Chapter 14

PESTICIDES

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INTRODUCTION

A *pesticide* is any substance or mixture of substances that prevents, destroys, repels, or mitigates any pest. A *pest* is any animal or plant that can injure the environment or the health of populations in that environment. This definition allows any of the following terrestrial or aquatic plant or animal life to be classified as pests: insects, rodents, nematodes, fungi, weeds, viruses, bacteria, or other microorganisms (except those on or within living humans or other animals). The administrator of the Environmental Protection Agency (EPA) determines which organisms qualify as pests.[1]

As part of a unified effort, all scientists, managers, and those who apply pesticides must consider the potential risks associated with the applications of pesticides before using them. Military goals are to (*a*) use pesticides judiciously and (*b*) minimize introducing these toxic materials into the environment. Nonchemical pest-control measures are given first consideration; chemical controls are initiated only if nonchemical control measures fail, or if the situation dictates that chemical controls are the only option.

Pesticides are unique among toxic materials: to be effective, they must be purposely introduced into the pests' environments. Not only other animals and plants but also humans share this environment with the pests. Excessive residues that result from misapplication and residues that migrate from target areas into areas of environmental concern, such as groundwater, are just two of the serious problems associated with pesticide use.

The risks of using pesticides must be weighed against the benefits. The problem has been and continues to be our inability to fully identify the risks associated with the introduction of pesticides into the environment. For example, the thinning of bird eggshells from the bioaccumulation of dichlorodiphenyltrichloroethane (DDT) and the controversy that surrounded the defoliant Agent Orange (a mixture of approximately 50% dichlorophenol [2,4-D] and 50% trichlorophenol [2,4,5-T], with trace amounts of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin [TCDD] contamination) after the Vietnam War were unanticipated pesticide risks. Although the acute effects on both the environment and human health may be known, there is a paucity of information on the chronic effects that result from long-term exposures to pesticide residues. Therefore, every precaution and form of protection must be taken whenever pesticides are used.

MILITARY USES OF PESTICIDES

Pesticides are necessary in the military to protect (*a*) human health, (*b*) products in storage, (*c*) natural resources, and (*d*) property, just as they are in civilian life. The military has an enormous investment in human resources, facilities, and natural resources, and adequate protection of this investment often requires the use of pesticides.

Protecting Human Health

The mission of the U.S. Army Medical Department (AMEDD) is to conserve the fighting strength. Because arthropod-borne diseases are major risks to human health, this mission requires that pesticides be used; worldwide contingency operations necessitate that AMEDD be prepared to protect its troops adequately against diseases such as malaria, typhus, plague, leishmaniasis, encephalitis, and dengue. In the United States, Lyme disease has emerged as an important tick-borne disease and has renewed the effort for using skin and clothing repellents to protect troops during field exercises. Pesticides used both as personal protection (such as repellents and pediculicides [louse powders]) and area control (such as mosquito larvicides and adulticides) are available to assist in preventing the spread of pest-borne diseases.

To protect against the health hazards associated with pesticides, the military must also conduct adequate risk-benefit analyses before using them. For example, herbicides were used as defoliants during the Vietnam War to help members of the U.S. military see the enemy in the dense jungle. Agent Orange was used widely. Its formulation was contaminated with dioxin, however, and because the contaminant is toxic, controversy raged for years in the United States over the use of Agent Orange. This controversy underscores the need for adequate risk-benefit analyses to be conducted when military forces could be present while pesticides are being applied or might be exposed to them after their application. Specifically, the assessment must evaluate the risk to the troops from the pest (arthropod-borne diseases or dense vegetation providing cover for enemy soldiers) versus the risks to troops if pesticides are used to minimize these

risks. If the benefits of using pesticides outweigh the risks associated with their use, then pesticides should be considered weapons.

Roosting birds can cause serious health problems in hospitals and dusty work areas. Bird feces can contain numerous pathogens that cause psittacosis and such mycotic diseases as histoplasmosis and cryptococcosis. These can be transmitted throughout a hospital via its ventilation system, especially if bird feces contaminate the ducting. When fecal-contaminated dust travels as suspended particulates in air and is inhaled, unprotected individuals can contract clinical illnesses such as mycoses or respiratory diseases, or develop skin lesions or subclinical infections manifested only by subtle changes in specific antibody titers.

The military uses more pesticides to control cockroaches than to control any other pest species. Cockroaches transmit disease organisms mechanically: this is the major reason for the continued effort to control them. They are associated with the spread of enteric diseases such as salmonellosis, dysentery, or typhoid. In addition, there is increasing evidence of allergies in humans, which has resulted from cohabiting indoors with cockroaches. While nonchemical control methods—such as appropriate sanitation and reduction of cockroach harborage—are far more effective in controlling cockroach populations, pesticide treatments in food areas and in military housing continue to be necessary.

Protecting Stored Products

The Stored Products Pest Management Program, conducted within the Department of Defense (DoD), consists of an integrated system of storage, quality assurance, and pest-management activities. These activities are designed to prevent or control insects and rodents that attack infestable stored products such as food and fiber items. Failure to comply with proper storage procedures may result in substantial economic losses caused by pest damage. Pesticides are an integral part of this program. Applied as residual treatments or airborne area sprays, pesticides provide a barrier between the pests and the stored products. Without such protection, insects (such as grain beetles, moths, and weevils) and rodents (such as mice and rats) would contaminate or destroy items such as flour, cereal, rice, and dried fruit.

Protecting Natural Resources and Military Property

The military, with millions of acres of land on its installations and bases, uses pesticides to protect valuable natural resources such as forests and wildlife and protect against pest populations that inhibit military activities or damage property. For example, trees are a valuable natural resource that need to be protected from the gypsy moth. Wooden buildings need to be protected from termites and other wood-destroying insects.

Populations of rodents such as prairie dogs or rats may exceed the natural carrying capacity of the area; rodenticides may be needed to reduce these populations, especially if the burrows impede the use of military equipment in the area or a plague outbreak should occur that may threaten human populations. In these instances, pesticides may be required to reduce the rodent population quickly, rather than rely on natural controls such as predation.

Pests such as birds that congregate near airports are hazardous to aircraft, crews, and passengers; an avicide can promptly reduce the hazard. Birds, particularly pigeons, can also become a serious problem when they roost in warehouses. In addition to their association with illness and contamination of stored foods, roosting birds' acidic feces can deface buildings and accelerate the deterioration of equipment.

Termites and other wood-destroying insects cause tremendous building damage and economic loss on military installations. However, as a result of the environmental persistence of the chemical constituents of pesticides and the potential for adverse human health effects from these constituents, the military uses of pesticides to control termites have changed from the use of persistent chlorinated hydrocarbon pesticides (such as chlordane) to less persistent pesticides (such as chlorpyrifos). These changes in termite management—more frequent applications of less persistent termiticides—have, paradoxically, increased the risk of exposure.

Protecting Against Exposure

The safe application of pesticides requires that precautions be taken to protect against acute or chronic exposures to pesticide residues that may cause poisoning. While acute pesticide poisoning symptoms are well documented, a paucity of information exists on effects of long-term exposure to pesticide residues. For this reason, protecting against the unknown chronic health effects, as well as acute health effects, warrants minimizing human exposure to pesticide residues.

Routes of Exposure

The purposeful introduction of pesticides into the environment can cause not only the worker who applies the pesticide (the applicator) but also unsuspect-

ing bystanders or passersby to be exposed to pesticide residues via (*a*) dermal contact, (*b*) inhalation, and (*c*) ingestion.

Dermal contact, the most frequent route of pesticide exposure, can occur during applications of liquid sprays, dusts, and granules. Preparing mixed or diluted solutions from concentrated pesticides may cause considerable dermal exposure if a spill occurs.

Pesticides can cause mild-to-severe skin injury depending on the particular pesticide and formulation involved. Severe internal poisoning may occur if sufficient pesticide is absorbed through the skin into the blood, and is transported to the internal organs.

Inhalational or respiratory exposures can also occur from pesticides during mixing or application, although this exposure route is usually much less likely than the dermal route. If inhaled, pesticides can be absorbed into the lungs and transported to other organs via the blood.

Ingestion is not usually a significant hazard for careful workers, but it can be a dangerous exposure route, especially if pesticide spray or dust is splashed into the mouth during mixing or application, or if contaminated foods or beverages are consumed. Pesticides can also be ingested if the applicator smokes while mixing or applying them. Ingested pesticides, after passing through the linings of the mouth, stomach, and intestine, are easily absorbed into the blood.

Reducing the Hazards

The hazards that pesticides present to human health are mitigated by using personal protective equipment (PPE) and the appropriate engineering controls; PPE must be used whenever pesticide exposure will occur in excess of accepted action levels[2] or the permissible exposure limit.[3] By consensus, unless otherwise defined, action levels are usually defined as a concentration equal to one-half the Occupational Safety and Health Administration's (OSHA's) permissible exposure limit (PEL), which is the statutory exposure limit. The American Conference of Governmental Industrial Hygienists (ACGIH) recommends acceptable exposure limits, known as Threshold Limit Values (TLVs, a registered trademark of the ACGIH).[2] Protection from exposure should be provided at whichever action level is lowest (either the limit required by OSHA or the limit recommended by the ACGIH).

Protecting Pesticide Workers

Protection against pesticide exposure to military personnel who apply pesticides is afforded by both engineering controls and PPE. Engineering controls are aimed at containing or reducing the spread of pesticides. These measures are particularly important for the activities performed in pest-control facilities, such as diluting and mixing pesticides. Engineering controls can pertain to the design of ventilating systems, plumbing, fire protection, emergency shower and eyewash fountains, and personnel locker and bathing facilities.

PPE provides a barrier that precludes or limits an individual's exposure to pesticides (Table 14-1). Depending on the pest-management operation being conducted, more than one type of PPE may be necessary. For example, a waterproof jacket and pants should be worn if a spraying operation could cause the required coveralls to become wet. In addition, label instructions may indicate that a specific respirator be used with that product. Such respirators might include a dust mask, canister-type gas mask, or self-contained breathing apparatus.

Training is essential for pesticide applicators, to prevent or reduce their potential exposures. Specific issues that must be addressed in training include the benefits of using engineering controls, as well as the appropriate selection and use of PPE. Other essential training issues include the hazards of specific pesticides, possible adverse health effects from exposure, emergency first aid, decontamination procedures, and emergency responses to spills. Workers must be informed that a subtle exposure hazard potential may be associated with pesticides that have long-lasting residues. The training must emphasize that workers could be chronically exposed to pesticides if engineering controls fail to operate properly or if the PPE is defective or worn improperly.

All workers who receive, handle, store, and apply pesticides must

- demonstrate proper handling of pesticides,
- know proper clean-up procedures for pesticide spills,
- initiate appropriate spill notification or reporting, and
- have access to a pesticide-spill kit.

Cleanup procedures, including a notification channel, should be posted in the vicinity of the kit. After training, workers should be able to demonstrate that they are capable of

- recognizing the inherent toxicity of the particular pesticide products they apply,
- using available engineering controls and recognizing when the controls are functioning

TABLE 14-1

PERSONAL PROTECTIVE EQUIPMENT (PPE)

PPE	Requirement
Apron	Waterproof, made from synthetic material or rubber; use for mixing pesticides.
Boots	Waterproof, made from synthetic material or rubber.
Clothing	Clean coveralls or outer clothing; change daily; waterproof jacket or pants if using liquid formulations. Do not wear over street clothes.
Faceshield	Use when handling or mixing.
Goggles or full-face respirator	Use when handling or applying.
Gloves	Waterproof, unlined, made from synthetic material or rubber.
Hat	Waterproof, wide-brimmed with nonabsorbent headband.
Respirator	Cartridge-type approved for pesticide vapors, unless label specifies another type (dust mask, self-contained breathing apparatus).

improperly,
- determining when PPE is necessary,
- properly donning and doffing PPE to limit exposure potential,
- properly disposing of unused pesticides, and
- properly decontaminating equipment.

Protecting Bystanders

It is equally important to protect other people from exposures that may occur during or after the application of pesticides. This type of exposure is insidious because the individual may not be aware of the pesticide and its potential exposure hazard. However, the hazard to these individuals is often largely reduced if appropriate techniques are followed during application and if diluted pesticides are used.

Those who apply pesticides to buildings (offices, homes, barracks, and so forth) should carefully advise the occupants of the potential hazards. The occupants should be instructed to alert the pesticide applicators if there are signs of inappropriate application such as wet spots or puddles. The occupants should also be carefully instructed concerning their time of reentry into the treated building and safety practices associated with baits and traps. Pesticides that have a significant residual time are hazardous to humans if application procedures have been faulty.

PREPARATION OF PESTICIDES

Pesticide chemicals as they are produced by the manufacturer are usually highly concentrated, will not mix well with water, and may not be chemically stable. To enhance storage, handling, and application of pesticides, *carriers* (solvents, clays, surfactants, or stabilizers) are added to the active ingredient to create a pesticide formulation.

Formulations

The most common pesticide formulations are (*a*) sprays, (*b*) dusts, (*c*) granules, (*d*) aerosols, and (*e*) fumigants. Sprays can be prepared from a number of liquid formulations with various carriers such as water, oil, and other adjuncts (Table 14-2). Dusts are finely ground materials of either undiluted pesticide or the pesticide mixed with an inert diluent. Granular pesticides are small pellets manufactured from inert clays that are sprayed with a solution of the pesticide. Aerosols are pressurized sprays that use a propellant to disperse the pesticide, while fumigants are gaseous forms of a pesticide.

Pesticides must be formulated to improve properties such as storage, mixing, application, efficacy, and safety before they can be used. For example, certain ingredients of pesticide formulations are designed to increase water solubility for their use as diluted sprays, or incorporated into solid matrices for their use as granules. The resulting product (or formulation) includes not only chemicals (in pure or technical-grade

TABLE 14-2

FORMULATIONS OF PESTICIDE SPRAYS

Formulation Type	Definition
Emulsifiable concentrate	Concentrated oil solution of technical-grade pesticide to which an emulsifier, a detergent-like material, is added. When added to water, the emulsifier causes the oil to disperse uniformly.
Wettable powder	Pesticide dusts to which a wetting agent is added to facilitate the mixing of the powder with water.
Flowable or sprayable suspension	Blend of a technical-grade pesticide with a dust diluent and a small quantity of water. This finely ground, wet formulation mixes well with water.
Water-soluble powder	Finely ground technical-grade pesticide that dissolves when added to water.
Oil solution	Technical-grade pesticide dissolved in oil and applied as an oil spray.
Ultra-low-volume concentrate	Technical-grade pesticide dissolved in a minimum of solvent. The high concentration of the pesticide's active ingredient (usually > 50%) is applied via special ground or aerial equipment that greatly reduces the volume of pesticide formulation applied.

form) that are active as pesticides but also chemicals that are inactive (or poorly effective) as pesticides. Inactive or inert ingredients also include chemicals that are added to the pesticide, and are intended to improve its distribution and use. In this context, the term inert refers to the pesticide's activity against specific pests and is unrelated to the chemical's inherent potential toxicity to other species, including humans. For example, the formulation's carrier (or vehicle), included to enhance the solubility in water, may be a petroleum-based product that has no direct effect on the pest, but which could be a hazard to those who apply the pesticides if they were to use the product improperly.

Technical-Grade Components

Most pesticides are produced through a series of complex chemical reactions that eventually result in chemically impure mixtures of reaction products. Even when chemically pure, chemicals are used to initiate the industrial process reactions for development of the final pesticide, and the resultant product mixture is chemically diverse. Similarly, naturally occurring pesticides extracted from biological sources are chemically complex mixtures with comparable physical and chemical solvent-extraction characteristics.

Technical-grade pesticide products are complex chemical mixtures that have been developed and licensed for incorporation into commercial pesticide formulations. Technical-grade products contain numerous related, intermediate, production-process-associated compounds. The production of chemically pure organic compounds is technically difficult, expensive, and usually unnecessary to afford acceptable practical activity for use against pests. As a result, technical-grade production chemicals are often used to formulate pesticides and therefore often demonstrate chemical impurities. Technical-grade products derived from controlled chemical reactions conform to a range of chemical diversity. The acceptable range of product purity is defined by the manufacturer's design quality control specifications for each intended use. As a result, chemical mixtures generated for incorporation into pesticide formulations, or subsequent sale for use, usually demonstrate a degree of acceptable variability in the final product.

It is imperative that healthcare providers recognize that pesticides are usually impure mixtures resulting from production-process chemicals that have been combined with other chemicals to produce the final formulation. As such, "pesticides" are not mixtures of pure, chemically discrete unreacted compounds, but are technical-grade quality mixtures, and have solvents or other chemicals added to improve their dispersion or solubility properties.

Similarly, it is important for healthcare providers to recognize that pesticide products stored beyond the

stated shelf life or released into the environment might be contaminated with decomposition products. The presence of technical-grade, intermediate compounds or degradation products can substantially alter the toxic effects of the chemical mixture (in comparison with the pure compound) on biological systems.

The complexity of potential problems can be formidable. For example, the use of chlordane as a termiticide in structures owned by all military services was challenged on the basis of possible long-term sequelae among potentially exposed military members and dependents. All services were required to determine the extent of use of chlordane on every installation, and to define the possible extent of exposures of all family members. It became immediately apparent that sampling and analysis for chlordane products required definition in order to evaluate the possibility for exposure.

The commercial pesticide product chlordane is a complex chemical during both its production and its environmental degradation (Figure 14-1). It is an example of the composition of a technical-grade pesticide. The product is no longer registered for sale to the public, but it is extremely persistent in the environment. As a result, it became the focus of substantial military interest during the 1980s. The controversy concerning potential acute and chronic health effects of this product on military members and their dependents will probably continue to resurface periodically. Therefore, a review of the chemical composition of chlordane serves both as a point of historical interest and as a practical demonstration of the complexity of human exposure and health-risk determination.

Toxicological testing of several of the individual components has resulted in the assignment of differential human-health risks from exposure to the separate compounds of technical-grade chlordane. For example, both chlordane and heptachlor demonstrate variable degrees of activity at the same target organs (ie, both are potential hepatotoxins). Reported differences in acute toxicity in rodents usually indicate that heptachlor is approximately 5-fold more potent than chlordane. In addition, heptachlor has been recognized as a substantially more potent carcinogen than chlordane.[4]

In addition to the concern for environmental degradation over time, the technical-grade composition of chlordane had been reported to change with time. Formulations of chlordane produced before 1951 are known as "early chlordane." The temporal differences in specific composition of technical grade may be related to differences between the incidence of reported hepatoma in mice in 1977 to 1979 and 1989. The later studies have failed to demonstrate an increased incidence of hepatoma reported in earlier studies.[5]

Toxicological and biological activity associated with chemical stereoisomers of the same chemical moiety have been documented for numerous compounds. As an example, the acute toxicity of permethrin is directly correlated with the *cis*/*trans* ratio, with most mammalian toxicity attributable to the *cis* isomer.[6,7]

The best-recognized example is probably the undesirable human toxicity associated with exposure to an intermediate, unwanted, contamination product found in a technical-grade, market formulation of Agent Orange (Figure 14-2). An intermediate compound in the production of the herbicide 2,4,5-trichlorophenol (2,4,5-T) was found to cause a positive response in the rabbit ear toxicology evaluation.[8] The compound that was subsequently identified as the cause of chloracne in humans and hyperkeratosis in livestock was the contaminant 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). The chemical TCDD is an undesired reaction

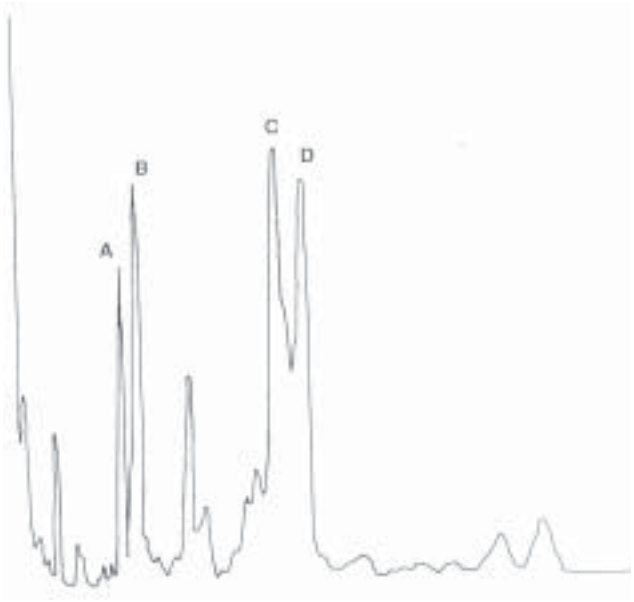

Fig. 14-1. A chromatogram is produced during the analysis of chlordane on federal installations. Careful review reveals a complex composition. Technical-grade chlordane has been identified and selectively defined for compound identification by the ratio of the percentage composition of four of the major components in the mixture. The four major components are electively labeled A, B, C, and D, based on their retention times—from shortest to longest, respectively—using carefully prescribed chromatographic specifications. Peak A is an otherwise unspecified chemical substance known as "compound C." Peak B represents the chemical compound heptachlor, peak C represents *trans*-chlordane, and peak D represents *cis*-chlordane. If the ratio of peaks A+B/C+D approximates 0.8 (range 0.4–1.6), the sample is accepted as representative of technical-grade chlordane.

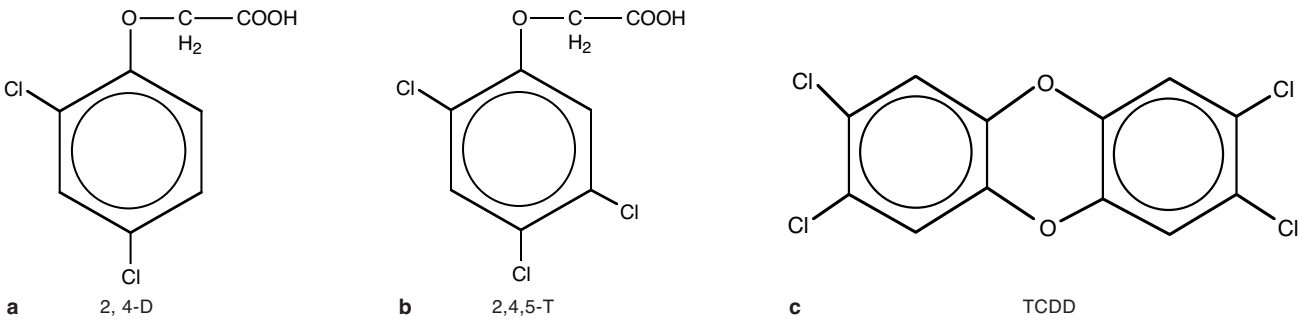

Fig. 14-2. Agent Orange. The chemical structures of the herbicides (**a**) dichlorophenoxyacetic acid (2,4-D) and (**b**) 2,4,5-trichlorophenoxyacetic acid (2,4,5-T); (**c**) represents the structure of the undesirable intermediate dioxin contaminant 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD).

product identified in the production of phenols and hexachlorophene, which is now often chemically removed from technical-grade products before they are formulated. TCDD has neither pesticide nor phenol activity. It is, however, by scientific consensus, the chemical believed to represent the main health hazard associated with exposure to Agent Orange. Another example of undesirable reactions associated with unreacted chemical intermediates was the dermal and respiratory toxicity identified for the chemical hexachlorocyclopentadiene, a contaminant of early chlordane. Specifications for chlordane produced after 1951 limited hexachlorocyclopentadiene concentrations to less than 1%, with a resultant decline in acute adverse dermal and respiratory effects.[5]

In addition to recognizing the differences in toxicity between separate compounds in the marketed pesticide formulation, it is important to recognize the possibility for chemical interactions that may result in exposure consequences for an individual. In selected cases of patient poisonings, healthcare providers may be required to carefully review the available toxicology database for a pesticide to determine if the testing has been done on the isolated, separate, chemical components, technical-grade chemicals, or pesticide formulations.

CLASSIFICATION AND TOXICITY OF PESTICIDES

Pesticides must be approved for use by and registered with the EPA. They can be classified in numerous ways, including their mechanism of action and their chemical structure.

Pesticides do not necessarily kill pests, but in fact may kill, repel, or attract them (Exhibit 14-1). Pesticides are also used as plant regulators, defoliants, and desiccants. Some pesticides are used as *chemosterilants*, which prohibit or limit propagation of the next pest generation. *Growth regulators* retard the growth of plants and insects; *defoliants* remove the leaves of plants; and *desiccants* enhance the destructive drying of plants. Even *antimicrobials* (which include disinfectants, sanitizers, and bacteriostatics) are classified as pesticides and must be registered with the EPA. However, for purposes of this chapter, the word *pesticide* is used in its more traditional sense and is limited to the major categories: insecticides, rodenticides, and herbicides (Table 14-3).

Specific toxicological evaluations to identify potential adverse biomedical responses that could affect workers who apply pesticides, the general public, and the environment are required before the EPA will

EXHIBIT 14-1

CLASSIFICATION OF PESTICIDES BY ACTIVITY

Amphibian and reptile poisons and repellents
Antimicrobial agents
Attractants
Bird poisons and repellents
Defoliants
Desiccants
Fish poisons and repellents
Fungicides
Herbicides
Insecticides
Invertebrate animal poisons and repellents
Mammal poisons and repellents
Plant regulators
Rodenticides
Slimicides

TABLE 14-3

CATEGORIES OF PESTICIDES

Category	Example	Category	Example
Insecticides		***Herbicides***	
Chlorinated hydrocarbons	DDT, lindane, aldrin, chlordane	Inorganic	ammonium sulfate, sodium tetraborate
Organophosphates	malathion, naled, dichlorvos, parathion	Organic arsenicals	cacodylic acid, disodium methanearsonate
Carbamates	carbaryl, propoxur, carbofuran	Phenoxyaliphatic acids	2,4-D; 2,4,5-T; silvex
Foramidines	chlordimeform, amitraz	Substituted amides	propanil, diphenamid, alachlor
Dinitrophenols	dinitrocresol, dinoseb	Nitroanilines and substituted ureas	benefin, trifluralin, monuron, diuron
Organotins	cyhexatin, fenbutatin-oxide	Carbamates	propham, terbucarb
Botanicals	pyrethrum, nicotine, rotenone	Thiocarbamates	pebulate, metham, butylate
Pyrethroids	allethrin, d-phenothrin, fenvalerate	Heterocyclic nitrogens	atrazine, simazine, prometon, picloram
Synergists	piperonyl butoxide, MGK 264	Aliphatic acids	dalapon, trichloroacetic acid (TCA)
Inorganics	sulfur, arsenic, boron	Arylaliphatic acids	dicamba, dimethyl tetrachloro-terephthalate (DPCA)
Fumigants	methyl bromide, ethylene oxide, ethylene dibromide	Phenol derivatives	dinoseb, pentachlorophenol
Microbials	*Bacillus thuringiensis*, Heliothis	Substituted nitriles	dichlobenil, bromoxynil
Insect growth regulators	methoprene, diflubenzuron	Bipyridyliums	diquat, paraquat
Repellents	diethyl-m-toluamide (DEET)		
Rodenticides			
Phosphorus	zinc phosphide, yellow phosphorus		
Coumarins	warfarin, fumarin		
Indanediones	pindone, diphacinone		
Botanicals	red squill, strychnine		
Organochlorines	endrin		

Source: Ware GW. *Fundamentals of Pesticides—A Self-instruction Guide.* Fresno, Calif: Thomson Publications; 1982.

register a pesticide. A number of specific types of toxicological evaluations are considered before EPA registration and as an integral part of the Agency's ongoing review. The classical descriptive toxicological tests are customarily divided into two broad categories: acute or chronic, based on the duration of exposure to the administered toxicant under study.

An acute toxicological evaluation is based on measured biological responses to a single dose (or occasionally several doses) of a test compound within a 24-hour period. When the toxicity of a compound is low, the necessary volume to achieve the required dose often cannot be administered as a single dose, but must be administered in repetitive doses given within that 24-hour period. The observation period following exposure is customarily 7 days, but effects may be recorded for up to several weeks following the administration of acute exposure doses in selected circumstances. The most common acute studies simply record lethal effects; however, some studies record observations of toxic signs such as ataxia, feeding difficulty, or lethargy. (Like its use in clinical medicine, a "sign" in animal studies is defined as a discrete event that can be seen by the observer.)

Toxicological effects are either *quantum* or *continuum* responses. A quantum response is a discrete, yes or no, all or none, numeric phenomenon such as lethal outcome. A continuum response is a graded

response associated with a normal, or accepted, numerical range as well as abnormal levels (those that are reported outside the normal range, such as quantitative concentrations of enzymes identified in a sample of whole blood).

The EPA requires carefully controlled performance and documentation of acute lethality studies, using selected animal models, before a pesticide product can be registered. A specific, acute, toxic response to exposure required by the EPA is the LD_{50} (the dose of the pesticide that is lethal to 50% of the test population of animals under specified test conditions).[1]

Other types of toxicological evaluations that may be useful during the EPA registration process require repetitive administration of test doses of the pesticide over progressively increasing periods of time. Based on the duration of repetitive dosing, toxicology tests have been categorized as subacute, subchronic, or chronic. Subacute toxicological evaluations employ repeated administration of doses of the test compound over a duration of several days to 1 month. Subchronic evaluations are defined as repetitive exposures administered over a period of 1 to 3 months, while chronic studies require administration of the toxicant for longer than 3 months. While subchronic evaluations are customarily used to identify effects of long-term, low-dose exposures on target organs, both subchronic and chronic exposures often focus on the occurrence of carcinogenicity as the measured response. A common form of chronic toxicological study is the 2-year, rodent-lifetime study.

Several additional kinds of evaluations may be required for scientists, regulators, and health professionals to more completely assess potential pesticide toxicity. These evaluations include screening tests for the in vivo or in vitro changes in genetic material that could subsequently be associated with possible carcinogenic sequelae. Of these studies, the most commonly performed screening tool is the Ames test. In this test, the use of a specific strain of histidine-requiring bacteria allows scientists to measure changes in growth and replicative ability of the organisms after exposure to the test compound (see also Chapter 9, Explosives and Propellants). As an adjunct, extracts of rat liver homogenate are added to the usual culture media to simulate the hepatic metabolism of the test material in the "activated" Ames test.

In simplistic terms, positive findings reported from the Ames test result from the interaction of genetic materials and the test pesticide or its activated product. Positive results are recorded following an increased number of bacterial colonies (genetically altered clones) on the test-compound-treated growth media, when compared with the number of colonies recorded on the control bacterial-growth medium. In other words, the potential of the test compound to affect genotoxic alterations is recorded as an increase in the number of colonies on the histidine-deficient, test-compound-treated media, compared to histidine-deficient control culture plates.

Other forms of possible toxicological evaluations include assessments for potential skin or eye effects (the rabbit Draize test), reproductive effects (dominant lethal or multigeneration tests), and human effects (patch testing or epidemiological studies). The approved uses and cumulative toxicity reports associated with any specific pesticide are monitored as an ongoing, continuous EPA administrative process. As a result of these routine reviews or pesticide-use complaints from the general public, a pesticide product registration may be revised or revoked based on accumulated toxicological data and human epidemiological experience.

Both acute and chronic adverse health effects from a host of possible, likely, presumed, and confirmed pesticide exposures have been reported in humans. When applied to the circumstances surrounding human exposures, and subsequent effects, the differentiation between acute and chronic human health effects is based on the total frequency and duration of the exposure profile. Acute exposure effects are those that occur after short-duration, high-concentration, or high-potency exposures. This type of exposure usually results from cutaneous contact during improper application or handling of the more potent pesticide products. Chronic exposures occur over extended periods, with the slow accumulation of the pesticide ultimately resulting in signs or symptoms of exposure. Chronic poisoning can occur as a result of partial failures of PPE, engineering controls, or worker complacency. As a result, repeated exposures to dilute or relatively nontoxic, but biologically cumulative, pesticide products can cause chronic poisoning in pesticide applicators.

"Chronic poisoning" is not comparable to the term "chronic health effect." The health effects associated with chronic poisoning may vary between transient, totally remitting signs or symptoms and permanent, adverse, health sequelae. For example, one who enjoys gardening could suffer exposure to chlordane retained in previously contaminated soil. As a result of the accumulated dose from exposures over time, the gardener could develop a nonspecific convulsive disorder. Correct diagnosis and removal from subsequent exposure could result in complete recovery without adverse sequelae. In comparison, a chronic health effect is a persistent, possibly unremitting consequence of either acute or chronic exposure.

Individuals who have adverse effects after either

acute or chronic exposures are routinely reported in the medical literature in the generic category of "pesticide poisoning." Information gleaned from animal-toxicity studies must be combined with the reported human health effects from pesticide exposure to compile comprehensive disease prevention and medical care programs. Data from both animal-toxicity studies and reported human health effects provide clinically useful information for employee occupational health promotion and symptomatic patient management.

Management of both asymptomatic, healthy workers and symptomatic, poisoned workers can be specifically tailored for the individual, based on the known chemical composition and associated toxic effects of the pesticides in question. Essential information related to biological monitoring, medical surveillance, patient examination, and medical management can be recommended and provided using available cumulative data. However, healthcare providers must exercise caution when human experiences with the pesticide products are limited, or when toxicology information is indirectly extrapolated from animal data without reference to compound-specific, relative interspecies variability.

In workers, acute toxic or chronic exposure effects can occur during manufacture, formulation, mixing, or application of pesticide products. If short-term exposures to high pesticide concentrations occur, the symptomatic onset of poisoning is usually rapid and easily correlated with the coincident exposure profile. In contrast, when relatively low-dose exposures occur over prolonged periods, the pathophysiological responses from the chronic-exposure profile may be extremely difficult to correlate clinically with pesticide-associated sequelae. For example, the etiology of seizure activity associated with acute poisoning during pesticide application is rather easily identified during a cursory history. But the cumulative, chronic retention of pesticide residues may not be recognized as the cause of seizures in the gardener who experiences subtle, prolonged exposures to carbamate pesticides during grounds maintenance, but who does not display the usual associated acetylcholinesterase depression.

Workers associated with pesticide application, the general population, and the environment can be affected either acutely or chronically by exposure to pesticide products or residual products of degradation. Chronic biomedical responses to low-level, long-term exposure profiles may range from no apparent adverse health impact to overt clinical signs of poisoning. The possibility of chronic health impacts resulting from subtle exposures provides the theoretical and philosophical bases for biological monitoring and medical surveillance in pesticide-associated workers.

Pesticides that resist biological degradation or have limited environmental translocation are said to be environmentally persistent; such pesticides can cause subtle, prolonged human exposures. There may be no known correlation between low-level exposures to residual pesticide concentrations and known health effects. However, residual levels of organochlorine insecticides that have low comparative acute toxicities have been associated with the onset of seizures in gardeners, and have been predicted to cause an increased risk for carcinogenicity in exposed populations.[4]

Acute and chronic adverse health effects based on the duration of exposure to pesticides have been reported in humans. Patients said to be "poisoned" or "intoxicated" have adverse clinical signs or symptoms following pesticide exposure. Acute poisoning can result from mixing and applying pesticides, when the exposure to relatively high concentrations of the pesticide occurs over a relatively short time. Obviously, this type of intoxication is of particular concern to individuals who manufacture, formulate, or apply pesticides. These are the workers most likely to be seen with the chronic toxic effects that result from long-term exposures to relatively small quantities of pesticides that produce no apparent acute adverse biomedical effect, but which produce an accumulative, detectable alteration with increasing exposure time.

Workers who apply pesticides and those in the general public who continually experience involuntary exposures secondary to environmental contamination can have adverse health effects from chronic exposure to pesticides. The public may be exposed to pesticide residues on foods, at work, during recreational activities, and in their homes. Pesticides that are resistant to environmental degradation may be extremely persistent and thus may result in prolonged exposure potentials. As noted previously, the environmental degradation products may vary depending on the specific pesticide and environmental circumstances (such as temperature, soil type, and moisture). As a result, it is not possible to make a generic statement concerning pesticide degradation and the possible, consequent, proportional environmental toxicity.

Toxic Categories and Labeling Requirements

When pesticides are registered with the EPA, they are assigned a toxicity category that indicates the degree of toxicity that has been determined by animal experimentation and documented instances of human poisoning. The toxicity classification includes four categories (I, II, III, and IV) for each of five hazard indicators: three related to the LD_{50} associated with

oral, inhalational, and dermal exposures; and two related to topical eye and skin exposure effects (Table 14-4).[9] Within these categories, a particular pesticide may be highly toxic for one hazard indicator, such as the oral LD_{50}, while it has only a slight degree of toxicity by another indicator, such as the dermal LD_{50}. In cases where hazard indicators differ, the most toxic hazard indicator determines the official EPA registration category.

The EPA also requires the use of *signal words* (DANGER, POISON, WARNING, CAUTION) on labels to indicate the potential hazard of the pesticide. The most toxic pesticides are classified as Category I and must display the signal word DANGER. Additionally, if this category is based on the oral, dermal, or inhalation LD_{50}, the product label must contain the word POISON in red on a contrasting background, and the skull-and-crossbones symbol, which is familiar to most adults. Category II pesticides are moderately toxic and are labeled WARNING. Pesticides in Categories III and IV are both labeled CAUTION. With few exceptions, all pesticides are also labeled, "Keep out of the reach of children."

The toxicity classification and corresponding labeling apply primarily to pesticides on the basis of their acute toxicity. If a pesticide is known to cause significant chronic toxic effects in humans (such as carcinogenicity or teratogenicity), the pesticide is also subject to a restricted-use classification, which is noted on the label. This classification requires that the pesticide be applied by or under the direct supervision of trained and certified pesticide applicators.

If medical personnel are aware of the different requirements for EPA registration and of the spectrum of potential adverse health effects that pesticides can cause, they can provide better medical care to patients who present with signs and symptoms of possible pesticide poisoning. Pesticide labels must include medically useful information, such as acute toxicology categorization and a statement of practical poisoning treatment. In addition, medical surveillance, patient examination, and biological monitoring can be specifically tailored to individuals who may be exposed to pesticides, based on the known toxicological effects. As a result of possible differences in toxicological responses between species, however, care must be exercised when toxicological information is extrapolated from the animal model to patients.

Comparative Hazards

The differences between organophosphorus and organochlorine pesticides can be used to illustrate the comparative levels of hazard and the relative potentials to cause adverse health effects (Table 14-5). Organochlorine insecticides were used extensively from the 1940s through the 1960s because they were highly efficacious and were generally less acutely toxic than organophosphorus compounds of the same period. The organochlorine derivatives have recently fallen

TABLE 14-4

TOXICITY CATEGORIES AND HAZARD INDICATORS OF PESTICIDES

Toxicity Category Label		Hazard Indicators					Signal Word on
No.	/Description	Oral LD_{50} mg/kg*	Inhal. LD_{50} mg/L*	Dermal LD_{50} mg/kg*	Eye Hazards	Skin Effects	
I	Highly toxic	< 50	< 0.2	< 200	Corrosive; corneal opacity not reversible within 7 d	Corrosive	DANGER POISON (only if Cat. I based on Oral, Inhal., and Dermal LD_{50}s)
II	Moderately toxic	50–500	0.2–2	200–2,000	Corneal opacity reversible within 7 d; irritation persisting for 7 d	Severe irritation at 72 h	WARNING
III	Slightly toxic	500–5,000	2–20	2,000–20,000	No corneal opacity; irritation reversible within 72 h	Moderate irritation at 72 h	CAUTION
IV	Practically nontoxic	5,000	> 20	> 20,000	No irritation	Mild or slight irritation at 72 h	CAUTION

*Numbers listed apply to the pure substance only; dilutions may be considerably less toxic

TABLE 14-5

SELECTED PESTICIDES: ACUTE LETHALITY LEVELS IN RATS

Pesticide	Acute Oral Lethality (mg/kg) (Rat LD_{50})
Organochlorines	
DDT (powder)	500–2500
Lindane	88–200
Chlordane	150–700
Aldrin	10–74
Organophosphoruses	
Schradan	9–42
Parathion	3–30
Dichlorvos	46–80

Sources: (1) Smith AG; Chlorinated hydrocarbon insecticides. In: Hayes WJ Jr, Laws ER Jr, eds. *Handbook of Pesticide Toxicology*. New York: Academic Press, Harcourt Brace Jovanovich; 1991; Chap 15. (2) Gallo MA, Lawryk NJ; Organic phosphorous pesticides. In: Hayes WJ Jr, Laws ER Jr, eds. *Handbook of Pesticide Toxicology*. New York: Academic Press, Harcourt Brace Jovanovich; 1991; Chap 16.

into disfavor, however, because of their persistence in the environment, tendency for bioaccumulation within the food chain, tendency to accumulate in human tissues, and possible potential to cause human carcinogenicity. Commonly used organochlorine pesticides of the early periods of production and use included DDT, lindane, aldrin, and chlordane.

An example of the perceived safety of the organochlorine class of pesticides is demonstrated by the large number of scientific studies directed toward the evaluation of DDT pharmacokinetics after oral administration in humans. DDT was administered to healthy human volunteers in single doses as high as 1,500 mg and, in separate studies, repetitive doses of 35 mg/person/day for 18 months.

In contrast, many of the early organophosphorus compounds were found to be highly toxic during acute exposure. Some were produced as weapons by several countries as nerve agents, a class of chemical warfare gases. Despite their demonstrated potency, several of the early organophosphorus compounds were developed and used as medications for treatment of myasthenia gravis and glaucoma. When the environmental persistence and the possibility of adverse, cumulative toxicity of the organochlorine compounds were recognized, however, their use fell into disfavor. Less toxic organophosphorus compounds were substituted because of their more rapid environmental biodegradation and increasing availability. Later, selected carbamate pesticides, which were less persistent and more specific against the targeted pests, were substituted for many of the organophosphorus compounds.

Hazard as a Function of Toxicity

The toxicity of a pesticide is not synonymous with the hazard associated with use of the chemical. The hazard involved in the application of a pesticide is a result of the interactions among three elements: toxicity, exposure, and time. This relationship is expressed by the equation

$$\text{Hazard} = \text{Toxicity} \bullet \text{Exposure} \bullet \text{Time}$$

where *hazard* is the risk of pesticide poisoning, *toxicity* is a measure of the pesticide's potential for harm, *exposure* is a multivariate function, and *time* is associated with the cumulative dose.[10] In addition to time, the exposure dosage is dependent on the physical state of the pesticide formulation, application technique, and degree of personal protection. The cumulative association between the exposure concentration and the duration of the exposure is often called the exposure dosage and is expressed by the abbreviation *Ct* (ie, *concentration* • *time*). If any of the three variables on the right side of the equation equal zero, the hazard also equals zero.

Although a pesticide's toxicity can never actually be zero, selection of an appropriate formulation can reduce the associated hazard. Toxicity can be decreased by selecting a pesticide with (*a*) a lower dermal toxicity, (*b*) a less toxic formulation, and (*c*) a lower concentration for application. As a practical example, a relatively toxic pesticide could represent a diminished hazard if it is applied in a very dilute form or in a formulation that restricts its skin absorption potential.

It is possible to reduce the hazard of application, based on the hazard equation, in several practical ways. For example, a pesticide applicator could elect to substitute malathion for parathion in an eradication effort. As another example, the use of appropriate engineering controls or PPE would serve to decrease the exposure and, therefore, diminish the hazard.

The physical state of a pesticide's formulation influences the degree of hazard associated with its use. In general, solids are less hazardous than liquids. Liquid emulsifiable concentrates are probably the most widely used formulations, but these can pose significant hazards due to the highly flammable solvents that may be in the product. The presence of solvents may result in an increased potential for dermal ab-

sorption. Of the liquid formulations, solutions penetrate skin more readily than suspensions.[10]

The exposure potential and correlated hazard potential are related to both the physical state of the pesticide formulation and the application technique employed. To minimize the hazard potential, the techniques and equipment should allow the pesticide to be directed as accurately as possible at the pest and should minimize the pesticide's unwanted drift or movement.

Indoor pesticide applications present greater exposure potentials to both the applicator and the occupants. Pesticides that are considered extremely hazardous should not be used indoors, especially if the product label does not contain the indoor application site.

Pesticide Selection

While efficacy is a major consideration in the selection of a pesticide, selection should be influenced equally by the inherent hazard, of which the acute toxicity of the active ingredient plays an important role. One simple method to evaluate the suitability of several pesticides is to compare the ratio of mammalian to pest toxicity. The higher the ratio of the LD_{50} for a mammal, such as a rat, and the lower the LD_{50} for a given pest, such as a German cockroach, the lower the potential hazard for humans. That is, the higher the mammalian LD_{50}, the safer the product may be for humans, while the lower the LD_{50} for a pest species, the less active ingredient may be required to control the pest. Although toxicity/efficacy ratios provide an indication of relative hazards, they do not provide information on the effectiveness of the pesticide against the pest in the field.

Other factors that influence the level of control that is achieved for a specific pest population include the pest's resistance to the pesticide, the application techniques, and the type of surfaces treated. For example, military use of the pesticide d-phenothrin was seriously hampered when cockroach resistance to this pesticide was found. The application of pesticides to cracks and crevices, rather than broad baseboard treatments, has been found to be more effective because the pesticide is placed in locations where the pest is more likely to be found. Some surfaces such as wood, concrete or surfaces painted with latex paint may absorb the pesticide application, reducing the amount of surface pesticide available when contacted by the pest.

Although oral and inhalational toxicities may be significant, dermal absorption may represent a more significant hazard to those who apply pesticides. Careful selection by comparing the dermal toxicities of selected pesticides and calculating dermal toxicity versus efficacy ratios may be helpful in keeping the applicators safe.

EXPOSURE EPIDEMIOLOGY

There are no published epidemiological data about pesticide exposures resulting from military applications. Because of the federal regulatory requirements, however, civilian and military applications of pesticides are similar; therefore, data accumulated through civilian reports may represent potential qualitative health effects in military applications.

The requirements for reporting medical data are stringent in California, especially for worker's compensation: health-effects data from patients with suspected acute pesticide poisonings have been collected and reported for more than 40 years.[11] As a result of the increasingly stringent medical reporting requirements, these data may be the best quantitative source on which to base estimates of the potential for symptomatic human pesticide exposures, both occupational and nonoccupational. The epidemiological value of the data is compromised (degraded), however, by a number of factors that influence the adequacy of the data collection. In an uncompromised quantitative ratio, the number of patients who demonstrated signs or symptoms caused by pesticide exposure (the numerator) would be compared to the total number of individuals with pesticide exposure (the denominator). Uncertainties that could influence the numerator include physiological differences among patients, failure of minimally or mildly symptomatic patients to seek healthcare, failure of medical personnel to report all pesticide-associated illnesses, and the possibility that the etiology of a presumed pesticide-associated illness is inaccurately assigned.

Even if technically flawed for strict scientific extrapolation, the California epidemiological data provide valuable insights into the magnitude of potential pesticide exposures and the subsequent health effects. Another indicator of the widespread potential for pesticide exposure (and the subsequent health effects) is the quantity sold: 268,749,526 kg of pesticides were sold in California in 1988.[11] The *California State Abstract* for 1989 estimates that the population of California was 28,314,000 in 1988; therefore, pesticide use would have approximated 9.5 kg of pesticide per Californian.

Of these quantities, approximately 49% were used in agriculture, 17% in the home or garden, 19% in industry, and 13% in institutions within the state. The *U.S. Census of Agriculture* for 1987 estimates that about 31 million acres were available for agricultural use in California in 1988. If all the purchased pesticides in the state were applied on agricultural land within its borders, approximately 8.7 kg would have been applied per agricultural acre.

The earliest summary of information that provides insight into the epidemiology of pesticide poisonings was collated in 1950. In that year, a total of 293 cases of reported occupational diseases were associated with agricultural chemicals.[11] Unfortunately, absolute numbers, rather than incidence rates, of poisonings were reported. For 1950, in California, the profile of the leading causes of pesticides poisoning was parathion (n=52), DDT (n=27), sulfur (n=21), arsenic (n=9), nicotine (n=8), and tetraethyl pyrophosphate (n=6).

The introduction of about 500 new EPA-registered pesticides between 1949 and 1970, associated with more carefully regulated use practices and withdrawal of registration for some compounds, resulted in a change in the exposure profile. In 1987, approximately 17,000 pesticide poisonings were reported in California; of these, 1,507 were occupational illnesses. Of the several hundred registered products identified, the most serious poisonings were reported from exposures to the cholinesterase inhibitors and methyl bromide.[11] The organophosphate insecticide parathion was the most frequently reported pesticide correlated with systemic poisonings (n=90) in California in data reported for the years 1982 through 1986; these data are similar to those reported in 1950. Mevinphos (n=58), methomyl (n=51), methamidophos (n=44), methyl bromide (n=32), sulfur (n=28), dimethoate (n=27), dinitrophenol (n=25), methidathion (n=22), and malathion (n=20) were the next-most-commonly reported compounds.[12]

The American Association of Poison Control Centers reported 1,581,540 human poison exposures in 1989. With respect to the poisonings caused by pesticides, insecticides were the most commonly reported class with regard to the frequency of poisoning report, number of patients treated in healthcare facilities, number of symptomatic patients, and number of patient lethalities (n=12). Of the insecticides, organophosphates were by far the most commonly reported poisons in all age groups and were associated with seven of the reported deaths. Arsenicals, the next-most-implicated class of pesticides, were associated with three deaths.[13]

PHARMACOLOGY OF PESTICIDES USED BY THE MILITARY

Like other chemicals, pesticides can be categorized a variety of ways. The characteristics pesticides are most commonly used for are (*a*) mechanism of action (eg, the cholinesterase-inhibiting substances); (*b*) chemical composition (eg, the chlorinated hydrocarbons); (*c*) target pest classes (eg, the rodenticides); and (*d*) source of derivation (eg, the botanical extracts). Although the pharmacology of pesticides is not militarily unique, medical officers need to be familiar with

- the classes of pesticides most frequently used by the military,
- their mechanisms of toxicity,
- the manifestations of acute poisoning,
- the antidote, reversal, or therapeutic intervention,
- the biological monitors and surveillance parameters, and
- the potential long-term effects.

Table 14-6 summarizes these aspects of the following pesticide classes: organophosphates, carbamates, chlorinated hydrocarbons, anticoagulants, boric acid, and the pyrethroids. This chapter treats only the major pesticides that are used by the military.

Information concerning the pharmacology of pesticides and the medical management of poisonings accumulates exponentially. Consequently, most military emergency rooms subscribe to information sources such as the POISONDEX Information System.[14] Information compiled from this source is the basis for much of the management practices that follow. The three-volume *Handbook of Pesticide Toxicology*, published in 1991, thoroughly reviews the current, scientific literature related to general pesticide toxicology.[15] Additional sources of information concerning pesticide toxicity and the emergency medical response to poisoning include

- local poison control centers;
- the EPA publication *Recognition and Management of Pesticide Poisonings*, which provides valuable information for emergency management of a wide range of pesticide intoxications;
- the National Pesticide Telecommunications Network (the telephone number is 1-800-858-7378); and
- the DoD Pesticide Hot Line (the telephone number is 1-410-671-3773).[16–18]

TABLE 14-6

MECHANISIMS OF ACTION AND RECOMMENDED MEDICAL MANAGEMENT OF SELECTED PESTICIDE CLASSES

Chemical Class	Mechanism of Action	Manifestations of Acute Poisoning
Organophosphate	Cholinesterase inhibition, phosphorylation, time-dependent aging	Muscarinic, nicotinic, and CNS effects
Carbamate	Cholinesterase inhibition, carbamylation (rapidly reversible without aging)	Muscarinic, nicotinic, and CNS effects
Chlorinated hydrocarbon Chlorinated ethane derivative (eg, DDT)	Na, K, Ca channels	Highly variable, nonspecific: psychological, sensory, motor
Chlorinated cyclodiene, (eg, dieldrin)	CNS stimulation (transmitter release at synapse)	Convulsions Cardiac arrythmias possible
Anticoagulant (rodenticide baits)	Antimetabolites of vitamin K	Internal hemorrhage Prolonged prothrombin times, depressed levels of factors II (prothrombin),VII, IX, X
Pyrethroid (repellants, insecticides)	Delayed closure of Na channels	Skin irritation, allergy Eye irritation, allergy Paresthesia Allergic bronchospasm Rare: salivation, tremor, vomiting, incoordination
Boric acid (roach control)	Metabolic acidosis Electrolyte abnormalities	Nausea, vomiting, diarrhea, anuria, electrolyte imbalance, tremors, convulsions, skin erythema progressing to desquamation

Cholinesterase-Inhibiting Insecticides

Military applications of insecticides are usually restricted to selected organophosphates (including chlor-pyrifos, parathion, diazinon, and malathion) and carba-mates (including aldicarb, propoxur, and carbaryl), which are cholinesterase inhibitors; and organochlorines and borate derivatives, which are discussed later in this chapter.

The toxicities of these insecticides vary widely depending on their route of absorption, pharmacological interactions after absorption, degree of metabolic degradation, degree of reversible enzymatic binding, and rate of excretion. Although these insecticides can also be absorbed via inhalation or ingestion, most occupational effects have been reported following dermal exposures.

Organophosphate and carbamate insecticides ex-

Antidote, Reversal, Therapeutic Intervention	Biological Monitor and Surveillance Parameter	Long-Term Effects
Atropine (antidote) 2-PAM Cl (reversal) Anticonvulsant	RBC acetylcholinesterase (AChE), (detectible acute or chronic decremental change from individual baseline) Plasma cholinesterase (detectible acute decremental change)	Delayed neuropathy possible Possible neurotoxic esterase effect
Atropine (antidote) 2-PAM Cl CONTRAINDICATED Anticonvulsant	RBC AChE (possible short-term, acute depression; usually near normal level)	None reported
No known antidote	Specific chemical analysis possible; standard levels unknown; results related to known toxic response case reports	Bioaccumulation in lipid tissues Environmental persistence
Anticonvulsant (cholestyramine may enhance biliary excretion of some compounds)	Chemical epoxides in some cases	Possible carcinogenesis
Vit. K_1 is the SPECIFIC ANTIDOTE (K_3 and K_4 ineffective), fresh blood for bleeding	Prothrombin time	Warfarin reported teratogenic
Topical corticosteroids Topical therapy Vit. E oil for paresthesia Antihistamines, occasionally bronchodilators or steroids No known antidote	None reported	Possible carcinogenesis
Syrup of ipecac for acute indigestion (charcoal not efficacious) convulsant, monitor EKG, Fluid management, dialysis Topical skin therapy	Serum borate level (mg/L blood) (0–7.2 = normal; < 340 mg/L rarely shows toxic effect)	No direct sequelae reported Anti-

ert their pharmacological influences as a result of their inhibition of a family of cholinesterase enzymes in various tissues. There are clear toxicological similarities between both classes of cholinesterase inhibitors, but there are also significant differences between their pharmacodynamic interactions and the recommended medical therapeutic managements. Regulatory controls introduced by the EPA, greater awareness of the associated hazards by applicators, and an intensive effort by pesticide producers to develop safer, more efficacious products, have resulted in a decline in both toxicity and the numbers of human poisonings associated with these chemicals. As a group, the ready availability, widespread use, and relatively toxic nature of the cholinesterase inhibitors still cause a number of human fatalities annually.[13,17]

To review, an enzyme is a protein molecule that induces chemical changes in another molecule with-

out being changed itself; therefore, an enzyme is a catalyst. The substrate is the molecule on which the enzyme exerts an influence and that is changed to generate the enzymatic reaction product. For example, the enzyme acetylcholinesterase catalyzes the hydrolytic chemical conversion of the neurotransmitter acetylcholine. An inhibitor is a chemical that competes with or prohibits the enzymatic interaction with the substrate. Many enzymes are named on the basis of the customary substrate or characteristic chemical reaction type, followed by the terminal identifier -*ase*. For example, the enzyme acetylcholinesterase catalyzes the hydrolytic chemical conversion of the neurotransmitter acetylcholine.

Cholinesterase enzymes are widely distributed within the body. They are localized within numerous tissues, fluids, and cells including heart muscle, cholinergic synapses, myoneural junctions, plasma, and erythrocytes. Although a number of different cholinesterase enzymes are known to be distributed through the body, this discussion will focus specifically on the enzyme acetylcholinesterase, the cholinesterase enzyme characteristically associated with the erythrocyte. A different enzyme of the cholinesterase class, pseudocholinesterase (also called butyrylcholine esterase), is found in the plasma fraction of whole blood. Although the chemical substrate interactions and substrate degradation mechanisms are similar between these two types of cholinesterase enzymes, they differ with respect to their preferred substrate, rate of enzymatic activity, site of production, and rate of regeneration after poisoning. These differences will be discussed later in this chapter, with reference to specific pesticide poisoning, emergency medical management, and occupational surveillance.

To catalyze the hydrolysis of acetylcholine, its preferred natural substrate, the acetylcholinesterase protein molecule utilizes a specific, selective binding site (Figure 14-3). The acetylcholine binding site is thought to be composed of two specific binding areas that have been identified on the enzyme molecule.[18] A negatively charged *anionic* site of the enzyme is believed to attract and form an electrostatic bond with the positively charged nitrogen atom of the choline molecule of the transmitter acetylcholine**.** The ionic bond, and secondary attractions between the methyl groups of the choline moiety, and surface of the enzyme molecule appear to be prerequisites to the bond formed between the protonated acidic carboxyl group of the acetylcholine ester molecule at the *esteratic* site.[19] In the process of acetylation, a covalent linkage forms between the transmitter and enzyme at the esteratic site of the enzyme. Under normal metabolic conditions, the enzyme-substrate complex rapidly dissociates to form a molecule of choline and an acetylated enzyme. The acetylated enzyme undergoes a hydrolytic reaction, releasing acetate and regenerating the active enzyme.

Cholinesterase-inhibiting insecticides preferentially bind with cholinesterase enzymes, and as a consequence, cause interference with the normal enzymatic activity. This causes acetylcholine, the substance responsible for impulse transmission, to accumulate. Poisoning occurs in exposed humans because of interactions between the inhibitors and the enzyme within central and peripheral cholinergic synapses and within myoneural junctions. As a consequence of its functional activity, this enzyme controls nerve-impulse transmission from nerve fibers to autonomic ganglia, muscle, glandular cells, and other nerve cells within the central nervous system (CNS). Should an individual be exposed to a sufficient dose of cholinesterase inhibitors, the loss of the enzyme function results in the accumulation of acetylcholine at the cholinergic receptor sites. The pathophysiological response to

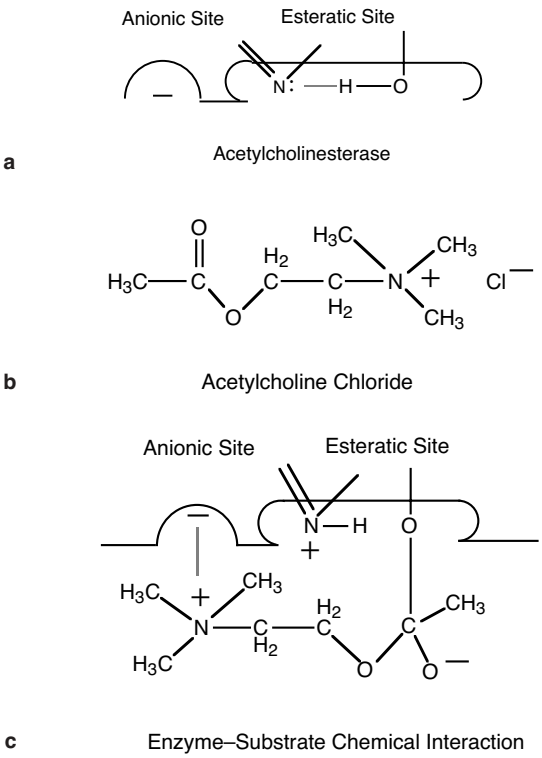

Fig. 14-3. These diagrams illustrate (**a**) the active site of the acetylcholinesterase molecule; (**b**) its usual natural substrate, acetylcholine chloride; and (**c**) the enzyme-substrate interaction. The electron-rich anionic site of the acetylcholinesterase molecule is represented as a negatively charged area; the serine residue at the esteratic site is represented in the hydroxylated state.

unimpeded overstimulation of neuromuscular tissues by acetylcholine is manifested by a spectrum of potential medical signs and symptoms related to the degree of poisoning. While clear toxicological similarities are demonstrable between the organophosphate and carbamate insecticides, there are significant differences between the pharmacodynamic interactions and recommended medical therapeutic management.

Organophosphates

The first organophosphate pesticide, the highly toxic compound tetraethyl pyrophosphate (TEPP), was introduced as an insecticide in 1939, although it was initially chemically synthesized and identified in 1894.[20] Closely related, highly toxic compounds later classified as nerve agents were identified during attempts to synthesize alternative pesticides and were secretly produced in Germany during World War II. Although they were never used as insecticides, warfare nerve gases such as tabun and soman were produced in substantial quantities and stored for possible use during the war. The partnership between applied toxicology and the chemical pesticide industry has resulted in the production and use of safer, more specific organophosphate pesticides for the target pest.

Many organophosphate pesticides have been developed, but those most commonly used for military applications are chlorpyrifos, diazinon, and malathion (Table 14-7).[20] Parathion is occasionally used; however, the EPA has currently been reviewing its registration. As a result of the intense scrutiny, the registration of parathion might be revised by the manufacturer with EPA approval, or revoked or revised by the EPA.

Route of Exposure. Most organophosphate insecticides are readily absorbed by all routes of exposure. Intentional ingestion of pesticide products is a commonly reported form of attempted suicide. Therefore, much of the information on medical management of organophosphate poisoning is derived from suicide attempts. Military scientific and medical experiences with the chemically similar nerve agent war gases have resulted in substantial contributions in the basic scientific literature and accumulated medical knowledge concerning organophosphate pesticides.

While some compounds such as mevinphos are more toxic when the exposure route is dermal, most of these compounds are more toxic if they are ingested. Some of the compounds, such as trichlorfon and diazinon, are severalfold more toxic if ingested or inhaled than if they absorbed through the skin. Chlorpyrifos and malathion are readily absorbed and may manifest equally toxic effects as a result of cutaneous contact, inhalation, and ingestion.[14]

Mechanism of Action. Much of the toxicological information concerning the mechanism of action of organophosphates has been gained through study of the more toxic chemicals such as the nerve agents and parathion.

Organophosphate insecticides interact with the esteratic site of the acetylcholinesterase enzyme molecule by the process of phosphorylation. The interaction, and subsequent chemical events that may occur between the enzyme and insecticide inhibitor, can be shown by the equation:

$$EOH + IL \leftrightarrow \{EOH\}\{IL\} \rightarrow L^- + H^+ + EOI \rightarrow EOH + I^- + L^-$$

where *EOH* represents the enzyme, *IL* represents the pesticide, *{EOH}{IL}* represents the reversible enzyme-insecticide complex, L^- represents the leaving group, H^+ represents the hydrogen ion, *EOI* represents the phosphorylated or carbamylated enzyme, and I^- represents the pesticide remnant that remains after hydrolytic dephosphorylation or decarbamylation has occurred.

Hepatic metabolic activity may influence organophosphate pesticide activity as a result of pesticide degradation, activation, or both.[4,16,20] In addition to the enzymatic degradation of organophosphate pesticides through the acetylcholinesterase pathway, hepatic metabolization of organophosphate insecticides is sometimes important in pesticide detoxification. Enzymes that perform phase I metabolic activation in the liver—through hydrolysis, oxidation, or reduction of the parent insecticide—are primarily localized with-in the hepatocyte endoplasmic reticulum. Hydrolytic, oxidation, or reduction rates and the types of metabolic products vary, depending on the particular pesticide. With some insecticides, breakdown may be sufficiently slow that temporary storage of the pesticide can occur in body fat. With other insecticides (eg, parathion, chlorpyrifos, and malathion), the metabolites of hepatic enzymatic pathways are more potent than the parent compound (the marketed pesticide). For example, the hepatic metabolites paraoxon and malaoxon cause much more pronounced toxic (cholinesterase inhibitory) effects than those produced by the parent compound.[4,16,20] For those compounds that are metabolically activated by the liver (including parathion, malathion, and chlorpyrifos), the onset of signs and symptoms may be delayed for several hours after exposure because the actual toxicity is almost exclusively due to its metabolic product, an oxygen analog.[14,19]

If the chemical reaction of the phosphorylated cholinesterase enzyme complex (EOI) results in hydrolytic dealkylation rather than dephosphorylation, an

TABLE 14-7

TOXICOLOGY OF SOME ORGANOPHOSPHATE INSECTICIDES

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*Values obtained in standardized tests in the same laboratory

†Maximum rate of intake (usually 3-mo, 2-yr feeding studies) that was tested and did *not* produce significant toxicologic effects (as listed in the monographs issued jointly by the Food and Agriculture Organization of the United Nations and the World Health Organization, as developed by joint meetings of expert panels on pesticide residues held annually, 1965–1972)

‡Acceptable daily intake (ADI) = the daily intake of a chemical that, during a lifetime, appears to provide the practical certainty that injury will not result (in man) during a lifetime of exposure. Figures taken from World Health Organization (1973).

Reprinted with permission from Murphy SD. Toxic effects of pesticides. In: Klaassen CD, Amdur MO, Doull J, eds. *Casarett and Doull's Toxicology: The Basic Science of Poisons*. 3rd ed. New York: McGraw-Hill; 1986: 529.

irreversible enzyme-phosphate product (phosphoryl adduct) is generated.[16] As a result, the enzyme cannot be regenerated and remains inactivated; that is, it is said to become *aged*. The reaction can be shown by the equation:

EOI —> alkyl group product + phosphoryl adduct

For example, in the enzymatic reaction with the organophosphate diisopropyl fluorophosphate (DFP), the initial enzyme-DFP complex releases its leaving group (fluoride) as a result of the hydrolytic reaction. The reaction results in the generation of the phosphorylation product, a diisopropylphosphoryl-enzyme complex and hydrofluoric acid. Subsequent hydrolytic dephosphorylation of the phosphorylated enzyme complex results in the release of a phosphoric acid derivative, diisopropyl phosphate, and the regeneration of the active enzyme. Because the rate of dephosphorylation is slow for the diisopropylphosphoryl-enzyme complex, an alternative degradation pathway through hydrolytic dealkylation is possible. As a consequence, the concentration of the enzyme-monoisopropyl phosphate complex (the aged enzyme) rises following DFP exposure. The rate of organophosphate-enzyme detoxification by hydrolytic dephosphorylation and resultant active enzyme regeneration strongly depends on the type of organophosphorus inhibitor involved. (In contrast, as a class, carbamate insecticides are considered *reversible* inhibitors of cholinesterase and are not associated with aging.[20])

Parathion is another organophosphate insecticide that ages the cholinesterase molecule (Figure 14-4). During the conversion process, parathion is metabolized to the active cholinesterase inhibitor, paraoxon, by desulfuration within the endoplasmic reticulum. Paraoxon reacts with the esteratic site of cholinesterase by phosphorylation. As a result of dearylation, *p*-nitrophenol is released as the leaving group from the initial, transient enzyme-insecticide complex. After dearylation, the phosphorylated-enzyme complex is very stable, with only limited subsequent hydrolysis to regenerate the active enzyme and release diethyl phosphate. Most of the phosphorylated complex is slowly converted to the extremely stable (aged) ethylphosphonate-enzyme adduct by dealkylation.[19,21]

Reactivation of a phosphorylated enzyme is possible using oxime therapy. However, reactivation of the aged enzyme-phosphorylated adduct complex is not possible and is, therefore, refractory to oxime therapy. The rate of pesticide-enzyme complex aging depends on the specific organophosphate inhibitor involved. For example, the nerve agent soman rapidly reacts with the enzyme through phosphorylation and the enzyme becomes aged within seconds to a few minutes. Other selected organophosphate-enzyme complexes may be reactivated 1 or 2 days after initial binding. The aged acetylcholinesterase associated with erythrocytes in the peripheral circulation is normally regenerated only as a consequence of erythrocyte

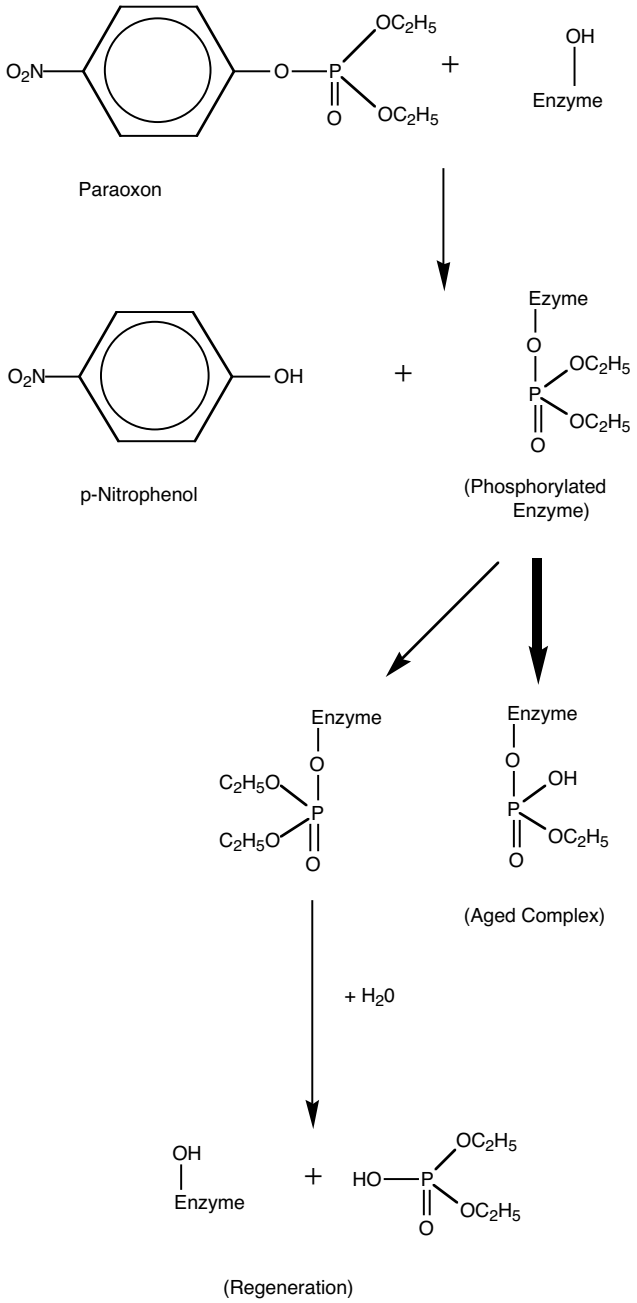


Fig. 14-4. The acetylcholinesterase molecule ages after organophosphate poisoning with parathion. The chemical reactions between paraoxon, the active chemical metabolite of parathion, and acetylcholinesterase favor enzyme aging; enzyme regeneration also occurs, but at a slower rate.

production and replacement in the circulation. Consistent with the life span of the mature erythrocyte, regeneration of erythrocyte-associated aged acetylcholinesterase occurs at a rate of about 1% per day.

Chlorpyrifos. Chlorpyrifos is one of the safer organophosphorus insecticides. When sufficient doses are absorbed to elicit a toxic response, however, chlorpyrifos produces clinical effects in humans that are indistinguishable from other organophosphorus compounds. In contrast to many organophosphate insecticides, chlorpyrifos is an active inhibitor of plasma cholinesterase, but is characterized as only a moderate inhibitor of the erythrocyte-associated enzyme. As a result, normal exposure causes selective depression of cholinesterase activity in the plasma rather than in erythrocytes. Depression of erythrocyte-enzyme levels is often seen, however, when systemic effects are clinically apparent.[14]

When ingested by humans, oral doses of chlorpyrifos of 0.03 mg/kg/day had no detectable effect on plasma cholinesterase (also called pseudocholinesterase) levels. Enzyme depression (inhibition) of 70% has been reported to cause only mild symptoms in some cases. Human subjects who ingested 0.1 mg of chlorpyrifos/kg/day for 4 weeks were found to have statistically significant decreases in plasma cholinesterase. Pest-control operators who were exposed to 8-hour time-weighted average (TWA) exposures of 27.6 mg of chlorpyrifos/m^3 of air revealed significant inhibition of plasma acetylcholinesterase when compared with age- and sex-matched controls; however, they had no clinical signs or symptoms of exposure.[14]

Information related to chronic neurological sequelae of chlorpyrifos exposure in humans is limited. An adult male ingested 300 mg/kg of chlorpyrifos. He exhibited varying degrees of severity of cholinergic signs for more than 2 weeks. Although his electrophysiological studies of peripheral nervous function were reportedly normal 1 month after ingestion, his neurotoxic esterase (lymphocytic neuropathy target esterase, NTE) was approximately 60% inhibited. About 2 weeks later, the patient complained of paresthesia and lower-extremity weakness. A clinical examination and laboratory evaluation demonstrated classical findings of delayed axonal peripheral neuropathy.[14]

Delayed neurotoxicity has been reported following chlorpyrifos administration in the standard hen assay; however, the effects were reported to be reversible.[19] Delayed neurotoxicity was not seen following administration in the mouse model.[14] However, it is the hen, not the mouse, that is considered to be the standard assay of neurotoxic effect.[1]

The delayed CNS neuropathy following acute exposures to the organophosphate insecticides may be slowly reversible or remain irreversible, associated with axonal degeneration. A delayed onset, mixed sensory-motor peripheral neuropathy has been reported, with onset between 6 and 21 days after malathion exposure. After malathion exposures, recovery from the delayed neuropathy may be slow or incomplete. After diazanon exposures, sensory-motor peripheral neuropathy has occurred; however, the onset of the neurological abnormalities may be delayed for several weeks. Recovery may be slow or incomplete.[14]

Organophosphorus ester–induced delayed neurotoxicity (OPIDN) is the classical clinical syndrome associated with organophosphate insecticides. The early clinical description of OPIDN was associated with workplace exposures to tri-*ortho* cresol phosphate. The clinical findings of OPIDN include a rapidly progressive paralysis of the lower and upper extremities with limited recovery. The classical pathological lesion occurs within the CNS and peripheral nervous system (PNS) and is characterized as axonal degeneration and demyelinization of the long motor and sensory neurons. (The adult female hen is the preferred and accepted scientific standard model for the study of neurotoxic effect.) Neurotoxic esterase has been reported to be the putative target of OPIDN. The enzyme 2´,3´-cyclic nucleotide 3´-phosphohydrolase (CNPase) has recently been reported as a sensitive indicator of myelin loss, and may be a sensitive indicator for OPIDN.[22]

Chlorpyrifos exposure did not result in teratogenic or fertility effects in the rat. Chlorpyrifos demonstrated no carcinogenic potential following chronic administration in studies using rats and mice. No changes in microbial mutation or sister chromatid exchanges have been reported following chlorpyrifos exposures. Semen quality changes have been reported in bulls exposed to chlorpyrifos.[14]

Parathion. In a human dose-response study, adults who consumed more than 6 mg of parathion per day for 30 days had some decrement in cholinesterase level. Several individuals who consumed more than 7.5 mg for 16 days had erythrocyte cholinesterase levels inhibited to 50% and 52% of pretest levels. No adverse signs or symptoms were noted in any of the study subjects. In a separate study, a total daily dosage of 0.078 mg/kg of parathion resulted in depression of both erythrocyte cholinesterase (16% decrease) and plasma cholinesterase (33% decrease) levels compared to baseline values. The no-effect daily dose of parathion administered to adults was between 0.058 and 0.078 mg/kg when administered over time durations between 25 and 70 days. The acute dose that could be lethal in an adult has been estimated to be 120 mg.[14]

Parathion has been shown to be fetotoxic, but not teratogenic, in laboratory studies. However, methyl parathion has been associated with human birth defects. Although parathion has demonstrated effects of possible genotoxicity in rodents (induced DNA alterations) and in vitro studies (Ames and sister chromatid exchange assays), it is not considered to be carcinogenic.[14]

Diazanon. In contrast to parathion, the estimated adult oral fatal dose for diazinon is approximately 25 g. In addition to cholinesterase inhibition, increased prothrombin time has been reported with both malathion and diazinon exposure.[14]

Malathion. Manifestations related to the degree of acute toxic response seen after malathion exposure depend on the total dose absorbed, manner of exposure, and duration of the exposure profile. The toxicity of malathion is probably due to its metabolic oxidation to malaoxon, which has been estimated to be approximately 1,000-fold more potent than malathion itself as a cholinesterase inhibitor. The cholinergic toxicity is regarded as the principle hazard associated with exposure. Malathion and its metabolites appear to affect both erythrocyte cholinesterase and serum butyrylcholine esterase enzymes. Malathion has relatively low acute toxicity: an oral dose of 24 mg/day was required to depress cholinesterase activities in adult volunteers. The estimated fatal oral dose exceeds 70 mg/kg.[14]

Malathion has been reported to cause mild skin and upper-respiratory irritation in humans, and repetitive exposures have been reported to cause allergic cutaneous sensitization. A case of transient renal dysfunction secondary to a malathion-induced, immune-complex nephropathy has been reported.[14]

Malathion exposure has been studied in human lymphoid cell culture. An increase in sister chromatid exchange was noted with increasing doses of cellular exposure. Metabolic activation with liver homogenate had no demonstrable effect on the exchange. At the highest dosage, cytotoxicity was demonstrated by the loss of approximately 50% of the cultured cells. A study of malathion-intoxicated individuals identified an increased frequency of chromatid breaks and unstable structural chromosomal aberrations. However, a causal association could not be demonstrated.[14]

Signs and Symptoms of Intoxication. Clinical signs and symptoms of organophosphate insecticide poisoning depend on the type and exposure dosage of the chemical pesticide involved and are usually reported within several hours of exposure (Table 14-8). The asymptomatic individual may have cholinesterase depression. Clinical signs of exposure vary from limited local effects to severe systemic effects such as coma.

TABLE 14-8

SIGNS AND SYMPTOMS OF ORGANOPHOSPHATE POISONING

Organ System	Effects
	Muscarinic (parasympathetic)
Visual	Dimness of vision, blurring of vision, unilateral or bilateral miosis
Respiratory	Rhinorrhea, breathing difficulty, cough, tightness of chest, bronchoconstriction, increased bronchial secretions, wheezing
Cardiovascular	Bradycardia, systemic hypotension, atrial or ventricular arrhythmia
Gastrointestinal	Salivation, nausea, vomiting, diarrhea, involuntary defecation
Cutaneous	Sweating
Genitourinary	Frequent, involuntary urination
	Nicotinic (sympathetic and neuromuscular)
PNS (ganglia)	Peripheral vasoconstriction, tachycardia, hypertension, hyperglycemia
Musculoskeletal (striated)	Localized or generalized fasciculation, respiratory insufficiency or paralysis, weakness, cramps, twitching
	CNS (mixed muscarinic and nicotinic)
CNS	Anxiety, giddiness, restlessness, headache, emotional lability, excessive dreaming, nightmares, confusion, tremor, ataxia, coma, cardiorespiratory depression, cyanosis, hypotension, convulsions, apnea

Signs and symptoms of acute cholinesterase inhibition and subsequent cholinergic intoxication are highly dose dependent. Direct skin contact can cause local fasciculation or sweating without other effect. Similarly, local ocular exposure to an organophosphate insecticide aerosol may cause unilateral or bilateral miosis without systemic manifestations.[14]

The systemic effects of this group of pesticides are the (*a*) muscarinic, (*b*) nicotinic, and (*c*) the combined, more severe CNS responses.[18]

Muscarinic Response. The classical postjunctional muscarinic response to acetylcholine stimulation is associated with activation of specific receptor sites of postganglionic parasympathetic effector cells. Postganglionic muscarinic receptors are found primarily in smooth muscle, exocrine glands, and the heart. Muscarinic signs and symptoms are associated with cardiac, ocular, pulmonary, cutaneous, genitourinary, and gastrointestinal manifestations. Severe bradycardia, miosis, wheezing associated with bronchoconstriction and bronchial secretions, sweating, involuntary urination, nausea, vomiting, diarrhea, and involuntary defecation are common muscarinic responses. Exposed workers may present with giddiness, complaints of blurred vision, headache, nausea, abdominal cramps, breathing discomfort, or with various degrees of more severe distress. Military medicine uses the acronym SLUDGE to aid rapid field recognition of the signs and symptoms of the muscarinic response: ***s***alivation, ***l***acrimation, ***u***rination, ***d***efecation, ***g***astrointestinal complaints, and ***e***mesis.

Atropine, in sufficient dosage, is an effective antidote for muscarinic signs associated with the cardiac, respiratory, and CNS responses. Atropinization causes the gastrointestinal and genitourinary effects to improve; however, atropinization is only partially efficacious because it neither results in enzyme regeneration nor affects nicotinic receptors.

Nicotinic Response. Nicotinic responses to acetylcholine occur at myoneural junctions of striated muscle, preganglionic autonomic synapses with ganglia, and within the CNS. Although several types of site-specific nicotinic receptors have been identified, the acetylcholine effect on nicotinic sites is independent of those differences. Muscular responses to stimulation of nicotinic receptors range from easy fatigue, mild weakness, twitching, or localized fasciculation, to severe, generalized fasciculations that result in respiratory embarrassment and cyanosis.

The effects of stimulation of the nicotinic receptors of sympathetic ganglia can result in pallor. At higher levels of sympathetic nicotinic stimulation, hypertension and hyperglycemia may occur. In addition, tachycardia that results from ganglionic nicotinic receptor stimulation, which overrides the bradycardic effects of muscarinic stimulation, may be observed. The nicotinic receptors of the CNS appear to be important in nicotine dependence; headaches, paresthesia, and tiredness have been reported with nicotine administration.[14] Other nicotinic actions on the CNS cause tremor, convulsions, initial respiratory stimulation followed by respiratory depression, and vomiting (the latter action being caused by direct action on the area postrema of the brain stem).[7]

Central Nervous System Response. Signs and symptoms of CNS poisoning include anxiety, apathy, toxic psychosis, restlessness, fatigue, headache, nightmares, tremors, seizures, and depression of cardiac and respiratory centers, which can progress to coma.[16,18] Atropinization and oxime therapy are efficacious for management of the CNS toxic effects. Anticonvulsants are indicated to provide therapeutic management of seizure control.

Chronic health effects from both high-dose, short-term and low-dose, chronic exposures to organophosphate compounds have been reported in humans.[16,23] Neuromuscular signs and symptoms associated with this neuropathy include paresthesias, easy fatigability, cramps, and may progress to gait abnormalities. Pathologically, the delayed peripheral neuropathy demonstrates peripheral demyelinization. The delayed peripheral effects may be related to organophosphate binding of a "neurotoxic esterase" enzyme.[16] Neurobehavioral signs and symptoms include many different complaints such as anxiety, depression, insomnia, and irritability. Most residual neurological symptoms appear to resolve within a year following acute intoxications.[18]

Parathion Intoxication. The onset of signs and symptoms induced by parathion has been uniformly accepted as the standard general description of organophosphate poisoning. It is important to recognize that the signs or symptoms can recur for days, despite therapeutically efficacious medical management. Careful patient monitoring and administration of indicated therapeutic management must be assured for days after parathion or other organophosphate poisoning.

Clinical signs and symptoms seen in children are most often seen by alterations of central neurological status. CNS depression, stupor, flaccidity, and coma are the most common signs in children. Dyspnea is commonly seen in children.

Ingestion usually results in nausea, followed by increased salivation, abdominal cramps, vomiting, and diarrhea. Hypothermia may occur as an early sign, but is not a usual finding. Alterations in mental status can manifest as confusion, anxiety, or giddiness.

Inhalation is usually followed by rhinorrhea, then

chest tightness as exposure doses increase. Although miosis may occur with eye pain, ciliary muscle spasm, and blurring of vision in topical or inhalation exposure, miosis is not a dependable sign for ingestion or cutaneous exposures. In fact, mydriasis is not an uncommon finding, possibly as a result of a sympathetic, reflex, adrenal response.

Although alveolitis, followed by progressive pulmonary fibrosis, has been reported in a parathion-intoxicated patient,[14] alveolitis and fibrosis are much more common following paraquat exposures.[24] Chemical alveolitis is probably associated with other chemicals in the pesticide formulation, rather than as a result of exposure to the cholinesterase-inhibiting insecticide itself.

CNS effects such as decreased vigilance, altered expressive language, diminished cognitive function, impaired memory, depression, anxiety, and irritability have been reported.[14] Other signs and symptoms may include visual hallucinations, auditory hallucinations, and psychosis.

Cardiac signs of organophosphate insecticide poisoning characteristically include bradycardia and hypotension, although reflex tachycardia, despite significant poisoning, has been reported. Heart rate, alone, is an unreliable sign for both the degree of exposure and efficacy of therapy. It has become increasingly apparent that acetylcholine in the coronary circulation can cause intense vasospasm resulting in atrial arrhythmias, hypotension, chest pain, and heart block.[14,25]

Acute respiratory failure is the major cause of death in organophosphate poisoned patients. Dyspnea, bronchorrhea, and tachypnea represent significant clinical signs of respiratory difficulty. Bronchospasm occurs as a typical pharmacological muscarinic effect. Respiratory responsiveness, such as diminished respiratory secretions and decreased ventilatory resistance are reliable indicators of inhalation toxicity and the efficacy of medical management. Delayed respiratory crisis may occur for 2 to 3 weeks following acute poisonings.[14]

Chlorpyrifos Intoxication. Muscular weakness, fatigability, and fasciculations are commonly reported in association with chlorpyrifos poisoning. They may be delayed in onset and paralysis may occur.[14]

Miosis, lacrimation, and blurred vision are common signs of chlorpyrifos poisoning. Mydriasis is unlikely, but has been reported in association with severe poisonings.[14] Excessive salivation is a common post-exposure sign.

Sweating is a common sign of chlorpyrifos exposure, but does not occur as a universal finding. Dermal irritation and sensitization have been reported but are uncommon. Other uncommon effects of exposure include a reported alteration in prothrombin time and the occurrence of hyperglycemia in severe poisoning.[14]

In addition to nausea, vomiting, and diarrhea, abdominal pain and fecal incontinence may occur with cholinesterase inhibition. Urinary frequency and, in severe cases, urinary incontinence have been reported.

Diazanon Intoxication. Nausea is often the first symptom that follows diazinon exposure. Other signs and symptoms range in severity from mild gastrointestinal or respiratory effects to cholinergic crisis. Vomiting, diarrhea, abdominal cramps, and salivation are commonly reported, especially with cutaneous or gastro-intestinal absorption. Inhalation exposures are more commonly associated with rhinorrhea and chest tightness. Ocular effects from exposure include tearing, miosis, ciliary muscle spasm, and eye pain. Paradoxical mydriasis has been reported with diazinon poisoning and probably is the result of a sympathetic reflex response.[14] Weakness, local fasciculations, drowsiness, dizziness, headache, and behavioral changes represent mild to moderate neuromuscular responses to exposure. Loss of muscular coordination, generalized twitching, and convulsions represent more severe neurological consequences of poisoning with diazinon.

Malathion Intoxication. It is important to note that symptoms occur after high-dose exposures to malathion, which are possible only in unusual circumstances such as an incorrect application. Inhalation of malathion results in ocular and respiratory effects as first signs of exposure. Ingestion results in a loss of appetite, nausea, vomiting, abdominal cramps, and diarrhea, which may appear within several hours. After skin absorption, local signs of sweating and twitching may occur within minutes or may be delayed for several hours. Severe signs may occur following exposure by all routes.

Clinical manifestations of malathion exposure in children may differ from the predominant signs and symptoms associated with adults exposure. CNS signs, such as CNS depression, stupor, loss of muscular tone, and coma are the most commonly reported signs of exposure in children; respiratory difficulty has also been reported.[14]

Other signs and symptoms have also been reported: fever may persist for several days; alterations in prothrombin time may occur; and hyperglycemia, glycosuria, and metabolic acidosis without ketosis have been reported associated with severe poisoning.[14]

Medical Treatment. If a strong likelihood of acute organophosphate poisoning exists, the patient should be treated immediately without waiting for laboratory results. The usual ABCs of emergency care apply:

healthcare providers must ensure that the patient has a patent airway, is breathing, and has adequate circulatory function without apparent hemorrhage. Oxygen should be provided, if the patient's condition indicates. Individuals who attend the victim should avoid direct contact with heavily contaminated clothing, vomitus, skin, and hair by wearing PPE such as rubber gloves (at a minimum).

Plasma and erythrocyte cholinesterase enzyme activities should be measured, but the degree of correlation between the levels of cholinesterase inhibition and clinical effects is imprecise. In some cases, a depression of only 50% of the enzyme activity may be associated with signs of cholinergic crisis. The correlation between cholinesterase levels and clinical effects is unreliable and should not be used for medical management.

In addition to the determinations of erythrocyte and plasma cholinesterase levels, some clinical laboratories may perform urinalyses for *p*-nitrophenol, the parathion leaving group. As with cholinesterase levels, the determination of parathion-metabolite levels is often not a readily available emergency test procedure. As a result, medical management of the parathion-poisoned patient should be directed by the patient's clinical responsiveness, with cholinesterase or pesticide-metabolite levels in urine serving only as subsequent measures of confirmation of exposure.

Clinical decisions concerning medical management must be based on the type and degree of signs exhibited by the acutely poisoned patient. Medical therapeutic intervention should not depend on the degree of depression of measured cholinesterase activity for the following reasons:

- The correlation between enzyme levels and clinical effects is poor.
- The test is not universally available.
- Laboratory report times are too time consuming.
- Baseline information is absent in many acute poisoning cases.

As a result, the measured enzyme inhibitions may confirm the diagnosis of cholinesterase inhibitor intoxication, but will not contribute substantially to acute patient management.

Asymptomatic patients with documented depression of cholinesterase levels should be carefully monitored, but they require no atropine unless signs and symptoms of poisoning evolve. Follow-up evaluations of cholinesterase levels for adequately treated or clinically stable asymptomatic patients whose levels have been acutely depressed may be done at weekly intervals unless the patient's condition dictates more frequent analyses.

Because early-onset respiratory depression and generalized convulsions are expected after serious exposures such as intentional ingestion, induction of emesis is contraindicated. If necessary, gastric aspiration or lavage can be performed. Protection of the airway is critical during nasogastric procedures and may be accomplished by cuffed endotracheal intubation. If lavage is performed, the return volume should approximate the amount of fluid administered.

In the management of ingestion, an activated charcoal slurry should be administered as quickly as possible. A total of 30 to 100 g of charcoal should be administered to adults, and 15 to 30 g to children.[14] Administration of a cathartic, either with the charcoal or separately, is recommended.

Atropine Therapy. In addition to respiratory distress, patients with severe signs of intoxication have profuse nasal, oral, and airway secretions. It is imperative to maintain control of a patent airway, using suction if necessary, until the degree of atropinization is adequate to control secretions and relieve bronchospasm. If hypoxia is suspected, administration of oxygen (if available) before atropine is injected is recommended. Atropine administration has been associated with the precipitation of ventricular fibrillation in hypoxic patients.

Atropine administration for symptomatic patients is imperative. Timely administration is crucial, regardless of the route of pesticide exposure. Atropine sulfate should be given intravenously, if possible, but is effective when injected intramuscularly, especially if administered via the current military Mark I atropine autoinjector. Signs of adequate atropine administration include drying of the airway secretions and improvement of respiratory efforts. Atropine administration should be continued as necessary until signs of organophosphate poisoning no longer recur, sometimes days after the acute poisoning event. The fever, disorientation, and delirium associated with atropine use reflect signs of excessive atropine administration; they indicate at least temporary discontinuation of atropine. Atropine administration does not affect acetylcholinesterase regeneration.

The typical adult dose of atropine is 2 to 4 mg, which can be administered every 10 to 15 minutes as needed. The dosage of atropine useful for managing a poisoned child is 0.05 mg/kg every 10 to 15 minutes as needed.[14] Treatment of cholinesterase inhibition is required for hours or days, depending on the individual patient and the circumstances of exposure. The treatment of patients poisoned with organophosphate insecticides may require a total of several grams of

atropine over the course of acute recovery from poisoning.

Oxime Therapy. There is no effective, medically approved antidote for the nicotinic effects of cholinesterase-inhibiting substances. If therapeutic intervention precedes enzyme aging, oxime therapy, such as administration of 2-pyridine aldoxime methyl chloride (2-PAM Cl), acts as a reversal compound (Figure 14-5). Improved levels of active enzyme within the acetylcholine-receptor regions results in improved disposition of free acetylcholine, with resultant improvement in the patient's signs and symptoms. Oxime therapy is recommended for patients with signs of severe pesticide intoxication such as severe twitching or fasciculation, significant weakness, or respiratory embarrassment.[16,23] 2-PAM Cl does not relieve bronchospasm or bronchorrhea, which are treated with concurrent administration of atropine.[23]

Pralidoxime Therapy. Pralidoxime therapy is often helpful in acute organophosphate poisonings. *It is imperative that pralidoxime be administered to severely poisoned patients* who have neuromuscular effects such as fasciculations, weakness, and respiratory paralysis. The typical dose for individuals who are 12 years old or older is 1 g of pralidoxime delivered intravenously over a minimum of 2 minutes. Children younger than 12 years of age should be given an intravenous dose of 20 to 30 mg/kg slowly, over at least 2 minutes.[14]

Pralidoxime is often helpful in acute organophosphate poisonings and is indicated in severe cases of organophosphate insecticide poisoning that are accompanied by profound weakness and respiratory depression. The recommended adult dose of pralidoxime is 1.0 g, administered intravenously, at a rate of 0.5 g/minute or infused in 250 mL of normal saline over 30 minutes. For initial management, the dose can be repeated up to three times. It may be administered in intervals of 6 to 12 hours if muscle weakness is not relieved or if the patient remains comatose. A continuous pralidoxime infusion (500 mg/h) may be administered; however, this alternative is considered to be controversial.[14]

For a poisoned child, pralidoxime may be administered intravenously at a dosage of 25 to 50 mg/kg over 30 minutes. Further administration may be necessary if muscle weakness and associated respiratory depression remain uncorrected.[14]

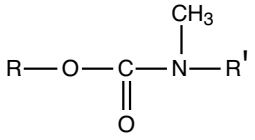
Anticonvulsant Therapy. Medical personnel should be prepared to promptly administer benzodiazapines (diazepam) as anticonvulsants for seizure activity associated with poisoning. The occurrence of clinically apparent convulsions has been recognized as a sign of neurological electrophysiological seizure activity. If convulsions occur, timely administration of diazepam as a direct intravenous bolus is imperative to preclude further neurological damage from hypoxia. The typical adult dose is 5 to 10 mg initially, which may be repeated every 15 minutes, as necessary, up to 30 mg. For the convulsing child, a dosage of 0.25 to 0.4 mg/kg up to 10 mg total dose is recommended. Intramuscular injections are slowly absorbed and should be avoided, if possible. If seizures are uncontrollable or recur, phenytoin or phenobarbital should be administered.[14] *Physostigmine, succinylcholine, or other cholinergic agents are contraindicated and should not be administered.*

Complications. Pulmonary edema may result from inhalation of pesticide formulations or occur as a complication of medical management. Oxygenation and ventilation must be maintained and arterial blood gases must be carefully monitored. If Po_2 remains low in spite of oxygen administration, it may be necessary to add positive end expiratory pressure (PEEP) or continuous positive airway pressure (CPAP). Careful fluid management is essential and a central line or Swan-Ganz catheter should be placed to monitor fluid status.

If significant inhalation exposure or coincident aspiration occurs, a baseline X ray should be obtained. This is especially important if the pesticide formulation was concentrated, contained irritant or hydrocarbon compounds, or was of unknown composition. Determining arterial blood gases and testing pulmonary function may be necessary during complicated medical management of some patients.

Hypotension may occur and should be treated by administering intravenous fluids and placing the patient in the Trendelenburg position, if necessary. Patients with blood pressure that is unresponsive to fluid administration may require careful pressure titration using dopamine (2–5 μg/kg/min) or norepinephrine (0.1–0.2 μg/kg/min).[14]

Carbamates



Carbamate insecticides are cholinesterase inhibitors (see Table 14-6). These compounds are an associated group of chemical esters with the general structural composition shown above, where *R* represents an oxime, alcohol, or phenol, and is the leaving group associated with inhibition of the cholinesterase molecule[16]; *R´* represents an N-methyl or hydrogen atom.[2,20,26] The most commonly used carbamates in

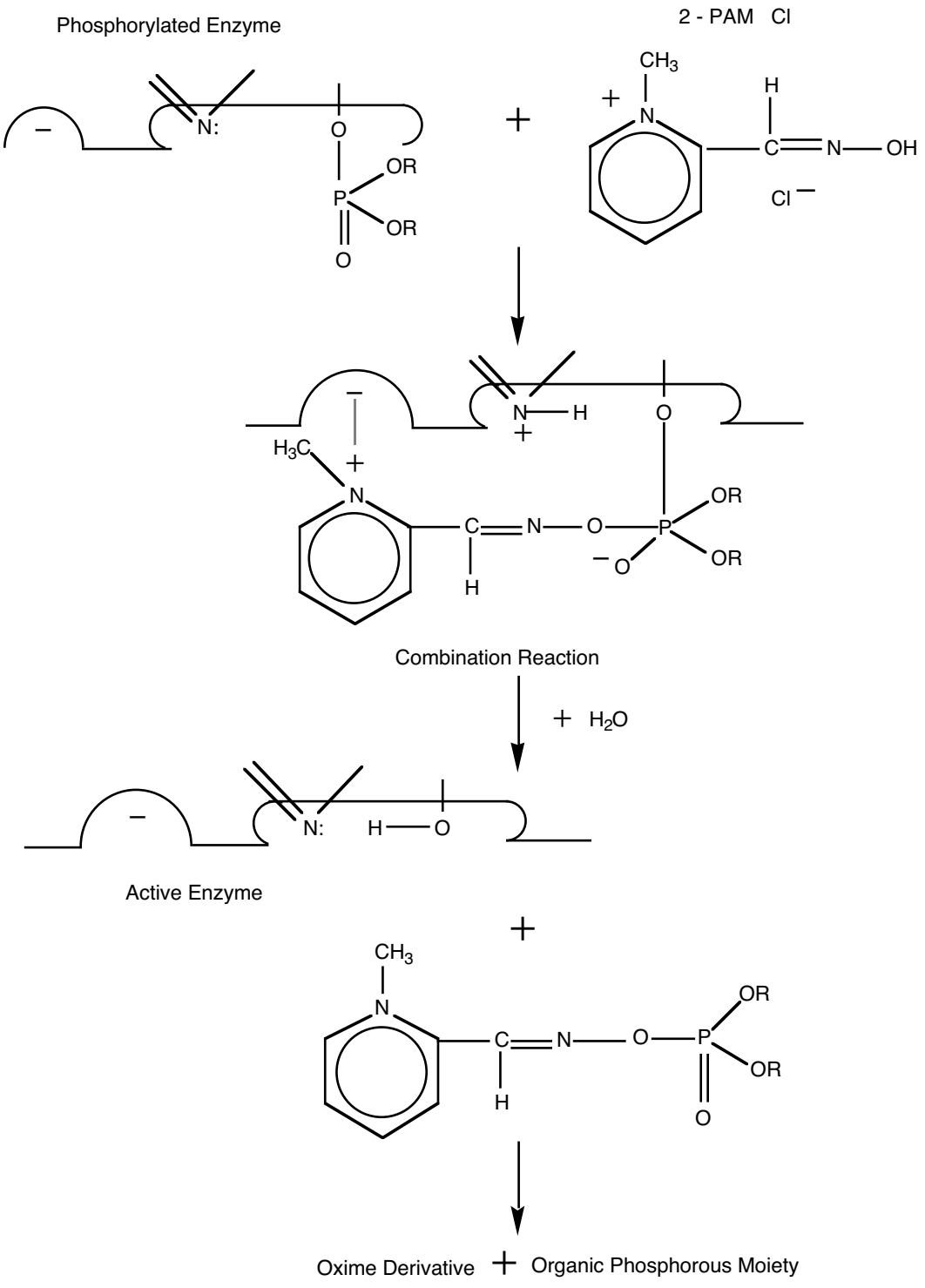


Fig. 14-5. If organophosphate-inhibited acetylcholinesterase is treated *before it ages* with pralidoxime chloride (2-PAM Cl, an oxime), the enzyme can be reactivated.

the military are carbaryl and propoxur, representatives of the N-methylcarbamate group (Table 14-9).[20]

Route of Exposure. Carbamates are absorbed via all routes of exposure, although dermal absorption is slight.[16] The degree of acute toxic effect depends on both the rapidity of absorption and the cumulative dose. Many carbamate insecticides have low dermal toxicity.[18]

Mechanism of Action. Inhibition of the acetylcholinesterase molecule by the N-methylcarbamate pesticide group differs from the phosphorylation reactions in organophosphate insecticides. In contrast to the rather stable organophosphate phosphorylation at the esteratic site, carbamylation of the enzyme appears to involve attachment of the carbamate at both the anionic and esteratic sites, which is similar to the action of acetylcholine. Because of the ready dissociation of the enzyme-carbamyl complex and the subsequent regeneration of the active enzyme molecule, carbamate compounds are rapidly reversible inhibitors of acetylcholinesterase.

Like other cholinesterase-inhibiting substances, carbamates are not directly measured in blood. Indirect measurement of exposure to carbamates is determined by measuring blood cholinesterase activity. Because the interaction between the carbamate and

TABLE 14-9

EXAMPLES OF RANGE OF ACUTE TOXICITIES OF SOME CARBAMATE INSECTICIDES

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*Values obtained in standardized tests in the same laboratory

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cholines-terase is spontaneously reversible, the residual cholinesterase activity usually fails to correlate with the clinical significance of the exposure.[14]

Rapid reversibility of the carbamylated enzyme complex decreases the duration of the clinical signs of poisoning, allows a wider dosage range between the onset of symptoms and death, and decreases the slight chance of documenting the level of depression of enzyme levels, unless a blood sample is analyzed almost immediately after exposure.[16,18,20]

Metabolism of carbaryl involves N-demethylation, hydroxylation, hydrolysis, and conjugation. Hydrolysis results in the urinary excretion of (*a*) 1-naphthol, which accounts for more than 20% of an administered dose, and (*b*) *p*-hydroxycarbamyl, which accounts for approximately 4% of the administered dose. Urinary concentration of 1-naphthol has been used as a biological exposure index of carbaryl exposure. Unexposed subjects have been reported to have urinary concentrations of 1-naphthol below 0.23 mg/L. Asymptomatic workers who were exposed to ambient air concentrations of carbaryl as high as 31 mg/m^3 were found to have urinary 1-naphthol concentrations of more than 42 mg/L. Although no standards have been established for carbaryl metabolites in urine, urinary 1-naphthol concentrations in excess of 4 mg/L of urine may represent significant exposure to carbaryl.[14]

Dose-dependent inhibitions of platelet aggregation and arachidonic acid metabolism in platelets have been demonstrated to be inhibited by carbamate insecticides. In these evaluations, the most potent carbamate compound found was carbaryl, which was shown to inhibit platelet aggregation and diminish products of the enzyme cyclooxygenase at concentrations as low as 10 μM. However, radiolabeled carbaryl was shown to bind covalently with numerous platelet proteins, in contrast to acetylsalicylic acid, which acetylates only a single platelet protein. Acetylsalicylic acid is known to specifically inhibit cyclooxygenase enzyme activity, which is similar to the action of carbaryl.[14]

Despite its widespread use by the World Health Organization as an insecticide to control the mosquito vector of malaria, only a few mild cases of propoxur poisoning have been reported. A human volunteer ingested 1.5 mg/kg of propoxur. The erythrocyte cholinesterase fell to 27% of the baseline within 15 minutes. The subject experienced nausea, vomiting, blurred vision, sweating, and tachycardia. By 2 hours following ingestion, the subject had no residual signs or symptoms and the enzyme levels were within normal limits. Adult humans have ingested single 90-mg doses without any apparent symptoms.[14]

Although delayed neurotoxicity has been reported with carbaryl exposure in one 75-year-old man, epidemiological studies of human carbaryl exposures have not demonstrated delayed neuropathy. Male human volunteers who ingested carbaryl dosages of 0.06 and 0.12 mg/kg for a study period of 6 weeks had no demonstrable changes in their electroencephalogram patterns. Inadequate data from human studies and the uncertain relevance of existing data from animal studies limit the final conclusions that can be drawn concerning delayed neurotoxic or myotoxic effects in human populations.[14]

Signs and Symptoms of Exposure. Much of what is known concerning the signs and symptoms of human exposures to carbamates has been based on studies of a closely related chemical compound, physostigmine.[26] The clinical signs and symptoms of carbamate poisoning are identical to those associated with organophosphate poisoning (see Table 14-6). Carbamates are believed to have a wide safety margin because the signs of cholinesterase poisoning, which resolve soon after the exposure is discontinued, are rapidly reversible. The most common signs and symptoms include lacrimation, salivation, miosis, convulsion, and death.[4]

Exposure to carbamate insecticides may lead to clinical manifestations of cholinergic crisis similar to those found with the organophosphate insecticides. The classic signs and symptoms associated with cholinergic activity may include increased salivation, lacrimation, urinary incontinence, diarrhea, gastro-intestinal cramping, and emesis. Clinical CNS signs and symptoms of carbamate poisoning are less intense and shorter in duration than those associated with comparable organophosphate pesticides.[14]

Ocular signs of exposure, including miosis, tearing, ciliary spasm, severe ocular or retroorbital pain, and diminished accommodation, may occur. Miosis may be either unilateral or bilateral and is often recognized by the patient as visual blurring, especially in a darkened room. Mydriasis may occur as a result of reflex adrenergic stimulation, although this is unusual.[14]

Respiratory responses to carbaryl intoxication include rhinorrhea, increased bronchial secretions, bronchospasm, wheezes, rhonchi, and rales. The patient may also experience chest tightness.

The major cutaneous sign associated with local dermal absorption is localized sweating. On careful observation of the skin, fasciculations may be observed in the underlying skeletal muscle.[14]

In addition to the localized fasciculations, other neuromuscular effects may include generalized loss of muscle tone, widespread muscular twitching, and overt convulsive activity, which can result from systemic stimulation. Other neurological responses include weakness, lassitude, incoordination, and slurred speech. Death is primarily the result of central respi-

ratory depression and paralysis, and is usually preceded by or associated with generalized convulsions, fecal or urinary incontinence or both, and coma.

In addition to the direct effects of the pesticide, bronchopulmonary sequelae may result from inhalation of the components of the pesticide formulation. For example, inhalation of the supposedly inert dust or the hydrocarbon vehicle may cause throat irritation, dyspnea, pneumonitis, or pulmonary edema.

If the individual who is exposed to the pesticide demonstrates cardiac effects, bradycardia is the most common sign; tachycardia can occur, however, possibly as a result of reflex response to bradycardia.

Disseminated intravascular coagulation and kidney damage have been reported, and delayed peripheral neuropathy, similar to that caused by some organophosphorus compounds, was reported in one case.[14]

With more severe exposures, mental confusion, loss of muscle coordination, tremors, or convulsions may occur. Death can result from respiratory arrest of CNS origin, paralysis of respiratory musculature, or intense bronchorrhea with bronchoconstriction.[14]

Medical Treatment. The administration of basic life-saving practices and decontamination of the skin with soap and water, if indicated by circumstances, are the essential elements of early first aid and medical care. Analysis of the plasma and erythrocyte cholinesterase levels are of no benefit in the medical management of these patients. Even in circumstances where depressed enzyme levels could be demonstrated, the delay in obtaining the results would severely compromise the usefulness of the enzyme levels as diagnostic and prognostic tools. Because the interaction between the carbamate pesticides and cholinesterase molecules is readily reversible, enzyme levels may be normal despite overt signs of poisoning. In addition, the tremendous variability between laboratory methodologies and reported cholinesterase activity units severely compromises meaningful interpretation of reported results in typical patients.

Induced emesis is not recommended following carbamate ingestion. After nasogastric suction has been performed, administration of activated charcoal and a cathartic is recommended. The adult dose of activated charcoal is usually between 30 and 100 g; for children, 15 to 30 g.[14]

Direct eye contact or splash should be treated by irrigation with copious amounts of water for at least 15 minutes. Medical evaluation is recommended in most circumstances, especially if signs of irritation such as pain, chemosis, lacrimation, or photophobia persist.

If significant inhalation exposure or coincident aspiration occur, a baseline chest X ray should be obtained. This is especially important if the pesticide formulation was concentrated, contained irritant or hydrocarbon compounds, or was of unknown composition.

Atropine administration for symptomatic patients is imperative. Timely administration is crucial, regardless of the route of pesticide exposure. Although best administered intravenously in life-threatening circumstances, atropine is also effective if administered intramuscularly, particularly if delivered by the atropine autoinjector. Atropine administration should be titrated to the patient's need based on resultant signs of atropinization. In cases of carbamate poisoning, the most reliable sign of atropine adequacy is the degree of drying of the pulmonary secretions.

The typical adult dose of 2 to 4 mg may be carefully administered every 10 to 15 minutes as needed. The dosage of atropine useful for the management of a poisoned child is 0.05 mg/kg every 10 to 15 minutes as needed.[14] The treatment of cholinesterase inhibition associated with carbamate poisoning may be required for hours or days, depending on the individual patient and the circumstances of exposure.

Clinically apparent convulsions have been accepted historically as a sign of neurological seizure activity. *If convulsions occur, timely administration of diazepam as a direct intravenous bolus is imperative.* The typical adult dose is 5 to 10 mg initially, which may be repeated every 15 minutes as needed up to 30 mg. For the convulsing child, the recommended dosage is 0.25 to 0.4 mg/kg, up to 10 mg total dose. Intramuscular injections are slowly absorbed and should be avoided, if possible. If seizures are uncontrollable or recur, phenytoin should be administered.[14] *Physostigmine administration is contraindicated, and its use should be avoided.*

The administration of pralidoxime is contraindicated in pure carbamate poisonings. The addition of oximes such as 2-PAM Cl markedly increase carbamate toxicity and may cause death.[16,18,27] Use of pralidoxime is controversial in carbamate poisonings that are complicated by other factors such as known organophosphate-combined poisoning or unknown circumstance of poisoning. Although atropine is effective against the muscarinic manifestations of carbamate poisoning, it is ineffective against the nicotinic manifestations.

However, some authorities recommend that pralidoxime should be given when life-threatening symptoms are present.[14] The recommended adult dose is 1.0 g administered intravenously at a rate of 0.5 g/min, or infused in 250 mL of normal saline over 30 minutes. The dose may be repeated up to three times for initial management. Praladoxime may be administered in intervals of 6 to 12 hours if muscle

weakness is not relieved. As an alternative, an infusion of 500 mg/hour may be administered.

For a poisoned child, pralidoxime may be administered intravenously at a dosage of 25 to 50 mg/kg over 30 minutes. Further administration may be necessary if muscle weakness and associated respiratory depression remain uncorrected.[14]

Organochlorine Insecticides

The four classes of organochlorine insecticides are (1) DDT and related derivatives of chlorinated diphenylethane; (2) cyclodienes, including dieldrin, heptachlor, and chlordane; (3) lindane (the gamma isomer of hexachlorocyclohexane); and (4) toxaphene (a mixture of chlorinated terpenes).[28] Substances in this group are known for their low biodegradability in the environment, accumulation in human and animal adipose tissues, and carcinogenicity in laboratory animals.

The acute toxicity and human hazard potential of organochlorine insecticides are highly variable and are influenced by the rate of exposure, route of exposure, and specific chemical compound (see Table 14-6). For example, dermal absorption is much greater of hexachlorocyclohexane (the technical grade includes the gamma isomer lindane) and the cyclodiene derivatives than for the ethane derivatives. The potential acute human toxicity hazard for these compounds is, from highest to lowest, endrin, aldrin, dieldrin, chlordane, toxaphene, chlordecone, heptachlor, DDT, and methoxychlor. Dicofol, methoxychlor, and hexachlorobenzene have limited CNS toxicity; however, in extreme overdoses, CNS depression may occur.[14]

Organochlorine insecticides are primary representatives of the broader group of chlorinated hydrocarbon pesticides. Other representatives of the chlorinated hydrocarbons have been used as fumigants, herbicides, fungicides, and nematocides.[5] The chemical structures and selected toxicological activities for representative organochlorine insecticides are found in Table 14-10 .

The precise mechanism of action of many of the organochlorine insecticides remains unknown.[16] Since 1944, DDT has been known to affect the nervous system; however, the precise mechanism of action remains incompletely described.[24] DDT is thought to exert its complex toxicological action through its impact on the fluxes of sodium, potassium, and calcium across the nerve cell membrane, but measurements of ionic potentials differ among species. In addition, in rabbit brain, DDT has been shown to inhibit the action of Na^{+}–K^{+}–Mg^{++} adenosine triphosphatase (ATPase), an enzyme responsible for ion movement in the nervous system.[24] The net effect of these ionic and enzymatic interactions is a slowed closing of the sodium channel, with prolongation of the hyperexcitable state of the nerve cell following nerve-impulse transmission.[28,29]

In contrast to DDT, lindane and the cyclodienes (eg, dieldrin) appear to exert their toxic effects at the nerve synapse, where their action results in increased spontaneous and evoked release of neurotransmitter.[28] Lindane and dieldrin act on the ganglion, rather than the axon, where increased membrane permeability to calcium was demonstrated. In addition, they appeared to inhibit Ca^{++}–Mg^{++} ATPase, which influences the rate of calcium extrusion. Dieldrin, lindane, and heptachlor epoxide have all recently been shown to be potent, competitive, stereospecific inhibitors of the picrotoxin receptor. As a result of this inhibition, γ-aminobutyric acid (GABA) and GABA-related transmission is affected. GABA-induced chloride permeability is inhibited, with the result that the nerve cell remains hyperexcitable after stimulation. DDT and mirex were not found to bind to the picrotoxin receptor.[28,30]

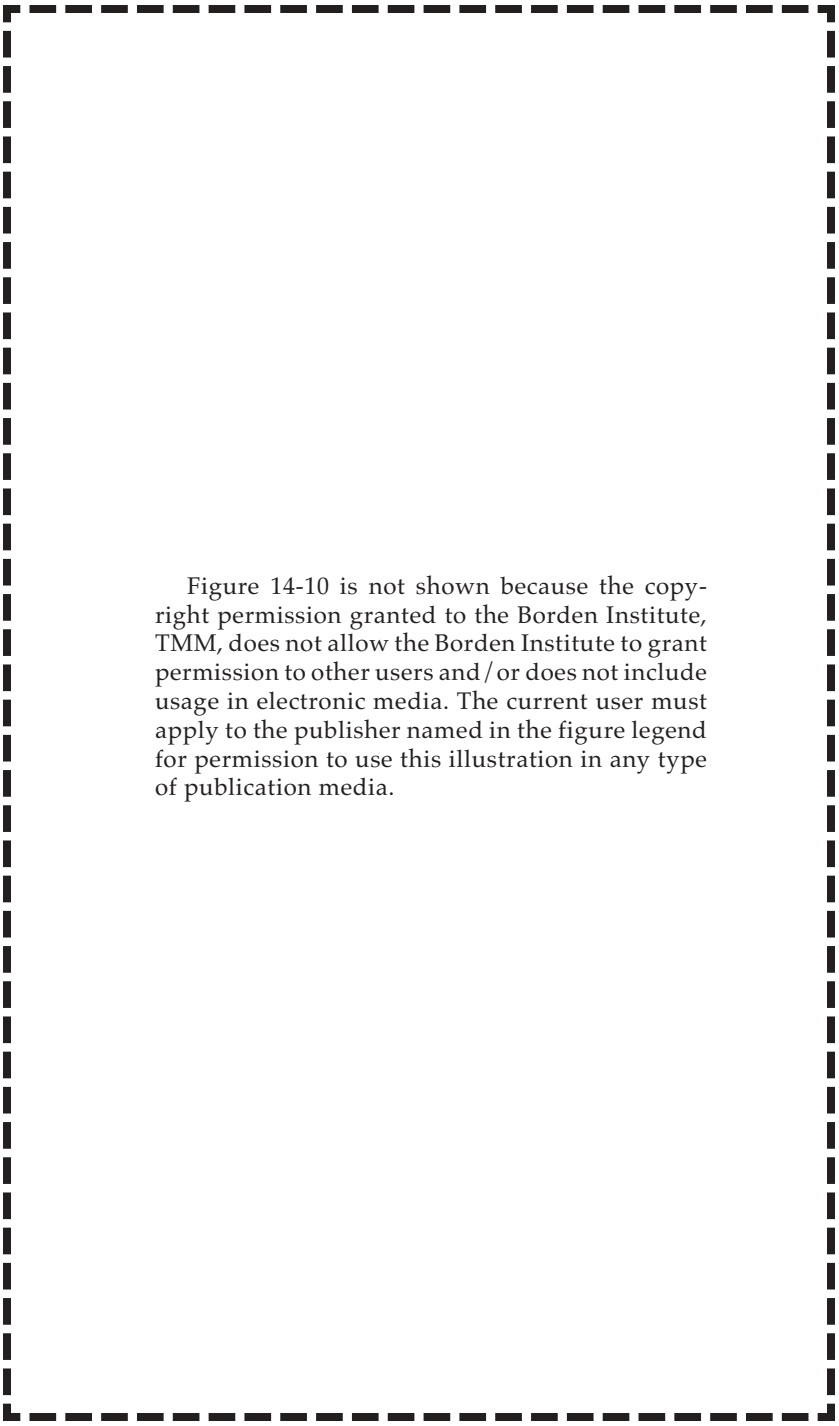
Animal experimentation and human epidemiological studies have demonstrated that chronic exposure to chlorinated hydrocarbons results in bioaccumulation in adipose tissues. Experimental observations within these test groups demonstrate significant differences in the metabolism and storage in the adipose tissue depots.

Numerous nonspecific signs and symptoms have been reported after acute organochlorine exposures. Sensory disturbances such as hyperesthesia or paresthesia may be either early or low-dose, acute effects of DDT poisoning. Headache, dizziness, vomiting, incoordination, and tremor may progress to myo-clonic jerking, convulsions, or both. Individuals who are exposed to cyclodienes may present with convulsions as the first sign of poisoning as long as 48 hours after acute exposure. Increased neuronal irritability results in excitation, convulsions, and possibly coma at high doses. Cardiac dysrhythmia may also occur.[16,23]

Several of the organochlorine insecticides (eg, aldrin and heptachlor) stimulate hepatic microsomal enzymes and undergo xenobiotic transformation through epoxide derivative intermediates (Figure 14-6). The development and storage of these intermediates, and, in animal models, evidence for their carcinogenic potential, have reinforced the concern that many of these compounds are suspect human carcinogens.[4] Histopathological changes have been noted in the livers of chlordecone workers; however, elevation of their hepatic enzymes indicative of damage was not observed. Reductions in sperm counts have been noted in workers who have been exposed to chlordecone and dichlorobromopropane. Blindness has been reported in sheep that have been exposed to

TABLE 14-10

TOXICOLOGY OF SELECTED ORGANOCHLORINE INSECTICIDES



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*Values obtained in standardized tests in the same laboratory

†Maximum rate of intake (usually 3-mo, 2-yr feeding studies) that was tested and did *not* produce significant toxicologic effects (as listed in the monographs issued jointly by the Food and Agriculture Organization of the United Nations and the World Health Organization, as developed by joint meetings of expert panels on pesticide residues held annually, 1965–1972)

‡Acceptable daily intake (ADI) = the daily intake of a chemical that, during a lifetime, appears to provide the practical certainty that injury will not result (in man) during a lifetime of exposure. Figures taken from World Health Organization (1973).

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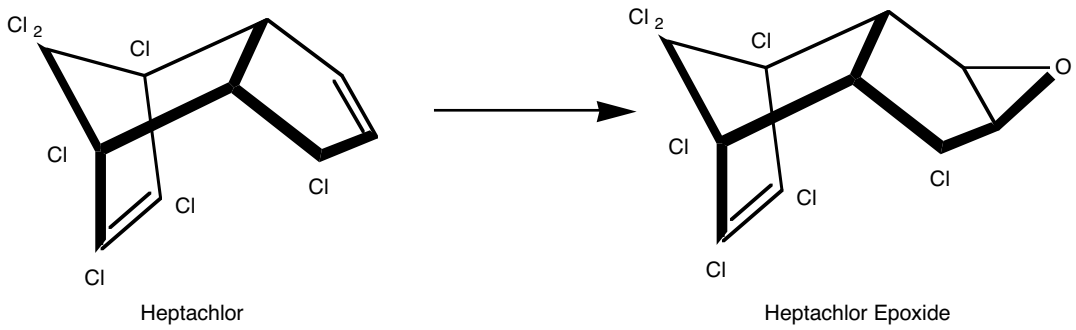


Fig. 14-6. When the parent pesticide compound *heptachlor* is metabolized by the hepatic P-450 enzyme system, the resultant metabolite *heptachlor epoxide*, a suspect carcinogen, is formed. The metabolism of chlordane to chlordane epoxide, also a suspect carcinogen, is similar.

endosulfan, and mirex has caused cataracts in the rodent model.[16,20,23] Chronic exposure to chlordecone has been associated with weight loss, weakness, tremor, slurred speech, cognitive changes, and abnormal liver-enzyme profiles.

Chlordane

Chlordane has been widely used as an environmentally persistent, highly effective termiticide. As a result of its efficacy and popularity, large numbers of pesticide operators and members of the general population have been exposed. The xenobiotic metabolism of chlordane has been evaluated in pest-control operators: chlordane and its metabolites (oxychlordane, heptachlor epoxide, and *trans*-nonachlor) were identified in the blood of some of the pest-control operators but not in the control subjects. The concentration of chlordane and its metabolites correlated well with the number of spraying days in the previous 3 months. As a result, the concentration of chlordane and its metabolites has been suggested as a biological monitor for chlordane-exposed workers. Although the chemical compounds can be identified at rather low concentrations in blood, no correlation between blood concentrations and health effects has been published. Consequently, the utility of the biological monitoring capability for chlordane and its metabolites remains speculative and is not routinely recommended.[14]

Purified chlordane has been reported to induce cytotoxic effects in human liver cell cultures. In that system, chlordane exposure resulted in growth inhibition and alterations of cellular morphology.

The fatal dose of chlordane for an adult has been estimated to be between 6 and 60 g. Onset of clinical signs and symptoms would be expected between 45 minutes and several hours.[14]

Route of Exposure. Chlordane and its formulations are lipophilic and may be readily absorbed following skin contact, inhalation, and ingestion. As a result of its widespread use, persistence, ease of cutaneous absorption, lipophilic nature, and preferred in vivo lipid-affiliated storage, the EPA identified almost ubiquitous presence of chlordane in samples of body fat and breast milk from human populations.[4]

Signs and Symptoms of Exposure. Because chlordane and related pesticides disrupt nervous system functions, patients may present with a spectrum of CNS-stimulation findings. The earliest signs of poisoning are related to increased sensitivity to stimuli. Hyperexcitability of the CNS usually manifests as nervousness, agitation, irritability, amnesia, and generalized hyperactive reflexes. Cycles of excitement followed by depression may occur repeatedly. More-severe signs include muscle twitching, tremor, incoordination, and ataxia. The most severe neurological signs include clonic convulsions, with or without coma.[14]

Respiratory depression may occur as an unusual result of chlordane intoxication. Aspiration of chlordane formulations that contain petroleum distillates may result in chemical pneumonitis.[14]

Gastrointestinal effects such as nausea, vomiting, and diarrhea have been reported following ingestion of chlordane. Extensive cutaneous contact may result in dermal irritation.[14]

The EPA considers chlordane and related compounds to be potential human carcinogens.[4] However, epidemiological studies of workers in the chlordane-producing industry have failed to identify an increased occurrence of cancer. Exposure to chlordane, heptachlor, or both has been related to aplastic anemia and acute leukemia in several cases, but the relationship between these chemicals and the adverse

health effects was inadequate to reflect a causal association. In another retrospective study, an uncertain cause-and-effect relationship was suggested between the occurrence of neuroblastoma in several children and possible chlordane or heptachlor exposure.[14]

In a prospective mortality study directed toward employees of a chlordane production plant, workers with the highest risk of exposure appeared to demonstrate an inverse relationship between exposure and cancer risk. The study identified an unexplained excess of deaths due to cerebrovascular disease.[14]

Medical Treatment. As with any pesticide-poisoned patient, basic life support and early decontamination procedures are essential elements of medical management. After the contaminated clothing has been removed, the patient should be decontaminated with soap and water, then topical alcohol, and then soap and water again.[14]

In alert patients, emesis should be induced with syrup of ipecac in cases of recent, substantial ingestion. In addition, administration of activated charcoal and a cathartic is recommended.[14]

As a consequence of the increased myocardial irritability associated with organochlorine poisoning, administration of epinephrine or other adrenergic amines may precipitate refractory ventricular arrhythmias.[14]

Seizure activity should immediately be treated with diazepam administered by intravenous bolus. The typical adult dose is 5 to 10 mg initially, which may be repeated every 15 minutes, as needed, up to a total dose of 30 mg. For seizure activity in a child, the recommended dosage of 0.25 to 0.4 mg/kg should be administered intravenously. In the child, diazepam doses may be repeated up to a total dose of 10 mg. Uncontrollable or recurrent seizures should be managed through administration of phenytoin.[14]

Excretion of chlordane (and a related organochlorine pesticide, chlordecone) may be accelerated by oral administration of cholestyramine, which fosters removal from the cycle of enterohepatic circulation. Dialysis, exchange transfusion, and hemoperfusion are probably ineffective.[14]

Heptachlor

Heptachlor epoxide has been identified as a metabolite of heptachlor in both animals and humans. In transformed human cell cultures, exposures both to heptachlor and to its epoxide induce unscheduled DNA synthesis, indicating possible genetic damage.[14] Heptachlor is absorbed following cutaneous contact, inhalation, and ingestion. The dose required to induce acute toxic effects in humans varies with the route and rate of exposure (see Figure 14-6).

Signs and Symptoms of Intoxication. Increased sensitivity to external stimuli and CNS hyperexcitability are the first adverse signs of exposure to heptachlor. Acute toxic signs of exposure include hyperactive reflexes, muscular twitching, tremors, ataxia, and clonic convulsions with or without coma. Respiratory depression may occur concurrently with convulsions. Repetitive cycles of excitability and depression may be seen. Cardiac irritability and contractility alterations can initiate dysrythmias.[23] Ingestion may cause nausea, vomiting, diarrhea, gastroenteritis, anorexia, or a delayed-onset hepatitis. Skin irritation has been reported following cutaneous contact.[14]

Aplastic anemia and neuroblastoma have been reported in patients following possible heptachlor exposures; however, a causal association has not been identified. If ingestion and subsequent aspiration of heptachlor pesticide formulations occurs, chemical pneumonitis should be anticipated.[14]

Medical Treatment. Patients contaminated with heptachlor should be decontaminated with soap and water. Some authorities recommend an alcohol wash following the soap and water, followed, in turn, by another soap and water wash. Three soap-and-water decontamination procedures have been recommended. Particular attention to decontaminating the hair is essential.[14]

Obtaining levels of chlorinated hydrocarbons or heptachlor in whole blood or serum is not useful in acute toxic exposures.[14] In most cases, blood levels of heptachlor or its metabolites reflect cumulative, rather than acute, exposures. Furthermore, these blood-chemistry analyses are usually not routinely available in most clinical laboratories. Because laboratory results will probably not be available to assist with early diagnosis or therapy, treatment must be based on a careful workplace—or intentional poisoning—historical profile. As with other organochlorine poisonings, if a history of heptachlor exposure is obtained, *the administration of adrenergic amines is to be avoided: they may increase myocardial irritability and precipitate refractory ventricular arrhythmias*.[14]

If an alert patient has ingested a possibly toxic dose of heptachlor, emesis should be induced with syrup of ipecac. Emesis is most effective within 30 minutes of ingestion of the poison. An activated charcoal slurry and cathartic should also be administered. Through interference with the enterohepatic circulation of the compound, cholestyramine has been reported to increase excretion of chlorinated hydrocarbons such as chlordecone and chlordane. Hemodialysis and ex-

change transfusion probably would not be effective therapeutic modalities for heptachlor poisonings.[14]

If seizures occur, diazepam should be carefully administered as an intravenous bolus of 5 to 10 mg. Diazepam may be repeated every 15 minutes, not to exceed a cumulative dose of 30 mg. If convulsions fail to respond to diazepam, or if they recur after initial therapy, phenytoin should be administered.[14]

Borate Insecticides

Boric acid, H_3BO_3, is also known as boracic acid or orthoboric acid. Its main use is as a common tablet formulation for pesticide management of cockroach infestation. Although the mechanism of action in humans is unknown, the end result is a metabolic acidosis with associated electrolyte abnormalities. Signs or symptoms of toxic exposure are not seen unless boron concentrations in the brain reach levels above 10 ppm (see Table 14-6).[31]

Routes of Exposure

Crawling children can be exposed to boric acid if pesticide applications of the powder or pellet formulations are careless or inappropriate. Intact skin provides an effective barrier to absorption. Abraded or burned skin allows efficient absorption, however, although no mechanism for enhanced absorption across abraded skin has been proposed.

Borates are well absorbed following ingestion. In rare instances, infants have been inadvertently poisoned when powder formulations were mixed in their infant formula.[31]

Signs and Symptoms of Exposure

The signs and symptoms associated with exposure to and absorption of borate insecticides include abdominal pain, nausea, protracted vomiting, diarrhea, and hematochezia. These have been associated with absorption across burned or abraded skin. Topical exposure has been associated with a bright erythematous rash that may progress to extreme exfoliation. Restlessness, headache, weakness, and tremors may precede convulsions in severely poisoned patients. Cyanosis and shock may precipitate acute renal failure associated with metabolic acidosis from boric acid in severe cases of intoxication. Poisoning may be confirmed by blood borate concentrations. Normal ranges in nonexposed individuals are between zero and 7.2 mg of borate per liter of blood with a mean of 1.4 mg/L. Concentrations lower than 340 mg/L have rarely been associated with toxicity. Urine borate tests may yield false-positive results.[16]

Medical Treatment

Potentially contaminated skin should be washed with soap and water. Treatment of boric acid poisoning includes administering syrup of ipecac to children who weigh less than 30 kg, if the child has ingested more than 200 mg/kg as an acute dose. Larger individuals who have ingested a dose of more than 6 g are also treated with syrup of ipecac. If acute doses exceed these levels, emergency medical specialists may prefer to use gastric lavage as an alternative to inducing emesis.[16]

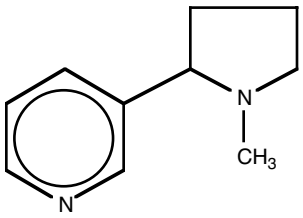
Activated charcoal does not absorb borate and should not be used unless there are special ingestion circumstances (eg, the ingestion of multiple substances). A blood sample drawn 2 to 3 hours after ingestion should be obtained to assess the severity of poisoning. If massive quantities have been ingested over several days, careful monitoring and medical management to prevent the adverse sequelae of metabolic acidosis and electrolyte abnormalities must be provided.[16] Excretion of boric acid is efficient and forced diuresis may afford some benefit. Exchange transfusion and peritoneal dialysis are efficacious.[31] Anticonvulsants are indicated for treatment of convulsions.[16]

Botanical Pesticides

Pesticides that are derived from living biological systems are chemically and pharmacologically diverse. In the broadest sense, this group includes relatively simple but potent molecules such as nicotine, complex proteinaceous poisons such as ricin, and the neurotoxin produced by *Clostridium botulinum,* which causes botulism. Many individuals share the common belief that a pesticide derived from natural sources has a greater margin of safety than a commercially manufactured pesticide. Carefully performed testing using standardized and accepted laboratory models has demonstrated, however, that some of the most potent poisons are derived from natural sources.

The mechanisms of action and possible antidote therapeutics for selected toxic compounds of biological origin have been carefully evaluated in the military's biological defense program. However, review and discussion of these toxins, their toxic mechanisms, and antidotes are not relevant to this discussion. Numerous pesticides derived from biological sources are available; however, the military uses only a few botanical derivatives such as the pyrethrins to eradicate or manage pests.

Nicotine



Nicotine is one of the most frequently recognized plant-derived pesticides. In addition to its commercial use as a fumigant and stomach poison for leaf-eating insects, its scientific use has provided valuable insight into the functions of the cholinergic components of the human nervous system. The toxicological mechanisms for cholinesterase inhibitors were clarified because of nicotine's cholinergic properties and reaction with specific sites (nicotinic receptors) within the CNS and PNS. Nicotine is not itself a cholinesterase inhibitor, but does have CNS, autonomic, and neuromuscular effects similar to excessive acetylcholine stimulation at nicotinic sites. Nicotine can exist in two isomeric forms: the synthetic R isomer is up to 8-fold more toxic than the natural S isomer.

There is no specific antidote for nicotine poisoning, but atropine administration may be somewhat efficacious in emergency medical management. In nicotine-poisoned dogs, artificial respiration has been shown to be life-saving if respiratory assistance was instituted prior to severe hypotension.[7]

Pyrethrum, Pyrethrins, and Pyrethroids

The insecticidal properties of the *Chrysanthemum* (Dalmatian pyrethrum flower) have been known for more than 100 years. Commercial growth of the flowers and production of the natural pyrethrum extracts (pyrethrins) made pyrethrum and pyrethrins available for domestic and agricultural pesticide use.[6] Widespread agricultural uses were initiated during the 1970s.[7] The naturally occurring pyrethrum components are produced from an oleoresin extract of dried chrysanthemum flowers and contain six active insecticidal ingredients collectively known as pyrethrins. These are used in a number of pesticide products, particularly aerosol products for indoor pest control. Advantages of pyrethrum and pyrethrins include their relatively low mammalian toxicity, rapid "knock down" and kill of pests, and the absence of environmental persistence. Disadvantages include the high cost of application and poor light stability.

As a result of efforts to decrease the unit production cost and to improve light stability, more than 1,000 synthetic compounds known as *pyrethroids* have been synthesized, some of which show significant structural differences and pest selectivities from the parent pyrethrum molecule (Figure 14-7).[7] Pyrethroids are light stable, biodegradable, and highly specific. For example, deltamethrin is approximately 3,000- to 5,000-fold more toxic to houseflies than to rats.[7,16,20,23]

Permethrin, one of the pyrethroid products, is a repellent that is used extensively by the military as a uniform impregnant (see Table 14-6). Some pyrethroids are approved for use as clothing spray formulations and others are used as pediculocides.

Route of Exposure. Pyrethrins are poorly absorbed via the dermis but appear to be well absorbed via the inhalational and ingestional routes. Although pyrethroids, if they are administered intravenously into laboratory animals, may cause extreme neurotoxic effects (convulsions), dermal and inhalation exposures are associated with only limited systemic toxicity.[16]

Mechanism of Action. Pyrethrins and pyrethroids have a high affinity for the sodium channel of the afferent neuron and produce their toxic effects as a consequence of neuronal hyperexcitability. As a consequence, pyrethroids cause a delay in channel closure, which results in a prolonged tail current of the action potential. The interaction slows the influx of sodium during the end of the depolarization phase, increases the depolarizing afterpotential, and results in repetitive discharges.[7,16,20] Pyrethroids are *open* channel blockers (ie, they selectively affect the active, or open, sodium channel). At high concentrations of pyrethroid, the nerve membrane may depolarize completely and excitability may be blocked.[7]

Allethrin and DDT have been shown to cause sodium channel effects in the lateral line organ of the toad. At the receptive portion of the peripheral afferent neuron, both chemicals cause a hyperexcitable stimulus response that results in the generation of a repetitive series of impulses. In the conductive portion of the afferent neuron, both compounds appear to impede the closing of the sodium channel, which results in an increased phase of hyperexcitability.[29]

Within the CNS, pyrethroids exhibit effects consistent with several mechanisms of action. Proposed CNS mechanisms of pyrethroid effects include antagonism of the GABA-transmitter pathway, modification of nicotinic cholinergic transmission, enhancement of norepinephrine release, and alteration of calcium-ion fluxes. The primary effects of pyrethroids may be the result of changes in the functional sodium channel activity of the afferent neuron; the toxic CNS effects appear to be secondary.[7]

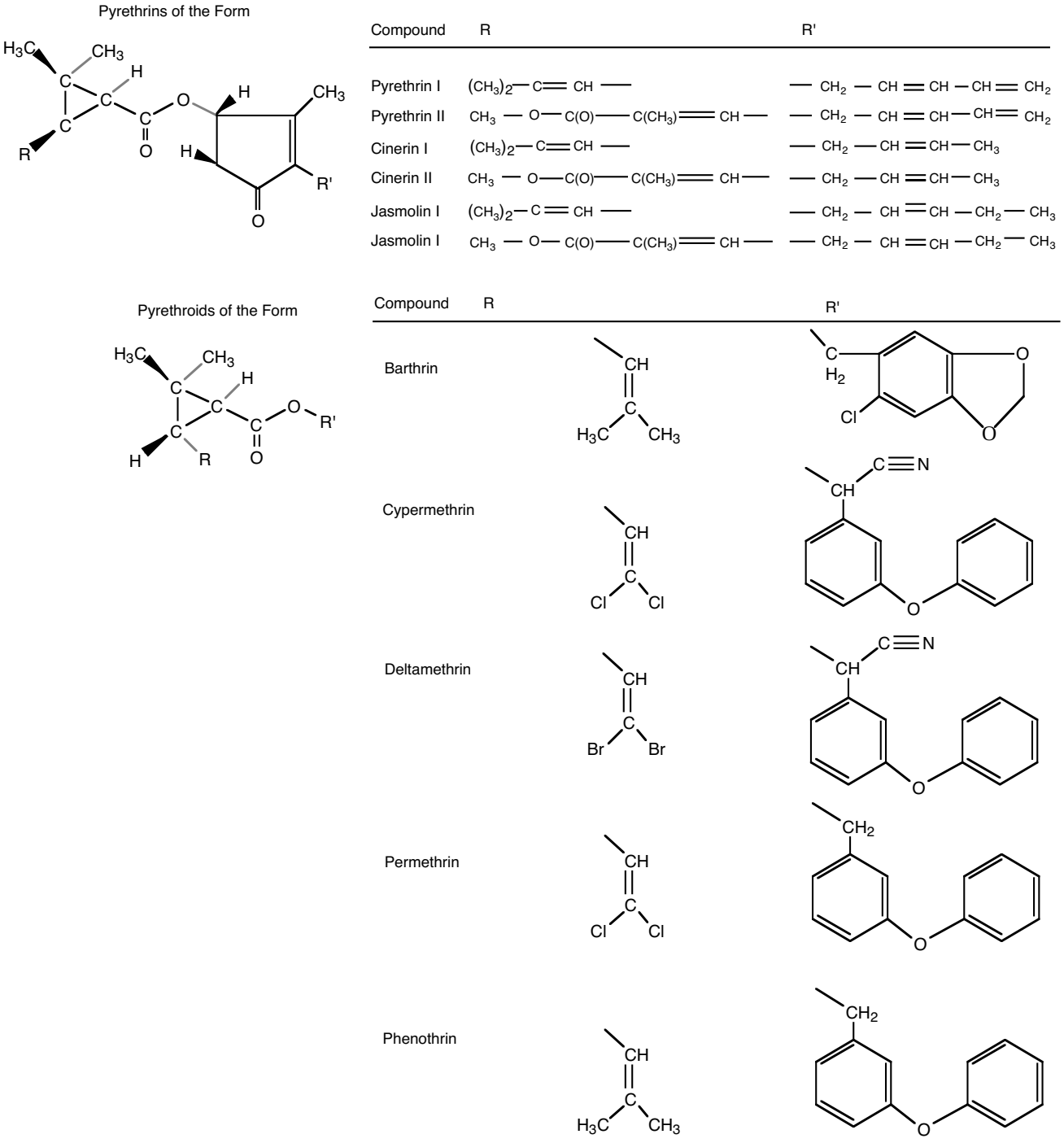


Fig. 14-7. The chemical structures for representative pyrethrin and pyrethroid pesticides. Source: Ray DE. Pesticides derived from plants and other organisms. In: Hayes WJ Jr and Laws ER Jr, eds. *Handbook of Pesticide Toxicology*. New York: Harcourt Brace Jovanovich, Academic Press Inc; 1991; Chap 13.

Each pyrethrin and pyrethroid compound may form at least four isomers, and interaction with the sodium channels is highly dependent on the isomeric form. Permethrin and pyrethrum form isomers at the third carbon of the cyclopropane ring, with the *cis* and *trans* forms both demonstrating insecticidal activity. In mammalian systems, however, the *cis* isomers are approximately 10-fold more potent than the *trans*.[7]

Crude pyrethrum is a dermal and respiratory allergen; the refined pyrethrin products are less sensitizing and less irritating. A strong cross-reactivity with ragweed pollen has been shown. Pyrethrins do not inhibit the enzyme cholinesterase.[7,16] The rapid rate of hydrolysis of both the natural and synthetic molecules within the hepatic circulation probably accounts for the low acute toxicity in mammals, compared to the selective toxicity for insects.[7,16,20]

Most authorities agree that topical and systemic toxicities of the pyrethroids should be considered separately. In addition, most agree that there are two distinct types of systemic poisoning syndromes.[6,7] The different syndromes have been used to separate most pyrethroid compounds into two groups, types I and II, based on their clinically different manifestations of poisonings. In the rodent, the type I syndrome (tremor) is first recognized by an increased aggressiveness, followed by the rapid onset of tremor, hyperactivity, hyperthermia, clonic convulsions, and death. The type II syndrome (choreoathetosis with salivation) begins with profuse salivation, followed by a coarse body tremor, spontaneous writhing, tonic-clonic convulsions, and death.[6]

Permethrin and cismethrin are examples of type I compounds. Effects of cismethrin poisoning can be induced by placing a small quantity of the chemical within the CNS; as a result, the poisoning effects are believed to arise from central stimulation. In contrast, type II compounds such as deltamethrin and cyfluthrin act on a broader range of tissues and produce a more complex poisoning syndrome.[7]

Signs and Symptoms of Exposure. Acute intoxication with pyrethroids is uncommon. Patients may present with signs or symptoms of allergic skin reaction, eye irritation, skin irritation, or pulmonary allergic mediated bronchospasm. Extreme doses may cause salivation, tremor, incoordination, vomiting, and diarrhea. Irritability to sound has also been reported. Paresthesia has been associated with exposure to pyrethroids in humans who have experienced effects through local volatilization or liquid contact. Facial discomfort is reported most commonly; however, paresthesia of the neck, forearms, and hands are sometimes noted. Heat, sweating, sun exposure, and moisture may aggravate symptomatology. Paresthesia, itching, and/or burning sensations may progress to numbness.[16] Possible long-term effects in humans include the potential for carcinogenesis.[32]

Medical Treatment. Rapid decontamination is a mainstay of therapy; therefore, contaminated skin should immediately be washed with soap and water. Antihistamines are efficacious in controlling most allergic reactions. Severe asthmatic reactions may require bronchodilators and corticosteroid therapy. Vitamin E oil preparations are effective in relieving symptoms of local paresthesia. Corn oil is somewhat helpful, but zinc oxide aggravates the sensation.[7,16] Contact dermatitis may require prolonged use of topical corticosteroid preparations.[16]

After acute ingestion, careful gastric lavage may be followed by administering activated charcoal and a cathartic. There are no approved antidotes.[16]

As a precautionary note, the EPA states that although several drugs have been useful in the treatment of intentionally poisoned animals, none has actually been tested in humans. Therefore, neither the efficacy nor the safety of the therapeutic compounds has been evaluated.[16]

Some authorities recommend that therapy should be directed toward managing the functional neuropathological effects (hyperthermia, choreoathetosis, and seizures) until the pyrethroids are metabolized. The sedatives phenobarbital and pentabarbitol are effective against type I neurological effects when administered in anesthetic concentrations. Clomethiazole has been shown to be beneficial in deltamethrin poisoning (type II), especially when used with diazepam and atropine. Diazepam, when used alone, was found to be of limited benefit in the rodent model and only moderately effective in the canine model.[7]

Rodenticides

Rats and mice may ingest or spoil large quantities of stored food. Rodents may also directly transmit disease and cause discomfort or disease through bites. In addition, rodent parasites can be disease vectors. Efforts to control the rodent population may be directed toward removal of harborage, introduction of predators, use of traps, and use of chemicals directed toward poisoning of the rodent species.

Although numerous chemical compounds have been listed as rodenticides, including thallium, strychnine, phosphorous, phenyl- (PNU) and thio- (ANTU) ureas, and red squill,[23] civilian and military uses are usually associated with the anticoagulant compounds because they have a wider margin of safety (see Table 14-6).

The anticoagulant dicoumarol, first isolated from spoiled, sweet-clover hay, was identified as a cause of

lethal hemorrhagic disease in cattle during the 1920s. The beneficial medical therapeutic and possible rodenticidal properties were readily recognized and several related compounds were rapidly synthesized. Warfarin, a synthetic analog, was introduced for clinical trial in 1952 and used to treat President Dwight D. Eisenhower in 1955.[33]

Anticoagulant rodenticides are typically applied as baits, either in liquid or solid form. Bait formulations must meet these four requirements: they must be (1) effective in small quantities, undetected by rodents; (2) formulated to avoid bait shyness; (3) lethal without the rodents' becoming suspicious of the cause; and (4) used in a concentration safe for accidental human ingestion or formulated in a concentration specific to the target species.[20]

Mechanism of Action

Regardless of the anticoagulant bait form, the active ingredient is a derivative of coumarin, such as warfarin or fumarin; or a derivative of 1,3-indanedione, such as pival or diphasin. These compounds have similar modes of action. They are highly toxic when pure, but are incorporated into bait formulations in low concentrations. For example, warfarin concentrations incorporated into most baits range between 0.025% and 0.05%. Although detectable reductions of prothrombin can be identified in rodents within 24 to 48 hours of initial ingestion, the onset of actual hemorrhage in rodents generally follows ingestion of 1 to 2 mg daily for one week.[16,23]

Coumarins and indanediones are effective anticoagulants. In addition to its anticoagulant properties, warfarin damages capillary integrity, which precipitates internal hemorrhage. Indanediones induce signs of neurological and cardiopulmonary injury in the rodent toxicological model, but have not been shown to cause neurological or cardiopulmonary effects in humans.[16,23]

Warfarin is an antimetabolite of vitamin K and as such, warfarin depresses the hepatic vitamin K–dependent synthesis of essential clotting factors II (prothrombin), VII, IX, and X. The antiprothrombin effect is the best known and is the basis for detection and assessment of clinical poisoning. Lengthened prothrombin time from a toxic dose of coumarins or indanediones usually reaches a maximum 36 to 72 hours after acute ingestion. Newly developed superwarfarin compounds are much more potent and their anticoagulation effects more persistent. Warfarin has also been identified as a human teratogen that causes microcephaly, brain malformations, optic atrophy, nasal hypoplasia, and mental retardation.[16,23]

Route of Exposure

Gastrointestinal absorption of anticoagulant rodenticides is efficient, with warfarin well absorbed within 2 to 3 hours of ingestion. In a study of 14 subject volunteers, warfarin was administered orally at a dosage of 1.5 mg/kg. Maximal concentrations of warfarin were measured in plasma between 2 and 12 hours after ingestion. The maximal decrease in prothrombin activity was demonstrated between 36 and 72 hours after ingestion.[33]

Dermal absorption is slow but measurable in the rodent. Dermal absorption has not been reported as a cause of human poisoning. Toxic ingestion may occur if the bait is unintentionally consumed by a child or is intentionally consumed in a suicide attempt.

Signs and Symptoms of Intoxication

Signs and symptoms of anticoagulant ingestion include epistaxis, bleeding gums, petechial rash, hematomas, hemarthrosis, cerebral hemorrhage, shock, and death.

Medical Treatment

Medical treatment is probably not required if only a few grams of bait are ingested. If larger amounts have been ingested, syrup of ipecac followed by activated charcoal and cathartics may be efficacious. If the amount of the anticoagulant rodenticide ingested is unknown, phytonadione (vitamin K_1) given orally will protect against the anticoagulant effect with minimal risk to the patient. Phytonadione specifically is required: vitamin K_3 and vitamin K_4 are not antidotes for these anticoagulants.

If the patient is bleeding actively, careful intravenous administration of vitamin K_1 consistent with the specified dosage-administration rates is indicated, recognizing that adverse reactions and fatalities have been reported in association with this procedure. Actively bleeding patients should receive fresh frozen plasma or fresh blood transfusions in cases of severe bleeding.

Prothrombin times may be helpful in judging the severity of intoxication if the ingestion occurred during the preceding 15 days. The peak prothrombin effect occurs after about 3 days and prothrombin times should be followed to document peak effect and recovery.[16,23]

Herbicides

The compound 2,4-dichlorophenoxyacetic acid (2,4-D) has been used as a growth-regulating substance

with herbicidal activity since the early 1940s (see Figure 14-2).[8] 2,4-D has only moderate oral toxicity when administered to a variety of animal species. Large doses cause death quickly in animals, probably as a result of ventricular fibrillation. Lower doses were associated with myotonia, ataxia, paralysis, and coma. Of the mammalian species tested, the dog was the most sensitive, with an oral LD_{50} of 100 mg/kg. The no-effect level in a 2-year canine study was approximately 12 mg/kg/day.[34]

Limited information is available with respect to human exposures and toxic doses. In humans, 100% of the radiolabeled dose administered by intravenous injection was recovered in the urine. In contrast, only 5.8% of the topically applied dose was excreted in the urine, suggesting that dermal absorption is limited.[34]

Route of Exposure

Workers exposed to herbicides via inhalation, ingestion, or dermal contact may experience clinical effects. Skin contact is the more common exposure route; however, dermal absorption is not efficient.[34] Inhalation and ingestion are also possible routes of exposure.[14]

Signs and Symptoms of Intoxication

Although a wide variety of clinical reactions to exposure is possible, depending on the exposure route and dose, irritant responses are most commonly reported effects of exposure.[14] Irritant responses have been reported from cutaneous contact, airborne or inhalation exposure, and ingestion. Chloracne from the dioxin contaminants in the related herbicide 2,4,5-T has been reported in heavily exposed workers (see Figure 14-2).

Eye, nose, and throat irritation may be associated with airborne exposures. Pulmonary edema has been reported following inhalation exposures. Ingestion has been reported to cause mouth, esophagus, and stomach irritation sometimes associated with vomiting and diarrhea. Elevated liver enzymes—lactic dehydrogenase (LDH), serum glutamic-oxalacetic transaminase (SGOT), and serum glutamic-pyruvic transaminase (SGPT)—have been reported.[14]

Neurological consequences of occupational exposures have been reported to include vertigo, headache, malaise, and paresthesias. Higher doses may produce muscle fasciculations, followed by profound muscle weakness and unconsciousness. Rhabdomyolysis and myotonia have been reported in severely poisoned persons.[14]

Tachycardia has been reported as a common manifestation of cardiac toxicity but the occurrence of actual arrhythmia has been uncommonly reported. Reported renal effects include albuminuria and azotemia.[14]

Headache, dizziness, stomach pains, nausea, leukopenia, fever, urinary incontinence, hypertonia, and constipation have been reported in humans after accidental or intentional ingestion. Skeletal muscle fasciculations have also been reported. Although myotonia is the most frequently identified sign of poisoning in animals, it is unusual in poisoned humans. Degeneration of the renal convoluted tubule, glomerular protein deposition, and limited fatty infiltration of the renal parenchyma have been reported in an accidental ingestion by a farmer.[34] Serious acute human poisonings have been reported after the ingestion of multigram doses.[14] An analog of 2,4-D, clofibrate, is used clinically to lower cholesterol levels.[34] These herbicides can be measured directly in plasma and urine by gas liquid chromatography. They do not affect cholinesterase levels.[14]

Medical Treatment

If eye exposure occurs following a splash, the eyes should be irrigated with copious amounts of water for at least 15 minutes. If a direct splash into the eyes has occurred, the patient should be taken to a medical treatment facility (MTF) for evaluation and necessary eye care.[14]

In cases of skin contact, the affected area should be thoroughly cleansed with soap and water. If acute irritation occurs, evaluation at the health clinic is indicated.[14]

Although massive overexposure could require the basic life-saving interventions such as airway management, this is usually unnecessary. Respiratory depression, hypotension, metabolic acidosis, hyperthermia, or seizures may occur in severely poisoned individuals.[14]

Emesis is indicated, using syrup of ipecac, if intentional ingestion has occurred and if the patient is conscious. This emetic is most effective when administered within 30 minutes of ingestion. Removal of the stomach contents via nasogastric intubation is indicated if the patient is obtunded, comatose, or convulsing. Activated charcoal administration and catharsis are recommended following ingestion of chlorphenoxy pesticides.[14]

If ingestion could result in toxic clinical manifestations, the following baseline determinations should be obtained: complete blood count, arterial pH, bicarbonate, serum creatinine, blood urea nitrogen (BUN), liver enzyme levels, urinary protein, myoglobin, and erythrocyte losses; urinary output should also be measured. Liver enzymes should be monitored to evalu-

ate the significance of possible hepatic injury. Because muscular tissue destruction may occur, baseline levels of serum creatine phosphokinase and myoglobin should be measured. Ongoing evaluations of liver enzymes and myoglobin levels should be performed following intentional ingestion. When significant myoglobinuria is seen, alkaline diuresis should be instituted to enhance elimination.[14] Alkaline diuresis appears to improve renal clearance of 2,4-D.

If inhalation has occurred in an enclosed area, the patient should be removed to fresh air. The patient may experience irritation of the respiratory tract as burning discomfort in the airway. Cough and respiratory distress may follow high-dose inhalation exposures as evidence of pulmonary edema. Bronchitis or pneumonitis may occur. Supplemental humidified oxygen or assisted ventilation may be required in extreme cases.[14] The treatment of 2,4-D exposure is symptomatic, with this exception: quinidine sulfate has been used in the management of tachycardia and may be helpful in treating the skeletal muscle dystonia.[34]

Many chronic adverse health effects from exposures to this group of pesticides have been alleged. However, in a 20-year follow-up of the health status of U.S. Air Force veterans who were exposed to herbicides in Vietnam, only basal cell carcinoma was more frequently identified among the herbicide handlers.[35] The possibility that the association was spurious has been noted.[36]

Sodium Arsenite

Sodium arsenite ($NaAsO_2$) is used as aqueous solution for weed control, and it has limited use as an insecticide.[16] Arsenical compounds demonstrate a spectrum of toxicity based on their chemical composition and arsenic valence state. The generally accepted order of toxicity is from the more toxic arsine (trivalent); through the organo-arsine derivatives, arsenites (trivalent); arsenoxides (trivalent); arsenates (pentavalent); other pentavalent organic compounds; arsonium metals (monovalent); to the least toxic, metallic arsenic. The active component of sodium arsenite is the arsenite, or trivalent arsenic, moiety. Arsenite has been shown to be much more toxic than the pentavalent form, arsenate.[14,16]

Mechanism of Action

Acute ingestion of more than 100 mg of the arsenite compound has been reported to be associated with significant toxicity. Ingestion of 200 mg of a related compound, arsenic trioxide, may be fatal in an adult.[14]

Sodium arsenite has been reported to be a potent cause of a number of cutaneous lesions, including corrosive ulceration. In addition, among pesticide applicators, it has been associated with erythema, papular dermatitis, and folliculitis. Among previously sensitized patients, some cases of folliculitis may actually be seen at low-exposure concentrations as a result of allergic cutaneous responsiveness. Ulceration of the hands, feet, and scrotum have been reported. While trivalent arsenic compounds are associated with skin corrosion, arsenic trioxide and pentoxide compounds are usually reported as skin sensitizers.[14]

Although arsenic compounds have been associated with both skin and pulmonary cancer in human epidemiological studies, arsenic has not yet been reported as a carcinogen in standard laboratory animal models. Arsenic is identified as a human carcinogen in the statutory occupational requirements promulgated by OSHA. The EPA has been actively reviewing the issue of potential carcinogenicity and has recently acted to withdraw product registrations.

Small doses of arsenic-containing compounds induce vasodilation. Increasing doses stimulate capillary dilatation and increase capillary permeability. Transudation of a large volume of plasma may cause profound hypotension with secondary arteriolar and myocardial damage. Abnormalities of the electrocardiographic record may persist for months following acute poisonings.[14]

Inorganic arsenicals cause increased blood flow through the bone marrow, which alters the marrow's cellular composition. Moderate doses of inorganic arsenicals depress the production of both erythrocytes and leukocytes, possibly through inhibitory actions on folic acid interactions.[14]

Inorganic arsenicals are considered to be potent hepatotoxins. Poisonings have been associated with central necrosis, fatty infiltration, and cirrhosis. Acute yellow atrophy and death may occur.

In a 1977 report concerning the state of California, 291 of 2,228 pesticide exposures involved sodium arsenite ingestion. Dosages as low as 1 mg/kg may induce serious toxicity and dosages as low as 2 mg/kg may be lethal.[14]

Route of Exposure

Acute poisonings are associated with both intentional and accidental ingestion. Chronic oral intoxication is associated with arsenical compounds used as medicaments. Skin contact may result in localized pathology but has not been associated with poisonings. Inhalational exposure is possible, depending on the exposure circumstances.[14]

Signs and Symptoms of Intoxication

Acute symptoms usually occur within 30 minutes to 1 hour from the time of ingestion unless simultaneously consumed food delays absorption. A garliclike odor may be noticeable in the breath or feces. Dysphagia, esophageal pain, stomach pain, colic, and profuse, watery—sometimes bloody—diarrhea have been reported. Dehydration, hypotension, tachycardia, and fluid and electrolyte disturbances are common. Hypovolemic shock, sometimes with associated intestinal blood loss, and cardiac abnormalities including tachycardia, QT interval prolongation, alterations in the T wave, and ventricular fibrillation have been reported in acute exposures. Chronic exposures have been associated with myocarditis.[14]

Acute exposures by direct contact with trivalent arsenic–containing compounds can cause eye, mouth, and skin corrosion. Chronic exposures have been associated with cutaneous and nasal septal ulcerations, and nasal septal perforations have been reported. Cutaneous responses to chronic arsenical exposures may include hyperpigmentation, keratoses, and epidermoid carcinomas.[14]

Acute arsenic exposures have been associated with CNS and PNS effects including alterations of mental status, convulsions, toxic delirium, chemical-induced encephalopathy, and delayed peripheral neuropathy. Hematuria and acute tubular necrosis have been reported complications of acute arsenic poisoning.[14]

Acute poisoning can cause hemolysis. Chronic arsenic exposures have been associated with bone marrow depression, pancytopenia, aplastic anemia, and leukemia.[14] Inorganic arsenicals may cross the placenta and have been associated with fetal death if chelation therapy was not prompt.[14]

Medical Treatment

Individuals with a history of possible acute arsenic ingestion require careful medical evaluation and timely medical management. A complete blood count, urinalysis, and baseline levels of serum electrolytes, liver enzymes, BUN, and creatinine should be obtained immediately. Urinary and blood arsenic levels should be obtained. A 24-hour urine specimen should be analyzed for arsenic excretion. Urinary arsenic excretions exceeding 100 μg have been reported to indicate abnormal excretory levels.[14] However, individuals who consume diets rich in seafood may excrete 200 μg or more of arsenic per day.[16] Individuals with possible surface contamination should be washed with soap and water. Decontamination of all areas, including the hair, should be thorough.[14,16]

Chest and abdominal X rays should be obtained for all patients being evaluated for arsenical ingestion. Timely, thorough gastric lavage is indicated for patients with acute, possibly toxic, ingestion. Whole-bowel irrigation has been recommended if radiography identifies arsenicals in the intestinal contents. Although activated charcoal has somewhat speculative benefit, its use is recommended following lavage. If there is no primary diarrhea associated with the arsenic ingestion, the administration of sodium sulfate as a cathartic should be considered.[14] Morphine may be administered in cases of intense abdominal pain.

Aggressive fluid and electrolyte management is required for individuals who ingest arsenicals, and is especially critical for those who are hypovolemic. A high output of alkaline urine should be maintained.[14] In some circumstances, pulmonary edema has been associated with arsenic poisoning.[14]

Symptomatic patients should be promptly treated with the chelating agents dimercaprol (2,3-dimercaptopropanol, also known as British anti-Lewisite [BAL]) and penicillamine. To avoid adverse effects from BAL administration, it should be administered intramuscularly at a rate of 3 to 5 mg/kg/dose every 4 to 12 hours. The dose requirement and frequency of administration should be correlated with the degree of arsenical poisoning. Tapered doses of BAL should be continued for 5 to 8 days in patients who are allergic to penicillin.[14] Another authority recommends somewhat lower dosages: 2.5 to 3.0 mg/kg/dose every 4 hours and tapered over about 2 weeks.[16]

As the signs and symptoms of acute arsenic poisoning subside as a consequence of BAL therapy, penicillamine should be prescribed as soon as possible for patients who have no history of penicillin allergy. For adults, the recommended dose for oral administration of D-penicillamine is 100 mg/kg/day up to 2 g daily, provided in four divided doses for a total of 5 days. The recommended dosage for children is 25 mg/kg/day in four divided doses daily, not to exceed a total of 2 g.[14] Another authority recommends, for children younger than 12 years, 100 mg/kg/day in 4 divided doses, not to exceed 1 g daily.[16]

Combined BAL and penicillamine therapy should be considered for severely poisoned patients. The dosages of chelating agents must be adjusted if renal complications occur as a result of the arsenic exposure. Hemodialysis may be necessary if renal function is impaired and if removal of the chelated arsenical complex is desired. Dimercaptosuccinic acid is currently being investigated as an alternative to BAL.[14]

Complications associated with the administration of BAL include acute signs and symptoms such as nausea, headache, restlessness, anxiety, paresthesia,

pain, tearing, tachycardia, and hypertension. In selected patients, antihistamines may be beneficial in managing these complications. Other common side effects from BAL administration include maculopapular rash, fever, depressed leukocyte counts, eosinophilia, lymphadenopathy, and joint pain. BAL therapy has also been implicated in a number of other, less common complications.[14,16]

PESTICIDE LEGISLATION

Numerous federal, state, local, and DoD regulations have been promulgated to ensure the proper use and disposition of pesticides. A brief history of federal pesticide legislation may help the reader understand the political concerns about pesticides.

Pesticide legislation is in a constant state of flux. Current laws continue to be amended and new laws continue to be enacted. The purpose of this legislation is to protect those who apply pesticides, the bystanders, and the environment from the harmful effects of pesticide residues. Therefore, all participants in the pesticide section of the occupational health program must be familiar with the current, pertinent military regulations and the requirements of federal, state, and local regulations.

The Federal Food, Drug, and Cosmetic Act

The first federal law regarding pesticides was the Food and Drug Act of 1906. It required that food shipped in interstate commerce be pure and wholesome. Although pesticide residues were not addressed in this act, their exclusion was eventually identified and the act was completely rewritten. The 1938 legislation was called the Federal Food, Drug, and Cosmetic Act; it established the allowable levels of pesticide residues on foods. This legislation was the federal government's first attempt to protect consumers from foods that had been contaminated with pesticides.

In 1954, Public Law 518, commonly called the Miller Amendment, amended the 1938 Federal Food, Drug, and Cosmetic Act. This amendment established pesticide *tolerances* (allowable residues on a raw agricultural commodity). The Miller Amendment stated that a commodity could be considered adulterated if (*a*) it contained a pesticide residue that had not been cleared for safety or (*b*) it exceeded the allowable tolerance.

The Food Additives Amendment, enacted in 1958, further amended the Federal Food, Drug, and Cosmetic Act in 1958; it regulated the use of food additives and established pesticide tolerances in processed foods. An extremely important part of this amendment was the Delaney Clause, which prohibited the use of a pesticide or a food additive that had been shown to cause malignant tumors in laboratory animals at any dose.

The Federal Insecticide, Fungicide, and Rodenticide Act

The first law regulating the transportation of pesticides in interstate commerce was enacted in 1910: the Federal Insecticide Act was designed to protect farmers from the distribution of fraudulent and substandard pesticide products. In 1947, the Federal Insecticide, Fungicide, and Rodenticide Act was enacted. It superseded the 1910 Act and required that pesticide products be registered and labeled with the U.S. Department of Agriculture before being shipped in interstate commerce. The Federal Insecticide, Fungicide, and Rodenticide Act also attempted to ensure the safe use of pesticides by requiring them to be labeled with

- the manufacturer's name and address;
- the name of the pesticide;
- the net contents;
- a statement of ingredients;
- warnings to prevent injury to humans and other animals, plants, and organisms that are not targets; and
- directions for use that would protect the user and the public.

In 1972, the most important revision of the Federal Insecticide, Fungicide, and Rodenticide Act was completed; this revision, entitled the Federal Environmental Pesticide Control Act, prohibited the use of any pesticide that was inconsistent with the warnings and directions on the label. In other words, *the label was the law*. Another provision of the 1972 revision regulated pesticides within states, not only those involved in interstate commerce; this was an important development in the regulation of pesticides on a national level.

The Federal Environmental Pesticide Control Act also required that pesticides be categorized as *General Use Pesticides* and *Restricted Use Pesticides*. General Use Pesticides are those pesticides that the public uses. Restricted Use Pesticides must be applied by, or under the direct supervision of, trained and certified personnel. A certification program was mandated within each state to train and certify the personnel who could apply the pesticides included in the Restricted Use category.

The Environmental Protection Agency

In 1969, the National Environmental Policy Act became a law and established the EPA. The legislation transferred the authority for pesticide regulation and registration from the U.S. Department of Agriculture to the EPA. At the same time, the authority to establish pesticide tolerances was transferred from the Food and Drug Administration to the EPA. However, the authority for enforcement of tolerances remains with the Food and Drug Administration.

Occupational Safety and Health Regulation

In 1970, the Williams-Steiger Occupational Safety and Health Act was enacted into law. OSHA was established as the regulatory authority to implement the act and establish policy under the U.S. Department of Labor. The National Institute for Occupational Safety and Health (NIOSH) was established, as an integral requirement of the act, to provide scientific guidance and recommendations for the regulatory authority. Executive Order 12196, dated 26 February 1980, required federal agencies to comply with OSHA requirements. OSHA promulgates regulatory requirements and documents the current annual requirement in the most recent volume of Title 29, Code of Federal Regulations (CFR), part 1910, *Occupational Safety and Health Standards*. OSHA publishes periodic updates and revisions of 29 CFR 1910 in the Federal Register (FR) and documents revisions to the published requirement or interim supplementation with new requirements. When the annual copy of the CFR is published, the new edition automatically incorporates all interim changes published in the periodic FR supplements. In addition to providing regulatory requirements, the CFR also documents the current, mandated PELs. In some cases, specific medical requirements are identified.

DoD Directive 1000.3 (29 March 1979, with Change 1, 17 April 1979) established military policy and provided implementation guidance for occupational safety and health. Health specific requirements for the Department of the Army (DA) are identified in Army Regulation (AR) 40-5, *Preventive Medicine, Health and Environment*.

For occupational health professionals to provide appropriate care for military employees and soldiers, they must be aware of the legal and regulatory requirements that direct the provisions for care. Federal legal requirements mandate that occupational illnesses and injuries are to be reported on the OSHA log. Army regulatory requirements specify that workers diagnosed with occupational illnesses, such as symptomatic pesticide-exposed workers, are to be identified in military occupational and safety health reports. State legal requirements are variable. Maryland and California are examples of states that require physicians who are licensed by the state to report all illnesses of occupational etiology.

THE U.S. ARMY PESTICIDE OCCUPATIONAL HEALTH PROGRAM

Any organization, installation, or activity that uses or stores pesticides must have an Occupational Health Program to monitor pesticide use and to implement procedures to protect the health of workers. The program addresses (*a*) health reports, records and forms, (*b*) protective equipment, (*c*) emergency medical treatment, (*d*) pesticide handling and applications, (*e*) pest-control equipment and facilities, (*f*) field occupational health, (*g*) medical surveillance, and (*h*) action levels for medical removal and return-to-work policies.

Health Reports, Records, and Forms

Command headquarters (eg, Health Services Command [HSC] or Army Materiel Command [AMC]) must be informed—through mandatory command health reports—of environmental releases and health-related problems involving pesticides. Environmental accidents resulting from the use, storage, or disposal of pesticides should be identified on any health report sent to the command headquarters. Confirmed or suspected health-related problems associated with occupational exposure to pesticides must also be reported. The purposes of the report are to (*a*) provide essential information about the circumstances associated with the problem, (*b*) identify additional resources that are necessary to solve the problem, and (*c*) provide information concerning problem resolution.

Extensive occupational health records, personnel records, and exposure monitoring records are required to provide and document the healthcare provided to all workers who handle pesticides (see Chapter 3, U.S. Army Health Programs and Services). The personnel office should work closely with the pesticide program management to assure that all job descriptions clearly delineate the worksite requirements and the medical conditions that cannot be accommodated in the pesticide-workshop environment.

After employment, preplacement examinations must be provided for pesticide applicators. These

document the patient's baseline health status and ensure that PPE can safely be used (eg, respirator fit and heat tolerance). Careful administrative management procedures must be provided to ensure that there is appropriate coordination between all health and safety personnel who are required to generate or maintain (or both) records related to employment.

Comprehensive records and forms should be maintained for all pest-control or pesticide-handling workers. To ensure that working conditions are in compliance with OSHA requirements, appropriate industrial hygiene site-visits, pesticide-applicator monitoring data, and safety-surveillance records are vitally important. Accurate sampling, analysis, recording, and interpretation are necessary in work areas where potential pesticide exposures may occur (eg, in pest-control shops and pesticide-storage warehouses). These results should also be prominently posted in the work area to notify employees and their supervisors.

An important method used to identify the need to mitigate exposure or to modify work practices is to obtain workplace data concerning pesticide concentrations associated with storage or use. As noted previously, the concentrations and durations of potential exposure to a pesticide are critical variables in this hazard evaluation. Exposure data should be carefully obtained by industrial hygienists when circumstances indicate that unacceptable exposures could occur in the workplace. The industrial hygienist should (*a*) collect data and keep a documented record, (*b*) formally notify the employee, area supervisor, and occupational healthcare provider, (*c*) identify corrective actions, and (*d*) ensure their implementation to reduce potential exposures, if monitoring data reveal concentrations of pesticides above the action level. Documented exposures above the action level and all pertinent information must be provided to the occupational health clinic in order to allow appropriate planning for medical care.

Individuals who are required to perform potentially hazardous operations (using engineering controls or PPE to mitigate or prevent their exposures) should also be afforded appropriate medical surveillance examinations to document that their health is maintained. The absence of adverse health effects among these workers may be useful to demonstrate the efficacy of engineering controls and PPE.

The health history obtained from employees prior to, periodically, and at the termination of employment must be carefully documented and retained for a minimum of 30 years after the termination of employment.[3] In addition, results from any atmospheric sampling should be included and retained in the military or civilian worker's medical records. These results should be identical to those that have been posted in the work area. The results of continuing medical surveillance or exposure-related medical examinations or clinical laboratory analyses must be carefully reviewed, compared with the preexisting information, and documented. Special care should be exercised to properly document and report workplace accidents, injuries, and illnesses in the medical records. Healthcare providers must ensure that Department of Labor forms for reporting illness or injury and compensation are completed in a timely fashion.

Emergency Medical Treatment

All employees who store, handle, and apply pesticides should be trained and able to practice emergency measures that ensure both the safe removal of exposed individuals from the contaminating source and their careful decontamination. All employees should receive some basic life-support training. Employees should demonstrate the appropriate use of PPE to preclude self-contamination and be able to implement the necessary procedures to assure that the spread of contamination will be limited.

Because pesticide antidotes are prescription medications, such antidotes should not be provided for employees to use unless the individual employees are properly trained and granted clinical privileges to provide emergency-response medical care. In certain circumstances where extremely toxic chemicals are involved—such as military nerve agents—employees may be allowed to carry the antidote, administer buddy aid, and inject themselves. Nonmedical personnel who are expected to use prescription antidotes and perform emergency care must learn to recognize the

- events that precipitate use,
- quantity and frequency of administration, and
- adverse effects associated with such use.

Unless access to first-aid kits can be carefully controlled, they are used only by trained individuals, or the work is being performed at a remote site, first-aid kits should not be available or used at the workplace. If managers decide that first-aid kits should be placed in work areas, medical personnel must approve the kits' contents, and pesticide workers must receive approved first-aid training. Procedures for safe first-aid kit use, kit resupply, accident reporting, and appropriate medical follow-up evaluation should be carefully documented.

The healthcare facilities that provide occupational health or general medical services must maintain a pharmaceutical inventory with necessary quantities of specific and appropriate antidotes, reversal agents,

and anticonvulsants. In addition, the facility must incorporate sufficient emergency-support equipment to manage an emergency situation, and healthcare providers must be properly trained and medically credentialed. Emergency-support agreements with nearby evacuation services and hospitals should be implemented and continuously revised to assure that timely support is available.

Pest-Control Equipment and Facilities

Industrial hygiene, safety, and occupational health personnel should ensure that (*a*) pest-control equipment is compatible with the pesticide formulation that is being applied, (*b*) the equipment is available and calibrated properly, and (*c*) the pesticides are transported properly. Engineering controls and PPE should be certified as operational. The appropriate care and use of the equipment should be documented. The following factors must also be considered in the transportation of pesticides:

- Vehicles used to transport pesticides, particularly pest-control vehicles, should be equipped with lockable storage areas and separate cabs for passengers.
- Transporting pesticides in the cabs should be prohibited.
- Vehicles assigned to the pest-control shop should be used only for pest-control activities.
- Pesticide spill kits should be placed on each vehicle.
- A portable eyewash should be available on vehicles that are located at remote pesticide-application sites.
- Emergency telephone numbers should be posted on pest-control vehicles.

Pesticide storage and mixing facilities must conform to not only federal workplace safety and health requirements, but also to state and local fire codes.[3,37] Pesticide labels, Material Safety Data Sheets, safety data prepared by the manufacturer, and a current pesticide inventory for the pesticides that are stored and in use should be available for the employees' review. Plans to adequately contain a pesticide fire at the facility should be prepared and updated annually. Copies should be provided to the local fire department, police department, hospitals, and safety offices.[38]

Pesticide Applications

Only personnel who are trained and certified should apply pesticides or supervise their application. Scheduled, periodic pesticide treatments should be prohibited unless a pest-control professional specifically approves, and these preventive treatments should be done only if surveillance has indicated past or current problems with pests. Furthermore, at least two pest controllers should perform pesticide operations such as fumigation that are particularly hazardous.

Food-handling areas and MTFs require special considerations for pest management; nonchemical pest-control methods should be attempted before chemical measures are considered. In food-preparation areas, pesticide treatments should be conducted only (*a*) when the food-preparation area is not in operation and (*b*) according to the pesticide label's instructions. Pesticides should not be applied routinely in MTFs, but *only* when the pest infestation warrants the use of a pesticide and then *only* administrative or storage areas should be treated. Pesticides should *not* be applied in patient-sensitive areas such as intensive care wards, emergency rooms, or infant nurseries. It is particularly important that pesticides *not* be applied in neonatal wards: infants have low blood cholinesterase; cholinesterase-inhibiting pesticides used in neonatal wards could cause serious health problems.

A pest-management coordinator should be appointed in each MTF. All pest sightings should be reported to the coordinator and any actions taken to control pests in the facility, including the use of pesticides, should be documented and maintained by the coordinator. Specific guidance for pest management operations in medical treatment facilities is provided in Armed Forces Pest Management Board Technical Information Memorandum 20.[39]

Medical Surveillance

Comprehensive medical surveillance is an essential element of a functional occupational health program. As a program element, the term *medical surveillance* is a misnomer. The surveillance element is composed of (*a*) general medical and specific occupational exposure history review, (b) target-organ-system-focused medical examination, (*c*) selected clinical laboratory analyses, and (*d*) medical intervention, depending on examination findings. In contrast to its use as a program element, in general preventive medicine the term medical surveillance is a separate, descriptive term. In that context, medical surveillance is a type of secondary prevention, directed toward identification of exposure effects at the time of organ-system injury, prior to the onset of permanent damage (impairment). For comparison, the term biological exposure index (BEI) is used as an element of primary prevention to identify and measure the specific chemi-

cal, or its metabolites, in biological fluids. Measurement of the chemical or its metabolite may not prove to be medically useful except to define whether a possible exposure has occurred. For the BEI to have maximal utility, a dose-response relationship for humans must have been determined for the chemical or metabolite that has been measured.

The toxicities of the chemical materials, the potential for cumulative effect, and the potentially serious medical consequences of long-term, low-dose exposures make a medical surveillance program essential for pesticide workers. The interdependent industrial hygiene, safety, and medical factors that exert important influences on the type and extent of medical surveillance programs, include

- the number, amount, and toxicity of the pesticides being handled;
- the potential hazards associated with the formulations;
- the potential hazards associated with the applications that are being performed;
- the presence or absence of a well-ventilated, properly designed and constructed pest-control shop or warehouse;
- the degree of compliance with procedures that are intended to minimize pesticide health hazards; and
- the extent of industrial hygiene surveys related to personnel exposures and the results that are obtained with a workplace environmental survey program.

As a tool to tailor medical surveillance for the individual pesticide worker, a health and safety hazard evaluation is necessary to fully analyze the cumulative importance of the factors. For example, potential exposures of pesticide workers are, as a rule, not restricted to one particular substance. Usually a number of pesticides, formulation components, solvents, and cleaning agents with very different modes of action and degrees of toxicity are used intermittently and simultaneously. The comprehensive set of employee-specific exposure possibilities represents the individual's *exposure profile*. A comprehensive medical surveillance program is optimally developed to identify the employee who has had a gradual decrement in cholinesterase as a result of ongoing organophosphate exposure before the worker experiences symptoms from the application of a carbamate insecticide.

Medical surveillance examinations—preplacement, periodic, and termination—should be specifically designed for each employee: the contents of the medical evaluation should be determined by the potential exposure profile of that employee. Specific medical surveillance tests or appropriate biological exposure indices should be identified for the employee on a case-by-case basis. If a generalized exposure potential to numerous chemicals exists, an extensive surveillance examination is usually required. The healthcare provider should coordinate with industrial hygienists, safety professionals, and supervisors to design specific examinations focused to the individual employee. Although coordination among these individuals fosters a better medical understanding of the workplace, the healthcare provider must remember to maintain the confidentiality of medical information.

Medical surveillance examinations of pesticide workers are provided for all employees who have the potential for exposure to pesticides in excess of either the statutory (29 CFR 1910) or the recommended exposure levels. The ACGIH annually publishes the current, revised set of recommended exposure limits and action levels. Both OSHA and ACGIH limits identify levels that should be safe for the traditional worker exposure (40 h/wk for the duration of employment). This examination is provided for any employee who has the potential to become exposed at or above the legal, regulatory, or advisory exposure levels despite the presence or use of engineering controls and PPE or if administrative work practices fail.

Preplacement Examination

Preplacement examinations are performed before an employee is assigned to the worksite. As a result of the Americans with Disabilities Act (ADA, which became effective in 1992, and by 1994 will cover companies with more than 15 employees), the character and type of examination performed prior to employment or job assignment has changed dramatically.[40] In short, before the statutory requirement was implemented, individuals presumed to be at increased risk from exposure could be excluded from employment or particular positions. Since the ADA became effective, however, it is illegal to refuse employment or placement for the individual who may be ill-suited to perform the job unless specific conditions of employment are published in the job description. If a potentially susceptible employee is hired in the absence of specific exclusions (conditions of employment), the work site must be reconfigured to accommodate the employee.

The preplacement examination for potential pesticide workers, performed by a physician or properly privileged and supervised healthcare provider, should include

- a comprehensive medical and work history;

- a physical examination with particular attention to the cardiovascular and respiratory system to evaluate the employee's ability to use respiratory protective equipment;
- an examination of the hepatic and renal systems to ensure that employees will not be unusually susceptible to ill effects from pesticides, formulation products, solvents, or cleaning materials;
- examinations of the musculoskeletal and nervous systems to identify preexisting neurological disorders, including
  - evaluations of PNS and CNS functions, and
  - mental status and limited neuropsychiatric evaluations;
- a chest X ray;
- spirometry, including
  - forced vital capacity (FVC) and
  - forced expiratory volume at 1 second (FEV_1);
- a complete blood count;
- liver function tests (such as SGOT and LDH);
- renal function tests (such as creatinine and BUN).

The preplacement examination may include a variety of other elements if indicated by the potential exposure profile. For example, for individuals who will be required to work with the organophosphate insecticides, one component of the examination is the determination of the baseline erythrocyte cholinesterase level. Subsequent analyses during periodic examinations or after suspected exposures will be evaluated by comparing with the baseline level.

The erythrocyte cholinesterase baseline determination is defined as the average value of three separate erythrocyte-associated cholinesterase measurements obtained during a 9- to 14-day period. Cholinesterase measurement methods must be subjected to judicious quality control procedures, both inside and outside the laboratory. Quality control is essential to assure consistently reproducible and reliable results. Laboratory consistency is critical because "normal" levels vary widely among individuals, but change very little over time in the same individual. Several methods have been developed for the analysis of cholinesterase levels.[41] Extreme care must be taken to ensure that all subsequent samples are analyzed by the same, carefully controlled, technique. Results of each test must be reviewed by an individual who has been granted clinical privileges to provide this type of care.

The erythrocyte cholinesterase baseline and all subsequent test results should be documented graphically (Figure 14-8). Individuals whose erythrocyte cholinesterase is depressed more than 25% should receive an immediate medical evaluation and then be removed from further exposure to cholinesterase inhibitors. Individuals can be cleared to return to work when the enzyme levels reach 80% of the patient's baseline.

Plasma cholinesterase (sometimes called pseudocholinesterase or butyrylcholinesterase) may be significantly changed with short-term, relatively high-dose exposures to cholinesterase inhibitors. The reactivation and replacement kinetics of the plasma-associated enzyme do not permit their being used in routine surveillance, although the plasma measurement can be used to confirm a very recent pesticide exposure.

Periodic Examinations

A physician or privileged healthcare provider should perform a periodic examination, based on the worker's potential for exposure to pesticide levels above the action levels identified by OSHA or the ACGIH. The examination should be focused within the scope of the preplacement examination and should be dependent on the potential exposure hazard. The frequency of this examination is arbitrary; it can range from annually to a frequency that depends on the worker's age and health. For example, an age-related examination could be performed on individuals with a minimal potential for pesticide exposure: workers younger than 40 years of age would be examined every 4 years; workers 40 to 49 years of age would be examined every 2 years; and workers 50 years and older would be examined annually.

Periodic examinations must be performed on workers who require PPE to verify that the level of protection is adequate. The examining healthcare provider is responsible for coordinating with the personnel who characterize and document exposure profiles so that appropriate and timely periodic examinations are provided to all appropriate workers.

The need for more extensive surveillance increases in situations when

- more toxic or hazardous pesticides are used,
- medical examinations indicate that more frequent monitoring is necessary, or
- a health- or safety-hazard evaluation reveals that potential pesticide exposures could affect workers' health.

If the medical surveillance program is extended because of potential—or actual—unfavorable working conditions, the extension should be considered as an interim measure until more-effective controls are installed.

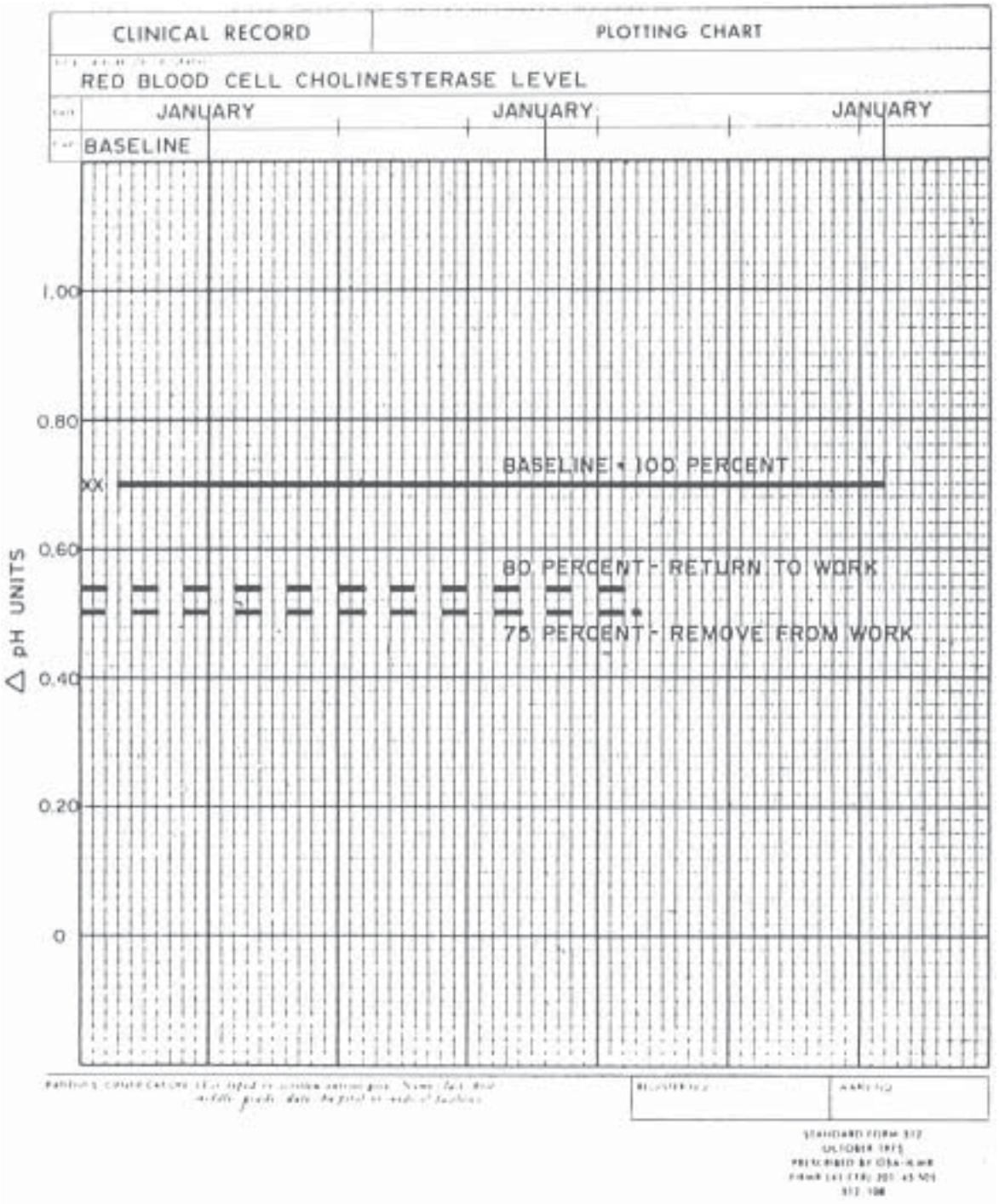


Fig. 14-8. The Clinical Record-Plotting Chart (SF 512) is an approved form for entry in a medical treatment facility's employee outpatient medical record. The graphic record should indicate an *action line*, (eg, a 20% depression from baseline values). When an employee approaches the action line, a set of patient-management practices, such as careful medical examination or return to work, may be implemented. A *medical removal line* should be drawn at the level of 25% depression. The change in pH (Δ pH units, the ordinate) is the difference in the pH of the erythrocyte environment before and after the addition of a buffer, as a measure of cholinesterase activity.

Regardless of the worker's age, a brief, focused interim review of history should be documented. A carefully elicited history of a general pesticide worker who has a wide potential for exposure, should, at a minimum, evaluate the organ systems mentioned in Table 14-11. Liver- and kidney-function tests and a complete blood count should be performed annually. If other occupational exposures exist (such as high noise levels from the vehicles or aircraft used for spraying pesticides), appropriate medical surveillance of the effects from these other occupational exposures should also be provided.

The frequency of periodic determinations of erythrocyte cholinesterase levels should be carefully planned for each individual, focusing on the potential for significant exposure to organophosphate insecticides or similar, militarily unique substances. If an emergency or a worker's breach of protection has caused an exposure, the results of the cholinesterase analysis should be charted immediately on the clinical graph and compared to the individual's baseline. In addition, a cholinesterase determination and comparison with the baseline are required when a symptomatic individual is evaluated.

Determinations of erythrocyte cholinesterase levels should be performed more frequently when workers are required to handle, store, mix, or use organophosphate insecticides. For example, if frequent applications are required during the summer, monthly determinations of the enzyme level should be documented as a prudent medical practice. In winter, if no potential exists for exposure, no determination of cholinesterase levels would be required.

The results of periodic examinations should be negative. If deviations from the normal baseline occur for occupationally related reasons, more frequent or more extensive examinations may be indicated. At the same time, an investigation should be initiated into the cause of the deviation, with specific attention directed toward engineering controls, PPE, and work practices.

Pretermination Examination

For employees who have been associated with pesticide use, pretermination examinations should be performed within 30 days of the termination of their employment. And as was previously discussed, the employee's total employment health history—obtained

TABLE 14-11

HISTORY AND PHYSICAL EXAMINATION FOR PESTICIDE WORKERS

Evaluation Categories	Areas of Emphasis
General History	Appetite, unexplained weight change, fatigue, work-site exposure potential
Visual	Acuity, need for prescription inserts, dimness and blurring of vision, unilateral or bilateral miosis, pressure, chemosis, allergic conjunctivitis
Respiratory	Rhinorrhea, breathing difficulty, cough, tightness of chest, bronchoconstriction, increased bronchial secretions, wheezing asthma, recurrent respiratory allergies, respirator wear (use test), claustrophobia, pulmonary-function testing, if needed
Cardiovascular	History of cardiovascular difficulty, atrial or ventricular arrhythmia, fainting, evidence of cardiac susceptibility, blood pressure history, family history
Gastrointestinal	History of ulcer or chronic bowel disease, neurological assessment for sphincter tone, history of incontinence or soiling
Cutaneous	Sweating disorders, heat tolerance, metabolic or genetic disorders, beard pattern, eczema, exfoliation, contact dermatitis, hematoma, easy bruising, petechiae
Genitourinary	Frequency, incontinence, history of renal disease
Musculoskeletal	Localized or generalized fasciculation, respiratory insufficiency (paralysis), weakness, cramps, twitching, strength, symmetry, family history
Nervous	Anxiety, giddiness, restlessness, depression, emotional lability, excessive dreaming, tremor, nightmares, confusion, headache, ataxia, apnea, convulsions, paresthesia, mental status exam, general neurological evaluation, affect, mood, memory, judgment
Hematological	Erythrocyte cholinesterase baseline (for organophosphates)

from preplacement, periodic, illness or injury, and pretermination examinations—must be retained for a minimum of 30 years.[3] All normal findings, together with any details of exposure and abnormal findings that could be ascribed to pesticide exposure, must be evaluated and documented before the employee's record is further disposed or retired.

Action Levels for Removal and Return-to-Work Policies

In general, any abnormal finding that could be related to pesticide exposure should cause the employee to be removed from further exposure until a complete evaluation is made with respect to the extent, cause, and significance of the finding. The employee's return to work should not be recommended if pesticide exposure could further harm the worker's health, *even if pesticide exposure did not cause the abnormality*. If the worker is found to have depressed levels of erythrocyte cholinesterase, which is fully reversible over time if no additional exposure occurs, the following policies should be adopted:

- The worker must be removed from work when the erythrocyte cholinesterase activity is depressed to 75% or less of its baseline value.
- The worker should be permitted to return to work when the erythrocyte cholinesterase activity has returned to 80% or more of its normal value, provided that this level is confirmed by a second test. In addition, the worker must be asymptomatic and have had no exposure to cholinesterase inhibitors for at least 1 week.
- The erythrocyte cholinesterase levels should not routinely be evaluated more frequently than once per week because the normal recovery rate is approximately 1% per day.

SUMMARY

Pesticides are used to prevent, destroy, or mitigate pests. To be effective, however, they must be applied into the pest's environment—the same environment shared by other animals, plants, and humans. To minimize adverse effects of pesticides to the environment or human health, the risks of applying a pesticide must be weighed against the benefits of its use. The inability to fully identify the risks associated with introducing pesticides into the environment is a continuing problem.

Although in some instances the acute effects may be known, there is a paucity of information on chronic effects that result from long-term exposures to pesticide residues—not only to those who apply pesticides but also to bystanders. For this reason, the safe application of pesticides requires that precautions be taken to protect against acute or chronic exposures to the residues. Human exposures to pesticides during their application are minimized by using PPE and appropriate engineering controls.

The pharmacology of pesticides is not militarily unique. However, medical officers need to be familiar with the mechanisms of toxicity, their signs and symptoms of intoxication, and the recommended medical management practices, occupational exposure surveillance end-points, and long-term effects. Medical officers also need to be familiar with the numerous pesticide-related federal, state, local, and DoD regulations.

The inherent hazards to humans, during and after pesticide application, dictate that a comprehensive occupational medicine program be implemented. This includes monitoring the workplace for pesticide use and disposition. In addition, the program provides mechanisms to investigate alleged incidents of pesticide exposure.

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