CHAPTER 16

Fungicides

Fungicides are extensively used in industry, agriculture and the home and garden for:

1. protection of seed grain during storage, shipment and germination;
2. protection of mature crops, berries, seedlings, flowers and grasses in the field, in storage and during shipment;
3. suppression of mildews that attack painted surfaces;
4. control of slime in paper pulps; and
5. protection of carpet and fabrics in the home.

Approximately 500 million pounds of fungicides are applied worldwide annually (see **Chapter 1, *Introduction***).

Fungicides vary enormously in their potential for causing adverse effects in humans. Historically, some of the most tragic epidemics of pesticide poisoning occurred by mistaken consumption of seed grain treated with organic mercury or hexachlorobenzene. However, most fungicides currently in use and registered for use in the United States are unlikely to cause frequent or severe acute systemic poisonings for several reasons: (1) many have low inherent toxicity in mammals and are inefficiently absorbed; (2) many are formulated as suspensions of wettable powders or granules, from which rapid, efficient absorption is unlikely; and (3) methods of application are such that relatively few individuals are intensively exposed. Apart from systemic poisonings, fungicides as a class also cause irritant injuries to skin and mucous membranes, as well as some dermal sensitization.

The following discussion considers the recognized adverse effects of widely used fungicides. In the case of those agents that have caused systemic poisoning, some recommendations for management of poisonings and injuries are provided. For those 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

Strobilurins

Thiocarbamates

Ethylene Bis Dithiocarbamates

Thiophthalimides

Triazoles

Copper Compounds

Organomercury Compounds

Organotin Compounds

Cadmium Compounds

Miscellaneous Organic Fungicides

HIGHLIGHTS

Numerous fungicides in use with varying levels of toxicity

Most are unlikely to cause systemic poisonings, exceptions being

- Organomercury compounds
- Triazoles
- Some copper compounds
- Isolated EBDC exceptions

Substituted Benzine

COMMERCIAL PRODUCTS

chloroneb (Terraneb SP)

chlorothalonil (Bravo, Clorto Caffaro, Clortosip, Daconil 2787, Exotherm Termil, Tuffcide, others)

dicloran (DCNA, Allisan, Clortran)

hexachlorobenzene (HCB, Anticarie, Ceku C.B., No Bunt)

PCNB, also known as pentachloronitrobenzene (PCNB, quintozene, Avicol, Earthcide, Folosan, Kobu, Kobutol, Pentagen, Tri-PCNB, terraclor, and others)

HIGHLIGHTS

No cases of human systemic poisoning have been reported in the medical literature for chloroneb, chlorothalonil, dicloran or PCNB

TREATMENT

Decontaminate skin and eyes

In cases where large amounts of HCB have been ingested, consider GI decontamination

SUBSTITUTED BENZENES

Toxicology

Chloroneb is supplied as wettable powder for treatment of soil and seed. This agent exhibits very low oral toxicity in mammals.[1] 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.[2,3,4,5] There is one report of immediate anaphylactoid reaction to skin contact.[6] Chlorothalonil is poorly absorbed across the skin and the gastrointestinal lining. In a man known to have atopic dermatitis and allergic rhinitis, occupational exposure to chlorothalonil was reported to induce asthma symptoms, which resolved following cessation of exposure.[7] No cases of systemic poisoning in humans have been reported in the published medical literature.

Dicloran, also known as DCNA, is formulated as wettable powder, dust, liquid and flowable powder. This broad-spectrum fungicide was widely used to protect perishable produce. It is absorbed through the skin by occupationally exposed workers, but promptly eliminated, at least partly, in the urine. Biotransformation products include dichloroaminophenol, which is an uncoupler of oxidative phosphorylation (enhances heat production). According to the EPA's Registration Eligibility Decision (RED), there is low oral toxicity to mammals (rat LD_{50} is 3,400 mg/kg). There have been no cases of human systemic poisoning reported in the medical literature.

Hexachlorobenezene (HCB) is principally formulated as dusts and powders. All registrations in the United States have been canceled. It differs chemically and toxicologically from hexachlorocyclohexane, the gamma isomer of which is also known as lindane, which is still used in limited amounts as an insecticide and as a pharmaceutical agent for the treatment of lice and scabies (see **Chapter 7, *Organochlorines***).

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.[8] 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.[8]

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 up to concentrations of about 5 µg per liter. Residues in food are the probable cause. Studies have suggested that adverse neurobehavioral effects in children may occur following exposure to hexachlorobenzene, and these are discussed in **Chapter 21, *Chronic Effects***.[9,10]

PCNB (also known as Pentachloronitrobenzene) is used to treat seed and soil. Formulations include emulsifiable concentrates, wettable powders and granules. Hexachlorobenzene is a minor contaminant to technical PCNB.

Systemic poisonings have not been reported in humans. Clearance in laboratory animals is chiefly biliary, with some conversion to pentachloroaniline, pentachlorophenol and other metabolites in the liver.[11,12] Although a methemoglobinemic effect is

suspected (as from nitrobenzene), this has not been reported in man or animals, nor has toxic porphyria (as from hexachlorobenzene) been reported.

Confirmation of Poisoning

Chloroneb, chlorothalonil, dicloran, HCB and PCNB all have described methods for analysis by chromatography, but those methods are not widely available. The trichlorophenol metabolites of HCB 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.

Treatment of Substituted Benzene Toxicosis

1. Wash off dermal contamination with soap and water. Remove contamination of the eyes by flushing with copious amounts of water. If irritation persists, specialized medical care should be obtained. See **Chapter 3, *General Principles***.

2. If a large amount of HCB has been ingested in the last few hours, and if copious vomiting has not already occurred, consider GI decontamination as outlined in **Chapter 3**. If contact with the toxicant has been minimal (for example, oral contamination only) promptly flushing out the mouth and observation are probably sufficient.

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

STROBILURIN FUNGICIDES

Strobilurin compounds are a relatively newer class of fungicides, discovered in the 1990s and introduced to the market in the late 1990s and early 2000s. They are used in agriculture to kill numerous types of pathogenic fungi including mildews, molds and rusts.

Toxicology

Strobilurin fungicidal activity inhibits mitochondrial respiration by disrupting the cytochrome complex, thus blocking electron transfer.[13] Strobilurin compounds work on a broad range of fungal pests and are now used on a wide range of crops, most notably corn, since 2004.[14]

These compounds have a relatively low acute toxicity; most have a reported LD_{50} oral of over 5,000 mg/kg, except orysastrobin and metominostrobin, with LD_{50} of 356 mg/kg and 708 mg/kg, respectively.[13,15] Few human data are available, though several separate incidents in July 2007 were reported by the CDC. All reports were based on pyraclostrobin. Toxic effects were considered minimal and short term, with resolution after patient was removed from exposure. Symptoms and signs included eye irritation, upper respiratory tract irritation, weakness, dizziness, purities, skin redness and chest pain. In one case, workers in an adjacent corn field were exposed and felt the droplets following aerial spraying, and the major symptoms reported in this incident were upper respiratory tract pain and chest pain.[14]

Strobilurin

COMMERCIAL PRODUCTS

azoxystrobin (Abound, Amistar, Azo-shield, Azotech, Azoxy, Banner Heritage, Dynasty, Dyna-shield, Graduate A+, Heritage, Protégé, Quadris, Quartet, Quilt, Renown, Soygard, Sporgard, Trio, Uniform)

kresoxim-methyl (Allegro, Cygnus, Sovran)

metominostrobin

orysastrobin

picoxystrobin (Benzeneacetic acid, Cygnus, Juwel, Mentor, Ogam, Stroby/Sovran)

pyraclostrobin (Bas, Cabrio, Cornet, Headline, Honor, Insignia, Opera, Pageant, Pristine, Stamina)

trifloxystrobin (Absolute, Armada, Chipco, Compass, Distinguish, Dyna-shield, Flint, Four way, Gem, Prosper, RTU-trifloxystrobin-metalaxyl, Stratego, Tartan, Three way, Trilex, USF)

HIGHLIGHTS

Widely used on many crops

Low acute toxicity

SIGNS & SYMPTOMS

Eye & respiratory irritation

Weakness, dizziness

TREATMENT

Supportive

Consider skin/eye decontamination

Thiocarbamate
COMMERCIAL PRODUCTS

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 Technical, Ziram F4, Zirberk, Zirex 90, Ziride, Zitox)

ferbam (Carbamate WDG, Ferbam, Ferberk, Hexaferb, Knockmate, Trifungol)

Confirmation of Poisoning

Tests to detect these compounds are not readily available.

Treatment of Strobilurin Toxicosis

Remove the patient from the source of exposure.

Provide supportive treatment directed to symptoms. Significant acute toxicity is not generally expected; therefore, exposure can be asymptomatic and symptoms usually do not warrant medical attention.

Consider skin decontamination as outlined in **Chapter 3, *General Principles***.

Flush eyes with water or normal saline. If eye irritation, redness or swelling persists for more than 15 minutes, recommend consultation with an ophthalmologist.

THIOCARBAMATES

Thiocarbamates are commonly formulated as dusts, wettable powders or water suspensions. They are used to protect seeds, seedlings, ornamentals, turf, vegetables and fruit including apples. Unlike the N-methyl carbamates (**Chapter 6**), 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, *Other Herbicides*.**

Metam-sodium, thiram and ziram and ferbam are the thiocarbamate pesticides. They are discussed individually.

Metam-sodium

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

Toxicology

Although animal feeding studies do not indicate high toxicity of **metam-sodium** by ingestion, its decomposition in water yields methyl isothiocyanate, a gas that is extremely irritating to the eyes and to respiratory mucous membranes including the lower respiratory tract/lungs. Inhalation of methyl isothiocyanate may cause pulmonary edema, manifesting with severe respiratory distress and coughing of bloody, frothy sputum. For this reason, metam-sodium must be used outdoors only, and stringent precautions must be taken to avoid inhalation of evolved gas. Metam-sodium can be very irritating to the skin.

Theoretically, exposure to metam-sodium may predispose the individual to "Antabuse" reactions if alcohol is ingested after exposure. Such occurrences have not been reported in the medical literature.

Confirmation of Poisoning

There are no tests for metam-sodium or its breakdown products in body fluids.

Treatment of Metam-sodium Toxicosis

Decontaminate skin and GI tract, as outlined in **Chapter 3, *General Principles***.

If pulmonary irritation or edema occurs 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 17, *Fumigants*** in the *Treatment of Fumigant Toxicosis* subsection beginning on page 166.

Metam-sodium is not a cholinesterase inhibitor. Atropine is not antidotal.

Thiram

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

Toxicology

Systemic human poisonings by **thiram** itself have been very few, probably due to limited absorption in most circumstances involving human exposure. Those that have been reported have been similar clinically to toxic reactions to **disulfiram** (Antabuse), the ethyl analogue of thiram that has been extensively used in alcohol aversion therapy.[16] 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 more toxic than disulfiram.

Neither thiram nor disulfiram is a cholinesterase inhibitor. 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 following ingestion of beverages containing alcohol among workers previously exposed to thiram.

Confirmation of Poisoning

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

Treatment of Thiram Toxicosis

Decontaminate skin and GI tract as outlined in **Chapter 3, *General Principles***.

Infuse appropriate intravenous fluids, especially if vomiting and diarrhea are severe. Monitor serum electrolytes and glucose and replace as needed.

Treatment of Acetaldehyde Toxicosis (Antabuse reaction)

Use oxygen inhalation, trendelenburg positioning and intravenous fluids, which are usually effective in relieving manifestations of "Antabuse" reactions.

Thiocarbamate

HIGHLIGHTS

Formulated as dusts, wettable powders, water suspensions

Less human health threat than insecticidal carbamates

SIGNS & SYMPTOMS

Skin, eye, respiratory irritation

For metam-sodium inhalation, respiratory distress, bloody sputum

May result in Antabuse-like reaction if alcohol is consumed after exposure

TREATMENT

Decontaminate skin and GI tract

For metam-sodium, treat pulmonary impacts as for fumigant toxicosis

For thiram, ziram and ferbam, IV fluids as needed

For Antabuse reaction, oxygen, IV fluids and trendelenburg positioning

EBDC Compound

COMMERCIAL PRODUCTS

maneb (Kypman 80, Manex 80, Maneba, Manex, M-Diphar, Sopranebe, Trimangol)

zineb* (Aspor, Dipher, Hexathane, Kypzin, Parzate C, Tritoftorol, Zebtox)

nabam (Chem Bam, DSE, Parzate, Spring Bak)

mancozeb (Manzeb, Dithane, Mancozin, Manzin, Nemispor, Penncozeb, Ziman-Dithane)

**All products canceled*

HIGHLIGHTS

Most products no longer in use

Low systemic toxicity

SIGNS & SYMPTOMS

Skin, eye, respiratory irritation

Possible behavioral, neurological symptoms

TREATMENT

Skin, eye decontamination

Consider GI decontamination

Consider hemodialysis for renal failure

Advise persons who have absorbed any significant amount of thiocarbamates to avoid alcoholic beverages for at least 3 weeks. Disposition of thiocarbamates is slow, and their inhibitory effects on enzymes are slowly reversible.

Ziram and Ferbam

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

Toxicology

Since **ziram** and **ferbam** are similar to thiram, it is reasonable to assume that similar toxic effects may occur, including irritation to the skin, respiratory tract and eyes. However, there are no reports of human poisoning in the medical literature. If absorbed in sufficient dosage, these metallothiocarbamates may theoretically predispose the patient to an "Antabuse" reaction following ingestion of alcohol. (See thiram.) No occurrences of this have been reported.

Confirmation of Poisoning

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

Treatment of Ziram and Ferbam Toxicosis

Decontaminate skin and GI tract as needed, as outlined in **Chapter 3, *General Principles***.

Treat as for thiram.

ETHYLENE BIS DITHIOCARBAMATES (EBDC COMPOUNDS)

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. Although some products, including maneb and mancozeb, were widely used in the 1990s and 2000s, particularly in agricultural settings and on golf courses, most of these products are no longer in use.

Toxicology

Maneb, zineb, nabam and **mancozeb** may cause irritation of the skin, respiratory tract and eyes. Some cases of chronic skin disease in occupationally exposed workers have been attributed to both maneb and zineb, possibly by sensitization.[17,18]

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. Maneb, mancozeb and metriam all are metabolized to the degradation product ethylene thiourea, which may have toxic properties of its own.[19]

Reports of acute systemic poisonings in humans have been rare. However, zineb precipitated an episode of hemolytic anemia in one worker presumably predisposed because of multiple red cell enzyme deficiencies.[20] Maneb toxicity has been reported in one person who developed acute renal failure and was treated with hemodialysis.[21] Behavioral and neurological symptoms may also occur following maneb poisoning. These include mental status changes, loss of consciousness and tonic-clonic seizures. These appear to improve with supportive care.[22,23] Symptoms similar to Parkinson's disease have also been reported in settings of chronic, occupational exposure, possibly due to the manganese component of maneb.[24] Animal studies suggest that following acute exposure at high doses, chronic symptoms similar to Parkinson's may also occur.[19]

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

Confirmation of Poisoning

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

Treatment of Ethylene Bis Dithiocarbamate Toxicosis

See treatment for substituted benzenes, page 145.

Should severe renal failure occur, consider hemodialysis.

THIOPHTHALIMIDES

Captan, captafol and folpet are widely used to protect seed, field crops and stored produce. They are formulated as dusts and wettable powders.

Toxicology

Captan, captafol and **folpet** are moderately irritating to the skin, eyes and respiratory tract. Dermal sensitization may occur; captafol has been associated with several episodes of occupational contact dermatitis.[25,26] Very few systemic poisonings by thiophthalimides have been reported in humans. Captafol has been reported to have exacerbated asthma after occupational exposure.[27] A 17-year-old who ingested captafol in a suicide attempt had symptoms including headache, nausea, weakness, numbness of upper limbs and substernal chest pain with an accompanying elevation in creatine kinase and aspartate aminotransferase, and inverted T waves on electrocardiogram. All abnormalities resolved with supportive care over a 72-hour period.[28]

Confirmation of Poisoning

Following oral exposure, captan fungicides are rapidly metabolized in the body to yield two metabolites that can be measured in the urine: tetrahydrophthalimide (THPI) and thiazolidine-2-thione-4-carboxilic acid (TTCA). Both are considered useful biomarkers for occupational exposure.[29]

Treatment of Thiophthalimide Toxicosis

See treatment for substituted benzenes, page 145.

Thiophthalimide

COMMERCIAL PRODUCTS

captan (Captanex, Captaf, Merpan, Orthocide, Vondcaptan)

captafol (Crisfolatan, Difolatan, Foltaf, Haipen, Merpafol, Mycodifol, Sanspor)

folpet (Folpan, Phaltan, Thiophal, Fungitrol II)

HIGHLIGHTS

Dusts, wettable powders

Used in seed & field crops, stored produce

Few systemic poisonings reported in the medical literature

SIGNS & SYMPTOMS

Skin, eye, respiratory irritation

TREATMENT

Skin, eye decontamination

Consider GI decontamination

Triazole
COMMERCIAL PRODUCTS

triadimefon (Bayleton, Amiral)

myclobutanil

propiconazole (Tilt)

flutriafol

HIGHLIGHTS

Moderate acute oral toxicity

Possible chronic effects

Low dermal toxicity

TREATMENT

Skin, eye decontamination

Consider GI decontamination

TRIAZOLE FUNGICIDES

Triazoles are supplied as wettable powder, emulsifiable concentrate, suspension concentrate, paste and dry flowable powder. Most triazoles are used on fruit, cereals, vegetables, coffee, ornamentals, sugarcane, pineapples and turf. (Another compound in this class is fluconazole, a pharmaceutical commonly used to treat fungal infections in humans.) Uses of triadimefon were voluntarily canceled by the registrant in 2008.

Toxicology

Triazole fungicides – **triadimefon**, **myclobutanil, propiconazole** and **flutriafol** – exhibit moderate acute oral toxicity in laboratory animals, but dermal toxicity is low. All except for triadimefon will cause hepatocyte hypertrophy in mice.[30] Eye exposure may cause irritation. Triadimefon is absorbed across the skin.

Animal data suggest that the triazole fungicides have some central nervous system effects. One study in rats demonstrated that flutriafol induces dopamine release. While this effect is not considered to result in acute toxicity, there is concern for chronic effects.[31] Triadimefon blocks reuptake of dopamine and has demonstrated hyperactivity in mice and rats.[32,33] It is expected that the findings in humans would be similar, although investigation of this has not been reported in the literature.

Confirmation of Poisoning

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

Treatment of Triazole Toxicosis

See treatment for substituted benzenes, page 145.

COPPER COMPOUNDS

Insoluble inorganic and organic copper compounds are formulated as wettable powders and dusts. Soluble inorganic and organic copper 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 in some countries, but their use has been discontinued in the United States. Toxicity of these is chiefly due to arsenic content (see **Chapter 15, *Arsenicals***). Another copper-arsenic compound, copper chromium arsenate, was formerly used as a wood preservative. That use was discontinued in 2003 on wood being used around the home or on playgrounds.[34]

Toxicology

The dust and powder preparations of **copper compounds** are irritating to the skin, respiratory tract and particularly the eyes. The soluble copper salts (such as the sulfate and acetate) are corrosive to mucous membranes and the cornea. Limited solubility and absorption probably account for generally low systemic toxicity of most compounds. The more absorbable organic copper compounds exhibit the greatest systemic toxicity in laboratory animals.

Most of what is known about mammalian toxicity of copper compounds has come from veterinary toxicology (livestock seem uniquely vulnerable) and poisonings in man due to deliberate ingestion of copper sulfate or to consumption of water or food that had been contained in copper vessels. The mechanism of toxicity is not clear, although copper appears to release an excess of the cupric ion.[35] This affects enzymes including G6PD and glutathione reductase, which can damage the erythrocyte membrane and produce hemolysis.[36,37] Other enzyme systems may also be affected, including nicotinamide-adenine dinucleotide phosphate (NADPH). 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.[38,39] As mentioned above, hemolysis can occur, resulting in circulatory collapse and shock and may be prolonged, particularly in patients with an existing condition such as G6PD deficiency. Methemoglobinemia has been reported in these cases, usually related to copper sulfate.[35,38,40,41] 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 deaths occurring more than 24 hours after poisoning.[42] A case report from China describes an adult male developing severe hemolysis and methemoglobinemia after ingestion of copper-8-hydroxyquinolate.[35]

Confirmation of Poisoning

Whole blood and serum copper levels can be measured, with a reported average red blood cell level in normal adults of 89 µg/dL and average serum level of 114 µg/dL.[43] Most reported cases of acute copper poisoning are at levels exceeding 200 µg/dL, and some as high as 1,650 µg/dL.[15,35,41]

Treatment of Copper Toxicosis

Management of poisonings by ingestion of copper-containing fungicides depends 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.

Decontaminate skin with soap and water. The eyes should be flushed free of irritating dust, powder or solution, using clean water or saline. If eye or dermal irritation persists, medical treatment should be obtained. Eye irritation may be severe.

Give water or milk as soon as possible to dilute the toxicant and mitigate corrosive action on the mouth, esophagus and gut. Do not be overly aggressive with the dilution to avoid accidental inducement of vomiting.[44] There is not a specific amount that should be given, although the Poisondex Editorial Board consensus is no more than 4 ounces in children and 8 ounces in adults.[42,44]

Do not induce emesis because the corrosive nature of some copper salts can cause further damage to the esophagus, although vomiting is usually spontaneous in acute copper ingestion. Further gastrointestinal decontamination should be determined on a case-by-case basis as outlined in the **Chapter 3**, ***General Principles***, understanding that gastric lavage may cause further damage.[42] Charcoal's adsorbent effectiveness has not been widely studied in metal poisonings.

CAUTION*: If corrosive action has been severe, it may be best to avoid gastric intubation, as this may pose a serious risk of esophageal perforation. It may be prudent to consider referral to a gastroenterologist for endoscopy, given the caustic nature of the ingestion.*

Copper Compound
COMMERCIAL PRODUCTS

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

SIGNS & SYMPTOMS

Skin, eye, respiratory irritation

TREATMENT

Skin, eye decontamination
Water or milk for GI dilution
IV fluids with glucose, electrolytes if systemic
Methylene blue for severe methemoglobinemia
Consider BAL

CONTRAINDICATED

Induced emesis, intubation

Organomercury
COMMERCIAL PRODUCTS

Methyl mercury compounds

methyl mercury hydroxide

acetate

propionate

pentachlorophenate

quinolinolate

Methoxyethyl mercury compounds

methoxyethyl mercury acetate (MEMA, Panogen, Panogen M)

methoxyethyl mercury chloride (MEMC, Emisan 6, Ceresan)

Phenylmercuric acetate

Agrosan, Shimmer-ex, Tag HL 331, Unisan

Setrete (Gallotox, PMAA) is phenyl mercury ammonium acetate

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.

Monitor plasma for evidence of hemolysis (free hemoglobin) and the red cells for methemoglobin. If methemoglobinemia is severe (>30%), or the patient is cyanotic, administer methylene blue.

Dosage of Methylene Blue

Adults/children 1-2 mg/kg/dose, given as a slow IV push over a few minutes, every 4 hours as needed.[42]

In patients with severe methemoglobinemia that is unresponsive to methylene blue, or those with G6PD deficiency, chelation (see below) and plasma exchange may be required.[35]

Administer morphine if the patient is in severe pain.

Consider administering BAL. The value of chelating agents in copper poisoning has not been established.[35,45] 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, but in the context of severe vomiting and/or mental status changes from an acute ingestion, BAL would be a more likely initial choice.[40,42] For a recommended schedule of dosage for initial therapy with BAL and subsequent d-penicillamine administration, see **Chapter 15**, ***Arsenicals***.

Although hemodialysis is indicated for patients with renal failure, copper is not effectively removed in the dialysate.[35,38]

ORGANOMERCURY COMPOUNDS

Methyl mercury and methoxyethyl mercury compounds and phenyl mercuric acetate fungicides have been formulated as aqueous solutions and dusts. They have been used chiefly as seed protectants and had historically been added to household paint. Use of alkyl mercury fungicides in the United States has been prohibited since the early 1990s. Phenyl mercuric acetate is no longer manufactured or used in the United States.

Toxicology

The mercurial fungicides — **methyl mercury** and **methoxyethyl mercury** compounds and **phenyl mercuric acetate** — are among the most toxic pesticides ever developed, in terms of both acute and chronic toxicity. 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.[46,47] Poisoning has also occurred from eating meat from animals fed mercury-treated seed.[48] 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 epithelium. Methyl mercury is selectively concentrated in the tissues of the nervous system and also in red blood cells. Other alkyl mercury compounds are probably distributed similarly. Excretion occurs almost entirely through the biliary system. The

whole body half-life of methyl mercury in humans ranges between 45 and 56 days.[49] Significant conversion of organic mercury to inorganic mercury occurs 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 in 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 been fatal and a large percentage of survivors have suffered severe, permanent neurologic damage.[46,47,48]

Phenyl mercuric acetate is not as extremely toxic as the alkyl mercury compounds and is not as efficiently absorbed from the gut as methyl mercury.[50] Phenyl mercuric acetate is used to prevent fungal growth in latex paint. A case of acrodynia in a child led to latex paint as a possible source for mercury exposure. Symptoms of acrodynia include fever, erythema and desquamation of hands and feet, muscular weakness, leg cramps and personality changes.[51] Phenyl mercuric compounds have been banned from latex paint since 1990.[52]

Confirmation of Poisoning

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

Treatment of Organomercury Toxicosis

Every possible precaution should be taken to avoid potentially life-threatening ingestions of organic mercury fungicides. Very little can be done to mitigate neurologic damage caused by organic mercurials.

The following are the basic steps in the management of organomercury poisoning:

Decontaminate skin and eyes, as discussed in **Chapter 3, *General Principles***.

Remove persons experiencing symptoms (metallic taste in mouth) after inhalation of volatile organic mercury compounds (methyl mercury is the most volatile) promptly from the contaminated environment and observe closely for indications of neurologic impairment. Every possible precaution should be taken to avoid further exposure to organic mercury compounds.

Consider gastrointestinal decontamination as outlined in **Chapter 3**.

Administer chelation therapy. Chelation is an essential part of the management of acute mercury poisoning. For dosages of specific agents, see **Chapter 15, *Arsenicals***. Succimer (DMSA) appears to be the most effective agent available in the United States. Dimercaprol (BAL) is contraindicated in these poisonings because of its potential to increase brain levels of mercury.[52] 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.[52] DMPS (2,3-dimercaptopropane-1-sulfonate acid) and NAP (n-acetyl-D,L-penicillamine) are probably also useful but are not currently approved for use in the United States.

Consider extracorporeal hemodialysis and hemoperfusion, although experience to date has not been encouraging.

Organomercury

HIGHLIGHTS

Extreme acute and chronic toxicity

Efficiently absorbed across gut and possibly skin

SIGNS & SYMPTOMS

Metallic taste in mouth

Numbness, tingling of digits & face

Tremor, headache, fatigue

Emotional lability, difficulty in thinking

Incoordination, slurred speech, hearing loss in more severe cases

TREATMENT

Skin, eye decontamination

Consider GI decontamination

Chelation with DMSA or other appropriate agent

CONTRAINDICATED

Use of BAL

Organotin Compound
COMMERCIAL PRODUCTS

triphenyl tin

fentin hydroxide (Suzu-H, Super Tin, Tubotin)

fentin chloride (Tinmate)

fentin acetate (Batasan, Brestan, Phenostat-A, Phentinoacetate, Suzu, TPTA)

HIGHLIGHTS

Wettable & flowable powders

Eye, skin, respiratory irritant

Most have been discontinued in U.S.

SIGNS & SYMPTOMS

Headache, nausea, vomiting, dizziness

Sometimes convulsions, loss of consciousness

Photophobia, mental disturbances

TREATMENT

Skin, eye decontamination

ICU supportive care for CNS effects

Consider GI decontamination for large ingestions

ORGANOTIN COMPOUNDS

Triphenyl tin, fentin hydroxide, fentin chloride and fentin acetate 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 in 1995). Tributyltin salts were at one time used as fungicides and antifouling agents on ships, but this use has been banned by most countries. They are somewhat more toxic by the oral route than triphenyltin, but toxic actions are otherwise probably similar. Most organotin compounds have been discontinued in the United States.

Toxicology

Triphenyl tin, fentin hydroxide, fentin chloride and **fentin acetate** 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 brain: 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 phenyl tin fungicides are less toxic than ethyl, dimethyl and trimethyl tin compounds that are used in the production of plastics. Signs and symptoms for poisoning from those compounds have included disorientation and other mental status changes, cerebral edema, neurologic damage and death in severely poisoned individuals.[34,53,54] No deaths and very few poisonings have been reported as a result of occupational exposures to phenyltin pesticides.

Treatment of Organotin Toxicosis

Remove skin contamination by washing with soap and water. Flush eyes free of contaminating material with clean water or saline. If irritation persists, expert medical treatment should be obtained.

Provide supportive care in an intensive care unit if neurological effects are evident.

If large amounts of phenyltin compound have been ingested in the past hour, take measures to decontaminate the gastrointestinal tract as outlined in **Chapter 3, *General Principles***.

BAL, penicillamine, or other chelating agents have not been effective in lowering tissue stores of organotin compounds in experimental animals.

CADMIUM COMPOUNDS

Cadmium chloride, **cadmium sulfate** and **cadmium succinate** 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. **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 United States have been discontinued. Cadmium exposure may also occur in the occupational setting from other sources and uses of the toxic metal.

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, headache 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.[55,56,57,58] 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.[59]

Confirmation of Poisoning

Cadmium can be measured in body fluids by several methods, including electrothermal atomic absorption spectroscopy, graphite furnace atomic spectrophotometry, and potentiometric stripping analysis.[60,61,62] 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 µg/dL suggest excessive exposure.[55] Urinary excretion in excess of 100 µg per day suggests an unusually high body burden.

Treatment of Cadmium Poisoning

Decontaminate skin and eyes as outlined in **Chapter 3, *General Principles***.

For severe reactions such as pulomonary edema and pneumonitis, use aggressive measures in an intensive care setting, including positive end-expiratory pressure mechanical ventilation, monitoring of blood gases and administration of diuretics, steroid medications and antibiotics.[55,63] Codeine sulfate may be needed to control cough and chest pain. Respiratory irritation resulting from inhalation of small amounts of cadmium dust may resolve spontaneously, requiring no treatment.

Consider decontaminating the lower GI tract as outlined in **Chapter 3** if retention of some cadmium is suspected. 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.

Administer intravenous fluids to overcome dehydration caused by vomiting and diarrhea. Fluids also 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.

Consider chelation therapy with calcium disodium EDTA for acute poisoning, depending on measured cadmium in blood and urine and the status of renal function. Chelation therapy has been shown to increase urinary excretion of cadmium. 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. Monitor urine protein and blood urea nitrogen and creatinine carefully during therapy.

Cadmium Compound

COMMERCIAL PRODUCTS

cadmium chloride (Caddy)

cadmium sulfate (generic, 14% solution)

cadmium succinate (Cadminate)

Miller 531 and Crag Turf Fungicide 531 (generic) were complexes of cadmium, calcium, copper, chromium, and zinc oxides

Kromad is a mixture of cadmium sebacate, potassium chromate, and thiram

Cad-Trete is a mixture of cadmium chloride and thiram

HIGHLIGHTS

Discontinued in U.S.

SIGNS & SYMPTOMS

Inhalation: Fever, cough, malaise, headache, abdominal pain

Ingestion: Nausea, vomiting, diarrhea, abdominal pain, tenesmus

TREATMENT

Skin, eye decontamination

Consider lower GI decontamination if retained

Aggressive ICU measures for severe reactions

IV fluids for dehydration

Miscellaneous Organic Fungicide
COMMERCIAL PRODUCTS

anilazine (Dyrene)

benomyl (Benlate, Tersan 1991, Benex)

cycloheximide (naramycin)

dodine (Carpene, Curitan, Melprex, Venturol)

iprodione (Rovral, Glycophene)

metalaxyl (Ridomil, Subdue)

etridiazole (Terrazole, Aaterra, Ethazol, Koban, Pansoil, Truban)

thiabendazole (Apl-Luster, Arbotect, Mertect, Tecto, Thibenzole)

triforine (Funginex, Saprol, Denarin)

Dosage of Calcium Disodium EDTA

- ***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.***[65]

Succimer (DMSA) has also been used in this poisoning but has not been demonstrated to be efficacious.

6. Because of the risk of renal injury by mobilized cadmium, do not use dimercaprol (BAL) for treatment of cadmium poisoning.

7. Monitor urinary protein and cells regularly and measure hepatocellular enzymes and creatinine for indications of injury to these organ systems.

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 follow.

Anilazine is supplied as wettable and flowable powders. It was used on vegetables, cereals, coffee, ornamentals and turf. No products are currently registered in the United States. 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 in the published medical literature.

Benomyl is a synthetic organic fungistat having little or no acute toxic effect in mammals. There are no active products in the United States. No systemic poisonings have been reported in humans in the published literature. Although the molecule contains a carbamate grouping, benomyl is not a cholinesterase inhibitor. It is poorly absorbed across skin, and what 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.[3,66]

Cycloheximide is formulated as wettable powders, sometimes combined with other fungicides. There are no registered products in the United States. Cycloheximide is a product of fungal culture, effective against fungal diseases of ornamentals and grasses. It is selectively toxic to rats and 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 in deliberately poisoned rats. Atropine, epinephrine, methoxyphenamine and hexamethonium all relieved the symptoms of poisoning, but did not improve survival.[67]

Dodine is formulated as a wettable powder. It is commonly applied to berries, nuts, peaches, apples, pears and trees afflicted with leaf blight. Dodine is a cationic surfactant with antifungal activity. It is absorbed across the skin. In animal studies, it causes severe irritation to the eye, and also is a skin irritant. Acute oral and dermal toxicity in laboratory animals is moderate. Poisonings in humans have not been reported in the published medical literature. Based on animal studies, ingestion would probably cause nausea, vomiting and diarrhea.[68]

Iprodione is supplied as wettable powder and other formulations. It is used on berries, grapes, fruit, vegetables, grasses and ornamentals. It is also used as seed dressing. Iprodione exhibits low acute oral and dermal toxicity in laboratory animals.[69] No human poisonings have been reported in the published medical literature.

Metalaxyl is supplied as emulsifiable and flowable concentrates. It is a systemic fungicide used to control soil-borne fungal diseases on fruit trees, cotton, hops, soybeans, peanuts, ornamentals and grasses. It is also used as seed dressing. It exhibits low acute oral and dermal toxicity in laboratory animals.[70] No human poisonings have been reported in the published medical literature.

Etridiazole is supplied as wettable powder and granules for application to soil as a fungicide and nitrification inhibitor. There are no registered products in the United States. Human poisonings have not been reported in the published literature.

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 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, headache and tinnitus.[71] Blood enzyme tests may indicate liver injury. Persons with liver and kidney disease may be unusually vulnerable to toxic effects. Adverse effects in humans from use of thiabendazole as a fungicide have not been reported in the published literature.

Triforine is supplied as emulsifiable concentrate and wettable powder. It is used on berries, fruit, vegetables and ornamentals. Mammals rapidly excrete it chiefly as a urinary metabolite. It exhibits low acute oral and dermal toxicity in laboratory animals.[72] No human poisonings have been reported in the published literature.

Confirmation of Poisoning

Laboratory tests for these organic fungicides or their metabolites in body fluids are not generally available.

Treatment of Organic Fungicide Toxicosis

See treatment for substituted benzenes, page 145.

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