2H_5)CH_2OH$	2–Ethylhexyl alcohol; important industrial solvent; toxicity similar to those of butyl alcohols

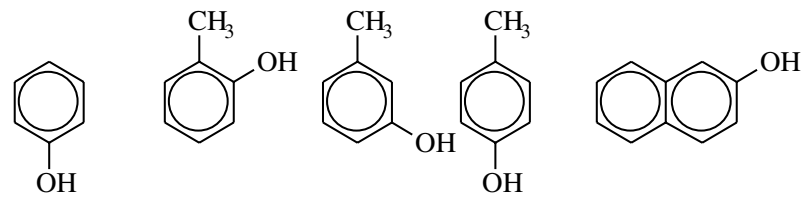


Figure 14.3 Major phenolic compounds.

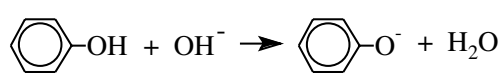
An important alcohol in toxicology studies is ***n*-octanol**, $CH_3(CH_2)_6CH_2OH$. This compound is applied to the measurement of the **octanol–water partition coefficient**, which is used to estimate how readily organic toxicants are transferred from water to lipids, a tendency usually associated with ability to cross cell membranes and cause toxic effects. As just one example, the octanol–water partition coefficient can be used to estimate the tendency of organic compounds to be taken up from water to the lipid gill tissue of fish.

14.3 PHENOLS

Phenols are aryl alcohols in which the –OH group is bonded to an aromatic hydrocarbon moiety. The simplest of these compounds is phenol, in which the hydrocarbon portion is the phenyl group. Figure 14.3 shows some of the more important phenolic compounds. Phenols have properties that are quite different from those of the aliphatic and olefinic alcohols. Many important phenolic compounds have nitro groups ($-NO_2$) and halogen atoms (particularly Cl) bonded to the aromatic rings. These substituents may strongly affect chemical and toxicological behavior; such compounds are discussed in Chapters 15 and 16.

14.3.1 Properties and Uses of Phenols

The physical properties of the phenols listed in Figure 14.3 are summarized briefly in Table 14.2. These phenolic compounds are weak acids that ionize to phenolate ions in the presence of base:



(14.3.1)

Table 14.2 Properties of Major Phenolic Compounds

Compound	Properties
Phenol	Carbolic acid; white solid; characteristic odor; mp, 41°C; bp, 182°C
m-Cresol	Often occurs mixed with *ortho*- and *para*- analogs as cresol or cresylic acid; light yellow liquid; mp, 11°C; bp, 203°C
o-Cresol	Solid; mp, 31°C; bp, 191°C
p-Cresol	Crystalline solid with phenolic odor; mp, 36°C; bp, 202°C
1-Naphthol	Alpha-naphthol; colorless solid; mp, 96°C; bp, 282°C
2-Naphthol	Beta-naphthol; mp, 122°C; bp, 288°C

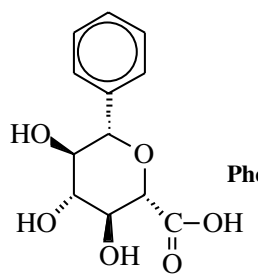
Phenols are extracted commercially from coal tar into aqueous base as the phenolate ions. The major commercial use of phenol is in the manufacture of phenolic resin polymers, usually with formaldehyde. Phenols and cresols are used as antiseptics and disinfectants in areas such as barns where the phenol odor can be tolerated. Phenol was the original antiseptic used on wounds and in surgery, starting with the work of Lord Lister in 1885.

14.3.2 Toxicology of Phenols

Generally, the phenols have similar toxicological effects. Phenol is a protoplasmic poison, so it damages all kinds of cells. Early medical studies that demonstrated asepsis with phenol revealed its toxicity as well. Phenol is alleged to have caused "an astonishing number of poisonings" since it came into general use.[6]

Fatal doses of phenol may be absorbed through the skin. Its acute toxicological effects are predominantly on the central nervous system. Death can occur as early as a half hour after exposure. Key organs damaged by chronic exposure to phenol include the spleen, pancreas, and kidneys. Lung edema can also occur.

Some phenol is eliminated from the body as the unchanged molecular compound, although most is metabolized prior to excretion. As noted in Section 7.2.1, phase II reactions in the body result in the conjugation of phenol to produce sulfates and glucuronides. These water-soluble metabolic products are eliminated via the kidneys. Urinary phenyl glucuronide may be measured to monitor exposure to phenol.[7]

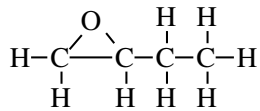


Phenyl glucuronide

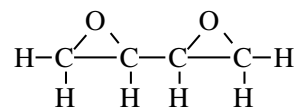
Oral doses of naphthols can be fatal. Acute poisoning by these compounds can cause severe gastrointestinal disturbances, kidney malfunction, circulatory system failure, and convulsions. Naphthols can be absorbed through the skin, one effect of which can be eye damage involving the cornea and lens.

14.4 OXIDES

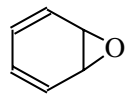
Hydrocarbon **oxides** are significant for both their uses and their toxic effects.[8] As shown for ethylene oxide (1,2-epoxyethane) in reactions 14.2.5 and 14.2.6 and propylene oxide (1,2-epoxypro-



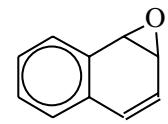
1,2-Epoxybutane (oxirane, ethyl)



1,2,3,4-Diepoxybutane (2,2'-bioxirane)



Benzene-1,2-oxide



Naphthalene-1,2-oxide

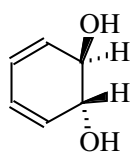
Figure 14.4 Some common epoxide compounds.

pane) in Figure 14.1, these compounds are characterized by an **epoxide** functional group consisting of an oxygen atom bridging two adjacent C atoms. As discussed in Section 4.2, the metabolic formation of such a group is called epoxidation and is a major type of the phase I reactions of xenobiotic compounds. In addition to ethylene and propylene oxides, four other common hydrocarbon oxides are shown in Figure 14.4.

Ethylene oxide (mp, –111°C; bp, 11°C) is a colorless, sweet-smelling, flammable, explosive gas. It is used as a chemical intermediate, sterilant, and fumigant. It has a moderate to high toxicity, is a mutagen, and is carcinogenic to experimental animals. When inhaled, ethylene oxide causes respiratory tract irritation, headache, drowsiness, and dyspnea. At higher levels, cyanosis, pulmonary edema, kidney damage, peripheral nerve damage, and death can result from inhalation of this compound. Animal studies have shown that inhalation of ethylene oxide causes a variety of tumors, raising concerns that it may be a human carcinogen.[8]

Propylene oxide (mp, –104°C; bp, 34°C) is a colorless, reactive, volatile liquid with uses similar to those of ethylene oxide. Its toxic effects are like those of ethylene oxide, though less severe. The properties of butylene oxide (liquid; bp, 63°C) are also similar to those of ethylene oxide. The oxidation product of 1,3-butadiene, 1,2,3,4-butadiene epoxide, is a direct-acting (primary) carcinogen.

As discussed in Section 13.5, benzene-1,2-oxide is an intermediate in the biochemical oxidation of benzene. It is probably responsible for the toxicity of benzene. It is hydrolyzed by the action of epoxide hydratase to the dihydrodiol shown below:

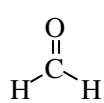


Benzene *trans*-1,2-dihydrodiol

Naphthalene-1,2-oxide is a metabolic intermediate in the oxidation of naphthalene mediated by cytochrome P-450.

14.5 FORMALDEHYDE

Aldehydes and ketones are compounds that contain the carbonyl (C=O) group. Of these compounds, **formaldehyde**,



Formaldehyde

is uniquely important for several reasons. Among these are that its physical and chemical properties are atypical of aldehydes in some important respects. Furthermore, it is widely used in a number of applications and exhibits toxicological chemical behavior that may differ substantially from that of other common aldehydes. Therefore, formaldehyde is discussed separately in this section. Other aldehydes and ketones are covered in the following section.

14.5.1 Properties and Uses of Formaldehyde

Formaldehyde (mp, –118°C; bp, –19°C) is a colorless gas with a pungent, suffocating odor. It is manufactured by the oxidation of methanol over a silver catalyst. Because it undergoes a number of important reactions in chemical synthesis and can be made at relatively low cost, formaldehyde is one of the most widely used industrial chemicals. In the pure form it polymerizes with itself to give hydroxyl compounds, ketones, and other aldehydes. Because of this tendency, commercial formaldehyde is marketed as a 37 to 50% aqueous solution containing some methanol called **formalin**. Formaldehyde is a synthesis intermediate in the production of resins (particularly phenolic resins), as well as a large number of synthetic organic compounds, such as chelating agents. Formalin is employed in antiseptics, fumigants, tissue and biological specimen preservatives, and embalming fluid.

14.5.2 Toxicity of Formaldehyde and Formalin

The fact that formaldehyde is produced by natural processes in the environment and in the body would suggest that it might not be very toxic. However, such is not the case in that formaldehyde exhibits a number of toxic effects.

Exposure to inhaled formaldehyde via the respiratory tract is usually to molecular formaldehyde vapor, whereas exposure by other routes is usually to formalin. Exposure to formaldehyde vapor can occur in industrial settings. In recent years, a great deal of concern has arisen over the potential for exposure in buildings to formaldehyde vapor evolved from insulating foams that were not properly formulated and cured or when these foams burn. Hypersensitivity can result from prolonged, continuous exposure to formaldehyde. Furthermore, animal experiments have shown formaldehyde to be a lung carcinogen.

The human LD_{50} for the ingestion of formalin has been estimated at around 45 g. Deaths have been caused by as little as about 30 g, and individuals have survived ingestion of about 120 g, although in at least one such case removal of the stomach was required. Ingestion results in violent gastrointestinal disturbances, including vomiting and diarrhea. Formaldehyde attacks the mucous membrane linings of both the respiratory and alimentary tracts and reacts strongly with functional groups in molecules.

Metabolically, formaldehyde is rapidly oxidized to formic acid (see Section 14.7), which is responsible in large part for its toxicity. Formaldehyde reacts by addition and condensation reactions with a variety of biocompounds, including DNA and proteins, and in so doing forms adducts and DNA–protein cross-links.[9] Formaldehyde is incorporated into proteins and nucleic acids as the $–CH_3$ group. Reactive formaldehyde has a short systemic lifetime of only about 1 min; its formic acid metabolic product has a longer metabolic lifetime.

14.6 ALDEHYDES AND KETONES

In **aldehydes** the carbonyl group, C=O, is attached to a C and H atom at the end of a hydrocarbon chain, and in a **ketone** it is bonded to two C atoms in the middle of a hydrocarbon chain or ring. The hydrocarbon portion of aldehydes and ketones may consist of saturated or unsaturated straight

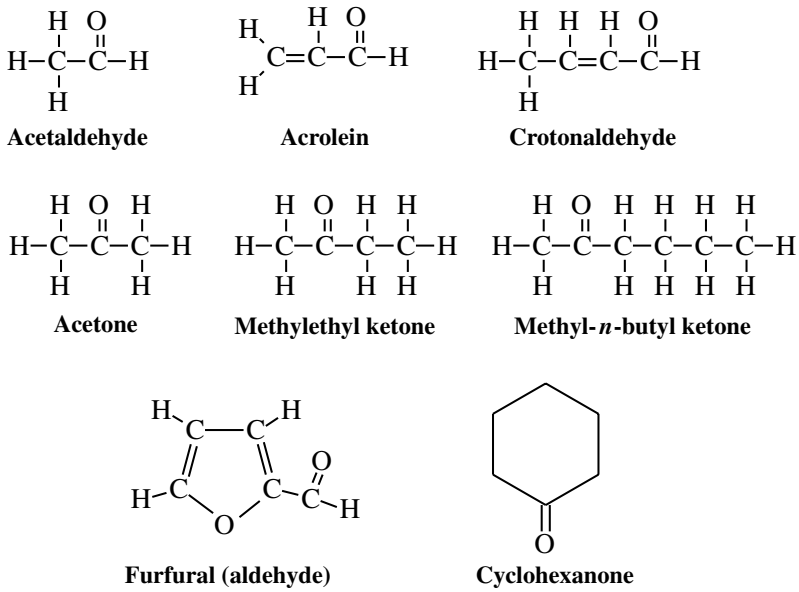


Figure 14.5 Aldehydes and ketones that are significant for their commercial uses and toxicological importance.

chains, branched chains, or rings. The structures of some important aldehydes and ketones are shown in Figure 14.5.

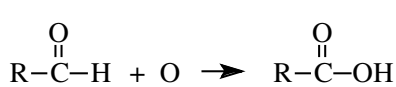
Both aldehydes and ketones are industrially important classes of chemicals. Aldehydes are reduced to make the corresponding alcohols and are used in the manufacture of resins, dyes, plasticizers, and alcohols. Some aldehydes are ingredients in perfumes and flavors. Several ketones are excellent solvents and are widely used for that purpose to dissolve gums, resins, laquers, nitrocellulose, and other substances.

14.6.1 Toxicities of Aldehydes and Ketones

In general, because of their water solubility and intensely irritating qualities, the lower aldehydes attack exposed moist tissue, particularly tissue in the eyes and mucous membranes of the upper respiratory tract. Because of their lower water solubility, the lower aldehydes can penetrate further into the respiratory tract and affect the lungs.

The toxicity of formaldehyde was discussed in the preceding section. The next higher aldehyde, acetaldehyde, is a colorless, volatile liquid (bp, 21°C). Toxicologically it acts as an irritant, and systemically as a narcotic to the central nervous system. Acrolein, a highly reactive alkenic aldehyde, is a colorless to light yellow liquid (bp, 52°C). It is a very reactive chemical that polymerizes readily. It is quite toxic by all routes of contact and ingestion. It has a choking odor and is extremely irritating to respiratory tract membranes. It is classified as an extreme lachrymator (substance that causes eyes to water). Because of this property, acrolein serves to warn of its own exposure. It can produce tissue necrosis, and direct contact with the eye can be especially hazardous. Crotonaldehyde is similarly dangerous and can cause burns to the eye cornea.

Metabolically, aldehydes are converted to the corresponding organic acids, as shown by the following general reaction:

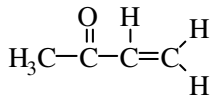


(14.6.1)

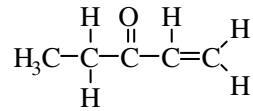
In mammals, the liver enzymes aldehyde dehydrogenase and aldehyde oxidase appear to be mainly responsible for this reaction.

Acetone is a liquid with a pleasant odor. It can act as a narcotic and dissolves fats from skin, causing dermatitis. Methyl-*n*-butyl ketone, a widely used solvent, is a mild neurotoxin. Methylethyl ketone is suspected of having caused neuropathic disorders in shoe factory workers.

Methylvinyl ketone and ethylvinyl ketone,



Methylvinyl ketone



Ethylvinyl ketone

are both classified as α,β-unsaturated ketones. These compounds and α,β-unsaturated aldehydes, of which acrolein is an example, are mutagenic and therefore potentially carcinogenic. Human exposure to these compounds can result from a number of sources, including industrial chemicals (a purpose for which methyvinyl ketone is widely used), metabolites of industrial chemicals, pesticide metabolites, natural products, and pollutants. Ethylvinyl ketone is an especially common contaminant of foods, having been detected in meat, dairy products, fruit juices, kiwi fruit, and other foods. Both of these ketones have been found to form adducts with the guanine moiety in deoxyguanosine nucleoside and in 2'-deoxyguanosine 5'-monophosphate nucleotide (see Section 3.7). When inhaled, methylvinyl ketone is classified as a reactive, direct-acting gaseous irritant.[10]

14.7 CARBOXYLIC ACIDS

Carboxylic acids contain the –C(O)OH functional group bound to an aliphatic, olefinic, or aromatic hydrocarbon moiety. This section deals with those carboxylic acids that contain only C, H, and O. Carboxylic acids that contain other elements, such as trichloroacetic acid (a strong acid) or deadly poisonous monofluoroacetic acid, are discussed in later chapters. Some of the more significant carboxylic acids are shown in Figure 14.6.

Carboxylic acids are the oxidation products of aldehydes and are often synthesized by that route. Some of the higher carboxylic acids are constituents of oil, fat, and wax esters, from which they are prepared by hydrolysis. Carboxylic acids have many applications. Formic acid is used as a relatively inexpensive acid to neutralize base, in the treatment of textiles, and as a reducing agent. Acetic and propionic acids are added to foods for flavor and as preservatives. Among numerous other applications, these acids are also used to make cellulose plastics. Stearic acid acts as a dispersive agent and accelerator activator in rubber manufacture. Sodium stearate is a major ingredient of most soaps. Many preservative and antiseptic formulations contain benzoic acid. Large quantities of phthalic acid are used to make phthalate ester plasticizers (see Section 14.10). Acrylic acid and methacrylic acid (acrylic acid in which the alpha-hydrogen has been replaced with a $–CH_3$ group; see Figure 14.6) are used in large quantities to make acrylic polymers.

14.7.1 Toxicology of Carboxylic Acids

Concentrated solutions of formic acid are corrosive to tissue, much like strong mineral acids. In Europe, decalcifier formulations containing about 75% formic acid have been marketed for removing mineral scale. Children ingesting this material have suffered corrosive lesions to mouth and esophageal tissue. Although acetic acid is widely used in food preparation as a 4 to 6% solution in vinegar, pure acetic acid (glacial acetic acid) is extremely corrosive to tissue that it contacts.

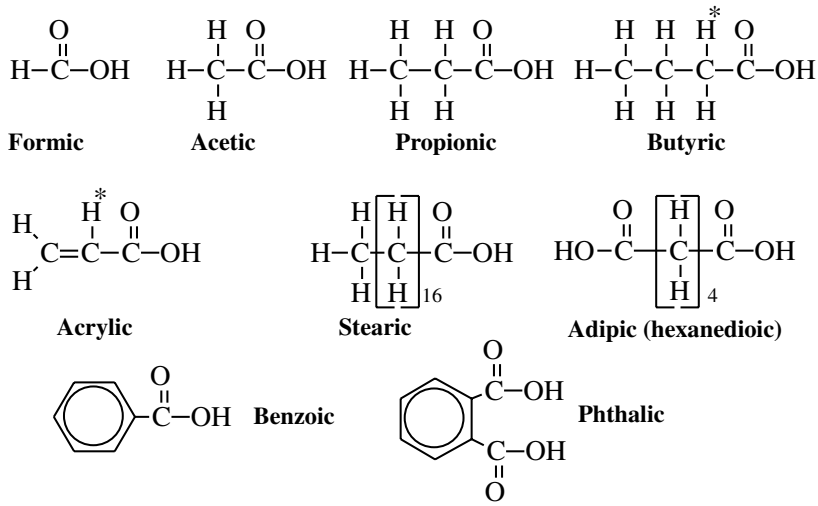


Figure 14.6 Some common carboxylic acids. The positions of the alpha-hydrogens have been marked with an asterisk for butyric and acrylic acids.

Acrylic and methacrylic acids are considered to be relatively toxic, both orally and by skin contact. In general, the presence of more than one carboxylic acid group per molecule, unsaturated bonds in the carbon skeleton, or the presence of a hydroxide group on the alpha-carbon position (see Figure 14.6) increases corrosivity and toxicity of carboxylic acids.

14.8 ETHERS

Three important classes of oxygenated organic compounds can be regarded as products of condensation of compounds containing the –OH group accompanied by a loss of H_2O, as shown by the following reaction:

$$R\text{–}OH + HO\text{–}R' \rightarrow R\text{–}O\text{–}R' + H_2O \qquad (14.8.1)$$

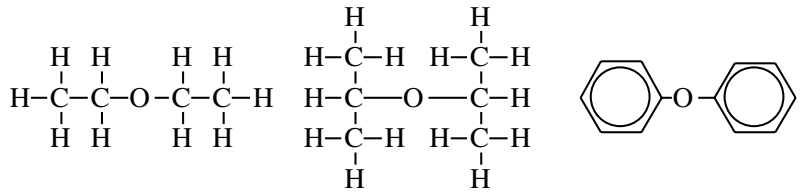
In this reaction, R–OH and HO–R' are either alcohols or carboxylic acids. When both are alcohols, R–O–R' is an ether; when one is an acid and the other an alcohol, the product is an ester; and when both are acids, an acid anhydride is produced. Ethers are discussed in this section, and the other two classes of products are discussed in the two sections that follow.

14.8.1 Examples and Uses of Ethers

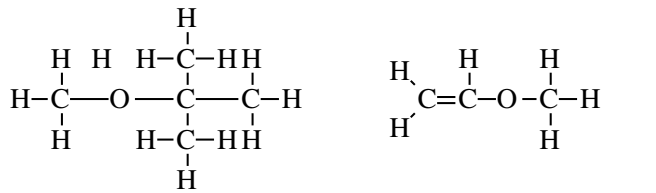
An ether consists of two hydrocarbon moieties linked by an oxygen atom, as shown in Figure 14.7. Although diethyl ether is highly flammable, ethers are generally not very reactive. This property enables their uses in applications where an unreactive organic solvent is required. Some ethers form explosive peroxides when exposed to air, as shown by the example of diethyl ether peroxide in Figure 14.7.

Ethers are prominent members of a class of organic substances widely used as solvents, including hydrocarbons, chlorinated hydrocarbons, and alcohols, as well as ethers. Because of the widespread use of such solvents, human exposure is particularly likely.

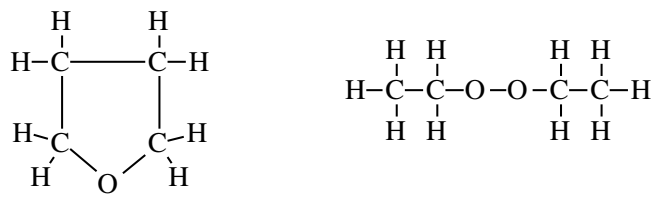
Diethyl ether (mp, –116°C; bp, 34.6°C) is the most commercially important ether. It is used as a reaction medium, solvent, and extractant. The production of methyl *tert*-butyl ether increased markedly during the 1990s because of its application as an antiknock ingredient of unleaded



Diethyl ether **Di-isopropyl ether** **Diphenyl ether**



Methyl *tert*-butyl ether **Vinyl methyl ether**



Tetrahydrofuran (cyclic ether) **Peroxide from diethyl ether**

Figure 14.7 Structures of some common ethers.

gasoline, but its uses in this application are now being curtailed because it has become a troublesome water pollutant.

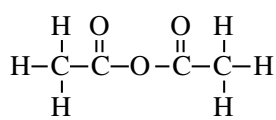
14.8.2 Toxicities of Ethers

Because of its volatility, the most likely route of exposure to diethyl ether is by inhalation. About 80% of this compound that gets into the body is eliminated unmetabolized as the vapor through the lungs. Diethyl ether is a central nervous system depressant, and for many years was the anesthetic of choice for surgery. At low doses, it causes drowsiness, intoxication, and stupor. Higher exposures result in unconsciousness and even death.

Compared to other classes of organic compounds, ethers have relatively low toxicities. This characteristic can be attributed to the low reactivity of the C–O–C functional group arising from the high strength of the carbon–oxygen bond. Like diethyl ether, several of the more volatile ethers affect the central nervous system. Hazards other than their toxicities tend to be relatively more important for ethers. These hazards are flammability and formation of explosive peroxides (especially with di-isopropyl ether).

14.9 ACID ANHYDRIDES

The most important carboxylic **acid anhydride** is acetic anhydride, the structure of which is



Acetic anhydride

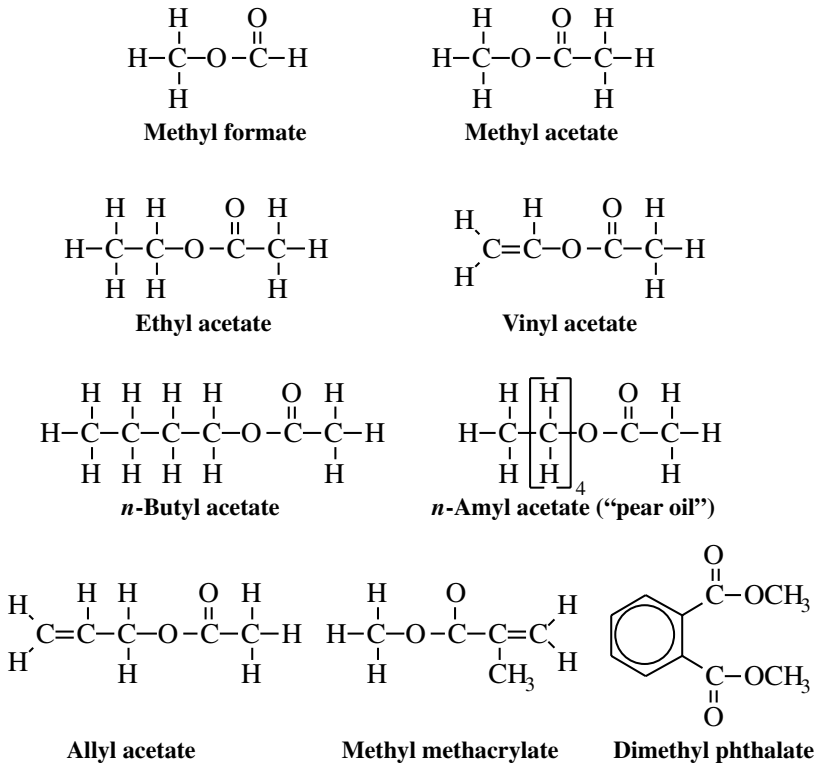


Figure 14.8 Some typical esters.

Annual world production of this chemical compound is on the order of a million metric tons. In chemical synthesis it functions as an acetylating agent (addition of $CH_3C(O)$ moiety). Its greatest single use is to make cellulose acetate, and it has additional applications in manufacturing textile sizing agents, the synthesis of salicylic acid (for aspirin manufacture), electrolytic polishing of aluminum, and the processing of semiconductor components.

14.9.1 Toxicological Considerations

In contrast to the relative safety of many ethers and esters, acetic anhydride is a systemic poison and especially corrosive to the skin, eyes, and upper respiratory tract. Levels in the air as low as 0.4 mg/m^3 adversely affect eyes, and contamination should be kept to less than one tenth that level in the workplace atmosphere. Blisters and burns that heal slowly result from skin exposure. Acetic anhydride has a very strong acetic acid odor that causes an intense burning sensation in the nose and throat that is accompanied by coughing. It is a powerful lachrymator. Fortunately, these unpleasant symptoms elicit a withdrawal response in exposed individuals.

14.10 ESTERS

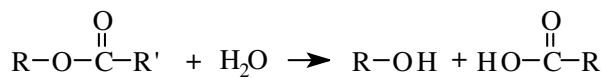
Esters, such as those shown in Figure 14.8, are formed from an alcohol and acid, the reverse of reaction 14.10.1. Esters exhibit a wide range of biochemical diversity, and large numbers of them occur naturally. Fats, oils, and waxes are esters, as are many of the compounds responsible for odors and flavors of fruits, flowers, and other natural products. It follows that many esters are not toxic. Synthetic versions of many of the esters that occur naturally are produced for purposes such as flavoring ingredients. A number of esters that are not natural products have been synthesized

for various purposes. Esters are used in industrial applications as solvents, plasticizers, lacquers, soaps, and surfactants. Figure 14.8 shows some representative esters.

Methyl formate has some industrial uses. It hydrolyzes in the body to methanol and formic acid.[11] Methyl acetate is a colorless liquid with a pleasant odor. It is used as a solvent and as an additive to give foods a fruit-like taste. Ethyl acetate is a liquid with a pleasant odor. Liquid vinyl acetate polymerizes when exposed to light to yield a solid polymer. Both *n*-butyl acetate and *n*-amyl acetate are relatively higher-boiling liquids than the esters mentioned above. Amyl acetate has a characteristic odor of bananas and pears. Methyl methacrylate is the monomer used to make some kinds of polymers noted for their transparency and resistance to weathering. Among their other applications, these polymers are used as substitutes for glass, particularly in automobile lights. Dimethyl phthalate is the simplest example of the environmentally important phthalate esters. Other significant members of this class of compounds are diethyl, di-*n*-butyl, di-*n*-octyl, bis(2-ethylhexyl), and butyl benzyl phthalates. Used in large quantities as plasticizers to improve the qualities of plastics, these compounds have become widespread environmental pollutants. The higher-molecular-mass phthalate compounds, especially, tend to be environmentally persistent.

14.10.1 Toxicities of Esters

The most common reaction of esters in exposed tissues is hydrolysis:



(14.10.1)

To a large extent, therefore, the toxicities of esters tend to be those of their hydrolysis products. Two physical characteristics of many esters that affect their toxicities are relatively high volatility, which promotes exposure by the pulmonary route, and good solvent action, which affects penetration and tends to dissolve body lipids. Many volatile esters exhibit asphyxiant and narcotic action. As expected for compounds that occur naturally in foods, some esters are nontoxic (in reasonable doses). However, some of the synthetic esters, such as allyl acetate, have relatively high toxicities. As an example of a specific toxic effect, vinyl acetate acts as a skin defatting agent.

Although environmentally persistent, most of the common phthalates have low toxicity ratings of 2 or 3, based on acute toxic effects. There is particular concern with regard to di-2-ethylhexyl phthalate used as a plasticizer in polyvinyl chloride plastic medical devices.[12] Dialysis patients and hemophiliacs who receive frequent blood transfusions are especially likely to receive potentially harmful levels of di-2-ethylhexyl phthalates from contact of fluids with such devices.

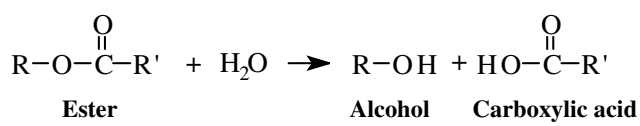
REFERENCES

1. Lanigan, R.S., Final report on the safety assessment of methyl alcohol, *Int. J. Toxicol.*, 20 (Suppl. 1), 57–85, 2001.
2. Eells, J. et al., Development and characterization of a rodent model of methanol-induced retinal and optic nerve toxicity, *Neurotoxicology*, 21, 321–330, 2000.
3. Glatthar, J., Seen, T., and Pieper, H.J., Investigations on reducing the methanol content in distilled spirits made of bartlett pears, *Deutsche Lebensmittel-Rundschau*, 97, 209–216, 2001.
4. Lumeng, L. and Crabb, D.W., Alcoholic liver disease, *Curr. Opin. Gastroenterol.*, 17, 211–220, 2001.
5. Brent, J., Current management of ethylene glycol poisoning, *Drugs*, 61, 979–988, 2001.
6. Gosselin, R.E., Smith, R.P., and Hodge, H.C., Phenol, in *Clinical Toxicology of Commercial Products*, 5th ed., Williams & Wilkins, Baltimore, 1984, pp. III-344–III-348.

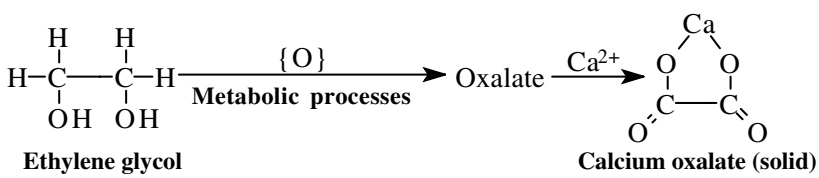
7. Staimer, N., Gee, S.J., and Hammock, B.D., Development of a class-selective enzyme immunoassay for urinary phenolic glucuronides, *Anal. Chim. Acta,* 441, 27–36, 2001.
8. Liteplo, R.G., Meek, M.E., and Bruce, W., Ethylene oxide: hazard characterization and exposure–response analysis, *Environ. Carcinog. Ecotoxicol. Rev.*, C19, 219–265, 2001.
9. Thrasher, J.D. and Kilburn, K.H., Embryo toxicity and teratogenicity of formaldehyde, *Arch. Environ. Health*, 56, 300–311, 2001.
10. Morgan, D.L. et al., Upper respiratory tract toxicity of inhaled methylvinyl ketone in F344 rats and B6C3F1 mice, *Toxicol. Sci.*, 58, 182–194, 2000.
11. Nihlen, A. and Droz, P.-O., Toxicokinetic modeling of methyl formate exposure and implications for biological monitoring, *Int. Arch. Occup. Environ. Health*, 73, 479–487, 2000.
12. Tickner, J.A. et al., Health risks posted by use of di-2-ethylhexyl phthalate (DEHP) in PVC medical devices: a critical review, *Am. J. Ind. Med.*, 39, 100–111, 2001.

QUESTIONS AND PROBLEMS

1. What are several of the bases for classifying organooxygen compounds?
2. In what respects are the chemical and toxicological chemical characteristics of methanol unique? What are some of the particular toxicological hazards of methanol?
3. What is the metabolic pathway of methanol degradation? How does this result in acidosis?
4. What are the major acute toxicological effects of ethanol? How is ethanol exposure usually measured or expressed? What is a particular chronic toxicological effect of long-term ethanol ingestion?
5. What are the metabolic products of ethanol oxidation in the body? How does the rate of ethanol metabolism compare to that of methanol metabolism?
6. What is the name of the long-chain alcohol $CH_3(CH_2)_6CH_2OH$? What is its water solubility? How is this alcohol used to describe bioaccumulation effects? What is the name of the parameter obtained using this alcohol to describe such effects?
7. In general, what are the toxicological characteristics of esters. Why is it reasonable to believe that many esters are not particularly toxic? What does the reaction below imply about the toxicities of esters?



8. What toxicological effect may result from the reaction below? Which organ is most susceptible to damage as a result?

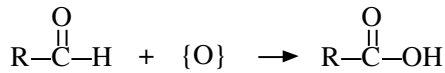


9. Match the following pertaining to organooxygen compounds:

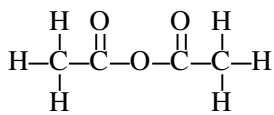
(a) $CH_3CHOHCH_3$	1. Olefinic alcohol
(b) $CH_2{=}CHCH_2OH$	2. *n*-Butanol
(c) $CH_3(CH_2)_2CH_2OH$	3. Used in bioaccumulation studies
(d) $CH_3(CH_2)_6CH_2OH$	4. Rubbing alcohol, food additive

10. What is shown by the following reaction? To what extent does this reaction occur?

11. Discuss the toxicology of phenol. Is it known to have many toxic effects? Why were so many people exposed around 100 years ago? What is meant by phenol being a protoplasmic poison?
12. What are epoxides? In what sense might they be regarded as ethers? Is there any way that epoxides may be formed from other kinds of compounds in the body? How might this occur?
13. What are the toxicological characteristics of formaldehyde? In what sense is the toxicological chemistry of formaldehyde unique? What is formalin? How is it related to formaldehyde? What metabolic phenomenon suggests that formaldehyde is not very toxic? Is this true?
14. What distinguishes an aldehyde from a ketone? From the material given in this chapter, can one conclude that there are any substantial differences in toxicities between aldehydes and ketones?
15. In large part because of the water solubility and intensely irritating qualities of the lower aldehydes, which kinds of tissue are these compounds most prone to attack?
16. Explain what is shown by the following general reaction in terms of the metabolism of an important class of toxic compounds:



17. Why is it reasonable to believe that many carboxylic acids have only limited toxicities? Give some examples of carboxylic acids that are quite toxic.
18. Ethers are often used in applications where an unreactive organic solvent is required. In what sense are ethers unreactive? How is this reflected in their toxicological chemistry?
19. What is the most likely route of exposure to diethyl ether? How is much of the diethyl ether that enters the body by this route subsequently eliminated?
20. What are some of the important chemical and toxicological characteristics of the compound shown below:



CHAPTER 15

Organonitrogen Compounds

15.1 INTRODUCTION

Nitrogen occurs in a wide variety of organic compounds of both synthetic and natural origin. This chapter discusses organic compounds that contain carbon, hydrogen, and nitrogen. Many significant organonitrogen compounds contain oxygen as well, and these are covered in later parts of the chapter. Not the least of the concerns regarding organonitrogen compounds is that a significant number of these compounds (including some aromatic amines and nitrosamines) are carcinogenic.

15.2 NONAROMATIC AMINES

15.2.1 Lower Aliphatic Amines

Amines may be regarded as derivatives of ammonia, NH_3, in which one to three of the H atoms have been replaced by hydrocarbon groups. When these groups are aliphatic groups of which none contains more than six C atoms, the compound may be classified as a **lower aliphatic amine**. Among the more commercially important of these amines are mono-, di-, and trimethylamine; mono-, di-, and triethylamine; dipropylamine; isopropylamine; butylamine; dibutylamine; diisobutylamine; cyclohexylamine; and dicyclohexylamine. Example structures are given in Figure 15.1.

The structures in Figure 15.1 indicate some important aspects of amines. Methylamine, methyl-2-propylamine, and triethylamine are primary, secondary, and tertiary amines, respectively. A primary amine has one hydrocarbon group substituted for H on NH_3, a secondary amine has two, and a tertiary amine has three. Dicyclohexylamine has two cycloalkane substituent groups attached and is a secondary amine. All of the aliphatic amines have strong odors. Of the compounds listed above as commercially important aliphatic amines, the methylamines and monoethylamine are gases under ambient conditions, whereas the others are colorless volatile liquids. The lower aliphatic amines are highly flammable. They are used primarily as intermediates in the manufacture of other chemicals, including polymers (rubber, plastics, textiles), agricultural chemicals, and medicinal chemicals.

The lower aliphatic amines are generally among the more toxic substances in routine, large-scale use. One of the reasons for their toxicity is that they are basic compounds and raise the pH of exposed tissue by hydrolysis with water in tissue, as shown by the following reaction:

$$R_3N + H_2O \rightarrow R_3NH^+ + OH^- \qquad (15.2.1)$$

Furthermore, these compounds are rapidly and easily taken into the body by all common exposure routes. The lower amines are corrosive to tissue and can cause tissue necrosis at the point of contact.

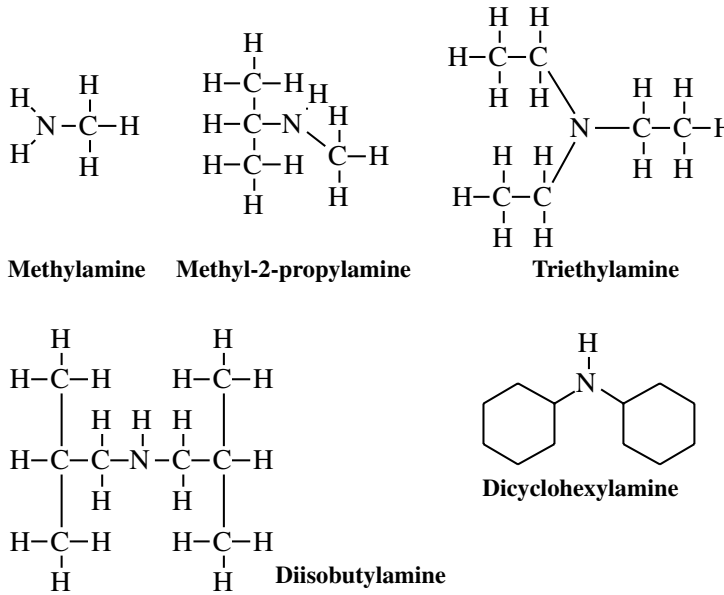


Figure 15.1 Examples of lower aliphatic amines.

Sensitive eye tissue is vulnerable to amines. These compounds can have systemic effects on many organs in the body. Necrosis of the liver and kidneys can occur, and exposed lungs can exhibit hemorrhage and edema. The immune system may become sensitized to amines.

Of the lower aliphatic amines, cyclohexylamine and dicyclohexylamine appear to have received the most attention for their toxicities. In addition to its caustic effects on eyes, mucous membranes, and skin, cyclohexylamine acts as a systemic poison. In humans the symptoms of systemic poisoning by this compound include nausea to the point of vomiting, anxiety, restlessness, and drowsiness. It adversely affects the female reproductive system. Dicyclohexylamine produces similar symptoms, but is considered to be more toxic. It is appreciably more likely to be absorbed in toxic levels through the skin, probably because of its less polar, more lipid-soluble nature.

15.2.2 Fatty Amines

Fatty amines are those containing alkyl groups having more than six carbon atoms. The commercial fatty amines are synthesized from fatty acids that occur in nature and are used as chemical intermediates. Other major uses of fatty amines and their derivatives include textile chemicals (particularly fabric softeners), emulsifiers for petroleum and asphalt, and flotation agents for ores.

Some attention has been given to the toxicity of octadecylamine, which contains a straight-chain, 18-carbon alkane group, because of its use as an anticorrosive agent in steam lines. There is some evidence to suggest that the compound is a primary skin sensitizer.

15.2.3 Alkyl Polyamines

Alkyl polyamines are those in which two or more amino groups are bonded to alkane moieties. The structures of the four most significant of these are shown in Figure 15.2. These compounds have a number of commercial uses, such as for solvents, emulsifiers, epoxy resin hardeners, stabilizers, and starting materials for dye synthesis. They also act as chelating agents; triethylene-tetramine is especially effective for this purpose. Largely as a result of their strong alkalinity, the alkyl polyamines tend to be skin, eye, and respiratory tract irritants. The lower homologues are relatively stronger irritants.

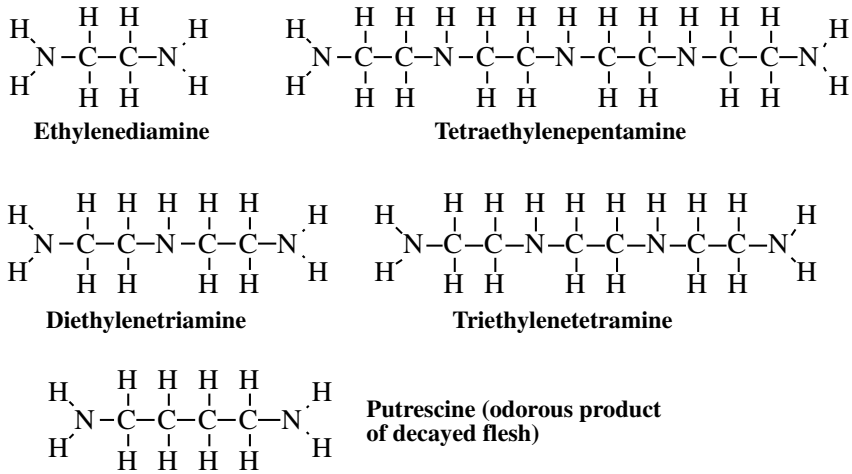


Figure 15.2 Alkyl polyamines in which two or more amino groups are bonded to an alkane group.

Of the common alkyl polyamines, ethylenediamine is the most notable because of its widespread use and toxicity. Although it has a toxicity rating of only three, it can be very damaging to the eyes and is a strong skin sensitizer. The dihydrochloride and dihydroiodide salts have some uses as human and veterinary pharmaceuticals. The former is administered to acidify urine, and the latter as an iodine source. Putrescine is a notoriously odorous naturally occurring substance produced by bacteria in decaying flesh.

15.2.4 Cyclic Amines

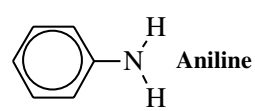
Four simple amines in which N atoms are contained in a ring structure are shown in Figure 15.3. Of the compounds shown in Figure 15.3, the first three are liquids under ambient conditions and have the higher toxicity hazards expected of liquid toxicants. All four compounds are colorless in the pure form, but pyrrole darkens upon standing. All are considered to be toxic via the oral, dermal, and inhalation routes. There is little likelihood of inhaling piperazine, except as a dust, because of its low volatility.

15.3 CARBOCYCLIC AROMATIC AMINES

Carbocyclic aromatic amines are those in which at least one substituent group is an aromatic ring containing only C atoms as part of the ring structure, and with one of the C atoms in the ring bonded directly to the amino group. There are numerous compounds with many industrial uses in this class of amines. They are of particular toxicological concern because several have been shown to cause cancer in the human bladder, ureter, and pelvis, and are suspected of being lung, liver, and prostate carcinogens.

15.3.1 Aniline

Aniline,



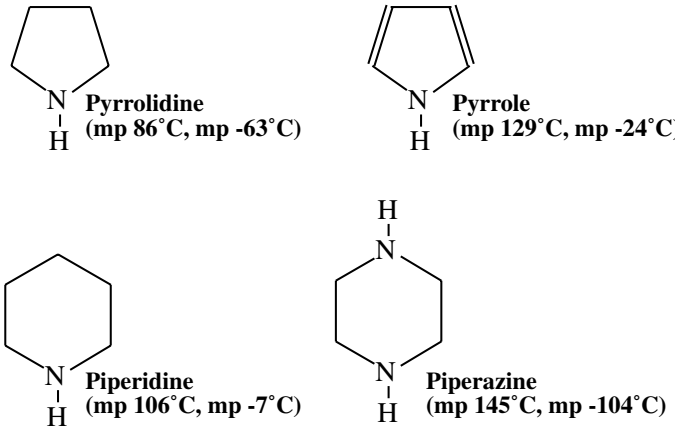


Figure 15.3 Some common cyclic amines.

has been an important industrial chemical for many decades. Currently, it is most widely used for the manufacture of polyurethanes and rubber, with lesser amounts consumed in the production of pesticides (herbicides, fungicides, insecticides, animal repellants), defoliants, dyes, antioxidants, antidegradants, and vulcanization accelerators. It is also an ingredient of some household products, such as polishes (stove and shoe), paints, varnishes, and marking inks. Aniline is a colorless liquid with an oily consistency and distinct odor; it freezes at –6.2°C and boils at 184.4°C.

Aniline is considered to be very toxic, with a toxicity rating of 4. It readily enters the body by inhalation, by ingestion, and through the skin. In its absorption and toxicological characteristics, aniline resembles nitrobenzene, which is discussed in Section 15.6. Aniline was the toxic agent responsible for affecting more than 20,000 people and killing 300 in Spain in 1981. Known as the Spanish toxic oil syndrome, this tragic epidemic was due to aniline-contaminated olive oil.[1]

The most common effect of aniline in humans is methemoglobinemia, caused by the oxidation of iron(II) in hemoglobin to iron(III), with the result that the hemoglobin can no longer transport oxygen in the body. This condition is characterized by cyanosis and a brown–black color of the blood. Unlike the condition caused by reversible binding of carbon monoxide to hemoglobin, oxygen therapy does not reverse the effects of methemoglobinemia. The effects can be reversed by the action of the methemoglobin reductase enzyme, as shown by the following reaction:

$$\text{HbFe(III)} \xrightarrow{\text{Methemoglobin reductase}} \text{HbFe(II)} \qquad (15.3.1)$$

Rodents (mice, rats, rabbits) have a higher activity of this enzyme than do humans, so that extrapolation of rodent experiments with methemoglobinemia to humans is usually inappropriate. Methylene blue can also bring about the reduction of HbFe(III) to HbFe(II) and is used as an antidote for aniline poisoning.

Methemoglobinemia has resulted from exposure to aniline used as a vehicle in indelible laundry-marking inks, particularly those used to mark diapers. This condition was first recognized in 1886, and cases were reported for many decades thereafter. Infants who develop methemoglobinemia from this source suffer a 5 to 10% mortality rate. The skin of infants (particularly in the genital area; see Section 6.4) is more permeable to aniline than that of adults, and infant blood is more susceptible to methemoglobinemia.

Aniline must undergo biotransformation to cause methemoglobinemia because pure aniline does not oxidize iron(II) in hemoglobin to iron(III) *in vitro*. It is believed that the actual toxic agents

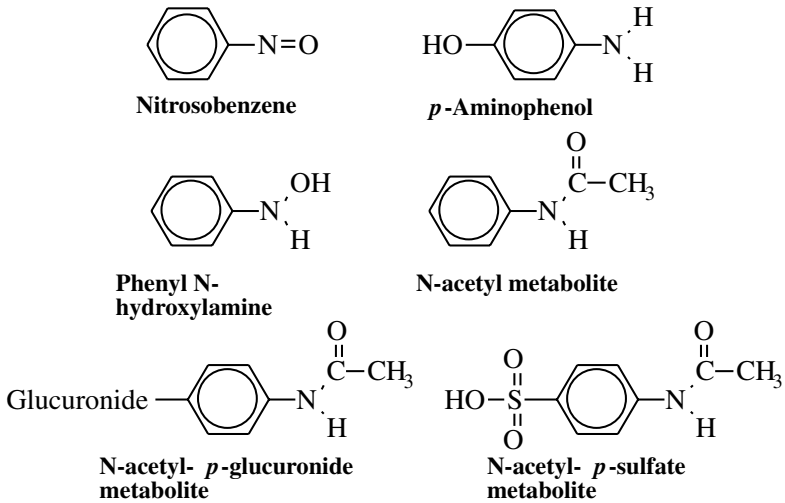
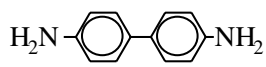


Figure 15.4 Metabolites of aniline that are toxic or excreted.

formed from aniline are nitrosobenzene, aminophenol, and phenyl N-hydroxylamine, shown in Figure 15.4. The hepatic detoxification mechanisms for aniline are not very effective. The metabolites of aniline excreted from the body are N-acetyl, N-acetyl-*p*-glucuronide, and N-acetyl-*p*-sulfate products, also shown in Figure 15.4.

15.3.2 Benzidine

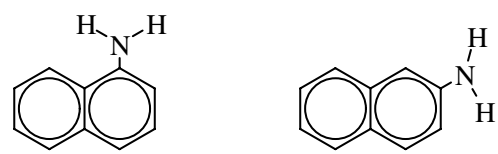
Benzidine, *p*-aminodiphenyl, is a solid compound that can be extracted from coal tar. It is highly toxic by oral ingestion, inhalation, and skin sorption and is one of the few proven human carcinogens. Its systemic effects include blood hemolysis, bone marrow depression, and kidney and liver damage.



Benzidine

15.3.3 Naphthylamines

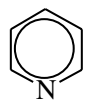
The two derivatives of naphthalene having single amino substituent groups are **1-naphthylamine** (alpha-naphthylamine) and **2-naphthylamine** (beta-naphthylamine). Both of these compounds are solids (lump, flake, dust) under normal conditions, although they may be encountered as liquids and vapors. Exposure can occur through inhalation, the gastrointestinal tract, or skin. Both compounds are highly toxic and are proven human bladder carcinogens.



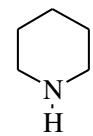
1-Naphthylamine **2-Naphthylamine**

15.4 PYRIDINE AND ITS DERIVATIVES

Pyridine is a colorless liquid mp, –42°C; bp, 115°C) with a sharp, penetrating odor that can perhaps best be described as terrible. It is an aromatic compound in which an N atom is part of a six-membered ring. The most important derivatives of pyridine are the mono-, di-, and trimethyl derivatives; the 2-vinyl and 4-vinyl derivatives; 5-ethyl-2-methylpyridine (MEP); and piperidine, also called hexahydropyridine (below):



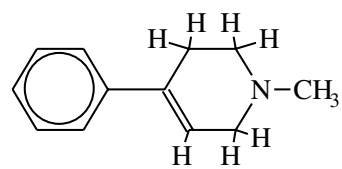
Pyridine



Piperidine

Pyridine and its substituted derivatives are recovered from coal tar. They tend to react like benzene and its analogous derivatives because of the aromatic ring. The major use of pyridine is as an initiator in the process by which rubber is vulcanized. Although considered moderately toxic, with a toxicity rating of three, pyridine has caused fatalities. Symptoms of acute pyridine poisoning from inhalation of the vapor have included eye irritation, nose and throat irritation, dizziness, abdominal discomfort, nausea, palpitations, and light-headedness.[2] Longer-term symptoms include diarrhea, anorexia, and fatigue. The major psychopathological effect of pyridine poisoning is mental depression.

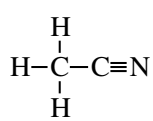
A notably toxic pyridine derivative is 1,2,3,6-tetrahydro-1-methyl-4-phenylpyridine (MPTP), which has the structural formula shown below:



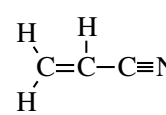
This compound is a protoxicant that readily crosses the blood–brain barrier, where it is acted on by the monoamine oxidase enzyme system to produce a positively charged neurotoxic species that cannot readily cross the blood–brain barrier to leave the brain. The result has been described as "selective neuronal death of the dopaminergic neurons in the zona compacta of the substantia nigra."[3] The symptoms of this disorder are very similar to Parkinson's disease, one of several common and devastating neurodegenerative diseases.

15.5 NITRILES

Nitriles are organic analogs of highly toxic hydrogen cyanide, HCN (see Section 11.2), where the H is replaced by a hydrocarbon moiety. The two most common nitriles are acetonitrile and acrylonitrile:



Acetonitrile



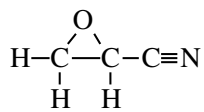
Acrylonitrile

Acetonitrile (mp, –45°C; bp, 81°C) is a colorless liquid with a mild odor. Because of its good solvent properties for many organic and inorganic compounds and its relatively low boiling point,

it has numerous industrial uses, particularly as a reaction medium that can be recovered. It is used as an organic solvent for lipophilic substances used in *in vitro* studies of metabolism of pharmaceutical agents.[4] Acetonitrile has a toxicity rating of 3 or 4; exposure can occur via the oral, pulmonary, and dermal routes. Although it is considered relatively safe, it is capable of causing human deaths, perhaps by metabolic release of cyanide.

Acrylonitrile is a colorless liquid with a peach-seed odor that is used in large quantities in the manufacture of acrylic fibers, dyes, and pharmaceutical chemicals. Containing both nitrile and C=C groups, acrylonitrile is a highly reactive compound with a strong tendency to polymerize. It has a toxicity rating of five, with a mode of toxic action resembling that of HCN. In addition to ingestion, it can be absorbed through the skin or by inhalation of the vapor. It causes blisters and arythema on exposed skin.

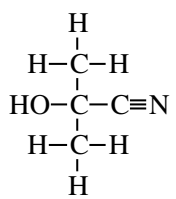
Because of its widespread industrial use and consequent worker exposure, the metabolism of acrylonitrile has been studied extensively.[5] There are two major pathways of acrylonitrile metabolism in humans. The first of these produces a glutathione conjugate and is considered to be detoxification. The second pathway produces cyanoethylene oxide,



Cyanoethylene oxide

followed by release of toxic cyanide, which inhibits enzymes responsible for respiration in tissue, thereby preventing tissue cells from utilizing oxygen. Acrylonitrile is a suspect carcinogen.

Acetone cyanohydrin (structure below) is an oxygen-containing nitrile that should be mentioned because of its extreme toxicity and widespread industrial applications. It is used to initiate polymerization reactions and in the synthesis of foaming agents, insecticides, and pharmaceutical compounds. A colorless liquid readily absorbed through the skin, it decomposes in the body to hydrogen cyanide, to which it should be considered toxicologically equivalent (toxicity rating, six) on a molecule-per-molecule basis.

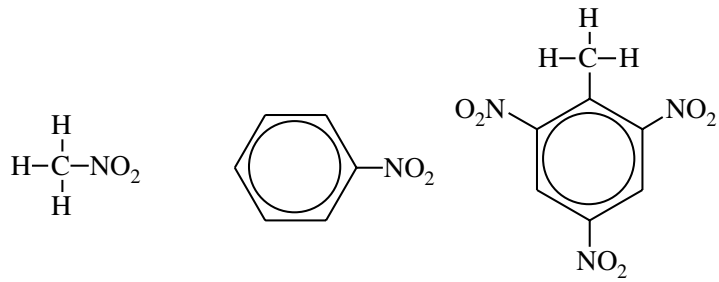


Acetone cyanohydrin

Nitriles are cyanogenic substances — substances that produce cyanide when metabolized. It is likely that nitriles are teratogens because of maternal production of cyanide in pregnant females. A study of the teratogenic effects on rats of saturated nitriles, including acetonitrile, propionitrile, and *n*-butyronitrile, and of unsaturated nitriles, including acrylonitrile, methacrylonitrile, allylnitrile, *cis*-2-pentenenitrile, and 2-chloroacrylonitrile, has shown a pattern of abnormal embryos similar to those observed from administration of inorganic cyanide.[6]

15.6 NITRO COMPOUNDS

The structures of three significant **nitro compounds**, which contain the $-NO_2$ functional group, are given in Figure 15.5.



Nitromethane **Nitrobenzene** **Trinitrotoluene (TNT)**

Figure 15.5 Some of the more important nitro compounds.

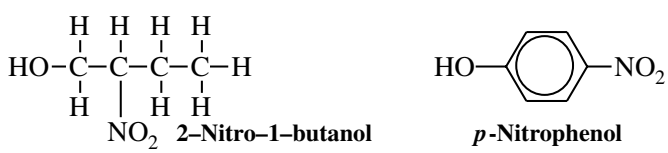
The lightest of the nitro compounds is **nitromethane**, an oily liquid (mp, –29°C; bp, 101°C). It has a toxicity rating of three. Symptoms of poisoning include anorexia, diarrhea, nausea, and vomiting. The organs that are most susceptible to damage from it are the kidneys and liver. Severe peripheral neuropathy has been reported in two workers strongly exposed to nitromethane for several weeks.[7]

Nitrobenzene is a pale yellow oily liquid (mp, 5.7°C; bp, 211°C) with an odor of bitter almonds or shoe polish. It is produced mainly for the manufacture of aniline. It can enter the body through all routes and has a toxicity rating of five. Its toxic action is much like that of aniline, including the conversion of hemoglobin to methemoglobin, which deprives tissue of oxygen. Cyanosis is a major symptom of nitrobenzene poisoning.

Trinitrotoluene (TNT) is a solid material widely used as a military explosive. It has a toxicity rating of three or four. It can damage the cells of many kinds of tissue, including those of bone marrow, kidney, and liver. Extensive knowledge of the toxicity of TNT was obtained during World War II in the crash program to manufacture huge quantities of it. Toxic hepatitis developed in some workers under age 30 exposed to TNT systemically, whereas aplastic anemia was observed in some older victims of exposure. In the United States during World War II, 22 cases of fatal TNT poisoning were documented (many more people were blown up during manufacture and handling).

15.6.1 Nitro Alcohols and Nitro Phenols

Nitro alcohols are nonaromatic compounds containing both –OH and $–NO_2$ groups. A typical example of such a compound is **2-nitro-1-butanol**, shown below. These compounds are used in chemical synthesis to introduce nitro functional groups or (after reduction) amino groups onto molecules. They tend to have low volatilities and moderate toxicities. The aromatic nitrophenol, ***p*-nitrophenol**, is an industrially important compound with toxicological properties resembling those of phenol and nitrobenzene.



2–Nitro–1–butanol ***p*-Nitrophenol**

15.6.2 Dinoseb

Dinoseb is a nitrophenolic compound, once widely used as an herbicide and plant desiccant, that is noted for its toxic effects. The chemical name of this compound is 4,6-dinitro-2-*sec*-butylphenol, and its structure is

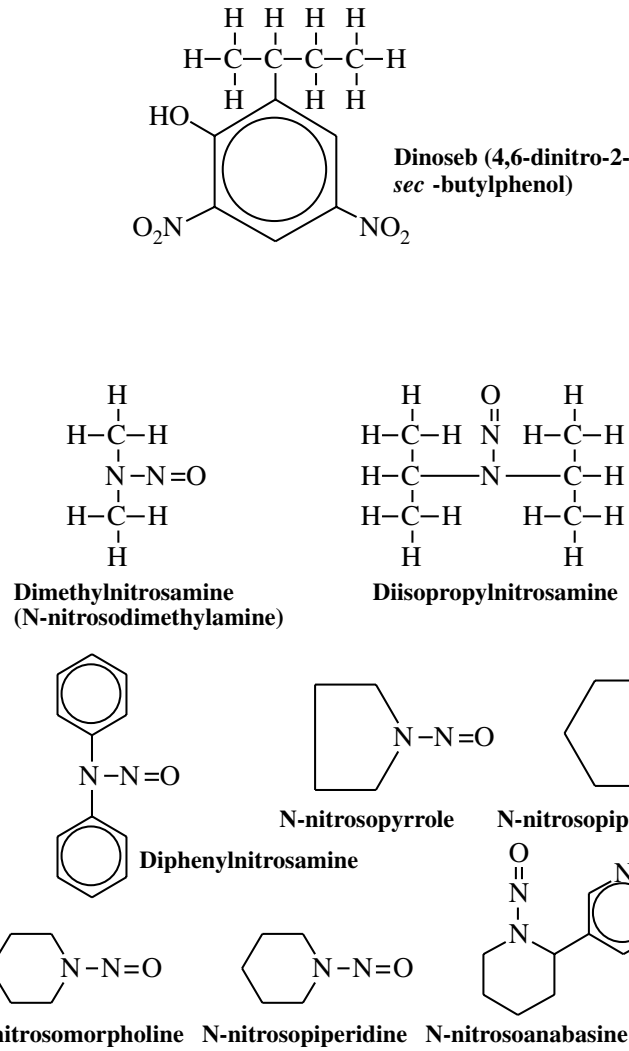


Figure 15.6 Examples of some important nitrosamines.

Dinoseb has a toxicity rating of five and is strongly suspected of causing birth defects in the children of women exposed to it early in pregnancy, as well as sterility in exposed men. In October 1986, the Environmental Protection Agency imposed an emergency ban on the use of the chemical, which was partially rescinded for the northwestern U.S. by court order early in 1987, although some uses were permitted, primarily in the northwestern U.S., through 1989. More than 10 years later, there were still controversies involving the cleanup of dinoseb-contaminated water in Washington State.[8]

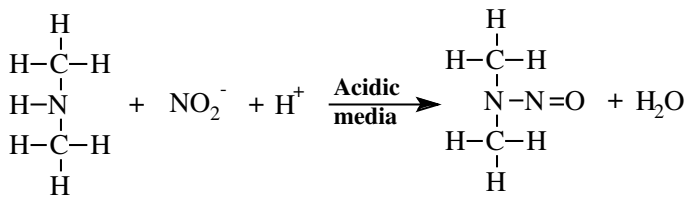
15.7 NITROSAMINES

N-nitroso compounds, commonly called **nitrosamines**, are a class of compounds containing the N–N=O functional group. They are of particular toxicological significance because most that have been tested have been shown to be carcinogenic. The structural formulas of some nitrosamines are shown in Figure 15.6.

Some nitrosamines have been used as solvents and as intermediates in chemical synthesis. They have been found in a variety of materials to which humans may be exposed, including beer, whiskey, and cutting oils used in machining.

By far the most significant toxicological effect of nitrosamines is their carcinogenicity, which may result from exposure to a single large dose or from chronic exposure to relatively small doses. Different nitrosamines cause cancer in different organs. The first nitrosamine extensively investigated for carcinogenicity was dimethylnitrosamine, once widely used as an industrial solvent. It was known to cause liver damage and jaundice in exposed workers, and studies starting in the 1950s subsequently revealed its carcinogenic nature. Dimethylnitrosamine was found to alkylate DNA, which is the mechanism of its carcinogenicity (the alkylation of DNA as a cause of cancer is noted in the discussion of biochemistry of carcinogesis in Section 7.8).

The common means of synthesizing nitrosamines is the low-pH reaction of a secondary amine and nitrite, as shown by the following example:



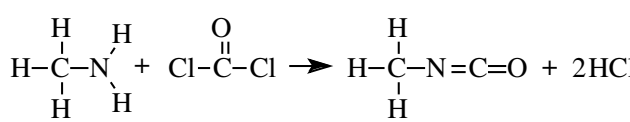
(15.7.1)

The possibility of this kind of reaction occurring *in vivo* and producing nitrosamines in the acidic medium of the stomach is some cause for concern over nitrites in the diet. Because of this possibility, nitrite levels have been reduced substantially in foods such as cured meats that formerly contained relatively high nitrite levels.

Tobacco (chewing tobacco and snuff) contains a variety of nitrosamines, including N-nitrosatabine, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, N-nitrosanabasine, N-nitrosopyrrolidine, N-nitronornicotine, N-nitrosopiperidine, and N-nitrosomorpholine (see examples in Figure 15.6). The enzymatic activation of these nitrosamines to mutagenic species has been studied using bacteria genetically activated to express the human enzymes responsible for such activation, cytochrome P-450 and NADPH–cytochrome P-450 reductase.[9]

15.8 ISOCYANATES AND METHYL ISOCYANATE

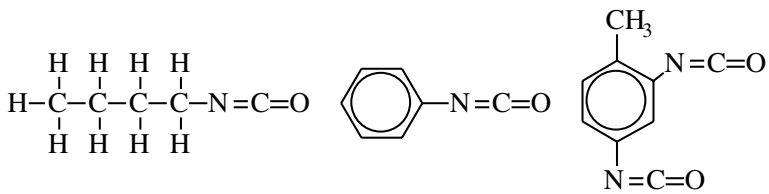
Isocyanates are compounds with the general formula R–N=C=O. They have numerous uses in chemical synthesis, particularly in the manufacture of polymers with carefully tuned specialty properties. Methyl isocyanate is a raw material in the manufacture of carbaryl insecticide. Methyl isocyanate (like other isocyanates) can be synthesized by the reaction of a primary amine with phosgene in a moderately complex process, represented by reaction 15.8.1. Structures of three significant isocyanates are given in Figure 15.7.



Methylamine **Phosgene** **Methyl isocyanate**

(15.8.1)

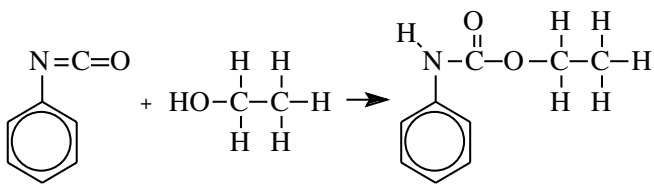
Both chemically and toxicologically, the most significant property of isocyanates is the high chemical reactivity of the isocyanate functional group. Industrially, the most significant such reaction is with alcohols to yield urethane (carbamate) compounds, as shown by reaction 15.8.2. Multiple



n-Butyl isocyanate **Phenyl isocyanate** **2,4-Toluene diisocyanate**

Figure 15.7 Examples of isocyanate compounds.

isocyanate and –OH groups in the reactant molecules enable formation of polymers. The chemical versatility of isocyanates and the usefulness of the products — such as polymers and pesticides — from which they are made have resulted in their widespread industrial production and consumption.

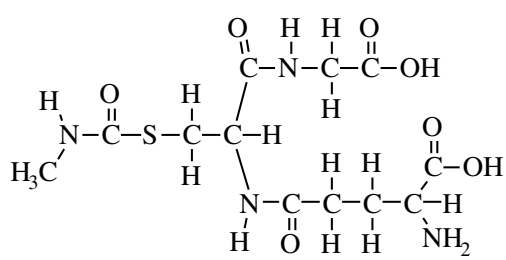


Phenyl isocyanate **A carbamate or urethane compound**

(15.8.2)

Methyl isocyanate was the toxic agent involved in the most catastrophic industrial accident of all time, which took place in Bhopal, India, on December 2, 1984. This accident occurred when water got into a tank of methyl isocyanate, causing an exothermic reaction that built up pressure and ruptured a safety valve. This resulted in the release to the atmosphere of 30 to 40 tons of the compound over an approximately 3-h period. Subsequent exposure of people resulted in approximately 3,500 deaths and almost 100,000 injuries.

Most of the deaths at Bhopal resulted from devastating pulmonary edema, which caused respiratory failure, leading to cardiac arrest. The major debilitating effects of methyl isocyanate on the Bhopal victims were on the lungs, with survivors suffering long-term shortness of breath and weakness from lung damage. However, victims also suffered symptoms of nausea and bodily pain, and numerous toxic effects have been observed in the victims. Changes in the immune systems (effects on numbers of T cells, T-helper cells, and lymphocyte mitogenesis responses) of victims exposed to methyl isocyanate were also observed. The tendency of the compound to function as a systemic poison was somewhat surprising in view of its chemical reactivity with water — its half-life is only about 2 min in aqueous solution — and appears to be the result of its ability to bind with small-molecule proteins and peptides. The most prominent among these is glutathione, a tripeptide described as a conjugating agent in Section 7.4.2; binding to hemoglobin may also be possible. Isocyanate reacts reversibly with –SH groups on glutathione, probably to form S-(N-methylcarbamoyl)glutathione:



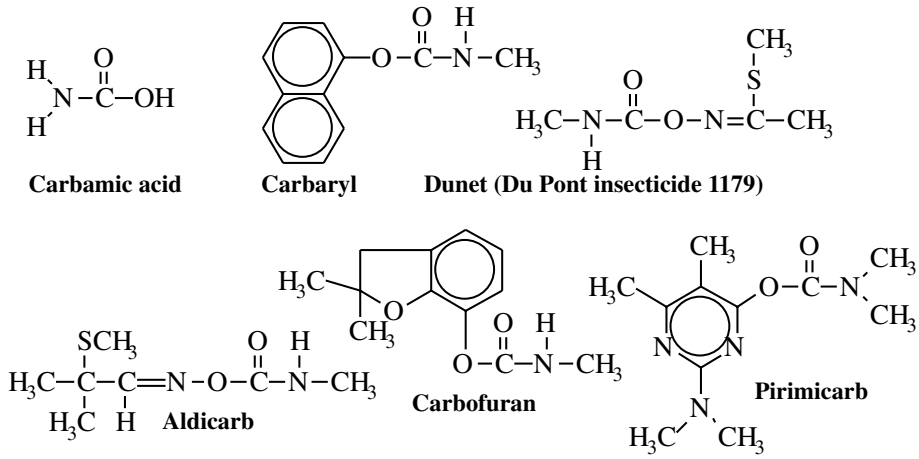


Figure 15.8 Carbamic acid and three insecticidal carbamates.

This complex can be transported to various organs in the body, where it releases isocyanate.

15.9 PESTICIDAL COMPOUNDS

A large number of organic compounds used as pesticides contain nitrogen. Space does not permit a detailed discussion of such compounds, but two general classes of them are cited here.

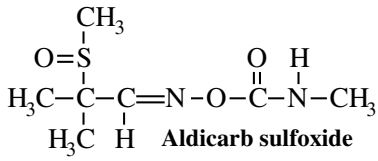
15.9.1 Carbamates

Pesticidal organic derivatives of carbamic acid, for which the formula is shown in Figure 15.8, are known collectively as **carbamates**. Some carbamate insecticides such as carbaryl, carbofuran, and pirimicarb have been in use for many years; others, including Dunet, are relatively recent. Carbamate pesticides have been widely used because some are more biodegradable than the formerly popular organochlorine insecticides and have lower dermal toxicities than most common organophosphate pesticides.

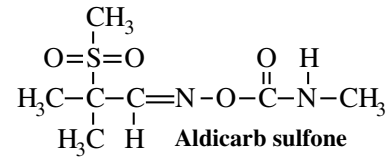
Carbaryl has been widely used as an insecticide on lawns or gardens. It has a low toxicity to mammals. **Carbofuran** has a high water solubility and acts as a plant systemic insecticide. It is taken up by the roots and leaves of plants so that insects feeding on the plant material are poisoned by the carbamate compound in it.

Pirimicarb has been widely used in agriculture as a systemic aphicide. Unlike many carbamates, it is rather persistent, with a strong tendency to bind to soil.

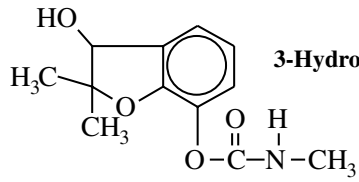
The toxic effects of carbamates to animals are due to the fact that these compounds inhibit acetylcholinesterase. Unlike some of the organophosphate insecticides (see Chapter 18), they do so without the need for undergoing a prior biotransformation and are therefore classified as direct inhibitors. Their inhibition of acetylcholinesterase is relatively reversible. Loss of acetylcholinesterase inhibition activity may result from hydrolysis of the carbamate ester, which can occur metabolically. In general, carbamates have a wide range between a dose that causes onset of poisoning symptoms and a fatal dose (see discussion of dose–response in Section 6.5). Although pirimicarb has a high systemic mammalian toxicity, its effects are mitigated by its low tendency to be absorbed through the skin. Using electrospray mass spectrometric analysis of urine samples, aldicarb sulfoxide and aldicarb sulfone metabolites of aldicarb and the 3-hydroxycarbofuran metabolite of carbofuran can be monitored as evidence of exposure to these insecticides:[10]



Aldicarb sulfoxide



Aldicarb sulfone



3-Hydroxycarbofuran

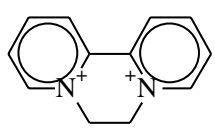
15.9.2 Bipyridilium Compounds

As shown by the structures in Figure 15.9, a bipyridilium compound contains two pyridine rings per molecule. The two important pesticidal compounds of this type are the herbicides **diquat** and **paraquat**; other members of this class of herbicides include chlormequat, morfamquat, and difenzoquat. Applied directly to plant tissue, these compounds rapidly destroy plant cells and give the plant a frostbitten appearance. However, they bind tenaciously to soil, especially the clay mineral fraction, which results in rapid loss of herbicidal activity so that sprayed fields can be planted within a day or two of herbicide application.

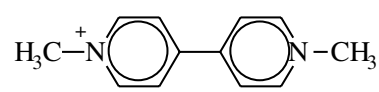
Paraquat, which was registered for use in 1965, is the most used of the bipyridilium herbicides. With a toxicity rating of five, it is reputed to have "been responsible for hundreds of human deaths."[11] Exposure to fatal or dangerous levels of paraquat can occur by all pathways, including inhalation of spray, skin contact, ingestion, and even suicidal hypodermic injections. Chronic health effects from long-term exposure are reputed to include pulmonary effects, skin cancer, and Parkinson's disease.[12] Despite these possibilities and its widespread application, paraquat is used safely without ill effects when proper procedures are followed.

Because of its widespread use as a herbicide, the possibility exists of substantial paraquat contamination of food. Drinking water contamination by paraquat has also been observed. The chronic effects of exposure to low levels of paraquat over extended periods of time are not well known. Acute exposure of animals to paraquat aerosols causes pulmonary fibrosis, and the lungs are affected even when exposure is through nonpulmonary routes. Paraquat affects enzyme activity. Acute exposure may cause variations in the levels of catecholamine, glucose, and insulin.

Although paraquat can be corrosive at the point of contact, it is a systemic poison that is devastating to a number of organs. The most prominent initial symptom of poisoning is vomiting, sometimes followed by diarrhea. Within a few days, dyspnea, cyanosis, and evidence of impairment of the kidneys, liver, and heart become obvious. In fatal cases, the lungs develop pulmonary fibrosis, often with pulmonary edema and hemorrhaging.



Diquat



Paraquat

Figure 15.9 The two major bipyridilium herbicides (cation forms).

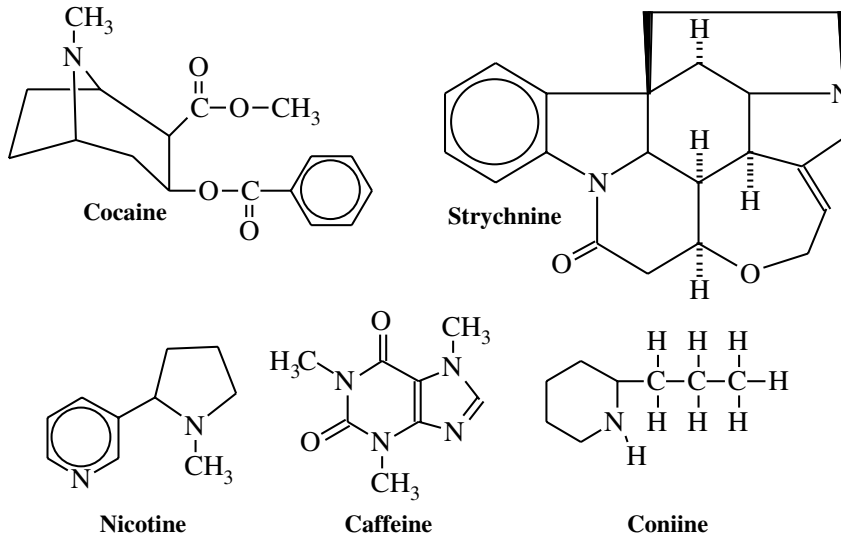
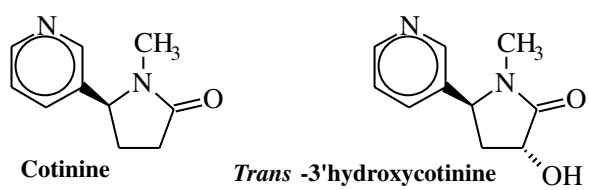


Figure 15.10 Structural formulas of typical alkaloids.

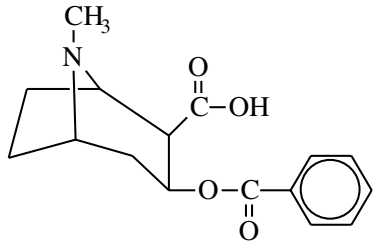
15.10 ALKALOIDS

Alkaloids are compounds of biosynthetic origin that contain nitrogen, usually in a heterocyclic ring. These compounds are produced by plants in which they are usually present as salts of organic acids. They tend to be basic and to have a variety of physiological effects. One of the more notorious alkaloids is cocaine, and alkaloidal strychnine is a deadly poison. The structural formulas of these compounds and three other alkaloids are given in Figure 15.10.

Among the alkaloids are some well-known (and dangerous) compounds. Nicotine is an agent in tobacco that has been described as "one of the most toxic of all poisons and (it) acts with great rapidity."[13] In 1988, the U.S. Surgeon General declared nicotine to be an addictive substance. Nicotine is metabolized to cotinine and *trans*-3'-hydroxycotinine,

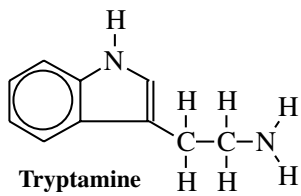


which may be detected in the urine of tobacco users. Coniine is the major toxic agent in poison hemlock (see Chapter 19). Alkaloidal strychnine is a powerful, fast-acting convulsant. Quinine and sterioisomeric quinidine are alkaloids that are effective antimalarial agents. Like some other alkaloids, caffeine contains oxygen. It is a stimulant that can be fatal to humans in a dose of about 10 g. Cocaine is currently the illicit drug of greatest concern. It is metabolized to benzoylecgonine, a compound in which the ester-linked $-OCH_3$ group in cocaine is replaced by the –OH group, which is detected in the urine of cocaine abusers.[14]

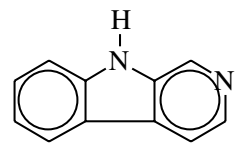


Benzoylecgonine

Alkaloids in feed crops, particularly grasses, can cause potentially fatal poisoning of livestock. Phalaris grasses used for pasture and forage in Australia have caused neurological and sudden death intoxication syndromes in livestock. Alkaloids similar to tryptamine and β-carboline have been implicated in these incidents.[15]



Tryptamine



β-Carboline

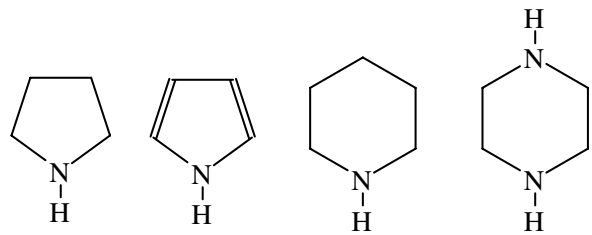
REFERENCES

1. Ladona, M.G. et al., Pharmacogenetic profile of xenobiotic enzyme metabolism in survivors of the Spanish toxic oil syndrome, *Environ. Health Perspect.*, 109, 369–375, 2001.
2. Pattanaik, U., Laa, S.B., and Bano, R., Accidental pyridine exposure: a workplace hazard, *Indian J. Occup. Health*, 42, 47–50, 1999.
3. Calne, D.B., Neurotoxins and degeneration in the central nervous system, *Neurotoxicology*, 12, 335–340, 1991.
4. Tang, C., Shou, M., and Rodrigues, D.A., Substrate-dependent effect of acetonitrile on human liver microsomal cytochrome P450 2C9 (CYP2C9) activity, *Drug Metab. Dispos.*, 28, 567–572, 2000.
5. Thier, R., Lewalter, J., and Bolt, H.M., Species differences in acrylonitrile metabolism and toxicity between experimental animals and humans based on observations in human accidental poisonings, *Arch. Toxicol.*, 74, 184–189, 2000.
6. Saillenfait, A.M. and Sabate, J.P., Comparative developmental toxicities of aliphatic nitriles: *in vivo* and *in vitro* observations, *Toxicol. Appl. Toxicol.*, 163, 149–163, 2000.
7. Page, E.H. et al., Peripheral neuropathy in workers exposed to nitromethane, *Am. J. Ind. Med.*, 40, 107–113, 2001.
8. Dinoseb cleanup: who pays the bill? Associated Press Newswires, February 24, 1999.
9. Fujita, K.-I. and Kamataki, T., Predicting the mutagenicity of tobacco-related N-nitrosamines in humans using 11 strains of *Salmonella typhimurium*, each coexpressing a form of human cytochrome P450 along with NADPH–cytochrome P450 reductase, *Environ. Mol. Mutag.,* 38, 339–346, 2001.
10. Fernandez, J.M., Vazquez, P.P., and Vidal, J.L.M., Analysis of N-methylcarbamate insecticides and some of their main metabolites in urine with liquid chromatography using diode array detection and electrospray mass spectrometry, *Anal. Chim. Acta*, 412, 131–139, 2000.
11. Gosselin, R.E., Smith, R.P., and Hodge, H.C., Paraquat, in *Clinical Toxicology of Commercial Products*, 5th ed., Williams & Wilkins, Baltimore, 1984, pp. III-328–III-336.
12. Wesseling, C. et al., Paraquat in developing countries, *Int. J. Occup. Environ. Health*, **7**, 275–286, 2001.
13. Gosselin, R.E., Smith, R.P., and Hodge, H.C., Nicotine, in *Clinical Toxicology of Commercial Products*, 5th ed., Williams & Wilkins, Baltimore, 1984, pp. III-311–III-314.

14. Cone, E.J. et al., Cocaine metabolism and urinary excretion after different routes of administration, *Ther. Drug Monit.*, 20, 556–560, 1998.
15. Anderton, N. et al., New alkaloids from Phalaris spp.: a cause for concern? in *Book of Abstracts, 216th ACS National Meeting*, American Chemical Society, Washington, D.C., AGFD-168, 1998.

QUESTIONS AND PROBLEMS

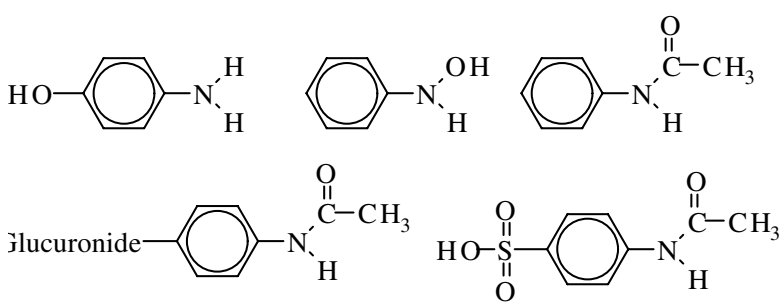
1. Describe the sense in which amines may be regarded as derivatives of ammonia, NH_3. Distinguish among primary, secondary, and tertiary amines.
2. How are the compounds shown in the following figure characterized or described? What are their main toxicological characteristics?



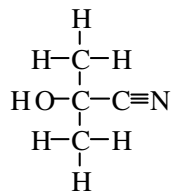
3. What is the structural formula of aniline? What are its major uses? Why is human exposure to aniline likely to be relatively common? How is aniline taken into the body?
4. Which other nitrogen-containing nonamine organonitrogen compound does aniline most resemble in its toxicological characteristics? What is its most common manifestation of toxicity? How does this affect the subject?
5. What are fatty amines? From which raw materials that occur in nature are they commonly synthesized?
6. What are alkyl polyamines?
7. Of the following, the statement that is **not** true is:
   (a) The lower amines are corrosive to tissue and can cause tissue necrosis at the point of contact.
   (b) The most common toxic effect of the lower aliphatic amines is that they cause methemoglobinemia.
   (c) Sensitive eye tissue is vulnerable to amines.
   (d) Necrosis of the liver and kidneys can occur from exposure to amines, and exposed lungs can exhibit hemorrhage and edema.
   (e) The immune system may become sensitized to amines.
8. Explain what the reaction below shows about the toxicity of amines.

$$R_3N + H_2O \rightarrow R_3NH^+ + OH^-$$

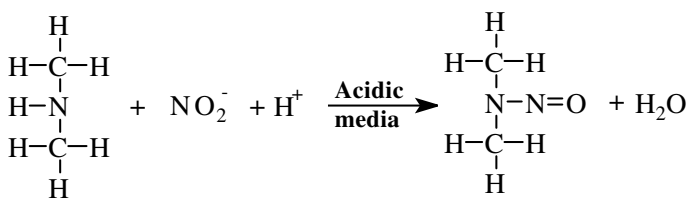
9. Consider the compounds with the structural formulas shown below. Which of these are believed to be the actual toxic agents involved in aniline poisoning? Which are the forms eliminated from the body?



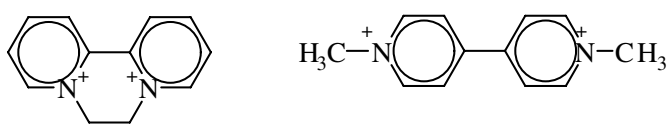
10. What are the two naphthylamines? How does exposure to these compounds occur? What is their toxic effect of most concern?
11. What is the structural formula of pyridine. Is it highly toxic? In what respect is it like benzene?
12. Of which common inorganic compound are nitriles analogs? Which common natural product produces this highly toxic inorganic compound? How does this occur?
13. Acetonitrile is not highly toxic. What does this say about its toxicological chemistry and metabolism in the body?
14. What are two reasons that the compound below is of particular concern?



15. Of which class of compounds is the N–N=O functional group characteristic? What is their most important toxicological characteristic?
16. Which class of compounds has the general formula R–N=C=O? Which of these is most notorious for an incident of poisoning? What happened?
17. What is the general formula of carbamates? Of which inorganic compound are they derivatives? How are carbamates used?
18. What does the reaction below illustrate?



19. For what purposes are the compounds below used? What are their toxicity characteristics?



20. What kinds of compounds are the following? What are their sources? What may be said about their toxicities?