Pesticides

74

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Pesticides are biocidal agents used to control a wide variety of organisms that pose a threat to health or compete for food or other materials (Table 74.1). Selective toxicity for the target pest is the principle of pesticide use, but because organisms are similar at the cellular or subcellular level, adverse human health effects may occur.

The earliest pesticides included metals such as arsenic, mercury, and lead. Some pesticides are inorganic chemicals, such as sulfur, and others are organic chemicals, such as the alkaloid nicotine derived from plants. After the discovery of dichlorodiphenyltrichloroethane (DDT) in 1939, the world witnessed an unprecedented increase in the search for and production of synthetic organic pesticides. Production of inorganic pesticides such as arsenicals has steadily declined since the 1940s. The prolonged ecologic half-life and lack of species selectivity of DDT and other organochlorine pesticides was recognized in the 1960s. These pesticide characteristics and concern about the effects of accumulation of organochlorines in human adipose tissue caused the banning or severe restriction of most of these agents in the United States and most of the world. In their place, newer synthetic pesticides, predominantly organophosphorus, carbamate, and pyrethrin compounds, have been developed and are now widely used. These agents cause less environmental damage through accumulation but are often more acutely toxic to humans and other animal species.

The manufacture, distribution, and handling of pesticides in the United States is regulated under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). The act, administered by the U.S. Environmental Protection Agency (EPA), was passed in 1947 and has been amended several times. There are nearly 900 active pesticides with different diluents and ingredients, configured in more than 20,000 formulations in use in the United States today. U.S. production is just over 1.2 billion pounds of conventional pesticides, and over 4.5 billion pounds of pesticides annually are applied in agriculture as well as in most household gardens today (1). The annual use of conventional pesticides has decreased 17.2% in the United States between 1979 and 1997 (1). Using National Discharge Survey data and American Poison Control Centers national data from 1985 to 1997, Klein-Schwartz and Smith (2) reported 341 fatalities and over 25,000 hospitalizations from agricultural and horticultural chemicals, making pesticide exposure an important public health problem. Ominously, a toxic organophosphate, the nerve gas sarin, was used by terrorists to attack large numbers of people in cities in Japan (3).

EXPOSURE

Environmental

Adverse effects of pesticides in the environment first received widespread attention in the 1960s with the publication of Rachel Carson's *Silent Spring* (4). Biomagnification of organochlorine compounds in the food chain leads to high residues, particularly in predaceous fish and birds. Elevated levels of DDT (and to a lesser degree, dieldrin) in several species of birds of prey lead to eggshell thinning and threaten species extinction. Because organochlorine compounds are not species specific, large populations of animal species may be at risk of chronic poisoning, which can lead to deleterious, long-term changes in the diversity of ecosystems in nature. Furthermore, pest species may develop increased tolerance or resistance to these specific pesticide compounds. Organochlorines have been largely replaced in developed countries by organophosphates and carbamate and pyrethrin compounds that

Table 74.1 Categories of Pesticide Agents and Target Organisms

Pesticide	Target
Acaricide	Mites
Algicide	Algae
Avicide	Birds
Bactericide	Bacteria
Defoliant	Leaves
Fungicide	Fungi
Herbicide	Weeds
Insecticide	Insects
Molluscide	Snails
Nematicide	Nematodes
Piscicide	Fish
Rodenticide	Rodents

rapidly hydrolyze in soil and on plants. Although organophosphates and carbamates do not accumulate significantly in the environment, they remain extremely toxic if used indiscriminately. A recent report of human DDT poisoning reminds us that, in many parts of the world, this pesticide remains in use (5).

Nonoccupational environmental exposures to pesticides in humans often result from household or garden use. Even schools can be the source for toxic pesticides exposures, leading to illness in both employees and students (6). The World Health Organization has estimated that more than 3 million cases of serious acute pesticide or insecticide poisoning occur worldwide annually, the majority being caused by organophosphates used for agriculture (7). There are an estimated 220,000 deaths annually from pesticides, and 99% of these deaths are in developing countries (7) despite the fact that only 20% to 25% of the global agrochemical use is in developing countries. Agriculture continues to be one of the most common areas of pesticide exposure in developing countries (8). The easy availability of pesticides and widespread use in many developing countries make them a common means of suicide and death, with some districts in Sri Lanka noting pesticide deaths exceeding all other causes of death (9).

In 2003, there were 97,677 pesticide poisonings in the United States reported to the American Association of Poison Control Centers (AAPCC) (10). This represented 4.1% of all reported poisoning, with over 50% of the poisonings occurring in children under 6 years old (10). Countries such as Turkey have reported percentages as high as 19% of poisonings as being related to pesticides (11). About 90% of homes in the United States use pesticides, with exposure resulting frequently from misuse or accident (12). Other environmental exposures may occur from water, air, or food. Low concentrations of pesticides have been detected in some groundwater sources, although these are not thought to pose serious health risks to the population at the levels detected (13).

Tolerance levels for pesticide residues in foods or the maximum residue levels allowed when pesticides are used according to the directions on the label are set by the EPA. The levels are based on toxicologic studies that attempt to balance the risks and benefits associated with the use of pesticides on human foodstuffs (14).

Although there is increasing public concern about pesticide residues in the food supply (e.g., Alar, a growth regulator, on apple crops), residues detected in fresh and processed foods are generally low. The U.S. Food and Drug Administration (FDA) tests a sample of food shipments for pesticide residues; only a small percentage are found to have levels above tolerances, and most samples have no detectable residue. The FDA also conducts the Total Diet Study, testing supermarket food items considered to represent the diet of U.S. consumers. Results from these analyses indicate that, in general, the dietary intake of pesticide residues is within acceptable tolerance. When pesticides are used on crops for which their use is not approved or are applied in an unapproved manner, however, outbreaks of foodborne pesticide illness may occur. This was the case with the 1985 outbreak caused by aldicarb-contaminated watermelons in the western United States (15).

The EPA conducted the National Human Adipose Tissue Survey annually beginning in 1969 to monitor levels of organochlorine pesticides, polychlorinated biphenyls (PCBs), and a few other compounds in tissues collected during surgery or at autopsy. These substances tend to bioaccumulate in adipose tissue, providing an excellent medium for detecting prevalence of exposure over a long period and body burden. Detectable residues of most of these compounds are found in a large proportion of tissue samples but in very low concentrations. This program was valuable in documenting time trends in body burdens. For example, levels of DDT and its metabolites and levels of PCBs decreased from the early 1970s, reflecting decreased use in the United States (16,17).

Occupational

Humans are exposed to pesticides in a variety of occupational settings, including agriculture, structural pest control (e.g., buildings), public health pest eradication programs, manufacture and formulation, transportation industries such as railroads and trucking, the florist industry, and hazardous waste treatment and cleanup. Many commercial products such as paints, cotton, and wood products have fungicides added to prevent degeneration. Herbicides are used heavily in maintaining roads and highways in developed countries.

Assessing exposure to pesticides in an occupational setting is a complex task. A worker may be exposed

unknowingly to clothing saturated with pesticides or by direct skin contact, but these amounts do not necessarily predict the actual dose, or amount absorbed into the body. Absorption may occur through inhalation, ingestion, or direct absorption on dermal surfaces. Detailed information on rates of absorption and knowledge of the pharmacokinetics of the compound in humans is often unavailable. Relating the absorbed dose to human health effects is often difficult or impossible. Work on biologic markers of pesticides may improve assessment of exposure and dose (18).

Accurate data do not exist on the incidence of acute illnesses secondary to pesticide poisoning, and even less is known about the chronic effects of pesticide exposure. While most acute pesticide-related illnesses and deaths in the past were caused by accidental agricultural exposure or attempted suicides, toxicologists and clinicians today must be alert to the illicit use of pesticides for criminal or terrorist activities. Health care providers must be able to recognize the immediate health effects of pesticides to establish diagnoses quickly and to begin treatment early. The number of deaths caused by pesticide poisoning in the United States is small, but acute pesticide-related illnesses are common. For example, in California, where pesticide-related illnesses must be reported, some 2,500 to 3,000 suspected pesticide illness are noted annually, of which half occur in agriculture. A recent analysis of the California Pesticide Illness Surveillance Program found that most intoxications followed domestic exposures and were not reported to the surveillance program, which primarily identified occupational exposures (19). Overall, the system was estimated to ascertain 50% of all poisonings but only 16% of nonagricultural occupational cases. Worldwide estimates for pesticide poisoning suggest the problem of acute toxicity and death is much greater in developing countries than in developed countries (7).

IMMEDIATE HEALTH EFFECTS

Organophosphate Insecticides

Millions of pounds of organophosphate pesticides are used worldwide in commercial farming, gardening, structural pest management, and vector control programs. The development of these agents is derived from the search for new chemical warfare or nerve gas agents in the 1930s. Although the organophosphate nerve agents such as sarin, tabun, and VX have not been used as insecticides, further research has shown that related, less potent compounds can be used successfully as insecticides (Fig. 74.1). The worldwide use of these organophosphate compounds has increased over the past 20 years due to increased use in the Third World and because their use results in less severe environmental impacts than the organochlorine insecticides. Because the organophosphate insecticides are less detrimental to the environment, they have largely replaced the organochlorine insecticides. Significant acute and chronic risk remains with the occupational exposure to these compounds (20). When suicide is associated with pesticide use, the agents now used are largely organophosphate insecticides (21).

Examples of organophosphate insecticides include parathion, chlorfenvinphos, diazinon, fenthion, dimethoate, monocrotophos, and malathion. These insecticides are commonly used in commercial farming, home gardening, pest control (e.g., flies), environmental control of vectors (e.g., mosquitoes), and the control of ectoparasites (e.g., fleas, lice). They may be combined with one or more other types of insecticides to potentiate their insecticidal action.

Organophosphate insecticides are efficiently absorbed by inhalation, ingestion, and skin penetration (22,23). Exposure by all three routes has been seen in occupational poisonings. The degree of toxicity varies considerably, depending on the route of exposure and the exposure concentration and dose. Organophosphate insecticides vary in potency. For example, the median lethal dose (LD_{50}) for parathion in humans is estimated to be 3 mg per kg, while that of malathion is 1,375 mg per kg.

The toxic manifestations of organophosphate insecticides result from the irreversible phosphorylation of the enzyme acetylcholinesterase found at the nerve–nerve synapse or nerve–muscle motor end plate where anionic binding of acetylcholine normally occurs (24). The loss of function of this enzyme allows flooding of the postsynaptic receptors with acetylcholine, leading to a cholinergic crisis in severe cases (25).

Acute Signs and Symptoms

Patients acutely intoxicated with organophosphates often present with a set of signs and symptoms. Recognition of these "toxidromes" helps the astute clinician establish the chemical class of the toxicant quickly and allows vital treatment to begin early. All too often, the clinician has only a history of exposure or a toxidrome to suggest organophosphate insecticide poisoning. The dramatic accounts of the Matsumoto sarin attack in 1994 and the notorious Tokyo subway sarin attack in 1995 should serve as valuable lessons to emergency room and hospital staff and prompt simulated disaster drills to prepare health care providers (3).

The organophosphate insecticide toxidrome can develop during the chemical exposure or be delayed some 4 to 12 hours after exposure. The key aspects of this toxidrome can be divided into muscarinic, nicotinic, and central nervous system overstimulation. Muscarinic overstimulation leads to hyperactivity of the parasympathetic system, including miosis, bradycardia, and hypersecretion of salivary, lacrimal, digestive, and

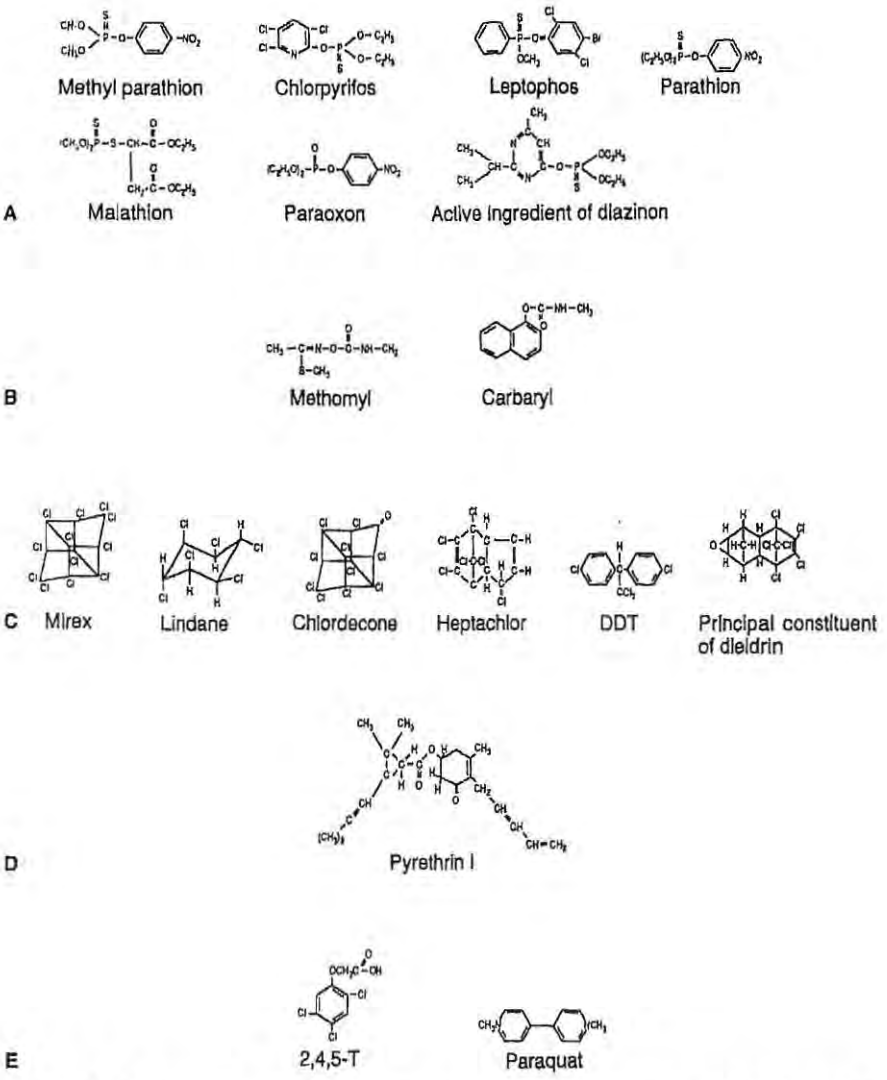

Figure 74.1 Chemical structure of some key classes of pesticides: organophosphate insecticides **(A)**, carbamate insecticides **(B)**, organochlorine insecticides **(C)**, pyrethroid insecticides **(D)**, and herbicides **(E)**.

bronchial glands. Accumulation of acetylcholine at the nicotinic synapses leads to blockade of nerve impulses in the central nervous system, at the autonomic ganglia, and at the skeletal muscle–nerve junction. The latter effects lead to motor end plate dysfunction (26). Nicotinic effects include muscle fasciculations that can be mistaken for seizure, cramps, and generalized muscle weakness. Depression of respiratory drive, delirium, loss of consciousness, and seizures are complications of central nervous system toxicity (22,27–31) (Table 74.2). The mnemonic *DUMBELS* (diarrhea, urination, miosis, bronchospasm, emesis, lacrimation, salivation) describes the signs of cholinergic (muscarinic) excess seen with organophosphate poisoning. Transient diabetes insipidus has been reported after severe malathion poisoning (32). A garlic odor may also be noted from the exposed patient or from the container of the pesticide. Recent data have suggested that visual changes, pancreatitis, and psychiatric findings are seen with acute organophosphate poisoning more commonly than previously recognized (33–36).

Establishing a diagnosis from acute or chronic low-dose exposure is particularly difficult in children. The typical muscarinic and nicotinic signs and symptoms of an acute organophosphate poisoning are often absent. Patients may present with neurobehavioral changes, hypertonicity, and even acute psychosis. To establish a more definitive diagnosis, clinicians should be aware that reliable reference laboratories are capable of detecting alkylphosphate metabolites of

Table 74.2
The Toxidrome of Acute Organophosphate and Carbamate Insecticide Poisoning

Central nervous system
Salivation[a]
Incontinence[a]
Convulsions[a]
Headache
Psychosis with delirium
Nausea
Dizziness
Restlessness with anxiety
Unconsciousness
Musculoskeletal system
Sweating[a]
Muscle twitching with fasciculations[a]
Weakness
Incoordination
Tremor
Paralysis
Gastrointestinal system
Diarrhea
Vomiting
Abdominal cramps
Acute pancreatitis
Vision
Miosis[a]
Blurred vision
Tearing
Ocular pain
Conjunctival injection
Respiratory system
Rhinorrhea[a]
Pulmonary edema[a]
Bronchorrhea[a]
Wheezing and chest tightness[a]
Respiratory muscle paralysis
Cardiovascular system
Bradycardia (parasympathetic stimulation)[a]
Sinus arrest
Early tachycardia (sympathetic ganglia stimulation)
Early hypertension (sympathetic ganglia stimulation)

[a]Key aspects of symptom complex or toxidrome.

organophosphates in plasma and urine, but the time and equipment necessary for this assay may limit its clinical usefulness (37–39).

Certain organophosphate insecticides have been associated with delayed and intermediate neurotoxicity syndromes (40–43). Characteristic manifestations include weakness, paralysis, and paresthesias in the distal lower extremities for the delayed syndrome; weakness of proximal limb muscles and muscles of respiration; and cranial nerve paralysis in the intermediate syndrome. Development of the delayed neuropathy is not associated with inhibition of neural or neuromuscular cholinesterases, as is the acute toxicity. It has been correlated with initial phosphorylation or inhibition of the neurotoxic esterase enzyme (NTE) (44,45). Symptoms usually occur within 2 to 3 weeks, with a denervation electromyographic pattern and a progressively irreversible to slowly reversible course over 6 to 12 months. The intermediate syndrome associated with organophosphate neurotoxicity was described in 10 patients (40). The time of onset was between 1 and 4 days after significant organophosphate insecticide poisoning, with proximal limb, neck, cranial, and respiratory muscle involvement. The electromyogram findings were described as tetanic fade. Recovery took between 4 and 18 days. Seven of 10 patients had respiratory difficulty, and four of 10 patients required mechanical ventilation. Most commonly, both delayed and intermediate neurotoxicity have been seen in survivors of massive organophosphate insecticide poisonings coming from Third World countries (42). Prolonged effects of muscle blocker agents have been reported in patients poisoned by organophosphate pesticides (46,47). Persistence of organophosphates measured in blood and in tissues at autopsy in humans has been demonstrated, particularly for the most lipid-soluble agents such as penthion and methidathion (48). The intermediate syndrome may also represent delayed organophosphate absorption or prolonged tissue half-life. Chronic neurologic and neuropsychological sequelae after organophosphate poisonings are complex and have been recently reviewed (49–53).

Laboratory Findings

Confirmatory laboratory tests include measurements of plasma and red blood cell (RBC) cholinesterase activities, which provide a measure of the inhibition of two types of cholinesterase enzymes in vivo. However, these studies may be available in a limited number of diagnostic laboratories. At least six different methods are available for measuring RBC and plasma cholinesterase levels. Consequently, interlaboratory variability may be great, and this variability may complicate the interpretation of results (54,55).

Plasma cholinesterase (pseudocholinesterase) is produced by the liver. It is a phase-reactant enzyme with baseline fluctuations due to many variables. Falsely lowered activity may be due to chronic or acute liver disease, chronic alcoholism, pregnancy, malnutrition, dermatomyositis, or concomitant poisoning with carbon disulfide and organic mercury compounds. Plasma cholinesterase levels decline and return faster than RBC or "true" cholinesterase levels. The 3% of the population who are genetically deficient in this enzyme are particularly vulnerable to the neuromuscular blocker succinylcholine and may be hypersensitive to organophosphate insecticides (56). Regeneration of activity is normally related to synthesis by the liver of new enzymes, and it may take 7 to 60 days to return to levels found prior to organophosphate insecticide exposure. RBC cholinesterase activity regenerates even more slowly because new RBCs must be released from the bone marrow to replace those with inactivated

cholinesterase enzyme (57). Because of this slow rate of renewal (0.5% to 1% per day), it can take 60 to 90 days for RBC cholinesterase levels to return to nearly baseline values.

RBC cholinesterase is the preferred measurement for documenting exposure and monitoring when exposed workers can return to handling organophosphate insecticides. Generally, RBC cholinesterase levels should be greater than 75% of baseline before workers are allowed to return.

More sensitive and specific blood and urine screens for the parent organophosphate insecticide compounds and metabolites exist, but they are not routinely available and often require detailed knowledge of the specific parent compound and specialized equipment (18,38,39).

Symptoms of organophosphate insecticide toxicity are usually not seen until 50% of baseline cholinesterase activity is inhibited, although this is not a reliable threshold. The large variability in normal cholinesterase levels also makes its interpretation difficult. Cases of poisoning and even deaths have been reported with depressions of less than 50%. Cholinesterase level is useful in clinical evaluation, but it must be done in association with a careful history and physical examination. Because baseline plasma cholinesterase levels are not usually available for an individual patient, serial determinations are useful in acute exposures. No clearly reliable association has been established between the magnitude of serum cholinesterase decrease and the severity of poisoning; it is simply a marker of organophosphate intoxication or poisoning. Nevertheless, most authorities consider mild exposure with minimal signs and symptoms to be associated with plasma cholinesterase levels of 20% to 50% of baseline. Moderate exposure, usually resulting in muscle fasciculations and miosis, is associated with plasma cholinesterase levels of 10% to 20% of baseline. Severe poisoning with life-threatening symptoms is associated with plasma cholinesterase levels of 0% to 10% of baseline. Some authors reported that prolonged severe depression of plasma cholinesterase has been associated with poor clinical outcomes after organophosphate poisoning (48). However, survival has been reported with extremely low plasma cholinesterase levels, leading some investigators to suggest that serum cholinesterase levels have no prognostic value in acute organophosphate poisoning. Identifying high-risk patients based on this enzyme measurement alone is not always reliable (58).

Leukocytosis with a leftward shift toward polymorphic neutrophils, hyperglycemia, ketoacidosis, glycosuria, albuminuria, and acetonuria have been reported with organophosphate poisoning, but these findings are neither specific nor sensitive enough for diagnostic purposes. Hyperamylasemia and other evidence of acute pancreatitis, such as computed tomographic imaging of the pancreas, have been reported following organophosphate poisoning (34–36).

Large, short-term doses of organophosphate insecticides have resulted in prominent electroencephalographic (EEG) changes and convulsions in humans and other primates. Studies have shown long-term (1 to 6 years) spectral shifts in beta voltage in sarin-exposed primates or accidentally exposed workers with serial EEG determinations. The usefulness, both in terms of specificity and sensitivity, of these EEG findings in the diagnosis of organophosphate poisoning has not been established (59). A case report noted reversible extrapyramidal Parkinson-like symptoms in a 14-year old complicating acute organophosphate insecticide poisoning (60). Cardiac toxicity can manifest as intraventricular conduction abnormalities, atrial dysrhythmias, and repetitive ventricular tachycardia such as torsades de pointes (61).

Treatment

The decision to treat a possible organophosphate poisoning is often based only on the history and physical examination findings. Initial management is directed at protecting and maintaining an open airway with respiratory support, including airway suctioning, endotracheal intubation, and mechanical ventilation with supplemental oxygen. Because organophosphate insecticides can easily cross the skin barrier, they pose a particularly insidious threat of secondary contamination to unprotected health care providers and emergency department personnel. Patients who arrive at an emergency department without having had appropriate decontamination should be decontaminated with large amounts of soap and water. Removing clothing potentially saturated with organophosphates is particularly important for both patient and health care provider. Clothing and other contaminated materials must be discarded as highly contaminated waste. Even wastewater from field or hospital decontamination must be handled carefully. Gastric decontamination with lavage followed by repeated doses of activated charcoal is indicated for enteric exposure and can reduce total and continued organophosphate exposure. Hemoperfusion removes only minimal amounts of the organophosphate insecticides (48).

For acutely ill patients, atropine sulfate in doses sufficient to reverse cholinergic (muscarinic) signs and symptoms is the primary pharmacologic treatment. A specific dose limit or an arbitrary dose goal is not practical. Careful titration with atropine while monitoring reversal of excessive parasympathetic stimulation is the standard of care. Initial doses of 0.4 to 2.0 mg atropine intravenously (IV) are repeated every 15 minutes until evidence of "atropinization" or muscarinic blockade, such as flushing, dry mouth, dilated pupils, and tachycardia, is seen (22). Repeated doses or continuous infusion of

atropine to maintain partial muscarinic blockade may be needed. Evidence of cholinergic excess, including miosis, nausea, and bradycardia, is used to govern atropine doses for several hours to days, depending on the severity of the organophosphate poisoning. Caution must be exercised when treating children with large doses of premixed atropine sulfate because large amounts of preservatives (e.g., alcohols) used to increase the shelf life of the drug can be toxic. Consultation with a pharmacist should allow formulation of a high-dose atropine sulfate solution that is preservative free. Other anticholinergic agents such as glycopyrrolate have been shown to be as effective as atropine in the treatment of organophosphate poisoning (62).

Pralidoxime (Protopam, 2-PAM) is a cholinesterase reactivator available in the United States that effectively reverses the phosphorylation of the RBC and neural cholinesterase enzyme when given within 24 to 48 hours of exposure. Other oximes that act in the same manner are available in Europe. Although it is generally accepted that oximes are important in the treatment of organophosphate poisonings, some reports have rejected their usefulness (63). It is believed that the sooner pralidoxime is given, the better the chances for cholinesterase reactivation. Pralidoxime is used in cases of moderate to severe organophosphate poisoning. Although pralidoxime can mitigate nicotinic and muscarinic effects of organophosphate poisoning, its actions will vary. It must be used concurrently with atropine sulfate. A dose of 1.0 to 2.0 g of pralidoxime (20 to 50 mg per kg for children) is administered IV over 30 minutes (22). Rapid injection can cause tachycardia, laryngeal spasm, muscle rigidity, transient neuromuscular blockade, and respiratory arrest (64). Giving repeated doses of pralidoxime at intervals of 2 to 12 hours or by constant IV infusion should be considered. Keeping plasma pralidoxime concentrations above 4 mg per L, which is the minimum plasma concentration required for therapeutic efficacy, is recommended (65). Loading doses of 4 mg per kg of pralidoxime followed by 3.2 mg/kg/hour have kept plasma levels above 4 mg per L (65). The final decision concerning pralidoxime dosing is governed by the severity of the poisoning symptoms (66–68). A recent Cochrane review of the clinical data on the use of oximes in organophosphate poisonings indicated a lack of data to conclude whether oximes are harmful or beneficial (69).

A unicenter, randomized, single-blind study of 89 organophosphate insecticide–poisoned patients showed benefit from treatment of 4 g per day of magnesium sulfate (70). Other adjunctive therapy such as gastric lavage in ventilated poisoned patients has been shown to improve outcomes in fasting patients after organophosphate poisoning (71). A study of 108 patients with severe dichlorvos poisoning showed an improvement in clinical response and a more rapid fall in blood levels after charcoal hemoperfusion (72). Other investigators have suggested that hemoperfusion may be useful only in severe organophosphate poisoning (73).

Seizures may not respond to atropine and pralidoxime. These patients are treated with IV diazepam or barbiturates. The use of IV diazepam has also been effective in the treatment of severe muscle fasciculations. Protection of the airway, aggressive control of seizures, mechanical ventilator support if necessary, early use of pralidoxime, and titration of atropine to effect are thought to be important to successful treatment of severe organophosphate pesticide poisoning.

N-Methyl Carbamate Insecticides

The carbamates, like the organophosphates, are used in commercial farming, home gardening, and control of domestic animal ectoparasites. Aldicarb, oxamyl, and methomyl are highly toxic carbamate insecticides; dioxacarb, carbaryl, and isoprocarb are less toxic. The carbamate insecticides are often used in combination with an organophosphate or pyrethroid insecticide.

Cases of aldicarb poisoning from ingestion of food and vegetables contaminated with the pesticides have been reported (74,75). Additionally, small case series and case reports have noted a spectrum of toxicity including death after aldicarb poisoning (76,77).

Carbamate insecticides are readily absorbed by inhalation or ingestion or through the skin. The *N*-methyl carbamate esters cause reversible inhibition of acetylcholinesterase. As in the case of organophosphates, postsynaptic cholinergic receptors are flooded with acetylcholine, resulting in a characteristic toxidrome. Unlike the phosphorylated enzyme, the carbamylated acetylcholinesterase enzyme can undergo spontaneous hydrolysis in vivo, which reactivates the enzyme. Less severe toxidromes of shorter duration can be expected from carbamate poisoning due to this hydrolysis.

Acute Signs and Symptoms

The diagnosis of carbamate poisoning is generally made by history and clinical presentation of the patient. The clinical toxidrome of carbamate poisoning is similar to that of organophosphates (Table 74.2). Symptoms typically develop within 15 minutes to 2 hours after exposure and usually last less than 24 hours. Central nervous system toxicity is less predominant because the *N*-methyl carbamates do not penetrate the blood–brain barrier well. However, carbamate poisoning in children was recently found to have a greater depressant effect on the central nervous system when compared to organophosphates (78). The cause of death is often acute respiratory failure from respiratory muscle fatigue, pulmonary edema, bronchorrhea, and bronchospasm. Central nervous system depression, seizures, and ventricular arrhythmias also increase morbidity and

mortality (79). Carbamate insecticide poisoning has been responsible for causing trauma-related deaths and injuries (80). When dealing with farm injuries, the clinician must consider the possibility of occult pesticide poisoning.

Laboratory Findings

Plasma and RBC cholinesterase enzyme measurements are less useful in cases of carbamate poisoning. Symptomatic patients whose blood samples are drawn within a few hours of exposure and absorption can exhibit depressed cholinesterase levels if the enzyme measurement is done rapidly. Enzyme reactivation can occur in vitro as well as in vivo, causing a rise in the enzyme activity before measurement. This makes clinical interpretation extremely difficult. Urine and blood analyses for parent compounds and metabolites have been described but are not often available (81). A radioimmunoassay has been described for carbamate insecticides that may resolve these problems if the assay becomes commercially available.

Treatment

Symptomatic treatment of the patient poisoned by carbamate insecticide includes aggressive respiratory support and atropine to reverse severe muscarinic manifestations. Because of the shorter duration of effect from in vivo hydrolysis, atropine treatment is usually required for less than 24 hours. The most important difference in treatment for carbamate and organophosphate poisoning involves pralidoxime. The use of pralidoxime may be relatively contraindicated in treating carbonyl poisonings because the carbamate–oxime complex may be a more potent cholinesterase inhibitor than carbonyl alone. Methomyl-induced carbamate poisoning has been treated with pralidoxime (82). After mixed or combined exposures involving both organophosphates and carbamate insecticides or in severe poisonings with an unidentified anticholinesterase agent, it is reasonable to administer pralidoxime (22).

Organochlorine Insecticides

Most of the organochlorine pesticides have been banned in the United States, principally because of their long ecologic half-lives, but a recent DDT poisoning report confirms that the toxic potential of this class continues (5). Organochlorine insecticides can be classified by chemical structure (Table 74.3). Lindane (γ-hexachlorocyclohexane) is one of the most commonly encountered organochlorine insecticides. It will be used as the prototype compound for discussing acute toxicity. It is available as a garden spray, structural and environmental pest control product, and scabicide (Kwell). The mechanism of toxicity is related to the ability of the organochlorine to alter ion fluxes, principally in nerve tissue. Although its use is decreasing, it continues to be a source of human poisoning (83,84). Evidence suggests that lindane produces antagonism of γ-aminobutyric acid–mediated inhibition in the central nervous system.

Table 74.3 Classification of Organochlorine Insecticides

Class	Brand Names
Dichlorodiphenylethanes	
DDT (1,1,1-trichloro-2,2-bis (p-chlorophenyl)ethane)	Anofex, Neocid
DDD (1,1,-dichloro-2,2-bis (p-chlorophenyl)ethane)	Rothane
Dicofol	Kelthane
Methoxychlor	Marlate
Hexachlorocyclohexanes	
Lindane (γ-hexaclorocyclohexane)	Kwell
Isotox	
Benzene hexachloride (mixed isomers)	BHC
Cyclodienes	
Endrin	Hexadrin
Aldrin	Aldrite, Drinox
Endosulfan	Thiodan
Dieldrin	Dieldrite
Toxaphene	Toxakil, Strobane-T
Heptachlor	Heptagram
Chlordane	Chlordan
Others	
Chlordecone	Kepone
Mirex	Dechlorane

BHC, Benzene hexachloride.

Organochlorine insecticides are easily absorbed through the lungs, gastrointestinal (GI) tract, and skin. As much as 10% of a topical dose of lindane is systemically absorbed. Because of the relatively large surface area–to–body weight ratio of infants, lindane poisoning has been reported to result from repeated therapeutic doses of lindane scabicide shampoo. The organochlorine insecticides are metabolized slowly and are excreted principally in the feces. Lindane accumulates in organs, including fat and tissue, but to a lesser extent than many of the other organochlorine insecticide. Lindane excretion takes several days, whereas most other organochlorine insecticides have much longer elimination half-lives. Lindane is partially dechlorinated and oxidized, yielding a series of conjugated chlorophenols and other oxidation products in the urine. Many of the organochlorine insecticides, including lindane and mirex, are capable of inducing liver microsomal enzymes (e.g., cytochrome P450–dependent mono-oxygenase system).

Immediate Signs and Symptoms

The neural excitation caused by the organochlorine insecticides leads to their primary toxic manifestations (Table 74.4). The toxidrome includes disturbances of

Table 74.4
Organochlorine Pesticide Poisoning Toxidrome

Sensory disturbances, hyperesthesia of face and extremities, paresthesia of face and extremities
Headache
Dizziness
Nausea and vomiting
Motor disturbances, muscle, weakness, incoordination, slurred speech, tremor, myoclonic jerking, involuntary eye movements
Mental confusion
Generalized tonic-clonic convulsions
Coma and respiratory depression

sensation, coordination, and mental status. Anorexia, malaise, headaches, myoclonic jerking, lethargy, tremor, hyperreflexia, motor hyperexcitability, oral paresthesia after ingestion, and convulsions of organochlorine pesticides have been associated with increased myocardial irritability and cardiac arrhythmias (85,86). Lindane has been rarely associated with aplastic anemia, agranulocytosis, disseminated intravascular coagulation, and proximal myopathy with myoglobinuria (87,88). A single case of self-poisoning with 1.0 mL of IV Thiodan (30% endosulfan in xylene) resulted in refractory grand mal seizures, increased liver enzyme levels, and acute rhabdomyolysis leading to proximal myopathy and acute renal failure. Motor seizures were controlled with IV midazolam and thiopentone. Both liver and renal dysfunction resolved with supportive intensive care unit treatment. Hemodialysis was not required, and the patient experienced a full recovery (84). A case of self-poisoning with oral endosulfan in kerosene resulted in seizures, respiratory failure, and terminal cardiac arrest (89). Organochlorine pesticide exposure has a significant neuroexcitatory effect on mammalian brains.

Laboratory Findings

Blood, tissue, and urine determinations of organochlorine pesticides and their metabolites are available from a limited number of laboratories. These levels are rarely useful in the clinical management of acute poisoning. The relatively rapid metabolism of lindane compared to many of the other organochlorine insecticides reduces the likelihood that the parent compound or metabolites will be detected in body fat, blood, urine, or human milk. Other organochlorine pesticides and their metabolites, such as DDT, dieldrin, mirex, and chlordecone, can remain in blood and tissue (particularly fat) for weeks or months. Persons exposed to lindane long term at work have had fat-to-serum concentration ratios of 220:1 (90). Workers exposed to lindane had whole-blood lindane levels of 0.02 to 0.45 ppm (91,92). Symptoms are unlikely in patients with whole-blood lindane levels as high as 20 to 30 ppm (93). EEG abnormalities have been noted after brief or long-term organochlorine exposure (94).

Treatment

GI decontamination with activated charcoal should be used for acute oral poisoning with organochlorine pesticides. For any exposure, skin decontamination and removal of contaminated clothing is essential. Treatment of convulsions may require ventilatory support and anticonvulsants such as diazepam, phenobarbital, or phenytoin. The organic solvents used to dispense organochlorine insecticides may result in aspiration pneumonitis and even acute respiratory failure. Because of the very long half-life of some organochlorine insecticides (e.g., chlordecone), the resin cholestyramine (3 to 8 g four times daily) has been shown to disrupt enterohepatic recirculation and significantly reduce the total body half-life of these insecticides (95). Cholestyramine has been advocated in the treatment of lindane poisoning (95). Repeated doses of activated charcoal over days to weeks may have the same effect, but this approach remains unproven, specifically with organochlorine insecticides.

Pyrethrum and Pyrethrin Insecticides

Pyrethrum is the natural derivative or oleoresin extract of dried *Chrysanthemum cinerariaefolium* flowers, which contain six active agents or pyrethrins (Fig. 74.1). Although pyrethrins I through VI make up crude pyrethrum extract, pyrethrins I and II are the most active. Because of the relatively high cost, high biodegradability, and light instability of natural pyrethrum, significant efforts over the last 20 to 25 years have resulted in the production of a number of synthetic pyrethroid derivatives. The synthetic pyrethroids are divided into two classes based on function or clinical effects of toxicity. Examples of type I pyrethroid include allethrin, permethrin, and cismethrin, whereas representative type II pyrethroids include fenvalerate, deltamethrin, and cypermethrin. Pyrethrum and pyrethrins are usually used in combination with synergistic compounds such as piperonyl butoxide and *n*-octyl bicycloheptene dicarboximide, which retard enzymatic degradation of the pyrethroids.

These insecticides have been used for more than 40 years and make up about 25% of the worldwide insecticide market (96). Commercial pesticide products with active pyrethroids often contain organophosphate or carbamate insecticides, in addition to the synergistic compounds that protect against degradation. In many of the indoor or household insecticide sprays, the pyrethrins, which cause a rapid paralytic or "knockdown" effect on insects, are often combined with longer acting insecticides to ensure lethality.

Because even the synthetic pyrethrins are expensive and have some light and heat instability, there is

relatively little commercial agricultural use of these agents. Because no active crop residues result from the application of pyrethrins, new pyrethrins may be marked for agricultural use in the future. Increasingly, pyrethrins are used as human scabicides because of their better tolerance compared to organochlorine agents such as lindane.

Signs and Symptoms

The pyrethroids alter nerve excitability by slowing nerve activation and by delaying sodium channel inactivation (96). This leads to type I pyrethroids (e.g., allethrin, bioullethrin) causing repetitive nerve discharge and can result in whole-body tremors and prostration ("T syndrome"). The type II pyrethroids (e.g., deltamethrin, fenvalerate) produce an even longer delay in sodium channel closure, resulting in persistent nerve depolarization and eventual blockage of axonal conduction. The type II pyrethroids may also alter and bind γ-aminobutyric acid receptor–mediated chloride channels.

Natural pyrethrum and its derivatives are less toxic to mammals than most other insecticides. Crude pyrethrum extracts contain dermal and respiratory allergens, which are probably other compounds than the active insecticide. These allergens produce the most common toxidrome (i.e., contact dermatitis, followed by rhinitis and asthma). An association or cross-reactivity with ragweed allergies has been noted (97). Because of the allergenic potential of pyrethrum extracts, anaphylactic or anaphylactoid reactions may occur in patients rechallenged with pyrethrum extracts or derivatives, but they have been rarely reported. The synthetic pyrethroids are less allergenic but have some irritant properties.

Systemic toxicity in mammals is reduced by rapid first-pass metabolism of pyrethrins by the liver. Pyrethrins are absorbed across the gut and by inhalation with poor bioavailability. Little dermal absorption occurs across intact skin. No modern-day pyrethrum fatalities have been reported; the estimated pyrethrum oral LD_{50} is over 1 g per kg.

Animals exposed to very large systemic doses of type I pyrethroids have demonstrated tremor in the limbs, which can gradually involve the entire body, with increased body temperature. Clinically, the toxicity is similar to massive exposure to the organochlorine DDT. Similarly, massive type II pyrethroid exposures have produced pronounced salivation, coarse whole-body tremors, and choreoathetosis with terminal seizures. In humans, large absorbed doses of these pyrethroids are thought to cause incoordination, tremor, salivation, vomiting, diarrhea, and rarely death (97–101). The α-cyano–containing type II pyrethroids have produced a unique cutaneous paresthesia several hours after cutaneous exposure. Many workers exposed to fenvalerate described a stinging or burning paresthesia, which sometimes progressed to numbness in the exposed face, neck, forearms, and hands. In fenvalerate-exposed workers, the symptoms lasted 12 to 18 hours but rarely beyond 24 hours. They were exacerbated by sweating and exposure to water, sun, or heat. The paresthesias are thought to be caused by contact with sensory nerve endings in the skin and are not thought to be allergic (102,103). In a study of licensed private pesticide applicators, neurologic symptoms were associated with organochlorine and organophosphate pesticides rather than with the use of pyrethroids (104). Developmental toxicity after pyrethroid exposure has recently been reviewed, but determining any relationship will require better designed and executed studies (96,105).

Large exposures of people to pyrethroids are usually secondary to oral exposure to commercial products, which usually contain many other synergistic chemicals. The toxicity of these other products is often the cause of the symptoms. The synergists piperonyl butoxide and *n*-octyl bicycloheptene dicarboximide exhibit little human toxicity. Acetylcholinesterase inhibitors, such as the organophosphate and carbamate insecticides, combined with pyrethroids in commercial products can cause significant human toxicity and require specific treatment, which has been described elsewhere in this chapter.

Because of a need to reduce mosquito vectors of West Nile Virus, public spraying of pyrethroids has occurred. Spraying of pyrethroids in New York City did not result in population-level increases in public hospital emergency department visits (106). Further studies in Mississippi, North Carolina, and Virginia failed to show significant pesticide exposure to humans after ultra low–volume pyrethroid spraying for West Nile Virus (107).

Laboratory Findings

No specific tests or routinely commercially available serum or tissue assays exist for detection of pyrethrum or synthetic pyrethrin compounds or their metabolites. Confirmation of absorption or cutaneous exposure is by clinical history and examination.

Treatment

Although there has been little systemic toxicity reported with pyrethroids in humans, GI decontamination, including the use of activated charcoal, is recommended. Aggressive decontamination of the eyes with water and the skin with soap and water is suggested. Further supportive care is rarely needed. Allergic reactions or responses may require antihistamines. Pulmonary allergic reactions may require bronchodilator treatment. Preventive care should include avoidance of pyrethrum-related allergens. Pyrethrum-induced contact dermatitis may require antihistamine and topical or systemic corticosteroid administration. Type II pyrethrin-induced cutaneous paresthesias can be avoided by reducing cutaneous and volatilized exposures. Topical vitamin E oil

preparations (*d*,1-a-tocopherol acetate) can modulate the cutaneous paresthesias to a greater degree than corn oil or petroleum jelly preparations (69). There is little experience treating systemic signs of pyrethroid-induced toxicity. Animal data suggest that atropine can modify pyrethroid-induced salivation and that diazepam or phenobarbital is effective against tremors and seizures. In a series of 573 cases of acute pyrethroid poisoning, one patient died after being given large doses of atropine for a condition misdiagnosed as acute organophosphate poisoning (99). In the same series, eight patients with pure pyrethroid poisoning developed atropine intoxication after receiving total atropine doses of 12 to 75 mg (99).

Paraquat and Diquat Herbicides

Paraquat (1,1'-dimethyl-4,4'bipyridylium) is a contact herbicide considered to have low potential for environmental toxicity because it is rapidly inactivated in the soil. Commercial or technical paraquat (or diquat, a related herbicide) products range in concentration from 20% to 50%, whereas home products are usually much less concentrated (0.2% solutions to 2.5% soluble granule formulation; Table 74.5). Home products are often formulated in combination with other herbicides. In a United Kingdom 6-year study of pesticide toxicity in the 1980s, paraquat was the cause for eight of the 10 reported deaths (108). A more recent study found that less than 5% of deaths and hospitalizations from pesticides in California were associated with paraquat or other herbicides (19). Most clinical toxicity has been associated with concentrated paraquat ingestions and suicide attempts (109). Toxicity has resulted from inhalation, skin absorption, and even vaginal absorption (110–112). Ingestion of more than 20 mg per kg (7.5 mL of a 20% solution) of paraquat is frequently lethal, with death caused by severe damage to the lung and other organs. Mild paraquat poisoning is associated with small doses (<20 mg per kg), severe poisoning is associated with doses between 20 and 40 mg per kg, and fulminant poisoning is seen with exposures of >40 mg per kg (113). The mortality rate after severe paraquat or diquat ingestion remains approximately 60% (114–116).

Table 74.5
Examples of Paraquat- and Diquat-containing Herbicide Products

Product	Herbicide	Content (%)
Gramoxone	Paraquat	29.1
Paraquat Plus	Paraquat	29.1
Ortho Paraquat	Paraquat	29.1
Ortho Spot Weed and Grass Killer	Paraquat	3.6
Ortho Weed Killer Concentrate	Diquat	35.3
Ortho Diquat 2-Spray	Diquat	35.3
Ortho Diquat Water Weed	Diquat	35.3
Weedtrine D	Diquat	8.53
Dexol Weed and Grass Killer	Diquat	0.23
Frank's Weed and Grass Killer	Diquat	0.23
Scotty's Weed and Grass Killer	Diquat	0.23

A recent study of general poisonings in Japan found that 16.1% were due to pesticides and herbicides, but 20 of the 23 deaths were associated with either paraquat or diquat (117). Selective concentration of paraquat in lungs (10 to 15 times greater than serum concentrations) accounts for this major lethal effect. The volume of distribution for paraquat is large (2 to 8 L per kg). Paraquat has been alleged, with little evidence, to cause lung damage to marijuana smokers in the United States who obtained their marijuana from paraquat-treated Mexican plants. Diquat is not selectively concentrated in the lungs, and pulmonary injury from exposures tends to be less severe. Survivors of paraquat poisoning frequently have abnormal restrictive lung defects from pulmonary fibrosis that will rarely improve over time (118). Risk factors for paraquat toxicity from agricultural exposures in California have been described (119). Chronic low-level occupational paraquat exposure was associated with subclinical gas exchange abnormalities, but the findings were inconsistent, with no clinically significant increases in interstitial thickening or restrictive lung disease among the population (120).

When a relatively low concentration of paraquat plus diquat replaced a product of high concentration of paraquat in Japan, deaths within 1 week from multiorgan failure and circulatory collapse were unchanged, but late deaths from respiratory failure were reduced (17.1% versus 6.3%); this was coupled with improved overall survival (23.4% versus 34.9%) (121). Damage to tissue and organs by paraquat or diquat is mediated on a molecular level by hydrogen peroxide and free radicals, including superoxide radicals and hydroxyl radicals, in reactions that may be catalyzed by transition metal ions (122). Supplemental oxygen can increase the generation of superoxide radicals and other free radicals in the lung, which, if not quenched by superoxide dismutase, can further free radical damage of molecular targets (e.g., proteins, lipids, and nucleic acids) (123).

Signs and Symptoms

Skin contact with paraquat or diquat leads to blistering, ulcerations, and discolored fingernails. Prolonged inhalation of spray droplets may cause nosebleeds, severe conjunctivitis, and severe shortness of breath. The caustic effects of paraquat result in esophageal and gastric erosions after ingestion. Extensive gastroenteritis with large amounts of mucosal sloughing can occur (Table 74.6). A case of severe diquat poisoning associated

Table 74.6 Paraquat Toxidrome

Clinical Finding	Prevalence (%)
Vomiting	100
Dysphagia	100
Oropharyngitis	100
Restlessness	90
Jaundice	80
Cyanosis	45
Hemoptysis	40
Diarrhea	5
Convulsions	5
Nail bed necrosis	5

with oral/esophageal burns, aggressive behavior, oliguric renal failure, and intracerebral bleeding was successfully managed with supportive care, and the patient demonstrated complete recovery (124). Death results from multisystem failure, including noncardiogenic pulmonary edema, acute renal failure, hepatic necrosis, adrenal hemorrhage, brain damage, and myocardial necrosis (115,125–128). Paraquat poisoning in pregnancy has resulted in high placental concentrations and fetal death (129). However, a recent report demonstrated maternal and fetal survival after a severe paraquat intoxication using charcoal hemoperfusion, "mega dose" cyclophosphamide, and methylprednisone pulse therapy (130).

Laboratory Findings

Determinations of plasma paraquat levels by radioimmunoassay and various chromatographic methods is available from specialized laboratories (131). Correlation among serum levels, interval after ingestion, and clinical outcome exist (Fig. 74.2) (132). A qualitative colorimetric method using 1% sodium dithionite and 1N sodium hydroxide to detect paraquat in urine has been described (131). To ensure accuracy, both positive and negative controls should be tested. An enzyme-linked immunosorbent assay (ELISA) recently was used for quantification of paraquat in urine and air-filter samples collected in a human-exposure study among farm workers in Costa Rica (133). A sample pretreatment consisted of removal of interfering substances using solid-phase extraction resin columns. The correlation between results for blind samples obtained using ELISA and liquid chromatography–mass spectrometry was significant ($r^2 = 0.945$ and 0.906 for spiked and field samples, respectively). The limit of quantification for this assay was 2 ng per mL (−1), which was able to distinguish exposed from nonexposed farm workers. A study of 21 patients poisoned by paraquat failed to find a correlation between exhaled ethane (a reflection of lipid peroxidation) and morbidity (decreased renal and pulmonary function) and mortality (134). Only the amount of paraquat ingested was a significant predictor of death (134).

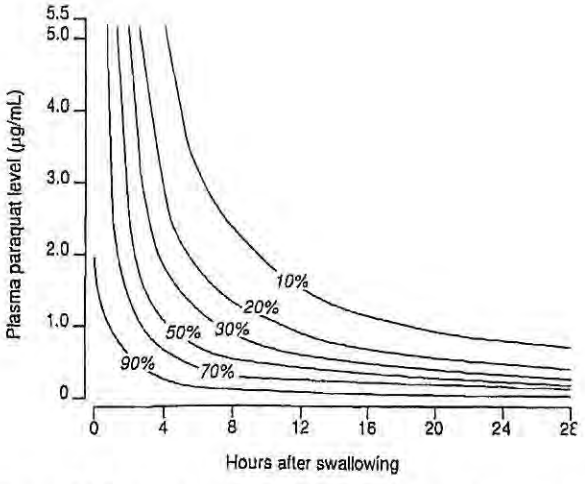

Figure 74.2 Graph demonstrating the relationship between the plasma concentrations of paraquat in micrograms per milliliter (*ordinate*), time after ingestion (*abscissa*), and the probability of survival. (From Sunder Ram Rao CV, Shreenivas R, Singh V, et al. Disseminated intravascular coagulation in a case of fatal lindane poisoning. *Vet Hum Toxicol.* 1988;30:132–134 with permission.)

In a series of 20 patients from Trinidad who were poisoned with paraquat (135), all were found to have elevated serum paraquat levels, blood urea nitrogen, and creatinine levels, as well as elevated liver function test values (e.g., bilirubin, glutamic-oxalate transaminase, and alkaline phosphatase). Hypokalemia was seen in 17 out of 20 paraquat-poisoned patients. Chest radiographs were abnormal in 45% of the cases, and urine tests for paraquat were positive in 90% of the cases.

Another review of 42 patients with severe paraquat poisoning found that those with serum paraquat levels above 3 μg per mL die, regardless of intervention (136). However, survival has been recently reported in a patient with a measured paraquat level of 28 μg per mL, but the patient received hemodialysis, early digestive decontamination, and antioxidant therapy (137). A fatal case of diquat poisoning occurred after exposure to 60 g of diquat. It resulted in progressive anuria, neurologic disorders, and cardiocirculatory collapse after 26 hours, with a serum level of 64 μg per mL at 4 hours (138).

Treatment

Although many treatments have been studied, no proven effective antidote exists (114,135,139). Early digestive decontamination and hemodialysis followed by antioxidant therapy with low doses of deferoxamine (100 mg per kg in 24 hours) to bind transition metal catalysts (such as iron and copper) and continuous IV infusion of acetylcysteine (300 mg/kg/day for 3 weeks) has been described for potentially fatal cases of paraquat poisoning with little controlled data to support the regimen (137). Whole-lung

radiation and single or bilateral lung transplantations must be considered experimental (140–144). Similarly, cyclophosphamide and steroids have not been proven to improve the outcome of paraquat- or diquat-poisoned patients. A severely paraquat- and diquat-poisoned patient was successfully treated with Fuller's earth, hemofiltration, *N*-acetylcysteine, methylprednisone, cyclophosphamide, vitamin E, colchicine, and continuous inhaled nitric oxide (145). Accepted therapy includes skin and eye decontamination with copious amounts of water. Immediate administration of an absorbent after ingestion is likely to improve the outcome of paraquat ingestion. Bentonite (75% suspension) or Fuller's earth (30% suspension) in an adult dose of 100 to 150 g are thought to be the most effective treatments (114,135). If these are not readily available, activated charcoal may be used. Because of the possible erosive changes in the esophagus, gastric intubation must be done with extreme care. Endoscopy may be required to avoid inadvertent perforation. Extracorporeal hemoperfusion (within hours of ingestion), peritoneal dialysis, and hemodialysis have been tried, with the latter two being useful only in electrolyte and hemodynamic management (114,146–151). In vitro studies using fresh pork blood have demonstrated higher paraquat clearance with hemoperfusion than with hemodialysis (152). Mechanical ventilation for acute respiratory failure (adult respiratory distress syndrome) and critical care support in an intensive care unit are often necessary in severely intoxicated patients. Beyond decontamination and supportive care, no specific effective antidote for paraquat poisoning has been demonstrated (113). A poor prognosis is expected in patients with multisystem failure.

Glyphosate

Glyphosate (N-phosphonomethyl glycine) is a nonselective, postemergent herbicide that is extremely effective against all green plants. Due to its effectiveness and rapid soil biodegradation, glyphosate has become one of the most widely used herbicides in the United States. Increased use in the future can be anticipated because glyphosate is one of the few nonselective herbicides for which genetically engineered crops have been developed. In 2004, the AAPCC reported 4,400 glyphosate exposures handled by U.S. poison control centers. Of these exposures, 94% were unintentional, and there was one death in a patient who ingested concentrated glyphosate (Roundup) in a suicide attempt (10).

Glyphosate-containing herbicides are marketed under a variety of different trade names. (e.g., Roundup, Bronco, Touchdown, Landmaster, Sonic, Rattler, Zero Weed Killer, etc.). These products are complex combinations of glyphosate, surfactants, salts, and even other herbicides. The surfactant component of the herbicide is added to aid glyphosate's penetration into plant leaves. The original and most commonly encountered commercial formulation is Roundup (manufactured by Monsanto), which contains the isopropylamine salt of glyphosate and the polyethoxylated tallow amine surfactant [polyethyleneamine (POEA)]. The dilute ready-to-use Roundup formulations contain between 0.5% and 5% glyphosate. The concentrate is sold as a 41% concentration and designed for a final dilution to a 1% solution. Interestingly, newer Roundup products marketed in the United States may contain both glyphosate and the unrelated poison, diquat, for more rapid weed "browing" effect.

Glyphosate is structurally related to the plant growth regulator glyphosine. It competitively inhibits the plant enzyme 5-enolpyruval shikimic acid 3-phosphate synthetase, which causes it to be a potent plant toxin. Its selectivity comes from the fact that there is no equivalent mammalian enzyme system. Previous animal studies have supported an excellent safety profile in mammals. Glyphosate has no acetylcholinesterase inhibitory activity. Because glyphosate-containing herbicides are complex mixtures, it is difficult to attribute human toxicity to any single ingredient. The surfactant is commonly considered to be more toxic than glyphosate itself and most likely is the primary cause of poisoning in significant human exposures. In one canine study, dogs infused with a mixture of surfactant and glyphosate or surfactant alone experienced myocardial suppression and hypotension. Those dogs receiving glyphosate alone remained normotensive (153,154). Because glyphosate is generally not encountered without its associated surfactant, separation of the two sources of clinical poisoning is impractical. Perhaps these exposures are most appropriately termed "glyphosate-surfactant" (G-S) poisonings (80,155). The exact mechanisms of toxicity and contribution of each component to poisoning is unknown.

In two lethal cases, glyphosate-trimesium (Touchdown) appeared to be significantly more toxic than Roundup. It is proposed that glyphosate-trimesium is more rapidly absorbed or has a unique mechanism of toxicity (156).

Signs and Symptoms

Common clinical findings reported after glyphosate herbicide (G-H) ingestion include GI distress (nausea, vomiting, diarrhea, abdominal pain, and GI bleeding), mucous membrane irritation, hypotension, pulmonary edema, respiratory distress, transient hepatic damage, renal insufficiency, and renal failure. Mild exposures may present with mild GI symptoms, while severe poisoning may result in refractory hypotension, shock, pulmonary edema requiring intubation, renal failure, coma, cardiac arrest, or death. Case series mortality rates after ingestion vary from 7.5% to 16.1% (80,157–159). In the study by Lee and Ransdell (80), the most common clinical features at presentation were sore throat (79.5%), nausea/vomiting (73.8%), and fever (41.2%).

While not all case reports of G-H poisoning have specified concentration, systemic poisoning associated with exposure to dilute (ready-to-use) products is unusual and unexpected. No known deaths have occurred from accidental ingestion of dilute G-H. Patients at high risk are those with exposure to concentrated G-H or intentional ingestion of any concentration.

It is unclear whether the pulmonary edema related to G-H poisoning is due to systemic toxicity of the agents or aspiration and direct pulmonary toxicity. Nevertheless, the pulmonary injury can be severe and may result in respiratory distress. In the study by Lee and Ransdell (80) of 131 patients, 13.7% presented with respiratory distress necessitating intubation. Several series report a delay in onset of serious symptoms, particularly pulmonary complications, of up to 12 to 72 hours (157–159).

Both glyphosate (157,158) and POEA are known to have GI corrosive effects. Chang et al. (60) performed upper GI endoscopy on 50 consecutive patients after G-H ingestion. Of these patients, 94% had findings of corrosive injury on endoscopy; 68% had injury involving the esophagus, and most of these were grade 2 injuries (56%). No severe grade 3 injuries were found in this study (160). Esophageal GI perforation has never been reported in relation to G-H ingestion. It appears that patients ingesting more than 100 mL are at greater risk for GI corrosive injury as well as systemic poisoning. Endoscopic evaluation for corrosive injury is warranted in all cases of intentional ingestion or in the presence of concerning symptoms.

Laboratory Findings

No specific serum, urine, or tissue assays exist for detection of POEA, glyphosate, or surfactant. Diagnosis of G-H intoxication depends on clinical history and examination. Findings of renal insufficiency (or failure), hyperkalemia, or metabolic acidosis suggest a severe poisoning. Liver enzyme elevations may also be present, although severe hepatotoxicity is not expected. Any findings of pulmonary involvement should prompt chest x-ray. In cases of Roundup exposure where renal toxicity is discovered, the treating physician should consider possible exposure to a combination product containing diquat (particularly when a dilute Roundup product is involved).

Treatment

Management after G-S exposure is primarily supportive. Topical G-H exposure warrants skin/eye decontamination; however, systemic toxicity is not expected because G-H is not well-absorbed dermally. GI decontamination is unnecessary after accidental ingestion of dilute (ready-to-use) G-H preparations because systemic toxicity is not expected. In cases of early presentation after intentional ingestion or ingestion of concentrated G-H, gastric decontamination with activated charcoal should be considered. Great care should be taken when administering activated charcoal because aspiration of G-S may induce pulmonary injury.

Findings of pulmonary edema should be treated with oxygen and ventilatory support as needed. Hypotension is treated with fluids and direct-acting vasopressors. Electrolytes, particularly potassium, should be checked and corrected if abnormal. Hemodialysis may be beneficial in cases of severe electrolyte abnormalities, metabolic acidosis, or renal failure. While a single case of survival after hemodialysis has been reported, there is no data to support routine hemodialysis after G-H poisoning (161).

Patients with symptoms of esophageal injury or intentional ingestion should receive endoscopic evaluation to assess for corrosive injury. Due to the possibility of delayed-onset pulmonary edema, patients should be observed for at least 12 to 24 hours following exposure.

FUMIGANTS

Fumigants are gases at ambient temperature or volatile liquids that are used to sterilize products, crops, structures, or soil. Fumigant pesticides have the advantage of being highly penetrating and relatively easy to apply. Most dissipate after use without toxic residues. Exposures may occur due to leaks in equipment, leaks from containment apparatus, premature reentry into a treated area, and occasionally suicidal ingestion. Poisonings are usually related to inhalational or skin exposure. In the United States, strict regulations govern the use of fumigant pesticides by licensed applicators.

There is a wide array of fumigant pesticides. Many are halogenated hydrocarbons and, as such, may cause general anesthetic effects, hepatotoxicity, and myocardial sensitization. These agents will not be described in this chapter. This section will cover some other relevant fumigants: phosphine, methyl bromide, and sulfuryl fluoride.

Phosphine

Phosphine (e.g., hydrogen phosphide, phosphorus trihydride) is a gas generated from aluminum or zinc phosphide upon exposure to water (or dilute acid). Aluminum phosphide is a commonly used fumigant for the treatment of grain elevators. Water is added to solid aluminum phosphide pellets, liberating the end-fumigant phosphine gas. Because phosphine has a density greater than air, it is able to descend through the grain, effectively treating the storage structure. Similar zinc phosphide products and baits are available as rodenticides. Ingestion of solid zinc phosphide causes liberation of phosphine gas within the stomach, resulting in poisoning. Phosphine gas exposure

has also been reported during acetylene gas production, certain semiconductor manufacture processes, and illegal methamphetamine synthesis.

Phosphine gas is colorless with a "fishy" (rotten fish) odor. The exact mechanism of phosphine toxicity is not clearly understood. Organs with the greatest oxygen requirement seem to be most affected. Based on animal studies, toxicity may be related to noncompetitive inhibition of cytochrome oxidase.

Signs and Symptoms

Phosphine gas inhalation is associated with cough, dyspnea, chest pain, and pulmonary edema. Symptom onset is usually rapid; however, delayed onset of pulmonary edema has been reported, necessitating an extended period of observation (after pulmonary exposure). Headache, dizziness, fatigue, and weakness have also been reported. GI symptoms including nausea, vomiting, abdominal pain, and hepatotoxicity are common findings. In cases of severe poisoning, hypotension, cardiac dysrhythmias, shock, convulsions, and coma may be seen (49,162–164).

Laboratory Findings

Diagnosis of phosphine poisoning is made based on history and physical examination findings. The clinician must maintain a high level of suspicion because delayed onset of pulmonary edema has been reported. No specific laboratory tests or levels are available. Chest x-ray, pulse oximetry, and blood gas measurements are helpful in monitoring patients for pulmonary toxicity. Electrolytes, creatinine, and hepatic transaminases should be checked.

Treatment

Treatment after possible phosphine poisoning is primarily supportive. Following exposure, patients should have clothing removed and skin decontamination performed if appropriate. Regardless of presenting symptoms, patients should be considered for admission for 24 to 48 hours due to delayed-onset pulmonary edema. Oxygen, ventilatory assistance, and positive end-expiratory pressure (PEEP) ventilation should be used to support pulmonary function as needed. In severe poisoning, hypotension should be treated with fluid and pressors. Convulsions are treated primarily with benzodiazepines. No specific antidote exists.

In cases of solid phosphide ingestion, gastric decontamination should be performed using single-dose activated charcoal and/or gastric lavage if presentation is rapid within 1 hour. One series reported benefit with gastric lavage performed early after ingestion (within 60 minutes) followed by IV magnesium sulfate (165). There are no definitive studies to confirm or refute this practice.

Methyl Bromide

Methyl bromide is an aliphatic, halogenated hydrocarbon used as both a structural and soil fumigant. It is also known under the names Bromomethane, Bromo-Gas, Methogas, Profume, Terr-O-Gas, and Zytox. Methyl bromide is a colorless and almost odorless gas at ambient temperatures. At very high concentrations, it has the odor of chloroform. Because of its poor warning properties, the irritant chloropicrin is often added to methyl bromide as an alerting agent. The EPA has recently been phasing out methyl bromide's use due to concerns regarding ozone depletion.

Previous exposures to methyl bromide have been caused by premature re-entry into tented areas, leaking from containment tents, and leaking of gas between structures through undiscovered conduits (166–170). The route of poisoning in these cases was pulmonary. One case of local and systemic toxicity has been reported related to dermal exposure (171). Methyl bromide causes primarily central nervous system toxic effects; however, its mechanism is not well understood. It is an alkylating agent, which may explain its toxicity. Bromide ions may contribute to toxicity but are not thought to be the primary means of acute poisoning (as opposed to chronic poisoning) because bromide levels do not correlate with clinical symptoms.

Signs and Symptoms

Methyl bromide is a vesicant agent and may cause blisters and skin burns upon topical exposure. Systemic poisoning after dermal exposure is uncommon. Inhalational exposure may result in respiratory tract irritation, cough, dyspnea, or lung injury related either to methyl bromide or the additive chloropicrin. Pulmonary exposure can also cause systemic symptoms including dizziness, blurry vision, headache, altered mental status, myoclonus, basal ganglia dysfunction, seizures, coma, and death. High-level exposures may cause narcosis and rapid death due to respiratory failure. Seizures may be refractory and difficult to control. Large exposures usually cause rapid onset of symptoms; however, delayed-onset toxicity, as late as 24 to 48 hours, has been reported in lower concentration exposures. Chronic neurologic symptoms may persist after acute poisoning. Partial or complete resolution of these symptoms may occur over months to years.

Laboratory Findings

Diagnosis of methyl bromide poisoning is made primarily based on history and physical examination. Specific methyl bromide levels can be obtained from serum, blood, or urine but are short lived and not commonly available. Elevated serum, blood, or urine bromide levels can be used to confirm suspected methyl bromide poisoning. Unfortunately, serum bromide

levels do not correlate well with clinical symptoms and do not aid in predicting outcome. Interestingly, bromide ions interfere with serum chloride assays. The finding of elevated chloride or a negative anion gap on chemistry panels is a clue that serum bromide may be high. One study reported the use of *S*-methylcysteine adduct testing to confirm exposure as long as 10 weeks after exposure (172).

Treatment

Patients should be immediately removed from the source of methyl bromide exposure and placed into fresh air. Clothing removal and skin decontamination should be performed when appropriate. Treatment of symptomatic poisoning is primarily supportive. There is no antidote for methyl bromide poisoning. Airway control should be performed when indicated for severe altered mental status. Benzodiazepines or barbiturates may be given for seizures. Hemodialysis has been attempted after methyl bromide poisoning (173,174). Hemodialysis is successful in lowering bromide levels but has had mixed effects on clinical symptoms. There is insufficient experience at this time to recommend routine hemodialysis after methyl bromide poisoning.

Sulfuryl Fluoride

Sulfuryl fluoride (e.g., sulfuryl difluoride, sulfuric oxyfluoride) is sold under the trade name Vikane. It is used primarily as a fumigant for the extermination of wood-boring insects. In the early 1990s, sulfuryl fluoride replaced methyl bromide as the most commonly used (tenting agent) fumigant for structural termite control. Because sulfuryl fluoride is a colorless, odorless gas, the irritant chloropicrin is often intentionally added in low concentrations as a warning agent. Exposures are usually related to occupational mishaps or premature reentry into a tented structure. The toxic mechanism of sulfuryl fluoride poisoning is not well understood but may be related to the release of fluoride ions.

Signs and Symptoms

In animal studies, low-dose sulfuryl fluoride exposures resulted in parasympathetic symptoms, like nausea, vomiting, diarrhea, abdominal cramping, salivation, and lacrimation. High-dose exposures cause loss of consciousness (versus incapacitation), seizures, and death (175). In human case reports, mucous membrane irritation, dyspnea, cough, pulmonary edema, nausea, vomiting, diarrhea, weakness, paresthesias, carpal-pedal tetany, seizures, cardiac dysrhythmias, and death have been reported (176,177). In severe poisonings, symptom onset appears to be rapid; however, fatalities may occur days after exposure. Life-threatening poisoning may cause pulmonary edema, seizures, metabolic acidosis, and/or cardiac dysrhythmias.

Laboratory Findings

No serum, urine, or tissue levels are commonly available. Diagnosis of sulfuryl fluoride poisoning is based on history and clinical examination. Elevated serum fluoride concentrations have been reported after poisoning. However, fluoride levels are not helpful for clinical management. Patients with symptomatic sulfuryl fluoride exposure should have serum electrolytes, including calcium, and creatinine checked. Chest x-ray is recommended in patients with any respiratory symptoms.

Treatment

Exposed patients should be immediately removed from the area into fresh air. Treatment of sulfuryl fluoride poisoning is primarily supportive. Hypotension is treated with fluids and direct-acting vasopressors. If seizures develop, benzodiazepines or barbiturates should be given. Pulmonary edema is treated with oxygen, ventilatory assistance, and PEEP. Similarly to fluoride poisoning, serum potassium and calcium should be checked immediately, and findings of hyperkalemia or hypocalcemia should be treated. If life-threatening cardiac dysrhythmias are discovered upon presentation, IV calcium and bicarbonate infusion should be considered. In one rat study, those animals pretreated with calcium prior to lethal sulfuryl fluoride exposure survived. Unfortunately, postexposure calcium treatment did not impact survival (175).

LONG-TERM HEALTH EFFECTS

Most acute effects of pesticide toxicity are well characterized, and the mechanisms of their pathogenesis have been established in many cases. Studies on long-term effects, which develop or persist long after the exposures that may have precipitated them, typically are less consistent in their findings and often raise more questions than they answer. The ability of pesticides to cause cancer, neurotoxicity, and adverse reproductive effects has been demonstrated in laboratory animals, but unambiguous clinical or epidemiologic evidence of effects in humans exists for only a few specific agents. For most pesticides, clinical or epidemiologic data are lacking on long-term health effects, or the data do not yet support clear evidence of causality.

Epidemiologic studies have focused principally on pesticide formulators and applicators as representing heavily exposed populations. Several population-based investigations have studied both cancer and reproductive outcomes, although most of these have been limited by ecologic methodology or poor estimates of pesticide exposure. In the remainder of this chapter, we focus on epidemiologic studies, including pertinent laboratory and clinical results, to clarify the effects of the various pesticides on health outcomes.

Issues of causation, particularly from long-term exposures, ideally require a combination of laboratory, clinical, and epidemiologic data. Laboratory studies may address the important question of biologic plausibility of associations observed in epidemiologic studies. The ability to assess exposure quantitatively through biomarkers will greatly improve the sensitivity and specificity of epidemiologic studies. Recognition of subcellular initial lesions that contribute to eventual development of degenerative diseases also will open new avenues to epidemiology. Until such studies are completed, prudent avoidance or minimization of exposure to all xenobiotics is the safest course.

Cancer

While farmers' mortality rates are lower than those of the general population for all causes combined and for smoking-related cancers, numerous studies of farmers have demonstrated above average death rates from particular cancers that are mostly not related to smoking. These studies, from several regions in the United States as well as countries in Europe, have most commonly observed increases in leukemia, non-Hodgkin's lymphoma (NHL), and multiple myeloma. Fewer studies have observed increases in Hodgkin's lymphoma and cancers of the brain, stomach, prostate, skin, and connective tissue (43,178–182). While some of these studies have linked cancer rates to pesticide use or other agricultural practices, all of the studies have serious problems of exposure misclassification. In addition, most farmers and farm workers are exposed to numerous pesticides and other potentially harmful substances, further complicating the conclusions from epidemiologic studies. The observed associations should be regarded provisionally and skeptically. Despite these difficulties, hematopoietic and lymphatic cancers consistently have been associated with farming and, in some cases, have been associated with geographic areas of higher pesticide use or with specific agricultural activities, such as corn production, associated with heavy pesticide use. More recently, epidemiologic studies have estimated exposure to specific pesticides (e.g., phenoxy herbicides) and evaluated their association with specific cancers (e.g., NHL).

A major epidemiologic approach to the question of pesticides and cancer has been to study occupational cohorts exposed to pesticides. Such studies have included pesticide manufacturers, structural pest control applicators, and agricultural applicators. These studies generally lack exact measurements of pesticide exposure in individuals, and multiple pesticide exposures often occur, especially among applicators. However, the studies do target populations that experience relatively frequent, intense, and prolonged exposures (183–185).

The Agricultural Health Study is a prospective cohort assessment of 52,393 private applicators (mostly farmers) and 32,345 spouses of farmers in Iowa and North Carolina (186–189). As with other farmer cohorts, overall mortality was very low in this population. The all-cause and all-cancer standardized mortality ratios for the cohort in 2000 (average follow-up time, 5.3 years) were 0.5 [95% confidence interval (CI), 0.5 to 0.5] and 0.6 (95% CI, 0.6 to 0.7), respectively (189). There was little variability in mortality with years of handling pesticides or other farming variables. Analyses of specific exposures within the cohort have suggested some associations of cancer with specific pesticides. For example, an analysis of alaclor exposure found a significantly increasing trend for incidence of all lymphohematopoietic cancers and lifetime exposure days to alaclor (190).

Recent indications that chlorinated pesticides and their contaminants may interact with hormone receptors (see Female Reproductive Effects section) have led to speculation about a possible role in the development of cancer of the breast. This work was catalyzed by a case-control study showing increased dichlorodiphenyldichloroethylene (DDE; a metabolite of DDT) in the sera of patients with breast cancer compared to controls (191). However, a larger nested case-control study conducted within a prospective cohort found no evidence of an association (192). A recent case-control study of agricultural workers in California found an association of breast cancer with quartiles of pesticide use (193), but overall, the epidemiologic data do not support an association between organochlorines and breast cancer (194–196).

In summary, overall mortality among pesticide-exposed populations is usually lower than for the general population, but epidemiologic studies continue to support the association of some cancers with specific pesticides. The large Agricultural Health Study cohort may help clarify some of these relationships, but it is limited by the geography and practices of its population.

Neurotoxicity

In most cases of acute neurotoxicity from pesticides, recovery is complete unless convulsions or other acute injuries occur. However, there is evidence that long-term pesticide exposure may result in some chronic neurologic effects. DDT and the other organochlorines are stored in fat tissue, so cumulative exposure may occur. With DDT, symptoms of chronic and acute toxicity are similar, such as anorexia, weakness, anxiety, and hyperexcitability (197). Persistent neurologic sequelae are most likely to follow acute organochlorine toxicity that is associated with convulsions (198). Polyneuropathy has been associated with chronic exposure to some organochlorine pesticides (199,200). Follow-up of adults and children years after chlordane was sprayed around the apartment complex in which they lived indicated impairment of

balance, reaction time, and immediate recall, among other test results (201).

The acute neurotoxic effects of the organophosphate and carbamate insecticides and the recently recognized intermediate syndrome have been discussed earlier. A delayed neuropathy has been observed in humans days to weeks following acute organophosphate insecticide exposure, termed the organophosphorus ester-induced chronic neurotoxicity (OPICN) syndrome. The OPICN syndrome is manifest by involvement of the longest nerve fibers and presents with progressive weakness, ataxia, and paralysis. Pathogenesis of this irreversible syndrome appears to involve inhibition of the NTE rather than of neural acetylcholinesterase (202,203), although inhibition of acetylcholinesterase has been an inevitable concomitant result. One study of neurologic sequelae following organophosphate poisoning found impaired visual attention and vibrotactile sensitivity among cases compared to controls (204). While this finding is provocative, it needs to be replicated with more complete follow-up and better estimates of exposure. Studies of long-term subtoxic exposure to chlorpyrifos in rats by injection or feeding have shown long-lasting neurobehavioral changes (205,206).

A cross-sectional analysis of neurologic symptoms among 18,782 pesticide applicators enrolled in the Agricultural Health Study found self-reported symptoms to be associated with lifetime days of insecticide use (50). The association was independent of recent pesticide poisoning. No tests of neurophysiologic function were performed. A study of neurobehavioral performance tests among preschool children from agricultural and nonagricultural communities in Oregon and North Carolina found poorer performance on some of the tests among the children from the agricultural community, but the study included no measures or estimates of pesticide exposure (207). Overall, these studies provide little specific insight into the association of chronic pesticide exposure and neuropsychological functioning.

The possibility that pesticide exposure may contribute to development of Parkinson's disease (PD) has been suggested following observations (208) that such exposure is more common among PD patients than among unaffected people from the same region. Specific features of PD have been reproduced in rodents following exposure to various toxicants including agricultural chemicals (e.g., rotenone, paraquat, maneb) (209). However, two recent case–control studies have failed to show statistically significant association of PD with specific pesticide or herbicide exposures (210,211).

Studies of neuropsychological effects in humans following acute organophosphate insecticide poisoning (204,212–214) have indicated a fairly consistent constellation of subjective disturbance and subclinical deficits. Persistent symptoms following acute toxicity include headache, dizziness, nausea, visual disturbances, weakness, confusion, agitation, and insomnia. The most consistent of positive measurable results has been elevation of the threshold for vibratory sensation. These symptoms may last weeks to months following cessation of exposure, persisting long after resolution of cholinergic signs (215). Cholinesterase depression is only variably associated with these persistent symptoms.

A variety of neurobehavioral symptoms has been associated with chronic low-dose exposure to organophosphate insecticides, but studies showing an association of objective outcomes with exposure are generally lacking. Symptoms observed among workers exposed long term to organophosphate insecticides include fatigue, memory deficits, nervousness, malaise, vision disturbances, and loss of concentration (197). There is supportive evidence from animal studies for chronic neurologic effects of organophosphate and other agrochemical exposures, but more carefully controlled studies are necessary in humans. The importance of acute versus chronic exposures is a major area of uncertainty.

Reproductive Toxicity

Male Reproduction

Chlordecone (Kepone) was an insecticide and fungicide produced from 1958 to 1975, when production was stopped because of toxicity in production workers (216). In animal studies, chlordecone causes testicular atrophy (217,218). Among the production workers in the Virginia Allied Chemical and Dye Corporation plant, chlordecone caused oligospermia and reduced sperm motility in several men, as well as neurotoxicity and several other clinical effects (216).

The recognition that spermatotoxicity could be caused by agrochemical exposure was dramatically demonstrated as evidenced by azoospermia and infertility among pesticide formulators exposed to the nematocide 1,2-dibromo-3-chloropropane (DBCP) in a California manufacturing plant (219,220). Additional studies demonstrated that reduced sperm counts were more commonly observed among workers in DBCP manufacturing than in applicators or farm workers (221–223). Follow-up studies of DBCP-exposed workers demonstrate recovery of spermatogenesis and fertility and, even in some cases, of azoospermia (223–225). The absence of a biomarker for DBCP and inadequate data on actual dose in epidemiologic studies limit understanding of dose-response relationships among exposed workers.

The study of infertility among men exposed to pesticides and other occupational agents is hindered by ignorance of the fundamental determinants and modifiers of spermatogenesis, the large individual and intrapersonal variability in semen parameters, and difficulty in conducting controlled epidemiologic investigations (226). Difficulties in obtaining accurate estimates of

pesticide exposures further hamper studies of their potential adverse reproductive effects.

Female Reproductive Effects

Few human studies directly address the effect of pesticides on female reproductive outcomes. Most of the epidemiologic studies have been descriptive or ecologic and do not provide direct support for causal associations with potential pesticide exposure. Furthermore, studies that have evaluated associations between birth defects and agricultural activity or pesticide use have generally been ecologic analyses and have been inconsistent in their results. Thus, they have done little more than raise concern about the effects of pesticides on female reproduction (227–229).

Organochlorines, including DDT, have been implicated in a variety of adverse reproductive outcomes. The mechanism is generally thought to be interaction with estrogen receptors, either directly or indirectly by metabolism to estrogen agonists. Abnormal menses and impaired fertility have been suggested effects of the organochlorines. Epidemiologic evidence has been inconsistent in studies of DDT and DDE with reproductive outcomes including ovarian function, premature delivery, spontaneous abortion, and stillbirths (43,230–232).

One study of a small but intense outbreak of congenital abnormalities provides persuasive evidence linking the event to consumption of fish treated for parasites with extraordinarily high doses of the organophosphate trichlorfon (233). Two case reports of malformations associated with prenatal exposure to organophosphates are anecdotal only, lacking any estimate of exposure magnitude (234,235).

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