CHAPTER 15

Fungicides

Fungicides are extensively used in industry, agriculture, and the home and garden for a number of purposes, including: protection of seed grain during storage, shipment, and germination; protection of mature crops, berries, seedlings, flowers, and grasses in the field, in storage, and during shipment; suppression of mildews that attack painted surfaces; control of slime in paper pulps; and protection of carpet and fabrics in the home.

Fungicides vary enormously in their potential for causing adverse effects in humans. Historically, some of the most tragic epidemics of pesticide poisoning occurred because of mistaken consumption of seed grain treated with organic mercury or hexachlorobenzene. However, most fungicides currently in use are unlikely to cause frequent or severe systemic poisonings for several reasons. First, many have low inherent toxicity in mammals and are inefficiently absorbed. Second, many fungicides are formulated as suspensions of wettable powders or granules, from which rapid, efficient absorption is unlikely. And third, methods of application are such that relatively few individuals are intensively exposed. Apart from systemic poisonings, fungicides as a class are probably responsible for a disproportionate number of irritant injuries to skin and mucous membranes, as well as dermal sensitization.

The following discussion covers the recognized adverse effects of widely used fungicides. For fungicides that have caused systemic poisoning, recommendations for management of poisonings and injuries are set forth. For fungicides not known to have caused systemic poisonings in the past, only general guidelines can be offered.

The discussion of fungicide-related adverse effects proceeds in this order:

- Substituted Benzenes
- Thiocarbamates
- Ethylene Bis Dithiocarbamates
- Thiophthalimides
- Copper Compounds
- Organomercury Compounds
- Organotin Compounds
- Cadmium Compounds
- Miscellaneous Organic Fungicides

HIGHLIGHTS

- Numerous fungicides in use with varying levels of toxicity
- Other than organomercury compounds, most fungicides are unlikely to be absorbed enough to cause systemic poisonings

Signs and Symptoms:

- Variable

Treatment:

- Dermal and eye decontamination
- GI decontamination
- Intravenous fluids

Contraindicated:

- Atropine. Fungicides are not cholinesterase inhibitors

Commercial Products

SUBSTITUTED BENZENES

chloroneb
- Terraneb SP

chlorothalonil
- Bravo
- Clorto Caffaro
- Clortosip
- Daconil 2787
- Exotherm Termil
- Tuffcide
- others

dicloran
- Allisan
- Clortran
- DCNA

hexachlorobenzene*
- Anticarie
- Ceku C.B.
- HCB
- No Bunt

pentachloronitrobenzene
- Avicol
- Earthcide
- Folosan
- Kobu
- Kobutol
- PCNB
- Pentagen
- quintozene
- Tri-PCNB
- others

* Discontinued in the U.S.

SUBSTITUTED BENZENES

Toxicology

Chloroneb is supplied as wettable powder for treatment of soil and seed. This agent exhibits very low oral toxicity in mammals. It may be moderately irritating to skin and mucous membranes. The metabolite dichloromethoxyphenol is excreted in the urine. No cases of systemic poisoning in humans have been reported.

Chlorothalonil is available as wettable powder, water dispersible granules, and flowable powders. Chlorothalonil has caused irritation of skin and mucous membranes of the eye and respiratory tract on contact. Cases of allergic contact dermatitis have been reported. There is one report of immediate anaphylactoid reaction to skin contact.[1] It is apparently poorly absorbed across the skin and the gastrointestinal lining. No cases of systemic poisoning in humans have been reported.

Dicloran is a broad-spectrum fungicide widely used to protect perishable produce. It is formulated as wettable powder, dusts, and flowable powders. Dicloran is absorbed by occupationally exposed workers, but it is promptly eliminated, at least partly in the urine. Biotransformation products include dichloroaminophenol, which is an uncoupler of oxidative phosphorylation (enhances heat production). Extraordinary doses of dicloran given to laboratory animals cause liver injury and corneal opacities.

Based on laboratory animal studies and effects of similar compounds, large doses might be expected to cause liver injury, pyrexia, corneal opacities, and possibly methemoglobinemia. None of these have been observed in humans exposed to DCNA.

Hexachlorobenzene. Principal formulations are dusts and powders. Hexachlorobenzene differs chemically and toxicologically from hexachlorocyclohexane, the gamma isomer of which (lindane) is still a widely-used insecticide.

Although this seed protectant fungicide has only slight irritant effects and relatively low single-dose toxicity, long-term ingestion of HCB-treated grain by Turkish farm dwellers in the late 1950s caused several thousand cases of toxic porphyria resembling porphyria cutanea tarda.[2] This condition was due to impaired hemoglobin synthesis, leading to toxic end-products (porphyrins) in body tissues. The disease was characterized by excretion of red-tinged (porphyrin-containing) urine, bullous lesions of light-exposed skin, scarring and atrophy of skin with overgrowth of hair, liver enlargement, loss of appetite, arthritic disease, and wasting of skeletal muscle mass. Although most adults ultimately recovered after they stopped consuming the HCB-treated grain, some infants nursed by affected mothers died.

Hexachlorobenzene is effectively dechlorinated and oxidized in humans; trichlorophenols are the major urinary excretion products. Disposition is sufficiently prompt that occupationally exposed workers usually show only slight

elevation of blood HCB concentrations. HCB is sometimes present in blood specimens from "non-occupationally exposed" persons in concentrations of up to 5 mcg per liter. Residues in food are the probable cause.

Pentachloronitrobenzene is used to dress seed and treat soil. Formulations include emulsifiable concentrates, wettable powders, and granules. Hexachlorobenzene is a minor contaminant to technical PCNB.

High concentrations in prolonged contact with skin have caused sensitization in some tested volunteers, but neither irritation nor sensitization has been reported in occupationally exposed workers. One case of conjunctivitis and keratitis occurred following eye contamination. This resolved slowly but completely.

Systemic poisonings have not been reported. Clearance in laboratory animals is slow, probably due to enterohepatic recirculation. Excretion is chiefly biliary, with some conversion to pentachloroaniline, pentachlorophenol, and other metabolites in the liver. Although a methemoglobinemic effect might be suspected (as from nitrobenzene), this has not been reported in humans or animals, nor has toxic porphyria (as from hexachlorobenzene) been reported.

Confirmation of Poisoning

Hexachlorobenzene (HCB) can be measured in blood by gas chromatography. Chlorophenol metabolites can be measured in the urine. Although inherited disease and a number of exogenous agents may cause porphyrins to appear in the urine, a test for porphyrins may be useful for toxicological diagnosis if there has been a known exposure to HCB or if a patient exhibits signs suggestive of porphyria cutanea tarda.

Gas chromatography can be used to measure PCNB and metabolites, chlorothalonil, and chloroneb, but the analysis is not widely available. Methods have also been described for analysis of dicloran, but they are not widely available.

Treatment

1. Skin decontamination. Dermal contamination should be washed off with soap and water. Flush contamination from the eyes with copious amounts of water. If irritation persists, specialized medical care should be obtained. See Chapter 2.

2. Gastrointestinal decontamination. If a large amount of the fungicide has been ingested in the last few hours, and if copious vomiting has not already occurred, it may be reasonable to consider GI decontamination. Activated charcoal can be used along with the addition of the cathartic sorbitol to the charcoal slurry. If sorbitol is given separately, it should be diluted with an equal volume of water before administration. No more than one dose of sorbitol is recommended and it should be used with caution in children and the elderly. See Chapter 2 for appropriate dosages.

Commercial Products

THIOCARBAMATES

ferbam
- Carbamate WDG
- Ferbam
- Ferberk
- Hexaferb
- Knockmate
- Trifungol

metam-sodium
- A7 Vapam
- Busan 1020
- Karbation
- Maposol
- Metam-Fluid BASF
- Nemasol
- Solasan 500
- Sometam
- Trimaton
- Vapam
- VPM

thiram
- Aules
- Chipco Thiram 75
- Fermide 850
- Fernasan
- Hexathir
- Mercuram
- Nomersam
- Polyram-Ultra
- Pomarsol forte
- Spotrete-F
- Spotrete WP 75
- Tetrapom
- Thimer
- Thioknock
- Thiotex
- Thiramad
- Thirasan
- Thiuramin
- Tirampa
- TMTD
- Trametan
- Tripomol
- Tuads

ziram
- Cuman
- Hexazir
- Mezene
- Tricarbamix
- Triscabol
- Vancide MZ-96
- Zincmate
- Ziram F4
- Ziram Technical
- Zirberk
- Zirex 90
- Ziride
- Zitox

If contact with the toxicant has been minimal (for example, oral contamination only, promptly flushed out of the mouth), administration of charcoal without a cathartic, followed by careful observation of the patient, probably represents optimal management.

3. Porphyria. Persons affected by porphyria should avoid sunlight, which exacerbates the dermal injury by porphyrins.

THIOCARBAMATES

Thiocarbamates are commonly formulated as dusts, wettable powders, or water suspensions. They are used to protect seeds, seedlings, ornamentals, turf, vegetables, fruit, and apples. Unlike the N-methyl carbamates (Chapter 5), thiocarbamates have very little insecticidal potency. A few exhibit weak anticholinesterase activity, but most have no significant effect on this enzyme. Overall, they are less of a threat to human health than the insecticidal carbamates. Fungicidal thiocarbamates are discussed in this section, while those used as herbicides are considered in Chapter 13.

METAM-SODIUM

Metam-sodium is formulated in aqueous solutions for application as a soil biocide and fumigant to kill fungi, bacteria, weed seeds, nematodes, and insects. All homeowner uses have been cancelled in the United States.

Toxicology

Metam-sodium can be very irritating to the skin. Poisonings by ingestion of metam-sodium have not been reported. Although animal feeding studies do not indicate extraordinary toxicity of metam-sodium by ingestion, its decomposition in water yields methyl isothiocyanate, a gas that is extremely irritating to respiratory mucous membranes, to the eyes, and to the lungs. Inhalation of methyl isothiocyanate may cause pulmonary edema (severe respiratory distress, coughing of bloody, frothy sputum). For this reason, metam-sodium is considered a fumigant. It must be used in outdoor settings only, and stringent precautions must be taken to avoid inhalation of evolved gas.

Theoretically, exposure to metam-sodium may predispose the individual to Antabuse reactions if alcohol is ingested after exposure. (See Thiram.) However, no such occurrences have been reported.

Confirmation of Poisoining

No tests for metam-sodium or its breakdown products in body fluids are available.

Treatment

1. Skin decontamination. Skin contamination should be washed off with soap and water. Flush contamination from the eyes with copious amounts of water to avoid burns and corneal injury. If dermal or eye irritation persists, specialized medical treatment should be obtained. See Chapter 2.

2. Gastrointestinal decontamination. If a large amount has been ingested recently, consider gastric emptying or charcoal and cathartic. See Chapter 2 for appropriate dosages.

3. Pulmonary edema. If pulmonary irritation or edema occur as a result of inhaling methyl isothiocyanate, transport the victim promptly to a medical facility. Treatment for pulmonary edema should proceed as outlined in Chapter 16, Fumigants.

4. Contraindicated: Metam-sodium is not a cholinesterase inhibitor. Atropine is not an antidote.

THIRAM

Thiram is a common component of latex and possibly responsible for some of the allergies attributed to latex.

Toxicology

Thiram dust is moderately irritating to human skin, eyes, and respiratory mucous membranes. Contact dermatitis has occurred in occupationally exposed workers. A few individuals have experienced sensitization to thiram.[3]

Systemic human poisonings by thiram itself have been very few, probably due to limited absorption in most circumstances involving human exposure. Those which have been reported have been similar clinically to toxic reactions to disulfiram (Antabuse), the ethyl analogue of thiram which has been extensively used in alcohol aversion therapy.[3] In laboratory animals, thiram at high dosage has effects similar to those of disulfiram (hyperactivity, ataxia, loss of muscle tone, dyspnea, and convulsions), but thiram appears to be about 10 times as toxic as disulfiram.

Neither thiram nor disulfiram are cholinesterase inhibitors. Both, however, inhibit the enzyme acetaldehyde dehydrogenase, which is critical to the conversion of acetaldehyde to acetic acid. This is the basis for the "Antabuse reaction" that occurs when ethanol is consumed by a person on regular disulfiram dosage. The reaction includes symptoms of nausea, vomiting, pounding headache, dizziness, faintness, mental confusion, dyspnea, chest and abdominal pain, profuse sweating, and skin rash. In rare instances, Antabuse reactions may have occurred in workers who drank alcohol after previously being exposed to thiram.

Confirmation of Poisoning

Urinary xanthurenic acid excretion has been used to monitor workers exposed to thiram. The test is not generally available.

Treatment: Thiram Toxicosis

1. Skin decontamination. Wash thiram from the skin with soap and water. Flush contamination from the eyes with copious amounts of clean water. If irritation of skin or eyes persists, specialized medical treatment should be obtained.

2. Gastrointestinal decontamination. If a large amount of thiram has been swallowed within 60 minutes of presentation, and effective vomiting has not already occurred, the stomach may be emptied by intubation, aspiration, and lavage, taking all precautions to protect the airway from aspiration of vomitus. Lavage should be followed by instillation of activated charcoal and cathartic. If only a small amount of thiram has been ingested and/or treatment has been delayed, oral administration of activated charcoal and cathartic probably represents optimal management.

3. Intravenous fluids. Appropriate IV fluids should be infused, especially if vomiting and diarrhea are severe. Serum electrolytes and glucose should be monitored and replaced as needed.

Treatment: Acetaldehyde Toxicosis (Antabuse Reaction)

1. Immediate management. Oxygen inhalation, Trendelenburg positioning, and intravenous fluids are usually effective in relieving manifestations of Antabuse reactions.

2. Alochol avoidance. Persons who have absorbed any significant amount of thiocarbamates must avoid alcoholic beverages for at least three weeks. Disposition of thiocarbamates is slow, and their inhibitory effects on enzymes are slowly reversible.

ZIRAM AND FERBAM

These are formulated as flowable and wettable powders, used widely on fruit and nut trees, apples, vegetables, and tobacco.

Toxicology

Dust from these fungicides is irritating to the skin, respiratory tract, and eyes. Prolonged inhalation of ziram is said to have caused neural and visual disturbances, and, in a single case of poisoning, a fatal hemolytic reaction. Theoretically, exposure to ziram or ferbam may predispose the individual to Antabuse reactions if alcohol is ingested after exposure. (See Thiram.) However, no such occurrences have been reported.

Confirmation of Poisoning

No tests for these fungicides or their breakdown products in body fluids are available.

Treatment

1. Skin decontamination. Skin contamination should be washed off with soap and water. Flush contamination from the eyes with copious amounts of water. If dermal or eye irritation persists, specialized medical treatment should be obtained. See Chapter 2.

2. Gastrointestinal decontamination. If substantial amounts of ferbam or ziram have been ingested recently, consideration should be given to gastric emptying. If dosage was small and/or several hours have elapsed since ingestion, oral administration of charcoal and a cathartic probably represents optimal management.

3. Hemolysis. If hemolysis occurs, intravenous fluids should be administered, and induction of diuresis considered.

ETHYLENE BIS DITHIOCARBAMATES (EBDC COMPOUNDS)

MANEB, ZINEB, NABAM, AND MANCOZEB

Maneb and zineb are formulated as wettable and flowable powders. Nabam is provided as a soluble powder and in water solution. Mancozeb is a coordination product of zinc ion and maneb. It is formulated as a dust and as wettable and liquid flowable powders.

Toxicology

These fungicides may cause irritation of the skin, respiratory tract, and eyes. Both maneb and zineb have apparently been responsible for some cases of chronic skin disease in occupationally exposed workers, possibly by sensitization.

Although marked adverse effects may follow injection of EBDC compounds into animals, systemic toxicity by oral and dermal routes is generally low. Nabam exhibits the greatest toxicity, probably due to its greater water solubility and absorbability. Maneb is moderately soluble in water, but mancozeb and zineb are essentially water insoluble. Absorption of the latter fungicides across skin and mucous membranes is probably very limited. Systemic poisonings of humans have been extremely rare. However, zineb apparently precipitated an episode of hemolytic anemia in one worker predisposed by reason of multiple red cell enzyme deficiencies.[4] Maneb exposure has been reported in one person who developed acute renal failure and was treated with hemodialysis.[5] Another person developed behavioral and neurological symptoms including tonic-clonic seizures after handling maneb. He recovered uneventfully with supportive care.[6]

The EBDC compounds are not inhibitors of cholinesterase or of acetaldehyde dehydrogenase. They do not induce cholinergic illness or "Antabuse" reactions.

Confirmation of Poisoining

No tests for these fungicides or their breakdown products in body fluids are available.

Treatment

See Treatment for Substituted Benzenes, p. 139.

THIOPHTHALIMIDES

CAPTAN, CAPTAFOL, AND FOLPET

These agents are widely used to protect seed, field crops, and stored produce. They are formulated as dusts and wettable powders. Captafol is no longer registered for use in the United States.

Toxicology

All of these fungicides are moderately irritating to the skin, eyes, and respiratory tract. Dermal sensitization may occur; captafol appears to have been responsible for several episodes of occupational contact dermatitis.[7,8] No systemic poisonings by thiophthalimides have been reported in humans, although captafol has been reported to have exacerbated asthma after occupational exposure.[9] Laboratory animals given very large doses of captan exhibit hypothermia, irritability, listlessness, anorexia, hyporeflexia, and oliguria, the latter with glycosuria and hematuria.

Confirmation of Poisoning

Captan fungicides are metabolized in the body to yield two metabolites that can be measured in the urine.[10]

Treatment

See Treatment for Substituted Benzenes, p. 139.

COPPER COMPOUNDS

INORGANIC AND ORGANIC COMPOUNDS

Insoluble compounds are formulated as wettable powders and dusts. Soluble salts are prepared as aqueous solutions. Some organometallic compounds are soluble in mineral oils.

A great many commercial copper-containing fungicides are available. Some are mixtures of copper compounds. Others include lime, other metals, and other fungicides. Compositions of specific products can usually be provided by manufacturers or by poison control centers.

Copper-arsenic compounds such as Paris green may still be used in agriculture outside the U.S. Toxicity of these compounds is chiefly due to arsenic content (see Chapter 14, Arsenical Pesticides).

Commercial Products

THIOPHTHALIMIDES

captafol*
- Crisfolatan
- Difolatan
- Foltaf
- Haipen
- Merpafol
- Mycodifol
- Sanspor

captan
- Captaf
- Captanex
- Merpan
- Orthocide
- Vondcaptan

folpet
- Folpan
- Fungitrol II
- Phaltan
- Thiophal

COPPER COMPOUNDS

Inorganic Copper Compounds

copper acetate
copper ammonium carbonate
copper carbonate, basic
copper hydroxide
copper lime dust
copper oxychloride
copper potassium sulfide
copper silicate
copper sulfate
cupric oxide
cuprous oxide
tribasic
- Bordeaux Mixture

Organic Copper Compunds

copper linoleate
copper naphthenate
copper oleate
copper phenyl salicylate
copper quinolinolate
copper resinate

* Discontinued in the U.S.

Toxicology

The dust and powder preparations of copper compounds are irritating to the skin, respiratory tract, and particularly to the eyes. Soluble copper salts (such as the sulfate and acetate) are corrosive to mucous membranes and the cornea. Limited solubility and absorption probably account for the generally low systemic toxicity of most compounds. The more absorbable organic copper compounds exhibit the greatest systemic toxicity in laboratory animals. Irritant effects from occupational exposures to copper-containing fungicides have been fairly frequent. Most of what is known about mammalian toxicity of copper compounds has come from veterinary toxicology (livestock seem uniquely vulnerable) and poisonings in humans due to deliberate ingestion of copper sulfate or to consumption of water or food that had been contained in copper vessels.

Early signs and symptoms of copper poisoning include a metallic taste, nausea, vomiting, and epigastric pain. In more severe poisonings, the gastrointestinal irritation will worsen with hemetemesis and melanotic stools. Jaundice and hepatomegaly are common.[11,12] Hemolysis can occur, resulting in circulatory collapse and shock. Methemoglobinemia has been reported in these cases.[11,13,14] Acute renal failure with oliguria can also occur. Shock is a primary cause of death early in the course, and renal failure and hepatic failure contribute to death more than 24 hours after poisoning.[15]

Treatment

Management of poisonings by ingestion of copper-containing fungicides depends entirely on the chemical nature of the compound: the strongly ionized salts present the greatest hazard; the oxides, hydroxides, oxychloride, and oxysulfate are less likely to cause severe systemic poisoning.

1. Skin decontamination. Dust and powder should be washed from the skin with soap and water. Flush the eyes free of irritating dust, powder, or solution, using clean water or saline. If eye or dermal irritation persists, specialized medical treatment should be obtained. Eye irritation may be severe. See Chapter 2.

2. Anti-corrosive. Give water or milk as soon as possible to dilute the toxicant and mitigate corrosive action on the mouth, esophagus, and gut.

3. Gastrointestinal decontamination. Vomiting is usually spontaneous in acute copper ingestion. Further induction of emesis is contraindicated because the corrosive nature of some copper salts can cause further damage to the esophagus. Further GI decontamination should be determined on a case-by-case basis, as outlined in Chapter 2. Gastric lavage may cause further damage.[15] Charcoal has not been widely studied in metal poisonings as an effective adsorbant.

Caution: Gastric intubation may pose a serious risk of esophageal perforation if corrosive action has been severe. In this event, it may be best to avoid gastric intubation.

4. Intravenous fluids. If indications of systemic illness appear, administer intravenous fluids containing glucose and electrolytes. Monitor fluid balance, and correct blood electrolyte concentrations as needed. If shock develops, give blood transfusions and vasopressor amines, as required.

5. Hemolysis. Monitor plasma for evidence of hemolysis (free hemoglobin) and the red cells for methemoglobin. If hemolysis occurs, alkalinize the urine to about pH 7.5 by adding sodium bicarbonate to the intravenous infusion fluid. Also, mannitol diuresis may be considered. If methemoglobinemia is severe (> 30%), or the patient is cyanotic, administer methylene blue. The dosage for adults/child is 1-2 mg/kg/dose, given as a slow IV push over a few minutes, every 4 hours as needed.[15]

6. Pain management. Severe pain may require the administration of morphine.

7. Chelating agents. The value of chelating agents in copper poisoning has not been established.[16] However, BAL appears to accelerate copper excretion and may alleviate illness. D-penicillamine is the treatment for Wilson's disease due to chronic copper toxicity; however, in the context of severe vomiting and/or mental status changes from an acute ingestion, BAL would be a more likely initial choice.[13,15] For a recommended schedule of dosage for initial therapy with BAL and subsequent penicillamine administration, see Chapter 14, Arsenical Pesticides.

8. Hemodialysis. Although hemodialysis is indicated for patients with renal failure, copper is not effectively removed in the dialysate.[11]

ORGANOMERCURY COMPOUNDS

METHYL MERCURY AND METHOXYETHYL MERCURY COMPOUNDS, PHENYLMERCURIC ACETATE

These fungicides have been formulated as aqueous solutions and dusts. They have been used chiefly as seed protectants. Use of alkyl mercury fungicides in the United States has been virtually prohibited for several years. Phenylmercuric acetate is no longer permitted to be used in the United States.

Commercial Products

ORGANOMERCURY COMPOUNDS

Methyl Mercury Compounds
methyl mercury acetate
propionate
quinolinolate

Methoxyethyl Mercury Compounds
methoxyethyl mercury acetate
MEMA
Panogen
Panogen M
methoxyethyl mercury chloride
Ceresan
Emisan 6
MEMC

Phenylmercuric Acetate
Agrosan
Setrete
Gallotox
PMAA
Shimmer-ex
Tag HL 331
Unisan

Toxicology

The mercurial fungicides are among the most toxic pesticides ever developed, for both chronic and acute hazards. Epidemics of severe, often fatal, neurologic disease have occurred when indigent residents of less developed countries consumed methyl mercury-treated grain intended for planting of crops.[17,18] Poisoning has also occurred from eating meat from animals fed mercury-treated seed.[19] Most of what is known of poisoning by organic mercurial fungicides has come from these occurrences.

Organic mercury compounds are efficiently absorbed across the gut and possibly across the skin. Volatile organic mercury is readily taken up across the pulmonary membrane. Methyl mercury is selectively concentrated in the tissue of the nervous system, and also in red blood cells. Other alkyl mercury compounds are probably distributed similarly. Excretion occurs almost entirely by way of the bile into the bowel. The residence half-life of methyl mercury in humans is about 65 days.[20] There is significant conversion of organic mercury to inorganic mercury in the red cell.

Early symptoms of poisoning are metallic taste in the mouth, numbness and tingling of the digits and face, tremor, headache, fatigue, emotional lability, and difficulty thinking. Manifestations of more severe poisoning are incoordination, slurred speech, loss of position sense, hearing loss, constriction of visual fields, spasticity or rigidity of muscle movements, and deterioration of mental capacity. Many poisonings caused by ingestion of organic mercurials have terminated fatally, and a large percentage of survivors have suffered severe permanent neurologic damage.[17-19]

Phenylmercuric acetate is not as extremely toxic as the alkyl mercury compounds. It is not as efficiently absorbed from the gut as methyl mercury.[21] Phenylmercuric acetate had been used to prevent fungal growth in latex paint. There have been reports of acrodynia in persons exposed to mercury vapor from use of interior latex paint. Symptoms include fever, erythema and desquamation of hands and feet, muscular weakness, leg cramps, and personality changes.[22] Phenylmercuric compounds have since been banned from latex paint.[20]

Confirmation of Poisoning

Mercury content of blood and tissues can be measured by atomic absorption spectrometry. Blood levels of 5 mcg/dL or greater are considered elevated for acute exposure.[21] Special procedures are needed for extraction and measurement of organic mercury compounds specifically.

Treatment

Every possible precaution should be taken to avoid exposure to organic mercury compounds. Ingestion of an organic mercury compound, even at low dosage, is life threatening, and management is difficult. Very little can be done to mitigate neurologic damage caused by organic mercurials.

Persons experiencing symptoms (metallic taste in mouth) after inhalation of volatile organic mercury compounds (methyl mercury is the most volatile) should be removed promptly from the contaminated environment and observed closely for indications of neurologic impairment. Following are the basic steps in management of poisoning:

1. Skin decontamination. Skin and hair contaminated by mercury-containing dust or solution should be cleansed with soap and water. Flush contamination from the eyes with clean water. If irritation persists, specialized medical care should be obtained. See Chapter 2.

2. Gastrointestinal decontamination. Consider gastrointestinal decontamination as outlined in Chapter 2.

3. Chelation is an essential part of the management of mercury poisoning. For dosages of specific agents, see Chapter 14, Arsenical Pesticides. Succimer (DMSA) appears to be the most effective agent available in the United States. Dimercaprol (BAL) is contraindicated in these poisonings due to its potential to increase brain levels of mercury.[20] EDTA is apparently of little value in poisonings by organic mercury. D-penicillamine is probably useful, is available in the United States, and has proven effective in reducing the residence half-life of methyl mercury in poisoned humans.[20] 2,3-dimercaptopropane-1-sulfonate acid (DMPS) and N-acetyl-D,L-penicillamine (NAP) are probably also useful but are not currently approved for use in the United States.

4. Hemodialysis. Extracorporeal hemodialysis and hemoperfusion may be considered, although experience to date has not been encouraging.

ORGANOTIN COMPOUNDS

These compounds are formulated as wettable and flowable powders for use mainly as fungicides to control blights on field crops and orchard trees. Fentin chloride was also prepared as an emulsifiable concentrate for use as a molluscicide (Aquatin 20 EC, discontinued 1995). Tributyltin salts are used as fungicides and antifouling agents on ships. They are somewhat more toxic by the oral route than triphenyltin, but toxic actions are otherwise probably similar.

Commercial Products

ORGANOTIN COMPOUNDS

fentin acetate*
- Batasan
- Brestan
- Phenostat-A
- Phentinoacetate
- Suzu
- TPTA

fentin chloride*
- Tinmate

fentin hydroxide
- Super Tin
- Suzu-H
- Tubotin

triphenyl tin

* Discontinued in the U.S.

Commercial Products

CADMIUM COMPOUNDS

cadmium chloride*
Caddy
cadmium succinate*
Cadminate
cadmium sulfate*
Cad-Trete
Crag Turf Fungicide
Kromad
Miller 531

* Discontinued in the U.S.

Toxicology

These agents are irritating to the eyes, respiratory tract, and skin. They are probably absorbed to a limited extent by the skin and gastrointestinal tract. Manifestations of toxicity are due principally to effects on the central nervous system: headache, nausea, vomiting, dizziness, and sometimes convulsions and loss of consciousness. Photophobia and mental disturbances occur. Epigastric pain is reported, even in poisoning caused by inhalation. Elevation of blood sugar, sufficient to cause glycosuria, has occurred in some cases. The phenyltin fungicides are less toxic than ethyltin compounds, which have caused cerebral edema, neurologic damage, and death in severely poisoned individuals who were exposed dermally to a medicinal compound of this type.[23] No deaths and very few poisonings have been reported as a result of occupational exposures to phenyltin compounds.

Treatment

1. Skin decontamination. Skin contamination should be removed by washing with soap and water. Flush contaminants from the eyes with clean water or saline. If irritation persists, specialized medical treatment should be obtained. See Chapter 2.

2. Gastrointestinal decontamination. If large amounts of phenyltin compound have been ingested in the past hour, measures may be taken to decontaminate the gastrointestinal tract, as outlined in Chapter 2.

3. Chelating agents. Neither BAL, penicillamine, nor other chelating agents have been effective in lowering tissue stores of organotin compounds in experimental animals.

CADMIUM COMPOUNDS

Cadmium salts have been used to treat fungal diseases affecting turf and the bark of orchard trees. They were formulated as solutions and emulsions. Miller 531 and Crag Turf Fungicide 531 were complexes of cadmium, calcium, copper, chromium, and zinc oxides. They are now marketed as a generic fungicide. Kromad is a mixture of cadmium sebacate, potassium chromate, and thiram. Cad-Trete is a mixture of cadmium chloride and thiram. All cadmium fungicides in the U.S. have been discontinued.

Toxicology

Cadmium salts and oxides are very irritating to the respiratory and gastrointestinal tracts. Inhaled cadmium dust or fumes can cause respiratory toxicity after a latency period of several hours, including a mild, self-limited illness of fever, cough, malaise, headaches, and abdominal pain, similar to metal fume fever. A more severe form of toxicity includes chemical pneumonitis, and is associated with labored breathing, chest pain, and a sometimes fatal hemorrhagic pulmonary edema.[24,25] Symptoms may persist for weeks.

Ingested cadmium causes nausea, vomiting, diarrhea, abdominal pain, and tenesmus. Relatively small inhaled and ingested doses produce serious symptoms. Protracted absorption of cadmium has led to renal damage (proteinuria and azotemia), anemia, liver injury (jaundice), and defective bone structure (pathologic fractures) in chronically exposed persons. Prolonged inhalation of cadmium dust has contributed to chronic obstructive pulmonary disease.[26]

Confirmation of Poisoning

Cadmium can be measured in body fluids by appropriate extraction, followed by flame absorption spectrometry. It is reported that blood cadmium concentrations tend to correlate with acute exposure and urine levels tend to reflect total body burden. Blood levels exceeding 5 mcg/dL suggest excessive exposure.[25] Urinary excretion in excess of 100 mcg per day suggests an unusually high body burden.

Treatment

1. Skin decontamination. Skin contamination should be removed by washing with soap and water. Flush contamination from the eyes with copious amounts of clean water or saline. If irritation persists, specialized medical treatment should be obtained. See Chapter 2.

2. Pulmonary edema. Respiratory irritation resulting from inhalation of small amounts of cadmium dust may resolve spontaneously, requiring no treatment. More severe reactions, including pulmonary edema and pneumonitis, may require aggressive measures, including positive pressure mechanical pulmonary ventilation, monitoring of blood gases, administration of diuretics, steroid medications, and antibiotics.[25] Codeine sulfate may be needed to control cough and chest pain.

3. Gastrointestinal decontamination. The irritant action of ingested cadmium products on the gastrointestinal tract is so strong that spontaneous vomiting and diarrhea often eliminate nearly all unabsorbed cadmium from the gut. If

Commercial Products

MISCELLANEOUS ORGANIC FUNGICIDES

anilazine*
Dyrene
benomyl
Benex
Benlate
Tersan 1991
cycloheximide*
naramycin
dodine
Carpene
Curitan
Melprex
Venturol
etridiazole
Aaterra
Ethazol
Koban
Pansoil
Terrazole
Truban
iprodione
Glycophene
Rovral
metalaxyl
Ridomil
Subdue
thiabendazole
Apl-Luster
Arbotect
Mertect
Tecto
Thibenzole
triadimefon
Amiral
Bayleton
triforine
Denarin
Funginex
Saprol

* Discontinued in the U.S.

retention of some cadmium in the lower GI tract is suspected, further gastrointestinal decontamination may be considered, as outlined in Chapter 2.

4. Intravenous fluids may be required to overcome dehydration caused by vomiting and diarrhea. Also, fluids limit cadmium toxicity affecting the kidneys and liver. However, great care must be taken to monitor fluid balance and blood electrolyte concentrations, so that failing renal function does not lead to fluid overload.

5. Chelation therapy with calcium disodium EDTA may be considered for acute poisoning, depending on measured cadmium in blood and urine, and the status of renal function. Its therapeutic value in cadmium poisoning has not been established, and use of the agent carries the risk that unduly rapid transfer of cadmium to the kidney may precipitate renal failure. Urine protein and blood urea nitrogen and creatinine should be carefully monitored during therapy. The dosage should be 75 mg/kg/day in three to six divided doses for 5 days. The total dose for the 5-day course should not exceed 500 mg/kg.[27] Succimer (DMSA) has also been used in this poisoning, but has not been demonstrated to be efficacious.

6. Contraindications: Dimercaprol (BAL) is not recommended for treatment of cadmium poisoning, chiefly because of the risk of renal injury by mobilized cadmium.

7. Liver function. Monitor urine content of protein and cells regularly, and perform liver function tests for indications of injury to these organs.

MISCELLANEOUS ORGANIC FUNGICIDES

Some modern organic fungicides are widely used. Reports of adverse effects on humans are few. Some of the known properties of these agents are listed below.

Anilazine is supplied as wettable and flowable powders. Used on vegetables, cereals, coffee, ornamentals, and turf. This product has caused skin irritation in exposed workers. Acute oral and dermal toxicity in laboratory animals is low. Human systemic poisonings have not been reported.

Benomyl is a synthetic organic fungistat having little or no acute toxic effect in mammals. No systemic poisonings have been reported in humans. Although the molecule contains a carbamate grouping, benomyl is not a cholinesterase inhibitor. It is poorly absorbed across skin; whatever is absorbed is promptly metabolized and excreted.

Skin injuries to exposed individuals have occurred, and dermal sensitization has been found among agricultural workers exposed to foliage residues.

Cycloheximide is formulated as wettable powder, sometimes combined with other fungicides. Cycloheximide is a product of fungal culture, effective against fungal diseases of ornamentals and grasses. It is selectively toxic to rats, much less toxic to dogs and monkeys. No human poisonings have been reported. Animals given toxic doses exhibit salivation, bloody diarrhea, tremors, and excitement, leading to coma and death due to cardiovascular collapse. Hydrocortisone increases the rate of survival of deliberately poisoned rats. Atropine, epinephrine, methoxyphenamine, and hexamethonium all relieved the symptoms of poisoning, but did not improve survival.

Dodine is formulated as a wettable powder. It is commonly applied to berries, nuts, peaches, apples, pears, and to trees afflicted with leaf blight. Dodine is a cationic surfactant with antifungal activity. It is absorbed across the skin and is irritating to skin, eyes, and gastrointestinal tract. Acute oral and dermal toxicity in laboratory animals is moderate. Poisonings in humans have not been reported. Based on animal studies, ingestion would probably cause nausea, vomiting, and diarrhea.

Iprodione is supplied as wettable powder and other formulations. It is used on berries, grapes, fruit, vegetables, grasses, and ornamentals, and as a seed dressing. Iprodione exhibits low acute oral and dermal toxicity in laboratory animals. No human poisonings have been reported.

Metalaxyl is supplied as emulsifiable and flowable concentrates. It is used to control soil-borne fungal diseases on fruit trees, cotton, hops, soybeans, peanuts, ornamentals and grasses. Also used as seed dressing. Metalaxyl exhibits low acute oral and dermal toxicity in laboratory animals. No human poisonings have been reported.

Etridiazole is supplied as wettable powder and granules for application to soil as a fungicide and nitrification inhibitor. Contact may result in irritation of skin and eyes. Systemic toxicity is low. Human poisonings have not been reported.

Thiabendazole is widely used as an agricultural fungicide, but most experience with its toxicology in humans has come from medicinal use against intestinal parasites. Oral doses administered for this purpose are far greater than those likely to be absorbed in the course of occupational exposure. Thiabendazole is rapidly metabolized and excreted in the urine, mostly as a conjugated hydroxy-metabolite. Symptoms and signs that sometimes follow ingestion are: dizziness, nausea, vomiting, diarrhea, epigastric distress, lethargy, fever, flushing, chills, rash and local edema, headache, tinnitus, paresthesia, and hypotension. Blood enzyme tests may indicate liver injury. Persons with liver and kidney disease may be unusually vulnerable to toxic effects. Adverse effects from use of thiabendazole as a fungicide have not been reported.

Triadimefon is supplied as wettable powder, emulsifiable concentrate, suspension concentrate, paste, and dry flowable powder. Used on fruit, cereals, vegetables, coffee, ornamentals, sugarcane, pineapple, and turf, triadimefon exhibits moderate acute oral toxicity in laboratory animals, but dermal toxicity is

low. It causes irritation if eyes are contaminated. Triadimefon is absorbed across the skin. Overexposures of humans are said to have resulted in hyperactivity followed by sedation.

Triforine is supplied as emulsifiable concentrate and wettable powder. Used on berries, fruit, vegetables, and ornamentals, triforine exhibits low acute oral and dermal toxicity in laboratory animals. Mammals rapidly excrete it chiefly as a urinary metabolite. No human poisonings have been reported.

Confirmation of Poisoining

There are no generally available laboratory tests for these organic fungicides or their metabolites in body fluids.

Treatment

See Treatment for Substituted Benzenes, p. 139.

References

1. Dannaker CJ, Maibach HI, and O'Malley M. Contact urticaria and anaphylaxis to the fungicide chlorothalonil. *Cutis* 1993;52:3120-5.
2. Peters HA, Gocmen A, Cripps DJ, et al. Epidemiology of hexachlorobenzene-induced porphyria in Turkey: Clinical and laboratory follow-up after 25 years. *Arch Neurol* 1992;39:744-9.
3. Dalvi RR. Toxicology of thiram (tetramethylthiuram disulfide): A review. *Vet Hum Toxicol* 1988;30:480-2.
4. Pinkhans J, Djaldetti M, Joshua H, et al. Sulfahemoglobinemia and acute hemolytic anemia with Heinz bodies following contact with a fungicide-zinc ethylene bisdithiocarbamate in a subject with glucose-6-phosphate dehydrogenase deficiency and hypocatalasemia. *Blood* 1963;21:484-93.
5. Koizumi A, Shiojima S, Omiya M, et al. Acute renal failure and maneb (manganouis ethylenebis[dithiocarbamate]) exposure. *JAMA* 1979;242:2583-5.
6. Israeli R, Sculsky M, and Tiberin P. Acute intoxication due to exposure to maneb and zineb: A case with behavioral and central nervous system changes. *Scand J Work Environ Health* 1983;9:47-51.
7. Peluso AM, Tardio M, Adamo F, et al. Multiple sensitization due to bis-dithiocarbamate and thiophthalimide pesticides. *Contact Dermatitis* 1991;25:327.
8. Vilaplana J and Romaguera C. Captan, a rare contact sensitizer in hairdressing. *Contact Dermatitis* 1993;29:107.
9. Royce S, Wald P, Sheppard D, et al. Occupational asthma in a pesticides manufacturing worker. *Chest* 1993;103:295-6.
10. Krieger RI and Thongsinthusak T. Captan metabolism in humans yields two biomarkers, tetrahydrophthalimide (THPI) and thiazolidine-2-thione-4-carboxylic acid (TTCA) in urine. *Drug Chem Toxicol* 1993;16:207-25.

11. Agarwal SK, Tiwari SC, and Dash SC. Spectrum of poisoning requiring haemodialysis in a tertiary care hospital in India. *Int J Artif Organs* 1993;16:20-3.
12. Lamont DL and Duflou JALC. Copper sulfate: Not a harmless chemical. *Am J Forensic Med Pathol* 1988;9:226-7.
13. Chugh KS, Singhal PC, and Sharma BK. Methemoglobinemia in acute copper sulfate poisoning. *Ann Intern Med* 1975;82:226-9.
14. Jantsch W, Kulig K, and Rumack BH. Massive copper sulfate ingestion resulting in hepatotoxicity. *Clin Toxicol* 1984-85;22:585-8.
15. POISINDEX®: Copper poisoning. Englewood, CO: Micromedex, 1998.
16. Hantson P, Lievens M, and Mahieu P. Accidental ingestion of a zinc and copper sulfate preparation. *Clin Toxicol* 1996;34:725-30.
17. Bakir F, Rustam H, Tikritis S, et al. Clinical and epidemiological aspects of methylmercury poisoning. *Postgrad Med J* 1980;56:1-10.
18. Grandjean P, Weihe P, and Nielsen JB. Methylmercury; Significance of intrauterine and postnatal exposures. *Clin Chem* 1994;40:1395-1400.
19. Snyder RD. Congenital mercury poisoning. *New Engl J Med* 1971;284:1014-5.
20. Clarkson TW. Mercury— An element of mystery. *New Engl J Med* 1990;323:1137-8.
21. Agency for Toxic Substances and Disease Registry. Mercury toxicity. *Am Fam Physician* 1992;46:1731-41.
22. Agocs MM, Etzel RA, Parrish RG, et al. Mercury exposure from interior latex paint. *New Engl J Med* 1990;323:1096-100.
23. Colosio C, Tomasini M, Cairoli S, et al. Occupational triphenyltin acetate poisoning: A case report. *Br J Ind Med* 1991;48:136-9.
24. Barnhart S and Rosenstock L. Cadmium chemical pneumonitis. *Chest* 1984;86:789-91.
25. Ando Y, Shibata E, Tsuchiyama F, et al. Elevated urinary cadmium concentrations in a patient with acute cadmium pneumonitis. *Scand J Work Environ Health* 1996;22:150-3.
26. Hendrick DJ. Occupational and chronic obstructive pulmonary disease (COPD). *Thorax* 1996;51:947-55.
27. Klaassen CD. Heavy metals and heavy metal antagonists. In: Gilman AG, Rall TW, Niew AS, et al (eds). Goodman and Gilman's The Pharmacological Basis of Therapeutics, 3rd ed. New York: Pergamon Press, 1990, pp. 1605-6.