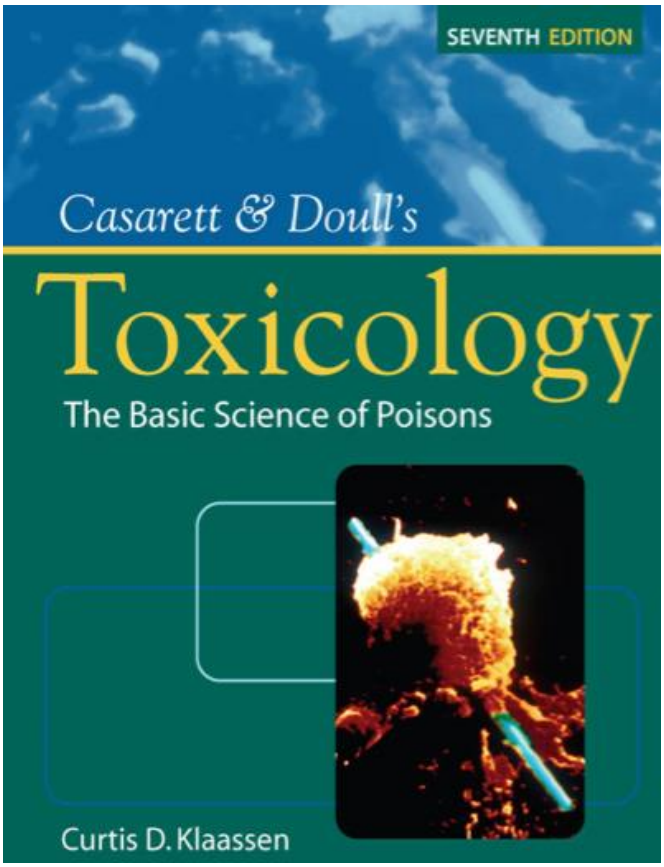
XENOBIÓTICOS

Resumen obtenido a partir de…



TOXICO 2020 (By CGL)

ÍNDICE

TOXIC AGENTS (XENOBIOTICS)

From: Principles of toxicology. By Eaton DL & Gilbert SG.

DEFINITION

One could define a poison as any agent capable of producing a deleterious response in a biological system, seriously injuring function or producing death. This is not, however, a useful working definition for the very simple reason that virtually every known chemical has the potential to produce injury or death if it is present in a sufficient amount. Paracelsus (1493–1541), a Swiss/German/Austrian physician, scientist, and philosopher, phrased this well when he noted, “What is there that is not poison? All things are poison and nothing [is] without poison. Solely the dose determines that a thing is not a poison.”

Toxic agents are classified in a variety of ways, depending on the interests and needs of the classifier. In this textbook, for example, toxic agents are discussed in terms of their target organs (liver, kidney, hematopoietic system, etc.), use (pesticide, solvent, food additive, etc.), source (animal and plant toxins), and effects (cancer, mutation, liver injury, etc.). The term toxin generally refers to toxic substances that are produced by biological systems such as plants, animals, fungi, or bacteria. The term toxicant is used in speaking of toxic substances that are produced by or are a by-product of anthropogenic (human-made) activities.

TOXIC EFFECTS OF PESTICIDES

By Lucio G. Costa

INTRODUCTION

Pesticides can be defined as any substance or mixture of substances intended for preventing, destroying, repelling, or mitigating pests. Pests can be insects, rodents, weeds, and a host of other unwanted organisms. Thus, pesticides occupy a rather unique position among the many chemicals that we encounter daily, in that they are deliberately added to the environment for the purpose of killing or injuring some form of life. Ideally, their injurious action would be highly specific for undesirable targets; in fact, however, most pesticides are not highly selective, but are generally toxic to many non-target species, including humans. Thus, the use of pesticides must minimize the possibility of exposure of nontarget organisms to injurious quantities of these chemicals. It is not uncommon for people to refer to pesticides as a single unitary class of chemicals, while in fact the term pesticide should be equated to that of pharmaceutical drugs. As there are dozens of drugs with different therapeutical indications and different mechanisms of action, several different classes of pesticides exist, with different uses, mechanisms and, hence, toxic effects in nontarget organisms. The most common classification of pesticides relies on the target species they act on. The four major classes (and their target pests) are those of insecticides (insects), herbicides (weeds), fungicides (fungi, molds), and rodenticides (rodents), but there are also acaricides (mites), molluscides (snails, other mollusks), miticides (mites), larvicides (larvae), and pediculocides (lice). In addition, for regulatory purposes, plant growth regulators, repellants, and attractants (pheromones) often also fallin this broad classification of chemicals. Furthermore, within each class, several subclasses exist, with substantially different chemical and toxicological characteristics. For example, among insecticides, one can find organophosphorus compounds, carbamates, organochlorines, pyrethroids, and many other chemicals.Even within each of these subclasses, significant differences can exist, as is the case, for example, of organochlorine compounds such as DDT, aldrin, or chlordecone. Thus, detailed knowledge of the toxicological characteristics of each chemical is needed to properly evaluate their potential risks for nontarget species.

The literature pertaining to the chemistry, development, nomenclature, biotransformation and degradation, environmental effects, toxicity in target and nontarget species, and mode of action of pesticides over the past 60 years is very extensive.

HISTORICAL DEVELOPMENTS

Pesticides have been used to a limited degree since ancient times. The Ebers Papyrus, written about 1500 b.c., lists preparations to expel fleas from the house. The oldest available record is Homer's mention (about1000b.c.) that Odysseus burned sulfur "...top urge the hall and the house and the court" (Odyssey XXII, 493–494). Pliny the Elder (a.d. 23–79) collected in his Natural History many anecdotes on the use of pesticides in the previous three to four centuries. Dioscorides, a Greek physician (a.d.40–90), knew of toxic properties of sulfur and arsenic. There are records showing that by a.d. 900 the Chinese were using arsenic sulfides to control garden insects. *Veratrum album* and *Veratrum nigrum*, two species of false hellebore, were used by the Romans as rodenticides. In 1669, the earliest known record of arsenic as an insecticide in the Western world mentioned its use with honey as an ant bait. Use of tobacco as contact insecticide for plant lice was mentioned later in the same century. Copper compounds were known since the early 1800s to have fungicidal value, and the Bordeaux mixture

(hydrated lime and copper sulfate) was first used in France in 1883. Hydrocyanic acid, known to the Egyptians and the Romans as a poison, was used as a fumigant in 1877 to kill museum pests in insect collections, and carbon-disulfide has been used as a fumigant since 1854. Even in this century, until the 1930s, pesticides were mainly of natural origins or inorganic compounds. Arsenicals have played a major role in pest control, first as insecticides, then as herbicides. Sulfur has been widely used as a fumigant since the early 1800s, and remains one of the most widely used fungicides as of today. Nicotine has been widely used as an insecticide all over the world, as has been rotenone, used as a fish poison in South America since 1725. Mercuric chloride was used as a fungicide since 1891, slowly replaced by phenyl-mercury and alkyl-mercury. Outbreaks of poisoning with the latter compounds have led to a ban on these chemicals.

The period between 1935 and 1950 was characterized by the development of major classes of pesticides, particularly insecticides. In 1939 Paul Müller found that DDT (dichlorodiphenyltrichloroethane), which had been first synthesized in 1874, acted as a poison on flies, mosquitoes, and other insects. DDT was commercialized in 1942 and was used extensively and successfully for the control of typhus epidemics and particularly of malaria. Together with DDT, other chlorinated hydrocarbon insecticides were developed.Intheearly1940s,scientists in England and France recognized the gamma isomer of hexa-chloro-cyclohexane, commonly known as lindane, which had been first synthesized in 1825 by Faraday, as a highly potent insecticide. Starting in the mid-1940s several other chlorinated insecticides were commercialized,including chlordane, heptachlor, aldrin, and dieldrin. The organo-phosphorus insecticides were first synthesized in Germany in the late 1930s. Gerhard Schrader, a chemist at the I. G. FarbenIndustrie in Germany, is considered the “father” of organophosphorus insecticides. The first one, tetraethylpyrophosphate (TEPP), was brought to the market in 1944, but had little success because of its instability in aqueous solution. Several thousand molecules were synthesized by Schrader, and one (code name E605) was eventually introduced into the agricultural market under the trade name parathion, to become one of the most widely employed insecticides in this class. During those years, compounds of much greater toxicity than parathion, such as sarin, soman, and tabun, were also synthesized as potential chemical warfare agents. The mechanisms of action of organophosphates, i.e., inhibition of acetylcholinesterase, was soon discovered, primarily by knowledge of the effects and mechanism of action of physostigmine. This alkaloid had been isolated in 1864 from Calabar beans, the seeds of *Physostigma venenosum*, a perennial plant in tropical West Africa, and its mode of action as a cholinesterase inhibitor was identified in 1926. Despite the early studies on physostigmine, the carbamates were introduced as insecticides only in the early 1950s. Though pyrethrum flower and extracts had been used for several centuries, pyrethrins were characterized only between 1910 and 1924. This led then to the development of synthetic pyrethroids, the first of which, allethrin, was followed by several others in the early 1970s, particularly because of the work of Michael Elliott in England and of scientists at Sumitomo Chemical Company in Japan. Several other classes of insecticides (e.g., avermectins, neonicotinoids, N-phenylpyrazoles) have also been developed in the past few decades.

The past 60 years have also seen the development of hundreds of other chemicals used as herbicides, fungicides, androdenticides. The development of thioureas, such as ANTU, and of anticoagulants such as warfarin, as rodenticides, dates back to the mid to late1940s. A few years later, two important fumigants were introduced, 1,2dichloropropeneandmethylbromide. In the1950s, phenyl-ureas and chlorophenoxy compounds were developed as herbicides, together with the fungicides captan and

folpet. Triazines, chloroacetanilides and paraquat, all widely used herbicides, came to the market in the 1960s, and so did the important class of dithiocarbamate fungicides, while the herbicide glyphosate was introduced in the mid-1970s.

ECONOMICS AND PUBLIC HEALTH

As with all chemicals, including therapeutic drugs, the use of pesticides must take into consideration the balance of the benefits that may be expected versus the possible risks of injury to human health or degradation of environmental quality. Pesticides play a major role in the control of vector-born e diseases, which represent a major threat to the health of large human populations. Pesticides of various types are used in the control of insects, rodents, and other pests that are involved in the life cycle of vector-borne diseases such as malaria, filariasis, yellowfever, viral-encephalitis, typhus, and many others. The case of DDT exemplifies the difficulty in striking a balance between benefits of its use and risks, in this case mainly to the environment. When introduced in 1942, DDT appeared to hold immense promise of benefit to agricultural economics and protection of public health against vector-borne diseases. For example, in the Italian province of Latina there were 175 new cases of malaria in 1944, but after a DDT spray control program was initiated, no new cases of malaria appeared by 1949. Indeed, at the time, the public health benefits of DDT were viewed so great that Mueller was awarded the Nobel prize in Medicine in1948.However, because of its bioaccumulation in the environment and its effects on bird reproduction, DDT was eventually banned in most countries by the mid-1970s. In South Africa, DDT was only banned in 1996, and at the time <10,000 cases of malaria were registered in that country. By the year 2000, cases of malaria had increased to 62,000, but with the reintroduction of DDT at the end of that year, cases were down to 12,500. There are still hundreds of millions of people in the world who are at risk from schistosomiasis, filariasis, and intestinal worm infestations, particularly in Africa and some Asian countries, and these major health problems require a continuous judicious use of pesticides.

In many parts of the world, excessive loss of food crops to insects or other pests may contribute to possible starvation, and use of pesticides seems to have a favorable cost-benefit relationship (Murphy, 1986). In developed countries, pesticides allow production of abundant, inexpensive, and attractive fruits and vegetables, as well as grains. In this case, cost-benefit considerations are based on economic considerations, particularly with regard to labor costs. Along with insecticides, herbicides and fungicides play a major role in this endeavor. Loss of harvested crops by postharvest infestation by insects, fungi, and rodents is also a major problem, that is dealt with by the use of fumigants and other pesticides. Pesticides, particularly herbicides, also find useful application in forestry, during re-forestation, as well as the clearing of roadways, train tracks and utilities' rights of way. In the urban setting, pesticides find multiple uses in the home and garden area, to control insects, weeds and other pests. It is estimated that 75% of households in the United States utilize some form of pesticides. These could include, for example, chemicals to control termite, cockroach or rodent infestations, herbicides to control weeds in the garden, or insect repellents.

Use of Pesticides

It is commonly believed that there is a continuous increase in the use of pesticides. While this is certainly true for the period 1950-1980, in the past twenty years or so, use of pesticides (as amount of active ingredient) has actually reached a plateau (Table 22-2). This is due in part to the utilization of more efficacious compounds, that require less active ingredients to be applied to obtain the same degree of pest control, and in part to

the introduction of integrated pest management approaches and organic farming, at least in the developed countries. Expenditures on pesticides, however, have increased, as new chemicals are more expensive than older ones. In the United States, almost half of the pesticides used are herbicides, while in other countries, particularly Africa, Asia, and Central America, there is also a substantial use of insecticides. Because the latter compounds are generally more acutely toxic, they contribute to the still large number of yearly pesticide poisonings (see below).

Pesticides are often, if not always, used as multiagent formulations, in which the active ingredient is present together with other ingredients to allow mixing, dilution, application, and stability. These other ingredients are lumped under the term “inert” or “other”. Though they do not have pesticidal action, such inert ingredients may not always be devoid of toxicity; thus, an ongoing task of manufacturers and regulatory agencies is to assure that inert ingredients do not pose any unreasonable risk of adverse health effects.

Exposure

Exposure to pesticides can occur via the oral or dermal routes or by inhalation. From a quantitative perspective, oral exposure lies on the extremes of a hypothetical dose–response curve. High oral doses, leading to severe poisoning and death, are achieved as are sult of pesticide ingestion for suicidal intents, or of accidental ingestion, commonly due to storage of pesticides in improper containers. Chronic low doses on the other hand, are consumed by the general population as pesticide residues in food, or as contaminants in drinking water. Regulations exist to ensure that pesticide residues are maintained at levels below those that would cause any adverse effects (see below). Workers involved in the production, transport, mixing and loading, and application of pesticides, as well as in harvesting of pesticide-sprayed crops, are at highest risk for pesticide exposure. The dermal route is thought in this case to offer the greatest potential for exposure, with a minor contribution of the respiratory route when aerosols or aerial spraying are used. In these latter cases, by standars or individuals living in proximity of the spraying may also be exposed because of off-target drifts. In the occupational setting, dermal exposure during normal handling or application of pesticides, or in case of accidental spillings, occurs in body areas not covered by protective clothing, such as the face or the hands. Furthermore, deposition of pesticides on clothing may lead to slow penetration through the tissue and/or to potential exposure of others, if clothes are not changed and washed upon termination of exposure. Several methodologies exist to assess exposure by passive dosimetry, such as the use of absorbent cloth or paper patches, of biosensors, or of tracers followed by video imaging. Biological monitoring is also used, to measure the absorbed dose of pesticides. Analysis of body fluids and excreta, usually urine, for parent compound or metabolites, can provide both a quantitative and a qualitative measurement of absorbed dose. The advantage of such approach over passive dosimetry is that it evaluates actual, rather than potential absorption, and integrates absorption from all routes of exposure. In some cases, modifications of biochemical parameters or a consequence of exposure can be measured as an indication of both exposure and of a biological effect. This is the case, for example, of measurements of plasma or erythrocyte cholinesterases upon exposure to organophosphorus insecticides.

Human Poisoning

Pesticides are not always selective for their intended target species, and adverse health effects can occur in nontarget species, including humans. In the general population and in occupationally exposed workers, a primary concern relates to a possible association

between pesticide exposure and increased risk of cancer. More recently, the acknowledgment that pesticide standards are based on healthy adults, and thus may not be sufficiently protective of susceptible populations, such as children, has led to new concerns, research, and regulations. Evidence that some pesticides may act as endocrine disruptors, possibly contributing to various adverse effects in humans, including cancer and reproductive and developmental toxicity, has also prompted additional concerns and initiatives. Yet, from a global perspective, the major problem with pesticides remains that of acute human poisoning. The World Health Organization (WHO) estimated that there are around three million hospital admissions for pesticide poisoning each year, that result in around 220,000 deaths (WHO, 1990). Most occur in developing countries, particularly in Southeast Asia, and a large percentage is due to intentional ingestion for suicide purposes. The WHO has recommended a classification of pesticides by hazard, where acute oral or dermal toxicities in rats were considered. An analysis of commercially available pesticides indicates that, as a class, insecticides are the most acutely toxic. Indeed, among the 74 active ingredients listed in Class 1A (Extremely hazardous) and Class 1B (Highly hazardous), 48 (65%) are insecticides, in particular organophosphates (IPCS, 2005). Rodenticides are also highly toxic to rats, but do not present the same hazard to humans. Indeed, warfarin, one of the most widely used rodenticides, is the same chemical used as an effective “blood thinner” (anticoagulant) for prevention of stroke and other blood clot related conditions. Herbicides, again as a class, have generally moderate to low acute toxicity, one exception being paraquat (which has a low dermal toxicity but causes fatal effects when ingested). Fungicides vary in their acute toxicity, but this is usually low.

Reports of human poisonings worldwide confirm this analysis. In Costa Rica between 1980 and 1986, 3330 individuals were hospitalized for pesticide poisoning, and 429 died. Cholinesterase inhibitors (organophosphates and carbamates) caused 63% of hospitalizations and 36% of deaths, while paraquat accounted for 24% of hospitalizations and 60% of deaths. Cholinesterase inhibitors also caused more than 70% of occupational accidents. Of 335 poisoning deaths in Manipal, India, in the 1990s, 70% were due to cholinesterase inhibitors. In Sri Lanka between1986 and 2000, hospital admissions for pesticide poisoning were 12–20 thousand/year, with approximately a 10% fatality rate (Roberts et al., 2003). Organophosphates and the organochlorine insecticide endosulfan (which was banned in 1998), were the compounds most commonly involved. The same pattern of poisoning can also be seen in developed countries. For example, in Greece, the number of poisonings ranged between 1200 and 1700/year during the periods 1988–1999. Of these, 40% were due to occupational exposure and 45% to accidental exposure. Organophosphates, carbamates and paraquat were again involved in the majority of cases. In a four year period in Japan, 346 cases of pesticide poisoning were reported; in this case 70% were due to suicide attempts. Again, cholinesterase inhibitors and paraquat were involved in more than 60% of poisonings. Death rate from poisoning with paraquat was over 70%, whereas it was <10%with the herbicides glyphosate orglufosinate.

INSECTICIDES

Insecticides play a most relevant role in the control of insect pests, particularly in developing countries. All of the chemical insecticides in use today are neurotoxicants, and act by poisoning the nervous systems of the target organisms. The central nervous system of insects is highly developed and not unlike that of mammals, and the peripheral nervous system, though less complex, also presents striking similarities. Thus, insecticides are mostly not species-selective with regard to targets of toxicity, and

mammals, including humans, are highly sensitive to their toxicity. When selectivity exists, this is often due to differences in detoxication pathways between insects and mammals, or to differential interactions with their target. As a class, insecticides have higher acute toxicity toward nontarget species compared to other pesticides. Some of them, most notably the organophosphates, are involved in a great number of human poisonings and deaths each year.

Molecular Targets of the Major Classes of Insecticides

TARGET	INSECTICIDE	EFFECT
Acetylcholinesterase	Organophosphates	Inhibition
	Carbamates	Inhibition
Sodium channels	Pyrethroids (Type I and II)	Activation
	DDT	Activation
	Dihydropyrazoles	Inhibition
Nicotinic acetylcholine receptors	Nicotine	Activation
	Neonicotinoids	Activation
GABA receptors-gated chloride channels	Cyclodienes	Inhibition
	Phenylpyrazoles	Inhibition
	Pyrethroids (Type II)	Inhibition
Glutamate-gated chloride channels[1]	Avermectins	Activation
Octopamine receptors[2]	Formamidines	Activation
Mitochondrial complex I	Rotenoids	Inhibition

[1]Found only in insects. In mammals avermectins activate $GABA_A$ receptors.
[2]In mammals, formamidines activate $alpha_2$-adrenoceptors.

INSECT REPELLENTS

Insect-transmitted diseases remain a major source of illness and death worldwide, as mosquitoes alone transmit disease to more than 700 million persons annually. Though insect-borne diseases represent a greater health problem in tropical and subtropical climates, no part of the world is immune to their risks. For example, in 1999, the West Nile virus, transmitted by mosquitoes, was detected for the first time in the western hemisphere. In the New York City area, 62 persons infected with the West Nile virus were hospitalized and seven died. Other arthropod-borne viral diseases (e.g.,equine encephalitis) and tick-borne diseases (e.g., Lyme disease) are also of concern; additionally, other insect bites can be associated with variable adverse health effects, from mild irritation and discomfort to possible allergic reactions. Insect repellents are thus widely used to provide protection toward insect bites. The best known and most widely used insect repellent is DEET. Botanical insect repellents based on citronella or oil of eucalyptus, and a biopesticide structurally similar to the aminoacid al anine a real so commercialized in Europe and the United States. A new compound, picaridin, has been recently approved for use as an insect repellent; it is effective against biting flies, mosquitoes, ticks and fleas, and has a very favorable toxicological profile.

HERBICIDES

Herbicides are chemicals that are capable of either killing or severely injuring plants. They represent a very broad array of chemical classes and act at a large number of sites of metabolic functions and energy transfer in plant cells. Some of the various mechanisms by which herbicides exert their biological effects are shown in Table 22-17, together with examples for each class. An other method of classification pertains to how and when herbicides are applied. Thus, preplanting herbicides are applied to the soil before a crop is seeded; preemergent herbicides are applied to the soil before the time of appearance of unwanted vegetation; and postemergent herbicides are applied to the soil or foliage after the germination of the crop and/or weeds. Herbicides are also divided according to the manner they are applied to plants. Contact herbicides are those that

affect the plant that was treated, while translocated herbicides are applied to the soil or to above-ground parts of the plant, and are absorbed and circulated to distant tissues. Nonselective herbicides will kill all vegetation, while selective compounds are those used to kill weeds without harming the crops. In the past decade, the development of herbicide-resistant crops through transgenic technology has allowed the use of nonselective compounds as selective herbicides (Duke, 2005). A final classification, of relevance to adverse health effects in nontarget species, relies, on the other hand, on chemical structures, as indicated below.

For the past several decades, herbicides have represented the most rapidly growing sector of the agrochemical market, and these compounds now represent almost half of the pesticides used in the United States and more than one-third of those utilized worldwide. This can be ascribed in part to movement to monocultural practices, where the risk of weed infestation has increased, and to mechanization of agricultural practices because of increased labor costs. In addition to agriculture and home and garden uses, herbicides are also widely utilized in forestry management and to clear roadsides, utilities' rights of way, and industrial areas.

In terms of general toxicity, herbicides, as a class, display relatively low acute toxicity, compared for example to most insecticides. There are exceptions, however, such as paraquat. A number of herbicides can cause dermal irritation and contact dermatitis, particularly in individuals prone to allergic reactions. Other compounds have generated much debate for their suspected carcinogenicity or neurotoxicity. The principal classes of herbicides associated with reported adverse health effects in humans are discussed below.

Some Mechanisms of Action of Herbicides

MECHANISM	CHEMICAL CLASSES (EXAMPLE)
Inhibition of photosynthesis	Triazines (atrazine), Substitued ureas (diuron), Uracils (bromacil)
Inhibition of respiration	Dinitrophenols
Auxin growth regulators	Phenoxy acids (2,4-D), Benzoic Acids (dicamba), Pyridine acids (picloram)
Inhibition of protein synthesis	Dinitroanilines
Inhibition of lipid synthesis	Aryloxyphenoxyproprionates (diclofop)
Inhibition of specific enzymes	
• Glutamine synthetase	Glufosinate
• Enolpyruvylshikimate -3-phosphate synthetase	Glyphosate
• Acetalase synthase	Sulfonylureas
Cell membrane disruptors	Bipyridyl derivatives (Paraquat)

FUNGICIDES

Fungal diseases are virtually impossible to control without chemical application. Fungicidal chemicals are derived from a variety of structures, from simple inorganic compounds, such as copper sulfate, to complex organic compounds. The majority of fungicides are surface or plant protectants, and are applied prior to potential infection by fungal spores, either to plants or to postharvest crops. Other fungicides can be used therapeutically, to cure plants when an infestation has already begun. Still others are used as systemic fungicides, that are absorbed and distributed throughout the plant.

With few exceptions, fungicides have low acute toxicity in mammals. However, several produce positive results in genotoxicity tests and some have carcinogenic potentials. The effects are often associated with the mechanisms by which these compounds act on their targets, the fungi. A 1987 evaluation by the National Research Council concluded that

fungicides, though accounting for only 7% of all pesticide sales, and less than 10% of all pounds of pesticides applied, accounted for about 60% of estimated dietary oncogenic risk. Some fungicides have been associated with severe epidemics of poisoning, and have thus been banned. Methylmercury was associated with poisoning in Iraq, when treated grains were consumed. Hexachlorobenzene (HCB), used in the1940–1950stotreatseedgrains, was associated with an epidemic of poisoning in Turkey from 1955 to 1959. HCB has a high cumulative toxicity and caused a syndrome called black sore, characterized by blistering and epidermolysis of the skin, pigmentation and scarring. HCB also causes porphyria as well as hepatomegaly and immunosuppression. The main classes of fungicides currently in use are: Captan and Folpet, Dithiocarbamates, Chlorothalonil, Benzimidazoles, Inorganic and Organometal Fungicides.

RODENTICIDES

Rats and mice can cause health and economic damages to humans. Rodents are vectors for several human diseases, including plague, endemic rickettsiosis, spirochetosis, and several others; they can occasionally bite people; they can consume large quantities of postharvest stored foods, and can contaminate foodstuff with urine, feces, and hair, that may cause diseases. Hence, there is a need to control rodent population. Limiting their access to feed and harborage, and trapping, are two approaches; however, rodenticides still play and will likely continue to play an important role in rodent control. To be effective, yet safe, rodenticides must satisfy several criteria: (1) the poison must be very effective in the target species once incorporated into bait in small quantity; (2) baits containing the poison must not excite bait shyness, so that the animal will continue to eat it; (3) the manner of death must be such that survivors do not become suspicious of its cause; and (4) it should be species-specific, with considerable lower toxicity to other animals.

The compounds used as rodenticides comprise a diverse range of chemical structures having a variety of mechanisms of action. The ultimate goal is to obtain the highest species selectivity; in some cases (e.g., norbormide) advantage has been taken of the physiology and biochemistry unique to rodents. With other rodenticides, the sites of action are common to most mammals, but advantage is taken of the habits of the pest animal and/or the usage, thereby minimizing toxicity for nontarget species. Because rodenticides are used in baits which are often placed in inaccessible places, widespread exposures or contaminations are unlikely. However, toxicologic problems can arise from acute accidental ingestions or from suicidal/homicidal attempts. In particular, poison centers receive thousands of calls every year related to accidental ingestions of rodenticide baits by children, most of which are resolved without serious consequences.

FUMIGANTS

A large number of compounds are used for soil fumigation or for fumigating postharvest commodities. They are active toward insects, mites, nematodes, weed seeds, fungi or rodents, and have in common the property of being in the gaseous form at the time they exert their pesticidal action. They can be liquids that readily vaporize (e.g., ethylene dibromide), solids that can release a toxic gas on reaction with water (e.g., phosphine released by aluminum phosphide), or gases (e.g., methyl bromide). For soil fumigation, the compound is injected directly into the soil, which is then covered with plastic sheeting, which is sealed. By eliminating unwanted pests, this treatment enhances the quality of the crops and increases yield. Fumigation of postharvest commodities, such as wheat, cereals, and fruits to eradicate pest infestations, typically occurs where the commodities

are stored (e.g., warehouses, grain elevators, ship holds). Compounds used as fumigants are usually nonselective, highly reactive, and cytotoxic. They provide a potential hazard from the standpoint of inhalation exposure, and to a minor degree for dermal exposure or ingestion, in case of solids or liquids. Several fumigants used in the past are no longer marketed because of toxicological concerns. These include, for example, carbon disulfide, which is neurotoxic; carbon tetrachloride, a potent hepatotoxicant; 1,2-dibromo-3-chloropropane, a male reproductive toxicant;andethylenedibromide,acarcinogen.Theirtoxicityisdiscussed in other sections of the book.

TOXIC EFFECTS OF METALS

By: Liu J, Goyer RA & Waalkes MP

INTRODUCTION

What is a Metal?

The definition of a metal is not inherently obvious and the differences between metallic and nonmetallic elements can be subtle. Metals are typically defined by physical properties of the element in the solid state, but they vary widely with the metallic element. General metal properties include high reflectivity (luster); high electrical conductivity; high thermal conductivity; and mechanical ductility and strength. A toxicologically important characteristic of metals is that they may react in biological systems by losing one or more electrons to form cations. In the periodic table, within a group there is often a gradual transition from nonmetallic to metallic properties going from lighter to heavier atoms (e.g., Group IVa transitions from carbon to lead). Many metals exhibit variable oxidation states. Various names are applied to subsets of metallic elements including alkalimetals (e.g., lithium and sodium), the alkaline earth metals (e.g., beryllium and magnesium), the transition (or heavy) metals (e.g., cadmium and zinc), and the metalloids (e.g., arsenic and antimony), which have characteristics between metal and nonmetals.

In the periodic table, over 75% of the elements are regarded as metals and eight are considered metalloids. This chapter discusses metals that have been reported to produce significant toxicity in humans. This discussion will include major toxic metals (e.g., lead, cadmium), essential metals (e.g., zinc, copper), medicinal metals (e.g., platinum, bismuth), and minor toxic metals including metals in emerging technology (e.g., indium, uranium). Metal Toxicology will also discuss toxic metalloids (e.g., arsenic, antimony) and certain nonmetallic elemental toxicants (e.g., selenium, fluoride). An overview of Metal Toxicology is shown in Fig. 23-1.

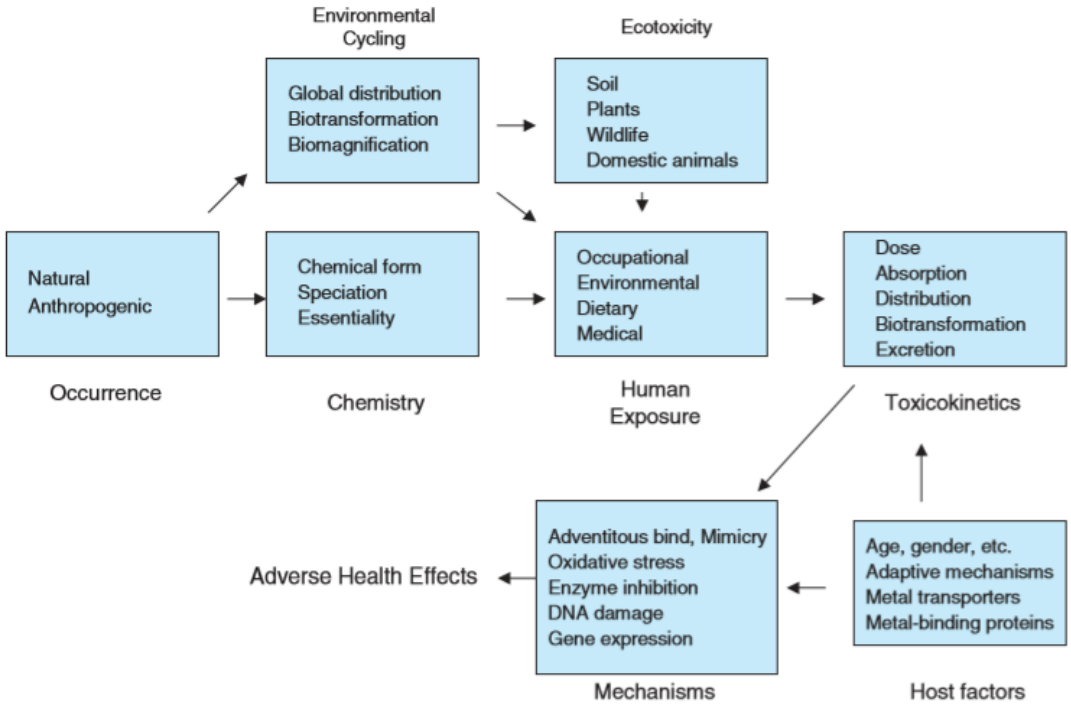


Figure 23-1. Overview of Metal Toxicology.

Metals as toxicants

The use of metals has been critical to the progress and success of human civilization. It would be difficult to image an advanced society without extensive utilization of metallic compounds. Metals are unique among pollutant toxicants in that they are all naturally occurring and, in many cases, are ubiquitous within the human environment. Thus, regardless of how safely metals are used in industrial processes or consumer products, some level of human exposure is inevitable. In addition, all life has evolved in the presence of metals and organisms have been forced to deal with these potentially toxic, yet omnipresent, elements. In fact, many metals have become essential to various biological processes. Essentiality goes hand-in-hand with intentional accumulation and safe transport, storage, and usage mechanisms. Nonetheless, even essential metals will become toxic with increasing exposure. It is often the case that the nonessential toxicant metals mimic essential metals and thereby gain access to, and potentially disrupt, key cellular functions. This can also account for bioaccumulation of toxic metals.

Metals differ from other toxic substances because, as elements, they are neither created nor destroyed by human endeavors. What human industry has accomplished is to concentrate metals in the biosphere. The anthropogenic contribution to the levels of metals in air, water, soil, and food is well recognized. Human use of metals can also alter the chemical form or speciation of an element and thereby impact toxic potential. With a few notable exceptions, most metals are only sparingly recycled once used. These factors combine to make metals very persistent in the human environment.

Metals are certainly one of the oldest toxicants known to humans due to their very early use. For instance, human use of lead probably started prior to 2000 b.c. The first description of abdominal colic in a man who extracted metals is credited to Hippocrates in 370 b.c. Arsenic and mercury are discussed by Theophrastus of Erebus (370–287bc), and Plinyand Elder (ad23– 79). Arsenic was used early on for decoration in Egyptian tomb sand as a “secret poison,” whereas mercury assumed almost a mystical stature in early science and was a large focus of alchemy. However, most of the use of the metals has occurred since the onset of the industrial revolution. In this regard, many of the metals of toxicological concern today were only relatively recently discovered. For instance, cadmium was first recognized in the early 1800s, and it was much later before the metal was widely used. The toxicological importance of some of the rarer or lesser used metals might well increase with new applications, such as chemotherapy and microelectronics, or other emerging technologies.

Historically, metal-toxicology largely concerned acute or overt, high-dose effects, such as abdominal colic from lead or the bloody diarrhea and uropenia after mercury ingestion. Because of advances in our understanding of potential toxicity of metals, and consequent improvements in industrial hygiene and stricter environmental standards, such acute high-dose effects are now uncommon. Focus has shifted to subtle, chronic, low-dose effects, in which cause and effect relationships may not be immediately clear. These might include a level of effect that causes a change in an important, but highly complex index of affected individual’s performance, such as lower than expected IQs due to childhood lead exposure. Other important chronic toxic effects include carcinogenesis, and several metals have emerged as human carcinogens. As signing responsibility for such toxicological effects can often be difficult, particularly when the endpoint in question lacks specificity, in that it may be a complex disease caused by a number of different chemicals or even combinations of chemicals. In addition, humans are never exposed to only a single metal, but rather to complex mixtures. The metals as a class of toxicants clearly present many challenges in toxicological research The elemental nature of metals

impacts their biotransformation and toxicity, as detoxification by destructive metabolism to subcomponents of lesser toxicity cannot occur with these atomic species. In essence, as elemental species metals are non-biodegradable. This indestructibility combined with bioaccumulation contributes to the high concern for metals as toxicants. Most elemental metals tend to form ionic bonds. However, biological conjugation to form organo metallic compounds can occur for various metals, particularly with metalloids, like arsenic, that show mixed carbonaceous and metallic qualities. The redox capacity of a given metal or metallic compound should also be considered as part of its metabolism. The metabolism of metals is intricate and subtle but can directly impact toxic potential.

Movement of Metals in the Environment

Metals are redistributed naturally in the environment by both geologic and biologic cycles. Rainwater dissolves rocks and ores and transports materials, including metals, to rivers and underground water (e.g., arsenic), depositing and stripping materials from adjacent soil and eventually transporting these substances to the ocean to be precipitated as sediment or taken up into forming rainwater to be relocated elsewhere. Biological cycles moving metals include biomagnification by plants and animals resulting in incorporation into food cycles. In comparison, human activity often intentionally shortens the residence time of metals in deposits, and can result in the formation of new, non-naturally occurring metallic compounds. For instance, cadmium distribution mainly comes from human activities. Human industry greatly enhances metal distribution in the global environment by discharge to soil, water, and air, as exemplified by the 200-fold increase in lead content of Greenland ice since the onset of the industrial revolution. Mercury undergoes global cycling with elevated levels being found far from points of discharge, as, for example, with mercury in the Arctic Ocean. Mercury also undergoes biomethylation and biomagnification by aquatic organisms.

Increased distribution of metals and metal compounds in the environment, especially through anthropogenic activities, raises increasing concern for ecotoxicological effects. Reports of metal intoxication are common in plants, aquatic organisms, invertebrates, fish, sea mammals, birds, and domestic animals. The ecotoxicity of various metals is discussed under each individual section. Mercury poisoning from consumption of fish containing high levels of methylmercury and cadmium poisoning from consumption of rice grown in soils contaminated with cadmium from industrial discharges are examples of human consequences from environmental pollution.

Not all human toxicity occurs from metals deposited in the biosphere by human activity. For example, chronic arsenic poisoning from high levels of naturally occurring inorganic arsenic in drinking water is a major health issue in many parts of the world. Endemic intoxication from excess fluoride, selenium, orthallium can all occur from natural high environmental levels.

Chemical Mechanisms of Metal Toxicology

The precise chemical basis of metal toxicology is inadequately understood but a uniform mechanism for all toxic metals is implausible because of the great variation in chemical properties and toxic endpoints. Chemically, metals in their ionic form can be very reactive and can interact with biological systems in a large variety of ways. Inthisregard,a cell presents numerous potential metal-binding ligands. For instance, metals like cadmium and mercury readily attach to sulfur in proteins as a preferred bio-ligand. Such adventitious binding is an important chemical mechanism by which exogenous metals exert toxic effects that can result in steric re-arrangement that impairs the function of

biomolecules. An example would be the inhibition of enzyme activity by metal interaction at sites other than the active center, such as the inhibition of heme synthesis enzymes by lead. The inhibition of biologically critical enzymes is an important molecular mechanism of metal toxicology.

The metals can show more specific forms of chemical attack through mimicry. In this regard the toxic metals may act as mimics of essential metals, binding to physiological sites that normally are reserved for an essential element. Owing to their rich chemistry, essential metals control, or are involved in, a variety of key metabolic and signaling functions. Through mimicry, the toxic metals may gain access to, and potentially disrupt a variety of important or even critical metal-mediated cellular functions. For example, mimicry for, and replacement of zinc, is a mechanism of toxicity for cadmium, copper, and nickel. Thallium mimics potassium and manganese mimics iron as a critical factor in their toxicity. Mimicry of arsenate and vanadate for phosphate allows for cellular transport of these toxic elements whereas selenate, molybdate, and chromate mimic sulfate and can compete for sulfate carriers and in chemical sulfation reactions. Organometallic compounds can also act as mimics of biological chemicals, as, for example, with methylmercury, which is transported by amino acid or organic anion transporters. Indeed, molecular or ionic mimicry at the level of transport is often a key event in metal toxicity.

Another key chemical reaction in metal toxicology is metal mediated oxidative damage. Many metals can directly act as catalytic centers for redox reactions with molecular oxygen or other endogenous oxidants, producing oxidative modification of biomolecules such as proteins or DNA. This may be a key step in the carcinogenicity of certain metals. Besides oxygen-based radicals, carbon- and sulfur-based radicals may also occur. Nickel and chromium are two examples of metals that act, at least in part, by generation of reactive oxygen species or other reactive intermediates. Alternatively, metals may displace redox active essential elements from their normal cellular ligands, which, in turn, may result in oxidative cellular damage. For instance, cadmium, which is not redox active, may well cause oxidative stress through the release of endogenous iron, an element with high redox activity.

Metals in their ionic form can be very reactive and form DNA and protein adducts in biological systems. For example, once hexavalent chromium enters the cell it is reduced by various intracellular reductants to give reactive trivalent chromium species that form DNA adducts or DNA-protein cross-links, events likely to be important in chromium genotoxicity. Metals can also induce an array of aberrant gene expression, which, in turn, produces adverse effects. For example, nickel can induce the expression of Cap43/NDRG1, under the control of the hypoxia-inducible transcription factor (HIF-1), which is thought to play a key role in nickel carcinogenesis. An array of aberrant hepatic gene expressions occurs in adult mice after in utero arsenic exposure, which could be an important molecular event in arsenic hepato-carcinogenesis.

Factors Impacting Metal Toxicity

The standard factors that impact the toxic potential of all chemicals apply to the metals as well. Exposure-related factors include dose, route of exposure, duration, and frequency of exposure. Because metals can be quite reactive, and the portal ofen try is often initially the organ most affected, as with the lung after inhalation.

Host-based factors that can impact metal toxicity include exposure, gender, and capacity for biotransformation. For instance, it is quite clear that younger subjects are often more sensitive to metal intoxication, as, for example, with the neurotoxicity of lead in children.

The major pathway of exposure to many toxic metals in children is food, and children consume more calories per pound of body weight than adults. Moreover, children have higher gastrointestinal absorption of metals, particularly lead. The rapid growth and proliferation in the perinate represent opportunities for toxic effects, including potentially carcinogenesis, of metallic agents, and several metals (e.g., arsenic, nickel, lead, and chromium) are transplacental carcinogens in rodents. Fetal-stage toxicity of metals is well documented, as with methylmercury, and many metals are teratogenic. For many inorganics there is no impediment to transplacental transport, as with lead or arsenic, and human fetal blood lead levels are similar to maternal levels. Elderly persons are also believed to be generally more susceptible to metal toxicity than younger adults. Recognition off actors that influence toxicity of a metal is important in determining risk, particularly in susceptible subpopulations.

Chemical-related factors directly impact the toxic potential of metals. This would include the precise metal compound and its valence state or speciation. For instance, methylmercury is a potent neurotoxin, whereas the inorganic mercurials primarily attack the kidney. Similarly, the oxidation state of chromium can differentiate the essential (naturally occurring trivalent chromium) from toxic species (hexavalent chromium).

Lifestyle factors such as smoking or alcohol ingestion may have direct or indirect impacts on the level of metal intoxication. For instance, cigarette smoke by itself contains many toxic metals, suchas cadmium, and it is thought that's moking will double the life time burden of cadmium in non occupationally exposed individuals. Other components of cigarette smoke may also influence pulmonary effects, as, for instance, with metals that are lung carcinogens. Alcohol ingestion may influence toxicity by altering diet, reducing essential mineral intake, and altering hepatic iron deposition. The composition of the diet can significantly alter gastrointestinal absorption of various dietary metals.

The essentiality of metals has direct bearing on the toxic potential of a metal. Any "free" ionic metal would be potentially toxic due to reactive potential. The need to accumulate essential metals dictates the evolution of systems for the safe transport, storage, and utilization as well as, within limits, elimination of excess. For example, metal-thionein is a metal-binding protein that may function in the homeostatic control of zinc, and may represent a storage or transport form of this metal. Such factor simply that a threshold would exist for toxicity due to essential metal exposure. In this regard, the essential metallic elements would be expected to show a "U"-shaped dose–response curve in that, at very low exposure levels, toxic adverse effects would occur from deficiency, but at high exposure levels toxicity also occurs. The nonessential toxic metals can mimic essential elements and disrupt homeostasis, as with cadmium which will potentially displace zinc to bind to zinc-dependent transcription factors and enzymes.

Adaptive mechanisms can be critical to the toxic effects of metals, and organisms have a variety of ways in which they can adapt to otherwise toxic metal insults. Typically, adaptation is acquired after the first few exposures and can be long lasting or transient after exposure cases. Adaptation can be at the level of uptake or excretion, or with some metals, through long-term storage in a toxicological inert form. For instance, it appears enhanced arsenic efflux is involved in acquired tolerance to the metalloid on the cellular level. Conversely, intentional sequestration of toxic metals is another adaptive tactic and examples of such longterm storage include lead-inclusion bodies, which form in various organs and contain protein-immobilized lead in a distinct cellular aggresome. These bodies are thought to be protective by limiting the level of free, and therefore toxic, lead within the cell, and the inability to form such bodies clearly increases the chronic toxic effects of lead, including carcinogenesis. Similarly, cadmium exposure causes the

overexpression of metallothionein which will sequester cadmium and reduce its toxicity as an adaptive mechanism. Metal exposure can also induce a cascade of molecular/genetic responses that may, in turn, reduce toxicity, such as with metal-induced oxidative stress responses. It is clear that acquired metal adaptation, although allowing immediate cellular survival, may in fact be a potential contributing factor in long-term toxicity. For instance, acquired self-tolerance to cadmium-or arsenic induced apoptosis may actually contribute to eventual carcinogenesis by allowing survival of damaged cells that would otherwise have been eliminated.

Biomarkers of Metal Exposure

Biomarkers of exposure, toxicity, and susceptibility are important in assessing the level of concern with metal intoxication. Exposure biomarkers, such as concentrations in blood or urine, have long been used with metals. Techniques in molecular toxicology have greatly expanded the possibilities for biomarkers. Thus, in the case of chromium, DNA–protein complexes may serve as a biomarker of both exposure and carcinogenic potential. The capacity for expression of genes that potentially play protective roles against metal toxicity, as, for example, with metallothionein and heme oxygenase, show promise as markers of both effect and susceptibility. The use of such biomarkers may well allow identification of particularly sensitive subpopulations.

Estimates of the relationship of exposure level to toxic effects for a particular metal are in many ways a measure of the dose– response relationships discussed in great detail earlier in this book. The dose of a metal is a multidimensional concept and is a function of time as well as concentration. The most toxicologically relevant definition of dose is the amount of active metal within cells of target organs. The active form is often presumed to be the free metal, but it is technically difficult or impossible to precisely determine.

A critical indicator of retention of a metal is its biological half-life, or the time it takes for the body or organ to excrete half of an accumulated amount. The biological half-life varies according to the metal as well as the organ or tissue. For example, the biological half-lives of cadmium in kidney and lead in bone are 20–30 years, whereas for some metals, such as arsenic or lithium, they are only a few hours to days. For many metals, more than one half-life is needed to fully describe the retention. The half-life of lead in blood is only a few weeks, as compared to the much longer half-life in bone. After inhalation of mercury vapor, at least two half-lives describe the retention in brain, one on the order of a few weeks and the other measured in years. Continued metal exposure clearly complicates retention kinetics.

Blood, urine, and hair are the most accessible tissues for quantifying metal exposure. Results from single measurements may reflect recent exposure or long-term or past exposure, depending on retention time in the particular tissue. Blood and urine concentrations usually, but not always, are reflective of more recent exposures and correlate with acute adverse effects. An exception is urinary cadmium, which may reflect kidney damage related to a renal cadmium accumulation over several decades. Hair can be useful in assessing variations in exposure to metals over the period of its growth. Analyses can be performed on segments of the hair, so that metal content of the newest growth can be compared with past exposures. Hair levels of mercury have been found to be a reliable measure of exposure to methylmercury. For most other metals, however, hair is not a reliable tissue for measuring exposure because of metal deposits from external contamination that may complicate analysis.

Metal-binding Proteins and Metal Transporters

Protein binding of metals is a critical aspect of essential and toxic metal metabolism. Many different types of proteins play roles in the disposition of metals in the body. Non specific binding to proteins, like serum albumin or hemoglobin, act in metal transport and tissue distribution. Metals vary in their preferred site of proteinaceous binding, and can attack a variety of amino acid residues. For instance, cysteine sulfurs are preferred by cadmium and mercury, and these residues are commonly involved with overall protein structure. In addition, proteins with specific metal-binding properties play special roles in the trafficking of specific essential metals, and toxic metals may interact with these proteins through mimicry. Metal-binding proteins are an important, emerging issue in the physiology and toxicology of metals and only a few examples are highlighted here.

The metallothioneins are a very important class of metal-binding proteins that function in essential metal homeostasis and metal detoxification. They are small (6000 Da), soluble, and rich in internally oriented thiol ligands. These thiol ligands provide the basis for high-affinity binding of several essential and toxic metals including zinc, cadmium, copper, and mercury. The metallo thioneins are highly inducible by a variety of metals or other stimulants. Metallo-thioneins clearly play an important role in metal toxicity, as illustrated in the discussion of cadmium below.

Transferrin is a glycoprotein that binds most of the ferric iron in plasma and helps transport iron across cell membranes. The protein also transports aluminum and manganese. Ferritin is primarily a storage protein for iron. It has been suggested that ferrin may serve as a general metal detoxicant protein, because it binds a variety of toxic metals including cadmium, zinc, beryllium, and aluminum.

Ceruloplasmin is a copper-containing glycoprotein oxidase in plasma that converts ferrous iron to ferric iron, which then binds to transferrin.Thisproteinalsostimulatesironuptakebyatransferrinindependent mechanism.

In all cells there are mechanisms for metalion homeostasis that frequently involve a balance between uptake and efflux systems. A rapidlyincreasingnumberofmetaltransportproteinsarebeingdiscoveredthattransportmetal sacrosscellmembranesandorganelles inside the cells. Metal transporters are important for cellular resistance to metals or metalloids. For instance, enhanced efflux via multidrug resistance protein pumps is involved in acquired tolerance to arsenic, whereas decreased influx via reduced calcium G-type channels is involved in acquired tolerance to cadmium. Over ten zinc transporters and four Zip family proteins are involved in cellular zinc transport, trafficking, and signaling. The importance of metal transporters in human diseases is well illustrated by Menkes disease and Wilson disease, which are caused by genetic mutations in the copper-transport protein gene ATP7A, resulting in copper deficiency (Menkes disease), or ATP7B, resulting in copper overload (Wilson disease).

Pharmacology of Metals

Metal and metal compounds have a long history of pharmacological use. Metallic agents, largely because of their potential toxicity, have been often used in chemotherapeutic settings. For instance, mercury was used in the treatment of syphilis as early as the 16th century. Similarly, Ehrlich’s magic bullet (arsphenamine) was an organo-arsenical. Today, many metallic chemicals remain valuable pharmacological tools in the treatment of human disease, as exemplified by the highly effective use of platinum compounds in cancer chemotherapy. In addition, gallium and titanium complexes are promising metal

compounds in cancer chemotherapy. Other medicinal metals used today include aluminum (antacids and buffered analgesics), bismuth (peptic ulcer and Helicobacter pylori associated gastritis), lithium (mania and bipolar disorders), and gold (arthritis).

Treatment of metal poisoning is sometimes used to prevent, or even attempt to reverse, toxicity. The typical strategy is to give metal chelators that will complex the metal and enhance its excretion. Most chelators are not specific and will interact with a number of metals, eliminating more than the metal of concern. In addition, the vast array of biological metal ligands is a formidable barrier to chelator efficacy. Metal chelation therapy should be considered a secondary alternative to reduction or prevention of toxic metal exposures. Such therapy can be used for many different metals including lead, mercury, iron, and arsenic. For detailed discussion on the pharmacology of chelation therapy.

Metal classification for toxic studies purposes

Toxic metals	Arsenic, Beryllium, Cadmium, Chromium, Lead, Mercury, Nickel.
Essential metals with potential for toxicity	Cobalt, Copper, Iron, Magnesium, Manganese, Molybdenum, Selenium, Trivalent Chromium, Zinc.
Metals related to medical therapy	Aluminium, Bismuth, Platinum.

TOXIC EFFECTS OF SOLVENTS AND VAPORS

By Bruckner JV, Anand S & Warren DA.

INTRODUCTION

The term solvent refers to a class of liquid organic chemicals of variable lipophilicity and volatility. These properties, coupled with small molecular size and lack of charge, make inhalation the major route of solvent exposure and provide for ready absorption across the lung, gastrointestinal (GI) tract, and skin. In general, the lipophilicity of solvents increases with increasing numbers of carbon and/or halogen atoms, while volatility decreases. Organic solvents are frequently used to dissolve, dilute, or disperse materials that are insoluble in water. As such they are widely employed as degreasers and as constituents of paints, varnishes, lacquers, inks, aerosol spray products, dyes, and adhesives. Other uses are as intermediates in chemical synthesis, and as fuels and fuel additives. Most organic solvents are refined from petroleum. Many such as naphthas and gasoline are complex mixtures, often consisting of hundreds of compounds. Early in the twentieth century, there were perhaps a dozen or so known and commonly used solvents. By 1981, this number had climbed to approximately 350.

Solvents are classified largely according to molecular structure or functional group. Classes of solvents include aliphatic hydrocarbons, many of which are chlorinated (i.e., halocarbons); aromatic hydrocarbons; alcohols; ethers; esters/acetates; amides/amines; aldehydes; ketones; and complex mixtures that defy classification. The main determinants of a solvent's inherent toxicity are: (1) its number of carbon atoms; (2) whether it is saturated or has double or triple bonds between adjacent carbon atoms; (3) its configuration (i.e., straight chain, branched chain, or cyclic); and (4) the presence of functional groups. Some class-wide generalizations regarding toxicity can be made. For example, the more lipophilic a hydrocarbon, the more potent a central nervous system (CNS) depressant it is; amides/amines tend to be potent sensitizers; aldehydes are particularly irritating; hydrocarbons that are extensively metabolized tend to be more cytotoxic/mutagenic; and many unsaturated, short-chain halocarbons are animal carcinogens. The toxicity of solvents within the same class can vary dramatically. For example, 1,1,1 tri chloroethane (TRI) and 1,1,2-trichloroethylene (TCE) are both halocarbons with three chlorine atoms, yet the unsaturated TCE is carcinogenic in the rat and mouse, but TRI is not. Similar results have been reported for 2,4- and 2,6-diaminotoluene in rodents, as only the 2,4 isomer is capable of inducing significant hepatocyte proliferation and liver tumors. Slight structural differences in solventmetabolitesarealsooftoxicologicalconsequence.Theperipheral neuropathy induced by n-hexane and 2-hexanone is dependent on the production of the γ-diketone metabolite, 2,5-hexanedione. Diketones lacking the gamma structure are not neurotoxic. Thus, subtle differences in chemical structure can translate into dramatic differences in toxicity.

Nearly everyone is exposed to solvents in the conduct of their normal activities. Consider, for example, a person who works in an aircraft factory as a metal degreaser (TCE exposure); drives to the neighborhood bar after work and has a few drinks (ethanol exposure) and cigarettes (benzene and styrene exposure); stops on the way home at a self-service filling station for gasoline (benzene, toluene, 1,3-butadiene exposure) and the dry cleaner's for laundry [tetrachloroethylene (PERC) exposure]; and after dinner enjoys his hobby of model shipbuilding that requires the use of glue (toluene exposure). While every one may not identify with the above scenario, detailed surveys of indoor and outdoor air, such as the EPA's Total Exposure Assessment Methodology (TEAM) and

National Human Exposure Assessment Survey (NHEXAS) studies, indicate that airborne solvent exposure is unavoidable. Drinking water is also a common source of solvent exposure due to discharge of solvents into surface and ground waters and the presence of disinfection by-products, including the animal carcinogen chloroform ($CHCl_3$). Trichloroacetic acid (TCA), and dichloroaceticacid (DCA), metabolites of TCE and PERC, are also common disinfection by products.

Environmental exposures to solvents in air and groundwater are frequent subjects of toxic tort litigation, despite concentrations that are typically in the low parts per billion (ppb) range. Multiple exposure pathways frequently exist (Fig. 24-1). Although not represented in Fig. 24-1, household use of solvent-contaminated water may result in solvent intake from inhalation and dermal absorption as well as ingestion. In many cases, environmental risk assessments require that risks be determined for physiologically diverse individuals who are exposed to several solvents by multiple exposure pathways. As an aid to the risk assessment process, the U.S. EPA has derived toxicity factors for many of the most toxic solvents. These toxicity factors are referred to as reference concentrations (RfCs), reference doses (RfDs), and cancer slope factors (CSFs). Values for a number of these are available from the EPA's online Integrated Risk Information System (IRIS). Additional sources of exposure guidelines for non-cancer end points are found in the Toxicologic Profiles of the U.S. Agency for Toxic Substances and Disease Registry (ATSDR). These profiles often contain minimal risk levels that are derived in a similar manner to EPA's RfCs and RfDs, but are frequently based on different critical studies or derived with different uncertainty factors.

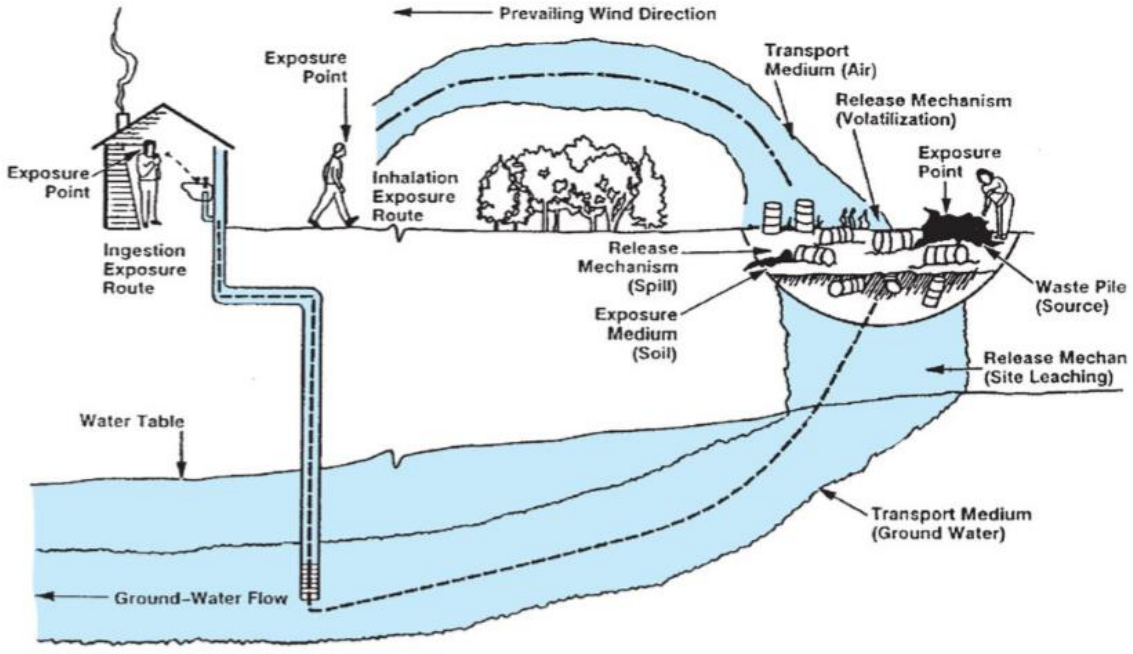


Figure 24-1. Solvent exposure pathways and media.

Occupational solvent exposures involve situations ranging from a secretary using type writer correction fluid to the load in gand off-loading of tanker trucks with thousands of gallons of gasoline. The greatest industrial use of solvents is as metal degreasers. This work environment is typically where the highest exposures occur, mainly via inhalation and secondarily via dermal contact. An estimated 10 million people are potentially exposed to organic solvents in the work place. Many of the most severe exposures to solvents have occurred as a result of their use in confined spaces with in adequate ventilation. While the U.S. Occupational Safety and Health Administration (OSHA) has

established legally enforceable permissible exposure limits (PELs) for over 100 solvents, most PELs are outdated. The majority of existing PELs were adopted from the list of threshold limit values (TLVs) published some years ago by the American Conference of Governmental Industrial Hygienists (ACGIH).Many current TLVs are more stringent than the PELs but do not carry the weight of law. Whereas the ACGIH's TLVs for an 8-hour workday, 40-hour workweek are designed to be protective for a working lifetime, its short-term exposure limits (STELs) and ceiling values are designed to protect against the acute effects of high-level, short-term solvent exposure. If warranted, ACGIH will assign a skin notation to a solvent, indicating that a significant contribution to overall exposure is possible by the dermal route, either by contact with vapors or direct skin contact with the liquid. Biological monitoring in the workplace should find increasing use as technologic advances are made, because it often provides a better measure of exposure than classic industrial hygiene monitoring. The ACGIH has published over 50 Biological Exposure Indices (BEIs), on which bases the safety of internal measures of exposure can be judged.

Most solvent exposures involve a mixture of chemicals, rather than a single compound. Our knowledge of the toxicity of solvent mixtures is rudimentary relative to the toxicology of individual solvents. While the assumption is frequently made that the toxic effects of multiple solvents are additive, solvents may also interact synergistically or antagonistically. For example, repetitive alcohol consumption induces certain cytochrome P450s (CYPs), and may therefore enhance the metabolic activation of other solvents to cytotoxic metabolites. Ethanol intake near the time of exposure to such solvents, in contrast, may competitively inhibit their metabolism and be protective. Another well-characterized example of solvent antagonism is the competitive metabolic interaction between benzene and toluene. Coexposure to these chemicals results in diminished benzene metabolism, genotoxicity, and erythropoietic toxicity relative to that which follows benzene exposure alone. It is now recognized that significant data gaps exist in the area of mixtures toxicology, and that these can be significant sources of uncertainty in risk assessments. Physiologically based toxicokinetic (PBTK) models are being developed by different research groups to predict the impact of metabolic induction and inhibition on the kinetics of individual components of specific mixtures.

Although some solvents are less hazardous than others, virtually all can cause adverse effects. Provided that the dose or concentration is sufficient, most have the potential to induce some level of narcosis and cause respiratory and mucous membrane irritation. A number of solvents are animal carcinogens, but only a handful have been classified as known human carcinogens. Herein lies a major challenge for toxicology—determining the human relevance of tumors observed in chronic, high-dose rodent studies. As with other chemicals, whether adverse health effects occur from solvent exposure is dependent on several factors: (1) toxicity of the solvent; (2) exposure route; (3) amount or rate of exposure; (4) duration of exposure; (5) individual susceptibility; and (6) interactions with other chemicals. Adverse health effects may occur acutely and be readily discernible, or they may be the result of chronic exposure and have insidious onset. Numerous epidemiologic studies of environmentally- and occupationally-exposed populations have been conducted for some solvents, but most human risk assessments remain heavily reliant upon extrapolation from high-dose animal studies. One must bear in mind that the toxic effects and their underlying mechanisms discussed herein may be operative only in certain animal species or strains and under certain exposure conditions. Care must therefore be taken in generalizing beyond the experimental conditions under which data are collected. While a relatively small number of commercially available solvents is discussed in this chapter, those selected for discussion are thought to best

demonstrate principles of solvent toxicology, are of particular commercial importance, and/or are currently garnering significant attention from the toxicological and regulatory communities.

IS THERE A SOLVENT-INDUCED CHRONIC ENCEPHALOPATHY?

The CNS-depressant effects of acute, high-level exposures and the potential for permanent neurologic damage in chronic solvent abusers are not a matter of debate. It is also clear that chronic, moderate-to-high-level exposure to a few solvents such as n-hexane and carbon disulfide can cause specific degenerative changes in the CNS or the peripheral nervous system (PNS). Far less clear is whether chronic, low-level exposure to virtually any solvent or solvent mixture can produce a pattern of neurologic dysfunction referred to as painters' syndrome, organic solvent syndrome, psychoorganic syndrome, and chronic solvent encephalopathy (CSE). CSE is characterized by nonspecific symptoms (e.g., headache, fatigue, mood disturbances, and sleep disorders) with or without changes in neuropsychological function. There is a reversible form of CSE referred to as neuroasthenic syndrome that consists of symptoms only, and both "mild" and "severe" forms accompanied by objective signs of neuropsychological dysfunction that mayor may not be fully reversible. This syndrome was first described in the Scandinavian occupational literature in the late 1970s in solvent-exposed painters. Since that time, numerous studies from Scandinavia have been published purporting that solvents as a class have chronic neurotoxic properties. These countries, as well as few others in Europe (i.e.,Germany, Austria, and Belgium) have passed legislation recognizing CSE as a compensable occupational disability. Scientists outside of Scandinavia, including many in the United States, have generally been less willing to recognize CSE as a legitimate disease state and have published studies to the contrary.

In response to the numerous reports of CSE, two conferences were convened in 1985. The first was held in Copenhagen by the Nordic Council of the World Health Organization.

The second, in Raleigh, NC, was attended by an international group of scientists from academia, industry, and government. The categorization scheme that resulted from the Raleigh meeting is presented in Table 24-1. The WHO scheme is similar. Among those who utilize the categorization scheme, it is generally believed that the most severe CSE category, type 3, results from repeated, severe intoxications like those experienced by solvent abusers. CSE types 1 and 2, on the other hand, are thought to be associated with prolonged, low-to-moderate-level exposure common to work environments. A major criticism of the categorization scheme is the lack of consideration of inhaled solvent concentration and exposure duration. While no consensus exists, even most CSE proponents believe that solvent exposure must occur for some 10 years before clinical symptoms are manifest. Citing growing acceptance of CSE outside of Scandinavia, some scientists and physicians advocate for refinement of existing diagnostic criteria and a unified categorization scheme.

CSE researchers typically rely upon self-reported symptoms and a clinical neuropsychological evaluation (Table 24-2), and to a much lesser extent on diagnostic tests such as electroencephalography and computerized brain tomography. It has been argued that the neuropsychological tests are of questionable validity, sensitivity, specificity, and predictive value. It has also been noted that many investigations of CSE are fraught with methodologic flaws. For example, CSE investigators frequently fail to measure premorbid function or intellect; employ a reference population; control adequately for the potential confounders of age, alcohol use, other CNS diseases, and

other chemicals; corroborate functional deficits with objective evidence of brain disease; and/or examine exposure– response relationships. The importance of doing so is best exemplified by the reanalysis of individuals originally reported in the seminal study by Arlien-Soborg et al. (1979) to have “painters’ syndrome. ”When the influences of age, education, and intelligence were considered, the previously reported reduction in neuropsychological test scores disappeared. Another example is that of Cherry et al. (1985), who demonstrated the importance of matching solvent-exposed and control groups for preexposure intellect before making a diagnosis of CSE. More recently, Albers et al. (2000) reportedly found no objective evidence of toxic encephalopathy among 52 railroad workers with long-term solvent exposure and diagnosis of CSE.

Table 24-1
Proposed Categories of Solvent-Induced Encephalopathy

CATEGORY	CLINICAL MANIFESTATIONS
Type 1	*Symptoms only*: The patient complains of nonspecific symptoms such as fatigability, memory impairment, difficulty in concentration, and loss of initiative. These symptoms are reversible if exposure is discontinued, and there is no objective evidence of neuropsychiatric dysfunction.
Type 2A	*Sustained personality or mood change*: There is a marked and sustained change in personality involving fatigue, emotional lability, impulse control, and general mood and motivation.
Type 2B	*Impairment in intellectual function*: There is difficulty in concentration, impairment of memory, and a decrease in learning capacity. These symptoms are accompanied by objective evidence of impairment. There may also be minor neurologic signs. The complete reversibility of type 2B is questionable.
Type 3	*Dementia*: In this condition, marked global deterioration in intellect and memory is often accompanied by neurologic signs and/or neuroradiologic findings. This condition is, at best, poorly reversible, but is generally nonprogressive once exposure has ceased.

Table 24-2
Functions that May Be Assessed in a Neuropsychological Evaluation

Psychomotor functions
Reaction time
Motor speed and dexterity
Eye-hand coordination
Sustained attention/concentration and perceptual speed
Verbal and nonverbal memory
Immediate memory
Delayed memory
Learning
Visual constructive ability
Conceptual ability
Evaluation of personality and affect

It is evident that resolution of the controversial issue of CSE will come only through the conduct of well-designed and controlled epidemiological studies, especially considering the absence of an appropriate animal model. Brief, but insightful reviews of CSE by Rosenberg (1995) and Schaumburg and Spencer (2000) have been published. These reviews conclude that the current literature, including the “landmark” North American study of 187 paint manufacturing workers (Bleecker et al., 1991), does not support chronic low-level solvent exposure as a cause of symptomatic CNS or PNS dysfunction. This does not preclude, however, the possibility that such exposure can be associated with subclinical cognitive dysfunction in the form of slight psychomotor and attentional deficit disorders.

SOLVENT ABUSE

Inhalants are volatile substances that can be inhaled to induce a psychoactive or mind-altering effect. Their abuse has become a major drug problem worldwide, particularly in disadvantaged populations and among adolescents. The epidemiology of inhalant abuse in the United States is receiving considerable attention, with almost one in five 8th graders claiming to have used inhalants according to the most recent National Institute on Drug Abuse (NIDA) sponsored survey. Solvents are among the most popular classes of drugs of abuse, given their presence in a multitude of inexpensive, readily available products that are legal to buy and possess. These products are used for common household and industrial purposes and include paint thinners and removers, dry-cleaning fluids, degreasers, gasoline, glues, typewriter fluid, nail polish remover, felt-tip marker fluids, and aerosols such as fabric protector sprays and spray paints. Solvents are often among the first drugs used by children and adolescents. Early use of inhalants is often a precursor to abuse of multiple illegal substances. Research suggests that adverse socioeconomic conditions, a history of child abuse, poor grades, and dropping out of school are all factors contributing to inhalant abuse.

Solvent abuse is a unique exposure situation in that participants repeatedly subject themselves to vapor concentrations high enough to produce effects that resemble alcohol intoxication. Solvents can be breathed in through the nose or the mouth by “sniffing” or “snorting” vapors from containers; spraying aerosols directly into the nose or mouth; “bagging” by inhaling vapors from substances sprayed or deposited inside a plastic or paper bag; or “huffing” from a solvent-soake drag stuffed into the mouth. Although dependent on the pattern of inhalation, blood levels of solvents typically peak minutes after inhalation begins, and the abuser can begin to experience intoxication after a matter of seconds. While intoxication may last only a few minutes, abusers frequently seek to prolong the “high” by inhaling repeatedly over the course of several hours. In extreme circumstances, death may be a consequence of cardiac arrhythmias, asphyxiation, and/or cachexia.

Relatively little is known about the neuropharmacology of abused solvents, although they appear to have much in common with the classical CNS-depressant drugs like ethanol and barbiturates, including the potential for tolerance and dependence. Commonly used solvents have been shown to alter the function of a variety of ligand-gated ion channels, including those activated by glycine, gamma-amino butyric acid(GABA) and N-methyld-aspartate (NMDA). Recent evidence links high-level toluene exposure in rats to increased dopaminergic neurotransmission within theme so limbic reward pathway, an effect thought to underlie the abuse potential of numerous drugs. Toluene, as well as TCE and TRI, have been shown to enhance serotonin-3 receptor function, which has also been implicated in the reinforcing properties of abused drugs.

Whereas the intoxicating effects achieved through acute solvent abuse are reversible, abuse may be continued for years and result in residual organ damage. For example, chronic abuse of products containing n-hexane and methyl-n-butyl ketone can cause peripheral neuropathies. Blood dyscrasias, liver damage, kidney injury, and hearing impairment are seen in patients who have abused solvents injurious to these organs. It has been known for some time that the brain is not spared residual damage, with long-term neurologic and psychological secuelae.

More recently, Rosenberg et al. (2002) reported increased incidences of neurologic and neuropsychological effects in chronic solvent abusers compared to a control group of chronic drug abusers. Solvent abusers did significantly worse on tests of working

memory and executive cognitive function, and a much higher percentage of the patients (44 vs. 25.5%) had structural abnormalities in subcortical regions of the brain (i.e., basal ganglia, cerebellum, pons, and thalamus) as visualized by MRI. Solvent abusers also showed moderate to severe, diffuse abnormality of the cerebral white matter, consistent with that seen in earlier studies of neuropsychologically impaired toluene abusers. Nearly two decades ago, Rosenberg and colleagues termed this condition “white matter dementia” (myelinated neurons are white in appearance) that was characterized primarily by diffuse cerebral, cerebellar and brainstem atrophy,and ventricular enlargement. More recently, dementia in toluene abusers has been referred to as “toluene leuko encephalopathy”. Leukoencephalopathy, also known as multifocal demyelinating disease, involves structural alteration of cerebral white matter, in which the myelin sheaths that cover nerve fibers are destroyed but axons are largely spared. Thus, toluene is among the long list of white matter toxins identified to date.

ENVIRONMENTAL CONTAMINATION

Widespread use of solvents has resulted in their dissemination throughout the environment (Fig. 24-1). Everyone is exposed daily to solvents, albeit in minute amounts. Because solvents as a chemical class are volatile, the preponderance of solvents entering the environment do so by evaporation. The majority of the more volatile organic chemicals (VOCs) volatilize when products containing them (e.g., aerosol propellants, paint thinners, cleaners, and soil fumigants) are used as intended. Solvent loss into the atmosphere also occurs during production, processing, storage, and transport activities, resulting in elevated concentrations in air in the proximity of point sources. Winds dilute and disperse solvent vapors across the world. Atmospheric concentrations of most VOCs are usually extremely low [i.e., nondetectable to nanograms or a few micrograms per cubic meter (m3) o fair]. Relatively high concentrations of certain solvents (e.g., 10–520 μg/m3, or 3–163 ppb of benzene) have been measured in urban areas, around petrochemical plants, and in the immediate vicinity of hazardous waste sites. Motor vehicle exhaust is a major contributor to hydrocarbon emissions.

Solvent contamination of drinking water supplies is of major health concern. Although the majority of a solvent spilled onto the ground evaporates, some may permeate the soil and migrate through it until reaching groundwater or an impermeable material. In years past, the more lipophilic solvents were generally regarded as water insoluble. It is now recognized that all solvents are soluble in water to some extent. Some (e.g., alcohols, ketones, glycols, and glycol ethers) are freely water soluble. Maximum solubilities of somecommonhydrocarbonsolventsrangefrom10mg/L(ppm)for n-hexane to 24,000 mg/L for bromo-chloromethane. High concentrations of VOCs are sometimes found in thee effluent of facilities of rubber producers, chemical companies, petrochemical plants, and paper mills. Concentrations diminish rapidly after VOCs enter bodies of water, primarily due to dilution and evaporation. VOCs in waters rise to the surface or sink to the bottom, according to their density. VOCs on the surface will largely evaporate. VOCs on the bottom must depend on solubilization in the water or upon mixing by current or wave action to reach the surface. VOCs in groundwater tend to remain trapped until the water reaches the surface, although some are subject to microbial modification. Concentrations in well water are rarely high enough for acute or subacute toxicity to be of concern. The very low levels of some solvents typically found in water have, however, caused a great deal of concern and debate about their carcinogenic potential.

Potential health effects of solvent contaminants of water have received considerable attention over the past 30+ years. A report by Mason and McKay (1974), of an increased

incidence of cancer in persons who drank water from the Mississippi River, prompted the EPA to analyze the water supply of New Orleans. The finding of some 76 synthetic organic chemicals, many of which were solvents, prompted passage of the Safe Drinking Water Act in 1974. CHC13 is the most frequently found VOC in finished drinking water supplies in the United States (ATSDR, 1997a). It and certain other trihalomethanes are formed by reaction of the chlorine added as a disinfectant with natural organic compounds present in the water. Levels of solvents found in drinking water in the United States are typically in the nanogram per liter (ppt) to microgram per liter (ppb) range, though concentrations in the low milligram per liter (ppm) range are found in water from wells situated in solvent plumes from hazardous waste sites and other point discharges. Of the thousands of chemicals found at hazardous waste sites, six of the ten most commonly present in groundwater are solvents.

People are subjected to solvents in environmental media by inhalation, ingestion, and skin contact. Considerable effort was devoted by the EPA, from 1979 to 1985, to assess personal exposure to solvents in different locales of the United States. TRI, PERC, benzene, xylenes, and ethylbenzene were most frequently found in highest concentrations (~1–32 μg/m3) in air. Exhaled breath levels of some chemicals (e.g., CHC13, ethylbenzene) corresponded to indoor air levels. Personal activities (e.g., smoking, visiting a dry cleaner and service station) and occupational exposures were believed to be largely responsible for relatively high exposures to other VOCs (e.g., benzene, toluene, xylenes, and PERC). Subsequent studies, accounting for all pertinent exposure pathways, were conducted by the EPA in the mid-1990s (Gordon et al., 1999). Elliott et al. (2006) recently reported indoor exposures to VOCs did not have adverse effects on the respiratory function of 953 adults surveyed, with the exception of 1,4-dichlorobenzene, a component of air fresheners, toilet bowl deodorants, and mothballs. CHCl3 was found to be the most prevalent VOC in drinking water. It should be recognized that CHCl3 and other VOCs volatilize to some degree during home water usage, particularly when the water is heated. Thus, a significant proportion of one's total exposure to VOCs in tap water can occur via inhalation, though the contribution of dermal exposure is relatively modest.

HEALTH EFFECTS OF RADIATION AND RADIACTIVE MATERIALS

By Harley NH

INTRODUCTION

Among all the branches of toxicology, ionizing radiation provides the most quantitative estimates of health detriments for humans and animals. Five large studies provide data on the health effects of radiation on people. These effects include those due to external X-rays and gamma-ray radiation and internal alpha radioactivity. The studies encompass radium exposures, including those sustained by radium dial painters, atom bomb survivors, patients irradiated with X-rays for ankylosing spondylitis, children irradiated with X-rays for tinea capitis (ringworm), and uranium miners exposed to radon and its short-lived daughter products. The latest data on radon risk comes from over 20 domestic studies of normal radon background. The major health effect subsequent to radiation exposure seen with statistical significance to date is cancer. Some heart and digestive disease has been observed in atom bomb survivors, but only at high dose levels (>0.5 Sv). The various types and the quantitative risks are described in subsequent sections.

All the studies provide a consistent picture of the risk of exposure to ionizing radiation. There are sufficient details in the studies of atom bomb, occupational, and medical exposures to estimate the risk from lifelong low-level environmental exposure. Natural background radiation is substantial, and only within the past two decades has the extent of the radiation insult to the global population from natural radiation and radioactivity been appreciated.

BASIC RADIATION CONCEPTS

The four main types of radiation are alpha particles, electrons (negatively charged beta particles or positively charged positrons), gamma rays, and X-rays. An atom can decay to a product element through the loss of a heavy (mass=4) charged (+2) alpha particle (He+2) that consists of two protons and two neutrons. The alpha particle is ejected from the nucleus with energy depending upon the element. After it loses its energy, it is a stable helium atom. An atom can decay by loss of a negatively or positively charged electron (e^-, a beta particle or e^+, a positron). Gamma radiation results when the nucleus releases excess energy, usually after an alpha, beta, or positron transition. X-rays occur whenever an inner-shell orbital electron is removed and rearrangement of the atomic electrons results, with the release of the element's characteristic X-ray energy.

There are several excellent textbooks describing the details of radiologic physics (Evans, 1955, 1982; Andrews, 1974; Turner, 1986; Shapiro, 2002; Cember, 1996).

Energy

The definition of an alpha or beta particle or a gamma ray arises from their energetic nuclear origin. Otherwise they are basically a helium atom, an electron, or a photon. Alpha particles and beta rays (or positrons) have kinetic energy as a result of their rapid motion when ejected from the nucleus. The energy is equal to:

$E = 1/2mV^2$

Where m is the mass of the particle and V the velocity of the particle.

Alpha particles have a low velocity compared with the speed of light, and calculations of alpha particle energy do not require any corrections for relativity. Most beta particles (or

positrons) have a Velocity near the speed of light, and the basic expression must be corrected for their increased relativistic mass. The energy equivalent of mass is calculated from Einstein's equation $E = mc^2$. Thus, rest mass of the electron is calculated as 0.511MeV and its total energy (increase in mass due to relativistic correction plus the rest mass) is equal to

$$E = 0.511/(1-v^2/c^2)+0.511$$

Where v is the velocity of the beta particle and c the speed of light.

Gamma rays and X-rays are pure electromagnetic radiation with energy equal to

$$E = hv$$

Where h is the Planck's constant (6.626×10^{-34} Js) and v the frequency of radiation.

The conventional energy units for ionizing radiation are the electron volt (eV) or multiples of this basic unit, kiloelectron volts (keV), and million electron volts (MeV). The conversion to the international system of units, the Systeme Internationale (SI), is currently taking place in many countries, and the more fundamental energy unit of the Joule (J) is slowly replacing the older unit. The relationship is

$$1\ \text{eV} = 1.6 \times 10^{-19}\ \text{J}$$

Alpha Particles

Alpha particles are helium nuclei (consist in g of two protons and two neutrons), with a charge of +2, that are ejected from the nucleus of an atom. When an alpha particle loses energy, its lows to the velocity of a gas atom and acquires two electrons from the vast sea of free electrons present in most media, and it becomes part of the normal background helium in the environment. All helium in nature is the result of alpha particle decay. The formula for alpha decay is

$$^{A}_{Z}X \rightarrow\ ^{A-4}_{Z-2}Y + \mathrm{He}^{2+} + \mathrm{gamma} + Q_{\alpha}$$

Where Z =atomic number and A =atomic weight.

The energy available in this decay is Qi and is equal to the mass difference of the parent and the two products. The energy is shared among the particles and the gamma ray if one is present.

The energy of alpha particles for most emitters lies in the range of 4–8 MeV. More energetical particles exist but are seen only in very short-lived emitters such as those formed by reactions occurring in particle accelerators. These particles are not considered in this chapter.

Although there may be several alpha particles with very similar energy emitted by a particular element such as radium, each particular alpha particle is monoenergetic, i.e., no continuous spectrum of energies exists, only discrete energies.

Alpha particles are massive relative to beta particles and most alpha particles cannot penetrate a thin sheet of paper. The range of an alpha particle in air is,

$$\text{Range (air)} = 0.325\ E^{3/2}\ \text{(cm)}$$

In tissue, the range is about 1/1000 of the range in air.

Beta Particles, Positrons, and Electron Capture

Beta particle decay occurs when a neutron in the nucleus of an element is effectively transformed into a proton and an electron. Subsequent ejection of the electron occurs, and the maximum energy of the beta particle equals the mass difference between the parent and the product nuclei. A gamma ray may also be present to share the energy, Q:

$$ {}^{A}_{Z}X \rightarrow {}^{A}_{Z+1}Y + \text{beta} + Q_{\beta} $$

Unlike alpha decay, in which each alpha particle is monoenergetic, beta particles are emitted with a continuous spectrum of energy from zero to the maximum energy available for the transition. The reason for this is that the total available energy is shared in each decay or transition by two particles: the beta particle and an antineutrino. The total energy released in each transition is constant, but the observed beta particles then appear as a spectrum. The residual energy is carried away by the antineutrino, which is a particle with essentially zero mass and charge that cannot be observed without extraordinarily complex instrumentation. The beta particle, by contrast, is readily observed with conventional nuclear counting equipment.

Positron emission is similar to beta particle emission but results from the effective nucleon transformation of a proton to a neutron plus a positively charged electron. The atomic number decreases rather than increases, as it does in beta decay.

The energy of the positron appears as a continuous spectrum, similar to that in beta decay, where the total energy available for decay is again shared between the positron and a neutrino. In the case of positron emission, the maximum energy of the emitted particle is the mass difference of the parent and product nuclide minus the energy needed to create two electron masses (1.02 MeV), whereas the maximum energy of the beta particle is the mass difference itself. This happens because in beta decay, the increase in the number of orbital electrons resulting from the increase in atomic number of the product nucleus cancels the mass of the electron lost in emitting the beta particle. This does not happen in positron decay, and there is an orbital electron lost as a result of the decrease in atomic number of the product and the loss of the electron mass in positron emission. Positron emission tomography (PET) scans are a useful diagnostic tool in nuclear medicine. The positron is an unstable particle and decays immediately to two 0.511 MeV photons emitted 180◦ from each other. The positron emitter is typically fluorine 18 (18F). The radionuclide is given in a solution that is taken up by the tissues of interest and coincidence counting of the two photons locates their tissue origin precisely.

Electron capture competes with positron decay, and the resulting product nucleus is the same nuclide. In electron capture, an orbiting electron is acquired by the nucleus, and the transformation of a proton plus the electron to form a neutron takes place. In some cases the energy available is released as a gamma-ray photon, but this is not necessary, and a monoenergetic neutrino may be emitted. If the 1.02 MeV required for positron decay is not available, positron decay is not kinetically possible and electron capture is the only mode observed.

Gamma-Ray (Photon) Emission

Gamma-ray emission is not a primary process except in rare instances, but it occurs in combination with alpha, beta, or positron emission or electron capture. Whenever the

ejected particle does not utilize all the available energy for decay, the nucleus contains the excess energy and is in an excited state. The excess energy is released as photon or gamma-ray emission coincident with the ejection of the particle.

One of the rare instances of pure gamma-ray emission is technetium 99m (99mTc), which has a 6.0-hour half-life and is widely used in diagnostic nuclear medicine for various organ scans. Its decay product, 99Tc, has a very long half-life (2.13×105 years), and as all 99Tc is ultimately released to the environment, a background of this nuclide is emerging.

$$^{99m}_{43}\mathrm{Tc} \rightarrow {}^{99}_{43}\mathrm{Tc} + \text{gamma (0.14 MeV)}$$

Internal Conversion

In many gamma ray emitters, a photon will not actually be emitted by the nucleus but the excess excitation energy will be transferred to an orbital electron. This electron is then ejected as a monoenergetic particle with energy equal to that of the photon minus the binding energy of the orbital electron. This process is known as internal conversion. In tables of nuclear data such as those of Browne et al. (1986), the ratio of the conversion process to the photon is given as e/γ. For example, the e/γ ratio for 99mTc is 0.11, and therefore the photon is emitted 90% of the time and the conversion electron is emitted 10% of the time. The internal conversion electron is a monoenergetic particle.

INTERACTION OF RADIATION WITH MATTER

Ionizing radiation,by definition, loses energy when passing through matter by producing ion pairs (an electron and a positively charged atom residue). A fraction of the energy loss raises atomic electrons to an excited state (excitation loss). The average energy needed to produce anion pair is given the notation W and is numerically equal to 33.85 eV in air. This energy is roughly two times the ionization potential of most gases or other elements because it includes the energy lost in the excitation process. It is not clear what role the excitation plays, for example, in damage to targets in the cellular DNA. Ionization, by contrast, can break bonds in DNA, causing even double strand breaks.

All particles and rays interact through their charge or field with atomic or free electrons in the medium through which they are passing. There is no interaction with the atomic nucleus except at energies above about 8 MeV, which is required for interactions that break apart the nucleus (spallation). Very high-energy cosmic-ray particles, for example, produce ^{3}H, ^{7}Be, ^{14}C, and ^{22}Na in the upper atmosphere by spallation of atmospheric oxygen and nitrogen.

Alpha and beta particles and gamma rays lose energy by ionization and excitation in somewhat different ways, as described in the following sections.

Alpha Particles

The alpha particle is a heavy charged particle with a mass that is 7300 times that of the electrons with which it interacts. The massive particle interacting with a small particle (the electron) has the interesting property that it can give a maximum velocity during energy transfer to the small particle of only two times the initial velocity of the heavy particle.

Although alpha particles can lose perhaps 10–20% of their energy in traveling 10 μm in tissue (1 cm in air), each interaction can impart only the small energy, given in the maximum, in Eq. (25-4). Thus, alpha particles are characterized by a high energy loss per unit path length and a high ionization density along the track length. This is called a high linear-energy-transfer (LET) or high-LET particle.

Beta Particles

The equations for beta particle energy loss in matter cannot be simplified, as in the case of alpha particles, because of three factors:

1. Even at low energies of a few tenths of a MeV, beta particles travel near the speed of light and relativistic effects (mass increase) must be considered.

2. Electrons interact with particles of the same mass in the medium (free or orbital electrons), so large energy losses per collision are possible.

3. Radiative or bremsstrahlung energy loss occurs when electrons or positrons are slowing down in matter. Such a loss also occurs with alpha particles, but the magnitude of this energy loss is negligible.

Gamma Rays

Photons do not have a mass or charge, as do alpha and beta particles. The interaction between a photon and matter therefore is controlled not by the electrostatic Coulomb fields but by interaction of the electric and magnetic field of the photon with the electron in the medium. There are three modes of interaction with the medium.

The Photoelectric Effect The photon interaction (energy exchange) with an orbital electron in the medium is complete, and the full energy of the photon is given to the electron minus the electron-binding energy.

The Compton Effect Part of the photon energy is transferred to an electron, and the photon scatters (usually at a small angle from its original path) (Evans,1955) with reduced energy.

Pair Production Pair production may occur whenever the photon energy is greater than the rest mass of two electrons, 2 (0.511MeV) = 1.02 MeV. The electromagnetic energy of the photon can be converted directly to an electron–positron pair, with any excess energy above 1.02 MeV appear in gas kinetic energy given to these particles.

Gamma Ray Energy Loss

The loss of photons and energy loss from a photon beam as it passes through matter are described by two coefficients. The attenuation coefficient determines the fractional loss of photons per unit distance (usually in normalized units of g/cm2, which is the linear distance times the density of the medium). The mass energy absorption coefficient determines the fractional energy deposition per unit distance traveled.

ABSORBED DOSE

Dose and Dose Rate

Absorbed dose is defined as the mean energy, e, imparted by ionizing radiation to matter of mass m. The unit for absorbed dose is gray (Gy).

Exposure often is confused with absorbed dose. Exposure is defined only in air for gamma rays or photons and is the charge of the ions of one sign when all electrons liberated by photons are completely stopped in air of mass. The unit of exposure is coulombs per kilogram of air.

Exposure and dose are used interchangeably in some publications, even though this is not correct.

Dose Rate

Dose rate is the dose expressed per unit time interval. The dose rate delivered to the thyroid by ^{99m}Tc for a nuclear medicine scan, for example, diminishes with time because of the 6.0-hour half-life of the nuclide. The total dose is a more pertinent quantity in this case because it can be related directly to risk and compared with the benefit of the thyroid scan.

In general, substances in the body are removed through biological processes as well as by radioactive decay; therefore, the effective half-life is shorter than the radiologic half-life.

Equivalent Dose

Ionizing radiation creates ion pairs in a substance such as air or tissue in relatively dense or sparse distribution depending upon the particle. Alpha particles with large mass produce relatively intense ionization tracks per unit distance relative to beta particles, and beta particles produce more dense ionization than gamma rays. The ability to produce more or less ionization per unit path in a medium is expressed by the linear energy transfer (LET). The LET in a substance such as water is readily calculated from the energy loss expressions in the previous sections.

The calculated LET from alpha and beta particles is much greater than it is for gamma rays. In considering the health or cellular effects of each particle or ray, it is necessary to normalize the various types of radiation. For a particular biological endpoint, such as cell death in an experiment with mouse fibroblasts, it is common to calculate a relative biological effectiveness (RBE). This is defined as the ratio of gamma ray dose that yields the same endpoint to the dose from the radiation under study, e.g., cell death.

Although giving the same dose to an organ from alpha particles as opposed to gamma rays would result in greater effects from the alpha particles, such refinement in the normalization of endpoints (cancer) in the human is not possible with the available data. An attempt to normalize human health effects from different types of radiation, i.e., to calculate an “equivalent” dose is made through the values for LET of the various types of radiation in water. The ratio of the LET for gamma to the radiation in question is defined as a radiation weighting factor, wr (formerly Q), and the normalized (or weighted) dose is called the equivalent dose. The unit for the equivalent dose is sievert (Sv).

PROPERTIES AND TOXICITIES OF ANIMALS VENOMS

By Watkings J

INTRODUCTION

The animal kingdom consists of more than 100,000 species spread through major phyla including arthropods, mollusks, chordates, etc. Venomous animals are capable of producing a poison in a highly developed exocrine gland or group of cells and can deliver their toxin during a biting or stinging act. The venom is the sum of all natural venomous substances produced in the animal. Poisonous animals have no mechanism or structure for the delivery of their poisons, and poisoning usually takes place through ingestion. Venomous or poisonous animals are widely distributed through out the animal kingdom, from the unicellular protistan Alexandrium (Gonyaulax) to certain mammals, including the platypus and the short-tailed shrew. At least 400 species of snakes are considered dangerous to humans. Myriad venomous and poisonous arthropods exist, and toxic marine animals are found in almost every sea and ocean.

Animal venom may play a role in offense, as in the capture and digestion of food, in the animal's defense, as in protection against predators or aggressors, or in both functions. In the snake, the venom provides a food-getting mechanism. Its secondary function is its defensive status. The presence of toxic venom in the snake is a superior complement to the animal's speed, size, concealment, or strength. In venomous spiders, toxin is used to paralyze the prey before the extraction of hemolymph and body fluids. The venom is not primarily designed to kill the prey, but it is only to immobilize the organism for feeding. The same can be said for the scorpions, although they to use their venom in defense. In the fishes, such as the scorpion fishes and stone fishes, and in elasmo branches, such as the stingray, the venom apparatus is generally used in the animal's defense. Venoms used in an offensive posture are generally associated with the oral pole, as in the snakes and spiders, while those used in a defensive function are usually associated with the aboral pole or with spines, as in the stingrays and scorpion fishes. Poisonous animals, on the other hand, usually derive their toxins through the food chain. As such, poison is often a metabolite produced by microorganisms, plants, or animals. Poisons are sometimes concentrated as they pass through the food chain from one animal to another.

PROPERTIES OF ANIMAL TOXINS

Venoms are very complex, containing polypeptides, high- and low molecular-weight proteins, amines, lipids, steroids, amino polysaccharides, quinones, glucosides, and free amino acids, as well as serotonin, histamine, and other substances. Some venoms may consist of more than a hundred proteins. The venom is a source of millions of peptides and proteins that act on myriad exogenous targets such as ion channels, receptors, and enzymes within cells and on the cell membrane. The venom is important for several reasons. First, the venom is a source of tools with which to study complex physiologic systems, such as the cardiovascular system, nervous system, coagulation, and homeostasis. Second, the venom is a source of potential new drugs, with at least five agents already on the market and dozens undergoing preclinical or clinical trials Third, additional knowledge on the composition and the function of venoms is hoped to favor development of improved protection against envenomations.

Novel instrument developments have permitted the greater application of mass spectrometry, coupled with various separation technologies, to tease out the complexity of natural venoms, thereby identifying the peptide and protein components of venom. The technology allows considerable resolution of extremely small amounts of venom.

Many snail venoms are studied by its fractionation. For example, cone snail venom was fractionated into numerous peptides with varying activities. Similar fractionations have been performed on many other venoms. Unfortunately, studying the chemistry, pharmacology, and toxicology of venoms requires isolating and dismantling the venoms and losing the synergy among multiple components. Nevertheless, advanced technology will permit peptide sequencing, and the characterization of post-translational modifications, such as glycosylation, and the discovery of new pharmacophores. Most venoms probably exert their effects on almost every cell and tissue, and their principal pharmacologic properties are usually determined by the amount of a fraction that accumulates at an activity site. It is clear from Table 26-1 that there is an extremely large range in the LD50 of different toxic compounds and venoms injected intravenously into mice.

Table 26-1
Intravenous LD_{50}s of Selected Toxins Determined in Mice

TOXIN SOURCE	COMMON NAME	LD_{50} (μg/kg)
Clostridium botulinum	Botulinum toxin	0.0003
Crotalus viridis helleri	Southern pacific rattlesnake	1.3
Crotalus adamanteus	Eastern diamondback	1.5
Oxyuranus scutellatus	Australian taipan	2
Crotalus atrox	Western diamondback	2.2
Agkistrodon piscivorus	Eastern cottonmouth	4
Agkistrodon contortrix	Copperhead	11
Androctonus australis	North African scorpion	17
Notechis scutatus	Australian tiger snake	25
Naja siamensis	Indochinese spitting cobra	75

SOURCES: Data from Mebs (2002) and Russell (2001).

The bioavailability of a venom is determined by its composition, molecular size, amount or concentration gradient, solubility, degree of ionization, and the rate of blood flow into that tissue, as well as the properties of the engulfing surface itself. The venom can be absorbed by active or passive transport, facilitated diffusion, or pinocytosis, among other physiologic mechanisms. Besides the bloodstream, the lymph circulation not only carries surplus interstitial fluid produced by the venom, but also transports larger molecular components and other particulates back to the bloodstream. Thus, the larger toxins of snake venoms, particularly those of Viperidae, probably enter the lymphatic network preferentially and then are transported to the central venous system in the neck. Because lymphatic capillaries, unlike blood capillaries, lack a basement membrane and have fibroelastic “anchoring filaments,” they can readily adjust their shape and size, facilitating absorption of excess interstitial fluid along with macromolecules of a venom.

The site of action and metabolism of venom is dependent on its diffusion and partitioning along the gradient between the plasma and the tissues where the components are deposited. Once the toxin reaches a particular site, its entry to that site is dependent on the rate of blood flow into that tissue, the mass of the structure, and the partition characteristics of the toxin between the blood and the particular tissue. Receptor sites appear to have highly variable degrees of sensitivity. In the case of complex venoms, there may be severalifnotmanyreceptorsites.Thereisalsoconsiderablevariability in the sensitivity of those sites for the different components of a venom.

A venom may also be metabolized in several or many different tissues before undergoing excretion. Some components of a venom are metabolized distant to the receptor site(s) and may never reach the primary receptor in a quantity sufficient to affect that site. The amount of a toxin that tissues can metabolize without endangering the organisms may also vary. Organs or tissues may contain enzymes that catalyze a host of reactions, including deleterious ones. Once a venom component is metabolically altered, the end substance is excreted primarily through the kidneys. The intestines play a minor role, and the contributions by the lungs and biliary system have not been determined. Excretion may be complicated by the direct action of the venom on the kidneys themselves.

ARTHROPODS

There are more than a million species of arthropods, generally divided into 25 orders, of which at least 12 are of importance to humans from an economic stand point. Medically, however, only about 10 orders are of significant venomous or poisonous importance. These include the arachnids (scorpions, spiders, whip scorpions, solpugids, mites, and ticks); the myriapods (centipedes and millipedes); the insects (water bugs, assassin bugs, and wheel bugs); beetles (blister beetles); Lepidoptera (butterflies, moths, and caterpillars), and Hymenoptera (ants, bees, and wasps). Several texts and papers that deal with venomous and poisonous arthropods are available (Bettini, 1978; Pick, 1986; Cohen and Quistad, 1998; Russell, 2001; Kuhn-Nentwig, 2003; Isbister et al., 2004).

The number of deaths from arthropod stings and bites is unknown. In Mexico, parts of Central and South America, North Africa, and India, deaths from scorpion stings, for instance, exceed several thousand a year. Spider bites probably do not account for more than 200 deaths a year worldwide. A common problem faced by physicians in suspected spider bites relates to the differential diagnosis. The arthropods most frequently involved in the misdiagnoses were ticks (including their embedded mouthparts), mites, bedbugs, fleas (infected flea bites), Lepidoptera insects, flies, vesicating beetles, water bugs, and various stinging Hymenoptera. Among the disease states that were confused with spider or arthropod bites or stings were erythema chronicum migrans, erythema nodosum, periarteritis nodosum, pyroderma gangrenosum, kerion cell-mediated response to a fungus, Stevens– Johnson syndrome, toxic epidermal necrolysis, herpes simplex, and purpura fulminans. Any arthropod may bite or sting and not eject venom. Finally, some arthropod venom poisonings accentuate the symptoms and signs of an existing undiagnosed subclinical disease.

ARACHNIDA

Scorpions

Of the more than 1000 species of scorpions, the stings of more than 75 can be considered of sufficient importance to warrant medical attention.

Spiders

Of the 30,000 or so species, at least 200 have been implicated in significant bites on humans. Spiders are predaceous, polyphagous arachnids that generally feed on insects or other arthropods. All spiders except the Uloboridae family possess a venom apparatus that produces neurotoxins designed to paralyze or kill prey.

Ticks

Many of the approximately 900 species of ticks are associated with disease in humans and wild and domesticated animals. Tick paralysis is caused by the saliva of certain ticks of the families Ixodidae, Argasidae, and Nuttalliellidae.

CHILOPODA (CENTIPEDES)

Found world wide, these elongated, many-segmented brownish yellow arthropods have a pair of walking legs on most segments, and they are fast moving, secretive, and nocturnal. They feed on other arthropods and even small vertebrates and birds. The first pair of legs behind the head is modified into poison jaws. Centipedes range in length from 3 mm to almost 300 mm. In the United States, the prevalent biting genus is a Scolopendra species. The venom is concentrated within the intracellular granules, discharged into vacuoles of the cytoplasm of the secretory cells, and moved by exocytosis into the lumen of the gland; from thence ducts carry the venom to the jaws.

The bite produces two tiny punctures, sharp pain, immediate bleeding, redness, and swelling often lasting for 24 hours. Localized tissue changes and necrosis have been reported, and severe envenomations may cause nausea and vomiting, changes in heart rate, vertigo, and headache. In the most severe cases, there can be mental disturbances.

DIPLOPODA (MILLIPEDES)

Ranging in length from 20 to 300 mm, these arthropods are cylindrical, worm-like creatures, to dark brown or black in color, and bearing two pairs of jointed legs per segment. In Australia and New Guinea particularly, the repellent secretions expelled from the sides of their bodies contain a toxin of quinone derivatives plus a variety of complex substances such as iodine and hydrocyanic acid, which the animal makes use of to produce hydrogen cyanide. Some species can spray these defensive secretions, and eye injuries are not uncommon. The lesions produced by millipedes consist of a burning or prickling sensation and development of a yellowish or brown-purple lesion; subsequently, a blister containing serosanguinous fluid forms, which may rupture. Eye contact can cause acute conjunctivitis, periorbital edema, keratosis, and much pain; such an injury must be treated immediately.

INSECTA

Heteroptera (True Bugs)

The clinically most important of the true bugs are the Reduviidae (the reduviids): the kissing bug, assassin bug, wheel bug, or cone nose bug of the genus Triatoma. Generally, they are parasites of rodents and common in the nest softwood rat or in wood piles. These are elongated bugs with freely movable, cone-shaped heads, and straight beaks. The most commonly involved species appear to be Triatoma protracta, Triatoma rubida, Triatoma magista, Reduvius personatus, and Arilus cristatus.

Hymenoptera (Ants, Bees, Wasps, and Hornets)

The Myrmecinae venoms are a mixture of amines, enzymes and proteinaceous materials, histamine, hyaluronidase, phospholipase A, and hemolysins, which hemolyze erythrocytes and mast cells.

Lepidoptera (Caterpillars, Moths, and Butterflies)

The urticating hairs, or setae, of caterpillars are effective defensive weapons that protect some species from predators. The setae are attached to unicellular poison gland sat the base of each hair. Both the larvae and the adults are capable of stinging, either by direct contact with the setae or indirectly when the creature becomes irritated.

MOLLUSCA (CONE SNAILS)

Human interest in this group of mollusks has been due to the beautiful patterns on their shells. Cone snails were known to Roman scholar sand natural history collectors, as the shells were often made into jewelry. The first record of fatality from cone snail sting may be found in the book of Rumphius from 1705. The genus Conus is a group of some 500 species of carnivorous predators found in marine habitats that use venom as a weapon for prey capture. Cone snails have a venom duct for synthesis and storage of venom and hollow harpoon-like teeth for injection of the venom.

There are probably over 100 different venom components per species. Components have become known as conotoxins, which may be rich in disulfide bonds, and cono peptides. Molecular targets include G-protein-coupled receptors and neuromuscular transporters, ligand- or voltage-gated ion channels. Some components have enzymatic activity.

REPTILES

Lizards

The Gila monster (Heloderma suspectum) and the beaded lizards (Helodermahorridum) are divided into five subspecies. These large, corpulent, relatively slow moving, and largely nocturnal reptiles have few enemies other than humans. They are far less dangerous than is generally believed. Their venom is transferred from venom glands in the lower jaw through ducts that discharge their contents near the base of the larger teeth of the lower jaw. The venom is then drawn up a long grooves in the teeth by capillary action. The venom of this lizard has serotonin, amine oxidase, phospholipase A, a bradykinin-releasing substance, helodermin, gilatoxin, and low proteolytic as well as high-hyaluronidase activities, but lacks phosphomonoesterase and phosphodiesterase, acetylcholinesterase, nucleotidase, ATPase, deoxyribonuclease, ribonuclease, amino acid oxidase, and fibrinogeno-coagulase activities. The clinical presentation of a helodermatid bite can include pain, edema, hypotension, nausea, vomiting, weakness, and diaphoresis.

Snakes

Snakes have a three chambered heart and rely almost exclusively upon an enlarge dright lung (that spans approximately half of the body length) for respiration. Of the approximately 2700 known species of snakes, about 20% are considered to be venomous. Venomous snakes primarily belong to the following families: Viperidae (vipers), Elapidae, Atractaspidae, and Colubridae. The vipers are further divided into subfamilies, and example of which is the Crotalinae, or pit vipers, which possess a pit between the eyes and no strils that serves as a heat sensor to detect warm-blooded animals. Some of the subfamilies are regarded as separate families altogether depending on the classification scheme. Overall the Colubridae are considered the largest venomous family, and are comprised of nearly 60% of all snakes. The Atractaspidae family, recently classified within the Viperidae, is known for burrowing into the ground and possessing the ability to expose their fangs without opening their mouth.

The Viperidae fang structure is regarded as the most developed and efficient means of venom, or toxin, delivery to prey. The venom gland is positioned at the base of a long (~30mm) hollow retractable fang. Muscle pressure on the gland determines the amount of venom released. Another highly developed venom delivery apparatus is characteristic of the spitting cobras, aptly named for their ability to project venom via glands that protrude from the base of the fang opening. Venom is carried toward the prey, or target, via forceful exhalation that is accompanied by a hissing sound. Toxin delivery via venom exposure is the primary mechanism by which snakes immobilize and kill their prey. Toxin type and specificity is dependent on the species; however, most venom comprises of complex networks of toxins that affect variable organ systems and interact with one another increasing the overall potency.

It is estimated that there are over 2.5 million snakebites annually, and that over 100,000 victims will die (White, 2005). Information resources available to physicians on management of snakebite victims may be found at the Clinical Toxinology Resources Website—www.toxinology.com or other appropriate references.

Actions of snake venoms can be said to be broad ranging in several areas. A simplistic approach would group toxin components as neurotoxins, coagulants, hemorrhagins, hemolytics, myotoxins, cytotoxins, and nephrotoxins. Neurotoxins produce neuromuscular paralysis ranging from dizziness to ptosis; to ophthalmoplegia, flaccid facial muscle paralysis, and inability to swallow; to paralysis of larger muscle groups; and finally to paralysis of respiratory muscles and death by asphyxiation. Coagulants may have initial procoagulant action that uses up clotting factors leading to bleeding. Coagulants may directly inhibit normal clotting at several places in the clotting cascade or via inhibition of platelet aggregation. In addition, some venom components may damage the endothelial lining of blood vessels leading to hemorrhage. Bite victims may show bleeding from nose or gums, the bite site, in saliva, urine, and stools. Myotoxins can directly impact muscle contraction leading to paralysis or cause rhabdomyolysis or the break down of skeletal muscle. Myoglobinuria, or a dark brown urine, and hyperkalemia may be noted. Cytotoxic agents have proteolytic or necrotic properties leading to the break down of tissue. Typical signs include massive swelling, pain, discoloration, blistering, bruising, and wound weeping. Sarafo toxins, which are found only in burrowing asps of Afro-Arabia, cause coronary artery constriction that can lead to reduced coronary blood flow, angina, and myocardial infarction. Finally, nephrotoxins can cause direct damage to kidney structures leading to bleeding, damage to several parts of the nephron, tissue oxygen deprivation, and renal failure.

ANTIVENOM

Antivenoms have been produced against most medically important snake, spider, scorpion, and marine toxins. Animals immunized with venom develop a variety of antibodies to the many antigens in the venom. Antivenom consists of venom-specific antisera or antibodies concentrated from immune serum to the venom. Antisera contain neutralizing antibodies: one antigen (monospecific) or several antigens (polyspecific). Monovalent antivenoms have a high neutralization capacity, which is desirable against the venom of a specific animal. Polyvalent antisera are typically used to cover several venoms, such as snakes from a geographic region. Polyvalent preparations usually required higher doses or volumes than monovalent antivenoms. Neutralization capacity of antivenom is highly variable as there are no enforced international standards. Antivenom may cross-react with venoms from distantly related species and may not react with venom from the intended species. Nevertheless, in general, the antibodies bind to the venom molecules, rendering them ineffective.

POTENTIAL CLINICAL APPLICATION OF VENOMS

Animal venoms are being used as research and clinical tools based upon their high affinity for specific targets and well-studied pharmacologic properties.

Other areas of active research indicate that animal venoms contain components that can reduce pain, can selectively kill specific cancers, may reduce the incidence of stroke via effects on blood coagulability, and function as antibiotics.

Another major area of investigation and success involves the venom components that act as enzyme inhibitors.

Venom toxins can also be used as a component of the toxin– receptor–antibody complex for diagnosis of autoimmune disorders.

TOXIC EFFECTS OF PLANTS

By Norton S.

INTRODUCTION

Plants may cause toxic effects as a result of inadvertent exposure on contact or accidental ingestion of the plant. Examples are “hay fever” (rhinitis) from exposure to airborne plant pollen and oral irritation, especially in children, from biting on a leaf of a plant such as dumb cane (Diffenbachia). Another source of toxicity may be from intentional ingestion of some herbs, especially when they are taken chronically. The possibility also exists for interactions of prescribed drugs with intake of herbal remedies. For example, the chemicals in some herbs affect hepatic cytochrome enzymes (Izzo and Ernst, 2001).

In recent years, information on bioactive chemicals in plants has grown steadily, partly from increased interest in herbal remedies and from interest in identifying novel approaches to medical problems. One result of the latter interest is that toxic effects of plants are being examined for potential usefulness in cancers. This chapter will be restricted primarily to consideration of the toxic effects of plants from unintentional exposure and some intentional exposures, with only brief mention of possible value of toxic bioactive components.

In the course of evolution, plants have been attacked by viruses, bacteria, and fungi, and have been eaten by animals of many kinds. In response, plants have developed various elegant defenses, including synthesis of antimicrobial chemicals and chemicals designed to repel animals by various means. Of the many species of plants that contain toxic chemicals, only a few can be described here. Selection is based on three considerations: frequency with which exposure occurs; importance and seriousness of the exposure; and the scientific understanding of the nature of the action of the chemical.

In considering any chemical synthesized by a plant it is important to note that there may be marked variability in the amount of a toxic chemical produced by a plant. The reasons for variability in concentration of toxic chemicals are several:

1. Different portions of the plant may contain different concentrations of a chemical. An example of localization of bioactive compounds is found in the bracken fern (Pteridium aquilinum) in which the carcinogenic terpene, ptaquiloside, is found in high concentrations in the fronds compared with the roots.

2. The age of the plant contributes to variability. Peak concentrations of bioactive compounds often are found at different periods of growth. For example, in lettuce (Lactuca species) the concentration of lactucin and other sesquiterpenes increases with maturation, reaching a peak in the latex when the flower stalk is forming.

3. Climate and soil influence the synthesis of some chemicals. For example, lichens produce carotenoids in direct relation to the amount of sunlight, with the advantage to the plant that carotenoids protect from excessive ultraviolet light.

4. Genetic differences within a species alter the ability of plants to synthesize a chemical. Synthesis of related toxic chemicals is found in some plants as a characteristic of a genus and sometimes as a familial characteristic. For example, species of Raunculus (buttercup) produce an acrid juice that releases the irritating chemical, anemonin. Some other genera of the same family (Ranunculaceae) also release anemonin.

TOXIC EFFECTS BY ORGANS

Tissue/organ	Clinical manifestation/Symptoms
Skin	Contact dermatitis:
	Allergic Dermatitis
	Photosensitivity
Respiratory Tract	Allergic Rhinitis
	Cough Reflex
	Toxin-Associated Pneumonia
Gastrointestinal System	Direct Irritant Effects (nausea, vomiting, and diarrhea)
	Antimitotic Effects
	Protein Synthesis Inhibition
Cardiovascular System	cardioactive glycosides
	ActionsonCardiacNerves
	Vasoactive Chemicals
Liver	Hepatocyte Damage
	Mushroom toxins
Kidney and Bladder	Carcinogens
	Kidney Tubular Degeneration: Acute/Chronic renal failure.
Blood and Bone Marrow	Anticoagulants
	BoneMarrowGenotoxicity
	Cyanogens
Nervous System	Epileptiform Seizures
	Excitatory Amino Acids
	Motor Neuron Demyelination
	Cerebellar Neurons
	Parasympathetic Stimulation
	Parasympathetic Block
	Sensory Neuron Block
Skeletal Muscle and Neuromuscular Junction (blockage)	
Bone and Tissue Calcification	
Reproduction	Abortifacients
Teratogenesis	Teratogens

Summarizing, a great variety of toxic chemicals have been produced by plants for their own protection from the environment and from predators, including pathogenic organisms. These defensive chemicals have been both deleterious and beneficial to humans. Throughout history a select number have been incorporated into therapy against disease and to combat morbidity, often with considerable success. Morphine from the latex of the opium poppy is an ancient historical example. If fungi are included with plants (as they are in this chapter), defensive chemicals of plants are responsible for some of our more successful therapies, such as antibiotics of the penicillin type and therapy for cancer. On balance, in spite of the long list of dangerous toxic chemicals from plants, it is fair to conclude that plants have proved therapeutically more useful than harmful to humans. Finally, there is simply the pleasure of scientific inquiry into the successful adaptations of plants to their complex and often hostile environments.