Chapter 201: Pesticides

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INTRODUCTION

Pesticides include insecticides, herbicides, and rodenticides.\(^1\) Pesticide toxicity results from intentional, accidental, and occupational exposures. More than 300,000 pesticide-poisoning deaths occur each year worldwide, with insecticides accounting for the majority of deaths.\(^2\) **Pesticides are marketed as multiple formulations, often under shared brand names; therefore, complex clinical syndromes can result from exposure to both active and other ingredients.** Ingredients in proprietary formulations, such as petroleum distillates, are inert to pests during typical exposures, but can be toxic to humans, especially with excessive amounts. Pesticides have class-specific toxicities, with many having both local and systemic effects. Management often includes consultation with a hazardous materials and toxins database or with a poison control center. Supportive care is of utmost importance in pesticide poisonings, but for some compounds, antidotes are essential.

The World Health Organization classifies pesticides according to toxicity based on the median lethal dose for oral and dermal exposure in rats. This classification has been criticized because human case-fatality rates display large variation for compounds within the same chemical and/or World Health Organization toxicity classification.\(^3\) **Toxicity classification should not be used to predict severity after human exposure.**

INSECTICIDES

Chemical insecticides are toxic to the nervous system, with acute and chronic manifestations, as well as delayed sequelae after acute exposure. Six major classes of insecticides are in common use (*Table 201-1*). Other compounds used to control insects include repellants.
TABLE 201-1

**Insecticides and Repellants**

<table>
<thead>
<tr>
<th>Insecticides</th>
<th>Repellants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organophosphates</td>
<td>Amitraz</td>
</tr>
<tr>
<td>Carbamates</td>
<td>$N,N$-diethyl-$3$-methylbenzamide (DEET)</td>
</tr>
<tr>
<td>Organochlorines</td>
<td></td>
</tr>
<tr>
<td>Pyrethrins/pyrethroids</td>
<td></td>
</tr>
<tr>
<td>Neonicotinoids</td>
<td></td>
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<tr>
<td>Nereistoxin analogs</td>
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</tbody>
</table>

**ORGANOPHOSPHATES**

Commonly used organophosphates include diazinon, acephate, malathion, parathion, and chlorpyrifos and many others in different countries. Organophosphate and carbamate compounds are the insecticides most commonly associated with systemic illness.\(^4\),\(^5\) Potency among organophosphates varies; highly potent compounds, such as parathion, are used primarily in agriculture, whereas those of intermediate potency, including coumaphos and trichlorfon, are used in animal care. Diazinon and chlorpyrifos were phased out from household use in the United States in 2000 due to neurotoxicity, particularly on the developing brains of children, but they continue to be used in many other parts of the world.\(^6\) The organophosphate structure can be modified into chemical agents of mass destruction (see chapter 8, Chemical Disasters).

Organophosphate poisoning results primarily from accidental exposure in the home, recently sprayed or fogged areas using pesticide applicators, agriculture, industry, and the transport of these products.\(^4\) Inadvertent exposure can occur from flea-dip products in pet groomers and children and from contaminated food. In addition, these chemicals are involved in intentional poisonings from homicides and suicides.\(^7\) Systemic absorption of organophosphates occurs by inhalation and after mucous membrane, transdermal, transconjunctival, and GI exposure.

**Pathophysiology**

Organophosphate and carbamate compounds inhibit the enzyme cholinesterase.\(^1\) Acetylcholinesterase (true or red blood cell acetylcholinesterase) is found primarily in erythrocyte membranes, nervous tissue, and...
skeletal muscle. Plasma cholinesterase (pseudocholinesterase or butyrylcholinesterase) is found in the serum, liver, pancreas, heart, and brain. Inhibition of cholinesterase leads to acetylcholine accumulation at nerve synapses and neuromuscular junctions, resulting in overstimulation of acetylcholine receptors. This initial overstimulation is followed by paralysis of cholinergic synaptic transmission in the CNS, in autonomic ganglia, at parasympathetic and some sympathetic nerve endings (e.g., sweat glands), and in somatic nerves. Excess acetylcholine results in a **cholinergic crisis** that manifests as a central and peripheral clinical toxidrome.

Organophosphate compounds bind irreversibly to acetylcholinesterase, thus inactivating the enzyme through the process of phosphorylation. **Aging** is a term describing the permanent, irreversible binding of the organophosphorus compound to the cholinesterase. The time to aging is highly variable among different agents and can range from minutes to a day or more. **Once aging occurs, the enzymatic activity of cholinesterase is permanently destroyed**, and new enzyme must be resynthesized over a period of weeks before clinical symptoms resolve and normal enzymatic function returns. **Antidotes must be given before aging occurs to be effective.**

**Clinical Features**

Clinical presentations depend on the specific agent involved, the quantity absorbed, and the route of exposure. Organophosphate insecticide poisoning can have substantial variability in clinical course, response to treatment, and outcome. Four clinical syndromes are described following organophosphate exposure: **acute poisoning, intermediate syndrome, chronic toxicity, and organophosphate-induced delayed neuropathy.**

In **acute organophosphate poisoning**, most poisoned patients are symptomatic within the first 8 hours and nearly all within the first 24 hours. Organophosphate agents such as malathion are associated with local irritation of the skin and respiratory tract with resulting dermatitis and wheezing, respectively, without evidence of systemic absorption.

Acute organophosphate poisoning results in CNS, muscarinic, nicotinic, and somatic motor manifestations (**Table 201-2**). In mild to moderate poisoning, symptoms occur in various combinations. Time to symptom onset varies according to exposure route; it is most rapid with inhalation and least rapid with transdermal absorption; however, dermatitis or skin excoriation may hasten this. Symptoms can occur within minutes after massive ingestion that is uniformly fatal.
CNS symptoms of cholinergic excess include anxiety, restlessness, emotional lability, tremor, headache, dizziness, mental confusion, delirium, hallucinations, and seizures. Coma with depression of respiratory and circulatory centers may result. Inhibition of acetylcholinesterase in the parasympathetic system produces muscarinic effects (Table 201-3).
### TABLE 201-3

**Mnemonics for the Muscarinic Effects of Cholinesterase Inhibition**

<table>
<thead>
<tr>
<th>Letter</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>S</td>
<td>Salivation</td>
</tr>
<tr>
<td>L</td>
<td>Lacrimation</td>
</tr>
<tr>
<td>U</td>
<td>Urinary incontinence</td>
</tr>
<tr>
<td>D</td>
<td>Defecation</td>
</tr>
<tr>
<td>G</td>
<td>GI pain</td>
</tr>
<tr>
<td>E</td>
<td>Emesis</td>
</tr>
<tr>
<td>D</td>
<td>Defecation</td>
</tr>
<tr>
<td>U</td>
<td>Urination</td>
</tr>
<tr>
<td>M</td>
<td>Muscle weakness, miosis</td>
</tr>
<tr>
<td>B</td>
<td>Bradycardia, bronchorrhea, bronchospasm</td>
</tr>
<tr>
<td>E</td>
<td>Emesis</td>
</tr>
<tr>
<td>L</td>
<td>Lacrimation</td>
</tr>
<tr>
<td>S</td>
<td>Salivation</td>
</tr>
<tr>
<td>&quot;Killer B's&quot;</td>
<td>Bradycardia, bronchorrhea, bronchospasm</td>
</tr>
</tbody>
</table>

Acetylcholine is the presynaptic neurotransmitter at nicotinic receptors in the sympathetic ganglia and adrenal medulla. Inhibition of acetylcholinesterase at these locations results in sympathetic stimulation, producing pallor, mydriasis, tachycardia, and hypertension. In most patients, parasympathetic stimulation usually predominates, but mixed autonomic effects are common.

Nicotinic stimulation at neuromuscular junctions results in muscle fasciculations, cramps, and muscle weakness. This syndrome may progress to paralysis and areflexia, making it difficult to detect seizure activity. Respiratory muscle paralysis can lead to ventilatory failure.
Abdominal pain is common with rare cases of pancreatitis and peritonitis. The clinical course may be complicated by broncho-aspiration of gastric contents contributing to respiratory distress. Many of these insecticide preparations contain hydrocarbons that act as solvents, and in cases of aspiration, they cause lipoid pneumonia, with severe respiratory failure.

More lipid-soluble organophosphates may not produce immediate symptoms of toxicity, but instead produce delayed sequelae. Low-grade chronic organophosphate exposures occur among farm workers, pesticide manufacturing plant workers, exterminators, and patients taking cholinergic ophthalmologic preparations. Symptoms and signs are often less dramatic and nonspecific, occurring without the cholinergic syndrome.

An intermediate syndrome may occur 1 to 5 days after an organophosphate exposure, reported in up to 40% of patients following ingestion. Clinical features include paralysis of neck flexor muscles, muscles innervated by the cranial nerves, proximal limb muscles, and respiratory muscles; respiratory support may be needed. Symptoms or signs of cholinergic excess are absent in this syndrome. Electromyography may assist in making the diagnosis. Aggressive, early antidote therapy and supportive measures may prevent or ameliorate the severity of this syndrome. Symptoms usually resolve within 7 days. Nerve gas poisoning has not been reported to cause the intermediate syndrome.

Chronic toxicity is seen primarily in agricultural workers with daily exposure, manifesting as symmetrical sensorimotor axonopathy. This mixed sensorimotor syndrome may begin with leg cramps and progress to weakness and paralysis, mimicking features of the Guillain-Barré syndrome.

Organophosphate-induced delayed neuropathy is characterized by cognitive dysfunction, impaired memory, mood changes, autonomic dysfunction, peripheral neuropathy, and extrapyramidal signs. Chronic fatigue syndrome and multiple chemical sensitivity have been reported in some patients, predominantly female, after exposure to very low doses of organophosphate insecticides. Children are at greater risk of toxicity when exposed due to smaller body size and lower baseline levels of cholinesterase activity.

Chemical warfare nerve agents, such as soman, sarin, tabun, and VX, are organophosphate compounds that inactivate acetylcholinesterases. They are rapid acting and extremely potent; death can occur within minutes of inhalation or dermal exposure, as occurred in the subway terrorist attack in Tokyo 1985. Soman ages within minutes, giving little time to administer antidotes.

**Diagnosis**

Diagnosis and treatment are based on history and the presence of a suggestive toxidrome; laboratory cholinesterase assays and reference laboratory testing for specific compounds take time and have limitations, and waiting for results delays administration of potentially life-saving therapy. Diagnosis is often difficult due to a constellation of clinical findings that can be variable in both acute and chronic poisonings. Point-of-care testing tools are in development.
Noting a characteristic hydrocarbon or garlic-like odor may assist in diagnosis. The cholinergic toxidrome may vary depending on the predominance of muscarinic, nicotinic, and CNS manifestations and the severity of the intoxication. Organophosphate insecticide poisoning should be considered in the differential diagnosis of a patient with altered mental status and pinpoint pupils. **Miosis and muscle fasciculations are considered reliable signs of organophosphate toxicity.**

Cholinesterase activity is used to assess potential toxicity, with red cell acetylcholinesterase enzymatic activity a more accurate indicator of synaptic cholinesterase inhibition, but plasma butyrylcholinesterase is easier to assay and more available (**Table 201-2**). The degree of cholinesterase inhibition necessary to produce symptomatic illness is variable, so although cholinesterase levels should correlate with toxicity, there is large individual variability in baseline measurements, and standardization of normal ranges among laboratories is poor, so deviation from a symptomatic patient's baseline may be significant when values are reported within the normal range for the testing laboratory.

When the cholinesterase function falls gradually, as in chronic exposure, clinical symptoms may be subtle. Plasma butyrylcholinesterase levels may be depressed in genetic variants, chronic disease states, liver dysfunction, cirrhosis, malnutrition and low serum albumin states, neoplasm, infection, and pregnancy. Red blood cell acetylcholinesterase is affected by factors that influence the circulating life of erythrocytes such as hemoglobinopathies. Unless pralidoxime is given before aging occurs, plasma butyrylcholinesterase takes up to 4 to 6 weeks and red blood cell acetylcholinesterase takes as long as 90 to 120 days to return to baseline after exposure.

Routine laboratory test abnormalities are nondiagnostic but may include evidence of pancreatitis, hypo- or hyperglycemia, leukocytosis, and abnormal liver function. In severe cases, a chest radiograph may show pulmonary edema. The ECG may be abnormal and correlate with the degree of toxicity and outcome. Common abnormalities include ventricular dysrhythmias, torsade de pointes, and idioventricular rhythms. Atrioventricular blocks and prolongation of the QT interval are common. A prolonged QT<sub>c</sub> interval correlates with severity and mortality in severe organophosphate poisoning. Electromyography may identify and quantify acetylcholinesterase inhibition at neuromuscular junctions.

**Treatment**

Treatment consists of airway control, intensive respiratory support, general supportive measures, decontamination, prevention of absorption, and the administration of antidotes (**Table 201-4**). Therapy should not be withheld pending determination of cholinesterase levels.
TABLE 201-4

Treatment for Organophosphate Poisoning

<table>
<thead>
<tr>
<th>Decontamination</th>
<th>Protective clothing must be worn to prevent secondary poisoning of healthcare workers. Handle and dispose of all clothes as hazardous waste. Wash patient with soap and water. Handle and dispose of water runoff as hazardous waste.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monitoring</td>
<td>Cardiac monitor, pulse oximeter, 100% oxygen.</td>
</tr>
<tr>
<td>Gastric lavage</td>
<td>No proven benefit (see text).</td>
</tr>
<tr>
<td>Activated charcoal</td>
<td>No proven benefit (see text).</td>
</tr>
<tr>
<td>Urinary alkalinization</td>
<td>No proven benefit (see text).</td>
</tr>
<tr>
<td><strong>Atropine</strong></td>
<td>1–3 milligrams IV in an adult or 0.01–0.04 milligram/kg IV (but never &lt;0.1 milligram per dose) in children. Repeat every 5 min until tracheobronchial secretions attenuate. Followed by continuous infusion to maintain the anticholinergic state. Dose varies from 0.4 to 4 milligrams/h IV infusion in adults.</td>
</tr>
<tr>
<td>Pralidoxime</td>
<td>No proven benefit (see text). 1–2 grams for adults or 20–40 milligrams/kg IV (up to 1 gram) in children, mixed with normal saline and infused over 5–10 min. Followed by continuous infusion: 500 milligrams/h in adults or 5–10 milligrams/kg per hour in children.</td>
</tr>
<tr>
<td>Seizures</td>
<td>Benzodiazepines IV.</td>
</tr>
</tbody>
</table>

In cases of acute cutaneous exposure, protective clothing must be worn to prevent secondary poisoning of healthcare workers. Neoprene or nitrile gloves should be used instead of latex. Patients with suspected exposure must be removed from the contaminated environment. All clothes and accessories must be removed completely, placed in plastic bags, and disposed of as hazardous materials. The patient is immediately decontaminated externally with copious amounts of a mild detergent such as dishwashing liquid and water. Decontamination includes the scalp, hair, fingernails, skin, conjunctivae, and skin folds. Body fluids should be treated as contaminated. Abrasion or irritation of the skin should be avoided.
Contaminated runoff water should be contained and disposed of as hazardous material. Instruments used can be decontaminated using chlorine bleach.

Patients with acute exposures should be placed on oxygen, a cardiac monitor, and pulse oximeter. A 100% nonrebreather mask will optimize oxygenation in the patient with excessive airway secretions and bronchospasm; however, atropine administration should not be delayed or withheld if oxygen is not immediately available. Gentle suction will assist in clearing airway secretions from hypersalivation, bronchorrhea, or emesis. Coma, seizures, respiratory failure, excessive respiratory secretions, or severe bronchospasm necessitate endotracheal intubation. An IV line should be established with baseline blood sampling and determination of cholinesterase levels. A nondepolarizing agent should be used when neuromuscular blockade is needed. Succinylcholine is metabolized by plasma butyrylcholinesterase, and therefore, prolonged paralysis may result. Hypotension is initially treated with fluid boluses of isotonic crystalloid.

Gastric lavage is widely used in Asia following organophosphate ingestion despite the lack of evidence for improved outcome. Given the sometimes rapid onset of symptoms after ingestion, it is unlikely that gastric lavage will be of benefit except in patients who present within 2 hours after a large ingestion. Activated charcoal is sometimes recommended because organophosphates do bind in vitro, although there is no evidence that single or multiple doses of activated charcoal improve patient outcome. Urinary alkalization is often used in Brazil and Iran for organophosphate poisoning, but there is no controlled evidence that shows benefit. Hemodialysis, hemofiltration, and hemoperfusion are of no proven value.

Atropine is the antidote for significant organophosphate poisonings (Table 201-4). Atropine, a competitive antagonist of acetylcholine at central and peripheral muscarinic receptors, will reverse the effects secondary to excessive cholinergic stimulation. The dose is repeated every 5 minutes until copious tracheobronchial secretions attenuate; large amounts may be necessary, in the order of hundreds of milligrams in massive ingestions. Pupillary dilatation is not a therapeutic end point. Tachycardia is not a contraindication to the use of atropine in organophosphorus poisoning because tachycardia can occur secondary to bronchospasm or bronchorrhea with hypoxia, which can be reversed with atropine.

The initial atropine should be IV when possible, but 2 to 6 milligrams IM should be considered when IV access is not possible. Normally, this initial dose of atropine should produce antimuscarinic symptoms; therefore, absence of anticholinergic symptoms after an initial dose is indicative of organophosphate poisoning. Once an effective amount of atropine has been given, an infusion should be started to maintain an anticholinergic state; the dose required varies according to severity, and prolonged therapy may be necessary. Importantly, atropine does not reverse muscle weakness.

Glycopyrrolate, an alternate anticholinergic agent, may be used, but dosing is not well defined, and there is no proven benefit compared to atropine. Nebulized atropine or ipratropium may be used to improve pulmonary symptoms. Glycopyrrolate and ipratropium do not cross the blood–brain barrier and are ineffective in treating central neurologic symptoms.
Compounds called oximes are used to displace organophosphates from the active site of acetylcholinesterase, thus reactivating the enzyme.\textsuperscript{9,18,19} Pralidoxime is the oxime in common use, ameliorating muscarinic, nicotinic, and CNS symptoms. Importantly, pralidoxime reverses muscle paralysis if given early, before aging occurs. If possible, blood samples for acetylcholinesterase levels are obtained before administration of pralidoxime, but it is important that pralidoxime be administered as soon as possible before permanent and irreversible aging occurs. Although pralidoxime is more effective in acute than in chronic intoxications, it is recommended for use even after >24 to 48 hours after exposure.

Response to pralidoxime therapy with a decrease in muscle weakness and fasciculations and relief of muscarinic effects with atropine usually occurs within 10 to 40 minutes of administration. Pralidoxime can also be given by the IM route. A continuous infusion is preferable to repeated bolus dosing if paralysis does not resolve after the initial dose or if paralysis returns. The pralidoxime dose recommended by the World Health Organization is a 30-milligram/kg IV bolus followed by an IV infusion of 8 milligrams/kg per hour.

Pralidoxime should be continued for 24 to 48 hours while monitoring acetylcholinesterase levels. Despite theoretical and experimental benefit and worldwide clinical use, current evidence is inadequate to show that oximes, such as pralidoxime, reduce mortality or complication rate in acute organophosphate poisoning.\textsuperscript{19,25,26} Pralidoxime is not recommended for asymptomatic patients or for patients with known carbamate exposures presenting with minimal symptoms.

Seizures are treated with airway protection, oxygen, atropine, and benzodiazepines.\textsuperscript{19} Atropine may prevent or abort seizures due to cholinergic overstimulation that occur within the first few minutes. Pulmonary edema and bronchospasm are treated with oxygen, intubation, positive-pressure ventilation, atropine, and pralidoxime. Succinylcholine, ester anesthetics, and β-adrenergic blockers may potentiate poisoning and should be avoided.

Disposition and Follow-Up

Minimal exposures may require only decontamination and 6 to 8 hours of observation in the ED to detect delayed effects. Reexposure should be avoided because sequential exposures can have cumulative toxicity, so patients returning to work should be limited from further exposure. All clothing, including shoes and belts, should be discarded properly as hazardous materials and not returned to the patient; recrudescence of poisoning has occurred from contaminated clothes and leather, even after washing or cleaning.\textsuperscript{21}

Admission to the intensive care unit is necessary for significant poisonings. Most patients respond to pralidoxime therapy with an increase in acetylcholinesterase levels within 48 hours. If there is no posthypoxic brain damage, and if the patient is treated early, symptomatic recovery occurs in 10 days. If toxins are fat soluble, the patient may be symptomatic for prolonged periods of time and dependent on continuous pralidoxime infusion. During this period, which may last weeks while awaiting resynthesis of new enzyme, supportive care and respiratory support may be needed. The end point of therapy is determined by the absence of signs and symptoms on withholding pralidoxime therapy.
Following an acute exposure, the patient may have neurologic sequelae, such as paresthesias or limb weakness, along with nonspecific symptoms lasting days to months.\(^\text{27}\) Death from organophosphate poisoning usually occurs in 24 hours in untreated patients, usually from respiratory failure secondary to paralysis of respiratory muscles,\(^\text{28}\) neurologic depression, or bronchorrhea.

**CARBAMATES**

The carbamate insecticides (aldicarb, carbofuran, carbaryl, ethienocarb, fenobucarb, oxamyl, methomyl, pirimicarb, propoxur, and trimethacarb) are cholinesterase inhibitors that are structurally related to the organophosphate compounds.\(^\text{1}\) These agents are primarily used as insecticides, but illegally imported rodenticides may contain aldicarb.\(^\text{29}\)

**Pathophysiology**

Carbamates can be toxic after dermal, inhalation, and GI exposure. Carbamates transiently and reversibly bind to and inhibit the cholinesterase enzyme. Regeneration of enzyme activity by dissociation of the carbamyl-cholinesterase bond occurs within minutes to a few hours involving rapid, spontaneous hydrolysis of the carbamate-cholinesterase bond. Therefore, aging does not occur, and as a major difference from organophosphate poisoning, new enzyme does not need to be synthesized before normal function is restored after carbamate poisoning.

**Clinical Features**

In adults, symptoms of acute carbamate poisoning are similar to the cholinergic syndrome observed with organophosphate agents but are of shorter duration. Because carbamates do not effectively penetrate the CNS in adults, less central toxicity is seen, and seizures do not occur. However, in children, presentation of acute carbamate poisoning differs, with a predominance of CNS depression and nicotinic effects. Carbamates can also produce the intermediate syndrome.\(^\text{12}\)

**Diagnosis**

Diagnosis is based on clinical history and findings. Measurement of acetylcholinesterase activity is generally not helpful because enzymatic activity may return spontaneously to normal 4 to 8 hours after a carbamate exposure.

**Treatment**

Initial treatment of carbamate poisoning is the same as for organophosphorus compounds. Atropine is the antidote of choice and is administered for muscarinic symptoms. Atropine is usually all that is necessary while waiting for the carbamylated acetylcholinesterase complex to dissociate spontaneously and recover function, usually within 24 hours. Therapy usually is not needed for more than 6 to 12 hours.
The use of pralidoxime in carbamate poisoning is controversial. The carbamate-binding half-life to cholinesterase is approximately 30 minutes, and irreversible binding does not occur; therefore, there is little need for pralidoxime. Human case reports and some but not all animal studies suggest that pralidoxime may potentiate the toxicity of carbamates, such as carbaryl. Therefore, pralidoxime should be avoided in known single-agent carbaryl poisonings. However, pralidoxime should be considered in mixed poisonings with an organophosphorus compound and a carbamate or if the type of insecticide is unknown.

Disposition and Follow-Up

Because carbamate poisonings have transient cholinesterase inhibition and rapid enzyme reactivation, the clinical course tends to be more benign than seen with organophosphates, and most patients recover completely within 24 hours. However, patients with depressed levels of consciousness have a significant mortality, and methomyl poisoning is associated with a high risk of cardiac arrest at presentation and subsequent death after resuscitation.

In mild poisonings, observation suffices, and the patient may be discharged with follow-up. Moderate poisonings necessitate 24 hours of observation that includes evaluation for possible concomitant exposure to or toxicity from inactive ingredients or vehicles such as hydrocarbons.

ORGANOCHLORINES

Dichlorodiphenyltrichloroethane (DDT) is the prototype insecticide of these chlorinated hydrocarbons. Chlordane, heptachlor, dieldrin, and aldrin are compounds used for termite and roach control. Most have been restricted or banned in the United States, Europe, and many other countries because of their persistence in the environment, long half-life in the human body, and toxicity. Worldwide, these insecticides continue to be used. Hexachlorocyclohexane (lindane) is a general garden organochlorine insecticide that is also used in some countries to treat scabies and head lice infestations. This compound is well absorbed by ingestion and inhalation. Dermal absorption occurs, particularly if the skin is abraded or repeated applications are used. Children and the elderly can develop neurotoxicity and seizures with therapeutic use of lindane.

Pathophysiology

Organochlorines are central neurologic stimulants that can be toxic after dermal, inhalation, and GI exposures. The physical state of the agent, whether a liquid or a solid, and the type of vehicle affect transdermal absorption. Organochlorines antagonize γ-aminobutyric acid–mediated inhibition of the central neurons, leading to hyperexcitability with repetitive neuronal discharges following the action potential. Organochlorines are highly lipid soluble and accumulate in human tissues. Most are capable of inducing the hepatic microsomal enzyme system. Therefore, the therapeutic efficacy of other chemicals and drugs that are inactivated by this system is reduced in the presence of organochlorines.

Clinical Features
Neurologic symptoms predominate in acute organochlorine intoxication. Mild poisoning presents with dizziness; ataxia; fatigue; malaise; headache; neurologic stimulation with hyperexcitability, irritability, and delirium; apprehension; tremulousness; myoclonus; and facial paresthesias. Fever is common. More severe exposures may result in seizures, coma, renal injury, and death. Seizures may occur early, without prodromal syndromes, and are usually short lived, although some patients may have status epilepticus.

Organochlorines are used dissolved in hydrocarbon solvents that, by themselves, can cause sedation, coma, and pneumonitis from aspiration. Sensitization of the myocardium to endogenous catecholamines with cardiac dysrhythmia can occur from both organochlorines and the solvents. Chronic neurotoxic effects from low-level exposure to the organochlorine compound chlordane include deficits in tests of balance, reaction time, and verbal recall.

A related agent, the halogenated pyrrole chlorfenapyr, has two unusual features. First, it is a prodrug that is converted into the active form after absorption by the insect. Second, it manifests biphasic neurotoxicity. Initial symptoms are nonspecific and include headaches, body aches, drowsiness, and weakness; these symptoms last for a few days, followed by a latent period of apparent recovery. Around the seventh day after ingestion, neurologic symptoms recur with rapidly progressing paralysis and stupor leading to coma with a fatal outcome. No treatment is effective once the delayed symptoms start. The requirement for metabolism to an active toxin and the latent period suggest it may be possible to develop an agent to inhibit this metabolic conversion and reduce the risk of progression to the delayed fatal neurologic course.

Diagnosis

History is important, and valuable information can be obtained from the package label regarding the product and vehicle involved. Laboratory evaluation generally is not helpful, but organochlorines can be detected in the serum and urine by specialty laboratories.

Treatment

Treatment includes administration of oxygen, with intubation indicated to treat hypoxia secondary to seizures, aspiration, and respiratory failure. Benzodiazepines are indicated for seizure control. Dysrhythmia control may be indicated, but epinephrine should be avoided because both organochlorines and organic solvents can sensitize the myocardium to endogenous catecholamines. Hyperthermia is managed by external cooling techniques. Removal of clothing and skin decontamination with mild detergent and water are important. Avoid using oils on the skin because they promote absorption. Activated charcoal and possibly gastric lavage in large, recent ingestions are potentially useful. The exchange resin cholestyramine is potentially useful for symptomatic patients exposed to chlordecone.

Disposition and Follow-Up

Exposed patients should be observed for 6 hours and admitted to the hospital if signs of toxicity develop or if ingestion involved a hydrocarbon.
PYRETHRINS AND PYRETHROIDS

Pyrethroid use and poisonings have increased since the phase-out of organophosphate insecticides for use in human dwellings. Pyrethrins are naturally occurring active extracts derived from the chrysanthemum plant. Pyrethroids are synthetic analogues of the pyrethrins with greater potency and environmental persistence, but are considered safer than organochlorine and organophosphate insecticides. Pyrethroids are used commonly as aerosols in automated insect sprays in public areas; therefore, inhalation is the most common source of exposure. These agents are available as dusts and liquids in a hydrocarbon base. Pyrethrins are common ingredients in over-the-counter household insecticides, pediculicides, and scabicides. They are rapidly metabolized and therefore are of low toxicity in humans.

Pathophysiology

Toxicity results from dermal absorption, inhalation, or ingestion. Pyrethroids block the sodium channel at the neuronal cell membrane, causing repetitive neuronal discharge. Additional effects include inhibition on γ-aminobutyric acid receptors, increased nicotinic cholinergic transmission, norepinephrine release, and interference with sodium–calcium exchange across cell membranes. Pyrethin antigens are cross-antigenic with ragweed pollen, so allergic reactions are common after exposure.

Clinical Features

These compounds can cause dermal, pulmonary, GI, and neurologic illness. Allergic hypersensitivity reactions are the most common effects of pyrethrins, producing dermatitis, bronchospasm, rhinitis, hypersensitivity pneumonitis, or anaphylaxis. Skin contact may lead to paresthesias and burning within 30 minutes of exposure that usually dissipates within 24 hours. These compounds are well absorbed but are rapidly metabolized in the liver, usually resulting in minimal systemic toxicity.

Systemic toxicity can occur from occupational poisonings and following large intentional ingestions. Features of systemic toxicity include fatigue and lethargy, nausea and vomiting, paresthesias, hyperexcitability, tremors, muscle fasciculations, pulmonary edema, respiratory failure, and seizures.

Diagnosis

Diagnosis is dependent on a history of exposure. Differential diagnosis includes allergic reactions and ingestions with neurologic stimulants. Laboratory tests have no diagnostic value.

Treatment

Treatment includes removal from exposure; dermal, ocular, and GI decontamination; treatment of allergic manifestations; and supportive care.

Disposition and Follow-Up
Disposition is usually related to the severity of asthmatic and allergic manifestations. The clinical course is usually benign, and hospitalization is not necessary for most accidental exposures.

**NEONICOTINOIDS**

Neonicotinoids are structurally similar to nicotine, acting as agonists at the postsynaptic acetylcholine receptor. Neonicotinoids have high affinity for the receptors within the insect CNS, producing paralysis and death. Commercially available agents from this family include imidacloprid, thiamethoxam, clothianidin, acetamiprid, thiacloprid, dinotefuran, and nitenpyram.

Data regarding human toxicity are limited to case reports. Toxicity from imidacloprid poisoning is relatively mild to moderate in most cases, with symptoms of nausea, emesis, diarrhea, and headache. However, uncommon cases of respiratory failure, encephalopathy, hypotension, rhabdomyolysis, and renal failure have occurred. Toxicity from acetamiprid poisoning has been associated with severe nausea and vomiting, muscle weakness, hypothermia, convulsions, and hypothermia. Treatment is supportive.

**NEREISTOXIN ANALOGS**

Analogs of nereistoxin are considered low-toxicity insecticides. Agents in common use include nensultap, cartap, thiocyclam and thiosultap. These insecticides induce neurotoxicity by promoting extracellular calcium influx and stimulating the release of intracellular calcium from the sarcoplasmic reticulum.

Case reports of toxicity from occupational skin exposure report nausea, vomiting, muscles tremors, dyspnea, and mydriasis. Intentional ingestions are associated with depressed level of consciousness, muscle fasciculations and spasms, seizures, hypotension, and hypoxia.

Animal studies suggest that sulfhydryl-containing compounds, such as l-cysteine, acetylcysteine, d-penicillamine, and dimercaprol, are effective antidotes, but human data are lacking, and suggested doses are conjectures. Recovery from severe toxicity associated with coma is possible, although death from multiple organ failure may occur.

**AMITRAZ**

Amitraz is a topical insecticide and acaricide, as well as an insect repellent. Amitraz is used as a spray on agricultural crops and as a wash-solution to treat ectoparasites found on farm animals, dogs, and cats. Amitraz possesses agonist activity at the postsynaptic \( \alpha_2 \)-adrenergic receptor, and interacts with the neuromodulator octopamine, inhibits monoamine oxidase, and impairs prostaglandin synthesis.

The clinical manifestations following human overdose include mental status depression, bradycardia, respiratory depression, miosis, hypotension, and hypothermia. Mechanical ventilation may be required, and with supportive therapy, recovery is expected.
\textbf{N,N-DIETHYL-3-METHYL BENZAMIDE (DEET)}

DEET is used extensively as an over-the-counter insect repellant that comes in a variety of product formulations ranging in concentrations from 5\% to 100\%. When used as directed, they are generally safe. Toxicity can occur with ingestion or prolonged exposure on covered or damaged skin. DEET is absorbed through the skin and is a neurotoxin that causes seizures after large ingestions and extensive dermal exposures of high-concentration products. Small children are most susceptible to systemic toxicity from skin absorption. Skin absorption occurs within 2 hours of topical application, but peak concentrations may be delayed several hours.

Systemic toxicity is rare but manifests as restlessness, insomnia, altered behavior, confusion, neurologic depression, slurred speech, ataxia, tremors, muscle cramps, hypertonia, and seizures occurring with or without prodrome. DEET-induced hypotension and bradycardia have been reported with heavy dermal or oral exposure. Treatment includes benzodiazepines for seizures, skin decontamination with mild detergent and water, and activated charcoal for recent ingestions. Most patients recover with supportive care.

**HERBICIDES**

Herbicides are used to kill weeds. Mechanisms of plant toxicity includes inhibition of photosynthesis, respiration, protein synthesis, or growth stimulation mimicking plant hormones called \textit{auxins}. Some classes pose a health hazard to humans (Table 201-5). Herbicidal formulations contain multiple ingredients such as organic solvents, surfactants, and preservatives that may have their own toxic effects; these may not be always disclosed on the product label.

\textbf{TABLE 201-5}

\begin{center}
Selected Herbicide Classes that Pose Potential Harm to Humans
\end{center}

<table>
<thead>
<tr>
<th>Chlorophenoxy compounds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bipyridyls: paraquat and diquat</td>
</tr>
<tr>
<td>Urea-substituted</td>
</tr>
<tr>
<td>Organophosphates</td>
</tr>
<tr>
<td>Glyphosate</td>
</tr>
</tbody>
</table>

\textbf{CHLOROPHENOXY HERBICIDES}

Chlorophenoxy herbicides are synthetic plant hormones. The most commonly used compounds are 2,4-dichlorophenoxyacetic acid (2,4-D) and 4-chloro-2-methylphenoxy-acetic acid. 2,4,5-Trichlorophenoxy \textit{acetic acid} (2,4,5-T) has been banned in the United States because of its contamination with 2,3,7,8-\textit{-tetrachlorodibenzo-\textit{p}-dioxin}. The aerially applied defoliant Agent Orange used during the Vietnam War was a
mixture of 2,4-D and 2,4,5-T. These compounds are effective against broadleaf plants and are used as weed killers on lawns and grain crops.

Pathophysiology

The metabolic pathway or mechanism related to human toxicity is unknown. Toxicity can result from dermal contact, inhalation, or ingestion. Systemic absorption can produce neurologic, cardiac, and skeletal muscle toxicity.

Clinical Features

Local exposure leads to eye and mucous membrane irritation that may last for days. After ingestion, nausea, vomiting, and diarrhea occur. Pulmonary toxicity may produce dyspnea, tachypnea, and signs of pulmonary edema. Cardiovascular findings include hypotension, tachycardia, and dysrhythmias. Mental status changes and seizures may occur. Muscle toxicity manifests as muscle tenderness, fasciculations, myotonia, and rhabdomyolysis. The patient may become hyperthermic. Peripheral neuropathy has been described in the recovery phase after acute exposure and with chronic exposure.

Diagnosis

Diagnosis is based on a history of exposure. Ancillary tests generally are nonspecific but may demonstrate a metabolic acidosis, rhabdomyolysis, or evidence of hepatorenal dysfunction. Toxin levels are not immediately available. Differential diagnosis includes other causes of acute myopathy.

Treatment

Treatment is supportive, including decontamination measures and respiratory support for myopathic-related respiratory failure.\textsuperscript{51,52} Urinary alkalinization will increase the elimination of these compounds and is recommended for severely poisoned patients.\textsuperscript{53} Hemodialysis can also be used to enhance chlorophenoxy herbicide clearance. Patients should be monitored for rhabdomyolysis and treated as necessary.

Disposition and Follow-Up

Severe toxicity and serious complications are not common following chlorophenoxy herbicides. Because toxic effects usually appear within 4 to 6 hours, patients with mild symptoms can be observed and discharged after that time. Significant toxicity warrants admission.

Bipyridyl Herbicides

The bipyridyl compounds, \textbf{paraquat and diquat}, are nonselective contact herbicides. Both are used widely and are responsible for significant morbidity if ingested.\textsuperscript{54} Paraquat is a fast-acting, nonselective herbicide. It is used for killing grass and weeds; is manufactured as a liquid, granules, or an aerosol; and is commonly
combined with diquat and other herbicides. Most products contain a blue dye, a stenchant, and an emetic. Ingestion is responsible for the majority of paraquat deaths,\(^5\) although deaths have been reported after transdermal exposure. Inhalation exposure to sprays can be very irritating to conjunctiva and the airway but are unlikely to cause systemic toxicity.

**Pathophysiology**

Paraquat is a severe local irritant and devastating systemic toxin.\(^5\) There is minimal transdermal absorption of paraquat in the absence of preexisting skin lesions. Ingested paraquat is absorbed rapidly, particularly if the stomach is empty. Plasma concentration peaks within minutes to 2 hours after ingestion. Paraquat is then distributed to most organs, with the highest concentrations found in the kidneys and lungs. A lethal oral dose of the 20% concentrate solution is about 10 to 20 mL in an adult and 4 to 5 mL in a child.

Paraquat actively accumulates in the alveolar cells of the lungs, where it is transformed into a reactive oxygen species, the superoxide radical.\(^5\) This anion is responsible for lipid peroxidation that leads to degradation of cell membranes, cell dysfunction, and necrosis. Lung injury has two phases. An initial destructive phase is characterized by loss of type I and type II alveolar cells, infiltration by inflammatory cells, and hemorrhage. These changes may be reversible. The later, proliferative phase is characterized by fibrosis in the interstitium and alveolar spaces. Paraquat and oxygen enhance each other's toxicity by sustaining the redox cycle. Myocardial injury and necrosis of the adrenal glands may occur.

Diquat has a similar structure and mechanism as paraquat. Formulations containing diquat do not contain the dye, stenching agent, or emetic usually added to paraquat. The lethal dose for diquat is similar to that of paraquat, but there is less occurrence of pulmonary injury and fibrosis because of diquat's lower affinity for pulmonary tissue. Diquat is caustic to the skin and GI tract, and exposure can result in renal and liver necrosis.

**Clinical Features**

Clinical features depend on the route of exposure and amount. Paraquat's severe caustic effects produce local skin irritation and ulceration of epithelial surfaces. Severe corrosive corneal injury may result from eye exposure. Upper respiratory tract exposure may result in mucosal injury and epistaxis. Inhalation may lead to cough, dyspnea, chest pain, pulmonary edema, epistaxis, and hemoptysis. Respiratory symptoms may persist for several weeks after inhalation exposure.

Ingestion causes GI irritation and mucosal damage with ulcerations (Table 201-6). A burning sensation of the lips or mouth may occur within a few minutes to hours followed by ulceration 1 to 2 days later. Nausea, vomiting, diarrhea, buccopharyngeal pain, esophageal pain, and abdominal pain may develop. Hypovolemia occurs from GI fluid losses and decreased oral intake.
### Table 201-6

**Paraquat Toxicity from Ingestion**

<table>
<thead>
<tr>
<th>Category</th>
<th>Clinical Features</th>
<th>Approximate Amount Ingested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>Asymptomatic or nausea, vomiting, and diarrhea. Renal and hepatic injury minimal or absent. Decreased pulmonary diffusion capacity may be present. Complete recovery expected.</td>
<td>&lt;20 milligrams/kg or &lt;7.5 mL of 20% concentrated solution in average adult</td>
</tr>
<tr>
<td>Severe</td>
<td>Initially nausea, vomiting, diarrhea, abdominal pain, mouth and throat ulceration. Positive colorimetric test for paraquat in the urine. 1–4 d: renal failure, hepatic impairment, hypotension. 1–2 wk: cough, hemoptysis, pleural effusion, pulmonary fibrosis. Survival possible, but majority of cases die within 2–3 wk from pulmonary failure.</td>
<td>Between 20 and 40 milligrams/kg or between 7.5 and 15 mL of 20% concentrated solution in average adult</td>
</tr>
<tr>
<td>Fulminant</td>
<td>Initially nausea, vomiting, diarrhea, and abdominal pain. Rapid development of renal and hepatic failure, GI ulceration, pancreatitis, toxic myocarditis, refractory hypotension, coma, convulsions. Death from cardiogenic shock and multiorgan failure within 1–4 d.</td>
<td>&gt;40–50 milligrams/kg or &gt;15–20 mL of 20% concentrated solution in average adult</td>
</tr>
</tbody>
</table>

Multisystem effects include GI tract corrosion, acute renal failure, cardiac failure, hepatic failure, and extensive pulmonary injury. The effects can be evident within a few hours following large ingestions, but, more typically, manifestations of renal failure and hepatocellular necrosis develop between the second and fifth days, with progressive pulmonary fibrosis leading to refractory hypoxemia 5 days to several weeks later. Metabolic (lactic) acidosis is common as a result of pulmonary effects (hypoxemia) and multisystem failure.

**Diagnosis**

Early diagnosis and therapy are important. Obtain details of the exposure, including accidental or intentional, route of exposure, concentration of the product, time of occurrence, and estimated amount. The differential diagnosis includes exposure to other corrosive agents and herbicides. Qualitative and
quantitative analyses for paraquat in urine and blood can assist in the diagnosis, and nomograms are used for predicting survival based on plasma paraquat concentration and time of ingestion. A commercially available semi-qualitative colorimetric test (Paraquat Test Kit; Syngenta CTL, Surrey, United Kingdom) can be done on urine or plasma to detect paraquat within a few hours after ingestion; such detection indicates potentially severe course. Serial pulmonary function tests, chest radiographs, and arterial blood gas determinations, including alveolar-arterial gradient, and arterial lactate may be used to monitor toxicity.

Laboratory abnormalities generally reflect multiorgan necrosis. Chest radiographs may show pneumomediastinum or pneumothorax due to corrosive rupture of the esophagus. Radiographic abnormalities of diffuse consolidation indicating parenchymal injury on the chest radiograph may not parallel the severity of clinical symptoms. Upper GI endoscopy should be performed to identify the extent and severity of mucosal lesions.

**Treatment**

The goal of early and vigorous decontamination is to prevent absorption and pulmonary toxicity. Any exposure to paraquat is a medical emergency, with hospitalization indicated even if the patient is asymptomatic. Early treatment is mainly supportive but is an important determinant of survival. Do not administer supplemental oxygen unless the patient is severely hypoxic, because added oxygen stimulates superoxide radical formation and promotes oxidative stress.

Remove clothing and decontaminate skin with mild detergent and water. Take care to avoid skin abrasions that may increase absorption. If there is conjunctival irritation, irrigate with copious amounts of water or saline. Fluid and electrolytic losses can occur from GI tract damage, vomiting, and cathartics. Maintain intravascular volume and urine output to prevent prerenal kidney injury. Pain associated with oropharyngeal lesions should be treated with opioids. Emesis is common, and there is no proven benefit to gastric lavage. In patients with pharyngeal or esophageal burns, prophylactic placement of a nasogastric tube for subsequent enteral nutrition is recommended.

Immediate GI decontamination with absorbents that bind paraquat is indicated in patients with a protected airway. A single dose of activated charcoal (1 to 2 grams/kg), diatomaceous fuller's earth (1 to 2 grams/kg in 15% aqueous suspension), or bentonite (1 to 2 grams/kg in a 7% aqueous slurry) should be used. Charcoal hemoperfusion can remove paraquat and has been recommended to be started as soon as possible and continued for 6 to 8 hours, but there is no evidence to show that prognosis is improved. Repeated pulse doses of glucocorticoids and cyclophosphamide may improve survival in severe cases.

Supportive care includes airway protection, maintaining intravascular volume, pain relief, treatment of renal failure and complications, and treatment of infection. Maintaining renal function will assist in avoiding toxic accumulation in other tissues.
Treatment for diquat poisoning is similar to that for paraquat, and despite the lower toxicity for diquat, mortality approaches 50% following intentional diquat ingestion.

Disposition and Follow-Up

Outcome is determined by the amount ingested; therefore, intentional ingestions tend to have a worse prognosis. Prognosis is worse ingesting a highly concentrated liquid formulation on an empty stomach. Conversely, ingestion of dilute solid formulations rarely cause death.

UREA-SUBSTITUTED HERBICIDES

Urea-substituted herbicides such as chlorimuron, diuron, fluometuron, and isoproturon are inhibitors of photosynthesis and have low systemic toxicity. In humans, methemoglobinuria may occur with ingestion. Treatment includes decontamination, supportive care, and treatment for methemoglobinemia with methylene blue, as appropriate (see chapter 207, "Dyshemoglobinemas").

ORGANOPHOSPHATE HERBICIDES

In addition to their use as insecticides, some organophosphate compounds are effective herbicides. Butiphos is used commonly as a cotton defoliant before mechanical harvesting. Treatment is identical to that for organophosphate insecticides.

GLYPHOSATE

Glyphosate is the active ingredient in many widely used preparations available for consumer use on lawns and gardens. A problem with lawn and garden chemicals is that some products sold using a common or group brand name may contain different active ingredients; a common brand name may contain either glyphosate or the more toxic herbicide diquat.

Glyphosate can produce severe toxicity with massive ingestions of the diluted product or ingestions of concentrated solutions. Preparations may contain the toxic surfactant polyoxyethyleneamine, which is a corrosive, and the combination is more toxic than glyphosate alone. Inhalational exposures cause respiratory irritation. Dermal absorption is poor, so symptomatic poisonings are generally from ingestion.

Clinical effects include mucous membrane irritation and erosions with nausea, vomiting, abdominal pain, and diarrhea. Widespread organ failure with refractory cardiovascular collapse and dysrhythmias has been reported. Respiratory distress requiring intubation, metabolic acidosis, tachycardia, renal failure, and hyperkalemia portend a fatal outcome.

Treatment includes activated charcoal following a recent ingestion and supportive care, with attention to support of oxygenation and ventilation, ameliorating complications due to the corrosive effects on the GI tract, treating hyperkalemia, and supporting the circulation. Intravenous lipid emulsion is reported as useful
in preventing hypotension\textsuperscript{64} and treating refractory hypotension.\textsuperscript{65} Hemodialysis may be supportive when severe acidosis and acute kidney injury are present.\textsuperscript{66}

Patients with small, asymptomatic ingestions can be discharged after 6 hours of observation. Significant GI symptoms, altered level of consciousness, hypoxemia, metabolic acidosis, and cardiovascular abnormalities indicate admission to an intensive care unit.

**RODENTICIDES**

A number of agents with distinct toxicities are used as rodenticides. Rodenticides are commonly classified based on whether they are anticoagulants or nonanticoagulants. Although intentional ingestions are often associated with significant morbidity and mortality, most unintentional exposures occur in young children and result in minimal or no toxicity.

**NONANTICOAGULANTS**

A number of nonanticoagulant rodenticides have been used throughout history. Many have been discontinued, although poisonings still occur from old product stored in garages, barns, and homes (Table 201-7).
<table>
<thead>
<tr>
<th>Rodenticide</th>
<th>Toxicity</th>
<th>Mechanism</th>
<th>Clinical Effects</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arsenic</td>
<td>Severe</td>
<td>Binds sulfhydryl groups on proteins</td>
<td>Dysphagia, muscle cramps, nausea and vomiting, bloody diarrhea, cardiovascular collapse, altered mental status, seizures, and late peripheral neuropathies</td>
<td>Gastric lavage, activated charcoal, catharsis, chelation therapy using succimer, dimercaprol, or penicillamine</td>
</tr>
<tr>
<td>Barium carbonate and other soluble forms such as barium chlorides, hydroxides, and sulfides</td>
<td>Severe</td>
<td>Depolarizing neuromuscular blockade</td>
<td>Onset occurs within 1–8 h with nausea, vomiting, diarrhea, abdominal pain, dysrhythmias, respiratory failure, muscular weakness, paresthesias, and paralysis</td>
<td>Gastric lavage with sodium or magnesium sulfate added to lavage solution to convert carbonate to less toxic sulfate; potassium replacement</td>
</tr>
<tr>
<td>Elemental or yellow phosphorus</td>
<td>Severe, early cardiac and neurologic toxicity is a poor prognostic sign</td>
<td>Caustic; uncouples oxidative phosphorylation</td>
<td>Skin irritation, cutaneous burns, oral burns, abdominal pain, hematemesis, possible &quot;smoking&quot; luminescent vomitus and stool, garlicky odor, direct toxic effects on the myocardium, kidney, and peripheral vessels, cardiovascular collapse; late neurologic depression with multisystem toxicity and hepatorenal syndrome</td>
<td>Gastric lavage with dilute potassium permanganate solution may convert phosphorus to less toxic phosphates; activated charcoal; avoid emesis</td>
</tr>
<tr>
<td>Rodenticide</td>
<td>Toxicity</td>
<td>Mechanism</td>
<td>Clinical Effects</td>
<td>Treatment</td>
</tr>
<tr>
<td>-------------------------------------------------</td>
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<td>---------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
</tr>
<tr>
<td><em>N</em>-3-Pyridylmethyl-<em>N</em>-p-nitrophenylurea (PNU or Vacor)</td>
<td>Severe</td>
<td>Destroys pancreatic β cells within hours of ingestion by interfering with nicotinamide metabolism</td>
<td>Within 24 h of ingestion, GI symptoms, perforation, autonomic nervous system dysfunction, insulin-deficient hyperglycemia or diabetic ketoacidosis, dysrhythmias, neuropathies</td>
<td>Nicotinamide (niacinamide) IV or IM is an antidote; lavage for recent ingestions; activated charcoal and <em>insulin</em> for treatment of hyperglycemia and ketoacidosis</td>
</tr>
<tr>
<td>Sodium fluoroacetate (SFA)</td>
<td>Severe</td>
<td>Blocks Krebs cycle</td>
<td>Nausea, vomiting, apprehension, lactic acidosis, seizures, coma, respiratory depression, cardiac dysrhythmias, and pulmonary edema; electrocardiographic abnormalities include ST-segment and T-wave changes, tachycardia, premature ventricular contractions, ventricular tachycardia, and ventricular fibrillation; hyperkalemia and hypocalcemia are common</td>
<td>Activated charcoal, seizure and dysrhythmia control, and supportive care; experimental regimens include glycerol monoacetate, calcium gluconate, sodium succinate, and ethanol loading; consultation with a toxicologist is recommended</td>
</tr>
<tr>
<td>Rodenticide</td>
<td>Toxicity</td>
<td>Mechanism</td>
<td>Clinical Effects</td>
<td>Treatment</td>
</tr>
<tr>
<td>------------</td>
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<td>----------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>Strychnine</td>
<td>Severe</td>
<td>Competitive antagonism of the inhibitory neurotransmitter glycine at the</td>
<td>Restlessness, muscle twitching, painful extensor spasms, opisthotonos, trismus,</td>
<td>Airway control, quiet environment (minimize sensory stimulation), and activated charcoal; avoid lavage (may precipitate seizures);</td>
</tr>
<tr>
<td></td>
<td></td>
<td>postsynaptic brainstem and spinal cord motor neuron</td>
<td>inability to swallow, and facial grimacing; medullary paralysis and death can follow</td>
<td>benzodiazepines, barbiturates, analgesia; neuromuscular blockage if necessary</td>
</tr>
<tr>
<td>Tetramine</td>
<td>Severe</td>
<td>Blocks γ-aminobutyric acid receptors in the CNS</td>
<td>Rapidly acting; initial features include headache, nausea, dizziness, fatigue,</td>
<td>The median lethal dose for tetramine is ~0.1 milligram/kg; 6–12 milligrams sufficient to kill an adult; no antidote; supportive care;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>anorexia, numbness, and listlessness; severe symptoms include loss of consciousness, seizures, and coma; death usually caused by respiratory failure</td>
<td>benzodiazepines or barbiturates for seizures</td>
</tr>
<tr>
<td>Rodenticide</td>
<td>Toxicity</td>
<td>Mechanism</td>
<td>Clinical Effects</td>
<td>Treatment</td>
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<tr>
<td>Thallium sulfate&lt;sup&gt;71&lt;/sup&gt;</td>
<td>Severe</td>
<td>Combines with mitochondrial sulfhydryl groups, interfering with oxidative phosphorylation</td>
<td>Early GI symptoms: nausea, vomiting, and abdominal pain; after 2–5 d, painful paresthesias, myalgias, muscle weakness, headache, lethargy, tremors, ataxia, delirium, seizures, and coma; death from respiratory failure and dysrhythmias; alopecia after approximately 2 wk; chronic neurologic sequelae</td>
<td>Supportive care; multiple doses of activated charcoal or Prussian blue (potassium ferric hexaniacinate) to interrupt enterohepatic circulation and increase elimination in stool; hemodialysis</td>
</tr>
<tr>
<td>Zinc or aluminium phosphide&lt;sup&gt;72,73,74,75,76&lt;/sup&gt;</td>
<td>Severe</td>
<td>Combines with water and stomach acid to produce phosphine gas; cellular toxicity and necrosis to the GI tract, kidney, and liver if ingested and to the lungs if inhaled</td>
<td>Immediate nausea, vomiting, epigastric pain, phosphorous or fishy breath, black vomitus, and GI irritation or ulceration; myocardial toxicity, shock, and acute lung injury; agitation, coma, seizures, hepatorenal injury, metabolic acidosis, hypocalcemia, tetany</td>
<td>Gastric lavage with potassium permanganate or combination coconut oil and sodium bicarbonate; magnesium sulfate IV&lt;sup&gt;77&lt;/sup&gt;; treat acidosis and hypocalcemia; consider acetylcysteine&lt;sup&gt;78&lt;/sup&gt;; supportive care</td>
</tr>
<tr>
<td>α-Naphthyl-thiourea (ANTU)</td>
<td>Moderate</td>
<td>Increases alveolar capillary permeability, causing pulmonary edema</td>
<td>Dyspnea, cyanosis, cough, pleuritic chest pain, noncardiogenic pulmonary edema, and pleural effusion</td>
<td>Supportive care; activated charcoal</td>
</tr>
<tr>
<td>Rodenticide</td>
<td>Toxicity</td>
<td>Mechanism</td>
<td>Clinical Effects</td>
<td>Treatment</td>
</tr>
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<td>-----------------------------------------</td>
<td>----------</td>
<td>---------------------------------------------------------------------------</td>
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<td>---------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Cholecalciferol (vitamin D₃)</td>
<td>Moderate</td>
<td>Mobilization of calcium from bones</td>
<td>Hypercalcemia, osteomalacia, and systemic metastatic calcifications</td>
<td>Treat hypercalcemia with IV normal saline, furosemide, steroids, calcitonin, and biphosphates as needed</td>
</tr>
<tr>
<td>Bromethalin</td>
<td>Low</td>
<td>Uncouples oxidative phosphorylation in CNS mitochondria, interrupting nerve conduction</td>
<td>Muscle tremors, myoclonic jerks, contractions of flexor muscles, ataxia, and focal motor seizures; personality changes, confusion, and coma</td>
<td>Decontamination; benzodiazepines for seizures</td>
</tr>
<tr>
<td>Norbormide or dicarboximide</td>
<td>Low</td>
<td>Irreversible smooth muscle vasoconstriction</td>
<td>Tissue hypoxia and ischemia</td>
<td>Supportive care; decontamination</td>
</tr>
<tr>
<td>Red squill</td>
<td>Low</td>
<td>Blocks sodium-potassium adenosine triphosphatase (similar to digoxin poisoning)</td>
<td>Nausea, protracted vomiting, diarrhea, abdominal pain; massive ingestion causes hyperkalemia, atrioventricular block, ventricular irritability with dysrhythmias, and death</td>
<td>Treat as digoxin toxicity (<em>atropine</em>, external pacing, digoxin-specific antibody fragments, activated charcoal)</td>
</tr>
</tbody>
</table>

**ANTICOAGULANTS**
Warfarin-type anticoagulants were the first generation of anticoagulant rodenticides and distributed commonly disguised as yellow corn meal or rolled oats. Most one-time warfarin rodenticide ingestions are insignificant accidental poisonings and do not cause any bleeding problems. Significant coagulopathy requires large amounts in a single exposure or a repetitive exposure over several days. Following a single large ingestion, onset of the anticoagulant effect takes place within 12 to 48 hours. Warfarin's biologic half-life is approximately 42 hours.

Therapy is not necessary for ingestion of a single mouthful of a warfarin rodenticide. For potentially toxic recent ingestion, consider activated charcoal. Obtain a baseline prothrombin time and INR determination and repeat it in 12 to 24 hours. Vitamin $K_1$ (phytonadione) administration is indicated if the INR is >2.0. The suggested total PO daily dose is 1 to 5 milligrams in children and 20 milligrams in adults, administered in two to four divided doses.

Second-generation superwarfarins and the indandione derivatives were introduced when rodent resistance to warfarin began to appear. They are currently responsible for approximately 80% of human rodenticide exposures reported in the United States. Their mechanisms are the same as that of warfarin, but they are more potent, have more prolonged anticoagulant activity, and therefore have the potential to be highly toxic. Poisonings involving the indandione derivatives pindone, diphacinone, chlorophacinone, and valone have toxic and clinical characteristics similar to those of the superwarfarins.

The superwarfarins include the 4-hydroxy-coumarins brodifacoum, diphenacoum, coumafuryl, and bromadoline. These are readily available over the counter as grain-based bait. After intentional ingestions, adults often develop a coagulopathy within 24 to 48 hours. Because the biologic half-life of brodifacoum is approximately 120 days, a single ingestion may result in marked anticoagulation effects for weeks to months. Intentional repeated ingestions can cause severe bleeding.

The diagnosis may not be readily apparent. Some patients may not report an intentional ingestion. Small children and depressed patients with an unexplained coagulopathy and/or bleeding should raise suspicion of superwarfarin poisoning. Although the prothrombin time and INR are usually monitored, large doses of warfarin can also cause prolongation of the activated partial thromboplastin time. Superwarfarins are not detected by warfarin assays, but specific serum assays are available in reference laboratories.

Unintentional superwarfarin ingestions in the pediatric patient are unlikely to result in significant toxicity. Obtain a baseline INR and repeat 24 and 48 hours after ingestion. For acute intentional ingestions, gastric lavage is indicated for early presentations, and activated charcoal should be administered. Obtain a baseline INR and repeat in 12 and 24 hours. If the INR is elevated but there is no active hemorrhage, oral vitamin $K_1$ is recommended. Because of the extended half-life of the anticoagulant, prolonged therapy with high doses of vitamin $K_1$ may be required to maintain hemostasis. Initial daily doses of 1 to 5 milligrams in children and 20 milligrams in adults are recommended with titration to maintain a normal INR. Doses up to 100
milligrams per day for 10 months have been reported. Upon discontinuation of vitamin K\textsubscript{1} therapy, serial INR determinations are required to ensure that further therapy is not needed.

Patients with acute hemorrhage may require repletion of volume losses with normal saline or blood transfusions. Fresh frozen plasma should be used if bleeding is severe or unresponsive to vitamin therapy. Vitamin K\textsubscript{1}, 10 milligrams, should be administered by slow IV infusion to minimize the risk of a hypotensive reaction. Forms of vitamin K other than vitamin K\textsubscript{1} are ineffective because the conversion of these other forms to the active form is blocked by superwarfarins. Administration of prothrombin complex concentrates or recombinant activated factor VII can be considered for patients with ongoing hemorrhage despite fresh frozen plasma and vitamin K\textsubscript{1} therapy.

For asymptomatic patients who have accidentally ingested a superwarfarin, follow-up in 24 and 48 hours for coagulation studies should be arranged. Prevention measures should be emphasized.

**CONSULTATION**

Consultation with a poison control center or medical toxicologist is recommended to assist in patient management and to collect data for surveillance reports. When consulting, precise communication of the specific product name from the container label is essential to identify both active and inert ingredients. As noted, confusion can arise because similar brand names are used for more than one agent.

**REFERENCES**

   [PubMed: 9220485]

   [PubMed: 17349229]

   [PubMed: 21048990]

   [PubMed: 16335577]

   [PubMed: 17389175]


[PubMed: 11141378]

[PubMed: 21327593]

[PubMed: 22786512]

[PubMed: 23816587]

[PubMed: 16390217]

[PubMed: 15862083]

[PubMed: 20136481]

[PubMed: 23869655]

[PubMed: 20569074]

[PubMed: 24400933]

[PubMed: 17288493]
[PubMed: 16340030]

[PubMed: 20678875]

[PubMed: 22315994]

[PubMed: 22865288]

[PubMed: 21887030]

[PubMed: 22450207]

[PubMed: 22687771]

[PubMed: 23109024]

[PubMed: 23351193]

[PubMed: 24550611]

[PubMed: 23148565]


**USEFUL WEB RESOURCES**

The American Academy of Clinical Toxicology—[http://www.clintox.org/index.cfm](http://www.clintox.org/index.cfm)

The American Association of Poison Control Centers—[http://www.aapcc.org/DNN](http://www.aapcc.org/DNN)

The Asia Pacific Association of Medical Toxicology—[http://www.asiatox.org](http://www.asiatox.org)

The European Association of Poisons Centres and Clinical Toxicologists—[http://www.eapcct.org](http://www.eapcct.org)

The South Asian Clinical Toxicology Research Collaboration—[http://www.sactrc.org](http://www.sactrc.org)

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