Basics of Environmental Toxicology

GERALD A. LEBLANC

26.1 INTRODUCTION

Industrial and agricultural endeavors are intimately associated with the extensive use of a wide array of chemicals. Historically chemical wastes generated through industrial processes were disposed of through flagrant release into the environment. Gasses quickly dispersed into the atmosphere; liquids were diluted into receiving waters and efficiently transported away from the site of generation. Similarly pesticides and other agricultural chemicals revolutionized farm and forest productivity. Potential adverse effects of the application of such chemicals to the environment were viewed as insignificant relative to the benefits bestowed by such practices. Then in 1962, a science writer for the US Fish and Wildlife Service, Rachel Carson, published a book that began by describing a world devoid of birds and from which the title *The Silent Spring* was inspired. In her book Ms. Carson graphically described incidents of massive fish and bird kills resulting from insecticide use in areas ranging from private residences to national forests. Further she inferred that such pollutant effects on wildlife may be heralding similar incipient effects on human health.

The resulting awakening of the general public to the hazards of chemicals in the environment spurred several landmark activities related to environmental protection, including Earth Day, organization of the US Environmental Protection Agency, and the enactment of several pieces of legislation aimed at regulating and limiting the release of chemicals into the environment. Appropriate regulation of the release of chemicals into the environment without applying unnecessarily stringent limitation on industry and agriculture requires a comprehensive understanding of the toxicological properties and consequences of release of the chemicals into the environment. It was from this need that modern environmental toxicology evolved.

Environmental toxicology is defined as the study of the fate and effects of chemicals in the environment. Although this definition would encompass toxic chemicals naturally found in the environment (i.e., animal venom, microbial and plant toxins), environmental toxicology is typically associated with the study of environmental chemicals of anthropogenic origin. Environmental toxicology can be divided into two subcategories:

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environmental health toxicology and ecotoxicology. Environmental health toxicology is the study of the adverse effects of environmental chemicals on human health, while ecotoxicology focuses upon the effects of environmental contaminants upon ecosystems and constituents thereof (fish, wildlife, etc.). Assessing the toxic effects of chemicals on humans involves the use of standard animal models (i.e., mouse and rat) as well as epidemiological evaluations of exposed human populations (i.e., farmers and factory workers). In contrast, ecotoxicology involves the study of the adverse effects of toxicants on myriad of organisms that compose ecosystems ranging from microorganisms to top predators. Further, comprehensive insight into the effects of chemicals in the environment requires assessments ancillary to toxicology such as the fate of the chemical in the environment (Chapter 27), and toxicant interactions with abiotic (nonliving) components of ecosystems. Comprehensive assessments of the adverse effects of environmental chemicals thus utilize expertise from many scientific disciplines. The ultimate goal of these assessments is elucidating the adverse effects of chemicals that are present in the environment (retrospective hazard assessment) and predicting any adverse effects of chemicals before they are discharged into the environment (prospective hazard assessment). The ecological hazard assessment process is discussed in Chapter 28.

Historically chemicals that have posed major environmental hazards tend to share three insidious characteristics: environmental persistence, the propensity to accumulate in living things, and high toxicity.

26.2 ENVIRONMENTAL PERSISTENCE

Many abiotic and biotic processes exist in nature that function in concert to eliminate (i.e., degrade) toxic chemicals. Accordingly many chemicals released into the environment pose minimal hazard simply because of their limited life span in the environment. Chemicals that have historically posed environmental hazard (i.e., DDT, PCBs, TCDD) resist degradative processes and accordingly persist in the environment for extremely long periods of time (Table 26.1). Continued disposal of persistent chemicals into the environment can result in their accumulation to environmental levels sufficient to pose toxicity. Such chemicals can continue to pose hazard long after their disposal into the environment has ceased. For example, significant contamination of Lake Ontario by the pesticide mirex occurred from the 1950s through the 1970s. Mass balance studies performed 20 years later revealed that 80% of the mirex deposited into the lake

Table 26.1 Environmental Half-lives of Some Chemical Contaminants

Contaminant	Half-life	Media
DDT	10 Years	Soil
TCDD	9 Years	Soil
Atrazine	25 Months	Water
Benzoperylene (PAH)	14 Months	Soil
Phenanthrene (PAH)	138 Days	Soil
Carbofuran	45 Days	Water

persisted. One decade following the contamination of Lake Apopka, Florida, with pesticides including DDT and diclofol, populations of alligators continued to experience severe reproductive impairment. Both biotic and abiotic processes contribute to the degradation of chemicals.

26.2.1 Abiotic Degradation

A plethora of environmental forces compromise the structural integrity of chemicals in the environment. Many prominent abiotic degradative processes occur due to the influences of light (photolysis) and water (hydrolysis).

Photolysis. Light, primarily in the ultraviolet range, has the potential to break chemical bonds and thus can contribute significantly to the degradation of some chemicals. Photolysis is most likely to occur in the atmosphere or surface waters where light intensity is greatest. Photolysis is dependent upon both the intensity of the light and the capacity of the pollutant molecules to absorb the light. Unsaturated aromatic compounds such as the polycyclic aromatic hydrocarbons tend to be highly susceptible to photolysis due to their high capacity to absorb light energy. Light energy can also facilitate the oxygenation of environmental contaminants via hydrolytic or oxidative processes. The photooxidation of the organophosphorus pesticide parathion is depicted in Figure 26.1.

Hydrolysis. Water, often in combination with light energy or heat, can break chemical bonds. Hydrolytic reactions commonly result in the insertion of an oxygen atom into the molecule with the commensurate loss of some component of the molecule. Ester bonds, such as those found in organophosphate pesticides (i.e., parathion; Figure 26.1), are highly susceptible to hydrolysis which dramatically lowers the environmental half-lives of these chemicals. Hydrolytic rates of chemicals are influenced by the temperature and pH of the aqueous media. Rates of hydrolysis increase with increasing temperature and with extremes in pH.

26.2.2 Biotic Degradation

While many environmental contaminants are susceptible to abiotic degradative processes, such processes often occur at extremely slow rates. Environmental degradation of chemical contaminants can occur at greatly accelerated rates through the action of microorganisms. Microorganisms (primarily bacteria and fungi) degrade chemicals in an effort to derive energy from these sources. These biotic degradative processes are enzyme mediated and typically occur at rates that far exceed abiotic degradation. Biotic degradative processes can lead to complete mineralization of chemicals to water, carbon dioxide, and basic inorganic constituents. Biotic degradation includes those processes associated with abiotic degradation (i.e., hydrolysis, oxidation) and processes such as the removal of chlorine atoms (dehalogenation), the scission of ringed structures (ring cleavage), and the removal of carbon chains (dealkylation). The process by which microorganisms are used to facilitate the removal of environmental contaminants is called bioremediation.

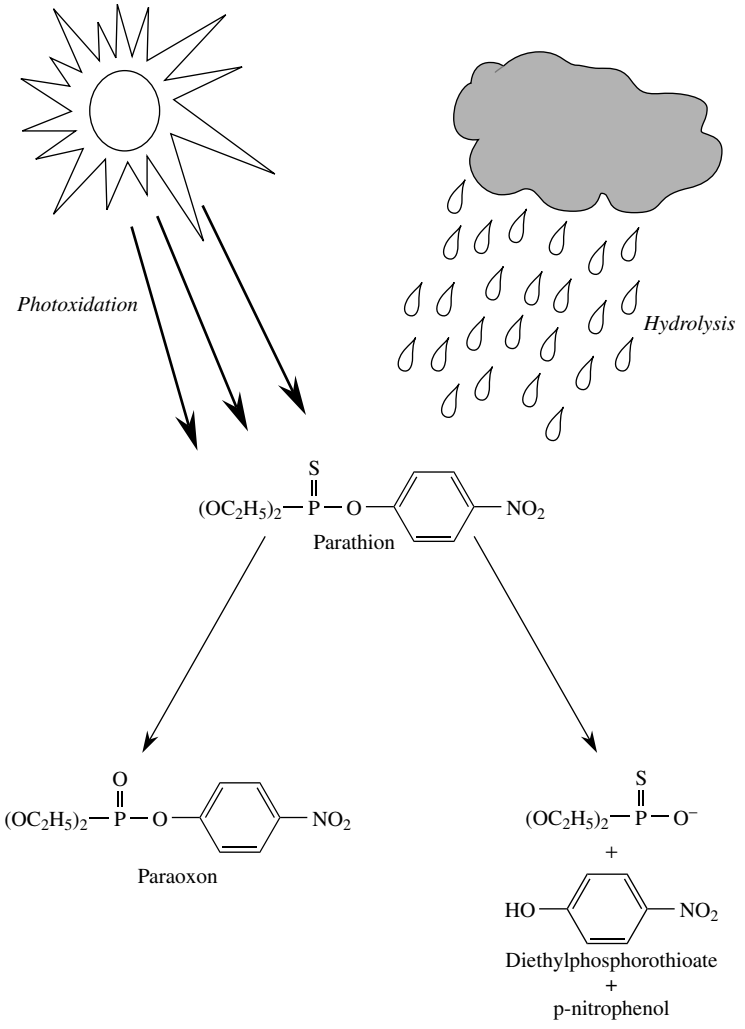

Figure 26.1 The effect of sunlight (photooxidation) and precipitation (hydrolysis) on the degradation of parathion.

26.2.3 Nondegradative Elimination Processes

Many processes are operative in the environment that contribute to the regional elimination of a contaminant by altering its distribution. Contaminants with sufficiently high vapor pressure can evaporate from contaminated terrestrial or aquatic compartments and be transferred through the atmosphere to new locations. Such processes of global distillation are considered largely responsible for the worldwide distribution of relatively volatile organochlorine pesticides such as lindane and hexachlorobenzene. Entrainment by wind and upper atmospheric currents of contaminant particles or dust onto which the contaminants are sorbed also contribute to contaminant redistribution. Sorption of contaminant to suspended solids in an aquatic environment with commensurate sedimentation can result with the removal of contaminants from the water

column and its redistribution into bottom sediments. Sediment sorption of contaminants greatly reduces bioavailability, since the propensity of a lipophilic chemical to partition from sediments to organisms is significantly less than its propensity to partition from water to organism. More highly water soluble contaminants can be removed and redistributed through runoff and soil percolation. For example, the herbicide atrazine is one of the most abundantly used pesticides in the United States. It is used to control broadleaf and weed grasses in both agriculture and landscaping. Atrazine is ubiquitous in surface waters due to its extensive use. A study of midwestern states revealed that atrazine was detectable in 92% of the reservoirs assayed. In addition atrazine has the propensity to migrate into groundwater because of its relatively high water solubility and low predilection to sorb to soil particles. Indeed, field studies have shown that surface application of atrazine typically results in the contamination of the aquifer below the application site. A more detailed account of the fate of chemicals in the environment is presented in Chapter 27.

26.3 BIOACCUMULATION

Environmental persistence alone does not render a chemical problematic in the environment. If the chemical cannot enter the body of organisms, then it would pose no threat of toxicity (see Chapter 6). Once absorbed, the chemical must accumulate in the body to sufficient levels to elicit toxicity. Bioaccumulation is defined as the process by which organisms accumulate chemicals both directly from the abiotic environment (i.e., water, air, soil) and from dietary sources (trophic transfer). Environmental chemicals are largely taken up by organisms by passive diffusion. Primary sites of uptake include membranes of the lungs, gills, and gastrointestinal tract. While integument (skin) and associated structures (scales, feathers, fur, etc.) provide a protective barrier against many environmental insults, significant dermal uptake of some chemicals can occur. Because the chemicals must traverse the lipid bilayer of membranes to enter the body, bioaccumulation potential of chemicals is positively correlated with lipid solubility (lipophilicity).

The aquatic environment is the major site at which lipophilic chemicals traverse the barrier between the abiotic environment and the biota. This is because (1) lakes, rivers, and oceans serve as sinks for these chemicals, and (2) aquatic organisms pass tremendous quantities of water across their respiratory membranes (i.e., gills) allowing for the efficient extraction of the chemicals from the water. Aquatic organisms can bioaccumulate lipophilic chemicals and attain body concentrations that are several orders of magnitude greater that the concentration of the chemical found in the environment (Table 26.2). The degree to which aquatic organisms accumulate xenobiotics from the environment is largely dependent on the lipid content of the organism, since body lipids serve as the primary site of retention of the chemicals (Figure 26.2).

Chemicals can also be transferred along food chains from prey organism to predator (trophic transfer). For highly lipophilic chemicals, this transfer can result in increasing concentrations of the chemical with each progressive link in the food chain (biomagnification). As depicted in Figure 26.3, a chemical that bioaccumulates by a factor of 2 regardless of whether the source of the contaminant is the water or food would have the potential to magnify at each trophic level leading to high levels in the birds of

Table 26.2 Bioaccumulation of Some Environmental Contaminants by Fish

Chemical	Bioaccumulation Factor[a]
DDT	127,000
TCDD	39,000
Endrin	6,800
Pentachlorobenzene	5,000
Lepthophos	750
Trichlorobenzene	183

Source: Data derived from G. A. LeBlanc, 1994, *Environ. Sci. Technol*. **28**: 154–160.

[a]Bioaccumulation factor is defined as the ratio of the chemical concentration in the fish and in the water at steady-state equilibrium.

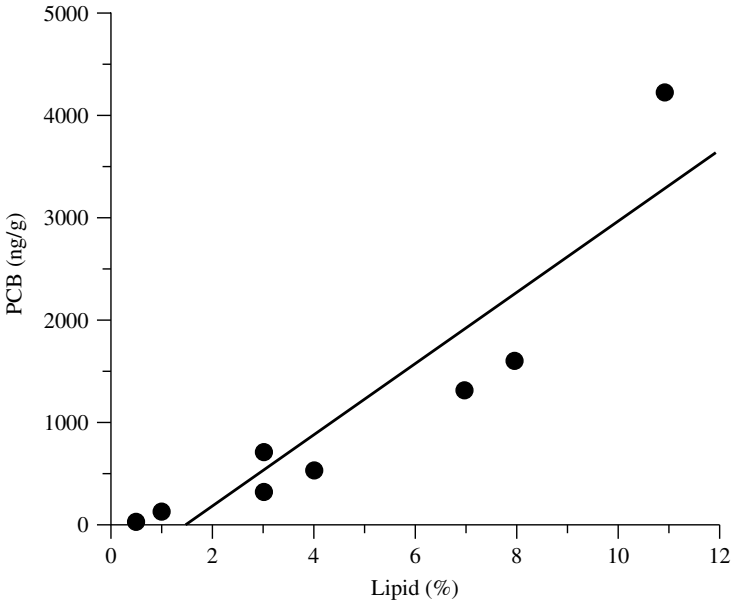

Figure 26.2 Relationship between lipid content of various organisms sampled from Lake Ontario and whole body PCB concentration (Data derived from B. G. Oliver and A. J. Niimi, *Environ. Sci. Technol*. **22**: 388–397, 1988.)

prey relative to that found in the abiotic environment. It should be noted that bioaccumulation is typically much greater from water than from food, and it is unlikely that an organism would accumulate a chemical to the same degree from both sources. The food-chain transfer of DDT was responsible for the decline in many bird-eating raptor populations that contributed to the decision to ban the use of this pesticide in the United States.

Bioaccumulation can lead to a delayed onset of toxicity, since the toxicant may be initially sequestered in lipid deposits but is mobilized to target sites of toxicity

BIOACCUMULATION OF ENVIRONMENTAL CHEMICALS

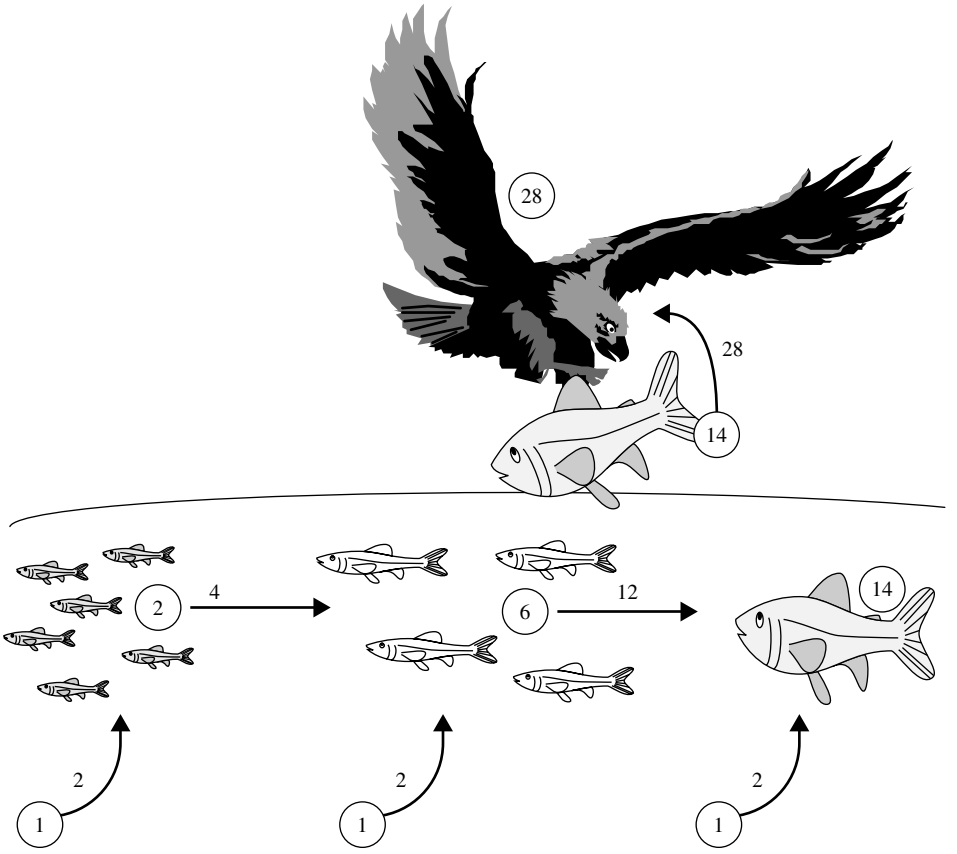

Figure 26.3 Bioaccumulation of a chemical along a generic food chain. In this simplistic paradigm, the amount of the chemical in the water is assigned an arbitrary concentration of 1, and it is assumed that the chemical will bioaccumulate either from the water to the fish or from one trophic level to another by a factor of 2. Circled numbers represent the concentration of chemical in the respective compartment. Numbers associated with arrows represent the concentration of chemical transferred from one compartment to another.

when these lipid stores are utilized. For example, lipid stores are often mobilized in preparation for reproduction. The loss of the lipid can result in the release of lipophilic toxicants rendering them available for toxic action. Such effects can result in mortality of adult organisms as they approach reproductive maturity. Lipophilic chemicals also can be transferred to offspring in lipids associated with the yolk of oviparous organisms or the milk of mammals, resulting in toxicity to offspring that was not evident in the parental organisms.

26.3.1 Factors That Influence Bioaccumulation

The propensity for an environmental contaminant to bioaccumulate is influenced by several factors. The first consideration is environmental persistence. The degree to

Table 26.3 Measured and Predicted Bioaccumulation Factors in Fish of Chemicals That Differ in Susceptibility to Biotransformation

Chemical	Susceptibility to Biotransformation	Bioaccumulation Factor	
		Predicted	Measured
Chlordane	Low	47,900	38,000
PCB	Low	36,300	42,600
Mirex	Low	21,900	18,200
Pentachloro-phenol	High	4,900	780
Tris(2,3-dibromo-propyl)phosphate	High	4,570	3

Source: Predicted bioaccumulation factors were based upon their relative lipophilicity as described by, D. Mackay, *Environ. Sci. Technol*. 1982, **16**: 274–278.

which a chemical bioaccumulates is dictated by the concentration present in the environment. Contaminants that are readily eliminated from the environment will generally not be available to bioaccumulate. An exception would be instances where the contaminant is continuously introduced into the environment (i.e., receiving water of an effluent discharge).

As discussed above, lipophilicity is a major determinant of the bioaccumulation potential of a chemical. However, lipophilic chemicals also have greater propensity to sorb to sediments, thus rendering them less available to bioaccumulate. For example, sorption of benzo[a]pyrene to humic acids reduced its propensity to bioaccumulate in sunfish by a factor of three. Fish from oligotrophic lakes, having low suspended solid levels, have been shown to accumulate more DDT than fish from eutrophic lakes that have high suspended solid contents.

Once absorbed by the organism, the fate of the contaminant will influence its bioaccumulation. Chemicals that are readily biotransformed (Chapter 7) are rendered more water soluble and less lipid soluble. The biotransformed chemical is thus less likely to be sequestered in lipid compartments and more likely to be eliminated from the body. As depicted in Table 26.3, chemicals that are susceptible to biotransformation, bioaccumulate much less than would be predicted based on lipophilicity. Conjugation of xenobiotics to glutathione and glucuronic acid (Chapter 7) can target the xenobiotic for biliary elimination through active transport processes thus greatly increasing the rate of elimination (Chapter 10). Differences in chemical elimination rates contribute to species differences in bioaccumulation.

26.4 TOXICITY

26.4.1 Acute Toxicity

Acute toxicity is defined as toxicity elicited as a result of short-term exposure to a toxicant. Incidences of acute toxicity in the environment are commonly associated with accident (i.e., derailment of a train resulting in leakage of a chemical into a river) or imprudent use of the chemical (i.e., aerial drift of a pesticide to nontarget areas). Discharge limits placed upon industrial and municipal wastes, when adhered to, have been generally successful in protecting against acute toxicity to organisms in waste-receiving areas. As discussed in Chapter 11, the acute toxicity of a chemical is commonly quantified as the LC50 or LD50. These measures do not provide any insight

Table 26.4 Ranking Scheme for Assessing the Acute Toxicity of Chemicals to Fish and Wildlife

Fish LC50 (mg/L)	Avian/Mammalian LD50 (mg/kg)	Toxicity Rank	Example Contaminant
>100	>5000	Relatively nontoxic	Barium
10–100	500–5000	Moderately toxic	Cadmium
1–10	50–500	Very toxic	1,4-Dichlorobenzene
<1	<50	Extremely toxic	Aldrin

into the environmentally acceptable levels of contaminants (a concentration that kills 50% of the exposed organisms is hardly tolerable). However, LC50 and LD50 values do provide statistically sound, reproducible measures of the relative acute toxicity of chemicals. LC50 and LD50 ranges for aquatic and terrestrial wildlife, respectively, and their interpretation are presented in Table 26.4.

Acute toxicity of environmental chemicals is determined experimentally with select species that serve as representatives of particular levels of trophic organization within an ecosystem (i.e., mammal, bird, fish, invertebrate, vascular plant, algae). For example, the US Environmental Protection Agency requires acute toxicity tests with representatives of at least eight different species of freshwater and marine organisms (16 tests) that include fish, invertebrates, and plants when establishing water quality criteria for a chemical. Attempts are often made to rank classes of organisms by toxicant sensitivity; however, no organism is consistently more or less susceptible to the acute toxicity of chemicals. Further the use of standard species in toxicity assessment presumes that these species are "representative" of the sensitivity of other members of that level of ecological organization. Such presumptions are often incorrect.

26.4.2 Mechanisms of Acute Toxicity

Environmental chemicals can elicit acute toxicity by many mechanisms. Provided below are example mechanisms that are particularly relevant to the types of chemicals that are more commonly responsible for acute toxicity in the environment at the present time.

Cholinesterase Inhibition. The inhibition of cholinesterase activity is characteristic of acute toxicity associated with organophosphate and carbamate pesticides (see Chapter 11 for more detail on cholinesterase inhibition). Forty to 80% inhibition of brain cholinesterase activity is typically reported in lethally poisoned fish. Acute toxicity resulting from cholinesterase inhibition is relatively common among incidents of acute poisoning of fish and birds due to the high volume usage of organophosphates and carbamates in applications such as lawn care, agriculture, and golf course maintenance. Cholinesterase inhibition in fish may occur following heavy rains in aquatic habitats adjacent to areas treated with the pesticides and subject to runoff from these areas. Acute toxicity to birds commonly occurs in birds that feed in areas following application of the pesticides.

Narcosis. A common means by which industrial chemicals elicit acute toxicity, particularly to aquatic organisms, is through narcosis. Narcosis occurs when a chemical accumulates in cellular membranes interfering with the normal function of the membranes. Typical responses to the narcosis are decreased activity, reduced reaction to external stimuli, and increased pigmentation (in fish). The effects are reversible, and nonmoribund organisms typically return to normal activity once the chemical is removed from the organism's environment. Prolonged narcosis can result in death. Approximately 60% of industrial chemicals that enter the aquatic environment elicit acute toxicity through narcosis. Chemicals that elicit toxicity via narcosis typically do not elicit toxicity at specific target sites and are sufficiently lipophilic to accumulate in the lipid phase or the lipid-aqueous interface of membranes to sufficient levels to disrupt membrane function. Chemicals that induce narcosis include alcohols, ketones, benzenes, ethers, and aldehydes.

Physical Effects. Perhaps most graphic among recent incidents of environmental acute toxicity is the physical effects of petroleum following oil spills. Slicks of oil on the surface of contaminated waters results in the coating of animals, such as birds and marine mammals, that frequent the air-water interface. Such a spill of unprecedented magnitude and consequence in the United States occurred on March 24, 1989, when the hull of the Exxon Valdez was ruptured on Bligh Reef in Prince William Sound, Alaska. Nearly 11 million gallons of crude oil spilled onto the nearshore waters killing more wildlife than any prior oil spill in history. Thousands of sea birds and mammals succumbed to the acute effects of the oil.

Hypothermia is considered a major cause of death of oiled marine birds and mammals. These organisms insulate themselves from the frigid waters by maintaining a layer of air among the spaces within their coat of fur or feathers. The oil penetrates the fur/feather barrier and purges the insulating air. As a result the animals rapidly succumb to hypothermia. In addition to hypothermia, these animals can also experience oil toxicosis. Inhalation of oil, as well as ingestion through feeding and preening, can result in the accumulation of hydrocarbons to toxic levels. Toxicity to sea otters has been correlated to degree of oiling and is characterized by pulmonary emphysema (bubbles of air within the connective tissue of the lungs), gastric hemorrhages, and liver damage.

26.4.3 Chronic Toxicity

Chronic toxicity is defined as toxicity elicited as a result of long-term exposure to a toxicant. Sublethal end points are generally associated with chronic toxicity. These include reproductive, immune, endocrine, and developmental dysfunction. However, chronic exposure also can result in direct mortality not observed during acute exposure. For example, chronic exposure of highly lipophilic chemicals can result in the eventual bioaccumulation of the chemical to concentrations that are lethal to the organisms. Or as discussed previously, mobilization of lipophilic toxicants from lipid compartments during reproduction may result in lethality. It is important to recognize that, while theoretically, all chemicals elicit acute toxicity at a sufficiently high dose, all chemicals are not chronically toxic. Chronic toxicity is measured by end points such as the highest level of the chemical that does not elicit toxicity during continuous, prolonged exposure (no observed effect level, NOEL), the lowest level of the chemical that elicits

Table 26.5 Acute and Chronic Toxicity of Pesticides Measured from Laboratory Exposures of Fish Species

Pesticide	LC50 (μg/L)	Acute Toxicity	Chronic Value (μg/L)	ACR	Chronic Toxicity
Endosulfan	166	Extremely toxic	4.3	39	Yes
Chlordecone	10	Extremely toxic	0.3	33	Yes
Malathion	3,000	Very toxic	340	8.8	No
Carbaryl	15,000	Moderately toxic	378	40	Yes

toxicity during continuous, prolonged exposure (lowest observed effect level, LOEL), or the chronic value (CV) which is the geometric mean of the NOEL and the LOEL. Chronic toxicity of a chemical is often judged by the acute : chronic ratio (ACR), which is calculated by dividing the acute LC50 value by the CV. Chemicals that have an ACR of less than 10 typically have low to no chronic toxicity associated with them (Table 26.5).

The following must always be considered when assessing the chronic toxicity of a chemical: (1) Simple numerical interpretations of chronic toxicity based on ACRs serve only as gross indicators of the potential chronic toxicity of the chemical. Laboratory exposures designed to establish chronic values most often focus upon a few general endpoints such as survival, growth, and reproductive capacity. Examination of more subtle end points of chronic toxicity may reveal significantly different chronic values. (2) Laboratory exposures are conducted with a few test species that are amenable to laboratory manipulation. The establishment of chronic and ACR values with these species should not be considered absolute. Toxicants may elicit chronic toxicity in some species and not in others. (3) Interactions among abiotic and biotic components of the environment may contribute to the chronic toxicity of chemicals, while such interactions may not occur in laboratory assessments of direct chemical toxicity. These considerations are exemplified in the following incidence of chronic toxicity of chemicals in the environment.

26.4.4 Species-Specific Chronic Toxicity

Tributyltin-Induced Imposex in Neogastropods. Scientists noted in the early 1970s that dogwhelks inhabiting the coast of England exhibited a hermaphroditic-like condition whereby females possessed a penis in addition to normal female genitalia. While hermaphroditism is a reproductive strategy utilized by some molluscan species, dogwhelks are dioecious. This pseudohermaphroditic condition, called imposex, has since been documented worldwide in over 140 species of neogastropods. Imposex has been implicated in reduced fecundity of neogastropod populations, population declines, and local extinction of affected populations.

The observation that imposex occurred primarily in marinas suggested causality with some contaminant originating from such facilities. Field experiments demonstrated that neogastropods transferred from pristine sites to marinas often developed imposex. Laboratory studies eventually implicated tributyltin, a biocide used in marine paints, as the cause of imposex. Tributyltin is toxic to most marine species evaluated in the

Table 26.6 Toxicity of Tributyltin to Aquatic Organisms

Species	Acute Toxicity (LC50, μg/L)	Chronic Toxicity (LOEL, μg/L)	Imposex (μg/L)
Daphnid	1.7	—	—
Polychaete worm	—	0.10	—
Copepod	1.0	0.023	—
Oyster	1.3	0.25	—
Dogwhelk	—	—	≤0.0010

laboratory at low parts-per-billion concentrations (Table 26.6). However, exposure of neogastropods to low parts-per-trillion concentrations can cause imposex (Table 26.6). Thus neogastropods are uniquely sensitive to the toxicity of tributyltin, with effects produced that were not evident in standard laboratory toxicity characterizations.

Atrazine-Induced Hermaphroditism in Frogs. The herbicide atrazine historically has been considered environmentally safe for use since the material has proved to be only slightly to moderately toxic in standard fish and wildlife toxicity evaluations. Measured atrazine levels in surface waters rarely exceed 0.04 mg/L. The acute and chronic toxicities of atrazine to aquatic organisms are typically in excess of 1 mg/L. Thus ample safety margins appear to exist for this compound. Recent studies with frogs have revealed that exposure to 0.0001 mg/L atrazine through the period of larval development caused the frogs to develop both a testis and an ovary. The toxicological significance of this chemical-induced hermaphroditic condition is not known. However, environmentally relevant levels of the herbicide appear to have the potential to adversely impact reproductive success of these organisms.

26.4.5 Abiotic and Biotic Interactions

Chlorofluorocarbons–Ozone–UV-B Radiation–Amphibian Interactions. The atmospheric release of chlorofluorocarbons has been implicated in the depletion of the earth's stratospheric ozone layer which serves as a filter against harmful ultraviolet radiation. Temporal increases in UV-B radiation have been documented and pose increasing risks of a variety of maladies to both plant and animal life.

Commensurate with the increase in UV-B radiation levels at the earth's surface has been the decline in many amphibian populations. Multiple causes may be responsible for these declines including loss of habitat, pollutants, and increased incidence of disease; however, recent studies suggest that increases in UV-B radiation may be a major contributor to the decline in some populations. Field surveys in the Cascade Mountains, Oregon, revealed a high incidence of mortality among embryos of the Cascades frog and western toad. Incubation of eggs, collected from the environment, in the laboratory along with the pond water in which the eggs were collected resulted in low mortality, suggesting that contaminants in the water were not directly responsible for the mortality. Furthermore placement of UV-B filters over the embryos, incubated under ambient environmental conditions, significantly increased viability of the embryos.

Several amphibian species were examined for photolyase activity. This enzyme is responsible for the repair of DNA damage caused by UV-B radiation. A more than

80-fold difference in photolyase activity was observed among the species examined. Photolyase activity was appreciably lower in species known to be experiencing population decline as compared to species showing stable population levels. Recent studies have also suggested that ambient UV-B radiation levels can enhance the susceptibility of amphibian embryos to mortality originating from fungal infection.

These observations suggest that chlorofluorocarbons may be contributing to the decline in amphibian populations. However, this toxicological effect is the result of abiotic interactions (i.e., chlorofluorocarbons depleting atmospheric ozone levels, which increase UV-B radiation penetration resulting in embryo mortality) (Figure 26.4). In addition abiotic (UV-B) and biotic (fungus) interactions may also be contributing to the toxicity. Such effects would not be predicted from direct laboratory assessments of the toxicity of chlorofluorocarbons to amphibians and highlight the necessity to consider possible indirect toxicity associated with environmental contaminants.

Masculinization of Fish due to Microbial Interactions with Kraft Pulpmill Effluent. Field surveys of mosquito fish populations in the state of Florida revealed populations containing females that exhibited male traits such as male-type mating behavior and the modification of the anal fin to resemble the sperm-transmitting gonopodium of males. Masculinized females were found to occur downstream of kraft pulpmill effluents suggesting that components of the effluent were responsible for the masculinizing effect. Direct toxicity assays performed with the effluent did not produce such effects. However, the inclusion of microorganisms along with the effluent resulted in masculinization. Further studies revealed that phytosterols present in the kraft pulpmill effluent can be converted to androgenic C19 steroids by microorganisms and these steroids are capable of masculinizing female fish (Figure 26.5).

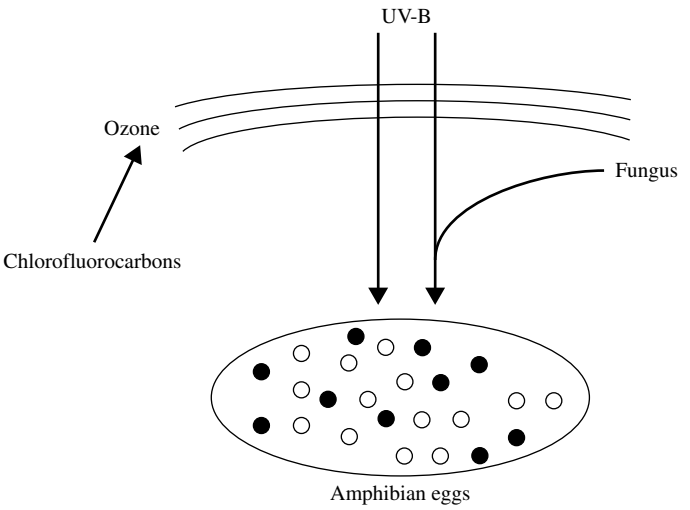

Figure 26.4 Abiotic and biotic interactions leading to the indirect toxicity of chlorofluorocarbons to amphibians. Atmospheric release of chlorofluorocarbons causes the depletion of the stratospheric ozone layer (abiotic-abiotic interaction). Depleted ozone allows for increased penetration of UV-B radiation (abiotic-abiotic interaction). UV-B radiation alone and in combination with fungus (abiotic-biotic interaction) causes increased mortality of amphibian embryos.

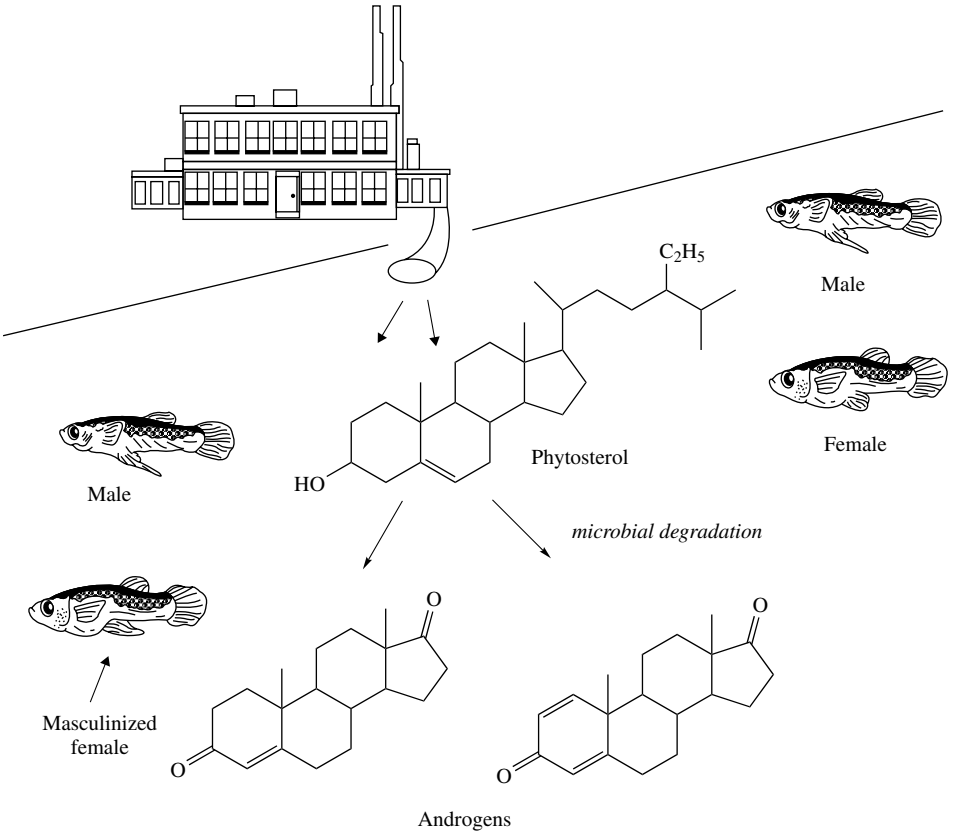

Figure 26.5 Indirect toxicity of kraft pulpmill effluent to mosquito fish. Phytosterols in the mill effluent are converted to C19 steroidal androgens through the action of microorganisms in the environment. These androgens masculinize both anatomy and behavior of female mosquito fish. An arrow identifies the modified anal fin on the masculinized female.

Thus abiotic (phytosterols) : biotic (microorganisms) interactions in the environment must occur before this occult toxicity associated with the kraft pulpmill effluent is unveiled.

Environmental Contaminants and Disease among Marine Mammals. Massive mortality have occurred over the past 20 years among populations of harbor seals, bottlenose dolphins, and other marine mammals worldwide. In many instances this mortality has been attributed to disease. For example, nearly 18,000 harbor seals died in the North, Irish, and Baltic seas in the late 1980s due to phocine distemper virus. Incidences of the disease outbreak were highest in areas containing high levels of pollutants, and seals that succumbed to the disease were found to have high tissue levels of polychlorinated biphenyls (PCBs). PCBs and other organochlorine chemicals such as DDT, hexachlorobenzene, and dieldrin have been shown to immunosuppress laboratory animals, and accumulation of these chemicals by the seals may have increased their susceptibility to the virus. This hypothesis was tested by feeding fish, caught either from a relatively pristine area or from a polluted coastal area, to seals for 93 weeks then

assessing the integrity of the immune system in the seals. Seals fed the contaminated fish did indeed have impaired immune responses lending credence to the hypothesis that organochlorine contaminants in the marine environment are rendering some species immunodeficient. Mortality occurs, not as a direct result of chemical toxicity, but due to increased susceptibility to pathogens.

26.5 CONCLUSION

Environmental toxicologists have learned a great deal about the effects of chemicals in the environment and the characteristics of chemicals that are responsible for the hazards they pose. Much of the information gained has been due to retrospective analyzes of the environmental consequences of the deposition of chemicals into the environment. Such analyzes have resulted in curtailing the release of demonstrated hazardous chemicals into the environment and provide benchmark information upon which the regulation of chemicals proposed for release into the environment can be based. The recognition that environmentally hazardous chemicals commonly share characteristics of persistence, potential to bioaccumulate, and high toxicity has resulted in development and use of chemicals that lack one or more of these characteristics yet fulfill societal needs previously served by hazardous chemicals. For example, recognition that persistence and propensity to bioaccumulate were largely responsible for the environmental hazards posed by many organochlorine pesticides led to the development and use of alternative classes of pesticides such as organophosphates, carbamates, and pyrethroids. While these chemicals all possess the toxicity necessary to function as pesticides, their lack of persistence and reduced propensity to bioaccumulate makes them more suitable for use in the environment.

Such advances in our understanding of the fate and effects of chemicals in the environmental does not imply that the role of environmental toxicologists in the twenty-first century will diminish. A dearth of information persist in areas vital to continued protection of natural resources against chemical insult. These include understanding (1) the unique susceptibilities of key species to the toxicity of different classes of chemicals, (2) the interactions of chemical contaminants with abiotic components of the environment that lead to increased toxicity, (3) the toxicological consequences of exposure to complex chemical mixtures, and (4) the consequences of toxicant effects on individuals with respect to ecosystem viability. Additionally continued research is needed to develop molecular and cellular biomarkers of toxicant exposure and effect that could be used to predict dire consequences to ecosystem before such effects are manifested at higher levels of biological organization. The role of the environmental toxicologist undoubtedly will increase in prospective activities aimed at reducing the risk associated with chemical contaminants in the environments before problems arise, and hopefully will decrease with respect to assessing damage caused by such environmental contaminants.

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CHAPTER 5

Classes of Toxicants: Use Classes

W. GREGORY COPE, ROSS B. LEIDY, and ERNEST HODGSON

5.1 INTRODUCTION

As discussed in Chapter 1, use classes include not only chemicals currently in use but also the toxicological aspects of the development of new chemicals for commercial use, chemicals produced as by-products of industrial processes, and chemicals resulting from the use and/or disposal of chemicals. Because any use class may include chemicals from several different chemical classes, this classification is not sufficient for mechanistic considerations. It is, however, essential for an understanding of the scope of toxicology and, in particular, is essential for many applied branches of toxicology such as exposure assessment, industrial hygiene, public health toxicology and regulatory toxicology.

5.2 METALS

5.2.1 History

Although most metals occur in nature in rocks, ores, soil, water, and air, levels are usually low and widely dispersed. In terms of human exposure and toxicological significance, it is anthropogenic activities that are most important because they increase the levels of metals at the site of human activities.

Metals have been used throughout much of human history to make utensils, machinery, and so on, and mining and smelting supplied metals for these uses. These activities increased environmental levels of metals. More recently metals have found a number of uses in industry, agriculture, and medicine. These activities have increased exposure not only to metal-related occupational workers but also to consumers of the various products.

Despite the wide range of metal toxicity and toxic properties, there are a number of toxicological features that are common to many metals. Some of the more important aspects are discussed briefly in the following sections. For a metal to exert its toxicity, it must cross the membrane and enter the cell. If the metal is in a lipid soluble form such as methylmercury, it readily penetrates the membrane; when bound to proteins

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such as cadmium-metallothionein, the metal is taken into the cell by endocytosis; other metals (e.g., lead) may be absorbed by passive diffusion. The toxic effects of metals usually involve interaction between the free metal and the cellular target. These targets tend to be specific biochemical processes and/or cellular and subcellular membranes.

5.2.2 Common Toxic Mechanisms and Sites of Action

Enzyme Inhibition/Activation. A major site of toxic action for metals is interaction with enzymes, resulting in either enzyme inhibition or activation. Two mechanisms are of particular importance: inhibition may occur as a result of interaction between the metal and sulfhydryl (SH) groups on the enzyme, or the metal may displace an essential metal cofactor of the enzyme. For example, lead may displace zinc in the zinc-dependent enzyme δ-aminolevulinic acid dehydratase (ALAD), thereby inhibiting the synthesis of heme, an important component of hemoglobin and heme-containing enzymes, such as cytochromes.

Subcellular Organelles. Toxic metals may disrupt the structure and function of a number of organelles. For example, enzymes associated with the endoplasmic reticulum may be inhibited, metals may be accumulated in the lysosomes, respiratory enzymes in the mitochondria may be inhibited, and metal inclusion bodies may be formed in the nucleus.

Carcinogenicity. A number of metals have been shown to be carcinogenic in humans or animals. Arsenic, certain chromium compounds, and nickel are known human carcinogens; beryllium, cadmium, and cisplatin are probable human carcinogens. The carcinogenic action, in some cases, is thought to result from the interaction of the metallic ions with DNA (see Chapter 11 for a detailed discussion of carcinogenesis).

Kidney. Because the kidney is the main excretory organ of the body, it is a common target organ for metal toxicity. Cadmium and mercury, in particular, are potent nephrotoxicants and are discussed more fully in the following sections and in Chapter 15.

Nervous System. The nervous system is also a common target of toxic metals; particularly, organic metal compounds (see Chapter 16). For example, methylmercury, because it is lipid soluble, readily crosses the blood-brain barrier and enters the nervous system. By contrast, inorganic mercury compounds, which are more water soluble, are less likely to enter the nervous system and are primarily nephrotoxicants. Likewise organic lead compounds are mainly neurotoxicants, whereas the first site of inorganic lead is enzyme inhibition (e.g., enzymes involved in heme synthesis).

Endocrine and Reproductive Effects. Because the male and female reproductive organs are under complex neuroendocrine and hormonal control, any toxicant that alters any of these processes can affect the reproductive system (see Chapters 17 and 20). In addition metals can act directly on the sex organs. Cadmium is known to produce testicular injury after acute exposure, and lead accumulation in the testes is associated with testicular degeneration, inhibition of spermatogenesis, and Leydig-cell atrophy.

Respiratory System. Occupational exposure to metals in the form of metal dust makes the respiratory system a likely target. Acute exposure may cause irritations and

inflammation of the respiratory tract, whereas chronic exposure may result in fibrosis (aluminum) or carcinogenesis (arsenic, chromium, nickel). Respiratory toxicants are discussed more fully in Chapter 18.

Metal-Binding Proteins. The toxicity of many metals such as cadmium, lead, and mercury depends on their transport and intracellular bioavailability. This availability is regulated to a degree by high-affinity binding to certain cytosolic proteins. Such ligands usually possess numerous SH binding sites that can outcompete other intracellular proteins and thus mediate intracellular metal bioavailability and toxicity. These intracellular "sinks" are capable of partially sequestering toxic metals away from sensitive organelles or proteins until their binding capacity is exceeded by the dose of the metal. *Metallothionein* (MT) is a low molecular weight metal-binding protein (approximately 7000 Da) that is particularly important in regulating the intracellular bioavailability of cadmium, copper, mercury, silver, and zinc. For example, in vivo exposure to cadmium results in the transport of cadmium in the blood by various high molecular weight proteins and uptake by the liver, followed by hepatic induction of MT. Subsequently cadmium can be found in the circulatory system bound to MT as the cadmium-metallothionein complex (CdMT).

5.2.3 Lead

Because of the long-term and widespread use of lead, it is one of the most ubiquitous of the toxic metals. Exposure may be through air, water, or food sources. In the United States the major industrial uses, such as in fuel additives and lead pigments in paints, have been phased out, but other uses, such as in batteries, have not been reduced. Other sources of lead include lead from pipes and glazed ceramic food containers.

Inorganic lead may be absorbed through the GI tract, the respiratory system, and the skin. Ingested inorganic lead is absorbed more efficiently from the GI tract of children than that of adults, readily crosses the placenta, and in children penetrates the blood-brain barrier. Initially, lead is distributed in the blood, liver, and kidney; after prolonged exposure, as much as 95% of the body burden of lead is found in bone tissue.

The main targets of lead toxicity are the hematopoietic system and the nervous system. Several of the enzymes involved in the synthesis of heme are sensitive to inhibition by lead, the two most susceptible enzymes being ALAD and heme synthetase (HS). Although clinical anemia occurs only after moderate exposure to lead, biochemical effects can be observed at lower levels. For this reason inhibition of ALAD or appearance in the urine of ALA can be used as an indication of lead exposure.

The nervous system is another important target tissue for lead toxicity, especially in infants and young children in whom the nervous system is still developing (Chapter 16). Even at low levels of exposure, children may show hyperactivity, decreased attention span, mental deficiencies, and impaired vision. At higher levels, encephalopathy may occur in both children and adults. Lead damages the arterioles and capillaries, resulting in cerebral edema and neuronal degeneration. Clinically this damage manifests itself as ataxia, stupor, coma, and convulsions.

Another system affected by lead is the reproductive system (Chapter 20). Lead exposure can cause male and female reproductive toxicity, miscarriages, and degenerate offspring.

5.2.4 Mercury

Mercury exists in the environment in three main chemical forms: elemental mercury (Hg^0), inorganic mercurous (Hg^+) and mercuric ($Hg2^+$) salts, and organic methylmercury (CH_3Hg) and dimethylmercury (CH_3HgCH_3) compounds. Elemental mercury, in the form of mercury vapor, is almost completely absorbed by the respiratory system, whereas ingested elemental mercury is not readily absorbed and is relatively harmless. Once absorbed, elemental mercury can cross the blood-brain barrier into the nervous system. Most exposure to elemental mercury tends to be from occupational sources.

Of more concern from environmental contamination is exposure to organic mercury compounds. Inorganic mercury may be converted to organic mercury through the action of sulfate-reducing bacteria, to produce methylmercury, a highly toxic form readily absorbed across membranes. Several large episodes of mercury poisoning have resulted from consuming seed grain treated with mercury fungicides or from eating fish contaminated with methylmercury. In Japan in the 1950s and 1960s wastes from a chemical and plastics plant containing mercury were drained into Minamata Bay. The mercury was converted to the readily absorbed methylmercury by bacteria in the aquatic sediments. Consumption of fish and shellfish by the local population resulted in numerous cases of mercury poisoning or Minamata disease. By 1970 at least 107 deaths had been attributed to mercury poisoning, and 800 cases of Minamata disease were confirmed. Even though the mothers appeared healthy, many infants born to mothers who had eaten contaminated fish developed cerebral palsy-like symptoms and mental deficiency. Organic mercury primarily affects the nervous system, with the fetal brain being more sensitive to the toxic effects of mercury than adults.

Inorganic mercury salts, however, are primarily nephrotoxicants, with the site of action being the proximal tubular cells. Mercury binds to SH groups of membrane proteins, affecting the integrity of the membrane and resulting in aliguria, anuria, and uremia.

5.2.5 Cadmium

Cadmium occurs in nature primarily in association with lead and zinc ores and is released near mines and smelters processing these ores. Industrially cadmium is used as a pigment in paints and plastics, in electroplating, and in making alloys and alkali storage batteries (e.g., nickel-cadmium batteries). Environmental exposure to cadmium is mainly from contamination of groundwater from smelting and industrial uses as well as the use of sewage sludge as a food-crop fertilizer. Grains, cereal products, and leafy vegetables usually constitute the main source of cadmium in food. Reference has already been made to the disease Itai-Itai resulting from consumption of cadmium-contaminated rice in Japan (see Chapter 4, Section 4.2.2).

Acute effects of exposure to cadmium result primarily from local irritation. After ingestion, the main effects are nausea, vomiting, and abdominal pain. Inhalation exposure may result in pulmonary edema and chemical pneumonitis.

Chronic effects are of particular concern because cadmium is very slowly excreted from the body, with a half-life of about 30 years. Thus low levels of exposure can result in considerable accumulation of cadmium. The main organ of damage following long-term exposure is the kidney, with the proximal tubules being the primary site of

action. Cadmium is present in the circulatory system bound primarily to the metal-binding protein, metallothionein, produced in the liver. Following glomerular filtration in the kidney, CdMT is re-absorbed efficiently by the proximal tubule cells, where it accumulates within the lysosomes. Subsequent degradation of the CdMT complex releases Cd^{+2}, which inhibits lysosomal function, resulting in cell injury.

5.2.6 Chromium

Because chromium occurs in ores, environmental levels are increased by mining, smelting, and industrial uses. Chromium is used in making stainless steel, various alloys, and pigments. The levels of this metal are generally very low in air, water, and food, and the major source of human exposure is occupational. Chromium occurs in a number of oxidation states from Cr^{+2} to Cr^{+6}, but only the trivalent (Cr^{+3}) and hexavalent (Cr^{+6}) forms are of biological significance. Although the trivalent compound is the most common form found in nature, the hexavalent form is of greater industrial importance. In addition hexavalent chromium, which is not water soluble, is more readily absorbed across cell membranes than is trivalent chromium. In vivo the hexavalent form is reduced to the trivalent form, which can complex with intracellular macromolecules, resulting in toxicity. Chromium is a known human carcinogen and induces lung cancers among exposed workers. The mechanism of chromium (Cr^{+6}) carcinogenicity in the lung is believed to be its reduction to Cr^{+3} and generation of reactive intermediates, leading to bronchogenic carcinoma.

5.2.7 Arsenic

In general, the levels of arsenic in air and water are low, and the major source of human exposure is food. In certain parts of Taiwan and South America, however, the water contains high levels of this metalloid, and the inhabitants often suffer from dermal hyperkeratosis and hyperpigmentation. Higher levels of exposure result in a more serious condition; gangrene of the lower extremities or "blackfoot disease." Cancer of the skin also occurs in these areas.

Approximately 80% of arsenic compounds are used in pesticides. Other uses include glassware, paints, and pigments. Arsine gas is used in the semiconductor industry. Arsenic compounds occur in three forms: (1) pentavalent, As^{+5}, organic or arsenate compounds (e.g., alkyl arsenates); (2) trivalent, As^{+3}, inorganic or arsenate compounds (e.g., sodium arsenate, arsenic trioxide); and (3) arsine gas, AsH_3, a colorless gas formed by the action of acids on arsenic. The most toxic form is arsine gas with a TLV-TWA of 0.05 ppm. Microorganisms in the environment convert arsenic to dimethylarsenate, which can accumulate in fish and shellfish, providing a source for human exposure. Arsenic compounds can also be present as contaminants in well water. Arsenite (As^{+3}) compounds are lipid soluble and can be absorbed following ingestion, inhalation, or skin contact. Within 24 hours of absorption, arsenic distributes over the body, where it binds to SH groups of tissue proteins. Only a small amount crosses the blood-brain barrier. Arsenic may also replace phosphorus in bone tissue and be stored for years.

After acute poisoning, severe GI gastrointestinal symptoms occur within 30 minutes to 2 hours. These include vomiting, watery and bloody diarrhea, severe abdominal pain,

Table 5.1 Examples of Chelating Drugs Used to Treat Metal Toxicity

British antilewisite (BAL[2,3–dimercaptopropanol]), dimercaprol
DMPS (2,3-dimercapto-1-propanesulfonic acid)
DMSA (meso-2,3-dimercaptosuccinic acid)
EDTA (ethylenediaminetetraacetic acid, calcium salt)
DTPA (diethylenetriaminepentaacetic acid, calcium salt)
DTC (dithiocarbamate)
Penicillamine (β-β-dimethylcysteine), hydrolytic product of penicillin

and burning esophageal pain. Vasodilatation, myocardial depression, cerebral edema, and distal peripheral neuropathy may also follow. Later stages of poisoning include jaundice and renal failure. Death usually results from circulatory failure within 24 hours to 4 days.

Chronic exposure results in nonspecific symptoms such as diarrhea, abdominal pain, hyperpigmentation, and hyperkeratosis. A symmetrical sensory neuropathy often follows. Late changes include gangrene of the extremities, anemia, and cancer of the skin, lung, and nasal tissue.

5.2.8 Treatment of Metal Poisoning

Treatment of metal exposure to prevent or reverse toxicity is done with chelating agents or antagonists. Chelation is the formation of a metal ion complex, in which the metal ion is associated with an electron donor ligand. Metals may react with O-, S-, and N-containing ligands (e.g., –OH, –COOH, –S–S–, and $–NH_2$). Chelating agents need to be able to reach sites of storage, form nontoxic complexes, not readily bind essential metals (e.g., calcium, zinc), and be easily excreted.

One of the first clinically useful chelating drugs was British antilewisite (BAL [2,3-dimercaptopropanol]), which was developed during World War II as an antagonist to arsenical war gases. BAL is a dithiol compound with two sulfur atoms on adjacent carbon atoms that compete with critical binding sites involved in arsenic toxicity. Although BAL will bind a number of toxic metals, it is also a potentially toxic drug with multiple side effects. In response to BAL's toxicity, several analogues have now been developed. Table 5.1 lists some of the more common chelating drugs in therapeutic use.

5.3 AGRICULTURAL CHEMICALS (PESTICIDES)

5.3.1 Introduction

Chemicals have been used to kill or control pests for centuries. The Chinese used arsenic to control insects, the early Romans used common salt to control weeds and sulfur to control insects. In the 1800s pyrethrin (i.e., compounds present in the flowers of the chrysanthemum, *Pyrethrum cineraefolium*) was found to have insecticidal properties. The roots of certain Derris plant species, (*D. elliptica* and *Lonchocarpus* spp.) were used by the Chinese and by South American natives as a fish poison. The active ingredient, rotenone, was isolated in 1895 and used for insect control. Another material

developed for insect control in the 1800s was Paris Green, a mixture of copper and arsenic salts. Fungi were controlled with Bordeaux Mixture, a combination of lime and copper sulfate.

However, it was not until the 1900s that the compounds we identify today as having pesticidal properties came into being. Petroleum oils, distilled from crude mineral oils were introduced in the 1920s to control scale insects and red spider mites. The 1940s saw the introduction of the chlorinated hydrocarbon insecticides such as DDT and the phenoxy acid herbicides such as 2,4-*D*). Natural compounds such as Red Squill, derived from the bulbs of red squill, *Urginea (Scilla) maritima*, were effective in controlling rodents. Triazine herbicides, such as atrazine, introduced in the late 1950s, dominated the world herbicide market for years. Synthetic pyrethrins or pyrethroid insecticides (e.g., resmethrin) became and continue to be widely used insecticides due to their low toxicity, enhanced persistence compared to the pyrethrins and low application rates. New families of fungicides, herbicides, and insecticides continue to be introduced into world markets as older compounds lose their popularity due to pest resistance or adverse health effects.

Pesticides are unusual among environmental pollutants in that they are used deliberately for the purpose of killing some form of life. Ideally pesticides should be highly selective, destroying target organisms while leaving nontarget organisms unharmed. In reality, most pesticides are not so selective. In considering the use of pesticides, the benefits must be weighed against the risk to human health and environmental quality. Among the benefits of pesticides are control of vector-borne diseases, increased agricultural productivity, and control of urban pests. A major risk is environmental contamination, especially translocation within the environment where pesticides might enter both food chains and natural water systems. Factors to be considered in this regard are persistence in the environment and potential for bioaccumulation.

5.3.2 Definitions and Terms

The term "agricultural chemicals" has largely been replaced by the term "pesticides," defined as economic poisons, regulated by federal and state laws, that are used to control, kill, or repel pests. Depending on what a compound is designed to do, pesticides have been subclassified into a number of categories (Table 5.2). The primary classes of pesticides in use today are fumigants, fungicides, herbicides, and insecticides with total US production of 1.2 billion pounds (1997: US Environmental Protection Agency's latest figures) and production of some 665 million pounds of wood preservatives. Table 5.3 describes the relative use of different classes of pesticides in the United States.

Generally, it takes some five to seven years to bring a pesticide to market once its pesticidal properties have been verified. Many tests must be conducted to determine such things as the compound's synthesis, its chemical and physical properties, and its efficacy. In addition, in order for registration for use by the US EPA, numerous toxicity tests are undertaken including those for acute toxicity, those for chronic effects such as reproductive anomalies, carcinogenesis, and neurological effects and those for environmental effects.

The mandated pesticide label contains a number of specified items, including the concentration and/or percentage of both the active (A.I.) and inert ingredients; proper mixing of the formulation with water to obtain the application rate of A.I., what the A.I.

Table 5.2 Classification of Pesticides, with Examples

Class	Principal Chemical Type	Example, Common Name
Algicide	Organotin	Brestar
Fungicide	Dicarboximide	Captan
	Chlorinated aromatic	Pentchlorophenol
	Dithiocarbamate	Maneb
	Mercurial	Phenylmercuric acetate
Herbicide	Amides, acetamides	Propanil
	Bipyridyl	Paraquat
	Carbamates, thiocarbamates	Barban
	Phenoxy	2,4-D
	Dinitrophenol	DNOC
	Dinitroaniline	Trifluralin
	Substitute urea	Monuron
	Triazine	Atrazine
Nematocide	Halogenated alkane	Ethylene dibromide (EDB)
Molluscicide	Chlorinated hydrocarbon	Bayluscide
Insecticide	Chlorinated hydrocarbons	
	DDT analogous	DDT
	Chlorinated alicyclic	BHC
	Cyclodiene	Aldrin
	Chlorinated terpenes	Toxaphene
	Organophosphorus	Chlorpyrifos
	Carbamate	Carbaryl
	Thiocyanate	Lethane
	Dinitrophenols	DNOC
	Fluoroacetate	Nissol
	Botanicals	
	Nicotinoids	Nicotine
	Rotenoids	Rotenone
	Pyrethroids	Pyrethrin
	Synthetic pyrethroids	Fenvalerate
	Synthetic nicotinoids	Imidacloprid
	Fiproles	Fipronil
	Juvenile hormone analogs	Methroprene
	Growth regulators	Dimilin
	Inorganics	
	Arsenicals	Lead arsenate
	Fluorides	Sodium fluoride
	Microbials	Thuricide, avermectin
Insecticide synergists	Methylenedioxyphenyl	Piperonyl butoxide
	Dicarboximides	MGK-264
Acaricides	Organosulfur	Ovex
	Formamidine	Chlordimeform
	Dinitrophenols	Dinex
	DDT analogs	Chlorbenzilate
Rodenticides	Anticoagulants	Warfarin
	Botanicals	
	Alkaloids	Strychine sulfate
	Glycosides	Scillaren A and B
	Fluorides	Fluoroacetate
	Inorganics	Thallium sulfate
	Thioureas	ANTU

will control, and how and when to apply it. In addition the label describes environmental hazards, proper storage of the material, re-entry intervals (REIs) for application sites, and the personal protective equipment (PPE) that must be worn during application or harvesting.

Depending on the toxicity, formulation concentration, and use patterns, pesticides can be classified as "general" or "restricted" use. A general use pesticide will cause no unreasonable, adverse effects when used according to the label and can be purchased and applied by anyone. A restricted use pesticide, defined as generally causing undesirable effects on the environment, applicator, or workers can only be purchased and applied by an individual who is licensed by the state.

The US EPA has developed "category use" definitions based on toxicity. Category I pesticides are highly hazardous, are classified as restricted use and have an oral LD50 less than or equal to 1.0/kg of body weight; category II pesticides are moderately toxic and have an oral LD50 less than or equal to 500 mg/kg; category III pesticides are generally nontoxic and have an oral LD50 less than or equal to 15,000 mg/kg. In addition the US EPA has developed a "carcinogenicity categorization" to classify pesticides for carcinogenicity.

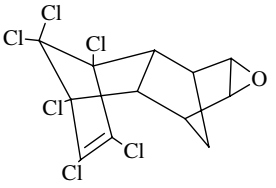
5.3.3 Organochlorine Insecticides

The chlorinated hydrocarbon insecticides were introduced in the 1940s and 1950s and include familiar insecticides such as DDT, methoxychlor, chlordane, heptachlor, aldrin, dieldrin, endrin, toxaphene, mirex, and lindane. The structures of two of the more familiar ones, DDT and dieldrin, are shown in Figure 5.1. The chlorinated hydrocarbons are neurotoxicants and cause acute effects by interfering with the transmission of nerve impulses. Although DDT was synthesized in 1874, its insecticidal properties were not noted until 1939, when Dr. Paul Mueller, a Swiss chemist, discovered its effectiveness as an insecticide and was awarded a Nobel Prize for his work. During World War II the United States used large quantities of DDT to control vector-borne diseases, such as typhus and malaria, to which US troops were exposed. After the war DDT use became widespread in agriculture, public health, and households. Its persistence, initially considered a desirable attribute, later became the basis for public concern. The publication of Rachel Carson's book *The Silent Spring* in 1962 stimulated this concern and eventually led to the ban of DDT and other chlorinated insecticides in the United States in 1972.

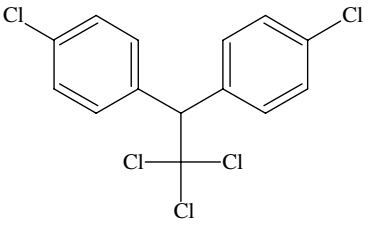
Table 5.3 Use Patterns of Pesticides in the United States

Class	Percentage of Total Pesticide Use
Herbicides	47
Insecticides	19
Fungicides	13
Others[a]	21

Note: Most recent data: for 1997, published by US EPA in 2001.
[a]Includes fumigants and wood preservates.



Dieldrin



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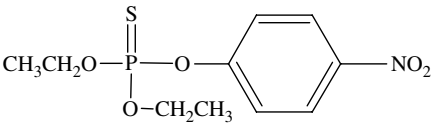
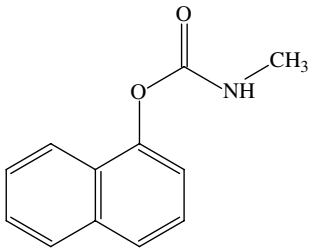
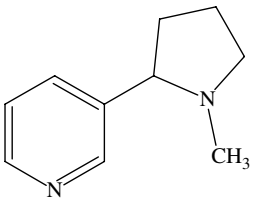


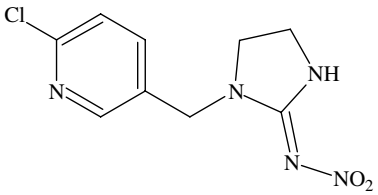
Parathion



Carbaryl



Nicotine



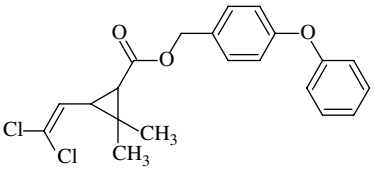
Imidacloprid

Figure 5.1 Some examples of chemical structures of common pesticides.

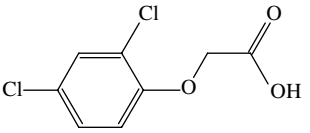
DDT, as well as other organochlorines, were used extensively from the 1940s through the 1960s in agriculture and mosquito control, particularly in the World Health Organization (WHO) malaria control programs. The cyclodiene insecticides, such as chlordane were used extensively as termiticides into the 1980s but were removed from the market due to measurable residue levels penetrating into interiors and allegedly causing health problems. Residue levels of chlorinated insecticides continue to be found in the environment and, although the concentrations are now so low as to approach the limit of delectability, there continues to be concern.

5.3.4 Organophosphorus Insecticides

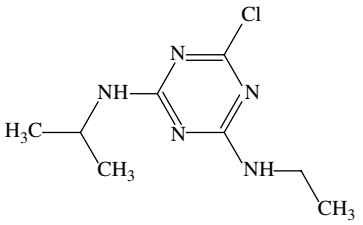
Organophosphorus pesticides (OPs) are phosphoric acid esters or thiophosphoric acid esters (Figure 5.1) and are among the most widely used pesticides for insect control. During the 1930s and 1940s Gerhard Schrader and coworkers began investigating OP compounds. They realized that the insecticidal properties of these compounds and by the end of the World War II had made many of the insecticidal OPs in use today,



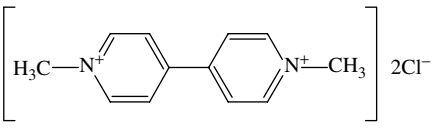
Permethrin



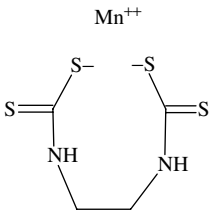
2,4-D



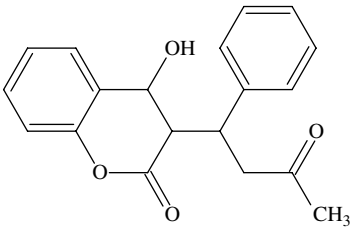
Atrazine



Paraquat



Maneb



Warfarin

Figure 5.1 (*continued*)

such as ethyl parathion [*O*,*O*-diethyl *O*-(4-nitrophenyl)phosphorothioate]. The first OP insecticide to find widespread use was tetraethylpyrophosphate (TEPP), approved in Germany in 1944 and marketed as a substitute for nicotine to control aphids. Because of its high mammalian toxicity and rapid hydrolysis in water, TEPP was replaced by other OP insecticides.

Chlorpyrifos [*O*,*O*-diethyl *O*-(3,5,6-trichloro-2-pyridinyl) phosphorothioate] became one of the largest selling insecticides in the world and had both agricultural and urban uses. The insecticide could be purchased for indoor use by homeowners, but health-related concerns caused USEPA to cancel home indoor and lawn application uses in 2001. The only exception is its continued use as a termiticide.

Parathion was another widely used insecticide due to its stability in aqueous solutions and its broad range of insecticidal activity. However, its high mammalian toxicity through all routes of exposure led to the development of less hazardous compounds. Malathion [diethyl (dimethoxythiophosphorylthio)succinate], in particular, has low mammalian toxicity because mammals possess certain enzymes, the carboxylesterases, that readily hydrolyze the carboxyester link, detoxifying the compound. Insects, by

contrast, do not readily hydrolyze this ester, and the result is its selective insecticidal action.

OPs are toxic because of their inhibition of the enzyme acetylcholinesterase. This enzyme inhibition results in the accumulation of acetylcholine in nerve tissue and effector organs, with the principal site of action being the peripheral nervous system (PNS) (see Chapter 16). In addition to acute effects, some OP compounds have been associated with delayed neurotoxicity, known as organophosphorus-induced delayed neuropathy (OPIDN). The characteristic clinical sign is bilateral paralysis of the distal muscles, predominantly of the lower extremities, occurring some 7 to 10 days following ingestion (see Chapter 16). Not all OP compounds cause delayed neuropathy. Among the pesticides associated with OPIDN are leptophos, mipafox, EPN, DEF, and trichlorfon. Testing is now required for OP substances prior to their use as insecticides.

The OP and carbamate insecticides are relatively nonpersistent in the environment. They are applied to the crop or directly to the soil as systemic insecticides, and they generally persist from only a few hours to several months. Thus these compounds, in contrast to the organochlorine insecticides, do not represent a serious problem as contaminants of soil and water and rarely enter the human food chain. Being esters, the compounds are susceptible to hydrolysis, and their breakdown products are generally nontoxic. Direct contamination of food by concentrated compounds has been the cause of poisoning episodes in several countries.

5.3.5 Carbamate Insecticides

The carbamate insecticides are esters of *N*-methyl (or occasionally *N*,*N*-dimethyl) carbamic acid (H_2NCOOH). The toxicity of the compound varies according to the phenol or alcohol group. One of the most widely used carbamate insecticides is carbaryl (1-napthyl methylcarbamate), a broad spectrum insecticide (Figure 5.1). It is used widely in agriculture, including home gardens where it generally is applied as a dust. Carbaryl is not considered to be a persistent compound, because it is readily hydrolyzed. Based on its formulation, it carries a toxicity classification of II or III with an oral LD50 of 250 mg/kg (rat) and a dermal LC50 of >2000 mg/kg.

An example of an extremely toxic carbamate is aldicarb [2-methyl-2-(methylthio) propionaldehyde]. Both oral and dermal routes are the primary portals of entry, and it has an oral LD50 of 1.0 mg/kg (rat)and a dermal LD50 of 20 mg/kg (rabbit). For this reason it is recommended for application to soils on crops such as cotton, citrus, and sweet potatoes. This compound moves readily through soil profiles and has contaminated groundwater supplies.

Like the OP insecticides, the mode of action of the carbamates is acetylcholinesterase inhibition with the important difference that the inhibition is more rapidly reversed than with OP compounds.

5.3.6 Botanical Insecticides

Extracts from plants have been used for centuries to control insects. Nicotine [(*S*)-3-(1-methyl-2-pyrrolidyl)pyridine] (Figure 5.1) is an alkaloid occurring in a number of plants and was first used as an insecticide in 1763. Nicotine is quite toxic orally as well as dermally. The acute oral LD50 of nicotine sulfate for rats is 83 mg/kg and

the dermal LD50 is 285 mg/kg. Symptoms of acute nicotine poisoning occur rapidly, and death may occur with a few minutes. In serious poisoning cases death results from respiratory failure due to paralysis of respiratory muscles. In therapy attention is focused primarily on support of respiration.

Pyrethrin is an extract from several types of chrysanthemum, and is one of the oldest insecticides used by humans. There are six esters and acids associated with this botanical insecticide. Pyrethrin is applied at low doses and is considered to be nonpersistent.

Mammalian toxicity to pyrethrins is quite low, apparently due to its rapid breakdown by liver microsomal enzymes and esterases. The acute LD50 to rats is about 1500 mg/kg. The most frequent reaction to pyrethrins is contact dermatitis and allergic respiratory reactions, probably as a result of other constituents in the formulation. Synthetic mimics of pyrethrins, known as the pyrethroids, were developed to overcome the lack of persistence.

5.3.7 Pyrethroid Insecticides

As stated, pyrethrins are not persistent, which led pesticide chemists to develop compounds of similar structure having insecticidal activity but being more persistent. This class of insecticides, known as pyrethroids, have greater insecticidal activity and are more photostable than pyrethrins. There are two broad classes of pyrethroids depending on whether the structure contains a cyclopropane ring [e.g., cypermethrin {(±)-α-cyano-3-phenoxybenzyl (±)-*cis*,*trans*-3-(2,2-dichlorovinyl_2,2-dimethyl cyclopropanecarboxylate)}] or whether this ring is absent in the molecule [e.g., fenvalerate{(*RS*)-α-cyano-3-phenoxybenzyl(*RS*)-2-(4-chlorophenyl)-3-methylbutyrate}]. They are generally applied at low doses (e.g., 30 g/Ha) and have low mammalian toxicities [e.g., cypermethrin, oral (aqueous suspension) LD50 of 4,123 mg/kg (rat) and dermal LD50 of >2000 mg/kg (rabbit)]. Pyrethroids are used in both agricultural and urban settings (e.g., termiticide; Figure 5.1).

Pyrethrins affect nerve membranes by modifying the sodium and potassium channels, resulting in depolarization of the membranes. Formulations of these insecticides frequently contain the insecticide synergist piperonyl butoxide [5-{2-(2-butoxyethoxy) ethoxymethyl}-6-propyl-1,3-benzodioxole], which acts to increase the efficacy of the insecticide by inhibiting the cytochrome P450 enzymes responsible for the breakdown of the insecticide.

5.3.8 New Insecticide Classes

There are new classes of insecticides that are applied at low dosages and are extremely effective but are relatively nontoxic to humans. One such class is the fiproles, and one of these receiving major attention is fipronil [(5-amino-1-(2,6-dichloro-4-(trifluoromethyl) phenyl)-4-((1,*R*,*S*)-(trifluoromethyl)su-1-*H*-pyrasole-3-carbonitrile)]. Although it is used on corn, it is becoming a popular termiticide because of its low application rate (ca. 0.01%) and long-term effectiveness. Another class of insecticides, the chloronicotinoids, is represented by imidacloprid [1-(6-chloro-3-pyridin-3-ylmethyl)-*N*-nitroimidazolidin-2-ylidenamine] (Figure 5.1), which also is applied at low dose rates to soil and effectively controls a number of insect species, including termites.

5.3.9 Herbicides

Herbicides control weeds and are the most widely used class of pesticides. The latest US EPA data show that some 578 million pounds of herbicides were used in the United States in 1997 and accounts for some 47% of pesticides used. This class of pesticide can be applied to crops using many strategies to eliminate or reduce weed populations. These include preplant incorporation, pre- and postemergent applications. New families of herbicides continue to be developed, and are applied at low doses, are relatively nonphytotoxic to beneficial plants and are environmentally friendly. Some of the newer families such as the imidazolinones inhibit the action of acetohydroxyacid synthase that produces branched-chain amino acids in plants. Because this enzyme is produced only in plants, these herbicides have low toxicities to mammals, fish, insects, and birds.

The potential for environmental contamination continues to come from families of herbicides that have been used for years. The chlorophenoxy herbicides such as 2,4-*D* (2,4-dichlorophenoxy acetic acid) and 2,4,5-*T* (2,4,5-trichlorophenoxy-acetic acid) (Figure 5.1) are systemic acting compounds to control broadleaf plants and have been in use since the 1940s. The oral toxicities of these compounds are low.

A mixture of 2,4-*D* and 2,4,5-*T*, known as Agent Orange, was used by the US military as a defoliant during the Vietnam conflict, and much controversy has arisen over claims by military personnel of long-term health effects. The chemical of major toxicological concern was identified as a contaminant, TCDD (2,3,7,8-tetrachlorodibenzo-*p*-dioxin), that was formed during the manufacturing process. TCDD is one of the most toxic synthetic substances known in laboratory animals. The LD50 for male rats is 0.022 mg/kg, and for female guinea pigs (the most sensitive species tested) the LD50 is 0.0006 mg/kg. In addition it is toxic to developing embryos in pregnant rats at a dose of only 1/400 of the LD50, and has been shown to cause birth defects at levels of 1 to 3 ng/kg of body weight. TCDD is a proven carcinogen in both mice and rats, with the liver being the primary target. This chemical has also been shown to alter the immune system and enhance susceptibility in exposed animals.

Another family of herbicides, the triazines, continues to cause concern to environmentalists and toxicologists because of the contamination of surface and groundwater supplies that become public drinking water. The herbicide, atrazine [6-chloro-*N*-ethyl-*N*-(1-methylethyl)-1,2,5-triazine-2,4-diamine (Figure 5.1) is used primarily on corn and has an MCL of 3.0 μg/L. This herbicide has been found in surface and groundwaters worldwide with widely varying concentrations (e.g., 1 to >130 μg/L). It, along with two other triazines, cyanazine [2-{{4-chloro-6-(ethylamino)-1,3,5-triazin-2-yl}amino}-2-methylpropanenitrile] and simazine (6-chloro-*N*,*N*-diethyl-1,3,5-triazine-2,4-diamine) (MCL of 4.0 μg/L). The uses of cyanazine were canceled in 2001 and no further use was permitted after 2002. Although relatively nontoxic [e.g., atrazine, oral LD50 of 3,100 mg/kg (rat)], the major concern with these types of compounds is their carcinogenic effects, and US EPA considers these three triazines as possible human carcinogens (category C).

A member of the bipyridylium family of herbicides is the compound paraquat (1,1-dimethyl-4,4-bipyridinium ion as the chloride salt) (Figure 5.1). It is a very water-soluble contact herbicide that is active against a broad range of plants and is used as a defoliant on many crops. The compound binds tightly to soil particles following

application and becomes inactivated. However, this compound is classified as a class I toxicant with an oral LD50 of 150 mg/kg (rat). Most poisoning cases, which are often fatal, are due to accidental or deliberate ingestion of paraquat. Toxicity results from lung injury resulting from both the preferential uptake of paraquat by the lungs and the redox cycling mechanism.

5.3.10 Fungicides

Every year fungi cause crop losses in the United States amounting to millions of dollars. In addition recent studies have shown that toxins and other airborne organic compounds released from fungi inhabiting the interior of dwellings probably are responsible for a number of adverse health effects. Compounds produced to combat these losses and adverse health effects are called fungicides, and a number of these families have been around for years.

The fungicide, chlorothalonil (tetrachloroisophthalonitrile), is a broad-spectrum fungicide which is used widely in urban environments. It is relatively cheap and controls some 140 species of organisms. As a result of the popularity of this compound, it is found routinely in surface waters entering public drinking water supplies. In the formulation that can be purchased by the general public, it is relatively nontoxic.

One family of fungicides that is of concern are the dithiocarbamates, sulfur derivatives of dithiocarbamic acid and include the metallic dimethyldithiocarbamates. The latter group includes mancozeb (a coordination product of zinc ion and manganese ethylene bisdithiocarbamate), maneb (manganese ethylenebisdithiocarbamate)(Figure 5.1), and zineb (zinc ethylenebisdithiocarbamate). All are effective fungicides and are used on a variety of crops including grapes, sugar beets, and ornamental plants. Although relatively nontoxic, they do hydrolyze producing known carcinogens such as ethylthiourea (ETU).

5.3.11 Rodenticides

This class of compounds is used to control rodents that cause yearly losses of 20% to 30% in grain and other food storage facilities. These pests harbor diseases in the form of fleas that carry bacteria and other organisms. A number of the rodenticides have been used for years and include warfarin [3-(α-acetonylbenzyl)-4-hydroxycoumarin] (Figure 5.1), an anticoagulant. This is a potent toxicant with an oral LD50 of 3.0 mg/kg (rat). As the rats navigate through narrow passages, they bruise themselves, developing small hemorrhages. Anticoagulants prevent the blood from clotting, and the animals bleed to death in about a week. Humans who are exposed to this class of compounds are given vitamin K, and if the poisoning is severe, blood transfusions as a treatment. Other rodenticides poison the animal and many times are applied along with an attractant such as peanut butter to overcome bait shyness. Fluoroacetamide is a fast acting poison with an oral LD50 (rat) of 15 mg/kg. This material is supplied as bait pellets or grains. ANTU ($\acute{\alpha}$ -naphthylthiourea), strychnine, and thallium salts are other fast acting poisons, and have been on the market for many years. Most of the rodenticides are classified as restricted use and are applied only by licensed pest

control operators. Human poisonings associated with rodenticides usually result from accidental or suicidal ingestion of the compounds.

5.3.12 Fumigants

Fumigants are extremely toxic gases used to protect stored products, especially grains, and to kill soil nematodes. These materials are applied to storage warehouses, freight cars, and houses infested with insects such as powder post beetles. They present a special hazard due to inhalation exposure and rapid diffusion into pulmonary blood; thus extreme care must be taken when handling and applying this class of pesticides. All fumigants are classified as restricted use compounds and require licensed applicators to handle them.

One of the most effective fumigants is methyl bromide. It essentially sterilizes soil when applied under a ground covering, because it kills insects, nematodes, and weed seed but also is used to fumigate warehouses. Overexposure to this compound causes respiratory distress, cardiac arrest, and central nervous effects. The inhalation LC50 is 0.06 mg/L (15 min) of air (rat) and 7900 ppm (1.5 h) (human). Methyl bromide has been classified as an ozone depleter under the Clean Air Act and is due to be phased out of use by 2005.

Chloropicrin (trichloronitromethane) is another soil/space fumigant that has been used for many years. It has an inhalation LC50 of 150 ppm (15 min). Thus it is highly toxic by inhalation, can injure the heart, and cause severe eye damage.

5.3.13 Conclusions

This section has covered only a few of the pesticides available today on the United States and world markets. An understanding of the basic chemical processes affected by pesticides has led to the discovery and production of new families of chemicals. Today's modern pesticide is generally safe to use if the directions on the label are followed. Advances in instrumentation and an understanding of how adverse health effects are produced have resulted in the production of many environmentally friendly but effective pesticides.

5.4 FOOD ADDITIVES AND CONTAMINANTS

Chemicals are added to food for a number of reasons: as preservatives with antibacterial, antifungal, or antioxidant properties; to change physical characteristics, particularly for processing; to change taste; to change color; and to change odor. In general, food additives have proved to be safe and without chronic toxicity. Many were introduced when toxicity testing was relatively unsophisticated, however, and some of these have been subsequently shown to be toxic. Table 5.4 gives examples of different types of organic food additives. Inorganics, the most important of which are nitrate and nitrite, are discussed later. Certainly hundreds, and possibly thousands, of food additives are in use worldwide, many with inadequate testing. The question of synergistic interactions between these compounds has not been explored adequately. Not all toxicants in food are synthetic; many examples of naturally occurring toxicants in the human diet are known, including carcinogens and mutagens.

Table 5.4 Examples of Organic Chemicals Used as Food Additives

Function	Class	Example
Preservatives	Antioxidants	Butylatedhydroxyanisole
		Ascorbic acid
	Fungistatic agents	Methyl *p*-benzoic acid
		Propionates
		Bactericides Sodium nitrite
Processing aids	Anticaking agents	Calcium silicate
		Sodium aluminosilicate
	Emulsifiers	Propylene glycol
		Monoglycerides
	Chelating agents	EDTA
		Sodium tartrate
	Stabilizers	Gum ghatti
		Sodium alginate
	Humectants	Propylene glycol
		Glycerol
Flavor and taste modification	Synthetic sweeteners	Saccharin
		Mannitol
		Aspartame
	Synthetic flavors	Piperonal
		Vanillin
Color modification	Synthetic dyes	Tartrazine (FD&C yellow5)
		Sunset Yellow
Nutritional supplements	Vitamins	Thiamin
		Vitamin D3
	Amino acids	Alanine
		Aspartic acid
	Inorganics	Manganese sulfate
		Zinc sulfate

5.5 TOXINS

5.5.1 History

A discussion of toxins first necessitates the understanding and distinction between the toxicological terms toxicant and toxin. A *toxicant* is any chemical, of natural or synthetic origin, capable of causing a deleterious effect on a living organism. A *toxin* is a toxicant that is produced by a living organism and is not used as a synonym for toxicant—all toxins are toxicants, but not all toxicants are toxins. Toxins, whether produced by animals, plants, insects, or microbes are generally metabolic products that have evolved as defense mechanisms for the purpose of repelling or killing predators or pathogens. The action of natural toxins has long been recognized and understood throughout human history. For example, ancient civilizations used natural toxins for both medicinal (therapeutic) and criminal purposes. Even today, we continue to discover and understand the toxicity of natural products, some for beneficial pharmaceutical or therapeutic purposes whose safety and efficacy are tested, and some for other less laudable purposes like biological or chemical warfare. Toxins may be

classified in various ways depending on interest and need, such as by target organ toxicity or mode of action, but are commonly classified according to source.

5.5.2 Microbial Toxins

The term "microbial toxin" is usually reserved by microbiologists for toxic substances produced by microorganisms that are of high molecular weight and have antigenic properties; toxic compounds produced by bacteria that do not fit these criteria are referred to simply as poisons. Many of the former are proteins or mucoproteins and may have a variety of enzymatic properties. They include some of the most toxic substances known, such as tetanus toxin, botulinus toxin, and diphtheria toxin. Bacterial toxins may be extremely toxic to mammals and may affect a variety of organ systems, including the nervous system and the cardiovascular system. A detailed account of their chemical nature and mode of action is beyond the scope of this volume.

The range of poisonous chemicals produced by bacteria is also large. Again, such compounds may also be used for beneficial purposes, for example, the insecticidal properties of *Bacillus thuringiensis*, due to a toxin, have been utilized in agriculture for some time.

5.5.3 Mycotoxins

The range of chemical structures and biologic activity among the broad class of fungal metabolites is large and cannot be summarized briefly. Mycotoxins do not constitute a separate chemical category, and they lack common molecular features.

Mycotoxins of most interest are those found in human food or in the feed of domestic animals. They include the ergot alkaloids produced by *Claviceps* sp., aflatoxins and related compounds produced by *Aspergillus* sp., and the tricothecenes produced by several genera of fungi imperfecti, primarily *Fusarium* sp.

The ergot alkaloids are known to affect the nervous system and to be vasoconstrictors. Historically they have been implicated in epidemics of both gangrenous and convulsive ergotism (St. Anthony's fire), although such epidemics no longer occur in humans due to increased knowledge of the cause and to more varied modern diets. Outbreaks of ergotism in livestock do still occur frequently, however. These compounds have also been used as abortifacients. The ergot alkaloids are derivatives of ergotine, the most active being, more specifically, amides of lysergic acid.

Aflatoxins are products of species of the genus *Aspergillus*, particularly *A flavus*, a common fungus found as a contaminant of grain, maize, peanuts, and so on. First implicated in poultry diseases such as Turkey-X disease, they were subsequently shown to cause cancer in experimental animals and, from epidemiological studies, in humans. Aflatoxin B1, the most toxic of the aflatoxins, must be activated enzymatically to exert its carcinogenic effect.

Tricothecenes are a large class of sesquiterpenoid fungal metabolites produced particularly by members of the genera *Fusarium* and *Tricoderma*. They are frequently acutely toxic, displaying bactericidal, fungicidal, and insecticidal activity, as well as causing various clinical symptoms in mammals, including diarrhea, anorexia, and ataxia. They have been implicated in natural intoxications in both humans and animals, such as Abakabi disease in Japan and Stachybotryotoxicosis in the former USSR, and

are the center of a continuing controversy concerning their possible use as chemical warfare agents.

Mycotoxins may also be used for beneficial purposes. The mycotoxin avermectin is currently generating considerable interest both as an insecticide and for the control of nematode parasites of domestic animals.

5.5.4 Algal Toxins

Algal toxins are broadly defined to represent the array chemicals derived from many species of cyanobacteria (blue-green bacteria), dinoflagellates, and diatoms. The toxins produced by these freshwater and marine organisms often accumulate in fish and shellfish inhabiting the surrounding waters, causing both human and animal poisonings, as well as overt fish kills. Unlike many of the microbial toxins, algal toxins are generally heat stable and, therefore, not altered by cooking methods, which increases the likelihood of human exposures and toxicity. Many of the more common algal toxins responsible for human poisonings worldwide are summarized herein.

Amnesic Shellfish Poisoning (ASP) was first identified in 1987 from Prince Edward Island, Canada after four people died from eating contaminated mussels. It is caused by domoic acid produced by several species of *Pseudonitzschia* diatoms. The main contamination problems include mussels, clams, and crabs of the Pacific Northwest of the United States and Canada.

Paralytic Shellfish Poisoning (PSP) was first determined to be a problem in 1942 after three people and many seabirds died from eating shellfish on the west coast of the United States, near the Columbia River. It is caused by the saxitoxin family (saxitoxin + 18 related compounds) produced by several species of *Alexandrium* dinoflagellates. The main contamination problems include mussels, clams, crabs, and fish of the Pacific Northwest and Northeast Atlantic.

Neurotoxic Shellfish Poisoning (NSP) is caused by a red-tide producer that was first identified in 1880 from Florida, with earlier historical references. It causes sickness in humans lasting several days. NSP is not fatal to humans; however, it is known to kill fish, invertebrates, seabirds, and marine mammals (e.g., manatees). It is caused by the brevetoxin family (brevetoxin + 10 related compounds produced by the dinoflagellate *Karenia brevis* a.k.a. *Gymnodinium breve*. The main contamination problems include oysters, clams, and other filter feeders of the Gulf of Mexico and southeast Atlantic, including North Carolina.

Diarrheic Shellfish Poisoning (DSP). Human poisonings were first identified in the 1960s. It causes sickness in humans lasting several days but is not fatal. It is caused by chemicals of the okadaic acid family (okadaic acid + 4 related compounds) produced by several species of *Dinophysis* dinoflagellates. The main contamination problems include mussels, clams, and other bivalves of the cold and warm temperate areas of the Atlantic and Pacific Oceans, mainly in Japan and Europe. Only two cases of DSP have been documented in North America.

Ciguatera Fish Poisoning (CFP) was first identified in 1511, CFP is a tropical-subtropical seafood poisoning that affects up to 50,000 people each year and is the most often reported foodborne disease of a chemical origin in the United States. Caused by consumption of reef fishes (e.g., grouper, snapper), sickness in

humans lasts several days to weeks, but the human fatality rate is low. It is caused by the ciguatoxin family (ciguatoxin + 3 or more related compounds) and produced by several species of dinoflagellates including *Gambierdiscus*, *Prorocentrum*, *and Ostreopsis*. The main contamination problems include herbivorous tropical reef fish worldwide.

Cyanobacterial (Blue-Green Bacteria) Toxins. Cyanobacterial poisonings were first recognized in the late 1800s. Human poisonings are rare; however, kills of livestock, other mammals, birds, fish, and aquatic invertebrates are common. It is caused by a variety of biotoxins and cytotoxins, including anatoxin, microcystin, and nodularin produced by several species of cyanobacteria, including *Anabaena*, *Aphanizomenon*, *Nodularia*, *Oscillatoria*, *and Microcystis*. The main contamination problems include all eutrophic freshwater rivers, lakes, and streams.

Ambush Predator (Pfiesteria piscicida and Toxic Pfiesteria Complex) Toxins. Members belonging to this group of organisms were first identified in 1991 from estuaries in North Carolina. They were believed to produce a toxin that has been implicated in several large fish kills and is suspect in causing adverse human health effects. However, the toxin or toxins are not yet identified and toxicity tests are not universally conclusive. Produced by several dinoflagellate species including, *Pfiesteria piscicida*, *Pfiesteria shumwayae*, and perhaps several other unidentified, un-named dinoflagellates belonging to the potentially toxic *Pfiesteria* complex. Main problems include major fish kills in North Carolina and Maryland and potential human health problems. The range may extend from the Gulf of Mexico to the Atlantic estuarine waters, including Florida, North Carolina, Maryland, and Delaware, and possibly outward to Europe.

5.5.5 Plant Toxins

The large array of toxic chemicals produced by plants (phytotoxins), usually referred to as secondary plant compounds, are often held to have evolved as defense mechanisms against herbivorous animals, particularly insects and mammals. These compounds may be repellent but not particularly toxic, or they may be acutely toxic to a wide range of organisms. They include sulfur compounds, lipids, phenols, alkaloids, glycosides, and many other types of chemicals. Many of the common drugs of abuse such as cocaine, caffeine, nicotine, morphine, and the cannabinoids are plant toxins. Many chemicals that have been shown to be toxic are constituents of plants that form part of the human diet. For example, the carcinogen safrole and related compounds are found in black pepper. Solanine and chaconine, which are cholinesterase inhibitors and possible teratogens, are found in potatoes, and quinines and phenols are widespread in food. Livestock poisoning by plants is still an important veterinary problem in some areas.

5.5.6 Animal Toxins

Some species from practically all phyla of animals produce toxins for either offensive or defensive purposes. Some are passively venomous, often following inadvertent ingestion, whereas others are actively venomous, injecting poisons through specially

adapted stings or mouthparts. It may be more appropriate to refer to the latter group only as venomous and to refer to the former simply as poisonous. The chemistry of animal toxins extends from enzymes and neurotoxic and cardiotoxic peptides and proteins to many small molecules such as biogenic amines, alkaloids, glycosides, terpenes, and others. In many cases the venoms are complex mixtures that include both proteins and small molecules and depend on the interaction of the components for the full expression of their toxic effect. For example, bee venom contains a biogenic amine, histamine, three peptides, and two enzymes (Table 5.5). The venoms and defensive secretions of insects may also contain many relatively simple toxicants or irritants such as formic acid, benzoquinone, and other quinines, or terpenes such as citronellal. Bites and stings from the Hymenoptera (ants, bees, wasps, and hornets) result in 5 to 60 fatal anaphylactic reactions each year in the United States. According to experts, about 0.3% to 3.0% of the US population experiences anaphylactic reactions from insect stings and bites.

Snake venoms have been studied extensively; their effects are due, in general, to toxins that are peptides with 60 to 70 amino acids. These toxins are cardiotoxic or neurotoxic, and their effects are usually accentuated by the phospholipases, peptidases, proteases, and other enzymes present in venoms. These enzymes may affect the blood-clotting mechanisms and damage blood vessels. Snake bites are responsible for less than 10 deaths per year in the United States but many thousand worldwide.

Many fish species, over 700 species worldwide, are either directly toxic or upon ingestion are poisonous to humans. A classic example is the toxin produced by the puffer fishes (*Sphaeroides* spp.) called tetrodotoxin (TTX). Tetrodotoxin is concentrated in the gonads, liver, intestine, and skin, and poisonings occurs most frequently in Japan and other Asian countries where the flesh, considered a delicacy, is eaten as "fugu." Death occurs within 5 to 30 minutes and the fatality rate is about 60%. TTX is an inhibitor of the voltage-sensitive Na channel (like saxitoxin); it may also be found in some salamanders and may be bacterial in origin.

Toxins and other natural products generally provide great benefit to society. For example, some of the most widely used drugs and therapeutics like streptomycin, the aminoglycoside antibiotic from soil bacteria, and acetylsalicylic acid (aspirin), the nonsteroidal anti-inflammatory from willow tree bark, are used by millions of people everyday to improve health and well-being. On the other hand, adverse encounters with toxins like fish and shellfish toxins, plant, and insect toxins do result in harm to humans.

Table 5.5 Some Components of Bee Venom

Compound	Effect
Biogenic amine	
Histamine	Pain, vasodilation, increased capillary permeability
Peptides	
Apamine	CNS effects
Melittin	Hemolytic, serotonin release, cardiotoxic
Mast cell degranulating peptide	Histamine release from mast cells
Enzymes	
Phospholipase A	Increased spreading and penetration of tissues
Hyaluronidase	

5.6 SOLVENTS

Although solvents are more a feature of the workplace they are also found in the home. In addition to cutaneous effects, such as defatting and local irritation, many have systemic toxic effects, including effects on the nervous system or, as with benzene, on the blood-forming elements. Commercial solvents are frequently complex mixtures and may include nitrogen- or sulfur-containing organics—gasoline and other oil-based products are examples of this. The common solvents fall into the following classes:

Aliphatic Hydrocarbons, such as hexane. These may be straight or branched-chain compounds and are often present in mixtures.

Halogenated Aliphatic Hydrocarbons. The best-known examples are methylene dichloride, chloroform, and carbon tetrachloride, although chlorinated ethylenes are also widely used.

Aliphatic Alcohols. Common examples are methanol and ethanol.

Glycols and Glycol Ethers. Ethylene and propylene glycols, for example, in antifreeze give rise to considerable exposure of the general public. Glycol ethers, such as methyl cellosolve, are also widely used.

Aromatic Hydrocarbons. Benzene is probably the one of greatest concern, but others, such as toluene, are also used.

5.7 THERAPEUTIC DRUGS

Although the study of the therapeutic properties of chemicals fall within the province of pharmacology, essentially all therapeutic drugs can be toxic, producing deleterious effects at some dose. The danger to the individual depends on several factors, including the nature of the toxic response, the dose necessary to produce the toxic response, and the relationship between the therapeutic dose and the toxic dose. Drug toxicity is affected by all of factors that affect the toxicity of other xenobiotics, including individual (genetic) variation, diet, age, and the presence of other exogenous chemicals.

Even when the risk of toxic side effects from a particular drug has been evaluated, it must be weighed against the expected benefits. The use of a very dangerous drug with only a narrow tolerance between the therapeutic and toxic doses may still be justified if it is the sole treatment for an otherwise fatal disease. However, a relatively safe drug may be inappropriate if safer compounds are available or if the condition being treated is trivial.

The three principal classes of cytotoxic agents used in the treatment of cancer all contain carcinogens, for example, Melphalen, a nitrogen mustard, adriamycin, an antitumor antibiotic, and methotrexate, an antimetabolite. Diethylstilbestrol (DES), a drug formerly widely used, has been associated with cancer of the cervix and vagina in the offspring of treated women.

Other toxic effects of drugs can be associated with almost every organ system. The stiffness of the joints accompanied by damage to the optic nerve (SMON—subacute myelo-optic neuropathy) that was common in Japan in the 1960s was apparently a toxic side effect of chloroquinol (Enterovioform), an antidiarrhea drug. Teratogenosis

can also be caused by drugs, with thalidomide being the most alarming example. Skin effects (dermatitis) are common side effects of drugs, an example being topically applied corticosteroids.

A number of toxic effects on the blood have been documented, including agranulocytosis caused by chlorpromazine, hemolytic anemia caused by methyldopa, and megaloblastic anemia caused by methotrexate. Toxic effects on the eye have been noted and range from retinotoxicity caused by thioridazine to glaucoma caused by systemic corticosteroids.

5.8 DRUGS OF ABUSE

All drugs are toxic at some dose. Drugs of abuse, however, either have no medicinal function or are taken at dose levels higher than would be required for therapy. Although some drugs of abuse may affect only higher nervous functions—mood, reaction time, and coordination—many produce physical dependence and have serious physical effects, with fatal overdoses being a frequent occurrence.

The drugs of abuse include central nervous system depressants such as ethanol, methaqualone (Quaalude), and secobarbital; central nervous system stimulants, such as cocaine, methamphetamine (speed), caffeine, and nicotine; opioids, such as heroin and mependine (demerol); and hallucinogens such as lysergic acid diethylamide (LSD), phencyclidine (PCP), and tetrahydrocannabinol, the most active principal of marijuana. A further complication of toxicological significance is that many drugs of abuse are synthesized in illegal and poorly equipped laboratories with little or no quality control. The resultant products are therefore often contaminated with compounds of unknown, but conceivably dangerous, toxicity. The structures of some of these chemicals are shown in Figure 5.2.

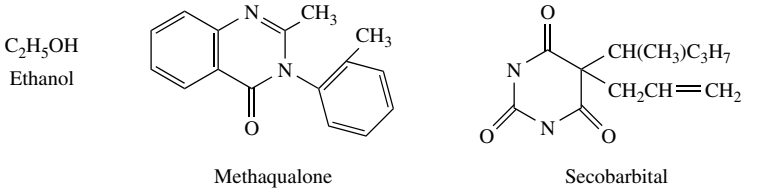
5.9 COMBUSTION PRODUCTS

While many air pollutants (see Chapter 4) are the products of natural or anthropomorphic combustion, some of the most important from the point of view of human health are polycyclic aromatic hydrocarbons. Although also found in natural products such as coal and crude oil, they are generally associated with incomplete combustion of organic materials and are found in smoke from wood, coal, oil, and tobacco, for example, as well as in broiled foods. Because some of them are carcinogens, they have been studied intensively from the point of view of metabolic activation, interactions with DNA, and other aspects of chemical carcinogenesis. Some are heterocyclic, containing nitrogen in at least one of the rings. Some representative structures of the most studied polycyclic aromatic hydrocarbons are shown in Figure 5.3.

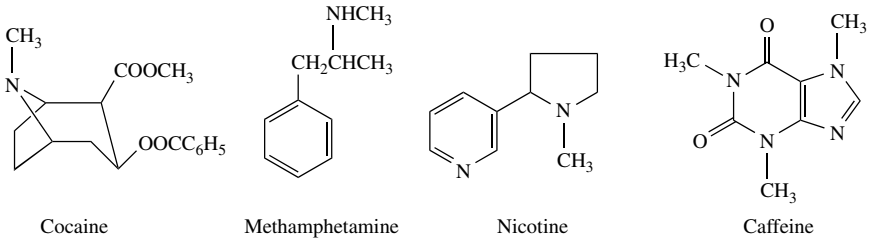
5.10 COSMETICS

The most common deleterious effects of modern cosmetics are occasional allergic reactions and contact dermatitis. The highly toxic and/or carcinogenic azo or aromatic

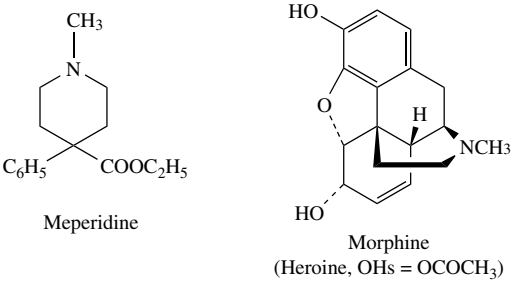
1. CNS Depressants



2. CNS Stimulants



3. Opioids



4. Hallucinogens

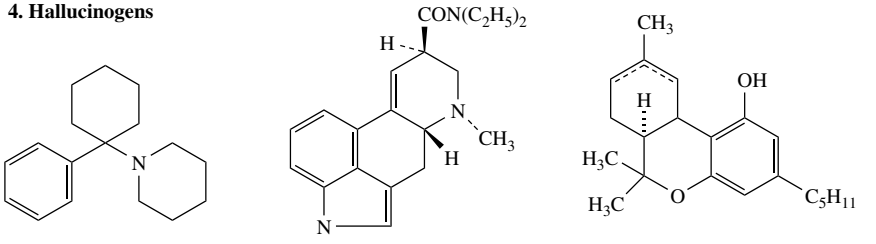
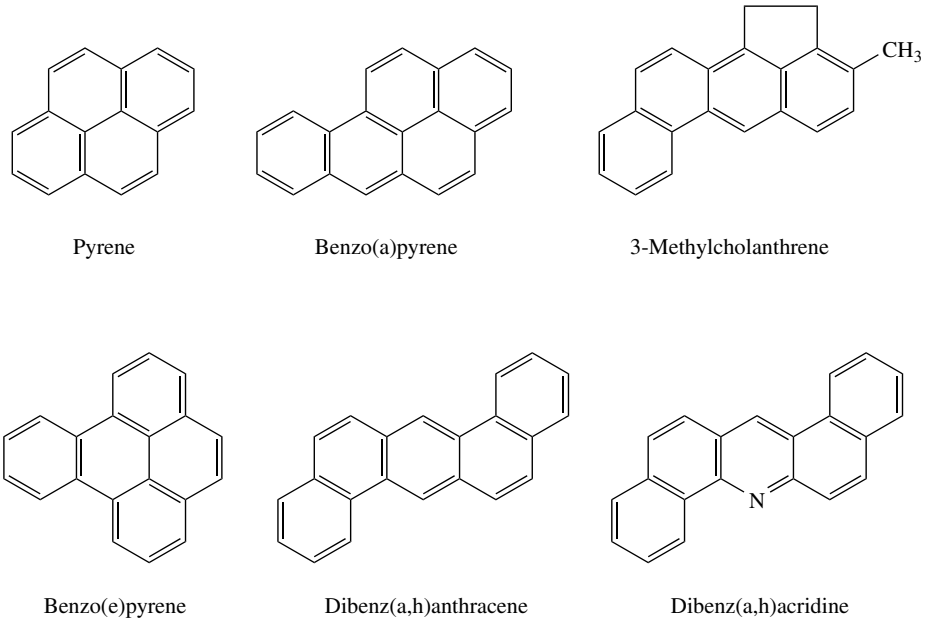


Figure 5.2 Some common drugs of abuse.

amine dyes are no longer in use, nor are the organometallics, used in even earlier times. Bromates, used in some cold-wave neutralizers, may be acutely toxic if ingested, as may the ethanol used as a solvent in hair dyes and perfumes. Thioglycolates and thioglycerol used in cold-wave lotion and depilatories and sodium hydroxide used in hair straighteners are also toxic on ingestion. Used as directed, cosmetics appear to



Pyrene | Benzo(a)pyrene | 3-Methylcholanthrene

Benzo(e)pyrene | Dibenz(a,h)anthracene | Dibenz(a,h)acridine

Figure 5.3 Some common polycyclic aromatic hydrocarbons.

present little risk of systemic poisoning, due in part to the deletion of ingredients now known to be toxic and in part to the small quantities absorbed.

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