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23 TOXICOLOGICAL CHEMISTRY OF CHEMICAL SUBSTANCES

23.1. INTRODUCTION

Toxicological chemistry, defined and discussed in Chapter 22, centers on the relationship between the chemical nature of toxicants and their toxicological effects. This chapter discusses this relationship with regard to some of the major pollutants and hazardous substances. The first section deals with toxicological aspects of elements (particularly heavy metals) the presence of which in a compound frequently means that the compound is toxic. It also discusses the toxicities of some commonly used elemental forms, such as the chemically uncombined elemental halogens. The following section discusses the toxicological chemistry of inorganic compounds, many of which are produced from industrial processes. It also provides a brief discussion of organometallic compounds.The last section deals with the toxicology of organic compounds. The toxicological properties of hydrocarbons and oxygen-containing organic compounds are discussed as well as other organic substances containing functional groups, such as alcohols and ketones. This section also discusses the toxicities of organic nitrogen, halide, sulfur, and phosphorous compounds, some of which are used as pesticides or military poisons.

ATSDR Toxicological Profiles

A very useful source of information about the toxicological chemistry of various kinds of toxic substances is published by the U. S. Department of Health and Human Services, Public Health Service Agency for Toxic Substances and Disease Registry ASTDR's Toxicological Profiles. These detailed documents are available on CD-ROM.[1] The substances covered are given in Table 23.1.

Table 23.1. Materials Listed by ATSDR[1]

Acetone	1,2-Dibromoethane	Naphthalene
Acrolein	1,4-Dichlorobenzene	Nickel
Acrylonitrile	3,3'-Dichlorobenzidine	Nitrobenzene
Aldrin/Dieldrin	1,1-Dichloroethane	2-Nitrophenol/ 4-Nitrophenol
Alpha-,Beta-,Gamma- and Delta-Hexachloro-cyclohexane	1,2-Dichloroethane	Otto Fuels
	1,1-Dichloroethene	Pentachlorophenol
	1,2-Dichloroethene	Phenol
Aluminum	1,3-Dichloropropene	Plutonium
Ammonia	Diethyl Phthalate	Polybrominated Biphenyls
Arsenic	1,3-Dinitrobenzene/ 1,3,5-Trinitrobenzene	
Asbestos	Dinitrocresols	Polychlorinated Biphenyls
Automotive Gasoline	Dinitrophenols	
Barium	2,4-Dinitrotoluene/ 2,6-Dinitrotoluene	Polycyclic Aromatic Hydrocarbons (PAH's)
Benzene		
Benzidine	1,2-Diphenylhydrazine	Radon
Beryllium	Disulfoton	RDX
Bis(2-Chloroethyl) Ether	Endosulfan	Selenium
Boron	Endrin	Silver
Bromomethane	Ethylbenzene	Stoddard Solvent
1,3-Butadiene	Ethylene Glycol and Propylene Glycol	1,1,2,2-Tetrachloroethane
2-Butanone		Tetrachloroethylene
Cadmium	Fluorides, Hydrogen Fluoride, and Fluorine	Tetryl
Carbon Disulfide		Thallium
Carbon Tetrachloride	Fuel Oils	Thorium
Chlordane	Heptachlor/Heptachlor Epoxide	Tin
Chlorobenzene		Titanium Tetrachloride
Chlorodibenzofurans		
Chloroethane	Hexachlorobenzene	Toluene
Chloroform	Hexachlorobutadiene	Toxaphene
Chloromethane	2-Hexanone	1,1,1-Trichloroethane
Chlorpyrifos	Hydraulic Fluids	1,1,2-Trichloroethane
Chromium	Isophorone	Trichloroethylene
Coal Tar Pitch, and Coal Tar Pitch Volatiles	Jet Fuels (Jp4 And Jp7)	2,4,6-Trichlorophenol
	Lead	2,4,6-Trinitrotoluene
Cobalt	Manganese	Uranium
Copper	Mercury	Used Mineral-Based Crankcase Oil
Cresols: *o*-Cresol, *p*-Cresol, *m*-Cresol	Methoxychlor	
	Methyl Parathion	Vanadium
Cyanide	Methyl Tert-Butyl Ether	Vinyl Acetate
4,4'-Ddt,4,4'-Dde,4,4'-Ddd	4, 4'-Methylenebis-(2-Chloroaniline) (MBOCA)	Vinyl Chloride
Di (2-Ethylhexyl) Phthalate		White Phosphorus
Di-N-Butylphthalate	Methylene Chloride	Wood Creosote, Coal Tar Creosote, Coal Tar
Diazinon	Mirex And chlordecone	
1,2-Dibromo-3-Chloropropane	N-Nitrosodi-N-Propylamine	Xylenes
	N-Nitrosodiphenylamine	Zinc

23.2. TOXIC ELEMENTS AND ELEMENTAL FORMS

Ozone

Ozone (O_3, see Chapters 9, 13, and 14) has several toxic effects. Air containing 1 ppm by volume ozone has a distinct odor. Inhalation of ozone at this level causes severe irritation and headache. Ozone irritates the eyes, upper respiratory system, and lungs. Inhalation of ozone can sometimes cause fatal pulmonary edema. *Pulmonary* refers to lungs and *edema* to an accumulation of fluid in tissue spaces; therefore, *pulmonary edema* is an abnormal accumulation of fluid in lung tissue. Chromosomal damage has been observed in subjects exposed to ozone.

Ozone generates free radicals in tissue. These reactive species can cause lipid peroxidation, oxidation of sulfhydryl (–SH) groups, and other destructive oxidation processes. Compounds that protect organisms from the effects of ozone include radical scavengers, antioxidants, and compounds containing sulfhydryl groups.

White Phosphorus

Elemental white phosphorus can enter the body by inhalation, by skin contact, or orally. It is a systemic poison, that is, one that is transported through the body to sites remote from its entry site. White phosphorus causes anemia, gastrointestinal system dysfunction, bone brittleness, and eye damage. Exposure also causes **phossy jaw**, a condition in which the jawbone deteriorates and becomes fractured.

Elemental Halogens

Elemental **fluorine** (F_2) is a pale yellow, highly reactive gas that is a strong oxidant. It is a toxic irritant and attacks skin, eye tissue, and the mucous membranes of the nose and respiratory tract. **Chlorine** (Cl_2) gas reacts in water to produce a strongly oxidizing solution. This reaction is responsible for some of the damage caused to the moist tissue lining the respiratory tract when the tissue is exposed to chlorine. The respiratory tract is rapidly irritated by exposure to 10-20 ppm of chlorine gas in air, causing acute discomfort that warns of the presence of the toxicant. Even brief exposure to 1,000 ppm of Cl_2 can be fatal.

Bromine (Br_2) is a volatile, dark red liquid that is toxic when inhaled or ingested. Like chlorine and fluorine, it is strongly irritating to the mucous tissue of the respiratory tract and eyes and may cause pulmonary edema. The toxicological hazard of bromine is limited somewhat because its irritating odor elicits a withdrawal response.

Elemental solid **iodine** (I_2) is irritating to the lungs much like bromine or chlorine. However, the relatively low vapor pressure of iodine limits exposure to I_2 vapor.

Heavy Metals

Heavy metals (Section 7.3) are toxic in their chemically combined forms and some, notably mercury, are toxic in the elemental form. The toxic properties of some of the most hazardous heavy metals and metalloids are discussed here.

Although not truly a *heavy* metal, **beryllium** (atomic mass 9.01) is one of the more hazardous toxic elements. Its most serious toxic effect is berylliosis, a condition manifested by lung fibrosis and pneumonitis, which may develop after a latency period of 5-20 years. Berylliumis is a hypersensitizing agent and exposure to it causes skin granulomas and ulcerated skin. Beryllium was used in the nuclear weapons program in the U. S., and it is believed that 500 to 1000 cases of beryllium poisoning have occurred or will occur in the future as a result of exposure to workers. In July 1999, the U. S. Department of Energy acknowledged these cases of beryllium poisoning and announced proposed legislation to compensate the victims in a program expected to cost up to $15 million at its peak.[2]

Cadmium adversely affects several important enzymes; it can also cause painful osteomalacia (bone disease) and kidney damage. Inhalation of cadmium oxide dusts and fumes results in cadmium pneumonitis characterized by edema and pulmonary epithelium necrosis (death of tissue lining lungs).

Lead, widely distributed as metallic lead, inorganic compounds, and organometallic compounds, has a number of toxic effects, including inhibition of the synthesis of hemoglobin. It also adversely affects the central and peripheral nervous systems and the kidneys. Its toxicological effects have been widely studied.

Arsenic is a metalloid which forms a number of toxic compounds. The toxic +3 oxide, As_2O_3, is absorbed through the lungs and intestines. Biochemically, arsenic acts to coagulate proteins, forms complexes with coenzymes, and inhibits the production of adenosine triphosphate (ATP) in essential metabolic processes involving the utilization of energy.

Arsenic is the toxic agent in one of the great environmental catastrophes of the last century, the result of its ingestion through well water in Bangladesh.[3] Several million of the wells in question were installed in Bangladesh starting in the 1970s using funds provided by the United Nations Children's Fund (UNICEF). Providing an abundant source of microbiologically safe drinking water, they were very successful in reducing water-borne diseases, especially cholera and dysentery. In 1992 a problem with arsenic contamination of many of the wells was shown to exist, and since that time tens of thousands of people have exhibited symptoms of arsenicosis, manifested by skin discoloration and other symptoms. It is likely that many more people in Bangladesh will become ill and die prematurely from arsenic poisoning.

Elemental **mercury** vapor can enter the body through inhalation and be carried by the bloodstream to the brain where it penetrates the blood-brain barrier. It disrupts metabolic processes in the brain causing tremor and psychopathological symptoms such as shyness, insomnia, depression, and irritability. Divalent ionic mercury, Hg^{2+}, damages the kidney. Organometallic mercury compounds such as dimethylmercury, $Hg(CH_3)_2$, are also very toxic.

23.3. TOXIC INORGANIC COMPOUNDS

Cyanide

Both **hydrogen cyanide** (HCN) and **cyanide salts** (which contain CN^- ion) are rapidly acting poisons; a dose of only 60–90 mg is sufficient to kill a human. Metabolically, cyanide bonds to iron(III) in iron-containing ferricytochrome oxidase

enzyme (see enzymes, Section 21.6), preventing its reduction to iron(II) in the oxidative phosphorylation process by which the body utilizes O_2. This prevents utilization of oxygen in cells, so that metabolic processes cease.

Carbon Monoxide

Carbon monoxide, **CO**, is a common cause of accidental poisonings. At CO levels in air of 10 parts per million (ppm) impairment of judgment and visual perception occur; exposure to 100 ppm causes dizziness, headache, and weariness; loss of consciousness occurs at 250 ppm; and inhalation of 1,000 ppm results in rapid death. Chronic long-term exposures to low levels of carbon monoxide are suspected of causing disorders of the respiratory system and the heart.

After entering the blood stream through the lungs, carbon monoxide reacts with hemoglobin (Hb) to convert oxyhemoglobin (O_2Hb) to carboxyhemoglobin (COHb):

$$O_2Hb + CO \rightarrow COHb + O_2 \qquad (23.3.1)$$

In this case, hemoglobin is the receptor (Section 22.7) acted on by the carbon monoxide toxicant. Carboxyhemoglobin is much more stable than oxyhemoglobin so that its formation prevents hemoglobin from carrying oxygen to body tissues.

Nitrogen Oxides

The two most common toxic oxides of nitrogen are NO and NO_2, of which the latter is regarded as the more toxic. Nitrogen dioxide causes severe irritation of the innermost parts of the lungs resulting in pulmonary edema. In cases of severe exposures, fatal bronchiolitis fibrosa obliterans may develop approximately three weeks after exposure to NO_2. Fatalities may result from even brief periods of inhalation of air containing 200–700 ppm of NO_2. Biochemically, NO_2 disrupts lactic dehydrogenase and some other enzyme systems, possibly acting much like ozone, a stronger oxidant mentioned in Section 23.2. Free radicals, particularly HO·, are likely formed in the body by the action of nitrogen dioxide and the compound probably causes **lipid peroxidation** in which the C=C double bonds in unsaturated body lipids are attacked by free radicals and undergo chain reactions in the presence of O_2, resulting in their oxidative destruction.

Nitrous oxide, N_2O is used as an oxidant gas and in dental surgery as a general anesthetic. This gas was once known as “laughing gas,” and was used in the late 1800s as a “recreational gas” at parties held by some of our not-so-staid Victorian ancestors. Nitrous oxide is a central nervous system depressant and can act as an asphyxiant.

Hydrogen Halides

Hydrogen halides (general formula HX, where X is F, Cl, Br, or I) are relatively toxic gases. The most widely used of these gases are HF and HCl; their toxicities are discussed here.

Hydrogen Fluoride

Hydrogen fluoride, (HF, mp -83.1˚C, bp 19.5˚C) is used as a clear, colorless liquid or gas or as a 30–60% aqueous solution of **hydrofluoric acid**, both referred to here as HF. Both are extreme irritants to any part of the body that they contact, causing ulcers in affected areas of the upper respiratory tract. Lesions caused by contact with HF heal poorly, and tend to develop gangrene.

Fluoride ion, F^-, is toxic in soluble fluoride salts, such as NaF, causing **fluorosis**, a condition characterized by bone abnormalities and mottled, soft teeth. Livestock are especially susceptible to poisoning from fluoride fallout on grazing land; severely afflicted animals become lame and even die. Industrial pollution has been a common source of toxic levels of fluoride. However, about 1 ppm of fluoride used in some drinking water supplies prevents tooth decay.

Hydrogen Chloride

Gaseous **hydrogen chloride** and its aqueous solution, called **hydrochloric acid**, both denoted as HCl, are much less toxic than HF. Hydrochloric acid is a natural physiological fluid present as a dilute solution in the stomachs of humans and other animals. However, inhalation of HCl vapor can cause spasms of the larynx as well as pulmonary edema and even death at high levels. The high affinity of hydrogen chloride vapor for water tends to dehydrate eye and respiratory tract tissue.

Interhalogen Compounds and Halogen Oxides

Interhalogen compounds, including ClF, BrCl, and BrF_3, are extremely reactive and are potent oxidants. They react with water to produce hydrohalic acid solutions (HF, HCl) and nascent oxygen {O}. Too reactive to enter biological systems in their original chemical state, interhalogen compounds tend to be powerful corrosive irritants that acidify, oxidize, and dehydrate tissue, much like those of the elemental forms of the elements from which they are composed. Because of these effects, skin, eyes, and mucous membranes of the mouth, throat, and pulmonary systems are especially susceptible to attack.

Major halogen oxides, including fluorine monoxide (OF_2), chlorine monoxide (Cl_2O), chlorine dioxide (ClO_2), chlorine heptoxide (Cl_2O_7), and bromine monoxide (Br_2O), tend to be unstable, highly reactive, and toxic compounds that pose hazards similar to those of the interhalogen compounds discussed above. Chlorine dioxide, the most commonly used halogen oxide, is employed for odor control and bleaching wood pulp. As a substitute for chlorine in water disinfection, it produces fewer undesirable chemical by-products, particularly trihalomethanes.

The most important of the oxyacids and their salts formed by halogens are hypochlorous acid, HOCl, and hypochlorites, such as NaOCl, used for bleaching and disinfection. The hypochlorites irritate eye, skin, and mucous membrane tissue because they react to produce active (nascent) oxygen ({O}) and acid as shown by the reaction below:

$$HClO \rightarrow H^+ + Cl^- + \{O\} \qquad (23.3.2)$$

Inorganic Compounds of Silicon

Silica (SiO_2, quartz) occurs in a variety of types of rocks such as sand, sandstone, and diatomaceous earth. **Silicosis** resulting from human exposure to silica dust from construction materials, sandblasting, and other sources has been a common occupational disease. A type of pulmonary fibrosis that causes lung nodules and makes victims more susceptible to pneumonia and other lung diseases, silicosis is one of the most common disabling conditions resulting from industrial exposure to hazardous substances. It can cause death from insufficient oxygen, or from heart failure in severe cases.

Silane, SiH_4, and disilane, H_3SiSiH_3, are examples of inorganic **silanes**, which have H-Si bonds. Numerous organic ("organometallic") silanes exist in which alkyl moieties are substituted for H. Little information is available regarding the toxicities of silanes.

Silicon tetrachloride, $SiCl_4$, is the only industrially significant compound of the **silicon tetrahalides**, a group of compounds with the general formula SiX_4, where X is a halogen. The two commercially produced **silicon halohydrides**, general formula $H_{4-x}SiX_x$, are dichlorosilane (SiH_2Cl_2) and trichlorosilane, ($SiHCl_3$). These compounds are used as intermediates in the synthesis of organosilicon compounds and in the production of high-purity silicon for semiconductors. Silicon tetrachloride and trichlorosilane, fuming liquids which react with water to give off HCl vapor, have suffocating odors and are irritants to eye, nasal, and lung tissue.

Asbestos

Asbestos is the name given to a group of fibrous silicate minerals, typically those of the serpentine group, for which the approximate chemical formula is $Mg_3(Si_2O_5)(OH)_4$. Asbestos has been widely used in structural materials, brake linings, insulation, and pipe manufacture. Inhalation of asbestos may cause 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) so that uses of asbestos have been severely curtailed and widespread programs have been undertaken to remove the material from buildings.

Inorganic Phosphorus Compounds

Phosphine (PH_3), a colorless gas that undergoes autoignition at 100˚C, is a potential hazard in industrial processes and in the laboratory. Symptoms of poisoning from potentially fatal phosphine gas include pulmonary tract irritation, depression of the central nervous system, fatigue, vomiting, and difficult, painful breathing.

Tetraphosphorus decoxide, P_4O_{10}, is produced as a fluffy white powder from the combustion of elemental phosphorus and reacts with water from air to form syrupy orthophosphoric acid. Because of the formation of acid by this reaction and its dehydrating action, P_4O_{10} is a corrosive irritant to skin, eyes and mucous membranes.

The most important of the **phosphorus halides**, general formulas PX_3 and PX_5, is phosphorus pentachloride used as a catalyst in organic synthesis, as a chlorinating agent, and as a raw material to make phosphorus oxychloride ($POCl_3$). Because they react violently with water to produce the corresponding hydrogen halides and oxo phosphorus acids,

$$PCl_5 + 4H_2O \rightarrow H_3PO_4 + 5HCl \qquad (23.3.3)$$

the phosphorus halides are strong irritants to eyes, skin, and mucous membranes.

The major **phosphorus oxyhalide** in commercial use is phosphorus oxychloride ($POCl_3$), a faintly yellow fuming liquid. Reacting with water to form toxic vapors of hydrochloric acid and phosphorous acid (H_3PO_3), phosphorus oxyhalide is a strong irritant to the eyes, skin, and mucous membranes.

Inorganic Compounds of Sulfur

A colorless gas with a foul, rotten-egg odor, **hydrogen sulfide** is very toxic. In some cases inhalation of H_2S kills faster than even hydrogen cyanide; rapid death ensues from exposure to air containing more than about 1000 ppm H_2S due to asphyxiation from respiratory system paralysis. Lower doses cause symptoms that include headache, dizziness, and excitement due to damage to the central nervous system. General debility is one of the numerous effects of chronic H_2S poisoning.

Sulfur dioxide, SO_2, dissolves in water, to produce sulfurous acid, H_2SO_3; hydrogen sulfite ion, HSO_3^-; and sulfite ion, SO_3^{2-}. Because of its water solubility, sulfur dioxide is largely removed in the upper respiratory tract. It is an irritant to the eyes, skin, mucous membranes, and respiratory tract. Some individuals are hypersensitive to sodium sulfite (Na_2SO_3), which has been used as a chemical food preservative. Because of threats to hypersensitive individuals, these uses were severely restricted in the U.S. in early 1990.

Number-one in synthetic chemical production, **sulfuric acid** (H_2SO_4) is a severely corrosive poison and dehydrating agent in the concentrated liquid form; it readily penetrates skin to reach subcutaneous tissue causing tissue necrosis with effects resembling those of severe thermal burns. Sulfuric acid fumes and mists irritate eye and respiratory tract tissue, and industrial exposure has even caused tooth erosion in workers.

The more important halides, oxides, and oxyhalides of sulfur are listed in Table 23.2. The major toxic effects of these compounds are given in the table.

Organometallic Compounds

The toxicological properties of some organometallic compounds—pharmaceutical organoarsenicals, organomercury fungicides, and tetraethyllead antiknock gasoline additives—that have been used for many years are well known. However, toxicological experience is lacking for many relatively new organometallic compounds that are now being used in semiconductors, as catalysts, and for chemical synthesis, so they should be treated with great caution until proven safe.

Table 23.2. Inorganic Sulfur Compounds

Compound name	Formula	Properties
Sulfur		
Monofluoride	S_2F_2	Colorless gas, mp -104˚C, bp 99˚C, toxicity similar to HF
Tetrafluoride	SF_4	Gas, bp -40˚C, mp -124˚C, powerful irritant
Hexafluoride	SF_6	Colorless gas, mp -51˚C, remarkably low toxicity 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/gas, mp -30˚C, Decom. below 0˚C, irritant
Trioxide	SO_3	Solid anhydride of sulfuric acid 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
Carbon disulfide	CS_2	Colorless liquid, industrial chemical, narcotic and central nervous system anesthetic

Organometallic compounds often behave in the body in ways totally unlike the inorganic forms of the metals that they contain. This is due in large part to the fact that, compared to inorganic forms, organometallic compounds have an organic nature and higher lipid solubility.

Organolead Compounds

Perhaps the most notable toxic organometallic compound is tetraethyllead, $Pb(C_2H_5)_4$, a colorless, oily liquid that was widely used as a gasoline additive to boost octane rating. Tetraethyllead has a strong affinity for lipids and can enter the body by all three common routes of inhalation, ingestion, and absorption through the skin. Acting differently from inorganic compounds in the body, it affects the central nervous system with symptoms such as fatigue, weakness, restlessness, ataxia, psychosis, and convulsions. Recovery from severe lead poisoning tends to be slow. In cases of fatal tetraethyllead poisoning, death has occurred as soon as one or two days after exposure.

Organotin Compounds

The greatest number of organometallic compounds in commercial use are those of tin—tributyltin chloride and related tributyltin (TBT) compounds. These compounds have bactericidal, fungicidal, and insecticidal properties. They have particular environmental significance because of their widespread applications as industrial biocides, now increasingly limited because of their environmental and toxicological effects.[4] Organotin compounds are readily absorbed through the skin, sometimes causing a skin rash. They probably bind with sulfur groups on proteins and appear to interfere with mitochondrial function.

Carbonyls

Metal carbonyls, regarded as extremely hazardous because of their toxicities include nickel tetracarbonyl ($Ni(CO)_4$), cobalt carbonyl, and iron pentacarbonyl. Some of the hazardous carbonyls are volatile and readily taken into the body through the respiratory tract or through the skin. The carbonyls affect tissue directly and they break down to toxic carbon monoxide and products of the metal, which have additional toxic effects.

Reaction Products of Organometallic Compounds

An example of the production of a toxic substance from the burning of an organometallic compound is provided by the combustion of diethylzinc:

$$Zn(C_2H_5)_2 + 7O_2 \rightarrow ZnO(s) + 5H_2O(g) + 4CO_2(g) \qquad (23.3.4)$$

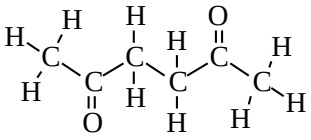
Zinc oxide is used as a healing agent and food additive. However, inhalation of zinc oxide fume particles produced by the combustion of zinc organometallic compounds causes zinc **metal fume fever**. This is an uncomfortable condition characterized by elevated temperature and "chills."

23.4. TOXICOLOGY OF ORGANIC COMPOUNDS

Alkane Hydrocarbons

Gaseous methane, ethane, propane, *n*-butane, and isobutane (both C_4H_{10}) are regarded as **simple asphyxiants** that form mixtures with air containing insufficient oxygen to support respiration. The most common toxicological occupational problem associated with the use of hydrocarbon liquids in the workplace is dermatitis, caused by dissolution of the fat portions of the skin and characterized by inflamed, dry, scaly skin. Inhalation of volatile liquid 5–8 carbon *n*-alkanes and branched-chain alkanes may cause central nervous system depression manifested by dizziness and loss of coordination. Exposure to *n*-hexane and cyclohexane results in 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). This has resulted in multiple disorders of the nervous

system (**polyneuropathy**) including muscle weakness and impaired sensory function of the hands and feet. In the body, *n*-hexane is metabolized to 2,5-hexanedione:



2,5-hexanedione

This Phase I oxidation product can be observed in urine of exposed individuals and is used as a biological monitor of exposure to *n*-hexane.[5]

Alkene and Alkyne Hydrocarbons

Ethylene, a widely used colorless gas with a somewhat sweet odor, acts as a simple asphyxiant and anesthetic to animals and is phytotoxic (toxic to plants). The toxicological properties of propylene (C_3H_6) are very similar to those of ethylene. Colorless, odorless, gaseous 1,3-butadiene is an irritant to eyes and respiratory system mucous membranes; at higher levels it can cause unconsciousness and even death. Acetylene, H-C≡C-H, is a colorless gas with a garlic odor. It acts as an asphyxiant and narcotic, causing headache, dizziness, and gastric disturbances. Some of these effects may be due to the presence of impurities in the commercial product.

Benzene and Aromatic Hydrocarbons

Inhaled benzene is readily absorbed by blood, from which it is strongly taken up by fatty tissues. For the non-metabolized compound, the process is reversible and benzene is excreted through the lungs. As shown in Figure 23.1, benzene is converted to phenol by a Phase I oxidation reaction (see Section 22.6) in the liver.

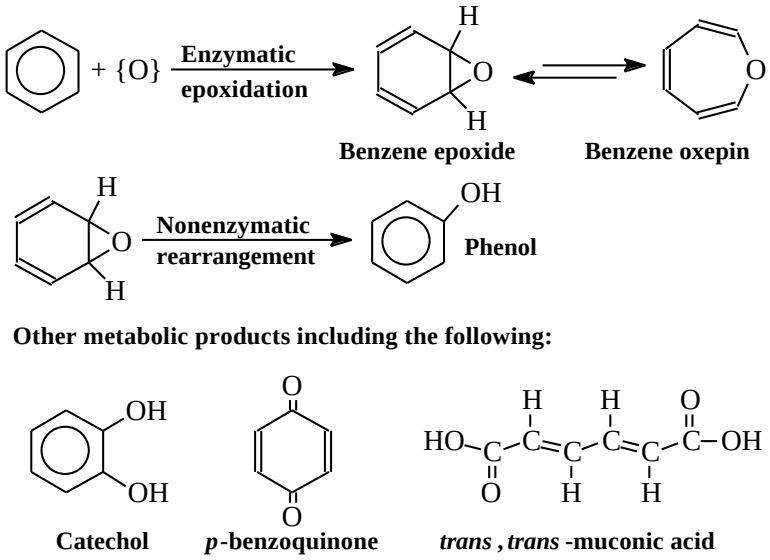


Figure 23.1. Conversion of benzene to phenol in the body.

The reactive and short-lived benzene epoxide intermediate known to occur in this reaction is probably responsible for much of the unique toxicity of benzene, which involves damage to bone marrow. In addition to phenol, several other oxygenated derivatives of benzene are produced when it is metabolized, as is *trans*,*trans*-muconic acid, produced by cleavage of the benzene ring.[6]

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 7 g/m^3 of benzene causes acute poisoning within an hour because of a narcotic effect upon the central nervous system manifested progressively by excitation, depression, respiratory system failure, and death. Inhalation of air containing more than about 60 g/m^3 of benzene can be fatal within a few minutes.

Long-term exposures to lower levels of benzene cause nonspecific symptoms, including fatigue, headache, and appetite loss. Chronic benzene poisoning causes blood abnormalities, including a lowered white cell count, an abnormal increase in blood lymphocytes (colorless corpuscles introduced to the blood from the lymph glands), anemia, a decrease in the number of blood platelets required for clotting (thrombocytopenia), and damage to bone marrow. It is thought that preleukemia, leukemia, or cancer may result.

Toluene

Toluene, a colorless liquid boiling at 101.4˚C, is classified as moderately toxic through inhalation or ingestion; it has a low toxicity by dermal exposure. Toluene can be tolerated without noticeable ill effects in ambient air up to 200 ppm. Exposure to 500 ppm may cause headache, nausea, lassitude, and impaired coordination without detectable physiological effects. Massive exposure to toluene has a narcotic effect, which can lead to coma. Because it possesses an aliphatic side chain that can be oxidized enzymatically to products that are readily excreted from the body (see the metabolic reaction scheme in Figure 23.2), toluene is much less toxic than benzene.

Naphthalene

As is the case with benzene, **naphthalene** undergoes a Phase I oxidation reaction that places an epoxide group on the aromatic ring. This process is followed by Phase II conjugation reactions to yield products that can be eliminated from the body in the urine.

Exposure to naphthalene can cause anemia and marked reductions in red cell count, hemoglobin, and hematocrit in individuals exhibiting genetic susceptibility to these conditions. Naphthalene causes skin irritation or severe dermatitis in sensitized individuals. Headaches, confusion, and vomiting may result from inhalation or ingestion of naphthalene. Death from kidney failure occurs in severe instances of poisoning.

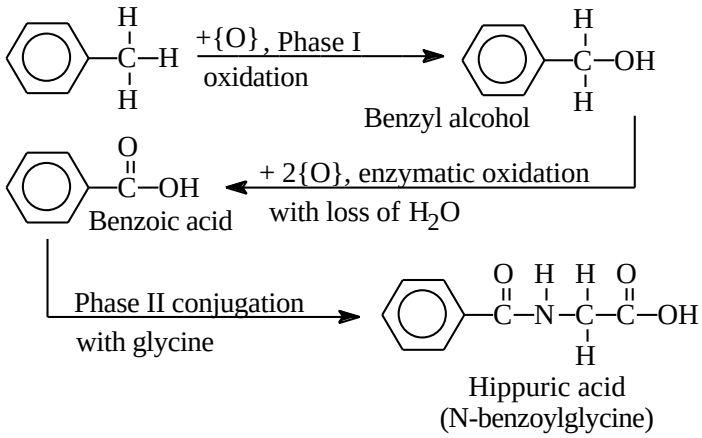


Figure 23.2. Metabolic oxidation of toluene with conjugation to hippuric acid, which is excreted with urine.

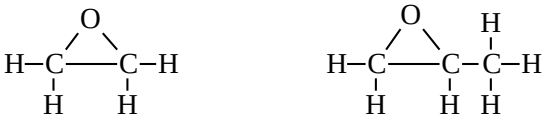
Polycyclic Aromatic Hydrocarbons

Benzo[a]pyrene (see Section 10.4) is the most studied of the polycyclic aromatic hydrocarbons (PAHs). Some metabolites of PAH compounds, particularly the 7,8-diol-9,10-epoxide of benzo[a]pyrene shown in Figure 23.3, are known to cause cancer. There are two stereoisomers of this metabolite, both of which are known to be potent mutagens and presumably can cause cancer.

Oxygen-Containing Organic Compounds

Oxides

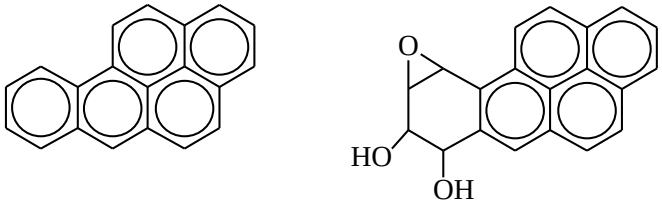
Hydrocarbon **oxides** such as ethylene oxide and propylene oxide,



Ethylene oxide **Propylene oxide**

which are characterized by an **epoxide** functional group bridging oxygen between two adjacent C atoms, are significant for both their uses and their toxic effects. Ethylene oxide, a gaseous colorless, sweet-smelling, flammable, explosive gas used as a chemical intermediate, sterilant, and fumigant, has a moderate to high toxicity, is a mutagen, and is carcinogenic to experimental animals. Inhalation of relatively low levels of this gas results in respiratory tract irritation, headache, drowsiness, and dyspnea, whereas exposure to higher levels causes cyanosis, pulmonary edema, kidney damage, peripheral nerve damage, and even death. Propylene oxide is a colorless, reactive, volatile liquid (bp 34˚C) with uses similar to those of ethylene

oxide and similar, though less severe, toxic effects. The toxicity of 1,2,3,4-butadiene epoxide, the oxidation product of 1,3-butadiene, is notable in that it is a direct–acting (primary) carcinogen.



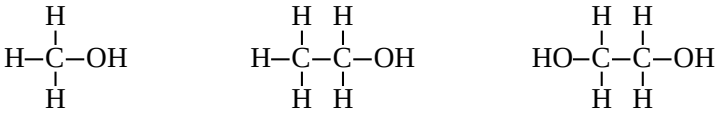
Benzo(a)pyrene

7,8-Diol-9,10-epoxide of benzo(a)pyrene

Figure 23.3. Benzo[a]pyrene and its carcinogenic metabolic product.

Alcohols

Human exposure to the three light alcohols shown in Figure 23.4. is common because they are widely used industrially and in consumer products.



Methanol Ethanol Ethylene glycol

Figure 23.4. **Alcohols** such as these three compounds are oxygenated compounds in which the hydroxyl functional group is attached to an alkyl or alkenyl hydrocarbon skeleton.

Methanol, which has caused many fatalities when ingested accidentally or consumed as a substitute for beverage ethanol, is metabolically oxidized to formaldehyde and formic acid. In addition to causing acidosis, these products affect the central nervous system and the optic nerve. Acute exposure to lethal doses causes an initially mild inebriation, followed in about 10–20 hours by unconsciousness, cardiac depression, and death. Sublethal exposures can cause blindness from deterioration of the optic nerve and retinal ganglion cells. Inhalation of methanol fumes may result in chronic, low-level exposure.

Ethanol is usually ingested through the gastrointestinal tract, but can be absorbed as vapor by the alveoli of the lungs. Ethanol is oxidized metabolically more rapidly than methanol, first to acetaldehyde (discussed later in this section), then to CO_2. Ethanol has numerous acute effects resulting from central nervous system depression. These range from decreased inhibitions and slowed reaction times at 0.05% blood ethanol, through intoxication, stupor, and—at more than 0.5% blood ethanol—death. Ethanol also has a number of chronic effects, of which the addictive condition of alcoholism and cirrhosis of the liver are the most prominent.[7]

Despite its widespread use in automobile cooling systems, exposure to ethylene glycol is limited by its low vapor pressure. However, inhalation of droplets of ethylene glycol can be very dangerous. In the body, ethylene glycol initially

stimulates the central nervous system, then depresses it. Glycolic acid, chemical formula $HOCH_2CO_2H$, formed as an intermediate metabolite in the metabolism of ethylene glycol, may cause acidemia, and oxalic acid produced by further oxidation may precipitate in the kidneys as solid calcium oxalate, CaC_2O_4, causing clogging.

Of the higher alcohols, 1-butanol is an irritant, but its toxicity is limited by its low vapor pressure. Unsaturated (alkenyl) allyl alcohol, $CH_2=CHCH_2OH$, has a pungent odor and is strongly irritating to eyes, mouth, and lungs.

Phenols

Figure 23.5 shows some of the more important phenolic compounds, aryl analogs of alcohols which have properties much different from those of the aliphatic and olefinic alcohols. Nitro groups ($-NO_2$) and halogen atoms (particularly Cl) bonded to the aromatic rings strongly affect the chemical and toxicological behavior of phenolic compounds.

Although the first antiseptic used on wounds and in surgery, phenol is a protoplasmic poison that damages all kinds of cells and is alleged to have caused "an astonishing number of poisonings" since it came into general use.[8] The acute toxicological effects of phenol are largely upon the central nervous system and death can occur as soon as one-half hour after exposure. Acute poisoning by phenol can cause severe gastrointestinal disturbances, kidney malfunction, circulatory system failure, lung edema, and convulsions. Fatal doses of phenol may be absorbed through the skin. Key organs damaged by chronic phenol exposure include the spleen, pancreas, and kidneys. The toxic effects of other phenols resemble those of phenol.

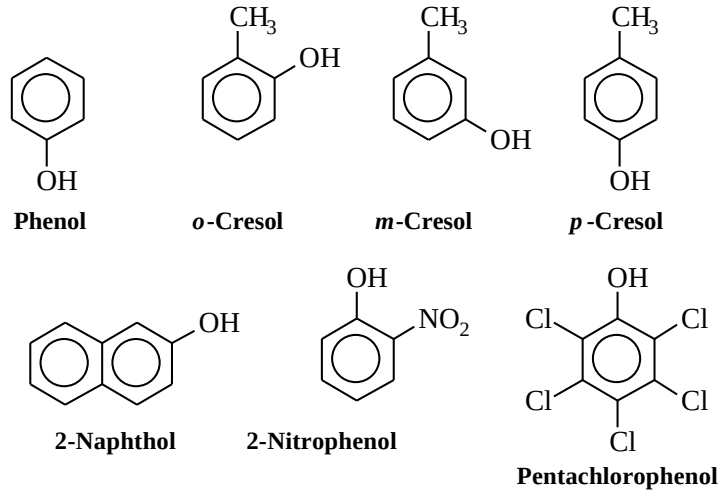


Figure 23.5. Some phenols and phenolic compounds.

Aldehydes and Ketones

Aldehydes and ketones are compounds that contain the carbonyl (C=O) group, as shown by the examples in Figure 23.6.

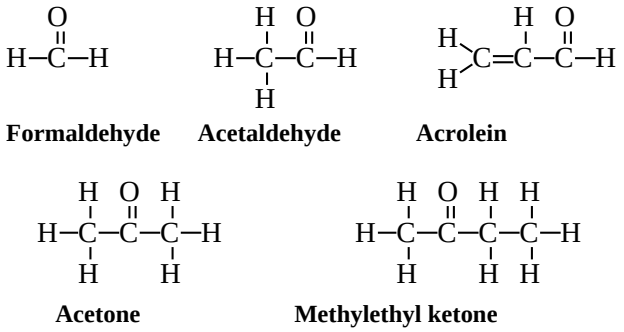


Figure 23.6. Commercially and toxicologically significant aldehydes and ketones.

Formaldehyde is uniquely important because of its widespread use and toxicity. In the pure form, formaldehyde is a colorless gas with a pungent, suffocating odor. It is commonly encountered as **formalin,** a 37–50% aqueous solution of formaldehyde containing some methanol. Exposure to inhaled formaldehyde via the respiratory tract is usually due to molecular formaldehyde vapor, whereas exposure by other routes is usually due to formalin. Prolonged, continuous exposure to formaldehyde can cause hypersensitivity. A severe irritant to the mucous membrane linings of both the respiratory and alimentary tracts, formaldehyde reacts strongly with functional groups in molecules. Formaldehyde has been shown to be a lung carcinogen in experimental animals. The toxicity of formaldehyde is largely due to its metabolic oxidation product, formic acid (see below).

The lower aldehydes are relatively water-soluble and intensely irritating. These compounds attack exposed moist tissue, particularly the eyes and mucous membranes of the upper respiratory tract. (Some of the irritating properties of photochemical smog, Chapter 13, are due to the presence of aldehydes.) However, aldehydes that are relatively less soluble can penetrate further into the respiratory tract and affect the lungs. Colorless, liquid acetaldehyde is relatively less toxic than acrolein and acts as an irritant and systemically as a narcotic to the central nervous system. Extremely irritating, lachrimating acrolein vapor has a choking odor and inhalation of it can cause severe damage to respiratory tract membranes. Tissue exposed to acrolein may undergo severe necrosis, and direct contact with the eye can be especially hazardous.

The ketones shown in Figure 23.6. are relatively less toxic than the aldehydes. Pleasant-smelling acetone can act as a narcotic; it causes dermatitis by dissolving fats from skin. Not many toxic effects have been attributed to methyl ethyl ketone. It is suspected of having caused neuropathic disorders in shoe factory workers.

Carboxylic Acids

Formic acid, HCO_2H, is a relatively strong acid that is corrosive to tissue. In Europe, decalcifier formulations for removing mineral scale that contain about 75% formic acid are sold; and children ingesting these solutions have suffered corrosive lesions to mouth and esophageal tissue. Although acetic acid as a 4–6% solution in

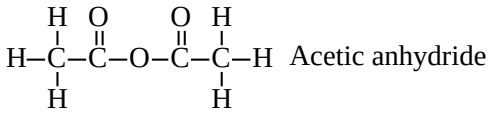
vinegar is an ingredient of many foods, pure acetic acid (glacial acetic acid) is extremely corrosive to tissue that it contacts. Ingestion of, or skin contact with acrylic acid can cause severe damage to tissues.

Ethers

The common ethers have relatively low toxicities because of the low reactivity of the C–O–C functional group which has very strong carbon-oxygen bonds. Exposure to volatile diethyl ether is usually by inhalation and about 80% of this compound that gets into the body is eliminated unmetabolized as the vapor through the lungs. Diethyl ether depresses the central nervous system and is a depressant widely used as an anesthetic for surgery. Low doses of diethyl ether cause drowsiness, intoxication, and stupor, whereas higher exposures cause unconsciousness and even death.

Acid Anhydrides

Strong-smelling, intensely lachrimating **acetic anhydride**,



is a systemic poison. It is very corrosive to the skin, eyes, and upper respiratory tract, causing blisters and burns that heal only slowly. Levels in the air should not exceed 0.04 mg/m^3, and adverse effects to the eyes have been observed at about 0.4 mg/m^3.

Esters

Many esters (Figure 23.7) have relatively high volatilities so that the pulmonary system is a major route of exposure. Because of their generally good solvent properties, esters penetrate tissues and tend to dissolve body lipids. For example, vinyl acetate acts as a skin defatting agent. Because they hydrolyze in water, ester toxicities tend to be the same as the toxicities of the acids and alcohols from which they were formed. Many volatile esters exhibit asphyxiant and narcotic action. Whereas many of the naturally occurring esters have insignificant toxicities at low doses, allyl acetate and some of the other synthetic esters are relatively toxic.

Insofar as potential health effects are concerned, di-(2-ethylhexyl) phthalate (DEHP) is arguably the ester of most concern. This is because of the use of this ester at levels of around 30% as a plasticizer to impart flexibility to poly(vinyl chloride) (PVC) plastic. As a consequence of the widespread use of DEHP-containing PVC plastics, DEHP has become a ubiquitous contaminant found in water, sediment, food, and biological samples. The most acute concern arises from its use in medical applications, particularly bags used to hold intravenous solutions administered to medical patients.[9] As a result of medical use, DEHP enters the blood of hemophiliacs, kidney dialysis patients, and premature and high-risk infants.[10] Although the acute toxic effects of DEHP are low, such widespread direct exposure of humans is worrisome.

Organonitrogen Compounds

Organonitrogen compounds constitute a large group of compounds with diverse toxicities. Examples of several of the kinds of organonitrogen compounds discussed here are given in Figure 23.8.

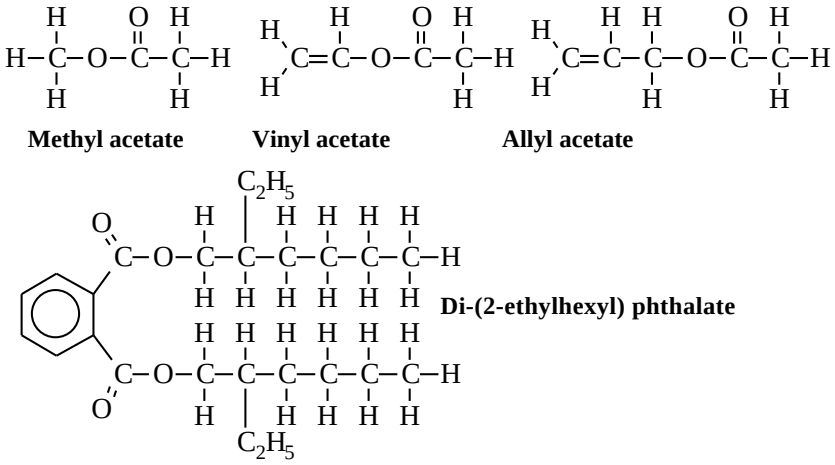


Figure 23.7. Examples of esters.

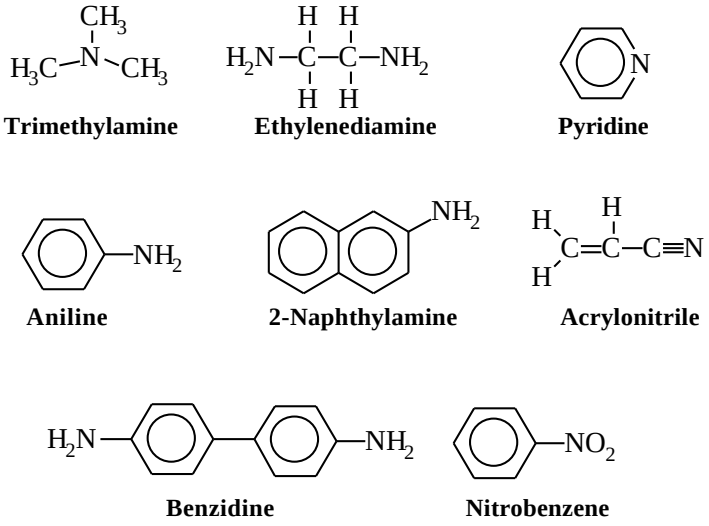


Figure 23.8. Some toxicologically significant organonitrogen compounds.

Aliphatic Amines

The lower amines, such as the methylamines, are rapidly and easily taken into the body by all common exposure routes. They are basic and react with water in tissue,

$$R_3N + H_2O \rightarrow R_3NH^+ + OH^- \quad (23.4.1)$$

raising the pH of the tissue to harmful levels, acting as corrosive poisons (especially to sensitive eye tissue), and causing tissue necrosis at the point of contact. Among the systemic effects of amines are necrosis of the liver and kidneys, lung hemorrhage and edema, and sensitization of the immune system. The lower amines are among the more toxic substances in routine, large-scale use.

Ethylenediamine is the most common of the **alkyl polyamines**, compounds in which two or more amino groups are bonded to alkane moieties. Its toxicity rating is only 3, but it is a strong skin sensitizer and can damage eye tissue.

Carbocyclic Aromatic Amines

Aniline is a widely used industrial chemical and is the simplest of the **carbocyclic aromatic amines**, a class of compounds in which at least one substituent group is an aromatic hydrocarbon ring bonded directly to the amino group. There are numerous compounds with many industrial uses in this class of amines. Some of the carbocyclic aromatic amines have been shown to cause cancer in the human bladder, ureter, and pelvis, and are suspected of being lung, liver, and prostate carcinogens. A very toxic colorless liquid with an oily consistency and distinct odor, aniline readily enters the body by inhalation, ingestion, and through the skin. Metabolically, aniline converts iron(II) in hemoglobin to iron(III). This causes a condition called **methemoglobinemia**, characterized by cyanosis and a brown-black color of the blood, in which the hemoglobin can no longer transport oxygen in the body. This condition is not reversed by oxygen therapy.

Both **1-naphthylamine** (α-naphthylamine) and **2-naphthylamine** (β-naphthylamine) are proven human bladder carcinogens. In addition to being a proven human carcinogen, **benzidine**, 4,4'-diaminobiphenyl, is highly toxic and has systemic effects that include blood hemolysis, bone marrow depression, and kidney and liver damage. It can be taken into the body orally, by inhalation into the lungs, and by skin sorption.

Pyridine

Pyridine, a colorless liquid with a sharp, penetrating, “terrible”odor, is an aromatic amine in which an N atom is part of a 6-membered ring. This widely used industrial chemical is only moderately toxic with a toxicity rating of 3. Symptoms of pyridine poisoning include anorexia, nausea, fatigue, and, in cases of chronic poisoning, mental depression. In a few rare cases pyridine poisoning has been fatal.

Nitriles

Nitriles contain the -C≡N functional group. Colorless, liquid **acetonitrile**, CH_3CN, is widely used in the chemical industry. With a toxicity rating of 3–4, acetonitrile is considered relatively safe, although it has caused human deaths, perhaps by metabolic release of cyanide. **Acrylonitrile**, a colorless liquid with a peach-seed (cyanide) odor, is highly reactive because it contains both nitrile and

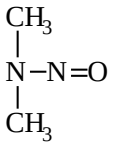
C=C groups. Ingested, absorbed through the skin, or inhaled as vapor, acrylonitrile metabolizes to release deadly HCN, which it resembles toxicologically.

Nitro Compounds

The simplest of the **nitro compounds**, **nitromethane** H_3CNO_2, is an oily liquid that causes anorexia, diarrhea, nausea, and vomiting, and damages the kidneys and liver. **Nitrobenzene**, a pale yellow, oily liquid with an odor of bitter almonds or shoe polish, can enter the body by all routes. It has a toxic action much like that of aniline, converting hemoglobin to methemoglobin, which cannot carry oxygen to body tissue. Nitrobenzene poisoning is manifested by cyanosis.

Nitrosamines

N-nitroso compounds (**nitrosamines**) contain the N–N=O functional group and have been found in a variety of materials to which humans may be exposed, including beer, whiskey, and cutting oils used in machining. Cancer may result from exposure to a single large dose or from chronic exposure to relatively small doses of some nitrosamines. Once widely used as an industrial solvent and known to cause liver damage and jaundice in exposed workers, dimethylnitrosamine was shown to be carcinogenic from studies starting in the 1950s.



Dimethylnitrosamine
(N-nitrosodimethylamine)

Isocyanates and Methyl Isocyanate

Compounds with the general formula R–N=C=O, **isocyanates** are widely used industrial chemicals noted for the high chemical and metabolic reactivity of their characteristic functional group. **Methyl isocyanate**, $H_3C–N=C=O$, was the toxic agent involved in the catastrophic industrial poisoning in Bhopal, India, on December 2, 1984, the worst industrial accident in history. In this incident several tons of methyl isocyanate were released, killing 2000 people and affecting about 100,000. The lungs of victims were attacked; survivors suffered long-term shortness of breath and weakness from lung damage, as well as numerous other toxic effects including nausea and bodily pain.

Organonitrogen Pesticides

Pesticidal *carbamates* are characterized by the structural skeleton of carbamic acid outlined by the dashed box in the structural formula of carbaryl in Figure 23.9. Widely used on lawns and gardens, insecticidal **carbaryl** has a low toxicity to mammals. Highly water-soluble **carbofuran** is a systemic insecticide in that it is taken up by the roots and leaves of plants; insects that feed on the leaves are poisoned. The toxic effects to animals of carbamates are due to the fact that they inhibit acetylcholinesterase directly without the need to first undergo biotransformation. This effect is relatively reversible because of metabolic hydrolysis of the carbamate ester.

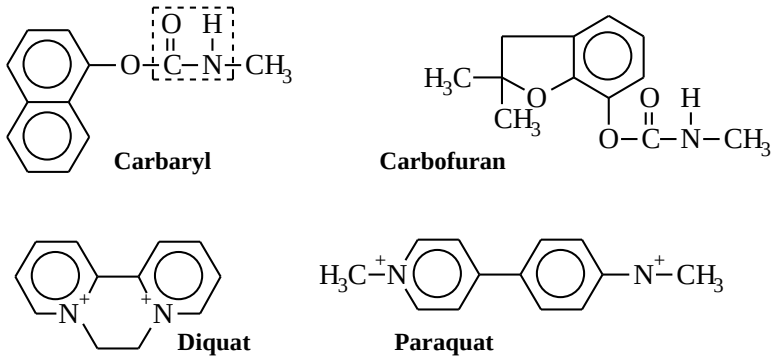


Figure 23.9. Examples of organonitrogen pesticides.

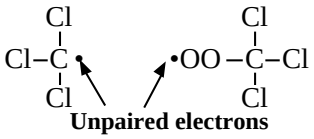
Reputed to have "been responsible for hundreds of human deaths,"[11] herbicidal **paraquat** has a toxicity rating of 5. Dangerous or even fatal acute exposures can occur by inhalation of spray, skin contact, and ingestion. Paraquat is a systemic poison that affects enzyme activity and is devastating to a number of organs. Pulmonary fibrosis results in animals that have inhaled paraquat aerosols, and the lungs are also adversely affected by nonpulmonary exposure. Acute exposure may cause variations in the levels of catecholamine, glucose, and insulin. The most prominent initial symptom of poisoning is vomiting, followed within a few days by dyspnea, cyanosis, and evidence of impairment of the kidneys, liver, and heart. Pulmonary fibrosis, often accompanied by pulmonary edema and hemorrhaging, is observed in fatal cases.

Organohalide Compounds

Alkyl Halides

The toxicities of alkyl halides, such as carbon tetrachloride, CCl_4, vary a great deal with the compound. Most of these compounds cause depression of the central nervous system, and individual compounds exhibit specific toxic effects.

During its many years of use as a consumer product, carbon tetrachloride compiled a grim record of toxic effects which led the U. S. Food and Drug Administration (FDA) to prohibit its household use in 1970. It is a systemic poison that affects the nervous system when inhaled, and the gastrointestinal tract, liver, and kidneys when ingested. The biochemical mechanism of carbon tetrachloride toxicity involves reactive radical species, including

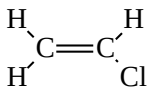


that react with biomolecules, such as proteins and DNA. The most damaging such reaction occurs in the liver as **lipid peroxidation**, consisting of the attack of free

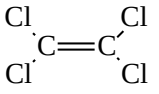
radicals on unsaturated lipid molecules, followed by oxidation of the lipids through a free radical mechanism.

Alkenyl Halides

The most significant **alkenyl** or **olefinic organohalides** are the lighter chlorinated compounds, such as vinyl chloride and tetrachloroethylene:



Vinyl chloride



Tetrachloroethylene

Because of their widespread use and disposal in the environment, the numerous acute and chronic toxic effects of the alkenyl halides are of considerable concern.

The central nervous system, respiratory system, liver, and blood and lymph systems are all affected by vinyl chloride exposure, which has been widespread because of this compound's use in poly(vinyl chloride) manufacture. Most notably, vinyl chloride is carcinogenic, causing a rare angiosarcoma of the liver. This deadly form of cancer has been observed in workers chronically exposed to vinyl chloride while cleaning autoclaves in the poly(vinyl chloride) fabrication industry. The alkenyl organohalide, 1,1-dichloroethylene, is a suspect human carcinogen based upon animal studies and its structural similarity to vinyl chloride The toxicities of both 1,2-dichloroethylene isomers are relatively low. These compounds act in different ways in that the *cis* isomer is an irritant and narcotic, whereas the *trans* isomer affects both the central nervous system and the gastrointestinal tract, causing weakness, tremors, cramps, and nausea. A suspect human carcinogen, trichloroethylene has caused liver carcinoma in experimental animals and is known to affect numerous body organs. Like other organohalide solvents, trichloroethylene causes skin dermatitis from dissolution of skin lipids, and it can affect the central nervous and respiratory systems, liver, kidneys, and heart. Symptoms of exposure include disturbed vision, headaches, nausea, cardiac arrhythmias, and burning/tingling sensations in the nerves (paresthesia). Tetrachloroethylene damages the liver, kidneys, and central nervous system. It is a suspect human carcinogen.

Aryl Halides

Individuals exposed to irritant monochlorobenzene by inhalation or skin contact suffer symptoms to the respiratory system, liver, skin, and eyes. Ingestion of this compound causes effects similar to those of toxic aniline, including incoordination, pallor, cyanosis, and eventual collapse.

The dichlorobenzenes are irritants that affect the same organs as monochlorobenzene. Some animal tests have suggested that 1,2-dichlorobenzene is a potential cancer-causing substance. *Para*-dichlorobenzene (1,4-dichlorobenzene), a chemical used in air fresheners and mothballs, has been known to cause profuse rhinitis (running nose), nausea, jaundice, liver cirrhosis, and weight loss associated with anorexia. It is not known to be a carcinogen. Its major urinary metabolite is 2,5-dichlorophenol, which is eliminated principally as the glucuronide or sulfate.[12]

Because of their once widespread use in electrical equipment, as hydraulic fluids, and in many other applications, polychlorinated biphenyls (PCBs, see Section 7.12) became widespread, extremely persistent environmental pollutants. PCBs have a strong tendency to undergo bioaccumulation in lipid tissue. Polybrominated biphenyl analogs (PBBs) were much less widely used and distributed. However, PBBs were involved in one major incident that resulted in catastrophic agricultural losses when livestock feed contaminated with PBB flame retardant caused massive livestock poisoning in Michigan in 1973.

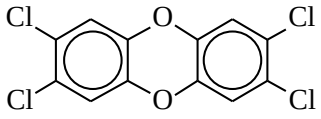
Organohalide Pesticides

Exhibiting a wide range of kind and degree of toxic effects, many organohalide insecticides (see Section 7.11) affect the central nervous system, causing tremor, irregular eye jerking, changes in personality, and loss of memory. Such symptoms are characteristic of acute DDT poisoning. However, the acute toxicity of DDT to humans is very low and, when used for the control of typhus and malaria in World War II, it was applied directly to people. The chlorinated cyclodiene insecticides—aldrin, dieldrin, endrin, chlordane, heptachlor, endosulfan, and isodrin—act on the brain, releasing betaine esters and causing headaches, dizziness, nausea, vomiting, jerking muscles, and convulsions. Dieldrin, chlordane, and heptachlor have caused liver cancer in test animals, and some chlorinated cyclodiene insecticides are teratogenic or fetotoxic. Because of these effects, aldrin, dieldrin, heptachlor, and—more recently—chlordane have been prohibited from use in the U. S.

The major **chlorophenoxy** herbicides are 2,4-dichlorophenoxyacetic acid (2,4-D), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T or Agent Orange), and Silvex. Large doses of 2,4-dichlorophenoxyacetic acid have been shown to cause nerve damage, (peripheral neuropathy), convulsions, and brain damage. According to a National Cancer Institute study,[13] Kansas farmers who had handled 2,4-D extensively have suffered 6 to 8 times the incidence of non-Hodgkins lymphoma as comparable unexposed populations. With a toxicity somewhat less than that of 2,4-D, Silvex is largely excreted unchanged in the urine. The toxic effects of 2,4,5-T (used as a herbicidal warfare chemical called "Agent Orange") have resulted from the presence of 2,3,7,8-tetrachloro-*p*-dioxin (TCDD, commonly known as "dioxin", discussed below), a manufacturing by-product. Autopsied carcasses of sheep poisoned by this herbicide have exhibited nephritis, hepatitis, and enteritis.

TCDD

Polychlorinated dibenzodioxins are compounds which have the same basic structure as that of TCDD (2,3,7,8-tetrachlorodibenzo-*p*-dioxin),



TCDD (2,3,7,8-tetrachloro-dibenzo-p-dioxin)

but have different numbers and locations of chlorine atoms on the ring structure. Extremely toxic to some animals, the toxicity of TCDD to humans is rather uncertain; it is known to cause a skin condition called chloracne. TCDD has been a

manufacturing by-product of some commercial products (see the discussion of 2,4,5-T, above), a contaminant identified in some municipal incineration emissions, and a widespread environmental pollutant from improper waste disposal. This compound has been released in a number of industrial accidents, the most massive of which exposed several tens of thousands of people to a cloud of chemical emissions spread over an approximately 3-square-mile area at the Givaudan-La Roche Icmesa manufacturing plant near Seveso, Italy, in 1976. On an encouraging note from a toxicological perspective, no abnormal occurrences of major malformations were found in a study of 15,291 children born in the area within 6 years after the release.[14]

Chlorinated Phenols

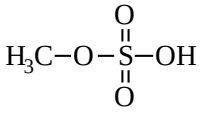
The chlorinated phenols used in largest quantities have been **pentachlorophenol** (Chapter 7) and the trichlorophenol isomers used as wood preservatives. Although exposure to these compounds has been correlated with liver malfunction and dermatitis, contaminant polychlorinated dibenzodioxins may have caused some of the observed effects.

Organosulfur compounds

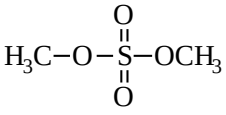
Despite the high toxicity of H_2S, not all organosulfur compounds are particularly toxic. Their hazards are often reduced by their strong, offensive odors that warn of their presence.

Inhalation of even very low concentrations of the alkyl **thiols**, such as methanethiol, H_3CSH, can cause nausea and headaches; higher levels can cause increased pulse rate, cold hands and feet, and cyanosis. In extreme cases, unconsciousness, coma, and death occur. Like H_2S, the alkyl thiols are precursors to cytochrome oxidase poisons.

An oily, water-soluble liquid, **methylsulfuric acid** is a strong irritant to skin, eyes, and mucous tissue. Colorless, odorless **dimethyl sulfate** is highly toxic and is a



Methylsulfuric acid



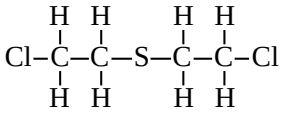
Dimethylsulfate

primary carcinogen that does not require bioactivation to cause cancer. Skin or mucous membranes exposed to dimethyl sulfate develop conjunctivitis and inflammation of nasal tissue and respiratory tract mucous membranes following an initial latent period during which few symptoms are observed. Damage to the liver and kidneys, pulmonary edema, cloudiness of the cornea, and death within 3–4 days can result from heavier exposures.

Sulfur Mustards

A typical example of deadly **sulfur mustards**, compounds used as military poisons, or "poison gases," is mustard oil (bis(2-chloroethyl)sulfide), the structure of

which is shown at the top of the next page. An experimental mutagen and primary carcinogen, mustard oil produces vapors that penetrate deep within tissue, resulting



Mustard oil

in destruction and damage at some depth from the point of contact; penetration is very rapid, so that efforts to remove the toxic agent from the exposed area are ineffective after 30 minutes. This military "blistering gas" poison causes tissue to become severely inflamed with lesions that often become infected. These lesions in the lung can cause death.

Organophosphorus Compounds

Organophosphorus compounds have varying degrees of toxicity. Some of these compounds, such as the "nerve gases" produced as industrial poisons, are deadly in minute quantities. The toxicities of major classes of organophosphate compounds are discussed in this section.

Organophosphate Esters

Some organophosphate esters are shown in Figure 23.10. **Trimethyl phosphate** is probably moderately toxic when ingested or absorbed through the skin, whereas moderately toxic **triethyl phosphate**, $(C_2H_5O)_3PO$, damages nerves and inhibits acetylcholinesterase. Notoriously toxic **tri-*o*-cresyl phosphate**, **TOCP,** apparently is metabolized to products that inhibit acetylcholinesterase. Exposure to TOCP causes degeneration of the neurons in the body's central and peripheral nervous systems with early symptoms of nausea, vomiting, and diarrhea accompanied by severe abdominal pain. About 1–3 weeks after these symptoms have subsided, peripheral paralysis develops manifested by "wrist drop" and "foot drop," followed by slow recovery, which may be complete or leave a permanent partial paralysis.

Briefly used in Germany as a substitute for insecticidal nicotine, **tetraethyl pyrophosphate**, **TEPP**, is a very potent acetylcholinesterase inhibitor. With a toxicity rating of 6 (supertoxic), TEPP is deadly to humans and other mammals.

Phosphorothionate and Phosphorodithioate Ester Insecticides

Because esters containing the P=S (thiono) group are resistant to nonenzymatic hydrolysis and are not as effective as P=O compounds in inhibiting acetylcholinesterase, they exhibit higher insect:mammal toxicity ratios than their nonsulfur analogs. Therefore, **phosphorothionate** and **phosphorodithioate** esters (Figure 23.11.) have been widely used as insecticides. The insecticidal activity of these compounds requires metabolic conversion of P=S to P=O (oxidative desulfuration). Environmentally, organophosphate insecticides are superior to many of the organochlorine insecticides because the organophosphates readily undergo biodegradation and do not bioaccumulate.

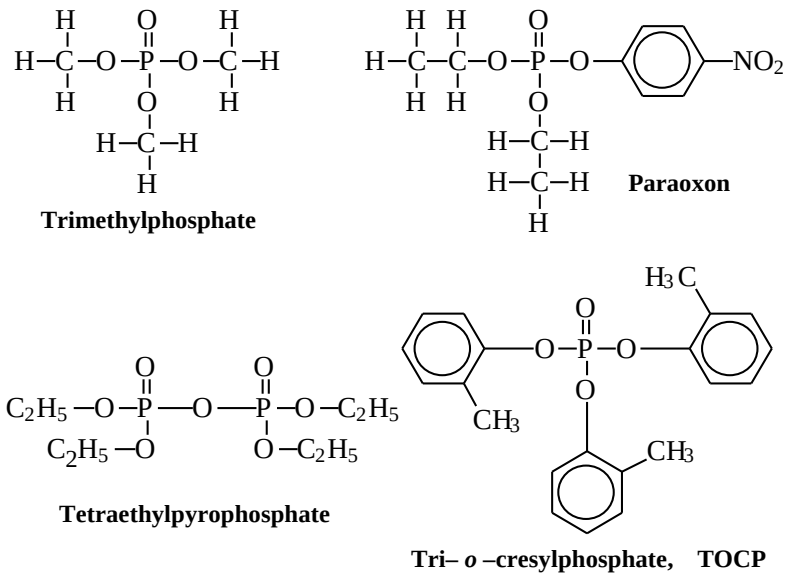


Figure 23.10. Some organophosphate esters.

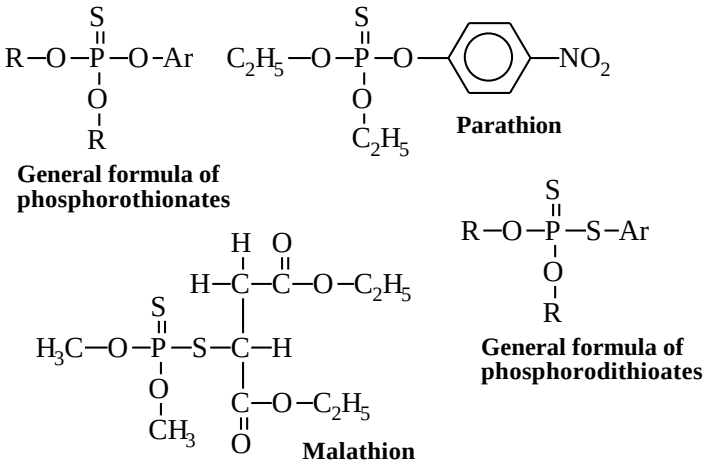


Figure 23.11. Phosphorothionate and phosphorodithioate ester insecticides. Malathion contains hydrolyzable carboxyester linkages.

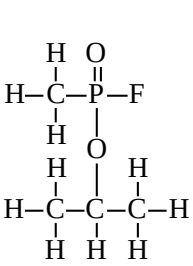
The first commercially successful phosphorothionate/phosphorodithioate ester insecticide was **parathion**, *O*,*O*-diethyl-*O*-*p*-nitrophenylphosphorothionate, first licensed for use in 1944. This insecticide has a toxicity rating of 6 (supertoxic). Since its use began, several hundred people have been killed by parathion, including 17 of 79 people exposed to contaminated flour in Jamaica in 1976. As little as 120 mg of parathion has been known to kill an adult human, and a dose of 2 mg has been fatal to a child. Most accidental poisonings have occurred by absorption through the

skin. Methylparathion (a closely related compound with methyl groups instead of ethyl groups) is regarded as extremely toxic, and in August 1999 the U. S. Environmental Protection Agency proposed severely curtailing its use. In order for parathion to have a toxic effect, it must be converted metabolically to paraoxon (Figure 23.10), which is a potent inhibitor of acetylcholinesterase. Because of the time required for this conversion, symptoms develop several hours after exposure, whereas the toxic effects of TEPP or paraoxon develop much more rapidly. Humans poisoned by parathion exhibit skin twitching and respiratory distress. In fatal cases, respiratory failure occurs due to central nervous system paralysis.

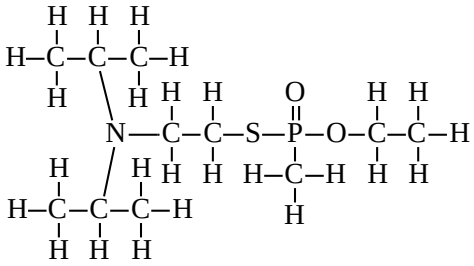
Malathion is the best known of the phosphorodithioate insecticides. It has a relatively high insect:mammal toxicity ratio because of its two carboxyester linkages which are hydrolyzable by carboxylase enzymes (possessed by mammals, but not insects) to relatively nontoxic products. For example, although malathion is a very effective insecticide, its LD_{50} for adult male rats is about 100 times that of parathion.

Organophosphorus Military Poisons

Powerful inhibitors of acetylcholinesterase enzyme, organophosphorus "nerve gas" military poisons include **Sarin** and **VX**, for which structural formulas are shown below. (The possibility that military poisons such as these might be used in war was a major concern during the 1991 Mid-East conflict, which, fortunately, ended without their being employed.) A systemic poison to the central nervous system that is readily absorbed as a liquid through the skin, Sarin may be lethal at doses as low as about 0.0l mg/kg; a single drop can kill a human.



Sarin



VX

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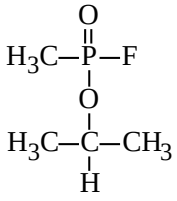
QUESTIONS AND PROBLEMS

1. List and discuss two elements that are invariably toxic in their elemental forms. For another element, list and discuss two elemental forms, one of which is quite toxic and the other of which is essential for the body. In what sense is even the toxic form of this element "essential for life?"
2. What is a toxic substance that bonds to iron(III) in iron-containing ferricytochrome oxidase enzyme, preventing its reduction to iron(II) in the oxidative phosphorylation process by which the body utilizes O_2?
3. What are interhalogen compounds, and which elemental forms do their toxic effects most closely resemble?
4. Name and describe the three health conditions that may be caused by inhalation of asbestos.
5. Why might tetraethyllead be classified as "the most notable toxic organometallic compound"?
6. What is the most common toxic effect commonly attributed to low-molar-mass alkanes?
7. Information about the toxicities of many substances to humans is lacking because of limited data on direct human exposure. (Volunteers to study human health effects of toxicants are in notably short supply.) However, there is a great deal of information available about human exposure to phenol and the adverse effects of such exposure. Explain.
8. Comment on the toxicity of the compound below:



9. What are neuropathic disorders? Why are organic solvents frequently the cause of such disorders?

10. What is a major metabolic effect of aniline? What is this effect called? How is it manifested?
11. What are the organic compounds characterized by the N–N=O functional group? What is their major effect on health?
12. What structural group is characteristic of carbamates? For what purpose are these compounds commonly used? What are their major advantages in such an application?
13. What is lipid peroxidation? Which common toxic substance is known to cause lipid peroxidation?
14. Biochemically, what do organophosphate esters such as parathion do that could classify them as “nerve poisons”?
15. Although benzene and toluene have a number of chemical similarities, their metabolisms and toxic effects are quite different. Explain.