RECOGNITION AND MANAGEMENT OF PESTICIDE POISONINGS

Fifth Edition, 1999

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Section I

GENERAL INFORMATION

CHAPTER 1

Introduction

This fifth edition of *Recognition and Management of Pesticide Poisonings* is an update and expansion of the 1989 fourth edition. The Office of Pesticide Programs of the United States Environmental Protection Agency has sponsored the series since 1973. The purpose of the manual is to provide health professionals with recently available information on the health hazards of pesticides currently in use, and current consensus recommendations for management of poisonings and injuries caused by them.

Pesticide poisoning is a commonly under-diagnosed illness in America today. Despite recommendations by the Institute of Medicine and others urging the integration of environmental medicine into medical education, health care providers generally receive a very limited amount of training in occupational and environmental health, and in pesticide-related illnesses, in particular.[1] The updating of this manual is part of a larger initiative of the U.S. Environmental Protection Agency, in conjunction with numerous federal agencies, associations of health professionals, and related organizations to help health care providers become better aware, educated, and trained in the area of pesticide-related health concerns. This larger initiative, entitled Pesticides and National Strategies for Health Care Providers, was launched in April 1998.

As with previous updates, this new edition incorporates new pesticide products that are not necessarily widely known among health professionals. The accumulated "use experience" of formulators, applicators, and field workers provides an expanding basis for judging safety and identifying the environmental and workplace hazards of old and new pesticides. Major episodes of adverse health effects reported in medical and scientific periodicals have been taken into account. This literature also contributes importantly to improved understanding of toxic mechanisms. Clinical toxicology is a dynamic field of medicine; new treatment methods are developed regularly, and the effectiveness of old as well as new modalities is subject to constant critical review.

There is general agreement that *prevention* of pesticide poisoning remains a much surer path to safety and health than reliance on treatment. In addition to the inherent toxicity of pesticides, none of the medical procedures or drugs used in treating poisonings is risk-free. In fact, many antidotes are toxic in their own right, and such apparently simple procedures as gastric intubation incur substantial risk. The clinical toxicologist must often weigh the hazards of various courses of action—sometimes including no treatment at all—against the risks of various interventions, such as gastric emptying, catharsis, administration

of intravenous fluids, or administration of an antidote, if available. Clinical management decisions have to be made promptly and, as often as not, on the basis of limited scientific and medical information. The complex circumstances of human poisonings rarely allow precise comparisons of alternative management. In no sense, then, are the treatment recommendations in this book infallible guides to successful outcomes. They are no more than consensus judgments of the best available clinical management options.

This manual deals almost entirely with short-term (acute) harmful effects of pesticides. Although obviously important, the subject of chronic effects is too complex to deal with exhaustively in a manual designed as guidance for emergency management. Nonetheless, appropriate treatment of serious exposures to pesticides represents an important step in avoiding chronic as well as acute disease.

The pesticides and commercial products mentioned in this manual do not represent the universe of pesticide products in existence. They were selected based on frequency of use and exposure, severity of toxicity, and prior experience with acute poisonings. Products are discussed in this manual that have been discontinued or whose U.S. pesticide registration has been revoked but are judged to still be of risk due to use elsewhere or where there is a probability of residual stocks. Agents long out of use in the U.S. and elsewhere were not included in the manual.

The amount of pesticide absorbed is a critical factor in making treatment decisions, and estimation of dosage in many circumstances of pesticide exposure remains difficult. The terms "small amount" and "large amount" used in this book are obviously ambiguous, but the quality of exposure information obtained rarely justifies more specific terminology.

Sometimes the circumstances of exposure are a rough guide to the amount absorbed. Exposure to spray drift properly diluted for field application is not likely to convey a large dose unless exposure has been prolonged. Spills of concentrated technical material onto the skin or clothing may well represent a large dose of pesticide unless the contamination is promptly removed. Brief dermal exposure to foliage residues of cholinesterase-inhibiting pesticides is not likely to lead to poisoning, but prolonged exposures may well do so. Suicidal ingestions almost always involve "large amounts," requiring the most aggressive management. Except in children, accidental pesticide ingestions are likely to be spat out or vomited. Ingestions of pesticides by children are the most difficult to evaluate. The therapist usually must base clinical management decisions on "worst case" assumptions of dosage. Childhood poisonings are still further complicated by the greater vulnerability of the very young, not only to pesticides themselves, but also to drugs and treatment procedures. The nature

Key Principles

General methods of managing pesticide poisonings are presented in Chapter 2 and reflect a broad base of clinical experience. The following key points deserve emphasis. The need to protect the airway from aspiration of vomitus cannot be overstated. Death has occasionally resulted from this complication, even following ingestions of substances having relatively low toxic potential. In poisonings by agents that depress central nervous system function or cause convulsions, early placement of a cuffed endotracheal tube (even when this requires light general anesthesia) may be life saving. Maintenance of adequate pulmonary gas exchange is another essential element of poisoning management that deserves constant reemphasis.

Gastric intubation, with aspiration and lavage, remains a useful method for removing poisons from the stomach shortly after they have been swallowed, but the time after ingestion during which lavage is likely to be beneficial is shorter than many clinical toxicologists have thought. Rarely are significant amounts of swallowed toxicants recovered more than 1-2 hours after ingestion, and, in many instances, the bulk of swallowed material passes into the duodenum and beyond in 15-30 minutes. In addition, the majority of controlled studies evaluating the effectiveness of gastric emptying procedures are done for ingestions of solid material (pills) rather than liquids.

Full advantage should be taken of new highly adsorbent charcoals that are effective in binding some pesticides in the gut. Unfortunately, charcoal does not adsorb all pesticides, and its efficiency against many of them is not known. In poisonings caused by large intakes of pesticide, hemodialysis and hemoperfusion over adsorbents continue to be tested as methods for reducing body burdens. Against some toxicants, these procedures appear valuable. Overall effectiveness appears to depend not only on efficiency of clearance from the blood, but also on the mobility of toxicant already distributed to tissues before the extracorporeal blood-purification procedure is started. The volume of distribution and avidity of tissue binding are important considerations in making such decisions. The critical determinant of success in using these systems may well be the speed with which they can be put into operation before tissue-damaging stores of toxicant have accumulated.

There remains a need for systematic reporting of pesticide poisonings to a central agency so that accurate statistics describing the frequency and circumstances of poisoning can be compiled, and efforts to limit these occurrences can be properly directed. In some countries there has been an increase in the use of pesticides as instruments of suicide and even homicide. Producers are now devoting considerable effort to modifying formulation and packaging to deter these misuses. This work is important because suicidal ingestions are often the most difficult pesticide poisonings to treat successfully.

Common Pesticide Poisonings

The pesticides most often implicated in poisonings, injuries, and illnesses, according to 1996 data from the American Association of Poison Control Center's Toxic Exposure Surveillance System, are listed below.

The list is based on symptomatic cases classified as minor, moderate, major, or fatal outcome for unintentional cases involving a single product. Numbers of cases are reported for both children under six years of age and for adults and older children. Suicide/homicide (intentional) cases have been excluded. Cases listed as organophosphates (and the other categories as well) may also include other insecticides such as carbamates and organochlorines in a single product.

PESTICIDES MOST OFTEN IMPLICATED IN SYMPTOMATIC ILLNESSES, 1996

Rank	Pesticide or Pesticide Class	Child < 6 years	Adults 6-19 yrs.	Total*
1	Organophosphates	700	3274	4002
2	Pyrethrins and pyrethroids**	1100	2850	3950
3	Pine oil disinfectants	1336	903	2246
4	Hypochlorite disinfectants	808	1291	2109
5	Insect repellents	1081	997	2086
6	Phenol disinfectants	630	405	1040
7	Carbamate insecticides	202	817	1030
8	Organochlorine insecticides	229	454	685
9	Phenoxy herbicides	63	387	453
10	Anticoagulant rodenticides	176	33	209
	All Other Pesticides	954	3604	4623
	Total all pesticides/disinfectants	7279	15,015	22,433

* Totals include a small number of cases with unknown age.
** Rough estimate: includes some veterinary products not classified by chemical type.

Source: American Association of Poison Control Centers, Toxic Exposure Surveillance System, 1996 data.

Approximately 90% of symptomatic cases involve only minor symptoms of the type that could typically be treated at home with dilution or just observation. However, seven of the top ten categories listed in the table above (organophosphates, pyrethrins/pyrethroids, hypochlorite disinfectants, carbamates, organochlorines, phenoxy herbicides, and anticoagulant rodenticides) are much more likely to require medical attention.

This list cannot be considered representative of all symptomatic poisonings

below). Denominator information on the population at risk (numbers exposed) would be needed to better understand the relative risk of different pesticides. However, the main purpose of these tables is to give physicians a sense of what types of cases they are most likely to see in their practice.

Although suicide cases make up roughly 3% of pesticide-related calls to Poison Control Centers, they may account for nearly 10% of the cases seen in a health care facility. The leading types of products involved in suicidal cases include anticoagulant rodenticides (20% of total suicide attempts), pine oil dis-

Format of this Manual

An effort has been made to format this book for quick reference by thorough indexing and minimal references to other pages or chapters. However, many different agents commonly require similar procedures in treating poisonings and it is not practical to repeat these protocols in every chapter. General principles for management of pesticide poisoning, including skin and eye decontamination, gastrointestinal decontamination, and control of convulsions are considered in Chapter 2, General Principles. These principles are referenced throughout.

Changes in this reformatted edition include: tabular listings of Commercial Products in each chapter, the addition of a new chapter on Disinfectants (Chapter 19), and the addition of a chapter on Environmental and Occupational History (Chapter 3), which places pesticide poisonings in the context of other environmental and occupational exposures, provides questionnaires designed to elicit exposure information, discusses resources available to the practitioner, and provides a list of governmental and non-government contacts and Web sites for more information. In addition, each chapter is referenced to key references in readily accessible current literature. Most references were selected as primary references in peer review journals, although some review papers are also included.

The contents of this book have been derived from many sources: published texts, current medical, toxicological, and pesticide product literature, and direct communications with experts in clinical toxicology and pesticide toxicology and environmental and occupational health specialists. A list of the major text sources follows this introduction.

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CHAPTER 2

General Principles in the Management of Acute Pesticide Poisonings

This chapter describes basic management techniques applicable to most acute pesticide poisonings. Where special considerations and treatments are required for a particular pesticide, they are addressed separately in the appropriate chapter.

Skin Decontamination

Decontamination must proceed concurrently with whatever resuscitative and antidotal measures are necessary to preserve life. Shower patient with soap and water, and shampoo hair to remove chemicals from skin and hair. If there are any indications of weakness, ataxia, or other neurologic impairment, clothing should be removed and a complete bath and shampoo given while the victim is recumbent. The possibility of pesticide sequestered under fingernails or in skin folds should not be overlooked.

Flush contaminating chemicals from eyes with copious amounts of clean water for 10-15 minutes. If eye irritation is present after decontamination, ophthalmologic consultation is appropriate.

Persons attending the victim should avoid direct contact with heavily contaminated clothing and vomitus. Contaminated clothing should be promptly removed, bagged, and laundered before returning. Shoes and other leather items cannot usually be decontaminated and should be discarded. Note that pesticides can contaminate the inside surfaces of gloves, boots, and headgear. Decontamination should especially be considered for emergency personnel such as ambulance drivers at the site of a spill or contamination. Wear rubber gloves while washing pesticide from skin and hair of patient. Latex and other surgical or precautionary gloves usually will not always adequately protect from pesticide contamination, so only rubber gloves are appropriate for this purpose.

Airway Protection

Ensure that a clear airway exists. Suction any oral secretions using a large bore suction device if necessary. Intubate the trachea if the patient has respiratory depression or if the patient appears obtunded or otherwise neurologically

impaired. Administer oxygen as necessary to maintain adequate tissue oxygenation. In severe poisonings, it may be necessary to mechanically support pulmonary ventilation for several days.

Note on Specific Pesticides: There are several special considerations with regard to certain pesticides. In **organophosphate** and **carbamate** poisoning, adequate tissue oxygenation is essential prior to administering atropine. As important, in **paraquat** and **diquat** poisoning, oxygen is **contraindicated**

2. Catharsis

Sorbitol and magnesium citrate are commonly used cathartic agents. Because magnesium citrate has not been studied as much, its use is not described here. Sorbitol is often included in charcoal formulations. It will increase gut motility to improve excretion of the charcoal-poison complex. The dosage of sorbitol is 1-2 g/kg as a one-time dose. Repeat doses of cathartics may result in fluid and electrolyte imbalances, particularly in children, and are therefore not recommended. Sorbitol is formulated in 70% and 35% solutions and usually packaged in 100 mL bottles. The gram dosage of sorbitol in a 100 mL bottle can be calculated by multiplying 100 (mL) x 0.7 (for 70% solution) x 1.285 g sorbitol/mL. Therefore the dose in mL is as follows:

Dosage of Sorbitol:

- *Adults:* 70% sorbitol, 1-2 mL/kg.
- *Children:* 35% sorbitol, 1.5-2.3 mL/kg (maximum dosage: 50 g).

Note on Specific Pesticides: Significant poisoning with organophosphates, carbamates, and arsenicals generally results in a profuse diarrhea. Poisoning with diquat and to a lesser extent paraquat results in an ileus. The use of sorbitol is not recommended in any of the above pesticide poisonings.

Position Statement: The administration of a cathartic alone has no role in the management of the poisoned patient. There are no definite indications for the use of cathartics in the management of the poisoned patient. Data are conflicting with regard to use in combination with activated charcoal, and its routine use is not endorsed. If a cathartic is used, it should be as a single dose in order to minimize adverse effects. There are numerous contraindications, including absent bowel sounds, abdominal trauma or surgery, or intestinal perforation or obstruction. It is also contraindicated in volume depletion,

Dosage of Activated Charcoal:

- *Adults and children over 12 years:* 25-100 g in 300-800 mL water.
- *Children under 12 years:* 25-50 g per dose.
- *Infants and toddlers under 20 kg*: 1 g per kg body weight.

Many activated charcoal formulations come premixed with sorbitol. Avoid giving more than one dose of sorbitol as a cathartic in infants and children due to the risk of rapid shifts of intravascular fluid.

Encourage the victim to swallow the adsorbent even though spontaneous vomiting continues. Antiemetic therapy may help control vomiting in adults or older

Dosage of Syrup of Ipecac:

- *Adolescents and adults:* 15-30 mL followed immediately with 240 mL of water.
- *Children 1-12 years:* 15 mL preceded or followed by 120 to 240 mL of water.
- *Infants 6 months to 12 months:* 5-10 mL preceded or followed by 120 to 240 mL of water.

Dose may be repeated in all age groups if emesis does not occur within 20-30 minutes.

Position Statement: Ipecac syrup should not be administered routinely in poisoned patients. If ipecac is used, it should be administered within 60 minutes of the ingestion. Even then, clinical studies have demonstrated no benefit from its use. It should be considered only in an alert conscious patient who has ingested a potentially toxic ingestion. Contraindications to its use include the following: patients with diminished airway protective reflexes, the ingestion of hydrocarbons with a high aspiration potential, the ingestion of a corrosive substance, or the ingestion of a substance in which advanced life support may be necessary within the next 60 minutes.[15]

5. Seizures

Lorazepam is increasingly being recognized as the drug of choice for status epilepticus, although there are few reports of its use with certain pesticides. One must be prepared to assist ventilation with lorazepam and any other medication used to control seizures. See dosage table on next page.

For organochlorine compounds, use of lorazepam has not been reported in the literature. Diazepam is often used for this, and is still used in other pesticide poisonings.

Dosage of Diazepam:

- *Adults:* 5-10 mg IV and repeat every 5-10 minutes to maximum of 30 mg.
- *Children:* 0.2-0.5 mg/kg IV every 5 minutes to maximum of 10 mg

Dosage of Lorazepam:

- *Adults:* 2-4 mg/dose given IV over 2-5 minutes. Repeat if necessary to a maximum of 8 mg in a 12 hour period.
- *Adolescents:* Same as adult dose, except maximum dose is 4 mg.
- *Children under 12 years:* 0.05-0.10 mg/kg IV over 2-5 minutes. Repeat if necessary .05 mg/kg 10-15 minutes after first dose, with a maximum dose of 4 mg.

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

Phenobarbital is an additional treatment option for seizure control. Dosage for **infants, children, and adults** is 15-20 mg/kg as an IV loading dose. An additional 5 mg/kg IV may be given every 15-30 minutes to a maximum of 30 mg/kg. The drug should be pushed no faster than 1 mg/kg/minute.

For seizure management, most patients respond well to usual management consisting of benzodiazepines, or phenytoin and phenobarbital.

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CHAPTER 3

Environmental and Occupational History

Pesticide poisonings may go unrecognized because of the failure to take a proper exposure history. This chapter is intended to remedy this often overlooked area by providing basic tools for taking a complete exposure history. In some situations where exposures are complex or multiple and/or symptoms atypical, it is important to consider consultation with clinical toxicologists or specialists in environmental and occupational medicine. Local Poison Control Centers should also be considered when there are questions about diagnosis and treatment.

Although this manual deals primarily with pesticide-related diseases and injury, the approach to identifying exposures is similar regardless of the specific hazard involved. It is important to ascertain whether other non-pesticide exposures are involved because of potential interactions between these hazards and the pesticide of interest (e.g., pesticide intoxication and heat stress in agricultural field workers). Thus, the following section on pesticide exposures should be seen in the context of an overall exposure assessment.

Most pesticide-related diseases have clinical presentations that are similar to common medical conditions and display nonspecific symptoms and physical signs. Knowledge of a patient's exposure to occupational and environmental factors is important for diagnostic, therapeutic, rehabilitative and public health purposes. Thus, it is essential to obtain an adequate history of any environmental or occupational exposure which could cause disease or exacerbate an existing medical condition.

In addition to the appropriate patient history-taking, one must also consider any other persons that may be similarly exposed in the home, work or community environment. Each environmental or occupational disease identified should be considered a potential sentinel health event which may require

that involve numerous exposed individuals, additional assistance can be obtained by contacting the state health department, state regulatory agency (e.g.,

effects, concurrent non-pesticide exposures need to be considered in the overall patient health assessment. Questions typical of a detailed interview are listed on the next several pages, preceded by special concerns in addressing exposures of children and agricultural workers. For further details on taking a history for all types of occupational and environmental hazards, consult the ATSDR monograph entitled "Taking an Exposure History"[1] or a general occupational and environmental medicine reference text.[2]

Special Patient Populations

Children

In comparison to adults, children may be at greater risk from pesticide exposures due to growth and developmental factors. Consideration of fetal, infant, toddler or child characteristics is helpful in an exposure evaluation: physical location, breathing zones, oxygen consumption, food consumption, types of foods consumed and normal behavioral development.[3] Furthermore, transplacental absorption and breast milk may pose additional routes of exposure. Although environmental (and, at times, occupational) exposure to pesticides is the focus of this chapter, the most significant hazard for children is unintentional ingestion.[4] Thus, it is very important to ask about pesticides used and stored in the home, day care facility, school, and play areas.

Agricultural Workers

Data from California's mandatory pesticide poisoning reporting system would imply an annual national estimate of 10,000-20,000 cases of farmworker poisoning.[5] However, it is believed that these figures still represent serious underreporting due to the lack of medical access for many farmworkers and misdiagnosis by some clinicians. For these high-risk patients, the exposure history should include specific questions about the agricultural work being done. For example:

- Are pesticides being used at home or work?
- Were the fields wet when you were picking?
- Was any spraying going on while you were working in the fields?
- Do you get sick during or after working in the fields?

The use of pesticides in the residence and taking home agricultural pesticides or contaminated work clothes that are not properly separated from other clothes may pose hazards for other household members as well.

Obtaining Additional Pesticide Information

In addition to the patient history, it is often helpful to obtain further information on suspect pesticide products. Two documents are useful starting points

DETAILED INTERVIEW FOR OCCUPATIONAL AND ENVIRONMENTAL EXPOSURES

(Questions marked in bold type are especially important for a pesticide exposure history)

(1) Adult Patient

OCCUPATIONAL EXPOSURE

- **What is your occupation?**

NON-OCCUPATIONAL EXPOSURES POTENTIALLY RELATED TO ILLNESS OR INJURY

- **Do you use tobacco?** If yes, in what forms (cigarettes, pipe, cigar, chewing tobacco)? About how many do you smoke or how much tobacco do you use per day? At what age did you start using tobacco? Are there other tobacco smokers in the home?
- **Do you drink alcohol?** How much per day or week? At what age did you start?
- **What medications or drugs are you taking?** *(Include prescription and non-prescription uses)*
- **Has anyone in the family worked with hazardous materials that they might have brought home (e.g., pesticides,** asbestos, lead)? (*If yes, inquire about household members potentially exposed.)*

(2) Pediatric Patient (questions asked of parent or guardian)

OCCUPATIONAL EXPOSURE

- **What is your occupation and that of other household members?** (If no employed individuals, go to next section)
- **Describe your work and what hazards you are exposed to (e.g., pesticides,** solvents or other chemicals, dust, fumes, metals, fibers, radiation, biologic agents, noise, heat, cold, vibration)

ENVIRONMENTAL EXPOSURE HISTORY

- **Are pesticides (e.g., bug or weed killers, flea and tick sprays, collars, powders, or shampoos) used in your home or garden or on your pet?**
- **Do you or any household member have a hobby with exposure to any hazardous materials (e.g., pesticides,** paints, ceramics, solvents, metals, glues**)?**
- **If pesticides are used:**
  - **Is a licensed pesticide applicator involved?**
  - **Are children allowed to play in areas recently treated with pesticides?**
  - **Where are the pesticides stored?**
  - **Is food handled properly (e.g., washing of raw fruits and vegetables)?**
- **Has the patient ever lived near a facility which could have contaminated the surrounding area** (e.g., mine, **plant**, smelter, **dump site**)?
- **Has the patient ever changed residence because of a health problem?**
- **Does the patient's drinking water come from a private well, city water supply, and/or grocery store?**
- Which of the following are in the patient's home: air conditioner/purifier, central heating (gas or oil), gas stove, electric stove, fireplace, wood stove, or humidifier?
- Is there recently acquired new furniture or carpet, or recent home remodeling in the patient's home?
- Has the home been weatherized recently?
- Approximately what year was the home built?

SYMPTOMS AND MEDICAL CONDITIONS

- **Does the timing of symptoms have any relationship to environmental activities listed above?**
- **Has any other household member or nearby neighbor suffered similar health problems?**

NON-OCCUPATIONAL EXPOSURES POTENTIALLY RELATED TO ILLNESS OR INJURY

- **Are there tobacco smokers in the home?** If yes, in what forms (cigarettes, pipe, cigar, chewing tobacco)?
- **What medications or drugs is the patient taking?** *(Include prescription and non-prescription uses)*
- **Has anyone in the family worked with hazardous materials that they might have brought home (e.g., pesticides,** asbestos, lead)? (*If yes, inquire about household members potentially exposed.)*

in the identification and evaluation of the pesticide exposure: the material safety data sheet (MSDS) and the pesticide label.

- **Material Safety Data Sheet (MSDS).** Under OSHA's Hazard Communications Standard (29 CFR 1910.1200), all chemical manufacturers are required to provide an MSDS for each hazardous chemical they produce or import. Employers are required to keep copies of MSDSs and make them available to the workers. The following items are contained in an MSDS:
  - Material identification
  - Ingredients and occupational exposure limits
  - Physical data
  - Fire and explosion data
  - Reactivity data
  - Health hazard data
  - Spill, leak, and disposal procedures
  - Special protection data
  - Special precautions and comments.

  These documents tend to have very limited information on health effects and some of the active ingredients may be omitted due to trade secret considerations. One cannot rely solely on an MSDS in making medical determinations.

- **Pesticide label.** EPA requires that all pesticide products bear labels that provide certain information. This information can help in evaluating pesticide health effects and necessary precautions. The items covered include the following:
  - Product name
  - Manufacturer
  - EPA registration number
  - Active ingredients
  - Precautionary statements:
    i. Human hazard signal words "Danger" (most hazardous), "Warning," and "Caution" (least hazardous)
    ii. Child hazard warning
    iii. Statement of practical treatment (signs and symptoms of poisoning, first aid, antidotes, and note to physicians in the event of a poisoning)
    iv. Hazards to humans and domestic animals
    v. Environmental hazards
    vi. Physical or chemical hazards

- Directions for use
- Name and address of manufacturer
- Net contents
- EPA registration number
- EPA establishment number
- Worker Protection Standard (WPS) designation, including restricted entry interval and personal protection equipment required (see WPS description on page 25).

The EPA registration number is useful when contacting EPA for information or when calling the National Pesticide Telecommunications Network hotline (see page 29). Pesticide labels may differ from one state to another based on area-specific considerations. Also, different formulations of the same active ingredients may result in different label information. The pesticide label lists information only for active ingredients (not for inert components) and rarely contains information on chronic health effects (e.g., cancer and neurologic, reproductive, and respiratory diseases).[6]

- Co-workers or others in the environment who are ill
- Timing of the problems
- Confirmation of physical exposure to the pesticide
- Environmental monitoring data
- Biomonitoring results
- Biological plausibility of the resulting health effect
- Ruling out non-pesticide exposures or pre-existing illnesses.

A concurrent non-pesticide exposure can either have no health effect, exacerbate an existing pesticide health effect, or solely cause the health effect in a patient. In the more complicated exposure scenarios, assistance should be sought from specialists in occupational and environmental health (see Information Resources on page 27).

Legal, Ethical, and Public Health Considerations

Following are some considerations related to government regulation of pesticides, ethical factors, and public health concerns that health care providers should be aware of in assessing a possible pesticide exposure.

Reporting Requirements

When evaluating a patient with a pesticide-related medical condition, it is important to understand the state-specific reporting requirements for the workers' compensation system (if there has been an occupational exposure) or surveillance system. Reporting a workers' compensation case can have significant implications for the worker being evaluated. If the clinician is not familiar with this system or is uncomfortable evaluating work-related health events, it is important to seek an occupational medicine consultation or make an appropriate referral.

At least six states have surveillance systems within their state health departments that cover both occupational and environmental pesticide poisonings: California, Florida, New York, Oregon, Texas, and Washington. These surveillance systems collect case reports on pesticide-related illness and injury from clinicians and other sources; conduct selected interviews, field investigations, and research projects; and function as a resource for pesticide information within their state. In some states, as noted earlier, pesticide case reporting is legally mandated.

Regulatory Agencies

Since its formation in 1970, EPA has been the lead agency for the regulation of pesticide use under the Federal Insecticide, Fungicide and Rodenticide Act. EPA's mandates include the registration of all pesticides used in the United States, setting restricted entry intervals, specification and approval of label in-

formation, and setting acceptable food and water tolerance levels. In addition, EPA works in partnership with state and tribal agencies to implement two field programs — the certification and training program for pesticide applicators and the agricultural worker protection standard — to protect workers and handlers from pesticide exposures. EPA sets national standards for certification of over 1 million private and commercial pesticide applicators.

The authority to enforce EPA regulations is delegated to the states. For example, calls concerning non-compliance with the worker protection standard can typically be made to the state agricultural department. In five states,

personal protective equipment for direct work with pesticides, and observe restricted entry interval (REI) times. (The REI is a required waiting period before workers can return to areas treated with pesticides.) Of special interest to health care providers, the WPS also requires agricultural employers to:

- Post an emergency medical facility address and phone number in a central location.
- Arrange immediate transport from the agricultural establishment to a medical facility for a pesticide-affected worker.
- Supply the affected worker and medical personnel with product name, EPA registration number, active ingredient, label medical information, a description of how the pesticide was used, and exposure information.

Ethical Considerations

Attempts to investigate an occupational pesticide exposure may call for obtaining further information from the worksite manager or owner. Any contact with the worksite should be taken in consultation with the patient because of the potential for retaliatory actions (such as loss of job or pay cuts). Ideally, a request for a workplace visit or more information about pesticide exposure at the workplace will occur with the patient's agreement. In situations where the health hazard is substantial and many individuals might be affected, a call to a state pesticide surveillance system (if available), agricultural health and safety center (if nearby), can provide the National Institute for Occupational Safety and Health (NIOSH) or state agricultural agency the assistance needed for a disease outbreak investigation.

Similarly, the discovery of pesticide contamination in a residence, school, daycare setting, food product, or other environmental site or product can have public health, financial, and legal consequences for the patient and other individuals (e.g., building owner, school district, food producer). It is prudent to discuss these situations and follow-up options with the patient as well as a knowledgeable environmental health specialist and appropriate state or local agencies.

Public Health Considerations

Health care providers are often the first to identify a sentinel health event that upon further investigation develops into a full-blown disease outbreak. A disease outbreak is defined as a statistically elevated rate of disease among a well-defined population as compared to a standard population. For example, complaints about infertility problems among workers at a dibromochloropropane (DBCP) manufacturing plant in California led to diagnoses of azoospermia (lack of sperm) or oligospermia (decreased sperm count) among a handful of otherwise healthy young men working at the plant.[7] An eventual disease outbreak investigation resulted in the first published report of a male reproductive toxicant in the workplace. At the time, DBCP was used as a nematocide; it has since been banned in the United States.

Disease outbreak investigations are conducted for all kinds of exposures

and health events, not only those in the occupational and environmental area. Usually, assistance from government or university experts is needed in the investigation, which may require access to information, expertise, and resources

materials in several languages are available.

Address: EPA – OPP
401 M Street SW (7506C)
Washington, DC 20460
Telephone: 703-305-7666
Web site: www.epa.gov/pesticides/safety

Occupational Safety and Health Administration (OSHA)

More than 100 million workers and 6.5 million employers are covered under the Occupational Safety and Health Act, which covers workers in pesticide manufacturing as well as other industries. OSHA and its state partners have approximately 2100 inspectors, plus investigators, standards writers, educators, physicians, and other staff in over 200 offices across the country. OSHA sets protective workplace standards, enforces the standards, and offers employers and employees technical assistance and consultation programs. Note that some states have their own OSHA plan.

Address: OSHA – US DOL
Room N3647
Constitution Ave NW
Washington, DC 20210
Telephone: 202-219-8021
Web site: www.osha.gov

Food and Drug Administration (FDA)

Drug and food pesticide issues.

Address: FDA
National Center for Toxicological Research
5600 Fishers Lane
Rockville, MD 20857
Telephone: 301-443-3170
Internet: gopher.nctr.fda.gov

USDA Extension Service

USDA's Extension Service works with its university partners, the state land-grant system, to provide farmers and ranchers information to reduce and prevent agricultural-related work incidents. The Pesticide Applicator Training program trains applicators in the safe use of pesticides and coordinates pesticide-related safety training programs.

Address: USDA
14th & Independence SW
Washington, DC 20250
Telephone: 202-720-2791
Web site: www.reeusda.gov

National Center for Environmental Health (NCEH), Centers for Disease Control (CDC)

NCEH provides expertise in environmental pesticide case surveillance and disease outbreak investigations.

Address: NCEH, CDC
Mailstop F29
4770 Buford Highway NE
Atlanta, GA 30341
Tel: 770-488-7030
Web site: www.cdc.gov/nceh/ncehhome.htm

National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control (CDC)

NIOSH is the federal agency responsible for conducting research on occupational disease and injury. NIOSH may investigate potentially hazardous working conditions upon request, makes recommendations on preventing workplace disease and injury, and provides training to occupational safety and health professionals.

Address: NIOSH
Humphrey Building, Room 715H
200 Independence Ave SW
Washington, DC 20201
Hotline: 1-800-356-4674
Web site: www.cdc.gov/niosh/homepage.html

NIOSH Agricultural Health and Safety Centers

NIOSH has funded eight Agricultural Health and Safety Centers throughout the country which involve clinicians and other health specialists in the area of pesticide-related illness and injury. The NIOSH-supported centers are:

University of California Agricultural Health and Safety Center
Old Davis Road
University of California
Davis, CA 95616
Tel: 916-752-4050

High Plains Intermountain Center for Agricultural Health and Safety
Colorado State University
Fort Collins, CO 80523
Tel: 970-491-6152

Great Plains Center for Agricultural Health
University of Iowa
Iowa City, IA 52242
Tel: 319-335-4415

Southeast Center for Agricultural Health and Injury Prevention
University of Kentucky
Department of Preventive Medicine
Lexington, KY 40536
Tel: 606-323-6836

Northeast Center for Agricultural and Occupational Health
One Atwell Road
Cooperstown, NY 13326
Tel: 607-547-6023

Southwest Center for Agricultural Health, Injury and Education
University of Texas
Health Center at Tyler
PO Box 2003
Tyler, TX 75710
Tel: 903-877-5896

Pacific Northwest Agricultural Safety and Health Center
University of Washington
Department of Environmental Health
Seattle, WA 98195
Tel: 206-543-0916

Midwest Center for Agricultural Research, Education and Disease and Injury Prevention
National Farm Medicine Center
Marshfield, WI 54449-5790
Tel: 715-389-3415

Non-Governmental Organizations:

National Pesticide Telecommunications Network

The National Pesticide Telecommunications Network (NPTN) is based at Oregon State University and is cooperatively sponsored by the University and EPA. NPTN serves as a source of objective, science-based pesticide information on a wide range of pesticide-related topics, such as recognition and management of pesticide poisonings, safety information, health and environmental effects, referrals for investigation of pesticide incidents and emergency treatment for both humans and animals, and cleanup and disposal procedures.

A toll-free telephone service provides pesticide information to callers in the continental United States, Puerto Rico, and the Virgin Islands. Additionally, pesticide questions and comments can be sent to an e-mail address. The Web site has links to other sites and databases for further information.

NPTN hotline:	1-800-858-7378
Hours of operation:	9:30 am – 7:30 pm E.S.T. daily except holidays
Web site:	http://ace.orst.edu/info/nptn/
E-mail address:	nptn@ace.orst.edu

Farmworker Justice Fund

The Farmworker Justice Fund can provide an appropriate referral to a network of legal services and nonprofit groups which represent farmworkers for free.

Address:	Farmworker Justice Fund 1111 19th Street, NW, Suite 1000 Washington, DC 20036
Telephone:	202-776-1757
E-mail address:	fjf@nclr.org

American Farm Bureau Federation
The AFBF is the nation's largest general farm organization. Information on how to contact individual state-based farm bureaus is available on their Web site.

Web site: www.fb.com

Association of Occupational and Environmental Clinics (AOEC)
This association is a network of 63 clinics representing more than 250 specialists.

Address: AOEC
1010 Vermont Ave, NW, Suite 513
Washington, DC 20005
Telephone: 202-347-4976
Web site: http://152.3.65.120/oem/aoec.htm

Poison Control Centers
For a list of state and regional poison control centers, or the nearest location, consult the NPTN Web site (http://ace.orst.edu/info/nptn).

Pesticide Information Databases:

Extension Toxicology Network (EXTOXNET)
http://ace.ace.orst.edu/info/extoxnet
The Extension Service's Toxicology Network, EXTOXNET, provides science-based information about pesticides to health care providers treating pesticide-related health concerns. Pesticide toxicological information is developed cooperatively by the University of California-Davis, Oregon State University, Michigan State University, Cornell University, and the University of Idaho.

IRIS
www.epa.gov/ngispgm3/iris
The Integrated Risk Information System – IRIS – is an electronic database, maintained by EPA, on human health effects that may result from exposure to various chemicals in the environment. IRIS is intended for those without extensive training in toxicology, but with some knowledge of health sciences. It provides hazard identification and dose-response assessment information. Combined with specific exposure information, the data in IRIS can be used for characterization of the public health risks of a chemical in a particular situation that can lead to a risk management decision designed to protect public health. Extensive supporting documentation available online.

Section II

INSECTICIDES

CHAPTER 4

Organophosphate Insecticides

Since the removal of organochlorine insecticides from use, organophosphate insecticides have become the most widely used insecticides available today. More than forty of them are currently registered for use and all run the risk of acute and subacute toxicity. Organophosphates are used in agriculture, in the home, in gardens, and in veterinary practice. All apparently share a common mechanism of cholinesterase inhibition and can cause similar symptoms. Because they share this mechanism, exposure to the same organophosphate by multiple routes or to multiple organophosphates by multiple routes can lead to serious additive toxicity. It is important to understand, however, that there is a wide range of toxicity in these agents and wide variation in cutaneous absorption, making specific identification and management quite important.

COMMERCIAL PRODUCTS

acephate
Orthene
azinphos-methyl+
Gusathion
Guthion
bensulide
Betasan
Lescosan
bomyl+
Swat
bromophos
Nexion
bromophos-ethyl
Nexagan
cadusafos
Apache
Ebufos
Rugby
carbophenothion+
Trithion
chlorethoxyfos
Fortress
chlorfenvinphos
Apachlor
Birlane
chlormephos+
Dotan
chlorphoxim
Baythion-C
chlorpyrifos
Brodan
Dursban
Lorsban
chlorthiophos+
Celathion
coumaphos+
Asuntol
Co-Ral
crotoxyphos
Ciodrin
Cypona
crufomate
Ruelene
cyanofenphos+
Surecide
cyanophos
Cyanox
cythioate
Cyflee
Proban
DEF
De-Green
E-Z-Off D
demeton+
systox
demeton-S-methyl
Duratox
Metasystoxl
dialifor+
Torak
diazinon
dichlorofenthion
VC-13 Nemacide
dichlorvos
DDVP
Vapona
dicrotophos+
Bidrin
dimefos+
Hanane
Pestox XIV
dimethoate
Cygon
DeFend
dioxathion+
Delnav
disulfoton+
Disyston
ditalimfos
edifenphos
endothion+
EPBP
S-Seven
EPN+
ethion
Ethanox
ethoprop
Mocap
ethyl parathion+
E605
Parathion
thiophos
etrimfos
Ekamet
famphur+
Bash
Bo-Ana
Famfos
fenamiphos+
Nemacur
fenitrothion
Accothion
Agrothion
Sumithion
fenophosphon+
Agritox
trichloronate
fensulfothion+
Dasanit
fenthion
Baytex
Entex
Tiguvon
fonofos+
Dyfonate
N-2790
formothion
Anthio
fosthietan+
Nem-A-Tak
heptenophos
Hostaquick
hiometon
Ekatin
hosalone
Zolone
IBP
Kitazin
iodofenphos
Nuvanol-N
isazofos
Brace
Miral
Triumph
isofenphos+
Amaze
Oftanol
isoxathion
E-48
Karphos
leptophos
Phosvel
malathion
Cythion
mephosfolan+
Cytrolane
merphos
Easy off-D
Folex
methamidophos+
Monitor
methidathion+
Supracide
Ultracide
methyl parathion+
E 601
Penncap-M
methyl trithion
mevinphos+
Duraphos
Phosdrin
mipafox+
Isopestox
Pestox XV
monocrotophos+
Azodrin
naled
Dibrom
oxydemeton-methyl
Metasystox-R
oxydeprofos
Metasystox-S
phencapton
G 28029
phenthoate
dimephenthoate
Phenthoate
phorate+
Rampart
Thimet
phosalone
Azofene
Zolone
phosfolan+
Cylan
Cyolane
phosmet
Imidan
Prolate
phosphamidon+
Dimecron
phostebupirim
Aztec
phoxim
Baythion
pirimiphos-ethyl
Primicid
pirimiphos-methyl
Actellic
profenofos
Curacron
propetamphos
Safrotin
propyl thiopyro-
phosphate+
Aspon
prothoate
Fac
pyrazophos
Afugan
Curamil
pyridaphenthion
Ofunack
quinalphos
Bayrusil
ronnel
Fenchlorphos
Korlan
schradan+
OMPA
sulfotep+
Bladafum
Dithione
Thiotepp
sulprofos
Bolstar
Helothion
temephos
Abate
Abathion
terbufos
Contraven
Counter
tetrachlorvinphos
Gardona
Rabon
tetraethyl pyrophos-
phate+
TEPP
triazophos
Hostathion
trichlorfon
Dipterex
Dylox
Neguvon
Proxol

+ Indicates high toxicity. Highly toxic organophosphates have listed oral LD_{50} values (rat) less than or equal to 50 mg/kg body weight. Most other organophosphates included in this table are considered moderately toxic, with LD_{50} values in excess of 50 mg/kg and less than 500 mg/kg.

Organophosphates are efficiently absorbed by inhalation, ingestion, and skin penetration. There is considerable variation in the relative absorption by these various routes. For instance, the oral LD_{50} of parathion in rats is between 3-8 mg/kg, which is quite toxic,[1,2] and essentially equivalent to dermal absorption with an LD_{50} of 8 mg/kg.[2] On the other hand, the toxicity of **phosalone** is much lower from the dermal route than the oral route, with rat LD_{50}s of 1500 mg/kg and 120 mg/kg, respectively.[2] In general, the highly toxic agents are more likely to have high-order dermal toxicity than the moderately toxic agents.

Chemical Classes: To some degree, the occurrence of poisoning depends on the rate at which the pesticide is absorbed. Breakdown occurs chiefly by

persist for weeks to years. These rare occurrences have been found shortly after an acute and often massive exposure, but in some cases, symptoms have persisted for months to years. Only a few of the many organophosphates used as pesticides have been implicated as causes of delayed neuropathy in humans. EPA guidelines require that organophosphate and carbamate compounds which are candidate pesticides be tested in susceptible animal species for this neurotoxic property.

Three epidemiologic studies with an exposed group and a control group also suggest that a proportion of patients acutely poisoned from any organo-

Signs and Symptoms of Poisoning

Symptoms of acute organophosphate poisoning develop during or after exposure, within minutes to hours, depending on the method of contact. Exposure by inhalation results in the fastest appearance of toxic symptoms, followed by the gastrointestinal route and finally the dermal route. All signs and symptoms are cholinergic in nature and affect muscarinic, nicotinic, and central nervous system receptors.[5] The critical symptoms in management are the respiratory symptoms. Sufficient muscular fasciculations and weakness are often observed as to require respiratory support; respiratory arrest can occur suddenly. Likewise, bronchorrhea and bronchospasm may often impede efforts at adequate oxygenation of the patient.

Bronchospasm and bronchorrhea can occur, producing tightness in the chest, wheezing, productive cough, and pulmonary edema. A life threatening severity of poisoning is signified by loss of consciousness, incontinence, convulsions, and respiratory depression. The primary cause of death is respiratory failure, and there usually is a secondary cardiovascular component. The classic cardiovascular sign is bradycardia which can progress to sinus arrest. However, this may be superseded by tachycardia and hypertension from nicotinic (sympathetic ganglia) stimulation.[19] Toxic myocardiopathy has been a prominent feature of some severe organophosphate poisonings.

Some of the most commonly reported early symptoms include headache, nausea, dizziness, and hypersecretion, the latter of which is manifested by sweating, salivation, lacrimation, and rhinorrhea. Muscle twitching, weakness, tremor, incoordination, vomiting, abdominal cramps, and diarrhea all signal worsening of the poisoned state. Miosis is often a helpful diagnostic sign and the patient may report blurred and/or dark vision. Anxiety and restlessness are prominent, as are a few reports of choreaform movements. Psychiatric symptoms including depression, memory loss, and confusion have been reported. Toxic psychosis, manifested as confusion or bizarre behavior, has been misdiagnosed as alcohol intoxication.

Children will often present with a slightly different clinical picture than adults. Some of the typical cholinergic signs of bradycardia, muscular fasciculations, lacrimation, and sweating were less common. Seizures (22%-25%) and mental status

Confirmation of Poisoning

If poisoning is probable, **treat the patient immediately. Do not wait for laboratory confirmation.**

Blood samples should be drawn to measure plasma pseudocholinesterase and red blood cell AChE levels. Depressions of plasma pseudocholinesterase and/or RBC acetylcholinersterase enzyme activities are generally available biochemical indicators of excessive organophosphate absorption. Certain organophosphates may selectively inhibit either plasma pseudocholinesterase or RBC acetylcholinesterase.[22] A minimum amount of organophosphate must be absorbed to depress blood cholinesterase activities, but enzyme activities, especially plasma pseudocholinesterase, may be lowered by dosages considerably less than are required to cause symptomatic poisoning. The enzyme depression is usually apparent within a few minutes or hours of significant absorption of organophosphate. Depression of the plasma enzyme generally persists several days to a few weeks. The RBC enzyme activity may not reach its minimum for several days, and usually remains depressed longer, sometimes 1-3 months, until new enzyme replaces that inactivated by organophosphate. The above table lists approximate lower limits of normal plasma and RBC cholinesterase activities of human blood, measured by several methods. **Lower levels usually indicate excessive absorption of a cholinesterase-inhibiting chemical.**

APPROXIMATE LOWER LIMITS OF NORMAL PLASMA AND RED CELL CHOLINESTERASE ACTIVITIES IN HUMANS*

Methods	Plasma	RBC	Blood	Whole units
pH (Michel)	0.45	0.55		ΔpH per mL per hr
pH Stat (Nabb-Whitfield)	2.3	8.0		μM per mL per min
BMC Reagent Set (Ellman-Boehringer)	1,875		3,000	mU per mL per min
Dupont ACA	<8			Units per mL
Garry-Routh (Micro)			Male 7.8 Female 5.8	μM-SH per 3mL per min
Technicon	2.0	8.0		μM per mL per min

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

In certain conditions, the activities of plasma and RBC cholinesterase are depressed in the absence of chemical inhibition. About 3% of individuals have a genetically determined low level of plasma pseudocholinesterase. These persons are particularly vulnerable to the action of the muscle-paralyzing drug succinylcholine (often administered to surgical patients), but not to organophosphates. Patients with hepatitis, cirrhosis, malnutrition, chronic alcoholism, and dermatomyositis exhibit low plasma cholinesterase activities. A number of toxicants, notably cocaine, carbon disulfide, benzalkonium salts, organic mercury compounds, ciguatoxins, and solanines may reduce plasma pseudocholinesterase activity. Early pregnancy, birth control pills, and metoclopramide may also cause some depression. The RBC acetylcholinesterase is less likely than the plasma enzyme to be affected by factors other than organophosphates. It is, however, reduced in certain rare conditions that damage the red cell membrane, such as hemolytic anemia.

The alkyl phosphates and phenols to which organophosphates are hydrolyzed in the body can often be detected in the urine during pesticide absorption and up to about 48 hours thereafter. These analyses are sometimes useful in identifying and quantifying the actual pesticide to which workers have been exposed. Urinary alkyl phosphate and phenol analyses can demonstrate organophosphate absorption at lower dosages than those required to depress cholinesterase activities and at much lower dosages than those required to produce symptoms and signs. Their presence may simply be a result of organophosphates in the food chain.

Detection of intact organophosphates in the blood is usually not possible except during or soon after absorption of a substantial amount. In general, organophosphates do not remain unhydrolyzed in the blood for more than a few minutes or hours, unless the quantity absorbed is large or the hydrolyzing liver enzymes are inhibited.

Treatment

2. Atropine sulfate. Administer atropine sulfate intravenously, or intramuscularly if intravenous injection is not possible. Remember that atropine can be administered through an endotracheal tube if initial IV access is difficult to obtain. Depending on the severity of poisoning, doses of atropine ranging from very low to as high as 300 mg per day may be required,[23] or even continuous infusion.[24,25] (See dosage on next page.)

The objective of atropine antidotal therapy is to antagonize the effects of excessive concentrations of acetylcholine at end-organs having muscarinic receptors. Atropine does not reactivate the cholinesterase enzyme or accelerate disposition of organophosphate. Recrudescence of poisoning may occur if tissue concentrations of organophosphate remain high when the effect of atropine wears off. Atropine is effective against muscarinic manifestations, but it is

Dosage of Atropine:

In *moderately severe poisoning* (hypersecretion and other end-organ manifestations without central nervous system depression), the following dosage schedules have been used:

- *Adults and children over 12 years:* 2.0-4.0 mg, repeated every 15 minutes until pulmonary secretions are controlled, which may be accompanied by other signs of atropinization, including flushing, dry mouth, dilated pupils, and tachycardia (pulse of 140 per minute). **Warning:** In cases of ingestion of liquid concentrates of organophosphate pesticides, hydrocarbon aspiration may complicate these

Dosage of Pralidoxime:

- *Adults and children over 12 years:* 1.0-2.0 g by intravenous infusion at a rate of no more than 0.2 g per minute. Slow administration of pralidoxime is strongly recommended and may be achieved by administering the

Contaminated clothing should be promptly removed, bagged, and laundered before returning. Contaminated leather shoes should be discarded. Note that the pesticide can contaminate the inside surfaces of gloves, boots, and headgear.

6. Gastrointestinal decontamination. If organophosphate has been ingested in quantity probably sufficient to cause poisoning, consideration should be given to gastrointestinal decontamination, as outlined in Chapter 2, General Principles. If the patient has already vomited, which is most likely in serious exposures, further efforts at GI decontamination may not be indicated. In significant ingestions, diarrhea and/or vomiting are so constant that charcoal adsorption and catharsis are not indicated.

7. Observation. Observe patient closely for at least 72 hours to ensure that symptoms (sweating, visual disturbances, vomiting, diarrhea, chest and abdominal distress, and sometimes pulmonary edema) do not recur as atropinization is withdrawn. In very severe poisonings by ingested organophosphates, particularly the more lipophilic and slowly hydrolyzed compounds, metabolic disposition of toxicant may require as many as 5-14 days. In some cases, this slow elimination may combine with profound cholinesterase inhibition to require atropinization for several days or even weeks. As dosage is reduced, the lung bases should be checked frequently for crackles. If crackles are heard, or if there is a return of miosis, bradycardia, sweating, or other cholinergic signs, atropinization must be re-established promptly.

8. Furosemide may be considered if pulmonary edema persists in the lungs even after full atropinization. It should not be used until the maximum benefit of atropine has been realized. Consult package insert for dosage and administration.

9. Pulmonary ventilation. Particularly in poisonings by large ingested doses of organophosphate, monitor pulmonary ventilation carefully, even after recovery from muscarinic symptomatology, to forestall respiratory failure. In some cases, respiratory failure has developed several days following organophosphate ingestion, and has persisted for days to weeks.

10. Hydrocarbon aspiration may complicate poisonings that involve inges-

12. Seizure control. Rarely, in severe organophosphate poisonings, convulsions occur despite therapy with atropine and pralidoxime. Insure that causes unrelated to pesticide toxicity are not responsible: head trauma, cerebral anoxia, or mixed poisoning. Drugs useful in controlling convulsions are discussed in Chapter 2. The benzodiazepines (diazepam or lorazepam) are the agents of choice as initial therapy.

13. Contraindications. The following drugs are contraindicated in nearly all

References

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CHAPTER 5

N-Methyl Carbamate Insecticides

HIGHLIGHTS

- Cause reversible carbamylation of AChE
- Muscarinic, nicotinic, CNS effects

Signs and Symptoms:

- Malaise, muscle weakness, dizziness, sweating
- Headache, salivation, nausea, vomiting, abdominal pain, diarrhea
- CNS depression, pulmonary edema in serious cases

Treatment:

- Clear airway, improve tissue oxygenation
- Administer atropine sulfate intravenously
- Proceed immediately with decontamination procedures

N-Methyl carbamate insecticides are widely used in homes, gardens, and agriculture. They share with organophosphates the capacity to inhibit cholinesterase enzymes and therefore share similar symptomatology during acute and chronic exposures. Likewise, exposure can occur by several routes in the same individual due to multiple uses, and there is likely to be additive toxicity with simultaneous exposure to organophosphates. However, due to the somewhat different affinity for cholinesterases, as compared to organophosphates, these poisonings are often somewhat easier to treat, as discussed later in this chapter.

Toxicology

The N-methyl carbamate esters cause reversible carbamylation of the acetylcholinesterase enzyme, allowing accumulation of acetylcholine, the neuromediator substance, at parasympathetic neuroeffector junctions (muscarinic effects), at skeletal muscle myoneural junctions and autonomic ganglia (nicotinic effects), and in the brain (CNS effects). The carbamyl-acetylcholinesterase combination dissociates more readily than the phosphoryl-acetylcholinesterase complex produced by organophosphate compounds. This lability has several important consequences: (1) it tends to limit the duration of N-methyl carbamate poisonings, (2) it accounts for the greater span between symptom-producing and lethal doses than in most organophosphate compounds, and (3) it frequently invalidates the measurement of blood cholinesterase activity as a diagnostic index of poisoning (see below).

N-methyl carbamates are absorbed by inhalation and ingestion and somewhat by skin penetration, although the latter tends to be the less toxic route. For example, carbofuran has a rat oral LD_{50} of 5 mg/kg, compared to a rat dermal LD_{50} of 120 mg/kg, which makes the oral route approximately 24 times more toxic when ingested.[1] N-methyl carbamates are hydrolyzed enzymatically by the liver; degradation products are excreted by the kidneys and the liver.

At cholinergic nerve junctions with smooth muscle and gland cells, high acetylcholine concentration causes muscle contraction and secretion, respectively. At skeletal muscle junctions, excess acetylcholine may be excitatory (cause muscle twitching), but may also weaken or paralyze the cell by depolarizing the end-plate. In the brain, elevated acetylcholine concentrations may cause sen-

Commercial Products

aldicarb+
- Temik

aminocarb+
- Matacil

bendiocarb+
- Dycarb
- Ficam
- Multamat
- Niomil
- Tattoo
- Turcam

bufencarb
- Bux
- metalkamate

carbaryl
- Dicarbam
- Sevin

carbofuran+
- Crisfuran
- Curaterr
- Furadan

cloethocarb+
- Lance

dimetan

Absorption of some N-methyl carbamates can be confirmed by analysis of urine for unique metabolites: alpha-naphthol from carbaryl, isopropoxyphenol from propoxur, carbofuran phenol from carbofuran, and aldicarb sulfone, sulfoxide, and nitrile from aldicarb. These complex analyses, when available, can be useful in identifying the responsible agent and following the course of carbamate disposition.

Treatment

Caution: Persons attending the victim should avoid direct contact with heavily contaminated clothing and vomitus. Wear rubber gloves while washing pesticide from skin and hair. Vinyl gloves provide no protection.

1. Airway protection. Ensure that a clear airway exists. Intubate the patient and aspirate the secretions with a large-bore suction device if necessary. Administer oxygen by mechanically assisted pulmonary ventilation if respiration is

Dosage of Atropine:

In *moderately severe poisoning*

3. Skin decontamination. In patients with contaminated skin, clothing, hair, and/or eyes, **decontamination must proceed concurrently with whatever resuscitative and antidotal measures are needed to preserve life.** Flush the chemical from eyes with copious amounts of clean water. For asymptomatic individuals who are alert and physically able, a prompt shower and shampoo may be appropriate for thorough skin decontamination, provided the patient is carefully observed to insure against sudden appearance of poisoning. If there are any indications of weakness ataxia or other neurologic impairment, clothing should be removed and a complete bath and shampoo given while the victim is recumbent, using copious amounts of soap and water. Attendants should wear rubber gloves as vinyl provides no protection against skin absorption. Wash the chemical from skin folds and from under fingernails.

Contaminated clothing should be promptly removed, bagged, and laundered before returning. Contaminated leather shoes should be discarded. Note that the pesticide can contaminate the inside surfaces of gloves, boots, and headgear.

4. Gastrointestinal decontamination. If N-methyl carbamate has been ingested in a quantity probably sufficient to cause poisoning, consideration should be given to gastrointestinal decontamination as outlined in Chapter 2. If the patient has presented with a recent ingestion and is still asymptomatic, adsorption of poison with activated charcoal may be beneficial. In significant ingestions, diarrhea and/or vomiting are so constant that charcoal adsorption and catharsis are not indicated. Attention should be given to oxygen, airway management, and atropine.

5. Urine sample. Save a urine sample for metabolite analysis if there is need to identify the agent responsible for the poisoning.

6. Pralidoxime is probably of little value in N-methyl carbamate poisonings, because atropine alone is effective. Although not indicated in isolated carbamate poisoning, pralidoxime appears to be useful in cases of mixed carbamate/organophosphate poisonings, and cases of an unknown pesticide with muscarinic symptoms on presentation.[7,8] See Chapter 4, Treatment section, p. 41.

7. Observation. Observe patient closely for at least 24 hours to ensure that symptoms (sweating, visual disturbances, vomiting, diarrhea, chest and abdominal distress, and sometimes pulmonary edema) do not recur as atropinization is withdrawn. The observation period should be longer in the case of a mixed pesticide ingestion, because of the prolonged and delayed symptoms associated with organophosphate poisoning. As the dosage of atropine is reduced over time, check the lung bases frequently for crackles. Atropinization must be re-established promptly, if crackles are heard, or if there is a return of miosis, sweating, or other signs of poisoning.

8. Furosemide may be considered for relief of pulmonary edema if crackles persist in the lungs even after full atropinization. It should not be considered

until the maximum effect of atropine has been achieved. Consult package insert for dosage and administration.

9. Pulmonary ventilation. Particularly in poisonings by large doses of N-methyl carbamates, monitor pulmonary ventilation carefully, even after recovery from muscarinic symptomatology, to forestall respiratory failure.

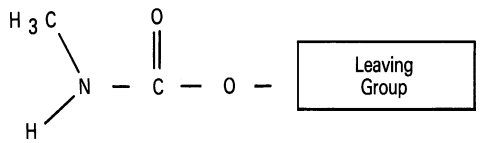
10. Cardiopulmonary monitoring. In severely poisoned patients, monitor cardiac status by continuous ECG recording.

11. Contraindications. The following drugs are probably contraindicated in nearly all N-methyl carbamate poisoning cases: morphine, succinlycholine, theophylline, phenothiazines, and reserpine. Adrenergic amines should be given only if there is a specific indication, such as marked hypotension.

12. Hydrocarbon aspiration may complicate poisonings that involve ingestion of liquid concentrates of some carbamates that are formulated in a petroleum product base. Pulmonary edema and poor oxygenation in these cases will not respond to atropine and should be treated as cases of acute respiratory distress syndrome.

13. Do not administer atropine prophylactically to workers exposed to N-methyl carbamate pesticides. Prophylactic dosage may mask early symptoms and signs of carbamate poisoning and thus allow the worker to continue exposure and possibly progress to more severe poisoning. Atropine itself may enhance the health hazards of the agricultural work setting: impaired heat loss due to reduced sweating and impaired ability to operate mechanical equipment due to blurred vision (mydriasis).

General Chemical Structure



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HIGHLIGHTS

Signs and Symptoms:

- Absorbed dose is stored in fat tissue
- Sensory disturbances: hyperesthesia and paresthesia, headache, dizziness, nausea, hyperexcitable state
- Convulsions

Metabolic dispositions of DDT and DDE (a DDT degradation product), the beta isomer of hexachlorocyclohexane, dieldrin, heptachlor epoxide, and mirex tend to be slow, leading to storage in body fat. Storable lipophilic compounds are likely to be excreted in maternal milk.[6,10,11] On the other hand, rapid metabolic dispositions of lindane, methoxychlor, dienochlor, endrin, chlorobenzilate, dicofol, toxaphene, perthane, and endosulfan reduce the likelihood that these organochlorines will be detected as residues in body fat, blood, or milk.

The chief acute toxic action of organochlorine pesticides is on the nervous system, where these compounds induce a hyperexcitable state in the brain.[12] This effect is manifest mainly as convulsions, sometimes limited to myoclonic jerking, but often expressed as violent seizures. Convulsions caused by cyclodienes may recur over periods of several days. Other less severe signs of neurologic toxicity such as paresthesias, tremor, ataxia, and hyperreflexia are also characteristic of acute organochlorine poisoning. Agents such as DDT and methoxychlor tend to cause the less severe effects, while the cyclodienes, mirex, and lindane are associated with the more severe seizures and fatalities.[7] Convulsions may cause death by interfering with pulmonary gas exchange and by generating severe metabolic acidosis.

High tissue concentrations of organochlorines increase myocardial irritability, predisposing to cardiac arrhythmia. When tissue organochlorine concentrations drop below threshold levels, recovery from the poisoning occurs. Organochlorines are not cholinesterase inhibitors.

High tissue levels of some organochlorines (notably DDT, DDE, and cyclodienes) have been shown to induce hepatic microsomal drug-metabolizing enzymes.[13] This tends to accelerate excretion of the pesticides themselves, but may also stimulate biotransformation of critical natural substances, such as steroid hormones and therapeutic drugs, occasionally necessitating re-evaluation of required dosages in persons intensively exposed to organochlorines. Human absorption of organochlorine sufficient to cause enzyme induction is likely to occur only as a result of prolonged intensive exposure.

potential, some organochlorines have lost registration for use in the United States or had their uses restricted. Although these effects are important, they are beyond the scope of this manual.

Signs and Symptoms of Poisoning

Early manifestations of poisoning by some organochlorine pesticides, particularly DDT, are often sensory disturbances: hyperesthesia and paresthesia of the face and extremities. Headache, dizziness, nausea, vomiting, incoordination, tremor, and mental confusion are also reported. More severe poisoning causes myoclonic jerking movements, then generalized tonic-clonic convulsions. Coma and respiratory depression may follow the seizures.

Poisoning by the cyclodienes and toxaphene is more likely to begin with the sudden onset of convulsions, and is often not preceded by the premonitory manifestations mentioned above. Seizures caused by cyclodienes may appear as long as 48 hours after exposure, and then may recur periodically over several days following the initial episode. Because lindane and toxaphene are more rapidly biotransformed in the body and excreted, they are less likely than diel-

hours, levels were 6 ng/mL and 5 ng/mL respectively. Findings from this study also provide evidence for increased absorption across abraded skin.[9] A child with severely abraded skin was treated for scabies and developed seizures. Three days after exposure, his lindane level was 54 ng/mL.[1] Most reports of acute

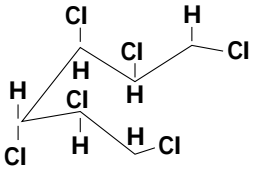
Seizures in patients caused by organochlorine toxicity are likely to be prolonged and difficult to control. Status epilepticus is common. For this reason, patients with seizures that do not respond immediately to anticonvulsants should

Dosage should be based on manifestations in the individual case and on information contained in the package insert.

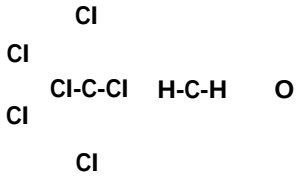
10. Cholestryamine resin accelerates the biliary-fecal excretion of the more slowly eliminated organochlorine compounds.[21] It is usually administered in 4 g doses, 4 times a day, before meals and at bedtime. The usual dose for children is 240 mg/kg/24 hours, divided Q 8 hours. The dose may be mixed with a pulpy fruit or liquid. It should never be given in its dry form and must always be administered with water, other liquids or a pulpy fruit. Prolonged treatment (several weeks or months) may be necessary.

11. Convalescence. During convalescence, enhance carbohydrate, protein, and vitamin intake by diet or parenteral therapy.

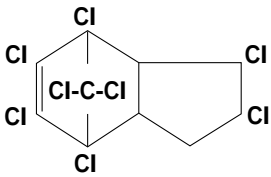
General Chemical Structures



Lindane



Dieldrin



Chlordane

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CHAPTER 7

Biologicals and Insecticides of Biological Origin

This chapter covers several widely-used insecticidal products of natural origin, as well as certain agents often identified as biological control agents. Of the many living control agents, only the bacterial agent *Bacillus thuringiensis* will be discussed in detail, since it is one of the most widely used. Many other agents, such as parasitic wasps and insects, are so host-specific that they pose little or no risk to human health. The agents are discussed in this chapter in alphabetic order.

AZADIRACHTIN

This biologically-obtained insecticide is derived from the Neem tree (*Azadirachta indica).* It is an insect growth regulator that interferes with the molting hormone ecdysone.

Toxicology

Azadirachtin causes severe dermal and gastrointestinal irritation. Central nervous system stimulation and depression have been seen. This agent is primarily used and manufactured in India; little use or exposures are expected in the United States.

Treatment

1. Skin decontamination. If skin exposure occurs, the skin should be thoroughly washed with soap and water.

2. Gastrointestinal decontamination. Due to the severe gastrointestinal irritation, gastric emptying and catharsis are not indicated. Consideration should be given to administration of activated charcoal as outlined in Chapter 2.

HIGHLIGHTS

- Derived from living systems
- *Bacillus thuringensis* is the most important live agent
- Generally of low order toxicity

Signs and Symptoms:

- Highly variable based on specific agents
- Several cause gastrointestinal irritation
- Nicotine and rotenone may have serious CNS effects
- Nicotine and sabadilla may have cardiovascular effects

Treatment:

- Specific to the agent
- Skin, eye, and GI decontamination may be indicated
- Nicotine, rotenone, and sabadilla require aggressive support

BACILLUS THURINGIENSIS

Several strains of *Bacillus thuringiensis* are pathogenic to some insects. The bacterial organisms are cultured, then harvested in spore form for use as insecticide. Production methods vary widely. Proteinaceous and nucleotide-like toxins generated by the vegetative forms (which infect insects) are responsible for the insecticidal effect. The spores are formulated as wettable powders, flowable concentrates, and granules for application to field crops and for control of mosquitoes and black flies.

Toxicology

Eugenol is similar in its clinical effects to phenol. Although it works as an anesthetic, in large doses it can cause burns to epithelial surfaces.[2] Sloughing of mucous membranes has occurred as an allergic reaction to a small dose applied topically in the mouth.[3] Gastric mucosal lesions have been reported in animals, but no lesions were seen on endoscopy after clove oil ingestion.[4] Large doses may result in coma and liver dysfunction.[5]

Treatment

Treatment is primarily supportive as there is no antidote. If mucosal burns are present, consider endoscopy to look for other ulcerations.

GIBBERELLIC ACID (Gibberellin, GA_3)

Gibberellic acid is not a pesticide, but it is commonly used in agricultural production as a growth-promoting agent. It is a metabolic product of a cultured fungus, formulated in tablets, granules, and liquid concentrates for application to soil beneath growing plants and trees.

Toxicology

Experimental animals tolerate large oral doses without apparent adverse effect. No human poisonings have been reported. Sensitization has not been reported, and irritant effects are not remarkable.

Treatment

1. Skin decontamination. Wash contamination from skin with soap and water. Flush contamination from eyes with clean water or saline. If irritation occurs, obtain medical treatment.

2. Gastrointestinal decontamination. If gibberellic acid has been swallowed, there is no reason to expect adverse effects.

NICOTINE

Nicotine is an alkaloid contained in the leaves of many species of plants, but is usually obtained commercially from tobacco. A 14% preparation of the free alkaloid is marketed as a greenhouse fumigant. Significant volatilization of nicotine occurs. Commercial nicotine insecticides have long been known as Black Leaf 40. This formulation was discontinued in 1992. Other currently

Commercial Products

(Continued)

- Rotacide
- Rotenone Solution FK-11
- Sypren-Fish

sabadilla

streptomycin
- Agri-Mycin 17
- Paushamycin, Tech.
- Plantomycin

*Discontinued in the U.S.

Treatment

1. Skin decontamination. If liquid or aerosol spray has come in contact with skin, wash the area thoroughly with soap and water. If eyes have been contaminated, flush them thoroughly with clean water or saline. If irritation persists, obtain specialized medical treatment.

If symptoms of poisoning appear during exposure to an airborne nicotine insecticide, remove the person from the contaminated environment immediately, wash any skin areas that may be contaminated, then transport the victim to the nearest treatment facility. Although mild poisoning may resolve without treatment, it is often difficult to predict the ultimate severity of poisoning at the onset.

2. Pulmonary ventilation. If there is any indication of loss of respiratory drive, maintain pulmonary ventilation by mechanical means, using supplemental oxygen if available, or mouth-to-mouth or mouth-to-nose methods if necessary. Toxic effects of nicotine other than respiratory depression are usually survivable. The importance of maintaining adequate gas exchange is therefore paramount.

3. Gastrointestinal decontamination. If a nicotine-containing product has been ingested recently, immediate steps must be taken to limit gastrointestinal absorption. If the patient is fully alert, immediate oral administration of activated charcoal as outlined in Chapter 2 is probably the best initial step in man-

Dosage of Atropine Sulfate:

- *Adults and children over 12 years:* 0.4-0.5 mg slowly IV, repeated every 5 minutes if necessary.
- *Children under 12 years:*

poor bioavailability probably accounts in large part for their relatively low mammalian toxicity. Dogs fed extraordinary doses exhibit tremor, ataxia, labored

ROTENONE

Although this natural substance is present in a number of plants, the source of most rotenone used in the United States is the dried derris root imported from Central and South America. It is formulated as dusts, powders, and sprays (less than 5% active ingredient) for use in gardens and on food crops. Many products contain piperonyl butoxide as synergist, and other pesticides are included in some commercial products. Rotenone degrades rapidly in the environment. Emulsions of rotenone are applied to lakes and ponds to kill fish.

Toxicology

Although rotenone is toxic to the nervous systems of insects, fish, and birds, commercial rotenone products have presented little hazard to humans over many decades. Neither fatalities nor systemic poisonings have been reported in relation to ordinary use. However, there is one report of a fatality in a child who ingested a product called Gallocide, which contains rotenone and etheral oils, including clove oil. She developed a gradual loss of consciousness over two hours and died of respiratory arrest.[17]

Numbness of oral mucous membranes has been reported in workers who got dust from the powdered derris root in their mouths. Dermatitis and respiratory tract irritation have also been reported in occupationally exposed persons.

When rotenone has been injected into animals, tremors, vomiting, incoordination, convulsions, and respiratory arrest have been observed. These effects have not been reported in occupationally exposed humans.

Treatment

1. Skin decontamination. Skin contamination should be removed by washing with soap and water. Eye contamination should be removed by flushing the eye thoroughly with clean water or saline. Dust in the mouth should be washed out. If irritation persists, medical treatment should be obtained.

2. Gastrointestinal decontamination. If a large amount of a rotenone-containing product has been swallowed and retained and the patient is seen within an hour of exposure, consideration should be given to gastric emptying. Whether or not gastric emptying is performed, consider use of activated charcoal as outlined in Chapter 2.

3. Respiratory support should be used as necessary if mental status changes and/or respiratory depression occurs.

SABADILLA (Veratrum alkaloid)

Sabadilla consists of the powdered ripe seeds of a South American lily. It is used as dust, with lime or sulfur, or dissolved in kerosene, mainly to kill ectoparasites on domestic animals and humans. Insecticidal alkaloids are those of the veratrum type. The concentration of alkaloids in commercial sabadilla is usually less than 0.5%. Little or no sabadilla is used in the United States today, but some is probably used in other countries. Most toxic encounters with veratrum alkaloid occur from the inadvertent ingestion of the plant.[18]

Toxicology

Sabadilla dust is very irritating to the upper respiratory tract, causing sneezing, and is also irritating to the skin. Veratrin alkaloids are apparently absorbed across the skin and gut, and probably by the lung as well. Veratrin alkaloids have a digitalis-like action on the heart muscles (impaired conduction and arrhythmia).

Although poisoning by medicinal veratrum preparations may have occurred in the past, systemic poisoning by sabadilla preparations used as insecticides has been very rare. The prominent symptoms of veratrum alkaloid poisoning are severe nausea and vomiting, followed by hypotension and bradycardia. Other arrythmias or A-V block may occur.[18,19]

Treatment

1. Skin decontamination. Contaminated skin should be washed thoroughly with soap and water. If eyes are affected, they should be flushed with copious amounts of clean water or saline. If skin or eye irritation persists, medical treatment should be obtained.

2. Gastrointestinal decontamination. If a large amount of sabadilla pesticide product has been ingested in the past hour and retained, consider gastric emptying. This may be followed by administration of charcoal. If only a small amount of

Dosage of Atropine Sulfate:

- *Adults and children over 12 years:* 0.4-0.5 mg slowly IV, repeated every 5 minutes if necessary.
- *Children under 12 years:* 0.01 mg/kg body weight, slowly IV, repeated every 5 minutes if necessary. (There is a minimum dose of 0.1 mg).

STREPTOMYCIN

Streptomycin sulfate and nitrate are used as pesticides for the control of a variety of commercially important bacterial plant pathogens. Streptomycin is an antibiotic derived from the growth of *Streptomyces griseus*.

Toxicology

This antibiotic shares a toxic profile with the aminoglycoside antibiotics commonly used to treat human diseases. Its major modes of toxicity are nephrotoxicity and ototoxicity. Fortunately, it is poorly absorbed from the gastrointestinal tract, so systemic toxicity is unlikely with ingestion.

Treatment

If a large amount of streptomycin has been ingested within one hour of the patient's receiving care, gastric emptying should be considered. Administration of activated charcoal, as outlined in Chapter 2, should be considered.

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CHAPTER 8

Other Insecticides, Acaricides, and Repellents

HIGHLIGHTS

- Multiple agents, with widely varying toxicity
- Careful history will usually reveal exposure history
- Agents of particular concern due to wide use are pyrethroids, diethyltoluamide, and borates

Signs and Symptoms:

- Variable and highly related to the specific agent
- Boric acid causes severe erythematous and exfoliative rash (boiled lobster appearance)
- Agents such as boric acid, diethyltoluamide, and pyrethroids should be suspected in cases of unusual nervous system symptoms

This chapter discusses insecticides, acaricides, and repellents that have toxicologic characteristics distinct from the insecticides discussed in previous chapters. Pesticides reviewed include: alkyl phthalates, benzyl benzoate, borates, chlordimeform, chlorobenzilate, cyhexatin, diethyltoluamide, fluorides, haloaromatic urea compounds, methoprene, propargite, pyrethroids, and sulfur.

ALKYL PHTHALATES

Dimethyl phthalate has been widely used as an insect repellent applied directly to the skin. Dibutylphthalate is impregnated into fabric for the same purpose. It is more resistant to laundering than dimethyl phthalate.

Toxicology

Dimethyl phthalate is strongly irritating to the eyes and mucous membranes. It has caused little or no irritation when applied to skin, and dermal absorption is apparently minimal. It has not caused sensitization. Tests in rodents have indicated low systemic toxicity, but large ingested doses cause gastrointestinal irritation, central nervous system depression, coma, and hypotension.

Treatment

No antidote is available. Supportive measures (hydration, oxygen if needed) are probably adequate to manage all but the most severe poisonings.

BENZYL BENZOATE

Toxicology

Incorporated into lotions and ointments, this agent has been used for many years in veterinary and human medicine against mites and lice. Apart from occasional cases of skin irritation, adverse effects have been few. The efficiency

of skin absorption is not known. Absorbed benzyl benzoate is rapidly biotransformed to hippuric acid which is excreted in the urine. When given in large doses to laboratory animals, benzyl benzoate causes excitement, incoordination, paralysis of the limbs, convulsions, respiratory paralysis, and death. No human poisonings have been reported.

Treatment

1. Skin decontamination. If significant irritant effect appears, medications should be discontinued and the skin cleansed with soap and water. Eye contamination should be treated by prolonged flushing with clean water or saline.

2. Gastrointestinal decontamination. If a potentially toxic amount has been swallowed and retained and the patient is seen soon after exposure, gastrointestinal decontamination should be considered as outlined in Chapter 2.

3. Seizures. If seizures occur, control may require anticonvulsant medication as outlined in Chapter 2.

BORIC ACID AND BORATES

Boric acid is formulated as tablets and powder to kill larvae in livestock confinement areas and cockroaches, ants, and other insects in residences. Rarely, solutions are sprayed as a nonselective herbicide.

Toxicology

Boric acid powders and pellets scattered on the floors of homes do present a hazard to children. Their frequent use for roach control increases access for ingestion. A series of 784 patients has been described with no fatalities and minimum toxicity. Only 12% of these patients had symptoms of toxicity, mostly to the gastrointestinal tract.[1] However, there have been some recent reports of fatal poisonings,[2,3] and a great many poisonings of newborns which occurred in the 1950s and 1960s often ended in death.[4,5] Historically, many poisonings have resulted from injudicious uses in human medicine aimed at suppressing bacterial growth, such as compresses for burns, powders for diaper rash, and irrigation solutions.[6,7] With the increased use of boric acid for roach control, suicidal or accidental ingestion is still likely to occur.[3,7]

Borax dust is moderately irritating to skin. Inhaled dust caused irritation of the respiratory tract among workers in a borax plant. Symptoms included nasal irritation, mucous membrane dryness, cough, shortness of breath, and chest tightness.[8,9]

Commercial Products

ALKYL PHTHALATES

dibutylphthalate
dimethyl phthalate
DMP

BENZYL BENZOATE

BORIC ACID AND BORATES

boric acid
sodium polyborates
Polybor 3
sodium tetraborate
decahydrate
Borax

CHLORDIMEFORM (nr)

CHLOROBENZILATE (nr)

Acaraben
Akar
Benzilan
Folbex

CYHEXATIN (nr)

Acarstin
Metaran
Oxotin
Pennstyl
Plictran

DIETHYLTOLUAMIDE (DEET)

Auton
Detamide
Metadelphene
MGK
Muskol
Off!
Skeeter Beater
Skeeter Cheater
Skintastic for Kids

FLUORIDES

sodium fluoride (wood protection only)
sodium fluosilicate (sodium silico fluoride) (nr)
Prodan
Safsan
sodium fluoaluminate
Cryolite
Kryocide
Prokil

(Continued on the next page)

When determining toxicity to boric acid from ingestion, it is important to distinguish between acute and chronic exposure. Chronic ingestion is more likely to cause significant toxicity than acute exposure.[1,2] Borates are well absorbed by the gut and by abraded or burned skin, but not by intact skin.[6] The kidney efficiently excretes them. The residence half-life in humans averages 13 hours, in a range of 4-28 hours.[1]

The gastrointestinal tract, skin, vascular system, and brain are the principal organs and tissues effected. Nausea, persistent vomiting, abdominal pain, and diarrhea reflect a toxic gastroenteritis.[1,2,7] Lethargy and headache may occur, but are more infrequent.[1] In severe poisonings, a beefy red skin rash, most often affecting palms, soles, buttocks, and scrotum, has been described. It has been characterized as a "boiled lobster appearance." The intense erythema is followed by extensive exfoliation.[2,5,10] This may be difficult to distinguish from staphylcoccal scalded skin syndrome.[10]

Headache, weakness, lethargy, restlessness, and tremors may occur, but are less frequent than gastrointestinal effects.[1] Seven infants who were exposed to a mixture of borax and honey on their pacifiers developed seizures.[11] Unconsciousness and respiratory depression signify life-threatening brain injury. Cyanosis, weak pulse, hypotension, and cold clammy skin indicate shock, which is sometimes the cause of death in borate poisoning.[2,3,7]

Acute renal failure (oliguria or anuria) may be a consequence of shock, of direct toxic action on renal tubule cells, or both. It occurs in severe borate poisoning.[2,3,5,10]

has been ingested and the patient is seen within one hour of exposure, gastrointestinal decontamination should be considered as outlined in Chapter 2. It is important to keep in mind that vomiting and diarrhea are common, and severe poisoning may be associated with seizures. Therefore induction of emesis by syrup of ipecac is probably contraindicated in these exposures. Catharsis is not indicated if diarrhea is present.

3. Intravenous fluids. If ingestion of borate has been massive (several grams), or has extended over several days, administer intravenous glucose and electrolyte solutions to sustain urinary excretion of borate. Monitor fluid balance and serum electrolytes (including bicarbonate capacity) regularly. Monitor cardiac

ized "hot" sensation, sleepiness, skin rash and desquamation, a sweet taste, and anorexia. Symptoms persisted for 2-8 weeks after exposure was terminated.[13] In a single case, methemoglobinemia was reported.[14] Chlordimeform is not a cholinesterase inhibitor. Chlordimeform has been voluntarily cancelled in the U.S. due to concerns regarding increased bladder cancer incidence seen in manufacturing workers.

Confirmation of Poisoning

Although methods do exist for measurement of urinary excretion products, these tests are not generally available.

Treatment

1. Precautions. Strenuous efforts should be made to protect against inhalation and dermal contact with chlordimeform because absorption is evidently efficient.

2. Skin decontamination. Wash skin with soap and water as outlined in

Toxicology

Chlorobenzilate is moderately irritating to the skin and eyes. Although structurally similar to DDT, chlorobenzilate is much more rapidly excreted following absorption, chiefly in the urine as the benzophenone and benzoic acid deriva-

Treatment

1. Skin decontamination. Wash skin with soap and water. Remove contamination from the eyes by prolonged flushing with clean water or saline.

2. Gastrointestinal decontamination. Management of poisonings by ingestion should proceed on the assumption that cyhexatin is toxic, even though rodent LD_{50} values are fairly high, and no human poisonings have been reported. Treatment should bee

Manifestations of toxic encephalopathy have been behavioral disorders including headache, restlessness, irritability, ataxia, rapid loss of consciousness, hypotension, and seizures. Some cases have shown flaccid paralysis and areflexia. Deaths have occurred following very large doses.[16,17,22] Blood levels of DEET found in fatal systemic poisonings have ranged from 168 to 240 mg per liter.[17] Interpretation of DEET toxicity in some fatal cases has been complicated by effects of simultaneously ingested ethanol, tranquilizers, and other drugs. One well-documented case of anaphylactic reaction to DEET has been reported. One fatal case of encephalopathy in a child heterozygous for ornithine carbamoyl transferase deficiency resembled Reyes syndrome, but the postmortem appearance of the liver was not characteristic of the syndrome.

Discretion should be exercised in recommending DEET for persons who have acne, psoriasis, an atopic predisposition, or other chronic skin condition. It should not be applied to any skin area that is likely to be opposed to another skin surface for a significant period of time (antecubital and popliteal fossae, inguinal areas).[22]

Great caution should be exercised in using DEET on children. Avoid repeated application day after day. Applications should be limited to exposed areas of skin, using as little repellent as possible and washing off after use. Do not apply to eyes and mouth and, with young children, do not apply to their hands. Low concentrations (10% or below) are effective and may be preferred in most situations. There are formulations labeled for children that have concentrations of 5 to 6.5% DEET.[25] If continuous repellent protection is necessary, DEET should be alternated with a repellent having another active ingredient. If headache or any kind of emotional or behavioral change occurs, use of DEET should be discontinued immediately.

Confirmation of Poisoning

Methods exist for measurement of DEET in blood and tissues and of metabolites in urine, but these are not widely available.

Treatment

1. Skin decontamination. Wash skin with soap and water as outlined in Chapter 2. Eye contamination should be removed by prolonged flushing of the eye with copious amounts of clean water or saline. If irritation persists, specialized medical treatment should be obtained. Topical steroids and oral antihistamines have been used for severe skin reactions that occasionally follow application of DEET.[21]

2. Gastrointestinal decontamination. If a substantial amount of DEET has been ingested within an hour of treatment, gastrointestinal decontamination should be considered as outlined in Chapter 2. Induced emesis is

usually considered contraindicated in these poisonings due to the rapid onset of seizures.

3. Seizures. Treatment is primarily supportive, with control of seizures by anticonvulsants, as outlined in Chapter 2. Persons surviving poisoning by ingestion of DEET have usually recovered within 36 hours or less.[16,17]

FLUORIDES

Sodium fluoride is a crystalline mineral once widely used in the United States for control of larvae and crawling insects in homes, barns, warehouses, and other storage areas. It is highly toxic to all plant and animal life. The only remaining use permitted is for wood treatement

Sodium fluosilicate (sodium silico fluoride) has been used to control ectoparasites on livestock, as well as crawling insects in homes and work buildings. It is approximately as toxic as sodium fluoride. All uses in the U.S. have been cancelled.

Sodium fluoaluminate (Cryolite) is a stable mineral containing fluoride. It is used as an insecticide on some vegetables and fruits. Cryolite has very low water solubility, does not yield fluoride ion on decomposition, and presents very little toxic hazard to mammals, including humans.

Hydrofluoric acid is an important industrial toxicant, but is not used as a pesticide. Sulfuryl fluoride is discussed in Chapter 16, Fumigants.

The toxic effects of fluoride in mammals are multiple, and all may threaten life. The primary effects from fluoride result from an inhibition of critical intracellular enzymes and the direct effect on ionized calcium in extra-cellular fluid. Hypocalcemia commonly occurs.[26, 28, 29, 30]

Ingested fluoride is transformed in the stomach to hydrofluoric acid, which

3. Calcium and magnesium. If the victim is fully alert, and if vomiting does not totally prevent swallowing of a neutralizing agent, prompt oral administration of **milk, calcium gluconate, or magnesium citrate** will precipitate fluoride ion in the gut and therefore may be life-saving. The milk provides the calcium ions that will bind to fluoride, thereby reducing absorption. Magnesium-based antacids have also been used to neutralize the acid and facilitate the production of poorly absorbed salts.[26] There are no data on the optimum amounts to be administered.

4. Blood analysis. A blood specimen should be drawn for serum electrolyte analysis for sodium, potassium, calcium, magnesium, fluoride, and bicarbonate capacity. Blood should also be drawn to type and cross match for blood transfusion.

5. Intravenous fluids (initially 5% dextrose in 0.9% saline) should be started to combat dehydration, shock, and metabolic acidosis. Fluid balance should be monitored closely to forestall fluid overload if renal failure occurs. If metabolic acidosis is detected, sodium bicarbonate should be administered to keep the urine alkaline as this may hasten excretion.[27] Intravenous fluids must be stopped if anuria or oliguria (less than 25-30 mL per hour) develops.

6. Hemodialysis should be reserved for compromised renal function.[26]

7. Monitor cardiac status by continuous electrocardiography. Ventricular arrhythmia may necessitate DC cardioversion.

8. Tetany. If overt or latent tetany occurs, or if hypocalcemia is demonstrated, or if it appears likely that a significant amount of fluoride has been absorbed, administer 10 mL of 10% **calcium gluconate** intravenously, at no more than 1 mL per minute.

Dosage of Calcium Gluconate:
Supplied as 100 mg/mL (10% solution)

- *Adults and children over 12 years:* 10 mL of 10% solution, given slowly, intravenously. Repeat as necessary.
- *Children under 12 years:* 200-500 mg/kg/24 hr divided Q6 hr. For cardiac arrest, 100 mg/kg/dose. Repeat dosage as needed.

9. Oxygen by mask should be administered for hypotension, shock, cardiac arrhythmia, or cyanosis. Shock may require administration of plasma or blood.

10. Acid Burns. Since these compounds can cause severe acid burns to the esophagus and stomach, patients should be referred for surgical evaluation and

METHOPRENE

Methoprene is a long chain hydrocarbon ester active as an insect growth regulator. It is effective against several insect species. Formulations include slow-release briquets, sprays, foggers, and baits.

Toxicology

Methoprene is neither an irritant nor a sensitizer in humans or laboratory

Treatment

Treatment of contamination and ingestions should proceed essentially as outlined for haloaromatic substituted urea.

PYRETHROIDS

These modern synthetic insecticides are similar chemically to natural pyrethrins, but modified to increase stability in the natural environment. They are now widely used in agriculture, in homes and gardens, and for treatment of ectoparasitic disease.

Pyrethroids are formulated as emulsifiable concentrates, wettable powders, granules, and concentrates for ultra low volume application. They may be combined with additional pesticides (sometimes highly toxic) in the technical product or tank-mixed with other pesticides at the time of application. AASTAR (discontinued 1992), for instance, was a combination of flucythrinate and phorate. Phorate is a highly toxic organophosphate. Nix and Elimite are permethrin creams applied to control human ectoparasites.

Toxicology

Certain pyrethroids exhibit striking neurotoxicity in laboratory animals when administered by intravenous injection, and some are toxic by the oral route. How-

tion of water enhance the disagreeable sensations. Sometimes the effect is noted within minutes of exposure, but a 1-2 hour delay in appearance of symptoms is more common.[36, 37] Sensations rarely persist more than 24 hours. Little or no inflammatory reaction is apparent where the paresthesia are reported; the effect is presumed to result from pyrethroid contact with sensory nerve endings in the skin. The paresthetic reaction is not allergic in nature, although sensitization and allergic responses have been reported as an independent phenomenon with pyrethroid exposure. Neither race, skin type, nor disposition to allergic disease affects the likelihood or severity of the reaction.

Persons treated with permethrin for lice or flea infestations sometimes experience itching and burning at the site of application, but this is chiefly an exacerbation of sensations caused by the parasites themselves, and is not typical of the paresthetic reaction described above.

Other signs and symptoms of toxicity include abnormal facial sensation, dizziness, salivation, headache, fatigue, vomiting, diarrhea, and irritability to sound and touch. In more severe cases, pulmonary edema and muscle fasciculations can develop.[35] Due to the inclusion of unique solvent ingredients, certain formulations of fluvalinate are corrosive to the eyes. Pyrethroids are not cholinesterase inhibitors. However, there have been some cases in which pyrethroid poisoning has been misdiagnosed as organophosphate poisoning, due to some of the similar presenting signs, and some patients have died from atropine toxicity.[35]

Treatment

1. Skin decontamination. Wash skin promptly with soap and water as outlined in Chapter 2. If irritant or paresthetic effects occur, obtain treatment by a physician. Because volatilization of pyrethroids apparently accounts for paresthesia affecting the face, strenuous measures should be taken (ventilation, protective face mask and hood) to avoid vapor contact with the face and eyes. Vitamin E oil preparations (dL-alpha tocopheryl acetate) are uniquely effective in preventing and stopping the paresthetic reaction.[37, 38] They are safe for application to the skin under field conditions. Corn oil is somewhat effective, but possible side effects with continuing use make it less suitable. Vaseline is less effective than corn oil. Zinc oxide actually worsens the reaction.

2. Eye contamination.

after exposure, consider gastrointestinal decontamination as outlined in Chapter 2. Based on observations in laboratory animals[34] and humans,[35] large ingestions of allethrin, cismethrin, fluvalinate, fenvalerate, or deltamethrin would be the most likely to generate neurotoxic manifestations.

If only small amounts of pyrethroid have been ingested, or if treatment has been delayed, oral administration of activated charcoal and cathartic probably represents optimal management. Do not give cathartic if patient has diarrhea or an ileus.

4. Other treatments. Several drugs are effective in relieving the pyrethroid neurotoxic manifestations observed in deliberately poisoned laboratory animals, but none has been tested in human poisonings. Therefore, neither efficacy nor safety under these circumstances is known. Furthermore, moderate neurotoxic symptoms and signs are likely to resolve spontaneously if they do occur.

5. Seizures. Any seizures should be treated as outlined in Chapter 2.

SULFUR

Elemental sulfur is an acaricide and fungicide widely used on orchard, ornamental, vegetable, grain, and other crops. It is prepared as dust in various particle sizes and applied as such, or it may be formulated with various minerals to improve flowability, or applied as an aqueous emulsion or wettable powder.

Toxicology

Elemental sulfur is moderately irritating to the skin and is associated with occupationally related irritant dermatitis.[39] Airborne dust is irritating to the eyes and the respiratory tract. In hot sunny environments, there may be some oxidation of foliage-deposited sulfur to gaseous sulfur oxides, which are very irritating to the eyes and respiratory tract.

Ingested sulfur powder induces catharsis, and has been used medicinally (usually with molasses) for that purpose. Some hydrogen sulfide is formed in the large intestine and this may present a degree of toxic hazard. The characteristic smell of rotten eggs may aid in the diagnosis. An adult has survived ingestion of 200 grams.[40]

Ingested colloidal sulfur is efficiently absorbed by the gut and is promptly excreted in the urine as inorganic sulfate.

Treatment

1. Skin decontamination. Wash skin with soap and water. Contamination of the eyes should be removed by prolonged flushing with clean saline or water. If eye irritation persists, obtain ophthamologic care.

2. Gastrointestinal decontamination.

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Section III

HERBICIDES

CHAPTER 9

Chlorophenoxy Herbicides

Chlorophenoxy compounds are sometimes mixed into commercial fertilizers to control growth of broadleaf weeds. Several hundred commercial products contain chlorophenoxy herbicides in various forms, concentrations, and combinations. In some cases, the same name is used for products with different ingredients. The exact composition must therefore be determined from the product label. Sodium, potassium, and alkylamine salts are commonly formulated as aqueous solutions, while the less water-soluble esters are applied as emulsions. Low molecular weight esters are more volatile than the acids, salts, or long-chain esters.

Toxicology

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

Chlorophenoxy compounds are well absorbed from the gastrointestinal tract.[1] They are less well absorbed from the lung. Cutaneous absorption appears to be minimal.[2] The compounds are not significantly stored in fat. Excretion occurs almost entirely by way of urine. Apart from some conjugation of the acids, there is limited biotransformation in the body.[1,2] The compounds are highly protein bound.[2] The average residence half-life of 2,4-D in humans is between 13 and 39 hours,[1,3,4,5] while that of 2,4,5-T is about 24 hours. Excretion is greatly enhanced in alkaline urine,[4,5,6] and with a half-life as prolonged as 70-90 hours with acidic urine.[6]

diographic changes, myotonia, muscle weakness, myoglobinuria, and elevated serum creatine phosphokinase, all reflecting injury to striated muscle. Chlorophenoxy acids are weak uncouplers of oxidative phosphorylation; therefore, extraordinary doses may produce hyperthermia from increased production of body heat.[5]

In the manufacture of some of these herbicides, other more toxic substances can be formed at excessive temperatures. These include chlorinated dibenzo dioxin (CDD) and chlorinated dibenzo furan (CDF). The 2,3,7,8-tetra CDD form is extraordinarily toxic to multiple mammalian tissues; it is formed only in the synthesis of 2,4,5-T. Hexa-, hepta-, and octa-compounds

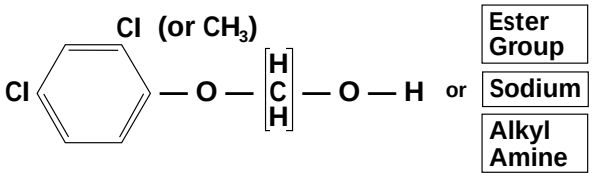
ably secondary to the metabolic acidosis that occurs. Muscle weakness and peripheral neuropathy have been reported after occupational exposure.[6] Con-

2. Respiratory protection. If any symptoms of illness occur during or following inhalation of spray, remove victim from contact with the material for at least 2-3 days. Allow subsequent contact with chlorophenoxy compounds only if effective respiratory protection is practiced.

3. Skin decontamination. Flush contaminating chemicals from eyes with

8. Follow-up clinical examination should include electromyographic and nerve conduction studies to detect any neuropathic changes and neuromuscular junction defects.

General Chemical Structure



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CHAPTER 10

Pentachlorophenol

Pentachlorophenol (PCP) is currently registered in the United States only as a restricted use pesticide for use as a wood preservative. PCP has been used as an herbicide, algacide, defoliant, wood preservative, germicide, fungicide, and molluscicide.[1] As a wood preservative, it is commonly applied as a 0.1% solution in mineral spirits, No. 2 fuel oil, or kerosene. It is used in pressure treatment of lumber at 5% concentration. Weed killers have contained higher concentrations.

Pentachlorophenol volatilizes from treated wood and fabric. It has a significant phenolic odor, which becomes quite strong when the material is heated. Excessively treated interior surfaces may be a source of exposure sufficient to cause irritation of eyes, nose, and throat.

Technical PCP contains lower chlorinated phenols (4-12%) plus traces of chlorobenzodioxins, chlorobenzofurans, and chlorobenzenes. Incomplete combustion of PCP-treated wood may lead to the formation of these compounds.

Toxicology

PCP is readily absorbed across the skin, the lungs, and the gastrointestinal lining. In animals, the dermal LD_{50} is of the same order of magnitude as the oral. With acute exposure it is rapidly excreted, mainly in the urine, as unchanged PCP and as PCP glucuronide. In chronic exposures, the elimination half-life has been reported to be very long, up to 20 days.[2] In another study, three volunteers took consecutive oral doses of PCP, and a half-life of 20 days was also found. The long half-life was attributed to the low urinary clearance because of high protein binding.[3] In the blood, a large fraction of absorbed PCP is protein-bound. It is widely distributed to other tissues in the body, including kidney, heart, and adrenal glands.

At certain concentrations, PCP is irritating to mucous membranes and skin. Contact dermatitis is common among workers having contact with PCP. In a study of employees involved in the manufacture of PCP, chloracne was found in 7% of the workers, and the risk was significantly higher among employees with documented skin contact compared to employees without skin contact.[4] Urticaria has also been reported as an uncommon response in exposed persons.

HIGHLIGHTS

- Absorbed by skin, lung, GI lining
- Fatalities reported, associated with intensive exposure in hot environments

Signs and Symptoms:

- Irritation of the nose, throat, and eyes
- Hyperthermia, muscle spasm, tremor, labored breathing, and chest tightness indicate serious poisoning

Treatment:

- No specific antidote
- Control fever, replace fluids, oxygen
- Decontaminate eyes, skin, hair, clothing
- Monitor cardiac status, control agitation

Contraindicated:

- Salicylates for fever control

The primary toxicological mechanism is increased cellular oxidative metabolism resulting from the uncoupling of oxidative phosphorylation. Heat production is increased and leads to clinical hyperthermia. This clinical state may mimic the signs and symptoms found in hyperthyroidism. Internally, large doses are toxic to the liver, kidneys, and nervous system.

Based on laboratory experimentation on animals, PCP has been reported to have fetotoxic and embrotoxic properties and to bind to various hormone receptors.[5,6] Epidemiological evidence suggests exposed persons may be at risk for miscarriages, reduced birth weight, and other malformations.[7,8]

Albuminuria, glycosuria, aminoaciduria, and elevated BUN reflect renal injury. Liver enlargement, anemia, and leukopenia have been reported in some intensively exposed workers. Elevated serum alkaline phosphatase, AST, and LDH enzymes indicate significant insult to the liver, including both cellular damage and some degree of biliary obstruction.

Signs and Symptoms of Poisoning

The most common effects of airborne PCP include local irritation of the nose, throat, and eyes, producing a stuffy nose, scratchy throat, and tearing. Dermal exposure is also common and may lead to irritation, contact dermatitis, or more rarely, diffuse urticaria or chloracne. Individual cases of exfoliative dermatitis of the hands and diffuse urticaria and angioedema of the hands have been reported in intensively exposed workers. Several infant deaths occurred in a nursery where a PCP-containing diaper rinse had been used.

Severe poisoning and death have occurred as a result of intensive PCP exposure. Acute poisoning occurs with systemic absorption which can occur by any route of sufficient dosage. Most occupational poisonings occur through dermal contact. Hyperthermia, muscle spasm, tremor, labored breathing, and chest tightness indicate serious poisoning. The patient may also complain of abdominal pain, and exhibit vomiting, restlessness, and mental confusion. Tachycardia and increased respiratory rate are usually apparent. Other commonly reported signs and symptoms of systemic poisoning include profuse sweating, weakness, dizziness, anorexia, and intense thirst. Workers exposed over long periods may experience weight loss.

Most adult fatalities have occurred in persons working in hot environments where hyperthermia is poorly tolerated. Cases of aplastic anemia and leukemia have been reported which were associated temporally with PCP exposure. Causal relationships in these cases were not established.[9] Peripheral neuropathies have also been reported in some cases of long-term occupational

Confirmation of Poisoning

If poisoning is strongly suspected on the basis of exposure, symptoms, and signs, **do not postpone treatment** until diagnosis is confirmed.

PCP can be measured in blood, urine, and adipose tissue by gas-liquid chromatography. Plasma levels can be much greater than urine levels (ratio of blood to urine is 1.0 to 2.5) so care must be taken in interpreting results.[10,11] There is no clear-cut determination of what constitutes an abnormally high level of PCP, and there is great variability among different references. Most information on the extent of serum levels in relation to toxicity is based on individual cases or small series of patients. Reports exist of asymptomatic infants with serum levels as high as 26 parts per million (ppm).[11,12] However, most reports of non-occupational exposure in the general public involve levels in the parts per billion range.[1,13-15] Food is probably the main source of this nanogram-level dosage.[1] Serum levels among occupationally exposed persons often exceed 1 ppm.[1] A report of a lethal case describes a plasma level of 16 ppm,[16] but most cases generally involve serum levels in the range of 100 ppm or higher.[11,17] It is reasonable to assume that levels greater than 1 ppm are consistent with an unusual exposure and that levels approaching 100 ppm are cause for great concern.

Treatment

1. Supportive treatment and hyperthermia control. There is no specific antidote to the poisoning; therefore treatment is supportive in nature including oxygen, fluid replacement, and most importantly, fever control.

Reduce elevated body temperature by physical means. Administer sponge baths and use fans to increase evaporation.[18] In fully conscious patients, administer cold, sugar-containing liquids by mouth as tolerated. Cooling blankets and ice packs to body surfaces may also be used.

Antipyretic therapy with salicylates is **strongly contraindicated** as salicylates also uncouple oxidative phosphorylation. Other antipyretics are thought to be of no use because of the peripherally mediated mechanism of hyperthermia in poisoning of this nature. Neither the safety nor the effectiveness of the other antipyretics has been tested.

Administer oxygen continuously by mask to minimize tissue anoxia. Unless there are manifestations of cerebral or pulmonary edema or of inadequate renal function, administer intravenous fluids to restore hydration and support physiologic mechanisms for heat loss and toxicant disposition. Monitor serum electrolytes, adjusting IV infusions to stabilize electrolyte concentrations. Follow urine contents of albumin and cells, and keep an accurate hourly record of intake/output to forestall fluid overload if renal function declines.

Caution: In the presence of cerebral edema and/or impaired renal function, intravenous fluids must be administered very cautiously to avoid increased

intracranial pressure and pulmonary edema. Central monitoring of venous and pulmonary wedge pressures may be indicated. Such critically ill patients should be treated in an intensive care unit.

2. Skin decontamination. Flush the chemical from eyes with copious amounts of clean water. Perform skin decontamination as described in Chapter 2.

3. Cardiopulmonary monitoring. In severe poisonings, monitor pulmonary status carefully to insure adequate gas exchange, and monitor cardiac status by ECG to detect arrhythmias. The toxicant itself and severe electrolyte disturbances may predispose to arrhythmias and myocardial weakness.

4. Neurological.

Chemical Structure

References

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2. Kalman DA and Horstman SW. Persistence of tetrachlorophenol and pentachlorophenol in exposed woodworkers. *J Toxicol Clin Toxicol* 1983;20:343.
3. Uhl S, Schmid P, and Schlatter C. Pharmacokinetics of pentachlorophenol in man. *Arch Toxicol* 1986;58:182-6.
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CHAPTER 11

Nitrophenolic and Nitrocresolic Herbicides

These highly toxic chemicals have many uses in agriculture worldwide, as herbicides (weed-killing and defoliation), acaricides, nematocides, ovicides, and fungicides. Relatively insoluble in water, most technical products are dissolved in organic solvents and formulated for spray application as emulsions. There are

Cataracts occur in laboratory animals given nitrophenols, and have occurred in humans, both as a result of ill-advised medicinal use and as a consequence of chronic, occupational exposure.[3] Cataract formation is sometimes accompanied by glaucoma.

Commercial Products

(Continued)

Dapacryl
Endosan
FMC 9044
Hoe 002784
Morrocid
NIA 9044
dinosulfon*
dinoterb acetate*
dinoterb salts*
dinoterbon*

* All U.S. registrations have been cancelled

Treatment

1. Supportive treatment and hyperthermia control. There is no specific antidote to poisoning with nitrophenolic or nitrocresolic herbicides. Treatment is supportive in nature and includes oxygen, fluid replacement, and temperature control.

Reduce elevated body temperature by physical means. Administer sponge baths and ice packs, and use a fan to promote air flow and evaporation.[7] In fully conscious patients, administer cold, sugar-containing liquids by mouth as tolerated.

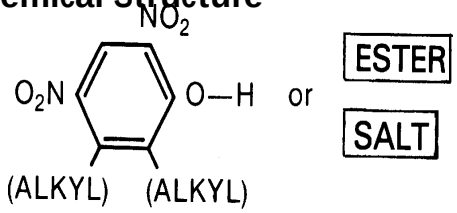
2. Contraindications. Antipyretic therapy with salicylates is strongly contraindicated as salicylates also uncouple oxidative phosphorylation. Other antipyretics are thought to be of no use because of the peripherally mediated mechanism of hyperthermia in poisoning of this nature. Neither the safety nor the effectiveness of other antipyretics has been tested.

Atropine is also absolutely contraindicated! It is essential not to confuse the clinical signs for dinitrophenol with manifestations for cholinesterase inhibition poisoning.[2]

3. Skin decontamination. If poisoning has been caused by contamination of body surfaces, bathe and shampoo contaminated skin and hair promptly and thoroughly with soap and water, or water alone if soap is not available. Wash the chemical from skin folds and from under fingernails. Care should be taken to prevent dermal contamination of hospital staff. See Chapter 2.

4. Other Treatment. Other aspects of treatment are identical to management of pentachlorophenol poisoning, detailed in Chapter 10.

General Chemical Structure



References

1. Leftwich RB, Floro JF, Neal RA, et al. Dinitrophenol poisoning: A diagnosis to consider in undiagnosed fever. *South Med J* 1982;75:182-5.
2. Finkel AJ. Herbicides: Dinitrophenols. In: Hamilton and Hardy's Industrial Toxicology, 4th ed. Boston: John Wright PSG, Inc., 1983, pp. 301-2.
3. Kurt TL, Anderson R, Petty C, et al. Dinitrophenol in weight loss: The poison center and public safety. *Vet Hum Toxicol* 1986;28:574-5.

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CHAPTER 12

Paraquat and Diquat

HIGHLIGHTS

- Life-threatening effects on GI tract, kidney, liver, heart, other organs
- Pulmonary fibrosis is the usual cause of death in paraquat poisoning (but not diquat)

Signs and Symptoms:

- Paraquat and diquat (ingestion): burning pain in the mouth, throat, chest,

The dipyridyl compounds paraquat and diquat are non-selective contact herbicides that are relatively widely-used, primarily in agriculture and by government agencies and industries for control of weeds. While paraquat is a restricted-use pesticide in most forms for most uses in the United States, its wide usage leads to significant potential for misuse and accidental and intentional poisonings. In the past few decades, paraquat has been a popular agent for suicide, but recent experience indicates a decline in such intentional poisonings. Paraquat and diquat are highly toxic compounds and management of poisonings requires a great deal of skill and knowledge of proper management procedures.

PARAQUAT

Toxicology

When ingested in adequate dosage (see below), paraquat has life-threatening effects on the gastrointestinal tract, kidney, liver, heart, and other organs. The LD_{50} in humans is approximately 3-5 mg/kg, which translates into as little as 10-15 mL of a 20% solution.[1,2]

The lung is the primary target organ of paraquat, and pulmonary effects represent the most lethal and least treatable manifestation of toxicity. However, toxicity from inhalation is rare. The primary mechanism is through the generation of free radicals with oxidative damage to lung tissue.[1,2] While acute pulmonary edema and early lung damage may occur within a few hours of severe acute exposures,[3,4] the delayed toxic damage of pulmonary fibrosis, the usual cause of death, most commonly occurs 7-14 days after the ingestion.[5] In patients who ingested a very large amount of concentrated solution (20%), some have died more rapidly (within 48 hours) from circulatory failure.[5]

Both types I and II pneumatocytes appear to selectively accumulate paraquat. Biotransformation of paraquat in these cells results in free-radical production with resulting lipid peroxidation and cell injury.[1,2,4] Hemorrhage proteinaceous edema fluid and leukocytes infiltrate the alveolar spaces, after which there is rapid proliferation of fibroblasts. There is a progressive decline in arterial oxygen tension and CO_2 diffusion capacity. Such a severe impairment of gas exchange causes progressive proliferation of fibrous connective tissue in the alveoli and eventual death from asphyxia and tissue anoxia.[6] One prospective study of survivors suggests

that some of the fibrous toxic damage may be reversible as evidence exists of markedly improved pulmonary function three months after survival.[7]

Local skin damage includes contact dermatitis. Prolonged contact will produce erythema, blistering, abrasion and ulceration, and fingernail changes.[8,9]

that methods for enhancing paraquat disposition several hours following ingestion have had little effect on mortality.

Cough, dyspnea, and tachypnea usually appear 2-4 days following paraquat ingestion, but may be delayed as long as 14 days. Progressive cyanosis and dyspnea reflect deteriorating gas exchange in the damaged lung. In some cases, the coughing up of frothy sputum (pulmonary edema) is the early and principal manifestation of paraquat lung injury.

Clinical experience has offered a rough dose-effect scale on which to base prognosis in cases of paraquat ingestion:[9]

- **Less than 20 mg** paraquat ion per kg body weight (less than 7.5 mL of 20% [w/v] paraquat concentrate): No symptoms or only gastrointestinal symptoms occur. Recovery is likely.
- **Twenty to 40 mg** paraquat ion per kg body weight (7.5-15.0 mL of 20% [w/v] paraquat concentrate): Pulmonary fibroplasia ensues. Death occurs in most cases, but may be delayed 2-3 weeks.
- **More than 40 mg** paraquat ion per kg body weight (more than 15.0 mL of 20% [w/v] paraquat concentrate): Multiple organ damage occurs as in class II, but is more rapidly progressive. Often characterized by marked ulceration of the oropharynx. Mortality is essentially 100% in 1-7 days.

Dermal signs are common among agriculture workers with acute paraquat toxicity. Particularly in concentrated form, paraquat causes localized injury to tissues with which it comes into contact. Fatal poisonings are reported to have occurred as a result of protracted dermal contamination by paraquat, but this is likely to occur only when the skin is abraded, eroded, or diseased, when more efficient systemic absorption can occur. With an intact dermal barrier, paraquat leaves the skin of the hands dry and fissured, can cause horizontal ridging of the fingernails, and may even result in the loss of fingernails. Prolonged contact with skin will create ulceration and abrasion, sufficient to allow systemic absorption.

In addition, some agriculture workers can be exposed through prolonged inhalation of spray droplets, and develop nosebleeds due to local damage. However, inhalation has not resulted in systemic toxicity, due to the low vapor pressure and lower concentration of paraquat field formulations. Eye contamination with diquat concentrate or stronger solutions results in severe conjunctivitis and sometimes protracted corneal opacification.

The hepatic injury from paraquat may be severe enough to cause jaundice, which signifies severe injury. However, hepatotoxicity is rarely a major determinant to clinical outcome. No other hepatic signs or symptoms are present other than the abnormal laboratory values mentioned in the Toxicology section.

DIQUAT

Toxicology

Diquat poisoning is much less common than paraquat poisoning, so that human reports and animal experimental data for diquat poisoning are less ex-

If the patient survives several hours or days, circulatory function may fail due to dehydration. Hypotension and tachycardia can occur, with shock resulting in death. Other cardiorespiratory problems may develop, such as toxic cardiomyopathy or a secondary infection such as bronchopneumonia.

Diquat is somewhat less damaging to the skin than paraquat, but irritant effects may appear following dermal contamination with the concentrate. There is probably significant absorption of diquat across abraded or ulcerated skin.

The great majority of poisonings by paraquat and diquat (discussed below) have been caused by ingestion with suicidal intent in most cases, particularly in Japan[11] and many developing countries. Since 1987, there has been a decline in most countries in the total numbers of suicidal deaths attributed to paraquat and diquat. Nearly all of the few poisonings caused by occupational exposure have been survived, but the mortality rate among persons who have swallowed paraquat or diquat remains high.[1,5] Avoidance of this mortality will probably have to rely on preventive strategies or on stopping gastrointestinal absorption very soon after the toxicant has been ingested.

Even though intestinal absorption of dipyridyls is relatively slow, lethal uptake by critical organs and tissues apparently occurs within 18 hours, and possibly within 6 hours, following ingestion of toxic quantities of paraquat or diquat. Bipyridyls have large volumes of distribution. Once distribution to tissues has occurred, measures to remove bipyridyls from the blood are very inefficient in reducing the total body burden.

Several strategies are being tested to reduce the frequency of these occurrences. These include the addition of emetics, stenching agents, gelling substances, and bittering agents such as sodim denatonium.

Confirmation of Poisoning: Paraquat and Diquat

At some treatment facilities, a simple colorimetric test is used to identify paraquat and diquat in the urine, and to give a rough indication of the magnitude of absorbed dose. To one volume of urine, add 0.5 volume of freshly prepared 1% sodium dithionite (sodium hydrosulfite) in one normal sodium hydroxide (1.0 N NaOH). Observe color at the end of one minute. A blue color indicates the presence of paraquat in excess of 0.5 mg per liter. Both positive and negative controls should be run to ensure that the dithionite has not undergone oxidation in storage.

When urine collected within 24 hours of paraquat ingestion is tested, the dithionite test appears to have some prognostic value: concentrations less than one milligram per liter (no color to light blue) generally predict survival, while concentrations in excess of one milligram per liter (navy blue to dark blue) often foretell a fatal outcome.

Diquat in urine yields a green color with the dithionite test. Although there is less experience with this test in diquat poisonings, the association of bad prognosis with intense color is probably similar.

Paraquat and diquat can be measured in blood and urine by spectrophotometric, gas chromatographic, liquid chromatographic, and radioimmunoassay methods. These tests are available in numerous clinical reference laboratories and sometimes by the manufacturing company. Survival is likely if plasma concentrations do not exceed 2.0, 0.6, 0.3, 0.16, and 0.1 mg per liter at 4, 6, 10, 16, and 24 hours, respectively, after ingestion.[15]

Treatment

1. Skin and eye decontamination. Flush skin immediately with copious amounts of water. Material splashed in the **eyes** must be removed by **prolonged irrigation** with clean water. Eye contamination should thereafter be treated by an ophthalmologist. Mild skin reactions usually respond if there is no further contact with the pesticide, but the irritation may take several weeks to resolve. Severe injuries with inflammation, cracking, secondary infection, or nail injury should be treated by a dermatologist.

2. Gastrointestinal decontamination. If paraquat or diquat have been ingested, **immediate administration of adsorbent** is the one therapeutic measure most likely to have a favorable effect. **Bentonite** (7.5% suspension) and **Fuller's Earth** (15% suspension) are highly effective, but sometimes not available.

Dosage of Bentonite and Fuller's Earth:

- *Adults and children over 12 years:* 100-150 g.
-

3. Samples. Secure a blood sample as soon as possible for paraquat analysis, and urine samples for either paraquat and/or diquat. Serial samples of urine for either agent and plasma for paraquat may be followed for prognostic information.

4. Respiration. Do not administer supplemental oxygen until the patient develops severe hypoxemia. High concentrations of oxygen in the lung increase the injury induced by paraquat, and possibly by diquat as well. There may be some advantage in placing the patient in a moderately hypoxic environment, i.e., 15%-16% oxygen, although the benefit of this treatment measure has not been established empirically in human poisonings. Inhalation of nitric oxide has been suggested as a method to maintain tissue oxygenation at low inspired oxygen concentrations, but its efficacy is unproven. When the lung injury is so far advanced that there is no expectation of recovery, oxygen may be given to relieve air hunger.

5. Intensive care. In serious poisonings, care should be provided in an intensive care setting, to allow proper monitoring of body functions and skilled

8. Seizure control. Convulsions and psychotic behavior sometimes encountered in diquat poisoning may be best controlled by lorazepam, given slowly intravenously, as outlined in Chapter 2. Control convulsions as outlined in Chapter 2.

9. Other drugs. Many drugs have been tested in animals or given in human bipyridyl poisonings without clear evidence of benefit or harm: corticosteroids, superoxide dismutase, propranolol, cyclophosphamide, vitamin E, riboflavin, niacin, ascorbic acid, clofibrate, desferrioxamine, acetylcysteine, and terpin hydrate. However, recent evidence regarding the use of **cyclophosphamide** and **methylprednisolone** may be effective in reducing the mortality associated with moderate to severe paraquat poisoning. Two studies found a reduced mortality associated with the treatment, while one study found no difference.[16] The dosages used for cyclophosphamide and methylprednisolone were 1 gram daily for two days and 1 gram daily for three days respectively, and were given after hemoperfusion. Each drug was administered as a two hour infusion, and white cell counts, serum creatinine levels, chest radiography, and liver function tests were monitored.[16]

10. Pain management. Morphine sulfate is usually required to control the pain associated with deep mucosal erosions of the mouth, pharynx, and esophagus, as well as abdominal pain from pancreatitis and enteritis. Mouthwashes, cold fluids, ice cream, or anesthetic lozenges may also help to relieve pain in the mouth and throat.

Dosage of Morphine Sulfate:

General Chemical Structures

References

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16. Lin JL, Wei MC, and Liu YC. Pulse therapy with cyclophosphamide and methyprednislone in patients with moderate to severe paraquat poisoning: A preliminary report. *Thorax* 1996;51:661-3.

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CHAPTER 13

Other Herbicides

Many herbicides are now available for use in agriculture and for lawn and garden weed control. This chapter discusses herbicides other than the chlorophenoxys, nitrophenols and chlorophenols, arsenicals, and dipyridyls, which are the subjects of separate chapters. Many modern herbicides kill weeds selectively by impairing metabolic processes that are unique to plant life. For this reason, their systemic toxicities in mammals are generally low. Nonetheless, some herbicides pose a significant risk of poisoning if handled carelessly, and many are irritating to eyes, skin, and mucous membranes.

For several good reasons, all of the herbicides mentioned in this chapter should be handled and applied only with full attention to safety measures that minimize personal contact. Many formulations contain adjuvants (stabilizers, penetrants, surfactants) that may have significant irritating and toxic effects. A number of premixed formulations contain two or more active ingredients; the companion pesticides may be more toxic than the principal herbicide. Good hygienic practice should not be disregarded just because a pesticide is reported to have a high LD_{50} in laboratory rodents.

Health professionals who may need to assess the consequences of prior exposure should understand the fate of these compounds after absorption by humans. The water-soluble herbicides are not retained in body tissues for long periods, as were the old lipophilic organochlorine insecticides, such as DDT. Most are excreted, mainly in the urine, within one to four days.

Toxicology

The table on the following pages lists the more commonly used herbicides not discussed elsewhere in this manual. The rat acute oral LD_{50} is given as a rough index of potential lethal toxicity. (If several values are reported by various sources, the lowest is recorded here.) The adverse effect information is drawn from many sources, including product labels, textbooks, published case histories, and some unpublished reports. The listing cannot be considered inclusive, either of herbicide products or of effects.

Aliphatic acids	trichloroacetic acid	TCA	5,000
	dichloropropionic acid (dalapon)	Dalapon, Revenge	970

TOXICITY OF COMMON HERBICIDES

Chemical Class	Generic Name	Proprietary Names	Acute Oral LD_{50} mg/kg	Known or Suspected Adverse Effects
Carbanilates	chlorpropham	Sprout-Nip Chloro-IPC	3,800	Skin irritants. May generate methemoglobin at high dosage.
Chloropyridinyl	triclopyr	Garlon, Turflon	630	Irritating to skin and eyes.
Cyclohexenone derivative	sethoxydim	Poast	3,125	Irritating to skin and eyes.
Dinitroamino-benzene derivative	butralin	Amex Tamex	12,600 >5,000	May be moderately irritating. These herbicides do not uncouple oxidative phosphorylation or generate methemoglobin.
	pendimethalin	Prowl, Stomp, Accotab, Herbodox, Go-Go-San, Wax Up	2,250	
	oryzalin	Surflan, Dirimal	>10,000	
Fluorodinitro-toluidine compounds	benfluralin	Benefin, Balan, Balfin, Quilan	>10,000	May be mildly irritating. These herbicides do not uncouple oxidative phosphorylation or generate methemoglobin.
	dinitramine	Cobex	3,000	
	ethalfluralin	Sonalan	>10,000	
	fluchloralin	Basalin	1,550	
	profluralin	Tolban	1,808	
	trifluralin	Treflan	>10,000	
Isoxazolidinone	clomazone	Command	1,369	May be moderately irritating.
Nicotinic acid isopropylamine derivative	imazapyr	Arsenal	>5,000	Irritating to eyes and skin. Does not contain arsenic.
Oxadiazolinone	oxadiazon	Ronstar	>3,500	Minimal toxic and irritant effects.
Phosphonates	glyphosate	Roundup, Glyfonox	4,300	Irritating to eyes, skin, and upper respiratory tract.
	fosamine ammonium	Krenite	>5,000	Irritating to eyes, skin, and upper respiratory tract.

Triazines	ametryn	Ametrex, Evik, Gesapax	1,750
	atrazine	Aatrex, Atranex, Crisazina	1,780
	cyanazine	Bladex, Fortrol	288
	desmetryn	Semeron	1,390
	metribuzin	Sencor, Lexone, Sencoral, Sencorex	1,100
	prometryn	Caparol, Gesagard, Prometrex	5.235
	propazine	Milo-Pro, Primatol, Prozinex	
	simazine	Gesatop, Princep, Caliber 90	
	terbuthylazine	Gardoprim, Primatol M	
	tertutryn	Ternit, Prebane, Terbutrex	
	prometon	Gesafram 50	
		Pramitol 25E	

Chemical Class	Generic Name	Proprietary Names	Acute Oral LD_{50} mg/kg	Known or Suspected Adverse Effects
Urea derivatives	chlorimuron ethyl			
	chlorotoluron			
	diuron			
	flumeturon			
	isoproturon			
	linuron			
	methabenz-thiazuron			

Confirmation of Poisoning

Although there are analytical methods for residues of many of the herbicides mentioned in this chapter and for some of the mammalian metabolites generated from them, these procedures are not generally available to confirm human absorption of the chemicals. Exposure must be determined from a recent history of occupational contact or accidental or deliberate ingestion.

Treatment

1. Skin decontamination. Skin contamination should be treated promptly by washing with soap and water. Contamination of the eyes should be treated immediately by prolonged flushing of the eyes with large amounts of clean water. If dermal or ocular irritation persists, medical attention should be obtained without delay. See Chapter 2.

2. Gastrointestinal decontamination. Ingestions of these herbicides are likely to be followed by vomiting and diarrhea due to their irritant properties. Management depends on: (1) the best estimate of the quantity ingested, (2) time elapsed since ingestion, and (3) the clinical status of the subject.

Activated charcoal is probably effective in limiting irritant effects and

4. Supportive measures are ordinarily sufficient for successful management of excessive exposures to these herbicides (endothall is an exception—see Chapter 18, p. 187). If the patient's condition deteriorates in spite of good supportive care, the operation of an alternative or additional toxicant should be suspected.

Section IV

OTHER PESTICIDES

CHAPTER 14

Arsenical Pesticides

Many arsenic compounds have been discontinued in the United States as a result of government regulations. However, arsenical pesticides are still widely available in some countries, and many homes and farms have leftover supplies that continue to represent some residual risk.

Arsine gas is discussed separately on page 132.

Toxicology

Arsenic is a natural element that has both metal and nonmetal physical/chemical properties. In some respects, it resembles nitrogen, phosphorus, antimony, and bismuth in its chemical behavior. In nature, it exists in elemental, trivalent (-3 or +3), and pentavalent (+5) states. It binds covalently with most nonmetals (notably oxygen and sulfur) and with metals (for example, calcium and lead). It forms stable trivalent and pentavalent organic compounds. In biochemical behavior, it resembles phosphorus, competing with phosphorus analogs for chemical binding sites.

Toxicity of the various arsenic compounds in mammals extends over a wide range, determined in part by the unique biochemical actions of each compound, but also by absorbability and efficiency of biotransformation and disposition. Overall, arsines present the greatest toxic hazard, followed closely by arsenites (inorganic trivalent compounds). Inorganic pentavalent compounds

nisms of toxicity are recognized: (1) reversible combination with thiol groups contained in tissue proteins and enzymes, and (2) substitution of arsenic anions for phosphate in many reactions, including those critical to oxidative phosphorylation. Arsenic is readily metabolized in the kidney to a methylated form, which is much less toxic and easily excreted. However, it is generally safest to manage cases of arsenical pesticide ingestion as though all forms are highly toxic.

The unique toxicology of arsine gas is described later in this chapter.

Signs and Symptoms of Poisoning

Manifestations of acute poisoning are distinguishable from those of chronic poisoning.

Acute arsenic poisoning: Symptoms and signs usually appear within one hour after ingestion, but may be delayed several hours. Garlic odor of the breath and feces may help to identify the toxicant in a severely poisoned patient. There is often a metallic taste in the mouth. Adverse gastrointestinal (GI) effects predominate, with vomiting, abdominal pain, and rice-water or bloody diarrhea being the most common. Other GI effects include inflammation, vesicle formation and eventual sloughing of the mucosa in the mouth, pharynx, and esophagus.[3] These effects result from the action of an arsenical metabolite on blood vessels generally, and the splanchnic vasculature in particular, causing dilation and increased capillary permeability.

The central nervous system is also commonly affected during acute exposure. Symptoms may begin with headache, dizziness, drowsiness, and confusion. Symptoms may progress to include muscle weakness and spasms, hypothermia, lethargy, delirium, coma, and convulsions.[1] Renal injury is manifest as proteinuria, hematuria, glycosuria, oliguria, casts in the urine, and, in severe poisoning, acute tubular necrosis. Cardiovascular manifestations include shock, cyanosis, and cardiac arrhythmia,[4,5] which are due to direct toxic action and electrolyte disturbances. Liver damage may be manifested by elevated liver enzymes and jaundice. Injury to blood-forming tissues may cause anemia, leukopenia, and thrombocytopenia.

Death usually occurs one to three days following onset of symptoms and is often the result of circulatory failure, although renal failure also may contribute.[1] If the patient survives, painful paresthesias, tingling, and numbness in the hands and feet may be experienced as a delayed sequela of acute exposure. This

weakness and fatigue can occur, as can anorexia and weight loss. Hyperpigmentation is a common sign, and tends to be accentuated in areas that are already more pigmented, such as the groin and areola. Hyperkeratosis is another very common sign, especially on the palms and soles.[8,9] Subcutaneous edema of the face, eyelids, and ankles, stomatitis, white striations across the nails (Mees lines), and sometimes loss of nails or hair are other signs of chronic, continuous exposure.[1,9] On occasion, these hyperkeratotic papules have undergone malignant transformation.[8] Years after exposure, dermatologic findings include squamous cell and basal cell carcinoma, often in sun-protected areas.

Neurologic symptoms are also common with chronic exposure. Peripheral neuropathy, manifested by paresthesia, pain, anesthesia, paresis, and ataxia, may be a prominent feature. It may often begin with sensory symptoms in the lower extremities and progress to muscular weakness and eventually paralysis and muscle wasting. Although less common, encephalopathy can develop with speech and mental disturbances very much like those seen in thiamine deficiency (Wernicke's syndrome).

Other organ systems are affected with arsenic toxicity. Liver injury reflected in hepatomegaly and jaundice may progress to cirrhosis, portal hypertension, and ascites. Arsenic has direct glomerular and tubular toxicity resulting in oliguria, proteinuria, and hematuria. Electrocardiographic abnormalities (prolongation of the Q-T interval) and peripheral vascular disease have been reported. The latter includes acrocyanosis, Raynaud's phenomenon, and frank gangrene.[1,10]

ever, a recent study supports that some of the arsenic released from mussels may contain higher amounts of arsenic trioxide than previously thought.[14] Urinary arsenic may be speciated into inorganic and organic fractions to help determine the source of the exposure and to help guide treatment.

Concentrations of arsenic in blood, urine, or other biologic materials can be measured by either wet or dry ashing, followed by colorimetric or atomic absorption spectrometric analysis. The latter method is preferred. Blood concentrations in excess of about 100 mcg per liter probably indicate excessive intake or occupational exposure, provided that seafood was not ingested before the sample was taken.[3,11,13,15] Blood samples tend to correlate with urine samples during the early stages of acute ingestion,[11] but because arsenic is rapidly cleared from the blood, the 24-hour urine sample remains the preferred method for detection and for ongoing monitoring.[1,11,13] Hair has been used for evaluation of chronic exposure. Levels in unexposed people are usually less than 1 mg/kg; levels in individuals with chronic poisoning range between 1 and 5 mg/kg.[15] Hair samples should be viewed with caution because external environmental contamination such as air pollution may artificially elevate arsenic levels.

Special tests for arsine toxicosis are described on page 132 under "Arsine Gas."

Treatment

The following discussion applies principally to poisonings by arsenicals in solid or dissolved form. Treatment of poisoning by arsine gas requires special measures described below on page 132.

1. Skin decontamination. Wash arsenical pesticide from skin and hair with copious amounts of soap and water. Flush contaminant from eyes with clean water. If irritation persists, specialized medical treatment should be obtained. See Chapter 2.

2. Gastrointestinal decontamination. If arsenical pesticide has been ingested within the first hour of treatment, consideration should be given to GI decontamination, as outlined in Chapter 2. Because poisoning by ingested arsenic almost always results in profuse diarrhea, it is generally not appropriate to administer a cathartic.

3. Intravenous fluids. Administer intravenous fluids to restore adequate hydration, support urine flow, and correct electrolyte imbalances. Monitor intake/output continuously to guard against fluid overload. If acute renal failure occurs, monitor blood electrolytes regularly. Blood transfusions and oxygen by mask may be needed to combat shock.

4. Cardiopulmonary monitoring. Monitor cardiac status by ECG to detect ventricular arrhythmias including prolonged Q-T interval and ventricular tachycardia, and toxic myocardiopathy (T wave inversion, long S-T interval).

5. Chelation therapy. Administration of Dimercaprol (BAL) is usually indicated in symptomatic arsenic poisonings, although DMPS, where available, may prove to be a better antidote. The following dosage schedule has proven to be effective in accelerating arsenic excretion.

Monitor urinary arsenic excretion while any chelating agent is being administered. When 24-hour excretion falls below 50 mcg per day, it usually is advisable to discontinue the chelation therapy.

RECOMMENDED INTRAMUSCULAR DOSAGE OF BAL (DIMERCAPROL) IN ARSENIC POISONING

	Severe Poisoning	Mild Poisoning
1st day	3.0 mg/kg q4h (6 injections)	2.5 mg/kg q6h (4 injections)
2nd day	3.0 mg/kg q4h (6 injections)	2.5 mg/kg q6h (4 injections)
3rd day	3.0 mg/kg q6h (4 injections)	2.5 mg/kg q12h (2 injections)
Each of the following days for 10 days, or	3.0 mg/kg q12 hr (2 injections)	2.5 mg/kg qd (1 injection)

Dosage of d-penicillamine:

- *Adults and children over 12 years:* 0.5 g every 6 hours, given 30-60 minutes before meals and at bedtime for about 5 days.
- *Children under 12 years:* 0.1 g/kg body weight, every 6 hours, given 30-60 minutes before meals and at bedtime for about 5 days. Not to exceed 1.0 g per day.

Caution: Adverse reactions to short-term therapy are rare. However, **persons allergic to penicillin should not receive d-penicillamine** as they may suffer allergic reactions to it.

Succimer (DMSA) has been shown to be an effective chelator of arsenic, though it is not labeled for this indication.[19] In Europe, DMPS has been used successfully in treatment of arsenic poisoning. In light of the lack of effectiveness of d-penicillamine, coupled with the low toxicity and high therapeutic index of DMPS and DMSA, it appears that the latter two agents may be the preferred method for chronic toxicity or when oral chelation is acceptable.[18,19]

Dosage of DMSA (Succimer):

- *Adults and Children:* 10 mg/kg every 8 hours for 5 days, followed by 10 mg/kg every 12 hours for an additional 14 days. (Maximum 500 mg per dose). Should be given with food.

Dosage of DMPS:

- *Adults:* 100 mg every 8 hours for 3 weeks to 9 months.

7. Hemodialysis. Extracorporeal hemodialysis, used in combination with

ARSINE GAS

Arsine is not used as a pesticide. However, some poisonings by arsine have occurred in pesticide manufacturing plants and metal refining operations when arsenicals came into contact with mineral acids or strong reducing agents.

Toxicology

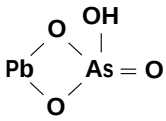
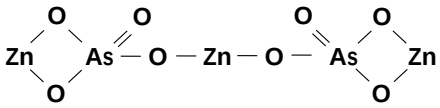
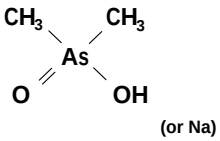
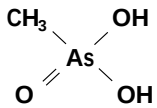
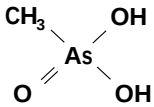
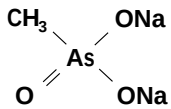
Arsine is a powerful **hemolysin,** a toxic action not exhibited by other arsenicals. In some individuals, very little inhalation exposure is required to cause a serious hemolytic reaction. Exposure times of 30 minutes at 25-50 parts per million are considered lethal.[20] Symptoms of poisoning usually appear 1-24 hours after exposure: headache, malaise, weakness, dizziness, dyspnea, nausea, abdominal pain, and vomiting. Dark red urine (hemoglobinuria) is often passed 4-6 hours after exposure. Usually 1-2 days after hemoglobinuria appears, jaundice is evident. Hemolytic anemia, sometimes profound, usually provides diagnostic confirmation and can cause severe weakness. Abdominal tenderness and liver enlargement are often apparent. Basophilic stippling of red cells, red cell fragments, and ghosts are seen in the blood smear. Methemoglobinemia and methemoglobinuria are evi-

INORGANIC TRIVALENT

Arsenic trioxide	"White arsenic." Arsenous oxide. Has been discontinued but still may be available from prior registrations.
Sodium arsenite	Sodanit, Prodalumnol Double. All uses discontinued in the U.S.
Calcium arsenite	Mono-calcium arsenite, London purple. Flowable powder for insecticidal use on fruit. All uses discontinued in the U.S.
Copper arsenite (Acid copper arsenite)	Wettable powder, for use as insecticide, wood preservative. All uses discontinued in the U.S.
Copper acetoarsenite	Insecticide. Paris green, Schweinfurt green, Emerald green, French green, Mitis green. No longer used in the U.S.; still used outside U.S.
Arsine	

INORGANIC PENTAVALENT

Arsenic acid	Hi-Yield Dessicant H-10, Zotox. Water solutions used as defoliants, herbicides, and
Sodium arsenate	

Calcium arsenate	
Lead arsenate 	Gypsine, Soprabel. Limited use in the U.S.; wettable powder used as insecticide outside the U.S.
Zinc arsenate 	Powder once used in U.S. as insecticide on potatoes and tomatoes.
ORGANIC (PENTAVALENT)	
Cacodylic acid (sodium cacodylate) 	Non-selective herbicide, defoliant, silvicide. Bolate, Bolls-Eye, Bophy, Dilic, Kack, Phytar 560, Rad-E-Cate 25, Salvo.
Methane arsonic acid 	MAA. Non-selective herbicide.
Monosodium methane arsonate 	MSMA. Non-selective herbicide, defoliant, silvicide. Ansar 170, Arsonate Liquid, Bueno 6, Daconate 6, Dal-E-Rad, Drexar 530, Herbi-All, Merge 823, Mesamate, Target MSMA, Trans-Vert, Weed-E-Rad, Weed-Hoe.
Disodium methane arsonate 	DSMA. Selective post-emergence herbicide, silvicide. Ansar 8100, Arrhenal, Arsinyl, Crab-E-Rad, Di-Tac, DMA, Methar 30, Sodar, Weed-E-Rad 360.
Monoammonium methane arsonate	MAMA. Selective post-emergence herbicide. No longer used in the U.S.

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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.

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. Formula-

Commercial Products

THIOCARBAMATES

ferbam
Carbamate WDG

Confirmation of Poisoining

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

Treatment

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 irri-

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.

Commercial Products

ETHYLENE BIS DITHIOCARBAMATES (EBDC COMPOUNDS)

mancozeb
- Dithane
- Mancozin
- manzeb
- Manzin
- Nemispor
- Penncozeb
- Ziman-Dithane

maneb
- Kypman 80
- Maneba
- Manex
- Manex 80
- M-Diphar
- Sopranebe
- Trimangol

nabam
- Chem Bam
- DSE
- Parzate
- Spring Bak

zineb
- Aspor
- Dipher
- Hexathane
- Kypzin
- Parzate C
- Tritoftorol
- Zebtox

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

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.

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 contamina-

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

Toxicology

Cadmium salts and oxides are very irritating to the respiratory and gas-

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.

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

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.

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CHAPTER 16

Fumigants

HIGHLIGHTS

- Easily absorbed in lung, gut, skin

Signs and Symptoms:

- Highly variable based on agent
- Many are irritants
- Carbon disulfide, chloroform, hydrogen cyanide, and naphthalene may have serious CNS effects
- Methyl bromide and aluminum phosphide (phosphine gas) cause pulmonary edema
- Hydrogen cyanide causes severe hypoxia without cyanosis in early stages

Treatment:

- Skin and eye decontamination
- Oxygen and diuresis for pulmonary edema
- Specific measures needed for various agents

Contraindicated:

- Ipecac should not be used in cyanide poisoning

Fumigants have remarkable capacities for diffusion, a property essential to their function. Some readily penetrate rubber and neoprene personal protective gear, as well as human skin. They are rapidly absorbed across the pulmonary membrane, gut, and skin. Special adsorbents are required in respirator canisters to protect exposed workers from airborne fumigant gases. Even these may not provide complete protection when air concentrations of fumigants are high.

The packaging and formulation of fumigants are complex. Fumigants which are gases at room temperature (methyl bromide, ethylene oxide, sulfur dioxide, hydrogen cyanide, sulfuryl fluoride) are provided in compressed gas cylinders. Liquids are marketed in cans or drums. Solids which sublime, such as naphthalene, must be packaged so as to prevent significant contact with air before they are used.

Mixtures of fumigants have several advantages. Carbon tetrachloride reduces the explosiveness of carbon disulfide and acrylonitrile. Chloropicrin, having a strong odor and irritant effect, is often added as a "warning agent" to other liquid fumigants.

Liquid halocarbons and carbon disulfide evaporate into the air while naphthalene sublimes. Paraformaldehyde slowly depolymerizes to formaldehyde. Aluminum phosphide slowly reacts with water vapor in the air to liberate phosphine, an extremely toxic gas. Metam sodium, also a fumigant, is covered under thiocarbamates in Chapter 15, Fungicides.

Toxicology *(in alphabetical order)*

Acrolein (acrylaldehyde) is an extremely irritating gas used as a fumigant and an aquatic herbicide. The vapor causes lacrimation and upper respiratory tract irritation, which may lead to laryngeal edema, bronchospasm, and delayed pulmonary edema. The consequences of ingestion are essentially the same as those that follow ingestion of formaldehyde. Contact with the skin may cause blistering.

Acrylonitrile is biotransformed in the body to hydrogen cyanide. Toxicity and mechanisms of poisoning are essentially the same as for cyanide (see under hydrogen cyanide below), except that acrylonitrile is irritating to the eyes and to the upper respiratory tract.

Carbon disulfide vapor is only moderately irritating to upper respiratory membranes, but it has an offensive "rotten cabbage" odor. Acute toxicity is due

chiefly to effects on the central nervous system. Inhalation of high concentrations for short periods has caused headache, dizziness, nausea, hallucinations,

Ethylene dibromide is a severe irritant to skin, eyes, and respiratory tract. The liquid causes blistering and erosion of skin, and is corrosive to the eyes. Once absorbed, it may cause pulmonary edema and central nervous system depression. Damage to testicular tissue has occurred in animals.[5] Long-term exposure may have some damaging effect on testicular tissue. Persons poisoned by ingestion have suffered chemical gastroenteritis, liver necrosis, and renal tubular damage. Death is usually due to respiratory or circulatory failure. A powerful disagreeable odor is advantageous in warning occupationally exposed workers of the presence of this gas.

Ethylene dichloride is moderately irritating to the eyes and respiratory tract. Respiratory symptoms may have a delayed onset. It depresses the central nervous system, induces cardiac arrhythmias, and damages the liver and kidney, in much the same way as carbon tetrachloride. Symptoms and signs of poisoning include headache, nausea, vomiting, dizziness, diarrhea, hypotension, cyanosis, and unconsciousness.

Ethylene oxide and propylene oxide are irritants to all tissues they contact. Aqueous solutions of ethylene oxide cause blistering and erosion of the affected skin. The area of skin may thereafter be sensitized to the fumigant. Inhalation of high concentrations is likely to cause pulmonary edema and cardiac arrhythmias. Headache, nausea, vomiting, weakness, and a persistent cough are common early manifestations of acute poisoning. Coughing of bloody, frothy sputum is characteristic of pulmonary edema.

Airborne **formaldehyde** is irritating to the eyes and to membranes of the upper respiratory tract. In some individuals, it is a potent sensitizer, causing allergic dermatitis. In addition, it has been associated with asthma-like symptoms, though there remains some controversy as to whether these represent true allergic asthma caused by formaldehyde.[6,7,8] High air concentrations may cause laryngeal edema, asthma, or tracheobronchitis, but apparently not pulmonary edema. Aqueous solutions in contact with the skin cause hardening and roughness, due to superficial coagulation of the keratin layer. Ingested formaldehyde attacks the membrane lining of the stomach and intestine, causing necrosis and ulceration. Absorbed formaldehyde is rapidly converted to formic acid. The latter is partly responsible for the metabolic acidosis that is characteristic of formaldehyde poisoning. Circulatory collapse and renal failure may follow the devastating effects of

one may also find an unusually high pO_2 on a venous blood gas.[9] Cyanosis is a late sign and indicates circulatory collapse.

The cells of the brain appear to be the most vulnerable to cyanide action. Presenting signs are nonspecific and can be found with many poisonings. Unconsciousness and death may occur immediately following inhalation of a high cyanide concentration, respiratory failure being the principal mechanism. Metabolic acidosis is another common presenting sign. Lesser exposures cause

treated fabric) may cause hemolysis, particularly in persons afflicted with glucose-6-phosphate dehydrogenase deficiency.

Sulfuryl fluoride has been used extensively for structural fumigation. Although use experience has generally been good, some fatalities have occurred when fumigated buildings have been prematurely reentered by unprotected individuals.[20] Since this material is heavier than air, fatal hypoxia may follow early reentry. Manifestations of poisoning have been nose, eye, and throat irritation, weakness, nausea, vomiting, dyspnea, cough, restlessness, muscle twitching, and seizures. Renal injury may induce proteinuria and azotemia.

Confirmation of Poisoning

There are no practical tests for absorbed **alkyl oxides, aldehydes,** or **phosphine** that would be helpful in diagnosis of poisoning.

Carbon disulfide can be measured in urine by gas chromatography, but the test is not generally available.

Cyanide ion from **cyanide** itself or **acrylonitrile** can be measured in whole blood and urine by an ion-specific electrode or by colorimetry. Symptoms of toxicity may appear at blood levels above 0.10 mg per liter.[10] Urine cyanide is usually less than 0.30 mg per liter in nonsmokers, but as much as 0.80 mg per liter in smokers. Thiocyanate, the metabolite of cyanide, can also be

chromatography. Many halocarbons can be measured in blood by gas chromatographic methods. Some can be measured in the expired air as well.

Paradichlorobenzene is metabolized mainly to 2,5-dichlorophenol, which is conjugated and excreted in the urine. This product can be measured chromatographically.

A serum fluoride concentration of 0.5 mg per liter was measured in one fatality from **sulfuryl fluoride** fumigation. Serum fluoride in persons not exceptionally exposed rarely exceeds 0.1 mg per liter.

Large industrial concerns sometimes monitor human absorption of halocarbons by analysis of expired air. Similar technology is available in some departments of anesthesiology. These analyses are rarely needed to identify the offending toxicant, because this is known from the exposure history. In managing

3. Respiration. If victim is not breathing, clear the airway of secretions and resuscitate with positive pressure oxygen apparatus. If this is not available, use chest compression to sustain respiration. If victim is pulseless, employ cardiac resuscitation.

4. Pulmonary edema. If pulmonary edema is evident, there are several measures available to sustain life. Medical judgment must be relied upon, however, in the management of each case. The following procedures are generally recommended:

- Put the victim in a sitting position with a backrest.
- Use intermittent and/or continuous positive pressure oxygen to relieve hypoxemia. (Do not give oxygen at greater concentrations or longer periods than necessary, because it may exaggerate the fumigant injury to lung tissue. Monitor arterial pO_2.)
- Slowly administer furosemide, 40 mg, intravenously (0.5-1 mg/kg in children up to 20 mg), to reduce venous load by inducing diuresis. Consult package insert for additional directions and warnings.

Some patients may benefit from careful administration of anxiolytic drugs. Whenever possible, such patients should be managed by intensivists in an intensive care center. Limit victim's physical activity for at least 4 weeks. Severe physical weakness usually indicates persistent pulmonary injury. Serial pulmonary function testing may be useful in assessing recovery.

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

6. Control convulsions. Seizures are most likely to occur in poisonings by methyl bromide, hydrogen cyanide, acrylonitrile, phosphine, and carbon disulfide. See Chapter 2 for seizure management. In some cases of methyl bromide, seizures have been refractory to benzodiazepines and diphenylhydantoin, and the authors resorted to anesthesia using thiopental.[11]

7. Gastrointestinal decontamination. If a fumigant liquid or solid has been ingested less than an hour prior to treatment, consider gastric emptying, followed by activated charcoal, as suggested in Chapter 2.

8. Fluid balance should be monitored, and urine sediment should be checked

9. Extracorporeal hemodialysis may be needed to regulate extracellular fluid composition if renal failure supervenes. It is probably not very effective in removing lipophilic fumigant compounds from blood, but it is, of course, effec-

lirubin in the plasma. Monitor fluid balance and blood electrolytes. If possible, monitor urinary excretion of naphthol to assess severity of poisoning and clinical progress.

If hemolysis is clinically significant, administer intravenous fluids to accelerate urinary excretion of the naphthol metabolite and protect the kidney from products of hemolysis. Use Ringer's lactate or sodium bicarbonate to keep urine pH above 7.5. Consider the use of mannitol or furosemide to promote diuresis. If urine flow declines, intravenous infusions must be stopped to prevent fluid overload and hemodialysis should be considered.[15] If anemia is severe, blood transfusions may be needed.

- **Phosphine Gas:** Recent experience in India suggests that therapy with magnesium sulfate may decrease the likelihood of a fatal outcome.[16,19,23] The mechanism is unclear, but may possibly be due to the membrane stabilization properties of magnesium in protecting the heart from fatal arrythmias. In one series of 90 patients, magnesium sulfate was found to decrease the mortality from 90% to 52%.[16] Two controlled studies have been done, one of which showed a reduction in mortality from 52% to 22%.[23] The other study found no effect on mortality.[24] The dosage for magnesium sulfate is: 3 grams during the first 3 hours as a continous infusion, followed by 6 grams per 24 hours for the next 3 to 5 days.[16]

- **Hydrogen Cyanide and Acrylonitrile**: Poisonings by hydrogen cyanide and acrylonitrile gases or liquids are treated essentially the same as poisoning by cyanide salts. Because cyanide is so promptly absorbed following ingestion, treatment should commence with prompt administration of oxygen and antidotes. Gastrointestinal decontamination should be considered if the patient presents within a short interval after ingestion, and **only** after the above life-saving treatment has commenced. Ipecac should be avoided due to the potential for rapid onset of loss of consciousness.

  The three antidotes — amyl nitrite, sodium nitrite, and sodium thiosulfate — are available as a kit called the Lilly Cyanide Antidote Kit, available from Eli Lilly and Company, Indianapolis, IN. The dosages vary between adults and children and are outlined below.

Dosage of Cyanide Antidotes

Adults:

- Administer **oxygen** continuously. Hyperbaric oxygen has been evaluated as effective in this condition.[25] If respiration fails, maintain pulmonary ventilation mechanically.
- Administer **amyl nitrite** ampules by inhalation for 15-30 seconds of every minute, while a fresh solution of 3% sodium nitrite is being prepared. This solution is ready prepared in commercial cyanide antidote kits.
- As soon as solution is available, inject intravenously 10 mL of 3% **sodium nitrite** solution over a 5-minute interval, keeping the needle in place.

Caution: Monitor pulse and blood pressure during administration of amyl nitrite and sodium nitrite. If systolic blood pressure falls below 80 mm Hg, slow or stop nitrite administration until blood pressure recovers.

- Follow sodium nitrite injection with an infusion of 50 mL of 25% aqueous solution of **sodium thiosulfate** administered over a 10-minute period. Initial adult dose should not exceed 12.5 g.
- If symptoms persist or recur, treatment by sodium nitrite and sodium thiosulfate should be repeated at half the dosages listed above.
- Measure hemoglobin and methemoglobin in blood. If more than 50% of total hemoglobin has been converted to methemoglobin, blood transfusion or exchange transfusion should be considered, because conversion back to normal hemoglobin proceeds slowly.

Children:

- Give amyl nitrite, oxygen, and mechanical respiratory support as recommended for adults. The following dosages of antidotes have been recommended for children.[26]
- Children over 25 kg body weight should receive adult dosages of sodium nitrite and sodium thiosulfate.
- Children less than 25 kg body weight should first have two 3-4 mL samples of blood drawn and then, through the same needle, receive 0.15-0.33 mL/kg up to 10 mL of the 3% solution of sodium nitrite injected over a 5-minute interval. Following sodium nitrite, administer an infusion of 1.65 mL/kg of 25% sodium thiosulfate at a rate of 3-5 mL per minute.

... continued

- At this point, determine the hemoglobin content of the pretreatment blood sample. If symptoms and signs of poisoning persist or return, give supplemental infusions of sodium nitrite and sodium thiosulfate based on hemoglobin level, as presented in the table. These recommended quantities are calculated to avoid life-threatening methemoglobinemia in anemic children. They are aimed at converting approximately 40% of circulating hemoglobin to methemoglobin. If possible, monitor blood methemoglobin concentrations as treatment proceeds.

RECOMMENDED DOSAGES OF SUPPLEMENTAL SODIUM NITRITE AND SODIUM THIOSULFATE BASED ON HEMOGLOBIN LEVEL

Initial Hemoglobin Concentration g/100 mL	Volume of 3% Sodium Nitrite mL/kg	Dose 25% Sodium Thiosulfate mL/kg
14.0	0.20	1.00
12.0	0.16	0.83
10.0	0.14	0.68
8.0	0.11	0.55

Although various cobalt salts, chelates, and organic combinations have shown some promise as antidotes to cyanide, they are not generally available in the United States. None has been shown to surpass the nitrite-thiosulfate regimen in effectiveness.

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CHAPTER 17

Rodenticides

A wide variety of materials are used as rodenticides. They pose particular risks for accidental poisonings for several reasons. First, as agents specifically designed to kill mammals, often their toxicity is very similar for the target rodents and for humans. (Warfarin and other anticoagulant rodenticides were initially developed to overcome this problem by creating compounds that were highly toxic to rodents, particularly after repeated exposures, but much less toxic to humans.) Second, since rodents usually share environments with humans and other mammals, the risk of accidental exposure is an integral part of the placement of baits for the rodents. Finally, as rodents have developed resistance to existing rodenticides, there is a continuous need to develop new and potentially more toxic rodenticides. As rodents have become resistant to warfarin baits, for example, the development of "superwarfarins" has increased the risk to humans.[1,2] It is important to be familiar with use patterns and development of more toxic compounds and to make every effort to identify the actual agent used in order to institute the most appropriate management for these poisonings.

COUMARINS AND INDANDIONES

Toxicology

in 36-72 hours.[1,4,5] Lengthened PT occurs in response to doses much lower

2. Vitamin K_1. A patient presenting within 24 hours after ingestion will likely have a normal PT. However, in a study of 110 children who were poisoned by superwarfarins, primarily brodifacoum, a child's PT was significantly more likely to be prolonged at 48 hours after having a normal PT at 24 hours.[5] Therefore, for suicidal ingestions with large amounts taken, if there is uncertainty about the amount of bait ingested or the general health of the patient, phytonadione (vitamin K_1

Dosage of Aquamephyton[R] (intramuscular):

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INORGANIC RODENTICIDES

Toxicology

Thallium sulfate is well absorbed from the gut and across the skin. It exhibits a very large volume of distribution (tissue uptake) and is distributed chiefly to the kidney and liver, both of which participate in thallium excretion. Most blood-borne thallium is in the red cells. Elimination half-life from blood in the adult human is about 1.9 days. Most authors report the LD_{50} in humans to be between 10 and 15 mg/kg.[10]

Unlike other inorganic rodenticides like yellow phosphorus and zinc phosphide, thallium poisoning tends to have a more insidious onset with a wide variety of toxic manifestations. Alopecia is a fairly consistent feature of thallium poisoning that is often helpful diagnostically; however, it occurs two weeks or more after poisoning and is not helpful early in the presentation.[10,11] In addition to hair loss, the gastrointestinal system, central nervous system, cardiovascular system, renal system, and skin are prominently affected by toxic intakes.

Early symptoms include abdominal pain, nausea, vomiting, bloody diarrhea, stomatitis, and salivation. Ileus may appear later on. Elevated liver enzymes may occur, indicating tissue damage. Other patients experience signs of central nervous system toxicity including headache, lethargy, muscle weakness, paresthesias, tremor, ptosis, and ataxia. These usually occur several days to more than a week after exposure.[10,12] Extremely painful paraesthesias, either in the presence or absence of gastrointestinal signs, may be the primary presenting complaint.[11,13] Myoclonic movements, convulsions, delirium, and coma reflect more severe neurologic involvement. Fever is a bad prognostic indication of brain damage.

Cardiovascular effects include early hypotension, due at least in part to a toxic myocardiopathy. Ventricular arrythmias may occur. Hypertension occurs later and is probably a result of vasoconstriction. The urine may show protein and red cells. Patients may also develop alveolar edema and hyaline membrane formation in the lungs, consistent with a diagnosis of Acute Respiratory Distress Syndrome.[14] Death from thallium poisoning may be caused by respiratory paralysis or cardiovascular collapse. Absorption of nonlethal doses of thallium has caused protracted painful neuropathies and paresis, optic nerve atrophy, persistent ataxia, dementia, seizures, and coma.[11]

Yellow phosphorus (also known as white phosphorus) is a corrosive agent and damages all tissues it comes in contact with, including skin and the gut lining. Initial symptoms usually reflect mucosal injury and occur a few minutes to 24 hours following ingestion. The first symptoms include severe vomiting and burning pain in the throat, chest, and abdomen. The emesis may be bloody (either red, brown, or black)[15] and on occasion may have a garlic smell.[16,17] In some cases, central nervous system signs such as lethargy, restlessness, and irrita-

Commercial Products

INORGANICS
thallium sulfate
yellow phosphorus
zinc phosphide
  Phosvin
  Ridall-Zinc
  Zinc-Tox

Yellow phosphorus is not sold in the United States. Zinc phosphide is still registered in the United States, and can be found in U.S. retail stores. Thallium sulfate is no longer registered for pesticidal use, but is used by government agencies only.

bility are the earliest symptoms, followed by symptoms of gastrointestinal injury. Shock and cardiopulmonary arrest leading to death may occur early in severe ingestions.[17]

Treatment: Thallium Sulfate

1. Gastrointestinal decontamination. If thallium sulfate was swallowed less than an hour prior to treatment, consider gastrointestinal decontamination as outlined in Chapter 2. Multiple doses of activated charcoal may be helpful in increasing thallium elimination.[13]

2. Electrolyte and glucose solutions should be given by intravenous infusion to support urinary excretion of thallium by diuresis. Monitor fluid balance carefully to insure that fluid overload does not occur. If shock develops, give whole blood, plasma, or plasma expanders. Pressor amines must be used very carefully in light of myocardial injury. Monitor ECG for arrhythmias.

3. Convulsions. Control seizures and myoclonic jerking as outlined in Chapter 2.

4. Combined hemodialysis and hemoperfusion has proven moderately

Caution: Highly toxic phosphine gas may evolve from emesis, lavage fluid, and feces of victims of these poisons. The patient's room should be well ventilated. Persons attending the patient must wear gloves to avoid contact with the phosphorus.

3. Lavage with 1:5000 potassium permanganate solution has been used in the management of ingested phosphorus compounds in the past; however, there is not sufficient evidence for its efficacy and we do not recommend it.

4. Catharsis is probably not indicated, but there may be some benefit in administering mineral oil. Dosage is 100 mL for adults and children over 12 years, and 1.5 mL/kg body weight in children under 12 years. Do not give vegetable oils or fats.

5. Transfusions. Combat shock and acidosis with transfusions of whole blood and appropriate intravenous fluids. Monitor fluid balance and central venous pressure to avoid fluid overload. Monitor blood electrolytes, glucose, and pH to guide choice of intravenous solutions. Administer 100% oxygen by mask or nasal tube.

6. Oxygen. Combat pulmonary edema with intermittent or continuous positive pressure oxygen.

7. Renal protection. Monitor urine albumin, glucose, and sediment to detect early renal injury. Extracorporeal hemodialysis will be required if acute renal failure occurs, but it does not enhance excretion of phosphorus. Monitor ECG to detect myocardial impairment.

8. Liver damage. Monitor serum alkaline phosphatase, LDH, ALT, AST, prothrombin time, and bilirubin to evaluate liver damage. Administer Aquamephyton^{R} (vitamin K_1) if prothrombin level declines.

9. Pain management. Morphine sulphate may be necessary to control pain. Adult dose: 2-15 mg IM/IV/SC Q 2-6 hours prn. Child's dose: 0.1-0.2 mg/kg/dose Q 2-4 hours.

10. Phosphine gas. For specific therapy due to phosphine gas, refer to the treatment of phosphine poisoning in Chapter 16, Fumigants.

CONVULSANTS

Toxicology

Crimidine is a synthetic chlorinated pyrimidine compound that, in adequate dosage, causes violent convulsions similar to those produced by strychnine.

Sodium fluoroacetate and fluoroacetamide are readily absorbed by the gut, but only to a limited extent across skin. The toxic mechanism is distinct from that of fluoride salts. Three molecules of fluoroacetate or fluoroacetamide are combined in the liver to form a molecule of fluorocitrate, which poisons critical enzymes of the tricarboxylic acid (Krebs) cycle, blocking cellular respiration. The heart, brain, and kidneys are the organs most prominently affected. The effect on the heart is to cause arrhythmias, progressing to ventricular fibrillation, which is a common cause of death. Metabolic acidosis, shock, electrolyte imbalance, and respiratory distress are all poor prognostic signs. Neurotoxicity is expressed as violent tonic-clonic convulsions, spasms, and rigor, sometimes not occurring for hours after ingestion.[21]

Strychnine is a natural toxin (nux vomica) which causes violent convulsions by direct excitatory action on the cells of the central nervous system, chiefly the spinal cord. Death is caused by convulsive interference with pulmonary function, by depression of respiratory center activity, or both. Strychnine is detoxified in the liver. Residence half-life is about 10 hours in humans. Onset of symptoms is usually within 15-20 minutes of ingestion. Lethal dose in adults is reported to be between 50 and 100 mg, although as little as 15 mg can kill a child.[22]

Confirmation of Poisoning

There are no generally available tests to confirm poisoning by the convulsant rodenticides.

Treatment: Sodium Fluoroacetate and Fluoroacetamide

Poisonings by these compounds have occurred almost entirely as a result of accidental and suicidal ingestions. If the poison was ingested shortly before treatment and convulsions have not yet occurred, the first step in treatment is to remove the toxicant from the gut. If the victim is already convulsing, however, it is necessary first to control the seizures before gastric lavage and catharsis are undertaken.

1. Control seizures as outlined in Chapter 2. Seizure activity from these compounds may be so severe that doses necessary for seizure control may paralyze respiration. For this reason, it is best to intubate the trachea as early as

Commercial Products

CONVULSANTS

crimidine
  Castrix
fluoroacetamide*
  Compound 1081
sodium fluoroacetate
  Compound 1080
strychnine

* Discontinued in the U.S.

Only specially trained personnel are allowed to use strychnine. Crimidine and sodium fluoroacetate are no longer registered for use as pesticides.

1. Control seizures as outlined in Chapter 2.

2. Gastrointestinal decontamination. Consider gastrointestinal decontamination if patient is seen within an hour of ingestion.

3. Administer intravenous fluids to support excretion of absorbed toxicants. Inclusion of sodium bicarbonate in the infusion fluid counteracts metabolic acidosis generated by convulsions. Effectiveness of hemodialysis and hemoperfusion has not been tested.

MISCELLANEOUS RODENTICIDES: RED SQUILL AND CHOLECALCIFEROL

Toxicology

Red squill is a little-used rodenticide, consisting of the inner portions of a small cabbage plant grown in eastern Mediterranean countries. Its toxic properties have been known since ancient times and are probably due to cardiac glycosides. For several reasons, mammals other than rodents are unlikely to be poisoned: (1) red squill is intensely nauseant, so that animals which vomit (rodents do not) are unlikely to retain the poison; (2) the glycoside is not efficiently absorbed from the gut; and (3) absorbed glycoside is rapidly excreted. Injection of the glycosides leads to effects typical of digitalis: alterations in cardiac impulse conduction and arrhythmias.

Cholecalciferol is the activated form of vitamin D (vitamin D_3). Its toxic effect is probably a combination of actions on liver, kidney, and possibly the myocardium, the last two toxicities being the result of hypercalcemia. Early symptoms and signs of vitamin D-induced hypercalcemia in humans are fatigue, weakness, headache, and nausea. Polyuria, polydipsia, proteinuria, and azotemia result from acute renal tubular injury by hypercalcemia. This is commonly the cause of death. Prolonged hypercalcemia results ultimately in nephrolithiasis and nephrocalcinosis. Azotemia occurs as renal tubular damage progresses.

Confirmation of Poisoning

Cholecalciferol intoxication is indicated by an elevated concentration of calcium (chiefly the unbound fraction) in the serum. There are no generally available tests for the other rodenticides or their biotransformation products.

Commercial Products

MISCELLANEOUS

cholecalciferol
- Muritan
- Quintox
- Rampage

red squill*
- Dethdiet
- Rodine

* Discontinued in the U.S.

Treatment: Red Squill

Red squill is unlikely to cause poisoning unless ingested at substantial dosage. The problem is usually self-correcting due to its intense emetic effect. If, for some reason, the squill is retained, syrup of ipecac, followed by 1-2 glasses of water, should be administered to initiate vomiting. Monitor cardiac status electrocardiographically.

Treatment: Cholecalciferol

Cholecalciferol at high dosage may cause severe poisoning and death. Human poisonings from its use as a rodenticide have not been reported, but vitamin D overdosage has occurred under clinical circumstances. Treatment is directed at limiting gastrointestinal absorption, accelerating excretion, and

The dose may be doubled if calcium-lowering effect is not sufficient. Calcium gluconate for intravenous injection should be immediately available if indica-

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CHAPTER 18

Miscellaneous Pesticides, Solvents, and Adjuvants

There are a variety of pesticides that do not fall into the broad categories described in other chapters in this manual. Many of them are widely used and are therefore associated with a high probability of human exposure. Some have significant toxicity as well as a likelihood of human exposure, and are of real concern. Many of the solvents and adjuvants used in the formulation of pesticides also present a high likelihood of human exposure. Such exposures can result in significant toxic effects that in many cases exceed the toxicity of the active pesticide ingredient(s). Furthermore, it is sometimes more difficult to obtain information about the solvents and adjuvants, complicating the issues of diagnosis and management.

4-AMINOPYRIDINE

Toxicology

4-Aminopyridine is a highly toxic white powder used as a bird repellent. It works by making one or two birds acutely ill, thus warning off the remaining birds by cries of distress. It is toxic to all vertebrates.[1] It is usually added to grain baits in 0.5%-3.0% concentration, but 25% and 50% concentrates in powdered sugar are available. Recent human exposure has come from its use as an investigational drug in the treatment of multiple sclerosis.[2,3] It is rapidly absorbed by the gut, less effectively across skin. The chief mechanism of toxicity is enhancement of cholinergic transmission in the nervous system through the release of acetylcholine both centrally and peripherally. Due to enhanced transmission at

Treatment

1. Skin decontamination. If skin or eye contamination has occurred, thorough washing of the skin or eyes is indicated. See Chapter 2.

2. Gastrointestinal decontamination. If the patient is seen within an hour of ingestion of a significant quantity of this compound, gastrointestinal decontamination should be considered, as outlined in Chapter 2. If treatment is delayed, immediate oral administration of charcoal and sorbitol may represent reasonable management.

3. Seizures may require anticonvulsant medication. See Chapter 2 for dosages.

4. Muscular spasms. Neuromuscular blockade with drugs such as d-tubocuarine, metocurine and pancuronium bromide have been used sucessfully to relieve the muscular spasms that occur with this agent. Such therapy must be provided in an intensive care setting.[1]

5. Dehydration should be treated with intravenous fluids if oral fluids cannot be retained.

CALCIUM CYANAMIDE

This synthetic compound is marketed as granules containing 44% calcium cyanamide, yielding 19.5% nitrogen. It is incorporated into soil to serve as fertilizer, fungicide, and herbicide. In contact with water, hydrogen cyanamide is released. Acidic conditions accelerate this reaction. Hydrogen cyanamide is a solid with considerable vapor pressure. It has toxic properties totally different from those of cyanide, and it does not degrade to cyanide.

Toxicology

Calcium cyanamide is only moderately irritating to skin, but hydrogen cyanamide is severely irritating and caustic to skin and the inhaled gas is strongly irritating to mucous membranes.[4] Dermal and mucosal lesions in the mouth, tongue, and upper esophagus have occurred after exposure. No systemic symptoms from dermal exposure have been reported.[5] Systemic poisonings have followed inhalation of hydrogen cyanamide and ingestion of the salt. Manifestations of poisoning include flushing, headache, vertigo, dyspnea, tachycardia, and hypotension, sometimes progressing to shock.[4] Because cyanamide is an inhibitor of acetaldehyde dehydrogenase, ingestion of alcohol exaggerates the symptoms. (A citrated form of cyanamide has been used in place of Antabuse in alcohol aversion therapy.)

Treatment

1. Skin decontamination. Skin contamination with either the calcium salt or the free form should be removed by washing with soap and water. Flush eyes with copious amounts of clean water. If skin or eye irritation persists, medical attention should be obtained promptly. See Chapter 2.

2. Gastrointestinal decontamination. If large doses have been ingested within an hour of exposure, gastrointestinal decontamination should be considered. If dosage was small or treatment is delayed, oral administration of activated charcoal and sorbitol probably represents reasonable management. See Chapter 2 for doses.

3. Hypotension or Antabuse-type reactions should be treated by placing the patient in the Trendelenburg position, giving intravenous fluids, including plasma or blood, if needed, and, if necessary, vasopressor drugs parenterally.

4. Atropine is not antidotal.

CREOSOTE

Creosote is obtained by distillation of the tar formed by heating wood or coal in the absence of oxygen. It is purified by extraction into oils. Creosote from wood consists mainly of guaiacol (methoxy phenol) and cresol (methyl phenol). Coal-derived creosote contains, in addition, some phenol, pyridine, and pyridinol. Creosote is extensively used as a wood preservative, usually by high-pressure impregnation of lumber. It has also been used as an animal dip and disinfectant. Much of human exposure is in the form of various phenol compounds.

Creosote is irritating to skin, eyes, and mucous membranes. Workers in contact with technical creosote or with treated timbers sometimes develop skin irritation, vesicular or papular eruptions, dermal pigmentation, and occasionally gangrene and skin cancer.[6] Photosensitization has been reported. Eye contamination has resulted in conjunctivitis and keratitis, sometimes resulting in corneal scarring. The constituents of creosote are efficiently absorbed across the skin, but systemic poisonings following dermal absorption have occurred very rarely. Absorption of ingested creosote from the gut occurs promptly, and there may be significant absorption of vapor by the lung. Conjugates of absorbed phenolic constituents are excreted mainly in the urine. Acute toxic effects are similar to those of lysol, but the corrosive nature of creosote is somewhat less because of greater dilution of phenol in the creosote.[7] Irritation of the gastrointestinal tract, toxic encephalopathy, and renal tubular injury are the principal effects. A chronic toxicosis from continuing gastrointestinal absorption (creosote used medicinally) has been described, consisting of gastroenteritis and visual disturbances.

Manifestations of acute systemic poisoning are salivation, vomiting, dyspnea, headache, dizziness, loss of pupillary reflexes, cyanosis, hypothermia, convulsions, and coma. Death is due to multi-organ system failure as patients develop shock, acidosis, respiratory depression, and anuric renal failure.

Confirmation of Poisoning

The presence of phenolic oxidation products imparts a dark, smoky color to the urine.[7] If there is suspicion of poisoning, addition of a few drops of ferric chloride solution to the urine yields a violet or blue color, indicating the presence of phenolic compounds.

Treatment

1. Skin decontamination. Stringent measures should be taken to avoid contamination of skin or eyes and inhalation of vapor. Skin contamination should be promptly washed off with soap and water. Remove eye contamination by washing with copious amounts of water, then obtain specialized medical attention promptly because corneal injury may be severe. See Chapter 2.

2. Gastrointestinal decontamination. If a significant amount of creosote has been ingested and the patient is alert and able to swallow, immediately administer a slurry of activated charcoal by mouth. Further efforts to limit absorption will depend on whether there has been corrosive injury to the esophagus. If pharyngeal redness and swelling are evident, neither induced emesis nor gastric lavage is advisable due to potential re-exposure of the esophagus to the creosote, or perforation of the esophagus from a gastric tube. For further information on gastric decontamination, including charcoal dosing, see Chapter 2.

3. Maintain pulmonary ventilation mechanically with oxygen, if necessary.

4. Blood and urine samples. Draw a blood sample to test for methemoglobinemia, to measure BUN and blood electrolytes, and to check for signs of liver injury (bilirubin, GGT, LDH, ALT, AST, and alkaline phosphatase). Examine the urine for protein and cells, and for "smoky" phenolic excretion products.

5. Intravenous fluids. Give fluids intravenously to correct dehydration and electrolyte disturbances. Include glucose to protect the liver and bicarbonate to relieve metabolic acidosis, as necessary. Monitor fluid balance carefully to signal discontinuation of intravenous fluids if renal failure occurs. Plasma or blood transfusion may be needed to overcome shock.

6. Monitor ECG to detect arrhythmias and/or conduction defects that may appear as manifestations of a toxic myocardiopathy.

7. Convulsions. Anticonvulsants may be needed to control seizures as outlined in Chapter 2.

8. Hemodialysis is not effective in accelerating disposition of phenol (or, presumably, creosote), but hemoperfusion over charcoal probably is effective.[8] This should be considered in severe creosote poisonings.

9. Methemoglobinemia is rarely severe, but intravenous administration of 1% methylene blue may be considered if 25-30% of hemoglobin is converted. Dose is 0.1 mL of 1% solution per kg body weight, given over no less than 10 minutes. Nausea, dizziness, and a transient increase in blood pressure may occur.

ENDOTHALL

As the free acid or as sodium, potassium, or amine salts, endothall is used as a contact herbicide, defoliant, aquatic herbicide, and algacide. It is formulated in aqueous solutions and granules at various strengths.

Toxicology

Endothall is irritating to the skin, eyes, and mucous membranes. It is well absorbed across abraded skin and from the gastrointestinal tract. Recognized systemic toxic mechanisms in mammals are: corrosive effects on the gastrointes-

3. Intubation. If there are indications of corrosive effects in the pharynx, gastric intubation should not be attempted because of the risk of esophageal perforation. Treatment procedures appropriate for ingestions of corrosives (strong acids and alkalis) may be necessary. Referral should be made to a surgeon or gastroenterologist for consideration of endoscopy.

4. Oxygen should be given by mask. If respiratory drive is weak, pulmonary ventilation may have to be supported mechanically.

5. Monitor blood pressure closely. Infusions of plasma, blood, other volume expanders, and pressors may be needed to combat shock.

6. Administer intravenous fluids to correct dehydration, stabilize electrolytes, provide sugar, and support mechanisms for toxicant disposition. Give vasoactive amines very carefully in light of possible myocardiopathy.

7. Convulsions. Seizures may require administration of diazepam and/or other anticonvulsants.

8. Hemodialysis. It is not known whether hemodialysis or hemoperfusion would be effective in removing endothall from the blood. This option should be considered if the patient's condition deteriorates despite supportive care.

METALDEHYDE

Toxicology

Metaldehyde is a four-unit cyclic polymer of acetaldehyde which has long been used to kill slugs and snails, which are attracted to it without the use of bait. Occasional poisonings of animals and children have resulted from ingestion of pellets intended as molluscicide, but tablets designed as a combustible fuel ("meta-fuel") have also been responsible for human poisonings.[10] Another form of exposure is "snow storm tablets," which the user places at the end of a lighted cigarette to create snow. Toxicity occurs through inhalation of metaldehyde fumes.[11] The biochemical mechanism of poisoning is not known. Both acetaldehyde and metaldehyde produced similar effects in dogs; however, acetaldehyde was not detected in the plasma or urine of the metaldehyde-poisoned dogs.[12]

Ingestion of a toxic dose is often followed shortly by nausea and vomiting. The other primary features of toxicity are pyrexia, generalized seizures, and mental status changes, sometimes leading to coma.[10,13] Other signs and symptoms that may occur include hypersalivation, facial flushing, dizziness, tachypnea, and acidosis.[10,11] Pneumonitis has followed inhalational exposure to

metaldehyde.[11] While most cases are dramatic with significant seizures and coma, fatal events are infrequent.[10,13] Poisoned animals show tremors, ataxia, hyperesthesia, salivation, ataxia, and seizures.[12] Autopsy findings in fatal human poisonings indicate severe damage to liver cells and renal tubular epithelium.

Confirmation of Poisoning

Metaldehyde can be measured in the blood and urine, although there are very few reports of levels among poisoned humans. One patient who had severe tonic clonic seizures and was comatose had a metaldehyde level in the serum of 125 mg/L with a half-life of 27 hours. This patient did not have detectable acetaldehyde in the serum.[13]

Treatment

1. Gastrointestinal decontamination. If ingestion occurred within an hour of treatment, consider gastrointestinal decontamination as outlined in Chapter 2. Activated charcoal may well be useful against metaldehyde.

2. Convulsions. If seizures occur, sedative anticonvulsants must be administered. See Chapter 2 for dosage.

3. Supportive treatment. Appropriate supportive treatment including intravenous fluids containing saline and glucose should be given. Sodium bicarbonate may be considered in the event of severe metabolic acidosis. Fluid balance and electrolytes must be monitored carefully to avoid fluid overload if renal failure supervenes.

4. Renal failure. There is no specific antidote for metaldehyde poisoning. Hemodialysis is probably not effective in removing metaldehyde, but must be instituted if renal failure occurs. The effectiveness of hemoperfusion has not been tested.

5. Liver function tests and urine sediment examination should be done to assess liver and kidney injury in poisoned patients.

SODIUM CHLORATE

Sodium chlorate is used in agriculture as a defoliant, nonselective contact herbicide, and semipermanent soil sterilant. Because of its explosive nature, it must be formulated with water-soluble fire retardant material, such as sodium metaborate, soda ash, magnesium chloride, or urea. It is usually applied in water solution.

Toxicology

Sodium chlorate is irritating to skin, eyes, and mucous membranes of the upper respiratory tract.[14] Dermal absorption is slight. Even though gastrointestinal absorption is also inefficient, severe (sometimes fatal) poisoning follows ingestion of a toxic dose, estimated at about 20 grams in the adult human. Excretion is chiefly in the urine. The principal mechanisms of toxicity are hemolysis, methemoglobin formation, cardiac arrhythmia (partly secondary to hyperkalemia), and renal tubular injury.[14,15]

The irritant action on the gut causes nausea, vomiting, and abdominal pain. Once absorbed, hemoglobin is rapidly oxidized to methemoglobin, and intravascular hemolysis occurs.[14] Cyanosis is prominent if methemoglobinemia is severe and may be the only presenting sign.[15] Acute tubular necrosis and hemoglobinuria may result from the hemolysis or direct toxic injury. Plasma and urine are dark brown from the presence of free hemoglobin and methemoglobin.[14,15,16]

less toxic chloride ion. It can be given orally or as an IV infusion over 60-90 minutes. The dose is 2-5 g dissolved in 200 mL of 5% sodium bicarbonate.[14]

5. Monitor blood pressure, fluid balance, blood electrolytes, BUN, methemoglobin, and bilirubin, as well as urine protein, cells and free hemoglobin content, and ECG. Widening of the QRS complex and prolongation of the PR interval indicate hyperkalemic cardiac toxicity.

6. Milk may be helpful in relieving the pain of gastric irritation.

7. Administer intravenous fluids to sustain chlorate excretion. Maintain urine pH in the alkaline range by adding sodium bicarbonate to the infusion fluid. Monitor urine production closely, so that intravenous fluids can be slowed or discontinued if renal failure occurs. Blood transfusion may be needed if hemolysis and methemoglobinemia are severe. Exchange transfusion has been recommended to enhance clearance and treat DIC.[16]

8. Hemodialysis may be life-saving in severe poisoning. It is effective in removing chlorate from the blood, provides a means to control hyperkalemia, and makes possible the control of extracellular fluid volume and composition while renal function remains impaired.

9. Methemoglobinemia. Administration of methylene blue to reverse methemoglobinemia may be considered if as much as 25-30% of hemoglobin is converted. Give intravenously 0.1 mL/kg body weight of a 1% solution over a period of at least 10 minutes. An increase in blood pressure, nausea, and dizziness may occur, but these effects are usually transient. As the use of this agent in chlorate poisoning has not proven beneficial in the past, it is still advisable to proceed to exchange transfusion as stated in #7.

SYNERGISTS: PIPERONYL BUTOXIDE

Synergists are chemical agents included in pesticide products to enhance the killing power of the active ingredients. The widely-used insecticide synergist, piperonyl butoxide, acts by inhibiting the enzymatic degradation of pyrethrins, rotenone, N-methyl carbamates, and possibly some other insecticides. There is limited dermal absorption on contact. Inherent toxicity in mammals is low. Large absorbed doses may theoretically enhance the toxic hazard of the rapidly metabolized insecticides used today, although inhibition of human drug-metabolizing enzymes by these agents has not actually been demonstrated. Their presence in pesticide products to which humans are exposed does not change

the basic approach to management of poisoning, except that some possibility of enhanced toxicity of the active insecticidal ingredients should be kept in mind.

SOLVENTS AND ADJUVANTS

Liquid materials in which pesticides are dissolved and the solids on which they are adsorbed (sometimes called carriers or vehicles) are selected by producers to achieve stability of the active ingredient, convenience in handling and application, and maximum killing power following application. Often, the particular solvents and adjuvants selected by pesticide manufacturers are responsible for giving their commercial products a competitive edge. For this reason, their inclusion in marketed products is usually proprietary information, not available to the general public except in emergencies. If a poisoning emergency exists, pesticide companies will usually cooperate in supplying physicians with information needed to provide treatment. Some companies will put the inert ingredients on the Material Safety Data Sheet (MSDS). The physician should seek this information to assist in evaluating all possible exposures. A direct request to the producer is the quickest way to secure this information. Physicians may also contact EPA directly for this information (tel: 703-305-7090) if needed for proper management of a case.

Petroleum distillates are the most commonly used solvents for lipophilic pesticides. Most insecticides are lipophilic. The distillates are mixtures of

foliage. Particle sizes are such that these dusts are usually trapped in the upper respiratory mucous when inhaled. When the mucous is swallowed, the particles desorb pesticide into gastrointestinal secretions. Dust formulations may, therefore, release enough of some pesticides to cause systemic poisonings.

Stickers and spreaders (film extenders) are organic substances added to formulations to disperse pesticide over treated foliage surfaces and enhance adhesion. The availability and persistence of residue on the leaf surfaces is thereby increased. Substances used include proteinaceous materials (milk products, wheat flour, blood albumin, gelatin), oils, gums, resins, clays, polyoxyethylene glycols, terpenes, and other viscid organics. Some also include sulfated alcohols, fatty acid esters, and alkyl and petroleum sulfonates. For persons exposed in the course of formulation or application of pesticides, these adjuvants probably add little or no toxic hazard to that inherent in the active pesticidal ingredients.

Emulsifiers serve to stabilize water-oil emulsions formed when water is added to technical hydrocarbon concentrates. Chemically, they resemble detergents (one part of the molecule lipophilic, the other hydrophilic). Long-chain

Treatment

Petroleum distillates are mineral hydrocarbons which undergo limited absorption across the gut. In general, clinical toxicologists do not recommend induced emesis or gastric lavage in treating ingestions of these materials, because of the serious risk of hydrocarbon pneumonitis if even tiny amounts of the liquid are aspirated into the lung. However, this injunction against emptying the stomach may be set aside when the petroleum distillate is a vehicle for toxic pesticides in significant concentration. In such cases, if the patient is seen within one hour of exposure, gastrointestinal decontamination should be considered.

Rapid respiration, cyanosis, tachycardia, and low-grade fever are the usual indications of frank hydrocarbon pneumonitis. Patients with presumed hydrocarbon pneumonitis, who are symptomatic, should usually be hospitalized, preferably in an intensive care setting. If the patient has pulmonary symptoms, a chest x-ray should be taken to detect or confirm signs of pneumonitis. In addition, the urine should be examined for protein, sugar, acetone, casts, and cells, and an ECG should be examined for arrhythmias and conduction defects. Mechanically assisted pulmonary ventilation with 100% oxygen may be required. Hydrocarbon pneumonitis is sometimes fatal, and survivors may require several weeks for full recovery. In milder cases, clinical improvement usually occurs within several days, although radiographic findings will remain abnormal for longer periods.[17]

The presence of chlorinated solvents in some formulations may add significantly to the toxic hazard, particularly if the product is ingested. Certain adjuvants are irritants to skin, eyes, and mucous membranes, and may account for the irritant properties of some products whose active ingredients do not have this effect. With these exceptions, however, the presence of adjuvants in most finished pesticide products probably does not enhance or reduce systemic mammalian toxicity to any great extent.

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CHAPTER 19

Disinfectants

HIGHLIGHTS

- Compounds are registered for medical or medicinal use rather than as pesticides
- Several are among the most frequently reported human poisonings in the U.S.
- Iodine is well absorbed through abraded or burned skin

Signs and Symptoms:

- Highly variable based on agent
- Many are irritants and corrosives
- Iodine causes neurological symptoms, shock, renal failure, and hyperkalemia
- Pine oil can cause aspiration pneumonia

Treatment:

Follow general principles of decontamination and supportive care

Contraindicated:

- Gastric emptying and decontamination procedures are contraindicated in poisonings due to corrosive agents and pine oil

A wide variety of disinfectant agents are used to destroy microorganisms and they differ greatly in their toxic effects. Most disinfectants can conveniently be grouped into a few categories, some of which are also represented in other classes of pesticides. Many of these materials are not registered as pesticides, but are registered for medical or medicinal use. This chapter reviews a few of the more common or more severely toxic disinfectants.

ALCOHOLS

Alcohols have a long history of use as disinfectants. Often disinfectants are mixtures, usually of ethanol and isopropyl alcohol (isopropanol). The alcohol most commonly used in households as a disinfectant is isopropyl alcohol, commonly marketed as a 70% solution. It is a clear, colorless liquid with an odor similar to ethanol.

Toxicology of Isopropyl Alcohol

Confirmation of Poisoning

Isopropyl alcohol can be measured in the blood and urine. Serum acetone can also be measured. Blood isopropyl alcohol levels of 128-200 mg/dL have been associated with death.

Treatment: Isopropyl Alcohol

1. Gastrointestinal decontamination. Since the onset of coma is often rapid with this poisoning, induced emesis is contraindicated, though spontaneous vomiting often occurs. If the patient has ingested a large amount, has not vomited, and is seen within one hour of exposure, consideration should be given to gastric emptying by lavage as outlined in Chapter 2.

Isopropyl alcohol is well adsorbed to charcoal, so activated charcoal should probably be administered, as outlined in Chapter 2.

2. Supportive care for hypotension and respiratory depression is critical to survival and should be administered whenever possible in an intensive care setting.

3. If **hypoglycemia** occurs, glucose administration is indicated in order to maintain normoglycemia.

4. Hemodialysis has been reported to be beneficial in patients with severe poisoning unresponsive to standard supportive therapy.[1,4]

ALDEHYDES

The two aldehydes most commonly used as disinfectants are formaldehyde and glutaraldehyde. Formaldehyde is discussed in Chapter 17, Fumigants. Glutaraldehyde is very similar to formaldehyde in its toxicity and treatment, although it is probably slightly less toxic. Glutaraldehyde is commonly prepared as an aqueous solution at a 2% concentration, and is slightly alkaline in this solution. It has been reported to cause respiratory irritation, resulting in rhinitis[5,6] and occupational asthma.[6,7,8] It has also resulted rarely in palpitations and tachycardia in human subjects. At high dosage, given orally, it results in gastrointestinal irritation with diarrhea, which may be hemorrhagic. Due to the irritant effects of glutaraldehyde, the wearing of personal protective equipment is required for the protection of skin (29 CFR 1910.132), and eyes (29 CFR 1910.133). OSHA standards require the use of appropriate respirators by employees that may be exposed to glutaraldehyde during routine or emergency work procedures (29 CFR 1910.134).

Commercial Products

ALCOHOLS
Isopropyl alcohol

ALDEHYDES
formaldehyde
glutaraldehyde

CATIONIC DETERGENTS

Treatment: Glutaraldehyde

1. Gastrointestinal decontamination. If a large amount has been ingested and retained, and the patient is seen within one hour of exposure, consider gastric emptying as described in Chapter 2. Administration of activated charcoal should be considered, as described in Chapter 2.

2. Oxygen. If patient has been in an area with strong odor of glutaraldehyde due to vaporization, remove to fresh air area and administer oxygen as needed.

3. Skin decontamination. If skin irritation is noted, vigorous skin decontamination is indicated. However, systemic toxicity from skin exposure appears unlikely.

CATIONIC DETERGENTS

Several cationic detergents are used as disinfectants. All share the capacity, in sufficient concentration, to behave as caustic agents, capable of causing rather

a high concentration solution is in contact with the eyes, profuse washing of the eyes is indicated followed by a careful exam of the corneas. If burns have occurred, appropriate ophthalmologic care should be provided.

2. Gastrointestinal decontamination. Gastric emptying and other methods of gastrointestinal decontamination are **contraindicated** in these poisonings. Some experts recommend cautious dilution with small amounts of milk or water.[9,13] Acidic solutions such as juices should never be offered for dilution.

solution mixed with tap water (10 mL in 2 liters water).[18] Liver toxicity can occur with large exposures.[17]

Treatment

1. Gastrointestinal decontamination. If ingestion of a large quantity has occurred within an hour and the patient has not vomited, gastrointestinal decontamination as described in Chapter 2 should be considered. If a highly concentrated solution has been ingested, manage as a caustic ingestion as described in the cationic detergents, without gastrointestinal decontamination.

2. Liver injury panel should be performed with large ingestions.

3. Eye decontamination. If eye exposure has occurred, the eyes should be vigorously irrigated and a careful ophthalmologic exam should be performed for corneal injury. If an injury has occurred, an ophthalmologic consultation should be obtained.

HYPOCHLORITES

Hypochlorites are implicated in a large proportion of the disinfectant poisonings reported to poison control centers in the United States. Most are solutions of sodium or calcium hypochlorite solutions. Chloramine, a disinfectant used by many municipal water supplies, is an infrequent cause of acute poisonings. Sodium and calcium hypochlorite solutions are of relatively low toxicity. They are mildly corrosive to the eyes,[19] and mucous membrane burns have been reported.[20] Significant poisonings are very infrequent with these agents in solution.[21]

When hypochlorite solutions are mixed with acids or ammonia solutions, chlorine or chloramine gas is produced, resulting in an irritant with pulmonary toxicity. Many brief exposures have led to transient symptoms requiring limited emergency department management.[22] However, in cases of prolonged exposure or exposure to high concentrations, there is the potential for severe toxic pneumonitis.[23] While severe injury may be the exception to the rule, great efforts should be made to discourage mixing of these materials with acid or ammonia.

Treatment

1. Gastric decontamination. After oral exposures, gastric emptying is not indicated. If a granular material is ingested, and the patient has symptomatic mucosal burns, referral to a surgeon or gastroenterologist for consideration of endoscopy and management may be appropriate.

2. Dilution with water or milk not to exceed approximately 15 mL/kg in a child or 120-240 mL in an adult is probably appropriate if vomiting has not occurred. Administration of acids is contraindicated, due to the risk or increasing generation of chlorine gas.

3. Eye decontamination. If eyes were exposed, they should be irrigated profusely with water or saline. If corneal burns are detected, referral to an ophthalmologist is appropriate.

4. Skin decontamination. Skin exposure should also be managed by copious water dilutions. See Chapter 2.

5. Fresh air.

tions, and seizures.[26] Hypotension, arrythmias, cyanosis, metabolic acidosis, shock, and acute renal failure occur in severe cases.[25,27,28] Hepatic injury, manifested by elevated serum transaminase levels, has also been reported with very high level exposures.[27] Hyperkalemia has occurred, and the serum chloride may be falsely elevated due to the presence of a second halide.[25]

Treatment: Povidone-Iodine

1. Skin decontamination. Remove skin contamination by vigorous washing with soap and water. See Chapter 2.

2. Gastrointestinal decontamination. If the patient is seen soon after a very large ingestion, and vomiting has not occurred, consider gastrointestinal decontamination, as outlined in Chapter 2. Consider single dose charcoal.

3. Iodine clearance

Toxicology of Cresols

Cresols, in common with phenol and other phenolic compounds, are highly corrosive to all surfaces. With ingestion of concentrated forms they cause severe corrosive injury to the mouth and upper gastrointestinal tract. Likewise, severe eye and skin caustic injuries can occur with cresol exposure.[29] Symptoms usually include nausea, vomiting, and diarrhea. Hypotension, myocardial failure, pulmonary edema, and neurological changes may also occur.[30] Liver and renal toxicity, methemoglobinemia, and hemolysis have all been reported.[30,31] After long-term, repeated exposure, contact dermatitis may complicate these exposures. These compounds are well absorbed from the gastrointestinal tract and are also significantly absorbed from the skin and by inhalation.

Treatment: Cresols

1. Gastrointestinal decontamination. Due to the corrosive nature of these compounds, gastrointestinal decontamination should not be attempted. Consideration of dilution with milk or water is appropriate if vomiting has not occurred.

2. Endoscopy. If a corrosive injury has occurred with burns to the mouth, or if there is a clear history of gastrointestinal exposure, endoscopy should be considered and a gastroenterologist or surgeon should be consulted for diagnosis and management.

3. Skin decontamination. If skin or eye contamination has occurred, copious irrigation should be performed. This should be followed by a careful eye examination for corneal burns. If corneal burns are noted, ophthalmologic consultation should be obtained.

4. Respiratory and circulatory support should be provided in accordance with sound medical management. If severe systemic symptoms persist, the patient should be treated in an intensive care unit, if possible.

Toxicology of Hexachlorophene

Hexachlorophene is well absorbed orally and dermally. Dermal exposures have led to severe toxicity and death in neonates, due to application to damaged skin, or repeated or high-concentration skin exposures.[32] Hexachlorophene should never be used as a disinfectant on open wounds or abraded or inflamed skin surfaces. In distinction to other phenolic compounds, this agent is not significantly caustic and exposure does not result in the severe caustic injuries seen with other phenolic chemicals.

Hexachlorophene is a potent neurotoxicant. It causes brain edema and spongy degeneration of white matter.[33] This neurotoxicity can be seen after acute or chronic exposures, either by skin absorption or ingestion. The nervous system symptoms are complex. Lethargy is an early manifestation, followed by muscular weakness, muscular fasciculation, irritability, cerebral edema, and paralysis, leading to coma and death. Seizures commonly occur in more severe cases.[32,34] Blindness and optic atrophy have been reported following exposure to hexachlorophene.[35]

In addition to the neurological effects, common early symptoms of poisoning are vomiting, diarrhea, and anorexia.[34] These findings have been accompanied in animals by significant hepatotoxicity.[36]

PINE OIL

Pine oil detergent and disinfectant solutions are among the most common poisonings reported to poison control centers in the U.S. A relatively high number of these are reported as serious or fatal. Pine oil is found in a variety of household and commercial cleaners and disinfectants. It is a mixture of monoterpenes derived from the distillation of wood from various pine species, with approximately 57% being alpha-pinene.[39] Its most common side effects in smaller dosage are irritation of mucous membranes, gastrointestinal irritation, mild respiratory and CNS depression, and renal toxicity. Larger ingestions can result in severe respiratory distress, cardiovascular collapse, and severe CNS effects. Renal failure and myoglobinuria have also been reported in severe poisonings.[40] Since even small ingestions can result in severe aspiration pneumonia, all ingestions should be considered potentially hazardous.

While many of the reported effects of poisoning with this agent are related to direct irritant effect on mucous membranes, gastrointestinal tract, and lung (by aspiration), some reports suggest significant absorption from oral and rectal exposures. Other reports suggest a lesser rate of absorption.[39] While alpha-terpineol can be measured in blood, there are no data relating levels to degree of toxicity. Consequently, this measure is not considered useful in guiding diagnosis and management.

Treatment

1. Gastrointestinal decontamination. Since there is a high risk of aspiration pneumonia, induced emesis is usually considered contraindicated in these poisonings. However, spontaneous emesis may occur due to direct irritation of the gastric mucosa.

If the patient is seen within an hour of ingestion and a large amount has been ingested, gastric emptying by intubation and lavage may be considered, as described in Chapter 2. However, some studies have suggested greater rates of complications with lavage than with ipecac-induced emesis.[40]

There is no evidence that activated charcoal is helpful in these poisonings. Likewise, though a variety of enhanced elimination methods have been proposed and tried, there is no evidence to support their efficacy.

2. Eye decontamination. If eye exposure has occurred, copious irrigation of the eyes is appropriate.

3. Pulmonary symptoms. The patient should be observed for at least six hours with any significant ingestion in order to observe the onset of any symptoms, particularly pulmonary symptoms. If any pulmonary symptoms are observed, the patient should have a chest film and measurement of oxygenation,

and hospitalization is appropriate. With severe pulmonary symptoms, transfer to an intensive care unit is usually appropriate. With severe aspiration, management should be handled as in any severe aspiration pneumonia, in accordance with accepted medical practice. Other severe systemic effects should be treated in accordance with accepted medical practice.

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Index of Signs and Symptoms

Presented in this chapter are lists of pesticides reported to have caused particular symptoms and signs, or combinations thereof, in poisoned individuals. The lists may help direct the attention of health professionals to possible toxic causes of the various disease manifestations, prompting inquiry into likelihood of exposure to the listed chemicals. If certain agents appear suspect, inquiry can then be made into the presence of additional manifestations typical of poisoning by those substances.

The limitations of this approach to diagnosis must be understood. First, all manifestations of illness have multiple causes, pesticidal and nonpesticidal. Second, there are no specific symptoms or signs that are invariably present in poisonings by particular pesticides. Third, many poisonings are characterized by unexpected manifestations.

Finally, neither route of exposure nor dosage of pesticide is taken into account in this listing. For example, effects of high-dose ingestion are not distinguished from effects of relatively low-dose dermal absorption, nor are topical effects distinguished from systemic dermal manifestations. The lists of pesticides can only be regarded as *clues* to prompt further inquiry by the interviewing professional.

The term manifestation means either symptom or sign. The word "poisoning" is used loosely in these headings to include topical as well as systemic effects. Pesticides which are relatively consistent in causing particular manifestations are listed in the middle column, headed "Characteristic of These Agents." Pesticides that have caused various conditions with less consistency, or are less prominent features of poisoning, are listed in the right-hand column, headed "Occurs with These Agents." Obviously, the distinction is not clear-cut.

Some symptoms (malaise, fatigue, dizziness) occur so commonly in poisoned individuals that they have little or no value in differential diagnosis, and are therefore not included in these tables.

MANIFESTATION	CHARACTERISTIC OF THESE AGENTS
Rotten egg odor	Sulfur
Hypothermia	Creosote Norbormide
Hyperthermia (fever, pyrexia)	Nitrophenols Pentachlorophenol
Chills	Phosphine Arsine
Hot sensations	Nitrophenols Chlordimeform
Myalgia	Paraquat
Thirst	
Anorexia	
Alcohol intolerance	
Sweet taste in the mouth	
Metallic taste in the mouth	
Salty, soapy taste In the mouth	

Skin

MANIFESTATION	CHARACTERISTIC OF THESE POISONINGS	OCCURS WITH THESE AGENTS
Irritation, Rash, Blistering, or Erosion (without sensitization)	Copper, organotin, cadmium compounds Metam sodium Paraquat Diquat Sodium chlorate Phosphorus Sulfur Glyphosate Propargite Sodium hypochlorite Quaternary ammonia Thiram Chlordimeform Cationic detergents Hexachlorphene Ethylene oxide Formaldehyde Acrolein Methyl bromide Ethylene dibromide Dibromochloropropane Dichloropropane Endothall Aliphatic acids	Pentachlorophenol Picloram Chlorophenoxy compounds Captan Rotenone Diethyltoluamide Creosote Fungicides Herbicides with irritant properties Petroleum distillate
Contact dermatitis	PCP Paraquat DEET Chlorhexidine Creosote Hexachlorphine Pyrethrins Chlorothalonil Thiram Thiophthalimides	
Flushing	Cyanamide Nitrophenols	Thiram plus alcohol
Dermal sensitization	Propachlor Propargite Ethylene oxide	Anflazine Chlorothalonil Barban Captafol Formaldehyde
Beefy red palms, soles	Borate	
Urticaria	Chlorhexidine PCP DEET	Fluoride Pentachlorophenol
Bullae	Liquid fumigants	Hexachlorobenzene

Pallor

Cyanosis

Yellow stain

Keratoses, brown discoloration

Ecchymoses

Jaundice

Excessive hair growth

Loss of hair

Loss of fingernails

Copper compounds
Organotin compounds
Cadmium compounds
Metam sodium
Paraquat
Diquat
Acrolein
Chloropicrin
Sulfur dioxide
Naphthalene
Formaldehyde
Ethylene oxide
Methyl bromide
Endothall
Toluene
Xylene

Organophosphates
Carbamate insecticides
Chloropicrin
Acrolein

Nitrophenols

Paraquat

Thallium

Organophosphates
Carbamate insecticides
Nicotine

Nervous System (continued)

MANIFESTATION	CHARACTERISTIC OF THESE POISONINGS	OCCURS WITH THESE AGENTS
Seizures/Convulsions (clonic-tonic) sometimes leading to coma	Organochlorines Strychnine Crimidine Sodium fluoroacetate Nicotine Cyanide Acrylonitrile Metaldehyde Thallium DEET Chlorobenzilate Carbon disulfide Phosphine Povidone-iodine Hexachlorophene Sodium chlorate Creosote Endothall Fluoride	Nitrophenols Pentachlorophenol Inorganic arsenicals Organotin compounds Diquat Borate Sulfuryl fluoride Methyl bromide Chlorophenoxy compounds Organophosphates Carbamate insecticides Aminopyridine
Muscle twitching	Organophosphates Carbamate insecticides Nicotine Sulfuryl fluoride	Organic mercury Chlorophenoxy compounds
Myotonia		Chlorophenoxy compounds
Tetany, carpopedal spasms	Fluoride Phosphides Phosphorus	
Tremor	Organic mercury Thallium Organophosphates Carbamate insecticides Nicotine Metaldehyde Borates	Pentachlorophenol Nitrophenole Thiram
Incoordination (including ataxia)	Halocarbon fumigants Organophosphates Carbamate insecticides Carbon disulfide Nicotine Thallium	Organic mercury Organochlorines
Paralysis Paresis, muscle weakness	Inorganic arsenicals Organophosphates Carbamate insecticides Nicotine	Organic mercury Diethyltoluamide
Hearing loss	Organic mercury	

Hypotension shock	Phosphorus	Inorganic arsenicals
	Phosphides	Nicotine (late)
	Phosphine	
	Sodium fluoride	
	Sodium chlorate	
	Borate	
	Thallium	
	Copper compounds	
	Endothall	
	Cyanamide	
Hypertension	Thallium (early)	
	Nicotine (early)	

Naphthalene

Gastrointestinal Tract and Liver

MANIFESTATION	CHARACTERISTIC OF THESE POISONINGS	OCCURS WITH THESE AGENTS
Nausea, vomiting, commonly followed by diarrhea	Organophosphates Carbamate insecticides Nicotine Arsenicals Fluoride Cadmium compounds Organotin compounds Copper compounds Sodium chlorate Borate Cyanide Chlorophenoxy compounds Phosphorus Phosphides Phosphine Carbon disulfide Chloropicrin Halocarbon fumigants Endothall Metaldehyde Thallium Red quill Diquat Naphthalene Methyl bromide Dibromochloropropane Veratrum alkaloid Thiram	Pentachlorophenol *B.thuringiensis* Cholecalciferol Thiram Ethylene dichloride Propane Ethylene oxide Cresol Many pesticides have some irritant property
Diarrhea (first)	Organophosphates Carbamates Pyrethoids Borates Sulfur Nicotine *B.thuringiensis* Thiram Cadmium	Cationic detergents Cresol Hexachlorophene Chlorophenoxy compounds
Diarrhea (bloody)	Fluoride Paraquat Diquat Thallium Coumarins Indandiones Endothall Arsenicals	Phosphorus Phosphides Cycloheximide

Gastrointestinal Tract and Liver (continued)

MANIFESTATION	CHARACTERISTIC OF THESE POISONINGS	OCCURS WITH THESE AGENTS
Abdominal pain	Organophosphates Carbamate insecticides Paraquat Diquat Nicotine Methaldehyde Fluoride Borate Phosphorous Phosphides Inorganic arsenicals Cadmium compounds Copper compounds Thallium Organotin compounds	Chlorophenoxy compounds Aliphatic acids Sodium chlorate Creosote Endothall Aminopyridine Coumarins Indandiones Fumigants (ingested) Cycloheximide
Stomatitis	Inorganic arsenicals Paraquat Diquat Copper compounds	Thallium
Salivation	Organophosphates Carbamate insecticides Nicotine Aminopyridine Sodium fluoride Cyanide Cadmium compounds	
Ileus	Thallium Diquat	

Liver

MANIFESTATION	CHARACTERISTIC OF THESE POISONINGS	OCCURS WITH THESE AGENTS
Enlargement	Copper compounds Sodium chlorate Phosphine Carbon tetrachloride Cholorform	Inorganic arsenicals Hexachlorobenzene
Jaundice – see section on Skin		

Kidney

MANIFESTATION	CHARACTERISTIC OF THESE POISONINGS	OCCURS WITH THESE AGENTS
Proteinuria Hematuria Sometimes leading to oliguria Acute renal failure with azotemia	Inorganic arsenicals Copper compounds Sodium fluoride Naphthalene Borate Nitrophenols Pentacholorphenol Sodium chlorate Sulfuryl fluoride Paraquat Diquat Arsine Ethylene dibromide	Cadmium compounds Phosphorus Phosphides Phosphine Chlorophenoxy compounds Creosote Organotin compounds
Dysuria, hematuria, pyuria	Chlordimeform	
Polyuria	Cholecalciferol	Fluoride
Hemoglobinuria	Naphthalene Sodium chlorate Arsine	
Wine-red urine (porphyrinuria	Hexachlorobenzene	
Smoky urine	Creosote	
Glycosuria		Organotin compounds
Ketonuria		Borate

Reproductive System

MANIFESTATION	CHARACTERISTIC OF THESE POISONINGS	OCCURS WITH THESE AGENTS
Low sperm count	Dibromochloropropane	Kepone

Hypocalcemia		
Hypercalcemia Carboxyhemoglobinemia Anemia Leukopenia, Thrombocytopenia Elevated LDH GOT, GPT, alkaline phosphatase, ALT, AST enzymes Depressed RBC Acetylcholinesterase and plasma pseudocholinesterase		

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