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Recognition and Management of Pesticide Poisonings

Third Edition

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RECOGNITION AND MANAGEMENT OF PESTICIDE POISONINGS

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INTRODUCTION

This manual is designed to help professionals responsible for the health of persons exposed to pesticides to recognize and treat properly poisonings by these substances. This third edition discusses many more compounds than were dealt with in previous editions, and it updates particular management methods according to recently published clinical literature.

No text or manual on so complex a topic can presume to take the place of good clinical judgment. But it is unrealistic to expect health professionals confronted with a pesticide poisoning emergency to assemble quickly the many details of toxicology, diagnosis, and treatment that are essential to optimal management. This manual provides such information in a concise format.

A deliberate effort has been made to suggest treatment that can be implemented (or at least initiated) in small hospitals and clinics where victims of pesticide poisonings are likely to be received. At the expense of some repetition, details of treatment have been spelled out sequentially for the common classes of chemical poisonings.

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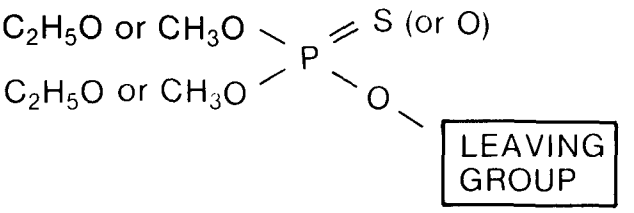
Chapter 1

ORGANOPHOSPHATE CHOLINESTERASE-INHIBITING PESTICIDES

GENERAL CHEMICAL STRUCTURE



COMMON COMMERCIAL PESTICIDE PRODUCTS*

Highly toxic: tetraethyl pyrophosphate (TEPP), phorate (Thimet), disulfoton† (Di-Syston), fensulfothion (Dasanit), demeton† (Systox), terbufos (Counter), mevinphos (Phosdrin), methidathion (Supracide), chlormephos (Dotan, MC2188), sulfotepp (Bladafum, Dithione), chlorthiophos (Celathion), monocrotophos (Azodrin), fonofos (Dyfonate), prothoate (Fac), fenamiphos (Nemacur), phosfolan (Cyolane), methyl parathion (Dalf, Penncap-M), schradan (OMPA), chlorfenvinphos (Birlane), ethyl parathion (Parathion, thiophos), azinphos-methyl (Guthion), phosphamidon (Dimecron), methamidophos (Monitor), dicrotophos (Bidrin), isofenphos (Amaze, Oftanol), bomyl (Swat), carbophenothion (Trithion), EPN, famphur, (Warbex, Bo-Ana, Famfos), fenophosphon (Agritox, trichloronate), dialifor (Torak), cyanofenphos (Surecide).

Moderately toxic: bromophos-ethyl (Nexagan), leptophos (Phosvel), dichlorvos (DDVP, Vapona), coumaphos (Co-Ral), ethoprop (Mocap), quinalphos (Bayrusil), triazophos (Hostathion), demeton-methyl† (Metasystox), propetamphos (Safrotin), chlorpyrifos (Lorsban, Dursban), sulprofos (Bolstar), dioxathion (Delnav), isoxathion (Karphos), phosalone (Zolone), thiometon (Ekatin), heptenophos (Hostaquick), crotoxyphos (Ciodrin), cythioate (Proban), phencapton (G28029), DEF (De-Green, E-Z-off D), ethion, dimethoate (Cygon, De-Fend), fenthion (Baytex, Entex, Tiguvon, Spotton, Lysoff), dichlofenthion (Mobilawn), EPBP (S-Seven),

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* These are listed approximately in order of descending toxicity. "Highly toxic" organophosphates have listed oral LD_{50} values (rat) less than 50 mg/kg; "moderately toxic" agents have LD_{50} values in excess of 50 mg/kg.

† These organophosphates are systemic; i.e., they are taken up by the plant and translocated into foliage and sometimes into the fruit.

diazinon (Spectracide), phosmet (Imidan, Prolate), formothion (Anthio), profenofos (Curacron), naled (Dibrom), phenthoate, trichlorfon (Dylox, Dipterex, Neguvon), pyrazophos (Afugan, Curamil), fenitrothion (Agrothion, Sumithion), cyanophos (Cyanox), pyridaphenthion (Ofunack), propylthiopyrophosphate (Aspon), acephate (Orthene), merphos (Folex), malathion (Cythion), etrimfos (Ekamet), phoxim (Baythion), pirimiphosmethyl (Actellic), iodofenphos (Nuvanol-N), bromophos (Nexion), tetrachlorvinphos (Gardona, Rabon), temephos (Abate, Abathion).

TOXICOLOGY

Organophosphates poison insects and mammals primarily by phosphorylation of the acetylcholinesterase enzyme at nerve endings. The enzyme is critical to normal transmission of nerve impulses from nerve fibers to innervated tissues. Some critical proportion of the tissue enzyme mass must be inactivated by phosphorylation before symptoms and signs of poisoning are manifest. At sufficient dosage, loss of enzyme function allows accumulation of acetylcholine (the impulse-transmitter substance) at cholinergic neuroeffector junctions (muscarinic effects), and at skeletal myoneural junctions and in autonomic ganglia (nicotinic effects). Organophosphates also impair nerve impulse transmission in the brain, causing disturbances in sensorium, motor function, behavior, and respiratory drive. Depression of respiration is the usual cause of death in organophosphate poisoning. Recovery depends ultimately on generation of new enzyme.

Organophosphates are efficiently absorbed by inhalation, ingestion, and skin penetration. To a degree, toxicity depends on the rate at which specific organophosphates are metabolized in the body (principally by hydrolysis in the liver), thus limiting the amount of pesticide available to attack acetylcholinesterase enzyme in other tissues.

Many organophosphates readily undergo conversion from -thions to -oxons (replacement of sulfur by oxygen). In general, -oxons are much more toxic than -thions. This conversion occurs in the environment under the influence of sunlight and in the body, mainly by the action of liver microsomes. Ultimately, both -oxons and -thions are inactivated by hydrolysis at the ester linkage, yielding alkyl phosphates and phenols which are readily excreted. The hydrolysis products present little toxic hazard.

One to two days after organophosphate absorption, depending on the specific organophosphate, some phosphorylated acetylcholinesterase enzyme can be de-phosphorylated (reactivated) by certain oxime antidotes. After this interval, the nature of the enzyme-phosphoryl bond changes, rendering the enzyme inactivation irreversible. New enzyme must then be generated.

Very rarely, organophosphate pesticides have produced a different type of neurotoxicity, consisting of damage to the myelin substance of peripheral nerves. This leads to a protracted peripheral neuropathy, characterized by numbness, pain, and weakness in the extremities, which persists for months or years. Organophosphates associated with these chronic illnesses have included

some whose acute toxic potential is low; i.e., there appears to be no relationship between acute toxicity and the likelihood of a chronic neuropathic effect. Particularly suspect as neurotoxic agents of this type are the phenylphosphonothioate series, cyanofenphos, EPN, leptophos, and EPBP.

Other unusual properties of specific organophosphates may render them more hazardous than basic toxicity data suggest. By-products can develop in long-stored malathion which strongly inhibit the hepatic enzymes operative in malathion catabolism, thus enhancing its toxicity. Certain organophosphates are exceptionally prone to storage in fat tissue, prolonging the need for antidote when stored pesticide is released back into the circulation. It is possible that other unrecognized factors modify the toxicity of organophosphates.

FREQUENT SYMPTOMS AND SIGNS OF POISONING

Symptoms of acute poisoning develop during exposure or within 12 hours (usually within four hours) of contact. **HEADACHE, DIZZINESS, WEAKNESS, INCOORDINATION, MUSCLE TWITCHING, TREMOR, NAUSEA, ABDOMINAL CRAMPS, DIARRHEA,** and **SWEATING** are common early symptoms. Blurred or dark vision, confusion, tightness in the chest, wheezing, productive cough, and **PULMONARY EDEMA** may occur. Incontinence, unconsciousness and convulsions indicate very severe poisoning. **SLOW HEARTBEAT,** salivation, and tearing are common. **TOXIC PSYCHOSIS,** with manic or bizarre behavior, has led to misdiagnosis of acute alcoholism. Slowing of the heartbeat may rarely progress to complete sinus arrest. **RESPIRATORY DEPRESSION** may be fatal. Continuing daily absorption of organophosphate at intermediate dosage may cause an **INFLUENZA-LIKE ILLNESS** characterized by weakness, anorexia, and malaise.

The very few individuals who have suffered peripheral neuropathy following organophosphate exposure exhibited diverse clinical courses. Onset of symptoms was generally slow, sometimes after an asymptomatic interval of several days following exposure. Principal symptoms have been numbness, tingling, pain and weakness of the arms and legs. Some recovered fully in a few weeks; a few others experienced muscle atrophy, leaving a degree of paresis and sensory loss.

CONFIRMATION OF DIAGNOSIS

CAUTION: If there are strong clinical indications of organophosphate poisoning, treat patient immediately. **DO NOT WAIT** for laboratory confirmation.

Depressions of plasma pseudocholinesterase and/or RBC acetylcholinesterase enzyme activities are the most satisfactory and generally available biochemical indices of excessive organophosphate absorption. A minimum amount of organophosphate must be absorbed to depress blood cholinesterase activities, but activities are lowered by dosage considerably less than are required to cause symptomatic poisoning. The enzyme depression is usually apparent immediately after, or within 12-24 hours of, significant absorption of

organophosphate. Depression of the plasma enzyme generally persists several days to a few weeks; the RBC enzyme activity usually remains depressed longer, sometimes 1-3 months. Table 1 lists **APPROXIMATE LOWER LIMITS OF NORMAL FOR PLASMA** and **RBC CHOLINESTERASE ACTIVITIES** of human blood, measured by generally available methods. **LOWER LEVELS usually** indicate excessive absorption of a cholinesterase-inhibiting chemical. Whenever possible, comparison of the test sample with a pre-exposure value offers the best confirmation of organophosphate absorption: a depression of 25% or more is strong evidence of excessive absorption.

In certain conditions, the activities of plasma and RBC cholinesterase are depressed in the absence of chemical inhibition. About 3% of individuals have a genetically determined low level of plasma cholinesterase. These persons are particularly vulnerable to the action of cholinesterase-inhibiting pesticides and to the drug succinylcholine, often administered to surgical patients. Patients with advanced liver disease, malnutrition, chronic alcoholism and dermatomyositis exhibit low plasma cholinesterase activities. A number of toxicants, notably carbon disulfide, benzalkonium salts, organic mercury compounds, ciguatoxins, and solanines may reduce plasma pseudocholinesterase activity. The RBC acetylcholinesterase is less likely than the plasma enzyme to be affected by factors other than organophosphates. It is reduced, however, in certain conditions that damage the red cell membrane, such as hemolytic anemias.

The alkyl phosphates and phenols to which organophosphates are hydrolyzed in the body can often be detected in the urine during pesticide absorption and up to 48 hours thereafter. These analyses are useful in identifying the actual pesticide to which workers have been exposed. Alkyl phosphate and phenol analyses can demonstrate organophosphate absorption at lower dosages than those required to depress cholinesterase activities.

Detection of intact organophosphates in the blood is usually not possible except after extreme exposures, such as ingestions of pesticide. Few organophosphates remain unhydrolyzed in the blood more than a few minutes or hours, unless the quantity absorbed is extraordinary or the hydrolyzing liver enzymes are inhibited.

TREATMENT

CAUTION: Persons attending the victim should avoid direct contact with heavily contaminated clothing and vomitus. Wear rubber gloves while washing pesticide from skin and hair.

1. Establish **CLEAR AIRWAY** by aspiration of secretions. Administer **OXYGEN** by mechanically assisted pulmonary ventilation. Improve tissue oxygenation as much as possible before administering atropine to minimize the risk of ventricular fibrillation.
2. Administer **ATROPINE SULFATE** intravenously, or intramuscularly, if IV injection is not possible. Atropine protects the muscarinic end-organs from excessive concentrations of acetylcholine. It does not reactivate the

TABLE 1. *Approximate Lower Limits of Normal Plasma and Red Cell Cholinesterase Activities in Humans**

METHOD	PLASMA	RBC	WHOLE BLOOD	UNITS
Δ pH (Michel)	0.45	0.55		Δ pH per hr per ml
pH Stat (Nabb-Whitfield)	2.3	8.0		μM per min per ml
ChE-tel (Pfizer)	40			ChE-tel units
A ChE-tel (Pfizer)		210		A ChE-tel units
BMC Reagent Set (Ellman-Boehringer)	1875		3000	mU per min per ml
1-Test Cholinesterase (EM Diagnostics)	3.6			Units per ml
Acholest Test Paper	>20			Minutes
Dupont ACA	< 8			Units per ml
Garry-Routh (Micro)			Male 7.8 Female 5.8	μM-SH per 3 min per ml
Merckotest			3.0	Units per ml
GLC Method (Cranmer)	2.1	8.2		μM per min per ml
Technicon	2.0	8.0		μM per min per ml

* Because measurement technique varies among laboratories, more accurate estimates of minimum normal values are usually provided by individual laboratories.

cholinesterase enzyme. Recrudescence of poisoning may occur if tissue concentrations of organophosphate remain high when the effect of atropine wears off. Atropine is the ideal antidote for muscarinic manifestations; it is ineffective against nicotinic actions: muscle weakness and twitching, and respiratory depression.

In **MODERATELY SEVERE** poisoning:

Adult dosage, including children over 12 years: 0.4-2.0 mg repeated every 15 minutes until atropinization is achieved: tachycardia (pulse of 140 per minute), flushing, dry mouth, dilated pupils. Maintain atropinization by repeated doses for 2-12 hours or longer depending on severity of poisoning. Râles in the lung bases indicate inadequate atropinization. Miosis, nausea, bradycardia, and other cholinergic manifestations are also indicative.

Dosage for children under 12 years: 0.05 mg/kg body weight, repeated every 15 minutes until atropinization is achieved. Maintain atropinization with repeated dosage of 0.02-0.05 mg/kg.

SEVERELY POISONED individuals may exhibit remarkable tolerance to atropine; two or more times the dosages suggested above may be

needed. Persons not poisoned or only slightly poisoned, however, may develop signs of atropine toxicity from such large dosages: **FEVER,** muscle fibrillations, and delirium are the main signs of atropine toxicity. If these signs appear while the patient is fully atropinized, atropine administration should be discontinued, at least temporarily.

3. Draw a **BLOOD SAMPLE** for **PLASMA** and **RBC CHOLINESTERASE** analysis.
4. Administer **PRALIDOXIME** (Protopam®-Ayerst, 2-PAM) in cases of severe poisoning by **organophosphate** pesticides in which respiratory depression, muscle weakness and twitchings are severe. When administered early (usually less than 36 hours after poisoning) pralidoxime relieves the nicotinic effects of poisoning.

   Note: Pralidoxime is of questionable value in poisonings by the cholinesterase-inhibiting **carbamate** compounds. (See Chapter 2).

   Adult dosage (including children over 12 years): 1.0 gm intravenously at *no more* than 0.5 gm per minute.

   Child's dose (under 12 years): 20-50 mg/kg (depending on severity of poisoning) intravenously, injecting *no more* than half the total dose per minute.

   Dosage of pralidoxime may be repeated in 1-2 hours, then at 10-12 hour intervals if needed. In very severe poisonings, dosage rates may be doubled.

   Note: *slow administration of pralidoxime is strongly recommended,* and may be achieved by administering the total dose in 250 ml 5% glucose solution over 30-60 minutes.

   If intravenous injection is not possible, pralidoxime may be given by deep intramuscular injection.

   CAUTION: Be prepared to assist pulmonary ventilation mechanically if respiration is depressed during and after pralidoxime injection.

5. **OBSERVE PATIENT CLOSELY** for *at least* 24 hours to insure that symptoms (sweating, visual disturbances, vomiting, diarrhea, chest and abdominal distress and sometimes **PULMONARY EDEMA**) do not recur as atropinization wears off. In very severe poisonings by ingested organophosphates, particularly the more lipophilic and slowly hydrolyzed compounds, metabolic disposition of toxicant may require as many as 5-10 days, during which atropinization must be maintained. Rising levels of blood cholinesterase activity are a useful signal that atropine dosage can be tapered off by lengthening the intervals between doses. As dosage is reduced, the lung bases should be checked frequently for râles. If râles are heard, or if there is a return of miosis, bradycardia, sweating or other cholinergic signs, atropinization must be re-established promptly.
6. **BATHE** and **SHAMPOO** victim with soap and water if there is any chance that **SKIN** and **HAIR** are contaminated.

7. **IF PESTICIDE HAS BEEN INGESTED** in quantity sufficient to cause poisoning, empty the stomach and intestine.

   A. **IF** victim is **ALERT** and respiration is not depressed, give **SYRUP OF IPECAC,** followed by 1-2 glasses of water to induce vomiting. **Adults** (12 years and over): 30 ml; **children** under 12 years: 15 ml.

      CAUTION: **OBSERVE** victim closely **AFTER** administering **IPECAC.** If consciousness level declines, or if vomiting has not occurred in 15 minutes, proceed immediately to **INTUBATE** the stomach.

      Following emesis, have victim drink a suspension of 30-50 gm **ACTIVATED CHARCOAL** in 3-4 ounces of water to limit absorption of toxicant remaining in the gut.

   B. **IF** victim is **OBTUNDED** or respiration is depressed, empty stomach by **INTUBATION, ASPIRATION,** and **LAVAGE,** using isotonic saline or 5% sodium bicarbonate. Because many pesticides are dissolved in petroleum distillates, emesis and intubation of the stomach involve a serious risk that solvent will be aspirated, leading to chemical pneumonitis. *For this reason:*

      (a). If victim is unconscious or obtunded and facilities are at hand, insert **ENDOTRACHEAL TUBE** (cuffed, if available) prior to gastric intubation.

      (b). Keep victim's **HEAD BELOW LEVEL OF STOMACH** during intubation and lavage (Trendelenburg, or left lateral decubitus, with head of table tipped downward). Keep victim's head turned to left.

      (c). **ASPIRATE PHARYNX** as regularly as possible to remove gagged or vomited stomach contents.
      After aspiration of gastric contents and washing of stomach, instill 30-50 gm of **ACTIVATED CHARCOAL** in 3-4 ounces of water through stomach tube to limit absorption of remaining toxicant.

   C. **SAVE A SAMPLE** of emesis, or the initial gastric washings, for chemical analysis.

   D. If bowel movement has not occurred in 4 hours, and if patient is fully conscious, give **SODIUM SULFATE,** 0.25 gm/kg, in 1-6 ounces water, as a cathartic. Magnesium sulfate and citrate are equally suitable at similar dosage if renal function is adequate. Retained magnesium may depress CNS function.

8. **DO NOT** give morphine, aminophylline, phenothiazines, reserpine, furosemide, or ethacrynic acid in poisonings by organophosphates.

9. Give adrenergic amines **ONLY** if there is a specific indication, such as marked hypotension.

10. Rarely, in severe organophosphate poisonings, **CONVULSIONS** occur which are unresponsive to atropine and pralidoxime. Insure that causes unrelated to pesticide toxicity are not responsible: head trauma, cerebral anoxia, or mixed poisoning. **DIAZEPAM** (Valium), 5-10 mg for adults, 0.1 mg/kg for children under 6 years or 23 kg is probably the safest and most reliable anticonvulsant to use under these circumstances. Give **SLOWLY** (no more than half the total dose per minute) intravenously. Severe protracted convulsions may require additional medication, as suggested in the chapter on *Solid Organochlorine Pesticides.*

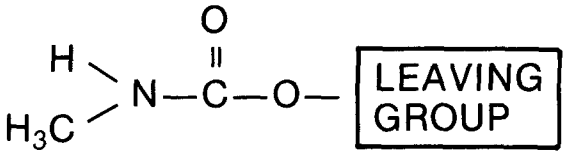
    CAUTION: Be prepared to assist pulmonary ventilation mechanically if respiration is depressed; to intubate the trachea, if laryngospasm occurs; and to counteract hypotensive reactions.

11. Persons who have been clinically poisoned by organophosphate pesticides should not be re-exposed to cholinesterase-inhibiting chemicals until symptoms and signs have resolved completely and blood cholinesterase activities have returned to at least 80 percent of pre-poisoning levels. If blood cholinesterase was not measured prior to poisoning, blood enzyme activities should reach at least minimum normal levels (Table 1) before the patient is returned to a pesticide-contaminated environment.
12. **DO NOT** administer atropine or pralidoxime prophylactically to workers exposed to organophosphate pesticides. It is neither practical nor medically sound to do so.

Chapter 2

CARBAMATE CHOLINESTERASE-INHIBITING PESTICIDES

GENERAL CHEMICAL STRUCTURE



COMMON COMMERCIAL PESTICIDE PRODUCTS*

Highly toxic:** aldicarb† (Temik), oxamyl (Vydate), carbofuran (Furadan), methomyl (Lannate, Nudrin), formetanate HCl (Carzol, Dicarzol), aminocarb (Matacil), dimetilan (Snip Fly Bands).

Moderately toxic*:** promecarb (Carbamult), methiocarb (Mesurol, Draza), propoxur (Baygon), pirimicarb (Pirimor, Aphox, Rapid), bufencarb (Bux), carbaryl (Sevin).

TOXICOLOGY

Insecticides of this class cause reversible carbamylation of acetylcholinesterase enzyme, allowing accumulation of acetylcholine at cholinergic neuroeffector junctions (muscarinic effects), and at skeletal muscle myoneural junctions and in autonomic ganglia (nicotinic effects). Poison also impairs CNS function. The carbamyl-enzyme combination dissociates more readily than the phosphorylated enzyme produced by organophosphate insecticides. This lability tends to mitigate the toxicity of carbamates, but also limits the usefulness of blood enzyme measurements in diagnosis of poisoning. Carbamates are absorbed by inhalation, ingestion, and dermal penetration. They are actively metabolized by the liver, and the degradation products are excreted by the liver and kidneys.

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* Listed approximately in order of decreasing toxicity.

** Acute oral LD_{50} in the rat less than 50 mg/kg.

*** Acute oral LD_{50} in the rat above 50 mg/kg.

† This carbamate is a systemic, i.e., it is taken up by the plant and translocated into foliage and sometimes into the fruit.

A few carbamate insecticides are formulated in methyl (wood) alcohol. In cases of ingestion of these formulations, the toxicology of the methanol must be taken fully into consideration: severe gastroenteric irritation, acidosis, CNS injury, and neuropathy.

FREQUENT SYMPTOMS AND SIGNS OF POISONING

DIARRHEA, NAUSEA, VOMITING, ABDOMINAL PAIN, PROFUSE SWEATING, SALIVATION, and **BLURRED VISION** are frequently reported. Other common symptoms have been dyspnea, tremor, muscle twitching, ataxia, and headache. Temporary paralysis of the extremities has also occurred. Most reported illnesses have not exceeded a few hours, and the prognosis is generally better than in organophosphate intoxications. However, in severe poisonings, one should anticipate the possibility of **RESPIRATORY DEPRESSION**, pulmonary edema, and convulsions. Continuing absorption of intermediate quantities may cause protracted **MALAISE**, weakness, and anorexia, resembling influenza.

CONFIRMATION OF DIAGNOSIS

CAUTION: If there is strong clinical evidence of poisoning, treat patient immediately. **DO NOT WAIT** for laboratory confirmation.

Depressions of plasma and/or RBC cholinesterase activities may be observed following absorption of extraordinary amounts of carbamate insecticide. However, enzyme activities commonly revert to normal within a few minutes or hours. They are not, therefore, reliable detectors of carbamate poisoning; i.e., intoxication may exist when blood cholinesterase activities are normal. The rapid methods for cholinesterase estimation (ACHOLTEST, ChE-tel, MERCKOTEST) are more likely to detect depressions than the longer test methods.

Table 1 in the chapter on **ORGANOPHOSPHATE PESTICIDES** lists the approximate lower limits of normal plasma and red cell cholinesterase-inhibiting carbamates. A normal value does not preclude carbamate insecticide poisoning. Whenever possible, comparison of the test sample with pre-exposure values offers the best confirmation of excessive carbamate absorption: a depression of 25% or more is strong evidence of excessive absorption.

Consult the chapter on **ORGANOPHOSPHATE PESTICIDES** for detailed interpretation of the blood cholinesterase tests.

Measurement of carbamate metabolites in urine within 48 hours of exposure represents a specific and sensitive method for confirming absorption of several pesticides of this class. A number of government and university laboratories in contact with poison control centers can perform these tests. Specimens for such analysis should be collected as promptly as possible after exposure.

TREATMENT

CAUTION: Persons attending the victim should avoid direct contact with heavily contaminated clothing and vomitus. Wear rubber gloves while decontaminating skin and hair.

1. Establish **CLEAR AIRWAY** and **TISSUE OXYGENATION** by aspiration of secretions, and if necessary, by assisted pulmonary ventilation with oxygen. Improve tissue oxygenation as much as possible before administering atropine to minimize the risk of ventricular fibrillation.
2. Administer **ATROPINE SULFATE** intravenously, or intramuscularly if IV injection is not possible. Atropine protects the end-organs from excessive concentrations of acetylcholine. It does not reactivate the cholinesterase enzyme. Recrudescence of poisoning may occur if tissue concentrations of carbamate remain high when the effect of atropine wears off. Atropine is the ideal antidote for muscarinic symptoms; it is ineffective against nicotinic actions such as muscle weakness and twitching, and respiratory depression.

   In **MODERATELY SEVERE** poisoning: **Adult dosage,** including children over 12 years: 0.4-2.0 mg repeated every 15 minutes until atropinization is achieved (tachycardia, flushing, dry mouth, mydriasis). Maintain atropinization by repeated doses for 2-12 hours, or longer, depending on severity of poisoning. The appearance of râles in the lung bases, miosis, salivation, nausea, bradycardia, are all indications of inadequate atropinization.

   Dosage for children under 12 years: 0.05 mg/kg body weight repeated every 15 minutes until atropinization is achieved. Maintain atropinization with repeated dosage of 0.02-0.05 mg/kg.

   SEVERELY POISONED individuals may exhibit remarkable tolerance to atropine; twice the doses suggested above may be needed. Persons not poisoned, or only slightly poisoned, may develop signs of atropine toxicity if large doses are given: **FEVER,** muscle fibrillations, and delirium. If these appear while the patient is fully atropinized, atropine should be discontinued, at least temporarily.
3. Pralidoxime (Protopam®-Ayerst, 2-PAM) is of doubtful value in poisonings by carbamate inhibitors of cholinesterase. Atropine alone is almost always an adequate antidote. Pralidoxime is probably contraindicated in poisonings by carbaryl, specifically. If victim of carbamate poisoning exhibits severe muscle weakness and/or respiratory depression, or if poisoning involves a combination of carbamate and organophosphate, a dilute solution of pralidoxime (total dose in 250 ml 5% glucose solution) may be given cautiously IV. The infusion should be terminated if patient's condition worsens. Pralidoxime **dosage:** adults, 1.0 gm; for children under 12 years, 20-50 mg/kg.
4. **OBSERVE** treated patients closely **at least 24 HOURS** to insure that symptoms (possibly pulmonary edema) do not recur as atropinization wears off. In very severe poisonings, metabolic disposition of toxicant

may require several hours or days during which atropinization must be maintained. Markedly lower levels of urinary metabolites indicate that atropine dosage can be tapered off. As dosage is reduced, check the lung bases frequently for râles. If râles are heard, or if nausea, salivation, or bradycardia returns, **RE-ESTABLISH ATROPINIZATION** promptly.

5. **BATHE** and **SHAMPOO** victim with soap and water if there is any chance that **SKIN** and **HAIR** are contaminated.
6. If pesticide has been **INGESTED** in quantity sufficient to cause poisoning, empty the stomach and intestine.

   A. If victim is alert and respiration is not depressed, give **SYRUP OF IPECAC,** followed by 1-2 glasses of water to induce vomiting; adults (including children over 12), 30 ml; children (under 12 years), 15 ml.

      CAUTION: **OBSERVE** victim closely **AFTER** administering **IPECAC.** If consciousness level declines, or if vomiting has not occurred in 15 minutes, proceed immediately to **INTUBATE** the stomach.

      Following emesis, have victim drink a suspension of 30-50 gm **ACTIVATED CHARCOAL** in 3-4 ounces of water to bind toxicant remaining in the gastrointestinal tract.

   B. **If** victim is **OBTUNDED** or respiration is depressed, empty stomach by **INTUBATION, ASPIRATION,** and **LAVAGE,** using isotonic saline or 5% sodium bicarbonate. Because many pesticides are dissolved in petroleum distillates, emesis and intubation of the stomach involve a serious risk that solvent will be aspirated, leading to chemical pneumonitis. For this reason:

      (a). If victim is unconscious or obtunded and facilities are at hand, insert **ENDOTRACHEAL TUBE** (cuffed, if available) prior to gastric intubation.

      (b). Keep victim's **HEAD BELOW LEVEL OF STOMACH** during intubation and lavage (Trendelenburg, or left lateral decubitus, with head of table tipped downward). Keep victim's head turned to left.

      (c). **ASPIRATE PHARYNX** as regularly as possible to remove gagged or vomited stomach contents.

      After aspiration of gastric contents and washing of stomach, instill 30-50 gm of **ACTIVATED CHARCOAL** in 3-4 ounces of water through the tube to limit absorption of remaining toxicant.

   C. **SAVE A SAMPLE** of emesis or initial gastric washings for chemical analysis.

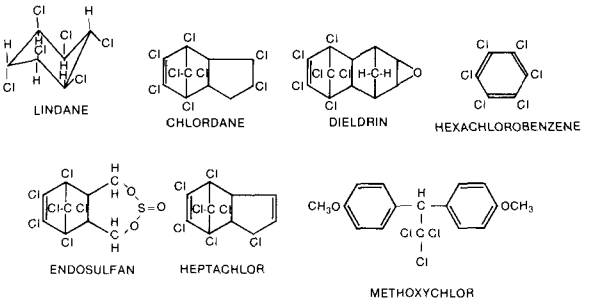
   D. If bowel movement has not occurred in 4 hours and patient is fully conscious, give **SODIUM SULFATE,** 0.25 gm/kg in 1-6 ounces of water, as a cathartic. Magnesium sulfate or citrate is equally suitable if renal function is satisfactory.

7. **DO NOT** give morphine, aminophylline, phenothiazines, reserpine, furosemide, or ethacrynic acid.
8. Give adrenergic amines **ONLY** if there is a specific indication, such as severe hypotension.
9. **CONVULSIONS** are **RARE** manifestations of poisoning by carbamates. If they occur, causes other than direct carbamate action should be considered: cerebral anoxia, head trauma, mixed poisoning. Although not tested in these circumstances, **DIAZEPAM** (Valium) is probably the anticonvulsant of choice. **Dosage** for adults and children over 6 years or 23 kg body weight is 5-10 mg given **slowly** intravenously (no more than half total dose per minute), or intramuscularly (deep). Dosage for children under 6 years or 23 kg body weight is 0.1 mg/kg. Repeat this dosage every 2-4 hours if needed to control convulsions. Be prepared to intubate and to assist pulmonary ventilaton mechanically if respiration is depressed. Hypotensive reactions may also occur.
10. Persons who have been clinically poisoned by carbamate pesticides should not be re-exposed to cholinesterase-inhibiting chemicals until symptoms and signs have resolved completely, and normal blood cholinesterase activities have been demonstrated.
11. **DO NOT** administer atropine prophylactically to workers exposed to carbamate insecticides. It is neither practical nor medically sound to do so.

Chapter 3

SOLID ORGANOCHLORINE PESTICIDES

CHEMICAL STRUCTURES



COMMON COMMERCIAL PESTICIDE PRODUCTS*

Highly toxic: endrin (Hexadrin), a stereoisomer of dieldrin.

Moderately toxic: aldrin (Aldrite, Drinox), endosulfan (Thiodan), dieldrin (Dieldrite), toxaphene (Toxakil, Strobane-T), lindane (Gammexane), benzene hexachloride (BHC, HCH), DDT (chlorophenothane), heptachlor, kepone, terpene polychlorinates (Strobane), chlordane (Chlordan), dicofol (Kelthane), chlorobenzilate (Acaraben), mirex, methoxychlor (Marlate), dienochlor (Pentac), hexachlorobenzene (HCB), ethylan (Perthane). All except HCB are insecticides or acaricides; HCB is a fungicide.

The U.S. Environmental Protection Agency has sharply curtailed the availability of many organochlorines, particularly DDT, dieldrin, and chlordane. Others, however, are still the active ingredients of various home and garden products and some agricultural and structural pest control agents. Hexachlorobenzene is used as a seed protectant. Lindane may no longer be used in continuous vaporizers, but it is the active ingredient of many products for pest control in the home and on the farm. It is the active ingredient of the scabicide Kwell®.

TOXICOLOGY

Most organochlorines are efficiently absorbed from the gut and across the skin. In adequate dosage, they interfere with axonic transmission of nerve impulses and, therefore, disrupt the function of the nervous system, principally that of the brain. This results in behavioral changes, sensory and equilibrium disturbances, involuntary muscle activity, and depression of vital centers, particularly those controlling respiration. Adequate doses of some organochlorines increase myocardial irritability, and stimulate synthesis of hepatic drug-metabolizing enzymes.

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* Listed approximately in order of decreasing toxicity.

Chlordane has apparently induced a few cases of self-limited megaloblastic anemia after protracted low-level exposures. The condition has resolved following termination of exposure.

Kepone has caused nervousness, tremor, incoordination, weakness and infertility in excessively exposed workers. Clinical improvement has occurred as the pesticide was excreted.

Endrin is more toxic to the liver and kidneys than the other organochlorines at comparable dosages.

Prolonged ingestion of HCB-treated grain produced porphyria cutanea tarda in several thousand Turkish citizens who mistakenly ate the seed grain. Disease was manifest as excretion of red urine, bullous dermatitis, hyperpigmentation, generalized hair growth, muscle wasting and liver enlargement. Slow improvement occurred when HCB ingestion was stopped.

A series of anecdotal reports of bone marrow injury has tended to indict lindane as a hematotoxic agent in certain predisposed individuals, but no relationship has been proved.

Lindane, methoxychlor, terpene polychlorinates, chlorobenzilate, dicofol, and the constituents of chlordane, except heptachlor and oxychlordane, are excreted rapidly by humans, usually within 3-4 days of ingestion. Dieldrin, aldrin, endrin, hexachlorobenzene, heptachlor, and oxychlordane are excreted within weeks to several months of absorption by humans. DDT, kepone, mirex, and the beta isomer of benzene hexachloride are excreted very slowly, requiring months or years for elimination. The excretion kinetics of perthane, kelthane, and dienochlor are not known. Because of their lipophilicity, all organochlorines are likely to be excreted in the milk of lactating women.

FREQUENT SYMPTOMS AND SIGNS OF POISONING

APPREHENSION, EXCITABILITY, DIZZINESS, HEADACHE, DISORIENTATION, WEAKNESS, PARESTHESIAE, muscle twitching, tremor, tonic and clonic **CONVULSIONS** (often epileptiform), and unconsciousness are the major manifestations. Soon after ingestion, nausea and vomiting commonly occur. When chemicals are absorbed dermally, apprehension, twitching, tremors, confusion, and convulsions may be the first symptoms. Respiratory depression is caused by the pesticide and by the petroleum solvents in which these pesticides are usually dissolved. Pallor occurs in moderate to severe poisoning. Cyanosis may result as convulsive activity interferes with respiration.

Even though convulsive activity may be severe, the prognosis in poisonings by these agents is far from hopeless. Although fatalities have occurred following absorption of large amounts of some organochlorines, there is a substantial likelihood of complete recovery if convulsions can be controlled, and vital functions sustained.

CONFIRMATION OF DIAGNOSIS

Pesticide and/or metabolites can usually be identified in blood or urine by gas-liquid chromatographic examination of samples taken within 72 hours of poisoning. These tests can be performed by some private laboratories, and by state health department and university laboratories supported by the U.S. Environmental Protection Agency. Such laboratories can be reached through poison control centers. Some chlorinated hydrocarbon pesticides (notably DDT) persist in the serum for weeks or months after absorption, but most are excreted in a few days. **DO NOT DELAY TREATMENT** of acute poisoning pending confirmatory blood analysis. Detection of chlorinated hydrocarbon residues in blood or tissues does not, of itself, indicate poisoning; actual concentrations are critical to a diagnosis of poisoning.

TREATMENT

1. Establish **CLEAR AIRWAY** and **TISSUE OXYGENATION** by aspiration of secretions, and, if necessary, by assisted pulmonary ventilation with oxygen.
2. **CONTROL CONVULSIONS. DIAZEPAM (VALIUM®)** is a valuable anticonvulsant.
   Adult dosage, including children over 6 years of age or 23 kg in weight: 5-10 mg (1-2 ml) slowly, intravenously (no faster than one ml per minute), or give total dose intramuscularly (deep). Repeat in 2-4 hours if needed.
   Dosage for children under 6 years or 23 kg in weight: 0.1 mg/kg (0.02 ml/kg) intravenously, no faster than half the total dose per minute, or give total dose intramuscularly (deep). Repeat in 2-4 hours if needed.

   CAUTION: Administer intravenous diazepam slowly to avoid irritation of the vein, hypotension, and respiratory depression.

   A. Persons suffering **SEVERE PROTRACTED CONVULSIONS** may require additional anticonvulsant medication. Agents that have been used successfully in the past are pentobarbital (Numbutal®), phenytoin (Dilantin®), thiopental (Pentothal®), and succinylcholine (Anectine®).

      CAUTION: Be prepared to maintain pulmonary ventilation mechanically if respiration is depressed during administration of anticonvulsants. Laryngospasm sometimes occurs during anticonvulsant therapy, and may necessitate tracheostomy.

      (a). **PENTOBARBITAL:** 5 mg/kg body weight, or 0.20 ml/kg body weight, using the usual 2.5% solution. If possible, inject solution intravenously, at a rate not exceeding 25 mg (one ml)

per minute until convulsions are controlled. If intravenous administration is not possible, give total dose rectally, not exceeding 5 mg/kg body weight (0.20 ml/kg of 2.5% solution).

(b). **PHENYTOIN:** loading dose 15-18 mg/kg. Maintenance dose 4-8 mg/kg q 4-24 hours as needed. Intramuscular administration is not recommended. Give IV slowly at no more than 20% total dose per minute.

(c). **THIOPENTAL (PENTOTHAL):** a solution of one gm in 500 ml of 5% glucose in water is given by intravenous drip at a rate just sufficient to suppress convulsions.

(d). **SUCCINYLCHOLINE:** occasionally, curarization may be required to stop seizures. Prior to curarization, the trachea must be intubated, and pulmonary ventilation maintained mechanically. Blood gases and pH must be monitored. A person experienced in general anesthesia should conduct these procedures.

3. **BATHE** and **SHAMPOO** the victim vigorously with soap and water if skin and hair have been contaminated.
4. **IF PESTICIDE HAS BEEN INGESTED** in quantity sufficient to cause poisoning, the stomach and intestine must be emptied.

A. **IF** victim is **ALERT** and gag reflex is not depressed, give **SYRUP OF IPECAC** to induce vomiting (adults and children 12 years and older: 30 ml; children under 12: 15 ml), followed by 1-2 glasses of water.

CAUTION: **OBSERVE** the **VICTIM** closely after administering **IPECAC.** If consciousness level declines, or if vomiting has not occurred in 15 minutes, proceed immediately to **INTUBATE** stomach.

Following emesis, have victim drink a suspension of 30-50 gm **ACTIVATED CHARCOAL** in 3-4 ounces of water to limit absorption of toxicant remaining in the gut.

B. If the victim is **NOT FULLY ALERT,** empty the stomach immediately by **INTUBATION, ASPIRATION,** and **LAVAGE,** using isotonic saline or 5% sodium bicarbonate. Because many pesticides are dissolved in petroleum distillates, emesis and intubation of the stomach involve a serious risk that solvent will be aspirated, leading to chemical pneumonitis. For this reason:

(a). If victim is unconscious or obtunded and if facilities are at hand, insert an **ENDOTRACHEAL TUBE** (cuffed, if available) prior to gastric intubation.

(b). Keep victim's **HEAD BELOW LEVEL OF STOMACH** and turned to left during intubation and lavage. (Trendelenburg, or left lateral decubitus, with head of table tipped downward).

(c). **ASPIRATE PHARYNX** as regularly as possible to remove gagged or vomited stomach contents.

C. After aspiration of gastric contents and washing of stomach, instill 30-50 gm of **ACTIVATED CHARCOAL** in 3-4 ounces of water through stomach tube to limit absorption of remaining toxicant. **DO NOT** instill milk, cream, or other substances containing vegetable or animal fats, which enhance absorption of chlorinated hydrocarbons.

D. **SAVE A SAMPLE** of emesis or gastric washings for chemical analysis.

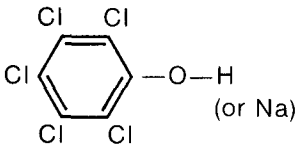
E. If bowel movement has not occurred in 4 hours and if patient is fully conscious, give **SODIUM SULFATE,** 0.25 gm/kg in 1-6 ounces of water, as a cathartic. Magnesium sulfate and citrate are as suitable as sodium sulfate if renal function is adequate. Retained magnesium may depress CNS function.

5. **DO NOT** give epinephrine or other adrenergic amines, because of the enhanced myocardial irritability induced by chlorinated hydrocarbons.
6. **CHOLESTYRAMINE** resin may accelerate the biliary-gastrointestinal excretion of the more slowly eliminated organochlorine compounds. This is usually administered in 3-8 gm doses, 4 times a day, before meals and at bedtime. Dose should be mixed with a pulpy fruit or liquid. Prolonged treatment (several weeks or months) may be necessary.
7. During convalescence, enhance **CARBOHYDRATE, PROTEIN,** and **VITAMIN** intake by diet or parenteral therapy to minimize injury to the liver.

Chapter 4

PENTACHLOROPHENOL

CHEMICAL STRUCTURE



COMMON COMMERCIAL PESTICIDE PRODUCTS

Pentachlorophenol or Sodium Pentachlorophenate, PCP, Dow Pentachlorophenol, Dowicide EC-7, Penchlorol, Pentacon, Penwar, Veg-I-Kill, penta, Wood Preserver, Wood Tox 140, Purina Insect Oil Concentrate, Gardon Termi Tox, Usol Cabin Oil, Certified Kiltrol-74 Weed Killer, Ciba-Geigy Ontrack OS3, 4 or 5, Ortho Triox Liquid Vegetation Killer, Black Leaf Grass Weed and Vegetation Killer Spray, DP-2 Antimicrobial, Priltox, Sinituho.

Pentachlorophenol is used as an herbicide, defoliant, wood preservative, germicide, fungicide, and molluscicide. It is an ingredient of many formulated mixtures sold for one or more of these purposes.

Pentachlorophenol volatilizes from treated wood and fabric. Excessively treated interior surfaces may represent a source of intensive PCP exposure.

TOXICOLOGY

Pentachlorophenol irritates the skin, eyes, and upper respiratory mucous membranes. It is efficiently absorbed across the skin, the lung, and the gastrointestinal lining. Like the nitrophenolic compounds, it stimulates cellular oxidative metabolism by uncoupling phosphorylation. In common with other phenols, it is toxic to the liver, kidney, and central nervous system. Impurities in the technical formulation may be responsible for chloracne in workers regularly exposed.

Most severe poisonings have occurred in workers exposed to hot environments. However, a major epidemic of poisoning occurred in an American hospital among newborn infants who absorbed PCP from treated diapers. Dehydration and metabolic acidosis are important features of poisoning in children.

Albuminuria, glycosuria, and elevated BUN reflect renal injury. Liver enlargement has been observed in some cases. Anemia and leukopenia have occurred in some chronically exposed workers, but leukocytosis is more commonly found in acute poisoning.

FREQUENT SYMPTOMS AND SIGNS OF POISONING

IRRITATION of nose, throat, eyes, and skin is the most common symptom of exposure to PCP. Severe or protracted exposure may result in **CONTACT DERMATITIS.** Intensive occupational exposure has resulted in chloracne.

PROFUSE SWEATING, HEADACHE, WEAKNESS, and **NAUSEA** are the most consistent presenting symptoms of systemic poisoning by absorbed PCP. **FEVER** is usually present but may be minimal or absent. **TACHYCARDIA, TACHYPNEA,** and **PAIN** in the **CHEST** and **ABDOMEN** are often prominent. **THIRST** is usually intense, but may be masked by nausea and vomiting. **DECLINING MENTAL ALERTNESS** may progress to stupor and/or convulsions. Protracted exposure may result in **WEIGHT LOSS** from increased basal metabolic rate.

CONFIRMATION OF DIAGNOSIS

PCP can be measured in blood, urine, and adipose tissue by gas-liquid chromatography. Up to about 100 parts per billion may be found in the blood and urine of persons having no recognized exposure. Based on studies of persons occupationally exposed to PCP, manifestations of systemic toxicity probably do not appear in adults until blood and urine concentrations reach at least one part per million (0.1 mg%, or 1,000 parts per billion).

If poisoning is strongly suspected on grounds of exposure, symptoms, and signs, **DO NOT POSTPONE TREATMENT** until diagnosis is confirmed.

TREATMENT

1. **BATHE** and **SHAMPOO** contaminated **SKIN** and **HAIR** promptly with soap and water, or water alone if soap is not available.
2. **FLUSH** chemical from **EYES** with copious amounts of clean water.
3. **IN EVENT OF SYSTEMIC POISONING:**
   A. **REDUCE ELEVATED BODY TEMPERATURE BY PHYSICAL MEANS.** Administer sponge baths and cover victim with low-temperature blankets. In fully conscious patients, administer cold, sugar-containing liquids by mouth as tolerated.
   B. Administer **OXYGEN** continuously by mask to minimize tissue anoxia.
   C. Unless there are manifestations of cerebral edema, administer **INTRAVENOUS FLUIDS** at maximum tolerated rates to enhance urinary excretion of toxicant and to support physiologic mechanisms for heat loss. Monitor fluid balance, blood electrolytes and sugar, adjusting IV infusions to stabilize electrolyte concentrations, Follow urine contents of albumin and cells. In the presence of **CEREBRAL EDEMA,** intravenous **FLUIDS** must be administered very **CAUTIOUSLY** to avoid increasing the cerebral injury.

D. Administer **SEDATIVES,** if necessary, to control apprehension and excitement. **DIAZEPAM®** (Valium) should be valuable, although its use has not been reported in this type of poisoning. Give slowly, intravenously, 5-10 mg in the adult, 0.1 mg/kg in children. Amobarbital or pentobarbital, 100-200 mg IM or slowly IV, every 4-6 hours may be needed. (Children's dose: up to 5 mg/kg.)

CAUTION: Be prepared to assist pulmonary ventilation mechanically in event of respiratory depression, and to counteract hypotensive reactions.

4. If toxicant has been **INGESTED,** evacuate the stomach and intestine.

A. If victim is alert and respiration is not depressed, give **SYRUP OF IPECAC,** followed by 1-2 glasses of water, to induce vomiting. (Adults, 12 years and older: 30 ml; children under 12: 15 ml).

CAUTION: **OBSERVE** the victim closely **AFTER** administering **IPECAC.** If consciousness level declines, or if vomiting has not occurred in 15 minutes, proceed immediately to **INTUBATE** the stomach.

Following emesis, have the victim drink a suspension of 30-50 gm **ACTIVATED CHARCOAL** in 3-4 ounces of water to bind toxicant remaining in the gastrointestinal tract.

B. If victim is not fully alert, empty the stomach immediately by **INTUBATION, ASPIRATION,** and **LAVAGE,** using isotonic saline or 5% sodium bicarbonate. Because PCP is commonly dissolved in petroleum distillates, emesis and intubation of the stomach involve a serious risk that solvent will be aspirated, leading to chemical pneumonitis. For this reason:

(a). If victim is unconscious or obtunded and facilities are at hand, insert an **ENDOTRACHEAL TUBE** (cuffed, if available) prior to gastric intubation.

(b). Keep victim's **HEAD BELOW LEVEL OF THE STOMACH,** turned to left, during intubation and lavage. (Trendelenburg, or left lateral decubitus, with head of table tipped downward).

(c). **ASPIRATE PHARYNX** as regularly as possible to remove gagged or vomited stomach contents.

(d). After aspiration of gastric contents and washing of stomach, instill 30 gm of **ACTIVATED CHARCOAL** in 3-4 ounces of water through a stomach tube to limit absorption of remaining toxicant. Do **NOT** instill milk, cream, or other materials containing vegetable or animal fats, which are likely to enhance absorption.

C. If bowel movement has not occurred in 4 hours and patient is fully conscious, give **SODIUM SULFATE** as a cathartic: 0.25 gm/kg body weight in 1-6 ounces of water. Magnesium sulfate and citrate

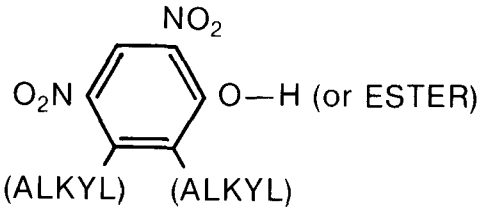
are equally suitable unless renal function is impaired; retention of magnesium may depress CNS function and alter myocardial irritability.

5. **DO NOT** administer atropine, aspirin, or other antipyretics to control fever. These are likely to enhance the toxicity of phenolic compounds.
6. During convalescence, administer high-calorie, high-vitamin diet to restore body fat and carbohydrate.
7. Discourage subsequent contact with the toxicant for at least 4 weeks to allow full restoration of normal metabolic processes.
8. **HEMODIALYSIS** and **HEMOPERFUSION** may be considered in PCP poisoning, although phenols are extensively bound to plasma protein. **EXCHANGE TRANSFUSION** was used to rescue the infants inadvertently poisoned by PCP in a hospital. Unless renal and liver functions are impaired, PCP is rapidly eliminated from the blood and tissues.

Chapter 5

NITROPHENOLIC AND NITROCRESOLIC HERBICIDES

GENERAL CHEMICAL STRUCTURE



COMMON COMMERCIAL PESTICIDE PRODUCTS

Dinitrophenol (Chemox PE), dinitrocresol (DNOC, DNC, Sinox, Chemsect DNOC, Elgetol 30, Nitrador, Selinon, Trifocide), dinoseb (DNBP, Dinitro, Basanite, Caldon, Chemox General, Chemox PE, Chemsect DNBP, Dinitro-3, Dinitro General, Dow General Weed Killer, Dow Selective Weed Killer, Dynamyte, Elgetol 318, Gebutox, Kiloseb, Nitropone C, Premerge 3, Sinox General, Subitex, Unicrop DNBP, Vertac Dinitro Weed Killer), dinosam (DNAP), dinoprop, dinoterbon, dinoterb, dinosulfon, binapacryl (Morocide, Endosan, Ambox, Dapacryl), dinobuton (Acrex, Dessin, Dinofen, Drawinol, Talan), dinopenton, dinocap (Crotothane, Karathane). Several combinations are widely used: Dyanap and Klean Krop = dinoseb + naptalam; Ancrack = sodium salts of dinoseb + naptalam; Naptro = dinitrophenol + naptalam.

TOXICOLOGY

These materials should be regarded as highly toxic to humans and animals. Most nitrophenols and nitrocresols are well absorbed from the gastrointestinal tract, across the skin, and by the lung when fine droplets are inhaled. Except in a few sensitive individuals, aromatic nitro-compounds are only moderately irritating to the skin. Like other phenols, they are toxic to the liver, kidney, and nervous system. The basic mechanism of toxicity is a stimulation of oxidative metabolism in cell mitochondria, by interference with the normal coupling of carbohydrate oxidation to phosphorylation (ADP to ATP). Increased oxidative metabolism leads to pyrexia, tachycardia, and dehydration, and ultimately depletes carbohydrate and fat stores. Most severe poisonings from absorption of these compounds have occurred in workers who were concurrently exposed to hot environments. Pyrexia and direct action on the brain cause cerebral edema, manifest clinically as a toxic psychosis and sometimes

convulsions. Liver parenchyma and renal tubules show degenerative changes. Albuminuria, pyuria, hematuria, and increased BUN are often prominent signs of renal injury.

Agranulocytosis has occurred in humans following large doses of dinitrophenol. Cataracts have occurred in some chronically poisoned laboratory species, but this effect has not been observed in humans.

Nitrophenols and nitrocresols are efficiently excreted by the kidneys, and there is some hepatic excretion into the bile. Unless the absorbed dose was extremely high, or kidney function is impaired, nearly complete elimination from the body can be expected within 3-4 days.

Death in nitrophenol poisoning is followed promptly by intense rigor mortis.

FREQUENT SYMPTOMS AND SIGNS OF POISONING

YELLOW STAINING of skin and hair often signify contact with a nitrophenolic chemical. Staining of the sclerae and urine indicate absorption of potentially toxic amounts. **PROFUSE SWEATING, HEADACHE, THIRST, MALAISE,** and **LASSITUDE** are the common early symptoms of poisoning. **WARM, FLUSHED SKIN, TACHYCARDIA,** and **FEVER** characterize a serious degree of poisoning. **APPREHENSION,** restlessness, anxiety, manic behavior, or unconsciousness reflect severe cerebral injury. **CONVULSIONS** occur in the most severe poisonings. Cyanosis, tachypnea and dyspnea result from stimulation of metabolism, pyrexia, and tissue anoxia. Weight loss occurs in persons chronically poisoned at low dosages.

CONFIRMATION OF DIAGNOSIS

Unmetabolized nitrophenols and nitrocresols can be identified spectrophotometrically, or by gas-liquid chromatography, in the serum and urine at concentrations well below those necessary to cause poisoning. If poisoning is probable, **DO NOT AWAIT CONFIRMATION** before commencing treatment.

TREATMENT

1. **WASH** contaminated **SKIN** and **HAIR** promptly with soap and water, or with water alone if soap is not available.
2. **FLUSH** chemical from **EYES** with copious amounts of clean water.
3. **IN EVENT OF SYSTEMIC POISONING:**
   A. **REDUCE ELEVATED BODY TEMPERATURE BY PHYSICAL MEANS.** Administer sponge baths and cover victim with low-temperature blankets. In fully conscious patients, administer cold, sugar-containing liquids by mouth as tolerated.
   B. Administer **OXYGEN** continuously by mask to minimize tissue anoxia.

C. Unless there are manifestations of cerebral edema, administer **INTRAVENOUS FLUIDS** at maximum tolerated rates to enhance urinary excretion of toxicant and to support physiologic mechanisms for heat loss. **IN** the presence of **CEREBRAL EDEMA**, intravenous **FLUIDS** must be administered very **CAUTIOUSLY** to avoid increasing the cerebral injury. Monitor fluid balance, blood electrolytes and sugar, adjusting IV infusions to stabilize electrolyte concentrations. Follow urine contents of albumin and cells. Follow serum alkaline phosphatase, GOT, and LDH to evaluate liver injury.

D. Administer **SEDATIVES**, if necessary, to control apprehension, excitement, and/or convulsions. Although not previously used in this type of poisoning, **DIAZEPAM** (Valium®) should help: adult dose, 5-10 mg **slowly** IV, or IM (deep); child's dose, 0.1 mg/kg. Repeat every 2-4 hours as needed. Amobarbital or pentobarbital may be needed. Dose in adults: 200 mg, IM or slowly IV, every 4-6 hours; child's dose: up to 5 mg/kg.

CAUTION: Be prepared to counteract respiratory depression and hypotension which may follow administration of anticonvulsants and sedatives.

4. If toxicant has been **INGESTED**, evacuate the stomach and intestine.

A. If victim is alert and respiration is not depressed, give **SYRUP** of **IPECAC**, followed by 1-2 glasses of water, to induce vomiting (adults 12 years and older: 30 ml; children under 12: 15 ml).

CAUTION: **OBSERVE** victim closely **AFTER** administering **IPECAC.** If consciousness level declines, or if vomiting has not occurred in 15 minutes, immediately **INTUBATE, ASPIRATE,** and **LAVAGE** the stomach.

Following emesis, have victim drink a suspension of 30-50 gm **ACTIVATED CHARCOAL** in 3-4 ounces of water to bind toxicant remaining in the gastrointestinal tract.

B. **IF VICTIM IS NOT FULLY ALERT,** empty the stomach immediately by **INTUBATION, ASPIRATION,** and **LAVAGE,** using isotonic saline or 5% sodium bicarbonate. Because these pesticides are usually dissolved in petroleum distillates, emesis and intubation of the stomach involve serious risk that solvent will be aspirated, leading to chemical pneumonitis. For this reason:

(a). If victim is unconscious or obtunded and facilities are at hand, insert an **ENDOTRACHEAL TUBE** (cuffed, if available) prior to gastric intubation.

(b). Keep victim's **HEAD BELOW LEVEL OF THE STOMACH** and turned to the left, during intubation and lavage (Trendelenburg, or left lateral decubitus, with head of table tipped downward).

(c). **ASPIRATE PHARYNX** as regularly as possible to remove gagged or vomited stomach contents.

(d). After aspiration of gastric contents and washing of stomach, instill 30-50 gm of **ACTIVATED CHARCOAL** in 3-4 ounces of water through the stomach tube to limit absorption of remaining toxicant. Do **NOT** instill cream, milk, or other materials containing vegetable or animal fats, as these are likely to enhance absorption.

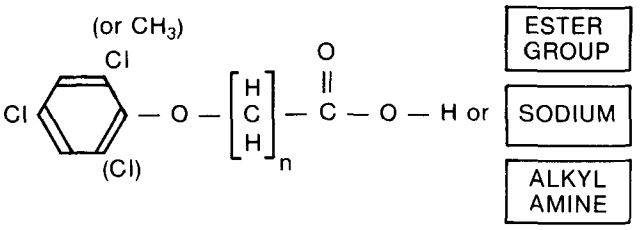
C. If bowel movement has not occurred in 4 hours, and if patient is fully conscious, give **SODIUM SULFATE** as a cathartic: 0.25 gm/kg body weight in 1-6 ounces of water. Magnesium sulfate and citrate are equally suitable unless renal function is impaired; retention of magnesium may depress CNS function and alter myocardial irritability.

5. **DO NOT** administer atropine, aspirin, or other antipyretics to control fever. Animal tests indicate that aspirin enhances, rather than reduces, the toxicity of nitrophenolic and nitrocresolic compounds.
6. During convalescence, administer high-calorie, high-vitamin diet to facilitate repletion of body fat and carbohydrate.
7. Discourage subsequent contact with the toxicant for at least 4 weeks, to allow full restoration of normal metabolic processes.
8. **HEMODIALYSIS** and **HEMOPERFUSION** may be considered in severe poisonings by aromatic nitro-compounds, although most phenols are extensively bound to plasma proteins. **EXCHANGE TRANSFUSION** is another option in poisonings characterized by impaired renal function. So long as renal and liver functions are intact, these compounds are efficiently excreted.

Chapter 6

CHLOROPHENOXY COMPOUNDS

GENERAL CHEMICAL STRUCTURE



COMMON COMMERCIAL PESTICIDE PRODUCTS

Several hundred commercial products contain chlorophenoxy herbicides in various concentrations and combinations. Following are names of widely advertised formulations. In some cases, the same name is used for products with different ingredients. Exact composition must therefore be determined from product label.

2,4-D, or 2,4-dichlorophenoxyacetic acid (Weedone†, Agrotec, Amoxone, Aqua-Kleen, BH 2,4-D, Chipco Turf Herbicide "D", Chloroxone, Crop Rider, D50, Dacamine 4D, Ded-Weed, Desormone, Dinoxol, DMA4, Dormone, Emulsamine BK, Emulsamine E-3, Envert DT or 171, Esteron 99 Concentrate, Esteron Four, Esteron Brush Killer, Estone, Fernoxone, Fernimine, Ferxone, Fernesta, Formula 40, Hedonal, Herbidal, Lawn-Keep, Macondray, Miracle, Netagrone 600, Pennamine D, Planotox, Plantgard, Rhodia, Salvo‡, Spritz-Hormin/2,4-D, Spritz-Hormit/2,4-D, Superormone Concentre, Super D Weedone, Transamine, U46, Verton 2D, Visko-Rhap, Weed-B-Gon, Weedar, Weed-Rhap, Weed Tox, Weedtrol, De broussaillant 600, Lithate, Dicotox, Field Clean Weed Killer). 2,4-DB is the butyric acid homologue of 2,4-D. Dichlorprop is the propionic acid homologue.

2,4,5-T or 2,4,5-trichlorophenoxyacetic acid (Brush-Rhap, Dacamine 4T, Debroussaillant Concentre, Ded-Weed Brush Killer, Esteron 245, Fence Rider, Forron, Inverton 245, Line Rider, Spontox, Super D Weedone, Tormona, Transamine, Trinoxol, Trioxone, U46, Veon 245, Verton 2T, Weedar, Weedone Envert T).

Common mixtures of 2,4-D and 2,4,5-T are: Dacamine 2D/2T, Esteron Brush Killer, Rhodia Low Volatile Brush Killer No. 2, U46 Special, Tributon, Visko-Rhap LV2D-2T, and Transamine.

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† A product of identical name containing pentachlorophenol (Chapter 4) as the active ingredient has been discontinued by Amchem Products Co.

‡ A product of identical name marketed by the Crystal Chemical Company contains cacodylic acid as the active ingredient (Chapter 10).

2,4,5-TP (Silvex) is the propionic acid homologue of 2,4,5-T. Kuron is a low volatile ester of 2,4,5-TP. 2,4,5-TB is the butyric acid homologue of 2,4,5-T. Fenac or chlorfenac is 2,3,6-trichlorophenylacetic acid. Dicamba (Banvel) is dichloroanisic acid. MCPA, MCPB, MCPB-Ethyl, MCPCA and MCPP (Mecoprop) are 2-methyl, 4-chlorophenoxy aliphatic acids and esters.

TOXICOLOGY

Some of the chlorophenoxy acids, salts, and esters are moderately irritating to skin, eyes, and respiratory and gastrointestinal linings. In a few individuals, local depigmentation has apparently resulted from prolonged and repeated dermal contact with chlorophenoxy materials.

The chlorophenoxy compounds are absorbed across the gut wall, lung, and skin. They are not significantly fat storable. Excretion occurs within hours, or at most, days, primarily in the urine.

Given in large doses to experimental animals, 2,4-D causes vomiting, diarrhea, anorexia, weight loss, ulcers of the mouth and pharynx, and toxic injury to the liver, kidneys, and central nervous system. Myotonia (stiffness and incoordination of hind extremities) develops in some species and is apparently due to CNS damage: demyelination has been observed in the dorsal columns of the cord, and EEG changes have indicated functional disturbances in the brains of heavily dosed experimental animals.

Ingestion of large amounts of chlorophenoxy acids has resulted in severe metabolic acidosis in humans. Such cases have been associated with electrocardiographic changes, myotonia, muscle weakness, myoglobinuria, and elevated serum creatine phosphokinase, all reflecting injury to striated muscle. Because chlorophenoxy acids are weak uncouplers of oxidative phosphorylation, extraordinary doses may produce hyperthermia from increased production of body heat.

PolyChlorinated DibenzoDioxin (CDD) compounds are generated in the synthesis of 2,4,5-T. The 2,3,7,8-Tetra CDD form is extraordinarily toxic to multiple mammalian tissues. Hexa- hepta-, and octa-compounds exhibit less systemic toxicity, but are the likely cause of chloracne (a chronic, disfiguring skin condition) seen in workers engaged in the manufacture of 2,4,5-T, and certain other chlorinated organic compounds. Although toxic effects, notably chloracne, have been observed in manufacturing plant workers, they have not been observed in formulators or applicators regularly exposed to 2,4,5-T.

The medical literature contains several reports of peripheral neuropathy following what seemed to be minor dermal exposures to 2,4-D. It is not certain that exposures to other neurotoxicants were entirely excluded in these cases. Single doses of 5 mg/kg body weight of 2,4-D and 2,4,5-T have been administered to human subjects without any adverse effects. One subject consumed 500 mg of 2,4-D per day for 3 weeks without experiencing symptoms or signs of illness.

FREQUENT SYMPTOMS AND SIGNS OF POISONING

Chlorophenoxy compounds are moderately **IRRITATING** to skin and mucous membranes. Inhalation of sprays may cause burning sensations in the nasopharynx and chest, and coughing may result. Prolonged inhalation sometimes causes dizziness.

When **INGESTED,** high concentrations of chlorophenoxy compounds may irritate the mouth, throat, and gastrointestinal tract. Prompt **EMESIS, CHEST PAIN** (from esophagitis), **ABDOMINAL PAIN,** and **DIARRHEA** commonly ensue. Injury to the GI tract does not usually progress to ulceration or perforation. Absorbed chlorophenoxy compounds have caused **FIBRILLARY MUSCLE TWITCHING,** skeletal muscle tenderness, and **MYOTONIA** (stiffness of muscles of the extremities). Ingestion of very large amounts has produced **METABOLIC ACIDOSIS,** fever, tachycardia, hyperventilation, vasodilatation and sweating. Particular cases have been characterized by coma and convulsions.

CONFIRMATION OF DIAGNOSIS

Gas-liquid chromatographic methods are available for detecting and measuring the chlorophenoxy compounds in blood and urine. These analyses are useful in confirming and assessing the magnitude of chlorophenoxy absorption. Urine samples should be collected as soon as possible after exposure because the herbicides may be almost completely excreted in 24-72 hours, depending on the extent of toxicant absorption. Analyses can be performed at special laboratories operated by state health departments, chemical companies, universities, and government facilities. If circumstances indicate strongly that excessive exposure to any of these compounds has occurred, initiate appropriate treatment measures immediately, not waiting for chemical confirmation of toxicant absorption.

TREATMENT

1. **BATHE** and **SHAMPOO** with soap and water to remove chemicals from skin and hair. Individuals with chronic skin disease or known sensitivity to chemicals should either avoid using these herbicides or take extraordinary measures to avoid contact.
2. **FLUSH** contaminating chemicals from eyes with copious amounts of clean water for 10-15 minutes.
3. If symptoms of illness occur during or following inhalation of spray, **REMOVE** victim **FROM CONTACT** with the material for at least two days. Allow subsequent contact with chlorophenoxy compounds only if effective respiratory protection is practiced.
4. IF substantial amounts of chlorophenoxy compounds have been **INGESTED,** spontaneous emesis usually occurs. Ordinarily, this empties the stomach as effectively as intubation and lavage. If vigorous emesis

has not occurred and **IF VICTIM IS FULLY ALERT,** induce **EMESIS** with **SYRUP OF IPECAC** (adults 12 years and older, 30 ml; children under 12 years, 15 ml), followed by 1-2 glasses of water. Following emesis, administer 30-50 gm of **ACTIVATED CHARCOAL** in a slurry of 6-8 ounces tap water, to limit absorption of herbicide remaining in the gut.

5. **IF CONSCIOUSNESS LEVEL IS DEPRESSED** or other signs of **NEUROTOXICITY** appear, **SUSPECT** additional or alternative ingested toxicants. Evacuate the stomach by **INTUBATION, ASPIRATION,** and **LAVAGE.** Because petroleum distillates are commonly included in chlorophenoxy formulations, gastric intubation incurs a risk of hydrocarbon pneumonitis from aspiration. For this reason:

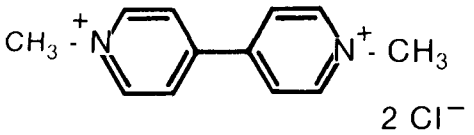
   A. If victim is unconscious or obtunded and facilities are at hand, insert an **ENDOTRACHEAL TUBE** (cuffed, if available) prior to gastric intubation.
   B. Keep victim's **HEAD BELOW LEVEL OF THE STOMACH** during intubation and lavage (Trendelenburg, or left lateral decubitus, with head of table tipped downward). Keep victim's head turned to left.
   C. **ASPIRATE PHARYNX** as regularly as possible to remove gagged or vomited stomach contents.

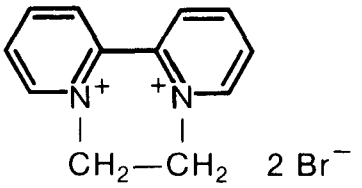
   After aspiration of gastric contents and washing of stomach, instill 30-50 gm of **ACTIVATED CHARCOAL** in 3-4 ounces of water through the stomach tube to limit absorption of remaining toxicant. Do **NOT** instill milk, cream, or other materials containing vegetable or animal fats, as these are likely to enhance absorption.
6. If bowel movement has not occurred in 4 hours and patient is fully conscious, give **SODIUM SULFATE,** 0.25 gm/kg, as a cathartic. Magnesium sulfate and citrate, in comparable dosages, are equally suitable if renal function is adequate. Retained magnesium may depress CNS function.
7. In **SEVERE POISONINGS** by very large amounts of ingested chlorophenoxy acids, forced **ALKALINE DIURESIS** may save the victim's life. Assess serum electrolyte concentrations, and serum and urine pH. If a metabolic acidosis is present, infuse solutions of sodium bicarbonate at rates sufficient to keep the urine distinctly alkaline, continuing until plasma concentrations of chlorophenoxy compounds are less than about 10 μg/ml. [Prescott, L F. et al., Br. J. Clin. Pharmacol. 7:11 (1979)]

Chapter 7

PARAQUAT AND DIQUAT

CHEMICAL STRUCTURES





PARAQUAT DIQUAT

COMMON COMMERCIAL PESTICIDE PRODUCTS

Paraquat products: paraquat dichloride (usually as a 21% concentrate). Other names: Ortho paraquat-CL, Crisquat, Dextrone X, Esgram. Mixtures: Priglone, Preeglone, Weedol—with diquat; Simpar, Terraklene—with simazine; Gramonol, Mofisal—with monolinuron; Pathclear—with diquat and simazine; TotaCol, Dexuron—with diuron.

Diquat products: diquat (Reglone, Reglox, Aquacide, Dextrone, Weedtrine-D). Mixtures: Priglone, Preeglone, Weedol—with paraquat; Pathclear—with paraquat and simazine.

TOXICOLOGY

These dipyridyls injure the epithelial tissues: skin, nails, cornea, liver, kidney, and the linings of the GI and respiratory tracts. In addition to direct irritant effects, injury may involve peroxidation of intracellular and extracellular phospholipids and inhibition of surfactant synthesis by lung tissue. These toxic properties may derive from the capacity of dipyridyls to generate free radicals in tissues. The injury is usually reversible; however, the pulmonary reaction which follows ingestion of paraquat is often fatal.

Certain injuries have followed occupational contact with paraquat. Contact with the concentrate may cause irritation and fissuring of the skin of the hands, and cracking, discoloration, and sometimes loss of the fingernails. Splashed in the eye, paraquat concentrate causes conjunctivitis and, if not promptly removed, may result in protracted opacification of the cornea.

Although nearly all systemic intoxications by paraquat have followed ingestion of the chemical, occasional poisonings have resulted from excessive dermal contact. Absorption of toxic amounts is much more likely to occur if the skin is abraded. Persons who have experienced extraordinary dermal contact with paraquat (especially the concentrate) should be examined, and tested for hazardous concentrations of the agent in the blood and urine (see section on Confirmation of Diagnosis).

Inhalation of dilute spray mist may irritate the upper respiratory passages, causing a scratchy throat and nosebleed. Effects induced by dilute paraquat sprays ordinarily resolve promptly following withdrawal from exposure.

If ingested, paraquat produces inflammation of the mouth and GI tract, sometimes progressing to ulceration within 1-4 days. Once absorbed, it damages the parenchymal cells of the liver and tubule cells of the kidney. In most instances, the victim survives these injuries. Paraquat is actively concentrated in the pneumocytes of lung tissue. Several days after ingestion these cells die, after which there is rapid proliferation of connective tissue cells which fill the alveolar spaces. Although some victims have survived, death from asphyxia usually occurs once this degree of lung damage has been sustained. In survivors, recovery of normal lung function requires weeks or months. In a few instances, ingestion of large quantities of paraquat has induced protracted pulmonary edema. Myocardial injury has also been noted in some poisonings.

Diquat appears less likely than paraquat to cause death. Information from suicidal ingestions and from orally dosed monkeys indicates that the principal target organs in diquat toxicity are the gastrointestinal tract, kidney, and liver. Diquat produces intense congestion and ulceration of the stomach and bowel. Fatty liver and acute renal tubular necrosis are produced by adequate doses. Smaller doses administered chronically have caused lens cataracts in animals. Diquat is not concentrated in lung tissue as paraquat is, and pulmonary lesions are limited to punctate hemorrhages. Hemorrhages in brain tissue have been reported after diquat ingestion.

FREQUENT SYMPTOMS AND SIGNS OF POISONING

The irritant effects of paraquat on skin, eye, and upper respiratory tract have been described under **TOXICOLOGY.**

The earliest (1-4 days) symptoms of injury and signs following ingestion of a toxic dose of **PARAQUAT** are burning **PAIN** (oral, substernal, abdominal), **NAUSEA, VOMITING, DIARRHEA,** and sometimes melena. Early symptoms are sometimes so mild that vigorous treatment is improperly delayed.

From 24-72 hours, indications of renal and hepatic insult appear. Albuminuria, hematuria, pyuria, and **ELEVATED BUN** and **CREATININE** may occur. **OLIGURIA** may develop, and this signals severe poisoning. **JAUNDICE** and elevations of serum GOT, GPT, LDH, and alkaline phosphatase reflect hepatocellular injury. These injuries are usually reversible, although severe renal tubular damage may require extracorporeal hemodialysis.

A progressive decline in arterial oxygen tension and CO diffusion capacity commonly precedes the appearance of pulmonary symptomatology. **COUGH, DYSPNEA,** and **TACHYPNEA** usually appear 72-96 hours after paraquat ingestion, but may be delayed as long as 14 days. Progressive **CYANOSIS** reflects deteriorating gas exchange caused by the fibrogenic reaction in the alveolar sacs. In a few cases, the production of **COPIOUS WATERY SPUTUM** (pulmonary edema) has followed ingestions of large amounts (200 ml) of paraquat or diquat concentrate.

DIQUAT INGESTION results in intense **NAUSEA, VOMITING,** and **DIARRHEA,** with accompanying dehydration, and in melena and hematemesis from gastrointestinal ulceration. **INCREASED** serum **BUN** and **CREATININE,** and **ANURIA** result from acute tubular necrosis. Serum GOT, GPT, and LDH and alkaline phosphatase elevations reflect liver injury. Early **COMA** has sometimes occurred following suicidal ingestion of large amounts and has also been noted in experimentally poisoned monkeys. This could be a consequence of profound dehydration, with electrolyte disturbances, or of diffuse hemorrhages in the central nervous system, as noted in one human poisoning.

CONFIRMATION OF DIAGNOSIS

Qualitative and quantitative methods for paraquat and diquat in blood and urine are available at some local, private, and government toxicology laboratories, and at the Chevron Environmental Health Center, Box 1272, Richmond, California 94802. The Chevron Chemical Company maintains a 24-hour toxicology consultation service through an emergency telephone number: (415) 233-3737. Sales representatives are prepared to deliver bentonite to virtually any location in the United States, and to arrange for the prompt delivery of biologic specimens for dipyridyl analysis to the Environmental Health Center. Company toxicologists are available 24 hours a day for assistance in management of poisonings by Chevron products.

TREATMENT

1. Contaminated **SKIN** must be **FLUSHED** with copious amounts of water. Material splashed in the **EYES** must be removed by **PROLONGED IRRIGATION** with clean water. Eye contamination should thereafter be treated by an ophthalmologist. Mild skin reactions usually respond to simple avoidance of further contact, but the irritation may take several weeks to resolve. Severe injuries, with cracking, secondary infection, or nail injury, should be treated by a dermatologist.
2. After a **DIPYRIDYL** compound has been **INGESTED,**

   EVACUATE the **STOMACH,** then **LOAD** the gastrointestinal tract with an effective **ADSORBENT,** to minimize toxicant absorption. *These measures must be undertaken immediately, even though the patient is free of signs of systemic toxicity, and even when, by all accounts, the ingested dose was probably small and was taken as long as several days prior to treatment.*

   INTUBATE the **STOMACH, ASPIRATE** contents, then **LAVAGE** with at least two liters of a slurry of **ADSORBENT** in normal saline. Then, slowly instill several hundred additional ml of adsorbent slurry, allowing the stomach and intestine to accommodate this volume without overdistension and vomiting.

A. The ideal adsorbent is **BENTONITE,** administered as a 7 gm per 100 ml suspension. If not immediately available, use **ACTIVATED CHARCOAL,** 30-50 gm in 300-400 ml of water, or any concentration that will flow through the tube. As soon as bentonite has been obtained, administer it as rapidly as the patient will tolerate it. If patient cannot swallow bentonite, administer it by stomach tube at the highest concentration that will flow through the tube.

B. Initiate **SALINE CATHARSIS.** Give **SODIUM SULFATE,** 0.25 gm/kg, and repeat in two hours if no bowel movement has occurred. Magnesium salts are probably contraindicated, because of the risk of magnesium retention in the presence of impaired renal function.

C. Continue administering bentonite suspension and sodium sulfate until the gut has been thoroughly flushed. This may require several days.

3. Secure samples of blood and urine for dipyridyl analysis. (See Confirmation of Diagnosis.)
4. Commence **INTRAVENOUS INFUSIONS** of glucose and electrolyte to minimize toxicant concentrations in the tissues, and expedite excretion of the dipyridyl. Attempt to establish a diuresis of 10-15 liters per day.

   CAUTION: Monitor fluid balance and electrolytes continuously to insure against fluid overload if acute tubular necrosis supervenes.

5. Although cases of paraquat poisoning have been successfully managed by forced diuresis regimens alone, it is more effective to use extracorporeal **HEMODIALYSIS** and/or **HEMOPERFUSION** over specially coated charcoal. This procedure for toxicant removal is best executed in tertiary care centers where blood levels of paraquat can be monitored regularly, and various complications of hemoperfusion can be detected and forestalled. The prognosis is generally good when blood levels do not exceed 0.05 to 0.10 ppm by 24-48 hours after paraquat ingestion.
6. **DO NOT ADMINISTER SUPPLEMENTAL OXYGEN** in paraquat poisoning. Increased levels of alveolar oxygen accelerate the pathologic process in the lung caused by paraquat. Some clinicians recommend maintaining the patient in an atmosphere of 15-16% oxygen as soon as possible, to retard the fibrogenic process.
7. The tubular necrosis produced by large doses of **DIQUAT** may require protracted **EXTRACORPOREAL HEMODIALYSIS.**
8. The topical injuries to mucous membranes produced by ingested dipyridyls are painful and may require topical local anesthetic.
9. The effectiveness of various medicines and procedures in paraquat poisoning remains uncertain. The free-radical scavenger superoxide dismutase is theoretically appropriate as an antidote, but is unproved. Corticosteroids are often given, and may be helpful. There is limited

laboratory evidence supporting the use of propranolol and expectorants: glyceryl guaicolate, anise oil, terpin hydrate, ammonium chloride and potassium iodide. One victim is thought to have benefited from a combination of azathioprine and potassium aminobenzoate. Lung transplant in one case of paraquat poisoning was not successful.

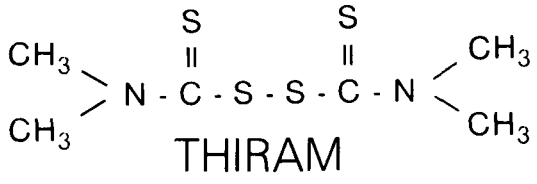
Chapter 8

DITHIOCARBAMATES AND THIOCARBAMATES

CHEMICAL STRUCTURES AND COMMON COMMERCIAL PRODUCTS

These functional classes include many fungicides and herbicides. There are several subclasses:

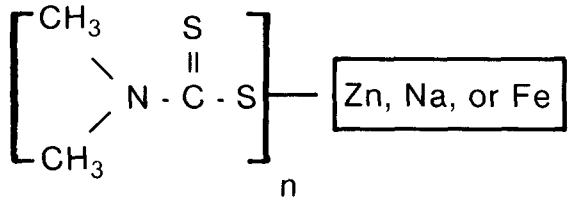
BIS DITHIOCARBAMATES



COMMERCIAL PRODUCTS

thiram (Arasan, Thiramad, Thirasan, Thylate, Tirampa, Pomarsol forte, TMTDS, Thiotex, Fernasan, Nomersan, Tersan, Thiuramin, Tuads, AAtack, Aules, Chipco Thiram 75, Fermide 850, Trametan, Hexathir, Mercuram, Polyram-Ultra, Spotrete, Tripomol, Tersan 75, Tetrapom, Thioknock). Thiram is a fungicide.

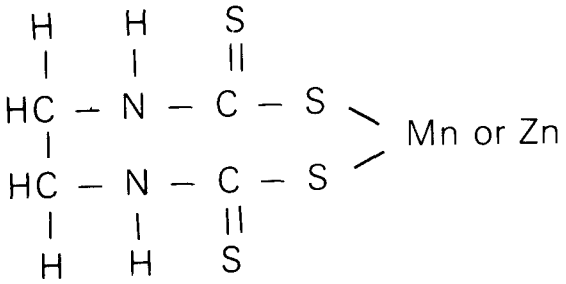
METALLO BIS DITHIOCARBAMATES



COMMERCIAL PRODUCTS

ziram (Z-C Spray, Carbazinc, Corozate, Cuman, Drupina 90, Fuclasin Ultra, Fuklasin, Fungostop, Hexazir, Mezene, Pomarsol Z Forte, Prodaram, Tricarbamix Z, Triscabol, Zerlate, Vancide MZ-96, Zincmate, Ziram Technical, Ziramvis, Zirasan 90, Zirberk, Zirex 90, Ziride); nabam (Dithane D14, Chem Bam, DSE, Nabasan, Parzate, Spring-Bak); ferbam (Ferberk, Hexaferb, Knockmate, Trifungol, Vancide FE-95). These chemicals are fungicides.

ETHYLENE BIS DITHIOCARBAMATES

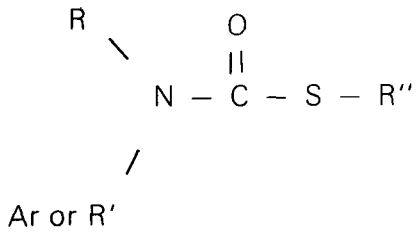


COMMERCIAL PRODUCTS

maneb (Dithane M22, Griffin Manex, Kypman 80, Manebgan, Manesan, Manzate, Nespor, Manzeb, Polyram M, Manzin, Tersan LSR, Trimangol, Tubothane, Vancide Maneb 80); zineb (Aspor, Dipher, Dithane Z-78, Hexathane, Kypzin, Lonacol, Parzate, Polyram Z, Tiezene, Tritoftorol, Zebtox, Zinosan).

These fungicides are often combined with thiram and with various inorganic salts of copper, manganese, and zinc in commercial preparations. Mancozeb (Dithane M45) is essentially a combination of maneb and zineb.

(MONO) THIOCARBAMATES



COMMERCIAL PRODUCTS

butylate (Sutan), cycloate (Ro-Neet), pebulate (Tillam), vernolate (Vernam, Surpass), EPTC (Eptam), diallate (Avadex), triallate (Far-Go, Avadex-BW). These chemicals are selective herbicides.

TOXICOLOGY

Although these agents have chemical similarities, the separate classes are metabolized differently by mammals, and effects on human health are also different.

In general, mammalian toxicity, as measured by oral dosing studies in laboratory rodents, is low. Occupational exposures have, however, caused acute adverse effects, and laboratory investigations have suggested potential chronic effects from some agents.

None of these agents is a cholinesterase inhibitor.

Thiram is irritating to skin and mucous membranes. It has sensitized some individuals, generally after contact with rubber products containing residues of thiram used as a curing agent.

The metallo dithiocarbamates and ethylene dithiocarbamates are moderately irritating to skin and the respiratory mucous membranes following contact with sprays or dusts.

Thiram is the methyl analogue of disulfiram (Antabuse), an agent used to condition alcoholics against beverage alcohol. Much more is known of the toxic effects of disulfiram than of thiram, although the acute toxicity of thiram in laboratory animals is substantially greater. Given to animals in extreme doses, disulfiram has caused gastrointestinal irritation, demyelinization of CNS tissues, and necrosis of liver, splenic, and kidney tissues. Peripheral neuropathy and psychotic reactions have occurred in humans taking large doses of disulfiram regularly.

Functional and anatomic CNS damage has been demonstrated in rats on high chronic dosage regimens of iron and zinc dimethyldithiocarbamates. Because all of these agents are degraded partly to carbon disulfide in the body, a role of this metabolite in neurotoxic effects is suspected.

Both thiram and disulfiram inhibit aldehyde dehydrogenase, and are therefore capable of inducing "Antabuse" reactions in persons who consume beverage alcohol following substantial absorption of dithiocarbamates. Reactions may have occurred rarely in workers who imbibed after extraordinary occupational exposure to thiram. Theoretically, the metallo dithiocarbamates may also predispose to an "Antabuse" reaction. Peripheral vasodilation is the main pathophysiologic feature of the disulfiram-alcohol reaction, probably due to high tissue levels of acetaldehyde. This may occasionally lead to shock, and even more rarely, to myocardial ischemia, cardiac arrhythmias, circulatory failure, and death. Animal experimentation has suggested certain other biochemical mechanisms of toxicity involving reaction products of ethanol and disulfiram.

The ethylene bis dithiocarbamates do not inhibit aldehyde dehydrogenase, and there is no evidence of neurotoxicity from them. They do, however, degrade in the environment, and in mammalian tissues, to ethylene thiourea, a compound known as a goitrogen and carcinogen in laboratory animals. This feature mandates extra care in the protection of harvesters, and in removal of residues from harvested crops.

Except for some moderate irritant effects on skin, respiratory tract, and eyes, the (mono) thiocarbamate herbicides do not appear to be highly toxic. Extreme doses in laboratory animals do produce paralysis. There is a very remote possibility of "Antabuse" reactions from ethanol following extraordinary exposure to these (mono) thiocarbamates. They do not form ethylene thiourea on degradation.

SYMPTOMS AND SIGNS OF POISONING

Thiram and metallo bis dithiocarbamates

Itching, redness, and eczematoid **DERMATITIS** have resulted when predisposed individuals have come into contact with these agents. Inhaled sprays and dusts have caused **NASAL STUFFINESS,** hoarseness, cough, and, rarely, pneumonitis. Repeated contact may produce sensitization. Ingestion of large amounts may produce nausea, **VOMITING,** and **DIARRHEA. HYPOTHERMIA** and ataxia are characteristic of poisoning. Muscle **WEAKNESS** and/or ascending paralysis may progress to respiratory paralysis if absorbed dosages are equivalent to those tested in experimental animals.

The reaction to beverage alcohol that may follow exceptional absorption of thiram and metallo bis dithiocarbamates is characterized by **FLUSHING, HEADACHE, SWEATING,** warm sensations, weakness, nasal congestion, labored breathing, tightness in the chest, tachycardia, palpitation, and hypotension. Extreme dosages may result in shock, convulsions, respiratory depression, and/or unconsciousness. Reactions are not likely to occur unless the absorbed dose is extraordinary.

Ethylene bis dithiocarbamates and (mono) thiocarbamates

Some of these agents are irritating to skin and respiratory mucous membranes, causing **ITCHING, SCRATCHY THROAT, SNEEZING,** and **COUGH,** if excessive amounts of spray or dust are inhaled. Apart from this effect, toxic potential is low. Neurotoxic and post-ethanol "Antabuse" reactions are not known to occur as a result of contact with these particular compounds.

CONFIRMATION OF DIAGNOSIS

Skin testing may be useful in identifying sensitization to these agents.

In general, these compounds are so rapidly metabolized in the body and excreted, that detection in blood is rarely possible. There are methods for detection of ethylene thiourea (from the ethylene bis dithiocarbamates) in urine.

TREATMENT

1. **WASH** contaminating chemical from **SKIN** and **HAIR** with soap and water. Persons sensitive to thiram (rubber-sensitive) should be permanently **REMOVED FROM CONTACT** with compounds of this nature.
2. **FLUSH** contaminant from **EYES** with fresh water for 10-15 minutes.
3. If **THIRAM** or **METALLO DITHIOCARBAMATE** compounds have been **INGESTED:**

A. If vigorous emesis has not already occurred and victim is fully alert, give **SYRUP OF IPECAC,** followed by 1-2 glasses of water to induce vomiting (adults, 12 years and older: 30 ml; children under 12: 15 ml).

CAUTION: **OBSERVE** victim closely **AFTER** administering **IPECAC.** If **CONSCIOUSNESS** level declines or vomiting has not occurred in 15 minutes, empty the stomach by **INTUBATION, ASPIRATION,** and **LAVAGE.**

B. **IF** consciousness level or respiration is **DEPRESSED,** empty the stomach by **INTUBATION, ASPIRATION,** and **LAVAGE,** using all available means to avoid aspiration of vomitus: left lateral Trendelenburg position, frequent aspiration of the pharynx and, in unconscious victims, tracheal intubation (using a cuffed tube) prior to gastric intubation.
After aspiration of the stomach and washing with isotonic saline or sodium bicarbonate, instill 30-50 gm of **ACTIVATED CHARCOAL** in 3-4 ounces of water through the stomach tube to limit absorption of remaining toxicant.

C. If the irritant properties of the toxicant fail to produce a bowel movement in 4 hours, administer **SODIUM** or **MAGNESIUM SULFATE** as a cathartic: 0.25 gm/kg body weight in 1-6 ounces of water.

D. Administer glucose-containing fluids intravenously to accelerate excretion of toxicant.

E. For adults and children over 12 years, inject 1.0 gm **ASCORBIC ACID** (Vitamin C) intravenously at a rate not exceeding 0.2 gm/minute. For children under 12, give 10-20 mg/kg body weight. As a hydrogen-donor, ascorbic acid may have significant antidotal action against absorbed, but unreacted, dithiocarbamate compounds.

F. The victim must **AVOID** consumption of any **ALCOHOLIC** beverage for 3 weeks. Gastrointestinal absorption of these substances is slow, and the enzyme inhibition which they cause is slowly reversed.

4. Management of a reaction to **ETHANOL,** following absorption of a **DITHIOCARBAMATE:**

A. Administer **100% OXYGEN** as long as the reaction continues. Oxygen usually gives substantial relief from the distressing symptoms of vasodilation and hypotension.

CAUTION: If respiration is depressed, administer oxygen by an intermittent positive pressure breathing device and observe the victim closely to maintain pulmonary ventilation mechanically in case of apnea.

B. Gastric evacuation, charcoal administration, catharsis, intravenous fluids, and ascorbic acid administration (3 A,B,C,D, and E) may be appropriate, depending on the amount of dithiocarbamate absorbed, the time interval between exposure and treatment, and the severity of symptoms.

C. If the victim has suffered from arteriosclerosis, myocardial insufficiency, diabetes, neuropathy, cirrhosis, or other severe chronic disease, **OBSERVE** him **CAREFULLY** for 48 hours to insure that complications (especially myocardial infarction, toxic psychosis, and neuropathy) are treated promptly.

5. If an **ETHYLENE BIS DITHIOCARBAMATE,** or (mono) **THIOCARBAMATE** have been ingested:

   A. Give **SYRUP OF IPECAC,** followed by 1-2 glasses of water, to induce vomiting (adults: 30 ml; children under 12 years: 15 ml). Following emesis, administer 30-50 gm **ACTIVATED CHARCOAL** to bind toxicant remaining in the gut.

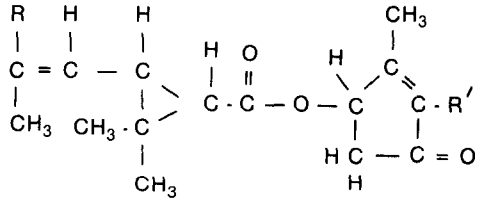
   B. Follow charcoal with **SODIUM** or **MAGNESIUM SULFATE,** 0.25 gm/kg, to remove toxicant from the gut by catharsis.

Chapter 9

PYRETHRUM, PYRETHRINS, PYRETHROIDS, AND PIPERONYL BUTOXIDE

Pyrethrum is the partly refined extract of the chrysanthemum flower which has been used as an insecticide for more than 60 years. Pyrethrins are the insecticidally active ingredients of pyrethrum, now known to consist of keto-alcohol esters of pyrethric and chrysanthemic acids. The alcohols are pyrethrolone, cinerolone, and jasmololone, whose respective esters are known as pyrethrins, cinerins, and jasmolins. Pyrethroids are synthetic compounds based structurally on the pyrethrin molecule but modified to improve stability in the natural environment (light, heat, etc.)

GENERAL CHEMICAL STRUCTURE



COMMON COMMERCIAL PESTICIDE PRODUCTS

Pyrethrins: There are several hundred commercial products containing pyrethrins and pyrethroids. Commonly, these products combine pyrethrins or pyrethroids with a synergist, such as piperonyl butoxide, and an additional pesticide, for increased killing power. Many of these combinations are packaged with a propellant in a spray can or bug-bomb.

Pyrethroids: Allethrin (Pynamin), barthrin, bioresmethrin, cypermethrin (Ripcord), decamethrin, fenothrin, fenpropanate, fenvalerate (Belmark, Pydrin), permethrin (Ambush, Ectiban, Pounce), phthalthrin or tetramethrin (Neo-Pynamin), resmethrin (Synthrin, Chrysron).

TOXICOLOGY

These esters rapidly paralyze the insect nervous system, making them famous for their quick "knockdown" effect. Mammalian toxicity, however, is extraordinarily low for pyrethrins and pyrethroids. Oral LD_{50} values for these compounds in rats are several hundred or thousand mg/kg body weight. There is apparently less efficient absorption of pyrethrins across the GI lining and

skin than across insect chitin, and much more rapid biodegradation (hydrolysis and oxidation) by the mammalian liver than by insect tissues.

Some of the less purified pyrethrum extracts contain allergenic substances that induce attacks of allergic rhinitis and asthma in humans. Rarely, hypersensitivity pneumonitis has followed pyrethrum inhalation.

Administered orally to rodents in extraordinary dosage, pyrethrins and pyrethroids cause nervous irritability, tremors, and motor ataxia. Bloody tears and urinary incontinence have also been observed. Manifestations of toxicity occur at much lower dosage following intravenous administration than after oral dosing. Chronic feeding of these chemicals induces an increase in liver size and bile duct hyperplasia. To date, neither pyrethrins nor pyrethroids have been identified as mutagenic, carcinogenic, or teratogenic.

Piperonyl butoxide inhibits the mixed function oxidase enzymes of the liver which catabolize pyrethrins and pyrethroids. The amount absorbed by humans during ordinary exposure is not likely to affect liver function measurably.

FREQUENT SYMPTOMS AND SIGNS OF UNDUE EXPOSURE

A **STUFFY, RUNNY NOSE** and scratchy throat from inhalation of partly purified pyrethrum extract is the most common adverse effect of these agents. Asthmatic **WHEEZING** may be precipitated by exposure of predisposed individuals.

Sudden bronchospasm, swelling of oral and laryngeal mucous membranes, and shock (anaphylaxis) have been reported after pyrethrum inhalation. Delayed appearance of dyspnea, cough and fever, with patchy lung infiltrates on x-ray, suggest hypersensitivity pneumonitis.

Nervous irritability, tremors, and ataxia have occurred rarely in persons who have had massive inhalation exposure to pyrethrins.

Halocarbon propellents in bug-bomb products present a risk of **CARDIAC ARRHYTHMIA** and possibly fibrillation if inhaled to excess. Hydrocarbons used as solvents in spray products are likely to result in **COUGH, FEVER,** and **CHEST PAIN** (hydrocarbon pneumonitis) if these liquids are inadvertently aspirated.

CONFIRMATION OF DIAGNOSIS

Skin tests sometimes identify sensitivity to pyrethrum. Neither pyrethrins nor pyrethroids inhibit cholinesterase enzymes. There are gas-chromatographic methods for identifying some of these insecticides in environmental samples, but they are not likely to be useful in diagnosing poisoning because of the rapid metabolism of the esters following absorption. There are no methods for identifying urinary metabolites.

TREATMENT

1. **WASH** contaminating pesticide from the **EYE** with copious amounts of water. Wash contaminated **SKIN** with soap and water.
2. For life-threatening allergic reaction to pyrethrum (severe **ASTHMA** or **ANAPHYLAXIS**), give 0.1 to 0.5 ml of 1:1000 **ADRENALIN** intramuscularly, or **slowly** intravenously. Repeat if necessary to relieve respiratory distress and maintain blood pressure. Intravenous **AMINOPHYLLINE** (10 ml, slowly) may be indicated. Give **HYDROCORTISONE** (50-100 mg), or equivalent steroid, intravenously.

   Less severe allergic reactions (rhinitis) can be managed with **ANTIHISTAMINES** and **DECONGESTANTS,** given orally.

   HYPERSENSITIVITY PNEUMONITIS may require oxygen, steroids, antibiotics and several days bedrest, depending on severity.
3. **INGESTION** of a **SMALL AMOUNT** of a pyrethrin or pyrethroid formulation is not likely to cause poisoning. **EXAMINE THE LABEL** to identify additional insecticides, which may be more toxic. **BASE TREATMENT ON THE MOST TOXIC** ingredients.

   A. If a formulation contains **ONLY** pyrethrins, or pyrethroids, and synergists, ingestion of a small amount (up to about 5 mg/kg) is probably best treated by large doses of **ACTIVATED CHARCOAL,** 30-50 gm in 3-4 ounces of water, followed by cathartic doses of **SODIUM** or **MAGNESIUM SULFATE,** 0.25 gm/kg body weight in 1-6 ounces of water.

4. If **LARGE AMOUNTS** of pyrethrin or pyrethroid formulation have been **INGESTED,** the stomach and intestine must be evacuated:

   A. **IF** victim is **ALERT** and respiration is not depressed, give **SYRUP OF IPECAC,** followed by 1-2 glasses of water, to induce vomiting (adults and children 12 years and older: 30 ml; children under 12 years: 15 ml).

      CAUTION: **OBSERVE VICTIM** closely **AFTER** administering **IPECAC.** If consciousness level declines or vomiting has not occurred in 15 minutes, **INTUBATE** the stomach immediately.

      Following emesis, have victim drink a suspension of 30-50 gm **ACTIVATED CHARCOAL** in 3-4 ounces of water to limit absorption of toxicant remaining in the gut.

   B. IF victim is **NOT FULLY ALERT,** empty stomach immediately by **INTUBATION, ASPIRATION,** and **LAVAGE,** using isotonic saline or 5% sodium bicarbonate. Because many pesticides are dissolved in petroleum distillates, emesis and intubation of the stomach involve a risk that solvent will be aspirated, leading to chemical pneumonitis. For this reason:

(a). If victim is unconscious or obtunded and facilities are at hand, insert an **ENDOTRACHEAL TUBE** (cuffed, if available) prior to gastric intubation.

(b). Keep victim's **HEAD BELOW LEVEL OF THE STOMACH** during intubation and lavage (Trendelenburg, or left lateral decubitus, with head of table tipped downward). Keep victim's head turned to left.

(c). **ASPIRATE PHARYNX** as regularly as possible to remove gagged or vomited stomach contents.

(d). After aspiration of gastric contents and washing of stomach, instill 30-50 gm of **ACTIVATED CHARCOAL** in 3-4 ounces of water through stomach tube to limit absorption of remaining toxicant.

(e). If bowel movement has not occurred in 4 hours and patient is fully conscious, give **SODIUM** or **MAGNESIUM SULFATE** as a cathartic: 0.25 gm/kg body weight in 1-6 ounces of water.

5. Do **NOT** administer or instill milk, cream, or other substances containing vegetable or animal fats, which enhance absorption of lipophilic substances, such as pyrethrins and pyrethroids.
6. **DIAZEPAM** (Valium®), 5-10 mg in adults, 0.1 mg/kg in children, given orally or **slowly** IV, should control nervousness and tremors in rare cases having these symptoms after extraordinary exposure to pyrethrins and pyrethroids.

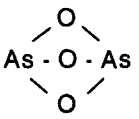
Chapter 10

ARSENICAL PESTICIDES

CHEMICAL STRUCTURES

INORGANIC ARSENICALS

Extremely Toxic



ARSENIC TRIOXIDE

$Na - O - As = O$

SODIUM ARSENITE

$K - O - As = O$

POTASSIUM ARSENITE

$Cu - (O - C(=O) - CH_3)_2$

$3Cu - (As\ O_2)_2$

COPPER ACETOARSENITE

$Ca(As\ O_2)_2$

CALCIUM ARSENITE

$Cu - (AsO_2)$
$|$
OH

COPPER ARSENITE

Highly Toxic

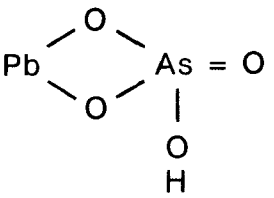
$Ca_3(As\ O_4)_2$

CALCIUM ARSENATE

$(HO)_3\ As = O$

ARSENIC ACID

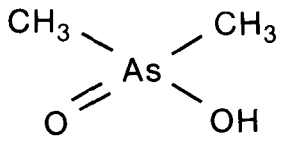
Moderately Toxic



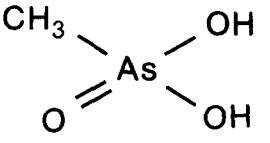
LEAD ARSENATE

ORGANIC ARSENICALS

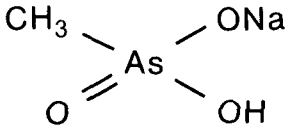
Moderately Toxic



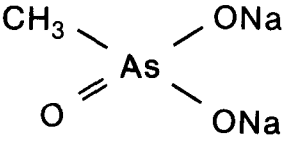
CACODYLIC ACID



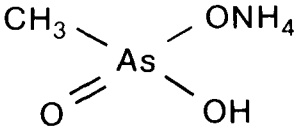
METHANE ARSONIC ACID
(MAA)



MONOSODIUM
METHYL ARSONATE
(MSMA)



DISODIUM
METHYL ARSONATE
(DSMA)



MONOAMMONIUM
METHANE ARSONATE

COMMON COMMERCIAL ARSENIC PRODUCTS

1.	Arsenic trioxide	"White arsenic," arsenious oxide (registered only for ant pastes, veterinary medicinals, and marine antifouling preparations).
2.	Sodium arsenite:	Chem Pels C, Chem-Sen 56, Kill-All, Penite, Prodalumnol Double.
3.	Calcium arsenite:	Mono-calcium arsenite.
4.	Copper arsenite:	Chemonite.
5.	Copper acetoarsenite:	Paris green, Schweinfurt green, emerald green, French green, mitis green.
6.	Arsenic acid:	Desiccant L-10, Hi-Yield Desiccant H-10.
7.	Sodium arsenate:	Jones Ant Killer, Terro Ant Killer.
8.	Calcium arsenate:	Pencal, Spra-cal, Security.
9.	Lead arsenate:	Gypsine, Security, Soprabel, Talbot.
10.	Methane arsonic acid:	MAA.
11.	Monosodium methyl arsonate:	MSMA, Ansar 17OHC, methane arsonate, Ansar 529HC, Arsonate liquid, Bueno 6, Daconate 6, Dal-E-Rad, Herb-All, Merge 823, Mesamate, Target MSMA, Trans-Vert, Weed-E-Rad, Weed-Hoe.
12.	Disodium methyl arsonate:	DSMA, Ansar 8100, methane arsonate, Ansar DSMA liquid, Arrhenal, Arsinyl, Chipco Crab Kleen, Crab-E-Rad, Dal-E-Rad 100, Di-Tac, DMA, DMA 100, Methar, Namate, Sodar, Weed-E-Rad, Weed-E-Rad 360, Weed-E-Rad DMA Powder, Weed-Hoe.
13.	Monoammonium methyl arsonate:	MAMA, monoammonium methanearsonate.
14.	Calcium acid methanearsonate:	CAMA, Super Crab-E-Rad-Calar, Super Dal-E-Rad "Calar".
15.	Cacodylic acid:	Dilic, Phytar 560, Rad-E-Cate 25, Salvo.† [Crystal Chemical Company)

† A product of identical name marketed by Crystal Chemical Company contains 2,4-D as the active ingredient (Chapter 6).

TOXICOLOGY

Although there may be some degree of dermal and pulmonary absorption of arsenical liquids and sprays, ingestion is the route of intake involved in virtually all acute poisonings by the solid arsenicals.

Inhalation of arsine gas (sometimes generated inadvertently in pesticide manufacturing plants) has caused serious illness and death by hemolytic action.

Generally, the organic (methylated) pentavalent arsenicals are considerably less toxic than the trivalent inorganic arsenicals. In fact, methylation is the principal mechanism of detoxification of inorganic arsenicals in mammals. The less soluble inorganic forms (notably lead arsenate, and even arsenic trioxide) present less hazard than the highly soluble salts such as sodium arsenite and copper acetoarsenite. But because gastric pH, gastrointestinal motility, and gut bacterial action can enhance the absorption and toxicity of ingested compounds, it is safest to manage cases of arsenic ingestion as though all forms of arsenic are highly toxic.

Trivalent arsenicals (or, more likely, an arsenious acid metabolite) bind efficiently to the functional thiol groups of many tissue components, including enzymes. The affinity for thiol groups in keratin accounts for the accumulation of arsenic in skin, nails, and hair in cases of chronic poisoning. When absorbed across the gut wall, these arsenicals injure the splanchnic vasculature, causing abdominal pain, colic, and diarrhea. Once absorbed into the blood, they cause toxic damage to the liver, kidneys, brain, bone marrow, and peripheral nerves. Liver injury is manifest as hepatomegaly, jaundice, and increase in circulating hepatocellular enzymes LDH and GOT. Renal damage is reflected in albuminuria, hematuria, pyuria, cylindruria, then azotemia. Acute tubular necrosis may occur in severe poisoning. Injury to blood-forming tissues can take the form of agranulocytosis, aplastic anemia, thrombocytopenia, or pancytopenia. Toxic encephalopathy may be manifest as speech and behavioral disturbances. Peripheral neuropathy occurs in both acute and chronic forms.

Sequelae of arsenic poisoning include cirrhosis, hypoplastic bone marrow, renal insufficiency, and peripheral neuropathy. Excessive exposures to arsenicals have caused hyperkeratosis and skin cancers. Excessive inhalation of dusts may cause bronchitis and pneumonia; protracted inhalation has been associated epidemiologically with increased occurrence of lung cancer.

FREQUENT SYMPTOMS AND SIGNS OF POISONING

ACUTE arsenic poisoning

COLIC, BURNING ABDOMINAL PAIN, VOMITING, and **WATERY** or **BLOODY DIARRHEA** are the primary manifestations of ingestion of solid arsenical poisons. Symptoms following ingestion of inorganic arsenicals are much more severe than those resulting from ingestion of pentavalent organic arsenicals. Symptoms are sometimes delayed for minutes or even hours after ingestion. **HEADACHE, DIZZINESS, MUSCLE SPASMS, DELIRIUM,**

and sometimes **CONVULSIONS** reflect direct injury to the central nervous system, as well as extracellular electrolyte disturbances and shock. A **GARLIC ODOR** to the breath and feces helps to identify the responsible toxicant. **SHOCK, TOXIC NEPHROSIS, HEPATITIS** (hepatomegaly and jaundice), and **NEUROLOGIC INJURY** (delirium, paralysis, respiratory depression) may progress to a fatal outcome.

SUBACUTE arsenic poisoning

Repeated intakes less than those necessary to produce severe acute symptoms are known to cause **CHRONIC HEADACHE, ABDOMINAL DISTRESS, SALIVATION, LOW-GRADE FEVER,** and **PERSISTENT** symptoms of **UPPER RESPIRATORY IRRITATION.** Stomatitis and garlicky breath are characteristic.

CHRONIC arsenic poisoning

Prolonged low intakes of arsenic cause peripheral neuropathy (**PARESTHESIAE, PAIN,** anesthesia, paresis, ataxia), encephalopathy (**APATHY,** disorientation), dermatologic disorders (**KERATOSES,** pigmentation, eczema, brittle nails, loss of hair), toxic hepatitis (**HEPATOMEGALY,** sometimes progressing to cirrhosis with ascites), and bone marrow injury (**ANEMIA,** leukopenia, **WEAKNESS**). Local **EDEMA,** frequently of the eyelids, characterizes some poisonings.

ACUTE arsine gas poisoning

The gas causes hemolysis of red blood cells, in addition to inhibition of cellular sulfhydryl respiratory enzymes. Hemolysis causes **HEMOGLOBINEMIA** and **HEMOGLOBINURIA.** This in turn, causes acute tubular necrosis. Early symptoms of poisoning (**CHILLS,** weakness, burning sensations) are followed by abdominal **CRAMPS,** vomiting, and prostration. Failing renal function deteriorates to **ANURIA.**

CONFIRMATION OF DIAGNOSIS

Measurement of 24-hour urinary excretion of arsenic is probably the best way to confirm excessive arsenic absorption, although methods for blood arsenic concentration are available. Persons on ordinary diets usually excrete less than 20 μg/day but diets rich in seafood may generate as much as 200 μg/day. Excretions above 100 μg/day should be viewed with suspicion and tests should be repeated. Excretions above 200 μg/day reflect a toxic intake, unless seafood was ingested. (The arsenic in seafood is apparently bound firmly to an organic moiety that renders the arsenic essentially nontoxic and highly excretable.)

The qualitative Gutzeit test for arsenic in the urine is available in most hospital laboratories, and is useful in identifying acute poisonings promptly.

Chronic storage of arsenic can be detected by analysis of hair or fingernails.

The hemoglobinuria caused by arsine is identified by finding free hemoglobin in fresh urine.

TREATMENT OF POISONING BY SOLID ARSENICALS

1. Flush contaminated **EYES, HAIR** and **SKIN** with copious amounts of fresh water. **WASH SKIN** and **HAIR** with soap and water.
2. In poisonings by **INGESTED ARSENICALS**

   A. **INTUBATE** the stomach, **ASPIRATE,** and **LAVAGE** with 3 liters of isotonic saline or 5% sodium bicarbonate. Use all possible precautions to avoid aspiration of vomitus:

      (1) If victim is unconscious or obtunded, insert an **ENDOTRACHEAL TUBE** (cuffed, if available) prior to gastric intubation.

      (2) Keep victim's **HEAD BELOW LEVEL OF THE STOMACH** during intubation (Trendelenburg, or left lateral decubitus, with head of table tipped downward). Keep victim's head turned to the left.

      (3) **ASPIRATE** pharynx as regularly as possible to remove gagged or vomited stomach contents.

   B. After lavage, **INSTILL** 30-50 gm **ACTIVATED CHARCOAL** in the smallest amount of water necessary to deliver the charcoal through the tube.

   C. If diarrhea or colic has not ensued within an hour of gastric lavage and charcoal administration, give **SODIUM SULFATE** as a cathartic 0.25 gm/kg body weight in 1-6 ounces of water.

3. An **ABDOMINAL X-RAY** film is useful in detecting concretions of the less soluble arsenicals (As_2O_3 and lead arsenate) in the gut. If not removed these may become a repository of slowly absorbed toxicant.
4. Administer **INTRAVENOUS ELECTROLYTE** and **GLUCOSE** solutions to maintain hydration and to accelerate toxicant excretion. **COMBAT SHOCK** with **TRANSFUSIONS** of **WHOLE BLOOD,** and by inhalation of 100% **OXYGEN.**

   CAUTION: Monitor urine flow via catheter. Monitor fluid balance, body weight, and/or central venous pressure to guard against fluid overload that may result if tubular necrosis (anuria) supervenes.

5. Administer **DIMERCAPROL** (BAL) and **PENICILLAMINE** to accelerate arsenic excretion.

   A. Give dimercaprol, 3-5 mg/kg q4h intramuscularly until abdominal pain and diarrhea subside and patient is regularly passing administered charcoal in the feces. **IF** victim is **ALLERGIC** to

PENICILLIN, continue dimercaprol therapy at 3-5 mg/kg q6h × 4 doses, then q12h × 2 doses, then q24h × 10 doses, monitoring urine arsenic excretion periodically to judge effectiveness.

CAUTION: **DIMERCAPROL** can cause troublesome side effects (hypertension, tachycardia, nausea, headache, paresthesiae and pain, lacrimation, sweating, anxiety, and restlessness). Although usually not so severe as to preclude treatment, they may require antihistaminic therapy.

B. **IF** victim is **NOT ALLERGIC** to **PENICILLIN,** oral **d-PENICILLAMINE** is the therapy of choice and should **REPLACE** dimercaprol treatment as soon as the feces are laden with charcoal, limiting gut absorption of arsenic. Adult dosage is 0.5 gm four times daily (2 gm/day), given before meals, for 5 days. Dosage for children is 0.025 gm/kg four times daily, not to exceed 2 gm/day for 5 days.

CAUTION: Although oral d-penicillamine therapy is usually better tolerated than intramuscular dimercaprol, serious reactions to it have occurred: the most common has been maculopapular rash, with fever, leukopenia, thrombocytopenia, eosinophilia, arthralgia and lymphadenopathy. It has also induced the nephrotic syndrome on occasion, and has caused thrombophlebitis, cheilosis, angioneurotic edema, and even fatal agranulocytosis in particular patients given the drug over long periods for conditions unrelated to arsenic poisoning. Penicillin sensitive individuals are likely to be sensitive to d-penicillamine.

(a). A single 5 day course of d-penicillamine therapy is usually sufficient. However, if symptoms recur after treatment, additional d-penicillamine should be given at a dosage just sufficient to abolish symptoms.

6. Intense abdominal pain may require morphine (adults, 12 years and older: 4-15 mg; children under 12 years: 0.1-0.2 mg/kg).
7. Severe poisoning (especially when renal function is impaired) may require **HEMODIALYSIS** to remove arsenic combined with dimercaprol from the blood, and to control extracellular fluid composition. **HEMOPERFUSION** may be useful, but its effectiveness has not been reported.

TREATMENT OF POISONING BY ARSINE GAS

1. **REMOVE** victim to **FRESH AIR.**
2. **MAINTAIN RESPIRATION** and **CIRCULATION** by resuscitation and cardiac massage, if necessary.

3. Administer **INTRAVENOUS FLUIDS** promptly to dilute free hemoglobin and minimize tubular injury. Include enough sodium bicarbonate to keep the urine alkaline.

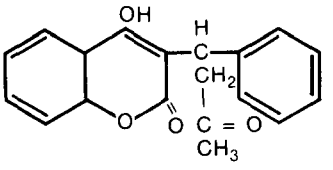
   CAUTION: Monitor urine flow via catheter. Monitor fluid balance, body weight, and/or central venous pressure to guard against fluid overload resulting from acute tubular necrosis.

4. Administer **DIMERCAPROL** as recommended in 5A even though it has only limited effect in arsine poisoning.
5. **EXCHANGE BLOOD TRANSFUSIONS** and **PERITONEAL DIALYSIS** have saved the lives of victims of arsine poisoning suffering acute tubular necrosis.

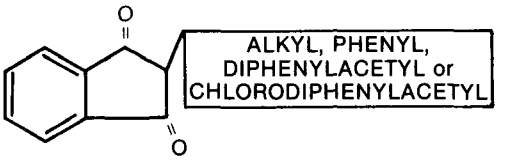
Chapter 11

RODENTICIDES

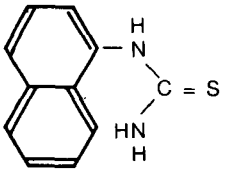
STRUCTURES OF PRINCIPAL COMPOUNDS



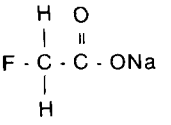
WARFARIN



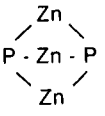
1,3 INDANDIONE



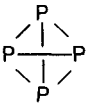
α - NAPHTHYL
THIOUREA



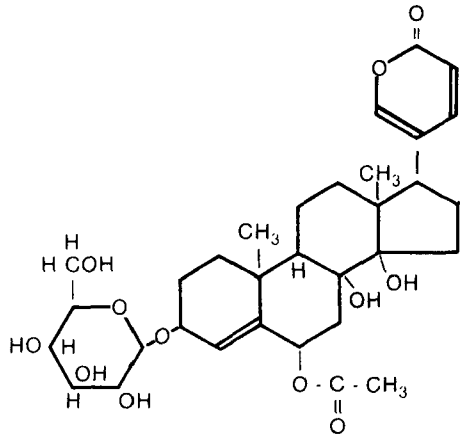
SODIUM
FLUOROACETATE



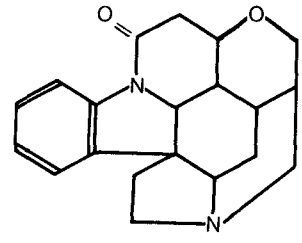
ZINC
PHOSPHIDE



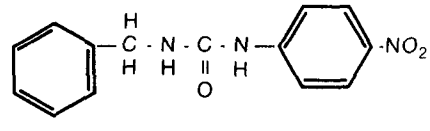
YELLOW
PHOSPHORUS



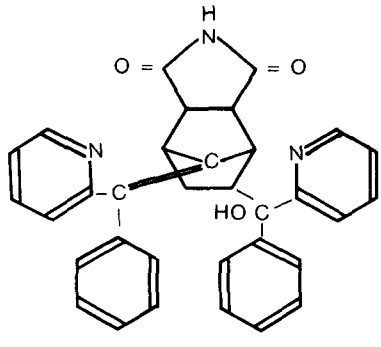
SCILLIROSIDE
(Active principle of Red Squill)



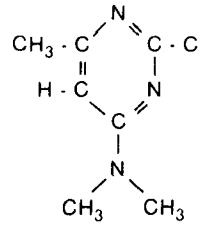
STRYCHNINE



RH- 787 (Active ingredient of VACOR and DLP-787)



NORBORMIDE



CRIMIDINE

COMMON COMMERCIAL RODENTICIDE PRODUCTS

Coumarins: warfarin, coumafene, zoocoumarin (Kypfarin, Ratox, RAX, Rodex, Tox-Hid, Warfarin Plus); coumafuryl (Tomarin, Fumarin); bromadiolone (Bromone, Super-Caid, Ratimus), coumachlor (Tomorin).

Indandiones: diphacinone (Diphacin, Promar, Ramik); chlorophacinone (Caid, Drat, Liphadione, Microzul, Ramucide, Ratomet, Raviac, Rozol, Topitox); pindone or pivaldione (Pival, Pivacin, Pivalyn, Tri-ban).

Other anticoagulant rodenticides of different structure: difenacoum (Ratak); brodifacoum (Talon).

Sodium fluoroacetate: 1080, Fratol, Yasoknock.

Zinc phosphide: Phosvin, Zinc-Tox.

Yellow phosphorus and **strychnine** have limited use and are generally identified by these long established common names.

Crimidine: Castrix.

RH-787: This product is no longer available for sale, but existing stocks present a continuing threat of poisoning. Commercial products are: Vacor Rat Killer (2% RH-787 in vehicle resembling corn meal); DLP-787 Bait (2% RH-787 in vehicle resembling corn meal); DLP-787 House Mouse Tracking Powder (10% RH-787 in a light green powder).

Red squill: Dethdiet, Rodine.

Antu: Krysid.

Norbormide: Shoxin, Raticate.

TOXICOLOGY

Rodent poisons are generally added to baits, i.e., grain or paste designed to encourage consumption. Safety for pets, domestic animals, and humans depends on the toxicity of the agents, concentration of active ingredients in the baits, and the likelihood that a toxic dose will be consumed by nontarget species. The *coumarins* are reasonably effective against pest rodents and have a good safety record. This is due mainly to the low concentration of active ingredient in the bait: about 100 gm of the commercial bait must be ingested to yield 25 mg of anticoagulant. This is important in evaluating suspected poisonings by anticoagulants, which are the most widely available rodenticides for public use.

Very small amounts of the extremely toxic rodenticides—sodium fluoroacetate, zinc phosphide, crimidine, strychnine, and yellow phosphorus—can cause fatal poisoning.

Vacor should be considered highly toxic. Ingestion of less than 1 gm by an adult has caused severe poisoning.

Antu, red squill, and norbormide present considerably less toxic hazard to humans and to domestic animals.

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† A rodenticide of identical trade name is still available in some areas which contains thallium sulfate as the active ingredient. Use of thallium in the United States is now restricted.

Coumarins, indandiones, and other anticoagulants: Gastrointestinal absorption of these toxicants is efficient, beginning within minutes of ingestion and continuing for 2 to 3 days. Apparently warfarin can also be absorbed across the skin, although the circumstances under which this occurred were extraordinary.

These agents depress the hepatic synthesis of substances essential to blood clotting: prothrombin (factor II) and factors VII, IX, and X. The antiprothrombin effect is best known, and provides the basis for detection and assessment of clinical poisoning. Direct damage to capillary permeability occurs concurrently. The ultimate effect of these actions is to induce widespread internal hemorrhage. This generally occurs in the rodent after several days of bait ingestion, although the modern products (diphacinone, chlorophacinone, pindone, difenacoum, and brodifacoum) may be lethal after fewer feedings. These modern agents should be considered more toxic than warfarin.

In rare instances, coumarin-type anticoagulants have caused ecchymosis and extensive skin necrosis in humans for reasons not related to excessive dosage.

Unlike the coumarin anticoagulants, the indandiones cause symptoms and signs of neurologic and cardiopulmonary injury in laboratory rats; these often lead to death before hemorrhage occurs. These actions may account for the somewhat greater toxicity of this class of anticoagulants. Neither cardiopulmonary nor neurologic symptoms or signs have been reported in human poisonings.

Lengthened prothrombin time from a toxic dose is usually evident within 24 hours of ingestion and reaches a maximum in 36 to 72 hours. Without intervention, hypoprothrombinemia may persist 10 to 15 days, depending on the agent and dosage. Prothrombin depression occurs in response to doses much lower than those necessary to cause hemorrhage.

Sodium fluoroacetate: the fluorocitrate metabolite of this poison blocks energy production in mammalian cells at the level of the tricarboxylic acid cycle. The critical sites of toxic effect in humans are the myocardium (where ventricular fibrillation is the usual cause of death) and the brain, where seizures are induced and respiration is depressed. Seizures, respiratory depression, and ventricular fibrillation are all causes of death.

Zinc phosphide: this inorganic compound produces severe gastrointestinal irritation. It degrades in the gut to phosphine gas which, when absorbed, causes pulmonary edema and severe liver, kidney, CNS, and myocardial injury.

Yellow phosphorus: this agent causes severe gastrointestinal irritation resulting in vomiting, diarrhea, and melena. Circulatory collapse may occur and prove irreversible. Liver necrosis and acute renal tubular necrosis are equally ominous threats to life. Hemorrhage, from hypoprothrombinemia, and cardiac arrest or fibrillation, account for some deaths.

Strychnine: this natural poison acts directly on the cells of the brain and spinal cord to cause convulsions. Death is caused by convulsive interference with pulmonary gas exchange, by depression of respiratory center activity, or both.

Crimidine: this is a synthetic pesticide which, although unrelated chemically to strychnine, exerts toxic effects similar to those of strychnine, producing violent convulsions and secondary tissue anoxia by its action on the CNS.

Vacor, DLP-787: the exact mechanism of RH-787 toxicity is not known although one established effect in rats is interference with nicotinamide metabolism. RH-787 has no anticoagulant action. Symptoms and signs in poisoned animals suggest toxic actions on the brain, peripheral nerves, myoneural junctions, pancreatic islet tissues, autonomic nervous system, and the conducting tissues of the heart. Abnormalities of renal and vascular function may be direct effects of poisoning, or they may reflect metabolic and autonomic nervous system disturbances, impaired vascular reactivity in particular.

Red squill: this biological agent is unlikely to present a serious toxic hazard to humans or other vomiting species, because 1) it usually induces prompt emesis, 2) it is poorly absorbed from the gut, and 3) the active principles are in low concentration, and are rapidly excreted. Natural squill contains digitalis-like glycosides, which might, theoretically, produce manifestations of digitalization in humans. The glycoside known as scilliroside is the probable cause of convulsive death in the rat; convulsions have not been observed in human poisonings.

Antu: this agent exhibits selective toxicity for the rat, causing pulmonary edema and pleural effusion. Only one human poisoning is recorded, and it was induced by a large suicidal dose. Vomiting was followed by dyspnea, cyanosis, and pulmonary râles, presumably reflecting pulmonary edema. The patient recovered.

Norbormide: this is selectively toxic to Norway and roof rats, which it kills by inducing a generalized, sudden, and intense vasoconstriction. Other varieties of rats are resistant, and the chemical is only moderately toxic to other mammals, including humans. Oral doses of 300 mg cause transient lowering of blood pressure and body temperature in humans.

FREQUENT SYMPTOMS AND SIGNS OF POISONING

Coumarins, indandiones, and other anticoagulants: In most cases of ingestion of anticoagulants, victims have remained asymptomatic, due to the small dosage taken. Even in cases involving ingestion of substantial amounts of anticoagulant compound (more often medication than rodenticide), hypoprothrombinemia has occurred without symptoms of poisoning. Hemorrhage appears only when extraordinary amounts have been absorbed. In reported cases, the anticoagulants were either taken deliberately, were absorbed over long periods out of neglect of elementary hygienic standards, or were ingested by starving indigents who used quantities of rodent bait as food.

Victims of large doses exhibit **HEMATURIA, NOSEBLEED, HEMATOMATA, BLEEDING GUMS,** and **MELENA. ABDOMINAL PAIN** and **BACK PAIN** probably reflect hemorrhage in the abdominal and retroperitoneal tissues. **WEAKNESS** occurs as a result of **ANEMIA. RENAL COLIC**

often complicates severe hematuria. Nasal and gastrointestinal hemorrhages have occasionally caused death from exsanguination.

Sodium fluoroacetate: A delay of several minutes or even hours may be expected before symptoms appear. Epigastric distress and vomiting often occur. Apprehension, **PARESTHESIAE** and hallucinations are the usual premonitory symptoms, leading to epileptiform **CONVULSIONS. CARDIAC IRREGULARITIES** (ectopic beats, pulsus alternans, ventricular tachycardia and fibrillation) appear after seizures commence. These are frequently fatal.

Zinc phosphide: Intense **NAUSEA,** abdominal pain, excitement, and chills are early symptoms. Tightness in the chest, **DYSPNEA** and **COUGH,** productive of **FROTHY SPUTUM,** reflect pulmonary edema. **SHOCK** from toxic myocarditis is common. If these conditions are survived, **JAUNDICE** from liver necrosis, and **ANURIA** from renal tubular injury are later complications. Hypocalcemic **TETANY** and **PURPURA** have occurred in some poisonings.

Yellow phosphorus: BURNING PAIN in the throat, chest, and abdomen reflect severe mucosal irritation. Vomiting and diarrhea ensue. Breath has garlicky odor. Feces may luminesce and "smoke" from phosphorus fumes. **SHOCK** often progresses to death in 1 to 2 days. The patient who survives may then be relatively symptom-free for several hours or even days, after which the delayed manifestations appear due to liver, CNS, myocardial and renal injury. Nausea and **VOMITING** persist. **HEMORRHAGE** at various sites reflects mainly depression of clotting-factor synthesis in the liver. **SHOCK** may be due to hemorrhage and/or toxic myocarditis. **CONVULSIONS,** delirium, and coma are common. **ANURIA** usually ensues as a result of direct nephrotoxic effect of phosphorus, enhanced by biliary nephrosis (hepatorenal syndrome).

Strychnine: Within 10 to 60 minutes of ingestion of an adequate dose (as little as 16 mg), the victim suffers **VIOLENT CONVULSIONS** caused by clonic, then tonic contraction of all the skeletal muscles of the body. Cyanosis develops promptly. Brief periods of relaxation may occur, followed by even more severe seizures. Opisthotonus is common, and the muscles of the face are drawn into a grimace. Death is usually due to **ASPHYXIA,** a consequence of convulsive spasm of the respiratory muscles.

Crimidine: Ingestion is followed promptly by **VIOLENT CONVULSIONS,** essentially like those caused by strychnine (see preceding paragraph).

Vacor, DLP-787: Minimum toxic and lethal doses in humans are not known. Ingested amounts less than one gram have proved severely toxic.

Symptoms may not appear for 4 to 48 hours after ingestion. Earliest symptoms are usually **NAUSEA,** vomiting, abdominal cramps, **CHILLS,** and **CONFUSION.** Later manifestations are aching and fine tremors of the extremities, dilated pupils, plantar hyperesthesia, **MUSCLE WEAKNESS,** dysphagia, chest pain, postural hypotension, anorexia, diarrhea, urinary retention, and **HYPOTHERMIA.** Subsequently, **DIABETES MELLITUS** commonly develops, manifest as glycosuria, polyuria, ketoacidosis, and dehydration. Death may result from respiratory failure, cardiovascular collapse, or ketoacidosis. Survivors of the acute phase of the poisoning are often

left with permanent sequelae: postural hypotension, diabetes mellitus, bladder dystonia (retention or frequency), bowel dystonia (constipation or diarrhea), and peripheral neuropathy.

Abnormal laboratory findings include hyperglycemia, glycosuria, ketosis (acidosis and electrolyte disturbances), and elevation of serum amylase and lipase activities.

Red squill: Nausea and **VOMITING** are the predominant effects. In the unlikely event that significant amounts of glycosides are absorbed, cardiac arrhythmias and slowing might be expected. Convulsions have not been observed in humans as they have in rats.

Antu: Pulmonary râles, **DYSPNEA** and cyanosis may be expected following ingestion of large amounts.

Norbormide: No human poisonings have been reported. Ingestion of 300 mg by an individual caused a slight fall in body temperature and blood pressure.

CONFIRMATION OF DIAGNOSIS

Coumarins, indandiones, and other anticoagulants: Increase of the prothrombin time (Quick) reflects a reduction in serum prothrombin concentration, and occurs in response to physiologically significant absorption of these toxicants. This widely available clinical test offers a sensitive and reliable diagnostic method for detecting a toxic effect of these compounds. Readily detectable change in prothrombin time appears within 24 to 48 hours of ingestion of anticoagulant.

Zinc phosphide and phosphorus: Zinc phosphide smells like rotten fish and imparts a garlicky odor to the breath. Luminescence of vomitus or feces indicates yellow phosphorus ingestion.

Other rodenticides: There are analytical methods available for identifying some remaining rodenticides in food or liquids suspected of contamination, in gastric contents, and sometimes in blood and urine. (See Sunshine, I., Handbook of Analytical Toxicology (1969) published by the Chemical Rubber Company, 18901 Cranwood Parkway, Cleveland, Ohio 44128.) These methods are generally complex and must be performed by a toxicology laboratory experienced in these tests. Analysis is often time-consuming, limiting the usefulness of the results in clinical management. Analyses may be important, however, for legal reasons.

TREATMENT

Coumarins, indandiones, and other anticoagulants

1. If only a few grains of anticoagulant bait have been ingested by an adult or child having no antecedent liver or blood clotting disease, treatment is probably unnecessary.

A. If there is uncertainty about the amount of bait ingested or the general health of the patient, **PHYTONADIONE** (vitamin K_1, Mephyton®) given orally protects against the anticoagulant effect of these rodenticides. For adults, give 15-25 mg; for children under 12, give 5-10 mg. Alternatively, a colloidal solution of phytonadione, Aquamephyton®, may be given intramuscularly. For adults, give 5-10 mg; for children under 12, give 1-5 mg.

CAUTION: **PHYTONADIONE,** specifically, is required. Neither vitamin K_3 (menadione, Hykinone®) nor vitamin K_4 (menadiol) is an antidote for these anticoagulants.

B. Whatever the doage, insure that patients (especially children) will be **CAREFULLY OBSERVED** for 4-5 days after ingestion. The indandiones and the more recently introduced anticoagulants have toxic effects apart from anticoagulation that are not yet well defined.

2. If **LARGE AMOUNTS** of anticoagulant were ingested in the preceding 2-3 hours, **INDUCE VOMITING** with **SYRUP OF IPECAC,** followed by 1-2 glasses of water. For adults, give 30 ml; for children under 12, 15 ml. Following emesis, give 30-50 gm **ACTIVATED CHARCOAL** in 4-6 ounces of water to limit absorption of anticoagulant remaining in the gut.
3. If anticoagulant has been ingested any time in the preceding 15 days, determination of **PROTHROMBIN TIME** provides a basis for judging the severity of poisoning.

   A. If the prothrombin time is lengthened, give Aquamephyton®, intramuscularly: **adult dose,** 5-10 mg; **child's dose:** 1-5 mg. Decide dose according to the degree of prothrombin time lengthening and, in children, the age and weight of the child.
   B. Repeat prothrombin time in 24 hours. If it has not decreased from the original value, repeat Aquamephyton® dosage.

4. If victim shows **SYMPTOMS** or **SIGNS** of **ANTICOAGULANT POISONING** (bleeding) in addition to hypoprothrombinemia, administer Aquamephyton® intramuscularly, up to 25 mg in the adult, and up to 0.6 mg/kg in children under 12 years. Phytonadione administration may be repeated in 24 hours if bleeding continues.

   A. In cases of **SEVERE BLEEDING,** it may be necessary to give Aquamephyton® intravenously. This is especially true if the bleeding tendency is so severe that intramuscular injection is likely to cause hematoma formation. Dosage is up to 25 mg in the adult, up to 0.6 mg/kg in children under 12 years. Repeat this dose in 24 hours if bleeding continues. Inject at rates not exceeding 5% of the total dose per minute. **INTRAVENOUS INFUSION** of the Aquamephyton® **DILUTED IN SALINE OR GLUCOSE SOLUTION** is recommended. Bleeding is usually controlled in 3-6 hours.

CAUTION: Adverse reactions, some fatal, have occurred from **INTRAVENOUS** phytonadione injections, even when recommended dosage limits and injection rates were observed. For this reason, the **INTRAVENOUS** route should be used **ONLY IN** cases of **SEVERE POISONING.** Flushing, dizziness, hypotension, dyspnea, and cyanosis have characterized adverse reactions.

B. Antidotal therapy **IN** cases of **SEVERE BLEEDING** should be supplemented with **TRANSFUSIONS** of **FRESH BLOOD** or **FRESH FROZEN PLASMA.** Use of fresh blood or plasma represents the most rapidly effective method of stopping hemorrhage due to these anticoagulants.

C. Determine **PROTHROMBIN TIMES** (and hemoglobin concentrations, if appropriate) every 6-12 hours to assess effectiveness of antihemorrhagic measures.

D. When normal blood coagulation is restored, it may be advisable to drain large hematomata.

E. Ferrous sulfate therapy may be appropriate in the recuperative period to rebuild lost erythrocyte mass.

Sodium fluoroacetate

1. If this substance has been **INGESTED,** empty the stomach immediately by **INTUBATION, ASPIRATION,** and **LAVAGE,** using 5% sodium bicarbonate. Before withdrawing the lavage tube, instill a slurry of 30-50 gm **ACTIVATED CHARCOAL.**
2. **MONITOR** cardiac rhythm by continuous **ELECTROCARDIOGRAPHY.**
3. **MONOACETIN** (glyceryl monoacetate) has antidotal properties in experimental animals. The liberated acetate competes successfully with fluorocitrate in the tricarboxylic acid cycle. However, there is no sterile pharmaceutical preparation of this compound: high-quality, fresh laboratory grade material must be used.

   A. If victim is fully conscious and not convulsing, administer 100 ml of monoacetin in 500 ml of water, by mouth. Repeat in one hour. (Arena, J. M. *Poisoning,* 1970.)

   B. If victim is obtunded, unconscious, or convulsing, give 0.1-0.5 ml/kg of undiluted monoacetin by deep intramuscular injection every half hour for 4-6 hours, rotating the injection sites to minimize pain and swelling. Monoacetin can also be given intravenously on the same schedule, using a 1:5 dilution in sterile isotonic saline.

CAUTION: The use of parenteral monoacetin is hazardous. Technical grade material contains glycerin which, in adequate dosage, may cause hemolysis, hypotension, convulsions, and paralysis. If a nonsterile solution is injected, the monoacetin should be cultured to guide the administration of antibiotics if sepsis develops.

4. **CONTROL CONVULSIONS**

A. Administer 100% **OXYGEN** by positive pressure to provide as much pulmonary gas exchange as possible, despite seizures.

B. **ANTICONVULSANT DRUGS**

CAUTION: It may be difficult or impossible to stop the seizure activity without stopping respiration. Be prepared to maintain pulmonary ventilation mechanically. Tracheostomy may be necessary if seizures are prolonged.

(a). Diazepam (VALIUM®) usually controls mild convulsions. For adults, give 5-10 mg, slowly, intravenously; for children under 6 years or 23 kg body weight, give 0.1 mg/kg body weight, slowly, IV. Repeat in 4-6 hours if necessary.

(b). Pentobarbital may be needed in addition to control severe convulsions. Dosage: 5 mg/kg body weight, or 0.20 ml/kg body weight, using the usual 2.5% solution. If possible, inject solution intravenously, at a rate not exceeding 25 mg (one ml) per minute until convulsions are controlled. If intravenous administration is not possible, give total dose by deep intramuscular injection, not exceeding 5 mg/kg body weight (0.20 ml/kg of 2.5% solution).

(c). Phenytoin (DILANTIN®) has prolonged anticonvulsant action. Dosage: loading dose 15-18 mg/kg. Maintenance dose 4-8 mg/kg q 4-24 hours as needed. Intramuscular administration is not recommended. Give IV slowly at no more than 20% total dose per minute.

(d). Thiopental (PENTOTHAL®), by continuous intravenous infusion, may help to control severe seizures. Dissolve one gram in 500 ml of glucose solution, and infuse at a rate just sufficient to stop seizures.

CAUTION: Laryngospasm is a complication of anticonvulsant therapy and may require tracheostomy.

(e). In some instances, curarization with succinylcholine or a similar agent is required to stop convulsions. This requires tracheal intubation or tracheostomy and mechanical pulmonary ventilation, with regular monitoring of blood gases and pH.

5. Many other agents tested in fluoroacetate poisoning are **NOT EFFECTIVE:** sodium acetate, calcium chloride, ethanol, propylene glycol, digitalis glycosides, di- and tri-acetates of glycerol.
6. Administer IV electrolyte solutions cautiously to avoid fluid overload in presence of a weak and irritable myocardium.

Zinc phosphide and yellow phosphorus

1. **WASH SKIN BURNS** due to yellow phosphorus with water and a 1% copper sulfate solution. Make sure all particles of phosphorus have been removed. Cover burned area with ointment.
2. Poisonings by **INGESTED** yellow phosphorus or zinc phosphide are extremely difficult to manage. The mortality rate of 50% is the result of either shock or pulmonary edema in the first few hours or days, or coma, seizures, and/or liver, kidney and myocardial damage in the ensuing days or weeks.

   CAUTION: Highly toxic phosphine gas may evolve from emesis, lavage fluid, and feces of victims of these poisons. The patient's room should be well ventilated.

   A. **INTUBATE** and **ASPIRATE** the stomach. **LAVAGE** with several quarts of 1:5000 potassium permanganate solution.

      CAUTION: Persons attending victim must avoid contact with yellow phosphorus, which causes skin burns.

   B. Combat shock and acidosis with **TRANSFUSIONS** of whole blood and **INFUSIONS** of glucose and electrolyte solutions. Monitor fluid balance and central venous pressure to avoid fluid overload. Monitor blood electrolytes and pH to guide choice of intravenous solutions.
   C. Administer 100% **OXYGEN** by mask or nasal tube.
   D. Combat pulmonary edema with intermittent or continuous **POSITIVE PRESSURE OXYGEN.**
   E. **MONITOR URINE** albumin, glucose, and sediment to detect early renal injury. Monitor EKG to detect myocardial impairment. Monitor serum alkaline phosphatase, LDH, prothrombin time, and bilirubin to evaluate liver damage.
   F. Include Aquamephyton® (vitamin K_1) in intravenous infusions if prothrombin level declines. Dosage of 10-50 mg per day may be required. Administer Aquamephyton® slowly, intravenously; stop infusion if flushing, cyanosis, paresthesiae, hypotension, or dyspnea occurs.
   G. **MORPHINE SULFATE,** 8-16 mg every few hours may be necessary to control pain. Child's dose: 0.1-0.2 mg/kg.
   H. **CONTROL CONVULSIONS** with diazepam, barbiturates, and/or phenytoin as suggested under *treatment of sodium fluoroacetate poisoning.*
   I. **CORTICOSTEROIDS** at high dosages may be beneficial.

Strychnine and crimidine

1. Administer **100% OXYGEN** by positive pressure.
2. **CONTROL CONVULSIONS.** This may be attempted with intravenous diazepam, barbiturates, and/or phenytoin, as described under *management of sodium fluoroacetate poisoning.*

   A. **CURARIZATION** is often required, using succinylcholine or similar agent. Tracheal intubation or tracheostomy and continuous mechanical pulmonary ventilation are necessary. Blood gases and pH must be monitored.

3. **FORCED DIURESIS** with mannitol accelerates the excretion of strychnine. Infusion of **SODIUM BICARBONATE** relieves metabolic acidosis. There may be some benefit from peritoneal dialysis, hemodialysis, and hemoperfusion.
4. Once seizures have been controlled, remove unabsorbed toxicant from the stomach by gastric **INTUBATION, ASPIRATION,** and **LAVAGE.** Leave a slurry of 30-50 gm **ACTIVATED CHARCOAL** in the stomach. Follow charcoal with **SODIUM** or **MAGNESIUM SULFATE,** 0.25 gm/kg, in 1-6 ounces of tap water, to induce catharsis. Repeat cathartic dosage as needed.

Vacor, DLP-787 (Active ingredient RH-787)

1. If toxicant was ingested recently, **EVACUATE** the **STOMACH** by **INTUBATION, ASPIRATION,** and **LAVAGE** with 2-3 liters isotonic saline.

   A. Before withdrawing stomach tube, instill 30-50 gm of **ACTIVATED CHARCOAL** as a slurry in 3-4 ounces of water, to limit absorption of remaining toxicant.
   B. As soon as patient can tolerate oral fluids after withdrawal of stomach tube, give **SODIUM** or **MAGNESIUM SULFATE,** 0.25 gm/kg body weight in 1-6 ounces of water to induce catharsis. Repeat dose in 4 hours if patient has had no bowel movement.

2. Administer **NICOTINAMIDE** (niacinamide) intravenously, slowly, or intramuscularly. For adults and children over 12 years, give 500 mg immediately, then repeat injections of 200-400 mg every 4 hours for 10-12 doses. Within this range, select the dose on the basis of body weight and the estimated quantity of RH-787 ingested. If manifestations of RH-787 toxicity appear, give nicotinamide by continuous IV infusion at about 100 mg per hour. There is probably no advantage in giving more than 3000 mg per day of nicotinamide.

   A. Dosage of nicotinamide for children under 12 years, or 23 kg, is about half the dosage suggested for adults.
   B. After 2-3 days of parenteral therapy, give nicotinamide by mouth, 100 mg four times daily, for 2 weeks.

3. **MONITOR** blood and urine sugar concentrations, serum alkaline phosphatase, amylase, LDH, and GOT activities, urine ketone concentrations, blood electrolytes and BUN. Examine the electrocardiogram for arrhythmias.
4. Unless the patient is able to void easily, put in place a **RETENTION CATHETER** to monitor urine flow and urinary glucose excretion.
5. Infuse **ELECTROLYTE SOLUTIONS** intravenously to accelerate toxicant excretion and correct errors in specific ion concentrations. If ketoacidosis appears, use bicarbonate or Ringer's-lactate to control acidosis.
6. If **DIABETIC KETOACIDOSIS** appears (ketonuria, metabolic acidosis, hyperglycemia) administer enough regular insulin to control the acidosis and hyperglycemia, as in naturally occurring diabetic ketosis. The diabetes resulting from RH-787 tends to be brittle and correspondingly difficult to control.
7. In all cases of ingestion of Vacor or DLP-787 (whether or not acute poisoning occurs), follow the patient's clinical status carefully for at least 6 months. Look for indications of diabetes mellitus (glycosuria, hyperglycemia), and for consequences of autonomic nervous system damage: orthostatic hypotension, urinary retention, constipation, diarrhea, abdominal cramping, pain and weakness in the limbs.

Red squill

1. Significant toxicity is not expected from this agent. If, for some reason, a significant amount is retained in the stomach, remove it by gastric **INTUBATION, ASPIRATION,** and **LAVAGE,** followed by 0.25 gm/kg **SODIUM** or **MAGNESIUM SULFATE** in 1-6 ounces water.
2. Monitor **ELECTROCARDIOGRAM** for arrhythmias and conduction disturbances characteristic of digitalis.

Antu

1. Significant toxicity is not expected from this agent. If an extraordinary amount has been ingested, empty the gut. Administer **SYRUP OF IPECAC,** then 1-2 glasses of water, to induce vomiting. Adult dose: 30 ml; dose for children under 12 years: 15 ml. Follow with 30-50 gm activated charcoal in 3-4 ounces of water, then 0.25 gm/kg **SODIUM** or **MAGNESIUM SULFATE** in 1-6 ounces water.
2. If dyspnea appears, administer **OXYGEN** by continuous flow or by intermittent **POSITIVE PRESSURE.**

Norbormide

1. Significant toxicity is not expected from this agent. If an extraordinary amount has been ingested, empty the gut. Administer **SYRUP OF**

IPECAC, then 1-2 glasses of water, to induce vomiting. Adult dose: 30 ml; dose for children under 12 years: 15 ml. Follow with 30-50 gm **ACTIVATED CHARCOAL** in 3-4 ounces of water, then 0.25 gm/kg **SODIUM** or **MAGNESIUM SULFATE** in 1-6 ounces water.

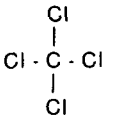
2. Monitor **BLOOD PRESSURE** and **BODY TEMPERATURE** for several hours, if a large amount has been absorbed.

Chapter 12

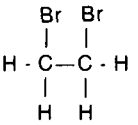
FUMIGANTS

CHEMICAL STRUCTURES

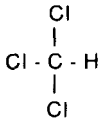
HALOCARBONS



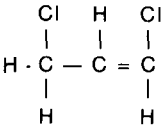
Carbon Tetrachloride



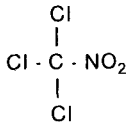
Ethylene Dibromide



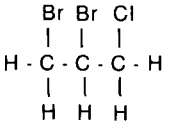
Chloroform



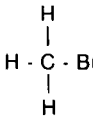
1,3-Dichloro-propene



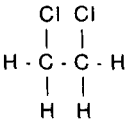
Chloropicrin



Dibromo-chloropropane

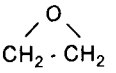


Methyl Bromide

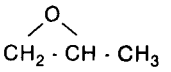


Ethylene Dichloride

OXIDES AND ALDEHYDES

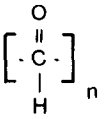


Ethylene Oxide

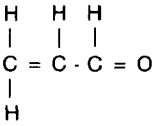


Propylene Oxide

Formaldehyde

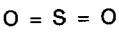


Paraformaldehyde

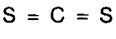


Acrolein

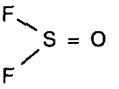
SULFUR AND PHOSPHORUS COMPOUNDS



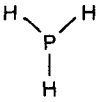
Sulfur Dioxide



Carbon Disulfide

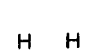


Sulfuryl Fluoride

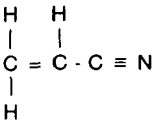


Phosphine (from Al≡ P+ H_2O)

CYANIDES



Hydrogen Cyanide



Acrylonitrile

COMMON COMMERCIAL FUMIGANT PRODUCTS

Chloroform, carbon tetrachloride, methyl bromide (Brom-O-Gas, Fumigant-1, Kayafume, Me Br, Meth-O-Gas, Pestmaster, Profume); chloropicrin (Acquinite, Chlor-O-Pic, Pic-Clor, Picfume, Tri-Clor); ethylene dichloride (EDC), ethylene dibromide (EDB, Bromofume, Celmide, Dowfume W-85, Kop-Fume, Nephis, Pestmaster EDB-85, Soilbrom); dichloroprop-ene and -ane (Telone, D-D), sulfuryl fluoride (Vikane), dibromochloropropane (DBCP).

The Dowfume fumigants manufactured by the Dow Chemical Company are mixtures of halocarbons, mainly EDC, EDB, carbon tetrachloride, Me Br, and chloropicrin, formulated to meet specific needs.

Ethylene oxide (ETO, oxirane); propylene oxide (epoxypropane); formaldehyde (Formalin is a 40% aqueous solution), propenal (Acrolein, Aqualin, Acrylaldehyde); carbon di- (or bi-) sulfide; hydrogen cyanide (prussic acid, Cyclon); acrylonitrile (ingredient of fumigant mixtures Acrylofume, Acritet, Carbacryl); aluminum phosphide (Phostoxin).

TOXICOLOGY

Fumigants have extraordinary power to penetrate the lining membranes of the respiratory and gastrointestinal tracts, and the skin. They also penetrate the rubber and plastics used in protective garb and they are not efficiently taken up by conventional adsorbents used in ordinary respirators. These properties make the protection of applicator personnel very difficult, essentially mandating methods of use that do not require on-site operator handling.

Because these chemicals are either gases or volatile liquids at room temperature, inhalation is the most common route of absorption. Dermal injury does follow contact with some fumigants, ranging in severity from a mild chemical burn to vesiculation and ulceration. Fumigant gases irritate the eyes; liquid fumigant may cause blindness from corneal ulceration.

Respiratory tract irritation is the most common and serious injury caused by fumigants. Some agents such as sulfur dioxide, chloropicrin, formaldehyde and acrolein cause so much irritation of the upper respiratory tract that the exposed individual is unlikely to inhale a quantity of fumigant capable of damaging the lung. Rarely, laryngeal edema or bronchospasm results from inhalation of high concentrations.

Other gases, such as methyl bromide, phosphine, and ethylene oxide, are not so irritating to the nose, eyes, throat, and bronchi, but cause serious injury to the cells lining the fine air sacs of the lung. Thus, they are more likely than other fumigants to induce pulmonary edema, a major cause of death from fumigant exposure.

In varying degrees, these fumigants depress the central nervous system. As in the case of the anesthetic chloroform, adequate dosage may lead to unconsciousness. Depression or cessation of respiration is a major hazard of acute inhalation exposure to fumigants. Acute exposures to methyl bromide have induced convulsions. Absorbed in lower concentrations over several consecutive

days, methyl bromide has impaired basal ganglion function in humans, causing ataxia for weeks or months after exposure. Protracted exposure to carbon disulfide has caused peripheral neuropathy and changes in CNS function (chronic encephalopathy) of chronically exposed workers.

The halocarbon fumigants increase the irritability of the heart muscle. Intensive exposures may lead to sudden death as a result of ventricular fibrillation.

Liver and kidney damage occurs commonly following excessive exposure to fumigants. Liver injury may take the form of fatty infiltration, diffuse necrosis or massive necrosis. Elevated serum levels of GOT, LDH, alkaline phosphatase, and bilirubin reflect hepatocellular injury. The fumigants may inflict direct injury on glomerular and tubular elements of the kidney, leading to functional proteinuria and glycosuria, or to acute renal failure, depending on severity of toxicant exposure. In addition, hyperbilirubinemia resulting from liver damage may compound the tubular injury (hepatorenal syndrome).

Inhaled phosphine gas (PH_3) and ingested metal phosphides cause pulmonary edema, CNS depression, toxic myocarditis, and circulatory collapse. Victims who survive these immediate actions suffer liver injury (fatty degeneration and necrosis) and acute renal tubular necrosis. Unlike its analogue arsine, phosphine is not hemolytic. Enzymatic mechanisms of toxicity are not known. Ingested metal phosphide (from which phosphine is generated) causes intense gastrointestinal irritation, followed by degenerative and necrotizing lesions of the liver, kidney, and heart. Death is often due either to cardiogenic shock or pulmonary edema.

Hydrogen cyanide (HCN) and its salts poison by inactivating the cytochrome oxidase of cells in critical tissues, primarily the heart and brain. Acrylonitrile degrades slowly to HCN in the body, and therefore acts primarily by the same mechanism, although the slow release of free cyanide renders it somewhat less toxic than HCN itself. Both HCN and acrylonitrile are sufficiently absorbable across the skin to cause poisoning in the absence of inhalation exposure. Manifestations of poisoning are due mainly to intracellular anoxia of brain tissue (leading to respiratory failure), and to the circulatory insufficiency that results from myocardial weakness. The liver has substantial capacity for converting cyanide to the less toxic thiocyanate, a metabolic conversion that is accelerated by therapeutically administered thiosulfate.

Dibromochloropropane has reportedly caused sterility in manufacturing plant workers and reduced sperm counts in highly exposed applicators.

FREQUENT SYMPTOMS AND SIGNS OF POISONING

HEADACHE, DIZZINESS, NAUSEA, and vomiting are prominent early symptoms of excessive exposure to these gases. Sulfur dioxide, formaldehyde, chloropicrin, and acrolein are strong irritants, causing **BURNING SENSATIONS** in the nose and throat, **TEARING, COUGH,** and sometimes hoarseness and wheezing. Exposures to methyl bromide, phosphine and ethylene oxide are more likely to produce prompt pulmonary edema: **COUGHING** of

copious amounts of **FROTHY FLUID,** associated with severe **SHORTNESS OF BREATH** and cyanosis. The remaining fumigants are less likely to cause respiratory tract injury.

DROWSINESS, TREMORS, double vision, and weakness are the common early manifestations of central nervous system impairment. Tremors may progress to myoclonic movements, then to generalized **SEIZURES, UNCONSCIOUSNESS,** and death. Protracted low level exposure to methyl bromide causes **ATAXIA** and impairment of manual coordination.

Injuries to the skin by liquid fumigants may be manifest as areas of redness or as **BLISTERS** which rupture, leaving raw skin or deep ulcers.

If ingested, the **LIQUID** forms of **HALOCARBONS** often cause pulmonary edema and **SHOCK** within a few moments. If victim survives, injuries to the brain, liver and kidney are life-threatening.

Longer-term low level inhalation of **CHLOROCARBONS** may cause liver damage, first manifest as **ANOREXIA,** then as **JAUNDICE.** Biochemical studies confirm hepatocellular injury.

Poisoning by excessive inhalation of **CARBON DISULFIDE** is characterized by **DIZZINESS,** headache, nausea, and sometimes disorientation, paresthesiae, hallucinations, and, rarely, convulsions. Protracted low level exposures produce **PAIN,** tingling, **WEAKNESS** of the extremities, and deterioration of mental functions.

Poisoning by **PHOSPHINE** gas is usually heralded by weakness, **TREMORS,** vomiting, a sense of pressure in the chest, **COUGH,** and dyspnea, sometimes progressing to **PULMONARY EDEMA.** Intense thirst results from hypotension and diarrhea. Severe poisonings lead to **CONVULSIONS,** coma, and death. Those who survive the acute phase suffer **LIVER INJURY** (elevation of serum GOT, LDH, and alkaline phosphatase, and sometimes, reduced prothrombin concentration, hemorrhage, and jaundice) and kidney damage (hematuria and sometimes anuria). Chronic exposures to lesser amounts have caused pain in the eyes and nose, nosebleeds, and abdominal pain.

Ingestion of **METAL PHOSPHIDES** leads promptly to **NAUSEA** and **VOMITING,** followed by injury to the lung, liver, kidney, heart and central nervous system. Hypocalcemic tetany (from hyperphosphatemia) and metabolic acidosis develop several hours after ingestion of solid phosphides.

Excessive inhalation of **SULFURYL FLUORIDE** may induce muscle twitching and convulsions. Persons repeatedly exposed risk injury to the lung (impaired pulmonary function) and kidney (proteinuria and azotemia).

Poisoning by **HYDROGEN CYANIDE** or **ACRYLONITRILE** may produce sudden **UNCONSCIOUSNESS** and respiratory arrest without warning symptoms. Lesser exposures cause **HEADACHE,** nausea, and a sense of constriction in the throat, followed by hyperpnea, dizziness, and apprehension. Pulse and respiratory movements then become weak, slow, and irregular as consciousness is lost. **CONVULSIONS,** either tonic or epileptiform, may supervene. Opisthotonus and trismus commonly appear, and sphincter control is usually lost. The heart often continues to beat after respiration has stopped. The skin generally remains pink.

CONFIRMATION OF DIAGNOSIS

Large industrial concerns monitor human absorption of halocarbons by analysis of expired air. Similar technology is available in many departments of anesthesiology. Such analyses are not often needed to identify the offending toxicant, because this is known from the exposure history. In managing difficult cases of poisoning, however, it may help to monitor breath concentrations of toxic gas.

Blood bromide concentrations† have some value in identifying poisonings by methyl bromide, and possibly ethylene dibromide, provided it can be established that the person exposed to the fumigant has not recently taken inorganic bromide medication. A level of organic bromide higher than 5 mg/100 ml indicates excessive absorption of fumigant. A blood concentration of more than 10 mg/100 ml of organic bromide represents a serious threat to health. A blood level of more than 15 mg/100 ml indicates an immediate threat to life.

Methods for detecting the organic oxides, aldehydes, sulfur dioxide, and phosphine are not generally available, but they are rarely needed. A simple method is available for detecting carbon disulfide in urine (Djuric et al. Brit. J. Indust. Med. 22:321-323. 1965). Cyanide can be detected and measured in blood and tissues, as can the thiocyanate metabolite in urine and saliva. Odors of gases on the victim's breath are sometimes helpful diagnostic clues: cyanide smells like bitter almonds, carbon disulfide like rotten cabbage, and phosphine somewhat like garlic or acetylene.

TREATMENT

1. **FLUSH** contaminating fumigant from the **SKIN** and **EYES** with copious amounts of water for at least 15 minutes. Contact with **LIQUID** fumigant can cause **BLINDNESS** or **DEATH.** Treat injuries **IMMEDIATELY.**
2. **REMOVE** victims of fumigant inhalation **TO FRESH AIR.** Even though initial symptoms and signs are mild, keep victim quiet, in a semireclining position. Reduction in physical activity reduces the likelihood of pulmonary edema.
3. If victim is not breathing, **RESUSCITATE** with positive pressure oxygen breathing apparatus, if available. If apparatus is not available, use mouth-to-mouth or mouth-to-nose methods. If victim is pulseless,use cardiac resuscitation.
4. If **PULMONARY EDEMA** is evident, there are several measures available to sustain life. Medical judgment must be relied upon, however, in the management of each case. The following procedures are generally recommended:

   A. Put the victim in a **SITTING** position with a backrest.

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† Conway, E. J. Microdiffusion Analysis and Volumetric Error, 3rd edition. Crosby Lockwood, London 1950.

B. Use intermittent and/or continuous positive pressure **OXYGEN** to relieve hypoxemia. (Do not give oxygen at greater concentrations or longer periods than necessary, because it may exaggerate the fumigant injury to lung tissue. Monitor arterial p O_2).

C. Apply **TOURNIQUETS** in rotation to arms and legs to limit venous return.

D. Administer **AMINOPHYLLINE** (0.25-0.50 gm) slowly, intravenously.

E. Administer **MORPHINE** in small doses (5-10 mg), slowly, intravenously, to allay anxiety and promote deeper respiratory excursions. Children's dose, 0.1-0.2 mg/kg.

F. Digitalization may be considered, but be alert to the serious risk of arrhythmias in an anoxic mycardium.

G. Slowly administer **FUROSEMIDE,** 40 mg, or **SODIUM ETHACRYNATE,** 50 mg, to reduce venous load by inducing diuresis.

H. **TRACHEOSTOMY** may be necessary in some cases to facilitate aspiration of large amounts of edema fluid.

I. Epinephrine, atropine, and expectorants are generally **NOT HELPFUL** and may complicate treatment.

J. **STEROIDS** at high dosage are usually recommended, although their effectiveness is unproved.

K. If secondary pneumonitis occurs, administer **ANTIBIOTICS.**

L. Watch for **RECURRENT PULMONARY EDEMA,** even up to 2 weeks after the initial episode. Limit victim's physical activity for at least 4 weeks. Severe physical weakness usually indicates persistent pulmonary injury. Serial pulmonary function testing may be useful in assessing recovery.

5. Combat **SHOCK** by placing victim in the Trendelenburg position and administering blood plasma and/or electrolyte and glucose solutions intravenously, with great care, to avoid pulmonary edema. Central venous pressure should be monitored continuously. Vasopressor amines must be given with great caution, because of the irritability of the myocardium.

6. Control **CONVULSIONS.** Seizures are most likely to occur in poisonings by methyl bromide, carbon disulfide, phosphine, metal phosphide, cyanide, and acrylonitrile.

A. Establish pulmonary gas exchange at the best possible level by administering 100% **OXYGEN** by IPPB.

B. In poisoning by **CYANIDE** and acrylonitrile, proceed directly with **ANTIDOTAL** therapy (see below, paragraph 10C).

C. Control convulsions caused by other agents with careful IV injection of **DIAZEPAM,** 5-10 mg in the adult, 0.1 mg/kg in children under 12 years. Repeat dosage in 4-6 hours if necessary.

CAUTION: Be prepared to maintain pulmonary ventilation mechanically, and to manage hypotension and cardiac arrhythmias.

D. In methyl bromide poisoning, it may be necessary to give diazepam or barbiturates orally for some time after the acute poisoning to control involuntary motor activity.

7. If **FUMIGANT LIQUIDS** have been **INGESTED,** quantities remaining in the gut must be removed as effectively as possible by gastric **INTUBATION, ASPIRATION,** and **LAVAGE.**

   A. **IF** victim is **UNCONSCIOUS,** put in place a cuffed endotracheal tube prior to gastric intubation.
   B. Place conscious victim in a left lateral Trendelenburg position for intubation, and aspirate the pharynx as effectively as possible to minimize likelihood of tracheal aspiration.
   C. After aspirating stomach contents, **LAVAGE** the stomach with 2-3 liters 0.9% saline or 5% sodium bicarbonate, containing 30-50 gm **ACTIVATED CHARCOAL.** After lavage, leave 30-50 gm activated charcoal in stomach before withdrawing tube.
   D. If diarrhea does not develop spontaneously, give **SODIUM SULFATE** orally, 0.25 mg/kg, to induce catharsis.

8. Intravenous **INFUSIONS** of **GLUCOSE** are valuable in limiting the hepatotoxicity of fumigants. Monitor central venous pressure to avoid precipitating, or aggravating, pulmonary edema by fluid overload.
9. **MONITOR** fumigant poisoning victims closely for recurrent pulmonary edema and bronchopneumonia. Chart fluid balance and check urine sediment regularly to detect incipient tubular necrosis. Measure serum alkaline phosphatase, LDH, and bilirubin to assess liver injury.
10. Certain **SPECIFIC MEASURES** are recommended in poisonings by particular fumigants:

   A. If given very soon after exposure to **METHYL BROMIDE,** there may be some value in administering **DIMERCAPROL** (BAL) in vegetable oil intramuscularly. For adults, give 3-5 mg/kg q6h for 4 doses.

      CAUTION: **DIMERCAPROL** may cause troublesome side effects (hypertension, tachycardia, nausea, headache, paresthesiae, pain, lacrimation, sweating, anxiety, and restlessness). Although usually not so severe as to preclude treatment, these manifestation may require antihistamine therapy for adequate control.

   B. Mild poisonings by **CARBON DISULFIDE** inhalation may be managed best by no more than careful observation, even though sensory hallucinations, delirium, and behavioral aberrations can be alarming. Severe poisonings may require specific measures:

      1. **CAFFEINE** and sodium benzoate (0.5 gm subcutaneously) may help to relieve CNS depression.

2. If manic behavior threatens the safety of the victim, **DIAZEPAM**, 5-10 mg, 0.1 mg/kg in children, administered cautiously, intravenously, may be helpful as a tranquilizer. Do not give catecholamine-releasing agents such as reserpine and amphetamines.

C. Poisonings by **HYDROGEN CYANIDE** and **ACRYLONITRILE** gases are treated in essentially the same way as poisoning by cyanide salts. In addition to the general treatment described earlier, specific **ANTIDOTES** are required. (See line 6 for pediatric regimen).

1. Administer **AMYL NITRITE** (perles) by inhalation for 15-30 seconds of every minute, while a fresh solution of 3% sodium nitrite is being prepared.
2. As soon as solution is available, inject intravenously 10 ml of 3% **SODIUM NITRITE** solution over a 2-4 minute interval, keeping the **NEEDLE IN PLACE.**

   CAUTION: Monitor **PULSE** and **BLOOD PRESSURE** during administration of amyl nitrite and sodium nitrite. If systolic blood pressure falls below 80 mm Hg, slow or stop nitrite administration until blood pressure recovers.

3. Follow sodium nitrite injection with an infusion of 50 ml of 25% aqueous solution of **SODIUM THIOSULFATE** administered over 10-minute period. Initial adult dose should not exceed 12.5 gm.
4. If symptoms persist or recur, treatment by sodium nitrite and sodium thiosulfate should be **REPEATED AT HALF THE DOSAGES** listed in paragraphs 2 and 3.
5. Measure hemoglobin and methemoglobin in blood. If more than 50% of total hemoglobin has been converted to methemoglobin, **BLOOD TRANSFUSION** or exchange transfusion should be considered, because conversion back to normal hemoglobin proceeds slowly.
6. Dosage of **ANTIDOTES** in **CHILDREN:**

   C. M. Berlin (Pediatrics 46:793-796, 1970) has recommended the following procedures in case of cyanide poisoning in children:

   (a) Children over 25 kg body weight should receive adult dosages of sodium nitrite and sodium thiosulfate.
   (b) Children less than 25 kg body weight should first have two 3-4 ml samples of blood drawn and then, through the same needle, receive 10 mg/kg (0.33 ml/kg of 3% solution) of **SODIUM NITRITE** injected over a 2-4 minute interval. Following sodium nitrite, administer an infusion of

1.65 ml/kg of 25% **SODIUM THIOSULFATE** at rate of 3-5 ml per minute.

(c) At this point, determine the hemoglobin content of the original blood sample. If symptoms and signs of poisoning persist or return, give *supplemental* infusions of sodium nitrite and sodium thiosulfate based on hemoglobin level, as presented in TABLE 2. (These recommended quantities are calculated to avoid life-threatening methemoglobinemia in anemic children).

TABLE 2. *Recommended dosages of supplemental sodium nitrite and sodium thiosulfate based on hemoglobin level.*

Initial Hemoglobin Concentration, gm/100 ml	Supplemental Volume of 3% Sodium Nitrite, ml/kg	Supplemental Volume of 25% Sodium Thiosulfate, ml/kg
14.0	0.26	1.28
13.0	0.21	1.05
12.0	0.17	0.83
11.0	0.12	0.60
10.0	0.07	0.38
9.0	0.04	0.23
8.0	0	0
7.0	0	0

(d) When possible, monitor **BLOOD LEVELS** of **METHEMOGLOBIN** to achieve approximately 40% conversion of hemoglobin to methemoglobin.

Chapter 13

MISCELLANEOUS PESTICIDES OF HIGH TOXICITY

Pesticides included in this chapter are not similar in chemical structure or toxicologic actions to the major classes of pesticidal toxicants (organophosphates, arsenicals, etc.) In general, they are not widely used and opportunities for serious human exposure are rare. However, those included here are characterized by either high toxicity or an important unique mechanism of toxic action. Occasional poisonings by these chemicals have occurred in humans and domestic animals.

4-aminopyridine (Avitrol, 4-AP)

This chemical, now used as a bird repellant, has caused severe poisoning in adult humans at dosages no greater than about 60 mg. This is only 2-3 times the dosage employed clinically in managing certain rare neuromuscular disorders. The principal pharmacologic action of 4-aminopyridine is to facilitate release of transmitter substances at neuroeffector junctions and at synapses throughout the nervous system.

Human poisonings have been characterized by thirst, nausea, dizziness, weakness, and intense diaphoresis, followed by toxic psychosis, ataxia, tremors, dyspnea, and tonic-clonic convulsions. Metabolic acidosis, leukocytosis, and elevations of serum GOT, LDH, and alkaline phosphatase were notable laboratory findings. EKG may show nonspecific ST-T wave changes.

Treatment

Promptly evacuate gut by intubation, lavage, activated charcoal administration, and saline catharsis. Control convulsions with diazepam. Initiate diuresis with intravenous infusions, including mannitol. To date, poisoning victims have recovered in 24-48 hours without severe sequelae.

Pancuronium is an antagonist of 4-aminopyridine, and can control seizures. It must be administered under the supervision of an anesthesiologist because of the likelihood of generalized paralysis. Propranolol may help to limit cardiac toxicity. Atropine controls the gastrointestinal symptoms.

Chlordimeform (Acaron, Fundal, Fundex, Galecron, Spanone)

Although the acute toxicity of this ovicidal agent is low (oral LD_{50} in the rat about 200 mg/kg), it is now known from an incident of excessive respiratory and dermal exposure to chlordimeform powder that it can cause acute illness and urinary bladder irritation. In all likelihood, the offending metabolite is 2-methyl-4-chloroaniline. Principal symptoms are dysuria, gross hematuria, urethral discharge, abdominal and back pain, and a hot sensation all over. Sleepiness, skin rash, anorexia, and a sweet taste in the mouth have also been

reported. Cystoscopic examination of victims of excessive exposure demonstrated acute hemorrhagic cystitis.

Methods are available for detecting the 2-methyl-4-chloroaniline metabolite in the urine.

Treatment

Flush contaminant from eyes and wash from skin. Symptoms resulting from undue occupational exposure resolve in a few days if exposure is terminated. If chlordimeform has been recently ingested, it should be removed from the gut either by administering Syrup of Ipecac, or by gastric intubation, aspiration, and lavage with 0.9% sodium chloride, followed by activated charcoal and sodium sulfate catharsis. Serial urinanalyses should be performed to assess injury to the urinary tract.

Copper salts and organic complexes (oxide, hydroxide, arsenite, carbonate, chloride, oxalate, phosphate, silicate, sulfate, zinc chromate, acetate, naphthenate, oleate, quinolinolate, and resinate).

These are commonly used as fungicides, either alone or in combination with other agents. There are several dozen proprietary products.

LD_{50} values vary from 6 to 1000 mg/kg, depending mainly on the solubility and degree of ionization of the copper compound.

Toxicity of copper-arsenite salts is due mainly to the arsenic content.

All of these salts irritate the skin and eyes and damage mucous membranes. When ingested, they are powerfully emetic: the stomach usually empties promptly and automatically in fully conscious individuals. When retained and absorbed, toxic injury affects the gastrointestinal lining, capillaries, brain, liver, kidney, and formed elements of the blood. Copper salts are hemolytic.

Manifestations of poisoning include burning pain in the chest and abdomen, intense nausea, vomiting, diarrhea, headache, sweating and shock. Later, the liver is enlarged. Jaundice may reflect hemolysis or liver damage or both. Anuria indicates kidney injury by copper and/or free hemoglobin. Death may occur from convulsions, coma, or hepatorenal failure. Elevated serum copper levels (maximum normal level is 125 μg per 100 ml) indicate severity of poisoning.

Treatment

Wash contaminated skin and flush eyes with copious amounts of water. If copper salts have been ingested, lavage the stomach with 0.1% potassium ferrocyanide, then instill a suspension of egg white. Intravenous fluids accelerate excretion. If signs of systemic poisoning develop, give dimercaprol (see Arsenical Pesticides for dosage) or penicillamine, 0.5 gm orally four times daily, if patient can retain oral medication. Shock may require blood transfusions and pain may require morphine. Exchange transfusions may be considered in severe poisonings. Renal failure may require protracted hemodialysis.

Cycloheximide (naramycin, Acti-dione, Actispray, Hizarocin)

This is an antibiotic fungicide of high toxicity: oral LD_{50} in rats is 2 mg/kg.

Dermal absorption is probably not efficient. When ingested, the agent causes excitement, tremors, salivation, diarrhea, and melena. Mechanisms of toxicity are not well defined, but probably include irritation of the gut, stimulation of sympathetic and parasympathetic nervous systems, renal injury, and damage to the adrenal cortex.

There are no chemical tests to confirm cycloheximide poisoning.

Treatment

Remove toxicant from gut by lavage. Instill activated charcoal, then a cathartic dose of sodium sulfate. Intravenous fluids accelerate excretion.

Hydrocortisone appears to be antidotal, particularly in combination with the adrenergic agent methoxyphenamine (Orthoxine®). Atropine relieves the cholinergic symptoms.

Endothall (Accelerate, Aquathol, Des-i-cate, Hydout, Hydrothol)

Acute oral LD_{50} of this herbicide is 51 mg/kg. Dermal absorption of the commonly used salts is probably slight. It is irritating to eyes, mucous membranes and skin, but it is not sensitizing. Mechanisms of systemic toxicity are not clear, but the central nervous system, heart, blood vessels, and gastrointestinal lining appear to be primary targets. Poisoned animals exhibit ataxia, convulsions, shock, and respiratory depression. Erosions and ulcers of the gastrointestinal tract follow ingestion.

There are no standard analytical methods for confirming poisoning.

Treatment

Wash contaminated skin and flush eyes with copious amounts of water. Instead of gastric evacuation following ingestion, administer cold milk or aluminum hydroxide gel. This may be followed by saline catharsis. There is no specific antidote. Shock may require blood transfusions. Use of adrenergic amines is probably hazardous in view of myocardial irritability.

Nicotine sulfate (Black Leaf 40)

This time-honored natural insecticide is still used in horticulture. Lethal dose in humans is about 60 mg. Nicotine preparations, especially those using the free alkaloid, are well absorbed across the gut wall, lung, and skin. Poisoning symptoms from excessive doses appear promptly. They are due to transient stimulation, then prolonged depression, of the central nervous system, autonomic ganglia, and motor end-plates of skeletal muscle. Central nervous system injury is manifest as headache, dizziness, incoordination, tremors, then clonic convulsions leading to tonic-extensor convulsions which are often fatal. In some instances, convulsive activity is minimal and death by respiratory arrest occurs within a few minutes. Effects on autonomic ganglia give rise to sweating, salivation, nausea, abdominal pain, diarrhea, and hypertension. The heart is usually slow, and often arrhythmic. Block of skeletal muscle motor end-plates causes profound weakness, then paralysis. Death may occur from respiratory depression or from shock.

Nicotine can be measured in blood and urine to confirm poisoning.

Treatment

Promptly wash contaminated skin and flush eyes with water. Ingestion of nicotine requires immediate gastric intubation, aspiration, and lavage, the latter preferably with 1.5% tannic acid solution, or 1:5000 potassium permanganate solution. Before withdrawing the lavage tube, instill 3-4 ounces of activated charcoal in a slurry of water. Diazepam and/or barbiturates may be required to control convulsions. Atropine and phenoxybenzamine (Dibenzaline®) may help to control the autonomic manifestations. Positive pressure ventilation of the lungs with oxygen may be necessary to sustain life when respiration is arrested.

Phenylmercuric salts. Most commonly used is phenylmercuric acetate (PMA, Agrosan, Cekusil, Gallotox, Hong Nien, Luquiphene, Mersolite, Phenmad, Phix, PMAS, Shimmer-ex)

Phenylmercuric acetate is a widely used fungicide. Acute oral LD_{50} in the rat is 22 mg/kg. Other salts are also highly toxic. They probably undergo some dermal absorption. Because of lower volatility and less penetration of the brain, they are somewhat less toxic than alkyl mercury compounds.

Early manifestations reflect injury to the central nervous system: ataxia, muscle weakness, visual impairment, and delirium. After a single moderate exposure, these symptoms usually resolve promptly. Repeated intensive exposures cause symptoms and signs resembling amyotrophic lateral sclerosis: weakness and incoordination of the arms, difficulty in swallowing and talking, weakness and spasticity of the legs. Concurrent or later manifestations of excessive absorption reflect renal injury: albuminuria, hematuria, azotemia, and sometimes acute tubular necrosis. Induction of nephrotic syndrome has been reported. This is characterized by massive albuminuria, generalized edema, and hypercholesterolemia.

Methods are available at specialized toxicology laboratories for measuring phenylmercuric compounds in urine.

Treatment

Wash contaminated skin and flush eyes with water. If ingested, remove the chemical from the gut by prompt gastric intubation, aspiration, and lavage with 5% sodium bicarbonate solution and instillation of activated charcoal, followed by catharsis with sodium or magnesium sulfate. Intravenous infusions of fluids accelerate excretion of mercurials and limit kidney damage. There is no specific antidote; dimercaprol is not very effective in limiting toxicity.

Sodium chlorate (De-Fol-Ate, Drexel Defol, Drop-Leaf, Fall, Grain Sorghum Harvest-Aid, Klorex, Kusatol, Tumbleaf)

Although the oral LD_{50} in the rat is high (1200 mg/kg), there have been several deaths from this herbicide-defoliant in the past decade. The principal mechanisms of toxicity are irritation of the gastrointestinal lining, central nervous system depression, hemolysis, oxidation of free hemoglobin to methemoglobin, and renal tubular injury. Dermal absorption is minimal. If ingested,

chlorate causes swelling of the oral and pharyngeal membranes and pain in the chest and abdomen. The victim is first restless, then apathetic. On the third or fourth day after ingestion, lumbar pain, albuminuria, hematuria, then anuria with azotemia, reflect renal injury. Death may be due to hyperkalemia (hemolysis), tissue anoxia (methemoglobinemia), or renal failure.

Although chlorate itself is not readily measured in the blood, free hemoglobin and methemoglobin in the plasma point to poisoning by an oxidizing agent.

Treatment

Remove from gut by prompt gastric intubation, aspiration, and lavage using 3 gm sodium thiosulfate in 300 ml 5% sodium bicarbonate. Instill 30-50 gm activated charcoal in a slurry. Pain may require narcotics. Both hemodialysis and exchange transfusions have been used successfully in treating poisonings. Methylene blue is of no value in reducing the extracellular methemoglobin. Intravenous infusions of 1% sodium thiosulfate (100-500 ml) limit the concentration of circulating chlorate. Monitor serum electrolytes. Hemodialysis may be needed to sustain life in the event of extensive renal tubular necrosis.

Sodium cyanide (Cymag)

Occasionally, this is used as a rodenticide. Toxicity is extreme, similar to that of hydrogen cyanide gas used as a fumigant. **CONSULT** Chapter 12 on **FUMIGANTS** (hydrogen cyanide) for toxicology, poisoning manifestations, diagnosis, and management. Cyanide salts are not adsorbed on activated charcoal.

Chapter 14

MISCELLANEOUS PESTICIDES OF LOW OR MODERATE TOXICITY

These compounds are included in the manual because their wide use generates inquiries as to their potential for causing adverse effects.

Description of the toxic potential of these chemicals as low or moderate does not preclude the need for cautious handling. Many agents have irritant properties, and individuals vary widely in their reactions to them. Certain predisposed persons may suffer dermal and respiratory illness from substances that have no effect on other persons or experimental animals. It is also true that the sum total of potential effects of a chemical, and by-products formed in synthesis and storage, plus the metabolites formed into vivo is never fully known. Reasonable precautions to avoid contact with pesticides are always recommended regardless of the reported toxicity of the principal active ingredient.

Lowest reported acute oral LD_{50} in the rat is cited in this listing as an indication of overall toxicity, manifest as killing power. The LD_{50} rating says nothing of dosages necessary to produce symptoms or signs, disease conditions characterized by long latency, subclinical biochemical effects, or other nonlethal effects on health. It is essential that high LD_{50} ratings not be interpreted as indications that the subject chemicals are innocuous.

Knowledge of use is sometimes helpful in identifying chemicals. Agents on this list are used as herbicides (H), fungicides (F), or insecticides (I).

There are many proprietary **MIXTURES** of these chemicals and it is common to tank mix many of them according to the grower's requirements. Intelligent management of exposures requires that the full list of active ingredients in mixtures be ascertained from the producer or applicator. In general, management is aimed at the most toxic ingredient.

Chemical Class	Generic Name	Use	LD_{50}	Proprietary Name	Known or Suspected Adverse Effects
Acetamides	allidochlor	H	750	Randox, CDAA	Moderately irritating to skin and eyes.
	metolachlor	H	2,780	Dual, Bicep, Primagram, Primextra	
Acetanilides	alachlor	H	1,800	Lasso, Lazo, Alanex	Mild irritant
	propachlor	H	710	Ramrod, Bexton	Dermal irritant and sensitizer
	propanil	H	1,384	DPA, Propanex, Riselect, Rosanil, Stam F34, Strel, Supernox, Surcopur, Surpur, Vertac	Mild irritant

Chemical Class	Generic Name	Use	LD_{50}	Proprietary Name	Known or Suspected Adverse Effects
Aliphatic Acids	dichloro-propionic acid	H	970	Dalapon, Dowpon, Crisapon, Basfapon	Skin and eye irritants
	trichloro-acetic acid	H	5,000	TCA	
Aluminofluoride salt	sodium fluoro-aluminate	I	>10,000	Cryolite, Kryocide	Slight irritant
Benzenes	hexachloro-benzene (perchloroben-zene)	F	10,000	HCB, No Bunt, Anticarie	Chronic ingestion causes porphyria cutanea tarda
	paradichloro-benzene	I	500	PDB, Paracide	Mild respiratory irritant and hepatotoxin
	pentachloro-nitrobenzene	F	1,700	PCNB, Terrachlor	Skin irritant
Benzoic and Benzilic Acid Derivatives	benzyl benzoate	I	1,700	Benzyl benzoate	Irritating to skin and eyes.
	chlorobenzilate	I	960	Acaraben, Akar, Benzilan, Kop-Mite, Benz-O-Chlor	
	trichloro-benzoic acid	H	1,370	Benzac, TBA, TCBA, Tribac	
Benzonitriles	chlorothalonil	F	10,000	Bravo, Daconil 2787	Moderately irritating to skin and respiratory tract
	dichlobenil	H	3,160	Casoron, Du-Sprex	
Carbamates	asulam	H	5,000	Asulox 40, Asulox F	Mild irritants. These carbamates do not inhibit cholinesterase enzyme.
	benomyl	F	10,000	Benlate, Tersan 1991	
	chlorpropham	H	3,800	Furloe, Chloro IPC, CIPC, Sprout Nip, Taterpex, Unicrop CIPC	
	terbucarb	H	34,000	Azak, Azac, Azar	
Carbanilate	barban	H	600	Carbyne, Neoban, Caryne	Irritant and dermal sensitizer.
Dicarboximides	captafol	F	6,200	Difolatan	Skin irritant
	captan	F	10,000	Captan, Merpan, Orthocide	Skin irritant
	folpet (thiophal)	F	10,000	Phaltan, Folpan	Skin irritant
Dinitrotoluidine Compounds	benefin	H	10,000	Benfluralin, Bethrodine, Balfin, Benefex, Quilan	Slightly to moderately irritating to skin, eyes, and mucous membranes. These agents do not uncouple oxidative phosphorylation.
	butralin	H	12,600	Amex	
	dinitroamine	H	3,700	Dinitramine, Cobex	
	fluchloralin	H	1,550	Basalin	
	isopropalin	H	5,000	Paarlan	
	oryzalin	H	10,000	Surflan, Rycelan, Ryzelan	
	pendimethalin	H	1,250	Prowl, Herbadox, Stomp	
	profluralin	H	1,808	Tolban, Pregard	

Chemical Class	Generic Name	Use	LD_{50}	Proprietary Name	Known or Suspected Adverse Effects
	trifluralin	H	>10,000	Treflan, Crisalina, Digermin, Elancolan, Ipersan	Slightly to to moderately irritating to skin, eyes, and mucous membranes. These agents do not uncouple oxidative phosphorylation.
Oxadiazolinone	oxadiazon	H	3,500	Ronstar	Irritating to skin and eyes
Phthalate	chlorthal-dimethyl	H	3,000	Dacthal, DCPA	Mild irritant
Picolinic acid Derivative	picloram	H	8,200	Tordon, Amdon	Irritating to skin, eyes, and respiratory tract
Pyridazinone	maleic hydrazide	Growth retardant	6,950	Burtolin, Chemform, De-Cut, De-Sprout, Regulox, KMH, Maintain, Stunt-Man	Slightly irritating
Phosphonomethyl glycine	glyphosate	H	4,300	Roundup	Irritant to eyes and respiratory tract
Thiadiazin (ol)	bentazon	H	2,063	Basagran	Moderately irritating to skin, eyes, respiratory tract. On ingestion, has caused vomiting, diarrhea, dyspnea, tremors, weakness.
	terrazole	F	1,077	Terrazole	Moderately irritating to skin, eyes, and respiratory tract.
Triazines	ametryn	H	1,750	Evik, Ametrex, Gesapax	Some triazines are mildly irritating to skin, eyes, and upper respiratory tract. Systemic toxicity is unlikely unless very large amounts have been ingested.
	anilazine	H	5,000	Dyrene, Direz, Kemate, Triasyn	
	atraton	H	1,465	Atratone, Gesatamin	
	atrazine	H	3,080	AAtrex, Atranex, Gesaprim, Primatol A, Atred, Crisazine, Vectal SC	
	cyanazine	H	334	Bladex, SD 15418	
	desmetryn	H	1,390	Semeron	
	isomethiozin	H	10,000	Tantizon	
	metribuzin	H	1,100	Sencor, Lexone, Sencorex, Sencoral	
	prometone	H	2,980	Pramitol, Gesafram-50, Prometon, Primatol 25E	
	prometryn	H	5,235	Caparol, Gesagard, Primatol Q, Prometrex	
	propazine	H	>5,000	Milogard, Gesamil, Primatol P, Prozinex	
	Simazine	H	>10,000	Princep, Gasatop, Simadex, Simanex	

Chemical Class	Generic Name	Use	LD_{50}	Proprietary Name	Known or Suspected Adverse Effects
Triazines	terbuthylazine	H	2,610	Primatol-M, Gardoprim, GS 13529	Some triazines are mildly irritating to skin, eyes, and upper respiratory tract Systemic toxicity is unlikely unless very large amounts have been ingested
	terbutryn	H	2,500	Igran, Terbutrex	
Uracils	bromacil	H	5,200	Hyvar X, Uragan, Urox B, Urox HX	Irritant to skin, eyes, and respiratory tract
	lenacil	H	11,000	Venzar	Moderately irritating
	terbacil	H	5,000	Sinbar	
Urea Derivatives	chloroxuron	H	3,700	Tenoran, Chloroxifenidim	Many substituted ureas are moderately irritating to skin, eyes, and mucous membranes.
	chlortoluron	H	10,000	Dicuran, Tolurex, Clortokem	
	difenoxuron	H	7,750	Lironion	
	diflubenzuron	I	4,640	Dimilin	
	diuron	H	3,400	Cekiuron, Crisuron, Dailon, Diater, Di-on, Diurex, Dirurol Dynex, Karmex, Unidron, Urox D, Vonduron	
	fluometuron	H	6,416	Cotoran, Lanex, Cottonex	
	isoproturon	H	1,826	Arelon, Belgran, Graminon, Tolkan	
	linuron	H	1,500	Afalon, Hoe 2810, Linurex, Lorox, Premalin, Sarclex	
	methabenzthiazuron	H	2,500	Tribunil	
	metobromuron	H	3,000	Patoran, Pattonex	
	metoxuron	H	3,200	Deftor, Dosanex, Dosaflo, Purivel	
	monolinuron	H	1,800	Aresin, Afesin, Arresin, Premalin	
	monuron	H	3,600	Monurex	
	neburon	H	11,000	Granurex, Kloben, Neburex	
	siduron	H	7,500	Tupersan	
	tebuthiuron	H	644	Spike	
	tetrafluoron	H	1,265	Tomilon	

TOXICOLOGY

Many of these compounds are primary irritants to skin, eyes, and respiratory tract. The ureas and uracils are perhaps the most common offenders, although captafol and chlorothalonil have apparently caused contact dermatitis in some agricultural workers. Propachlor is a dermal sensitizer in predisposed individuals.

Although hexachlorobenzene has low acute toxicity, long-term ingestion of HCB-treated seed grain caused an epidemic of porphyria cutanea tarda among Turkish farm families in the 1950's. No such effect has been found in HCB handlers in the United States.

Given to cattle in extreme dosage, some triazines have caused neuromuscular abnormalities and damage to internal organs. It is unlikely that domestic animals would consume these amounts voluntarily, and still less likely that humans would be exposed to such extreme dosage.

CONFIRMATION OF ABSORPTION

The benzene derivatives and benzonitriles can be identified in plasma by gas-liquid chromatography. Methods for benzoic acid and triazine metabolites in urine have been developed. Analytical methods used for agricultural residues of the remaining compounds might be adapted to analysis of gastric contents or skin wipings. Samples must be collected within hours of exposure, because most of these chemicals are promptly excreted.

It is unlikely that such analyses will be required in cases of human exposure to these agents. In the event that workers experiencing protracted heavy exposure develop suspicious manifestations of injury or toxicity, urine or blood analyses may help to confirm chemical absorption. Tests may be conducted in private or university laboratories, or laboratories supported by the state or federal government, i.e., the United States Environmental Protection Agency or Occupational Safety and Health Administration.

TREATMENT

1. **WASH** contaminated **SKIN** with soap and water.
2. **FLUSH** contaminated **EYES** with copious amounts of fresh water for 15 minutes.
3. **INGESTIONS** of **SMALL** amounts (less than 10 mg/kg body weight) occurring less than an hour before treatment, are probably best treated by:
   A. **SYRUP OF IPECAC,** followed by 1-2 glasses of water. Dose for adults and children over 12 years: 30 ml. Dose for children under 12 years: 15 ml.
   B. **ACTIVATED CHARCOAL**
   Administer 30-50 gm as a slurry in tap water, after vomiting stops.
   C. **SODIUM OR MAGNESIUM SULFATE,** 0.25 gm/kg in tap water, as a cathartic.

4. **INGESTIONS** of **LARGE** amounts (more than 10 mg/kg) occurring less than an hour before treatment, should probably be treated by gastric lavage:

   A. **INTUBATE** stomach and **ASPIRATE** contents.
   B. **LAVAGE** stomach with slurry of **ACTIVATED CHARCOAL** in 0.9% saline. Leave 30-50 gm activated charcoal in the stomach before withdrawing tube.
   C. **SODIUM SULFATE,** 0.25 gm/kg in tap water, as a cathartic.

      CAUTION: Hydrocarbons (kerosene, petroleum distillates) are included in some formulations of these chemicals. Ingestion of very **LARGE AMOUNTS** may cause CNS depression. In this case, **IPECAC IS CONTRAINDICATED.** Also, gastric intubation incurs a risk of **HYDROCARBON PNEUMONITIS.** For this reason observe the following precautions:

      (1) If the victim is unconscious or obtunded and facilities are at hand, insert an **ENDOTRACHEAL TUBE** (cuffed, if available) prior to gastric intubation.
      (2) Keep victim's **HEAD BELOW LEVEL OF STOMACH** during intubation and lavage (Trendelenburg, or left lateral decubitus, with head of table tipped downward). Keep victim's head turned to the left.
      (3) **ASPIRATE PHARYNX** as regularly as possible to remove gagged or vomited stomach contents.

5. **INGESTIONS** occurring **MORE THAN** an **HOUR** before treatment are probably best treated only by **ACTIVATED CHARCOAL,** 30-50 gm, and **SODIUM** or **MAGNESIUM SULFATE,** 0.25 gm/kg, as described above.
6. There are no specific antidotes for these chemicals. Because manifestations of toxicity do occasionally occur in peculiarly predisposed individuals, **MAINTAIN CONTACT** with victim for at least 72 hours so that unexpected adverse effects can be treated promptly.

INDEX TO PESTICIDE POISONINGS BY SYMPTOMS AND SIGNS

A listing of pesticides capable of causing specific symptoms and signs may be of some help to professionals confronted with illnesses possibly caused by pesticides. However, the limitations of this kind of index should be clearly understood. Rarely are particular manifestations *always* present in poisonings by a given chemical, and many poisonings are characterized by unexpected symptoms. Furthermore, there are usually many causes of particular symptoms and signs.

The purpose of these lists is, therefore, only to direct the professional's attention to a series of chemicals possibly responsible for various symptoms and signs, based on past experience. Starting from the major presenting feature of the illness, the interviewer can inquire closely into possible exposures to the principal causative toxicants, and then, if appropriate, assemble more substantive evidence for or against a poisoning diagnosis, e.g., concurrence of multiple manifestations of specific poisonings, and laboratory test findings.

Not all manifestations of illness are included. Some symptoms, such as dizziness and weakness, are caused by so many chemicals by either direct or indirect mechanisms that they have little value diagnostically.

This approach to clinical toxicology has been developed by Alan K. Done, M.D., of Wayne State School of Medicine. His general format of classification (Solving the Poison Puzzle, *Emergency Medicine,* February 1979) is used in the following tables. Chemicals appearing in the lists headed "Characteristic of These Poisonings" have been substantially consistent in producing the symptoms or signs identified in the left column. Agents listed in the column headed "Occurs in These Poisonings" are found with sufficient frequency to deserve mention, but the association is not highly consistent.

MANIFESTATIONS	CHARACTERISTIC OF THESE POISONINGS	OCCURS IN THESE POISONINGS
General		
Breath odor of.		
Garlic	Arsenic Phosphorus Phosphides Phosphine	
Bitter almonds	Cyanide	
Rotten cabbage	Carbon disulfide	
Fever	Nitro-, chloro- phenols	Chlorophenoxy compounds
Hypothermia	Vacor	
Myalgia		Chlorophenoxy compounds
Chills	Arsine Vacor	

MANIFESTATIONS	CHARACTERISTIC OF THESE POISONINGS	OCCURS IN THESE POISONINGS
Thirst	Nitro-, chloro-, phenols Aminopyridine Phosphine	
Anorexia	Organophosphates Carbamate insecticides Nicotine	Fumigants Nitro-, chloro-, phenols Arsenicals
Hot sensations	Chlordimeform Arsine	
Skin and Mucous Membranes		
Dry, cracked skin of hands	Paraquat Petroleum distillates Weed oil	
Loss of nails	Paraquat	
Brittle nails	Inorganic arsenicals	
Loss of hair	Thallium Inorganic arsenicals	
Sweating	Organosphates Carbamate insecticides Nitro-, chloro- phenols Nicotine Aminopyridine	
Pallor	Organchlorines	Anticoagulant rodenticides
Cyanosis	Paraquat Strychnine Crimidine Nicotine Sodium fluoroacetate	Organophosphates Carbamate insecticides Organochlorines
Scratchy throat and irritated eyes	Sulfur dioxide Acrolein Chloropicrin Nitro-, chloro- phenols Formaldehyde Pyrethrins Copper compounds Endothall Sodium chlorate Methyl bromide	Paraquat Bisdithiocarbamates Ethylene bisdithiocarbamates Chloroaliphatic acids
Blisters or burns	Phosphorus	Liquid methyl bromide or ethylene oxide
Rash	Sulfur Thiram Propachlor Barban	Picloram Difolatan Captan Chlorothalonil Nitro-, chloro- phenols Many other herbicides and fungicides
Yellow stain	Nitrophenols	
Ecchymoses	Anticoagulant rodenticides Phosphorus Phosphides	
Keratoses	Inorganic arsenicals	

MANIFESTATIONS	CHARACTERISTIC OF THESE POISONINGS	OCCURS IN THESE POISONINGS
Jaundice	Phosphorus Phosphides Phosphine Halocarbon fumigants	Paraquat Inorganic arsenicals
Central Nervous System		
Headache	Organophosphates Carbamate insecticides Organochlorines Fumigants Nicotine Inorganic arsenicals	Nitrophenols Chlorophenols
Ataxia	Organophosphates Carbamate insecticides *Endothall* Nicotine Phenyl mercuric acetate	Fumigants Inorganic arsenicals *Organochlorines*
Convulsions	Organochlorines Strychnine Crimidine Phosphorus Cyanide Sodium fluoroacetate Nicotine Aminopyridine Endothall	Nitro-, chloro- phenols Organophosphates Carbamate insecticides Sulfuryl fluoride
Muscle twitching	Organophosphates Carbamate insecticides Sulfuryl fluoride	Chlorophenoxy compounds
Tremors	Organophosphates Carbamates insecticides Phosphine Aminopyridine Cycloheximide Nicotine	Pyrethrins Nitro-, chloro- phenols Bentazon Sulfuryl fluoride
Mental confusion	Organophosphates Carbamate insecticides Nitrophenols Chlorophenols Cyanide Organochlorines Vacor Sodium fluoroacetate Carbon disulfide Aminopyridine Cycloheximide	Strychnine Crimidine Nicotine Inorganic arsenicals
Sudden unconsciousness	Cyanide	Organophosphates Diquat Carbamate insecticides Halocarbon fumigants
Central Nervous System		
Tingling and numbness in the extremities	Carbon disulfide Vacor Sodium fluoroacetate	Inorganic arsenicals
Tetany	Phosphorus Phosphides	
Myotonia		Chlorophenoxy compounds

MANIFESTATIONS	CHARACTERISTIC OF THESE POISONINGS	OCCURS IN THESE POISONINGS
Miosis	Organophosphates Carbamate insecticides	
Gastrointestinal Tract		
Nausea, vomiting, abdominal cramps, diarrhea	Organophosphates Carbamate insecticides Diquat Phosphorus Phosphides Phosphine Inorganic arsenicals Arsine Fumigants Red squill Cycloheximide Endothall Nicotine Chlorates Copper Compounds	Organochlorines Chloro-, nitro- phenols Bisdithiocarbamates Ethylene bisdithiocarbamates Chlorophenoxy compounds *Organic arsenicals* Paraquat Bentazon Chloroaliphatic acids
Salivation	Organophosphates Carbamate insecticides Cycloheximide Nicotine	
Respiratory System		
Stuffy nose, wheezing	Pyrethrum Bisdithiocarbamates plus alcohol	
Nosebleed		Paraquat
Coughing frothy sputum (pulmonary edema)	Methyl bromide Phosphine Phosphorus Phosphides Ethylene oxide	Organophosphates Carbamate insecticides ANTU
Rhinorrhea	Organophosphates Carbamate insecticides Fumigants	
Tachypnea	Nitro-, chloro- phenols	
Respiratory depression	Organophosphates Carbamate insecticides Fumigants Cyanide Acrylonitrile Nicotine Endothall Sodium chlorate	Organochlorines
Labored breathing	Methyl bromide Organophosphates Carbamate insecticides Phosphine Phosphides Phosphorus	Sulfuryl fluoride
Chest pain	Fumigants Sodium chlorate	Organophosphates Carbamate insecticides Chlorophenoxy herbicides Nitro-, chloro- phenols Chloroaliphatic acids

MANIFESTATIONS	CHARACTERISTIC OF THESE POISONINGS	OCCURS IN THESE POISONINGS
Cardiovascular System		
Bradycardia	Organophosphates Carbamate insecticides Cyanide	
Tachycardia	Nitrophenols Chlorophenols	Organochlorines
Hypotension, shock	Phosphorus Phosphides Phosphine Vacor Endothall Cyanide	Bisdithiocarbamates plus alcohol Inorganic arsenicals Anticoagulant rodenticides
Irregular heart beat	Sodium fluoroacetate Halocarbon fumigants Endothall	Organochlorines Red squill
Hypertension	Nicotine	
Renal System		
Renal failure	Arsine Fumigants Cycloheximide Chlorates	Paraquat Diquat Inorganic arsenicals Copper compounds
Urinary frequency, dysuria	Chlordimeform Vacor	
Renal colic	Anticoagulant rodenticides Chlorates	
Blood		
Anemia	Naphthalene Anticoagulant rodenticides	Inorganic arsenicals
Leukopenia		Nitrophenols Inorganic arsenicals
Hypoprothrombinemia	Anticoagulant rodenticides	
Depressed cholinesterase enzyme activities	Organophosphates	Carbamate insecticides (large dosage)
Methemoglobinemia	Chlorates	
Free hemoglobin in plasma	Naphthalene Arsine Copper compounds Sodium chlorate	
Elevated alkaline phosphatase, GOT, LDH	Halocarbon fumigants Inorganic arsenicals Diquat Paraquat Aminopyridine	Endrin
Elevated blood bromide	Methyl bromide	
Hyperbilirubinemia	Paraquat Diquat Phosphine Phosphorus Phosphides Copper compounds Inorganic arsenicals	Halocarbon fumigants

MANIFESTATIONS	CHARACTERISTIC OF THESE POISONINGS	OCCURS IN THESE POISONINGS
Elevated BUN, creatinine	Paraquat Diquat Fumigants Chlorates Inorganic arsenicals	Sulfuryl fluoride Nitro-, chloro-, phenols
Hyperkalemia	Naphthalene Chlorates Copper compounds	
Urine		
Proteinuria	Diquat Paraquat Nitro-, chloro-, phenols Fumigants Cycloheximide Copper compounds Phenyl mercuric acetate Sodium chlorate	Endothall Sulfuryl fluoride
Hematuria	Anticoagulant rodenticides Sodium chlorate Cycloheximide Chlordimeform	Chlordimeform Fumigants Paraquat Diquat
Ketonuria	Vacor Aminopyridine	Phosphorus Phosphides
Hemoglobinuria	Naphthalene Arsine Sodium chlorate	
Myoglobinuria		Chlorophenoxy compounds
Porphyrinuria	Hexachlorobenzene	
Bilirubinuria	Halocarbon fumigants Phosphorus Phosphides Phosphine	
Glycosuria	Vacor	
Feces		
Blood present (melena)	Diquat Sodium chlorate Anticoagulant rodenticides Phosphorus Phosphides Endothall Cycloheximide	Paraquat
Luminescence	Phosphorus	
Semen		
Low sperm count		Dibromochloropropane Kepone

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