HIGHLIGHTS

Multiple agents with widely varying toxicity

Agents of concern include borates, fluorides, pyrethroids

Neonicotinoids are a newer class that merits attention due to widespread use and toxicity

SIGNS & SYMPTOMS

Variable and highly related to the specific agent

Boric acid, fluorides, n-phenylpyrazones and neonicotinoids should be suspected in cases with CNS symptoms

TREATMENT

Specific to agent

Skin/eye decontamination

Consider GI decontamination based on quantity and time interval factors

Severe CNS symptoms may require intensive care management

CHAPTER 9

Other Insecticides and Acaricides

This chapter concerns insecticides and acaricides having toxicologic characteristics distinct from the insecticides discussed in previous chapters. It discusses benzyl benzoate, borates, chlordimeform, chlorobenzilate, cyhexatin, fluorides, fipronil (an n-phenylpyrazone insecticide), haloaromatic substituted urea compounds, methoprene, neonicotinoids, propargite and sulfur.

BENZYL BENZOATE

Incorporated into lotions and ointments, this agent has been used for many years in veterinary and human medicine against mites and lice.

Toxicology

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 that is excreted in the urine. Oral toxicity in animals is low, with LD_{50} values in the 2-3 grams/kg range in rats and cats. When given in large doses to laboratory animals, benzyl benzoate causes excitement, incoordination, paralysis of the limbs, convulsions, respiratory paralysis and death.[1] Very few human exposures have been reported to the National Poison Data System.

Treatment

1. If significant irritant effect appears, discontinue use of product and cleanse skin with soap and water. Treat eye contamination by irrigating exposed eyes with copious amounts of clean water or saline for at least 15 minutes. Remove contact lenses, if present, prior to irrigation. If irritation persists after irrigation, obtain specialized medical treatment in a healthcare facility.

2. If a potentially toxic amount has been swallowed and retained and the patient is seen soon after exposure, consider gastrointestinal decontamination. If seizures occur, control may require treatment with benzodiazepines.

BORIC ACID AND BORATES

Boric acid and borate products can be formulated as tablets and powder to kill larvae in livestock confinement areas and cockroaches in residences. Rarely, solutions are sprayed as a nonselective herbicide.

Toxicology

When determining toxicity of **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.[2,3] **Borates** are well absorbed by the gut and by abraded or burned skin, but not by intact skin.[4] The kidney efficiently excretes them. The residence half-life in humans averages 13 hours, in a range of 4-28 hours.[2]

Signs and Symptoms of Poisoning

Generally, boric acid is of lower toxicity when compared to other insecticides that are widely used in the United States. A series of 784 patients has been described with no fatalities and minimal toxicity. Only 12% of these patients had symptoms of toxicity, mostly to the gastrointestinal tract.[2] However, fatal poisonings have been reported.[3,5,6] A large number of poisonings in newborns occurred in the 1950s and 1960s and often resulted in death.[7,8] 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.[4,9]

Boric acid powders and pellets scattered on the floors of homes can present a hazard to children. Their frequent use for roach control increases access for ingestion. Consequently, cases of suicidal or accidental ingestion continue to be reported in the medical literature.[5,6,10,11,12] One toddler died following a massive ingestion of boric acid powder that had been stored in a bathroom cabinet.[5] An 82-year-old man accidentally ingested 30 mL of boric acid instead of the magnesium sulfate he was supposed to take for a colonoscopy prep.[10] Three cases of apparent suicide attempts in adults have been reported.[11,12,13] 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.[14,15]

The gastrointestinal tract, renal system, skin, vascular system and brain are the principal organs and tissues affected. Nausea, persistent vomiting, abdominal pain and diarrhea reflect a toxic gastroenteritis.[2,3,9] 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.[3,8,11,16] This may be difficult to distinguish from staphylococcal scalded skin syndrome.[16] Reversible alopecia has been reported following exposure to boric acid and related compounds.[17,18,19]

Headache, agitation, weakness, lethargy, restlessness and tremors may occur, but are less frequent than gastrointestinal effects.[2,10] Seven infants who were exposed to a mixture of borax and honey on their pacifiers developed seizures.[20] 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.[3,6,9] Hypotension and at times hypertension may occur even in milder cases where victims fully recover.[10,11]

Acute renal failure (oliguria or anuria) may be a consequence of shock, of direct toxic action on renal tubule cells, or possibly of both. It occurs in severe borate poisoning.[3,6,8,16] Metabolic acidosis may be a consequence of the acid itself, seizure activity or metabolic abnormalities.[3] Fever is sometimes present in the absence of infection.

Confirmation of Poisoning

Borate can be measured in serum by colorimetric methods, as well by high temperature atomic spectrometric methods. Studies of serum levels of boric acid and boron in non-poisoned individuals ranged from 0.0 to 0.2 mg/dL in adults and from 0.0 to 0.125 mg/dL in children.[9,21,22] Levels reported in toxic incidents have varied widely and it is felt that serum levels are of little use in guiding therapy.[2,9,21]

Boric Acid/Borates

COMMERCIAL PRODUCTS

Boric acid, sodium tetraborate decahydrate, sodium polyborates (discontinued 1992)

HIGHLIGHTS

Chronic ingestion more likely to cause significant toxicity than acute

Absorbed by gut and abraded/burned (not intact) skin

SIGNS & SYMPTOMS

Nausea, vomiting, abdominal pain, diarrhea

Severe poisonings: erythema ("boiled lobster") and exfoliation

CNS symptoms may be present

TREATMENT

Skin/eye decontamination

Consider GI contamination

Large or protracted ingestion may require IV fluids and cardiac monitoring

Treatment

1. Decontaminate the skin with soap and water as outlined in **Chapter 3, *General Principles***. Treat eye contamination by irrigating the exposed eye(s) with copious amounts of clean water or saline for at least 15 minutes. Remove contact lenses, if present, prior to irrigation. If irritation persists after irrigation, send patient for specialized medical treatment in a healthcare facility.

2. In acute poisonings, if a large amount has been ingested and the patient is seen within 1 hour of exposure, gastrointestinal decontamination may be considered as outlined in **Chapter 3**. It is important to keep in mind that vomiting and diarrhea are common, and severe poisoning may be associated with seizures.

3. If massive ingestion of borate (several grams) has occurred or if borate ingestion has extended over several days, administer IV fluids such as D5NS or Lactated Ringers to sustain urinary excretion of borate. Monitor fluid balance and serum electrolytes (including acid base status) regularly. Monitor cardiac status by ECG. Test the urine for protein and cells to detect renal injury, and monitor serum concentration of borate if possible. Metabolic acidosis may be treated with sodium bicarbonate. If shock develops, treat as appropriate. Administer oxygen continuously. If oliguria (less than 25-30 mL urine formed per hour) occurs, intravenous fluids must be slowed or stopped to avoid overloading the circulation. Such patients should usually be referred to a center capable of providing intensive care for critically ill patients.

4. Consider hemodialysis in severe poisonings, if patient fails to respond to conventional therapy. Dialysis has been demonstrated to enhance the clearance of boric acid even in the presence of normal renal function.[2,7,10,12] There is no consensus on its use. Forced diuresis has also been successfully used in early stages of poisoning.[13]

   Peritoneal dialysis was performed historically in borate poisoning and thought to be as effective as, and safer than, exchange transfusion in removing borate.[8,23] Exchange transfusion has been reported to be effective in chronic exposures. No large study of efficacy has been done. Exchange transfusion and peritoneal dialysis are rarely used today in acute poison management.[2]

5. Control seizures as recommended for other agents and as outlined in **Chapter 3**.

CHLORDIMEFORM

Formulations are emulsifiable concentrates and water-soluble powders. Chlordimeform demonstrates good dermal absorption and can be inhaled. It is an ovicide and acaricide. All registrations in the United States are currently canceled.

Toxicology

In a reported episode of occupational exposure to **chlordimeform**, several workers developed hematuria. Hemorrhagic cystitis, probably due to chloraniline biodegradation products, was the source of the blood in the urine. Symptoms reported by the affected workers included gross hematuria, dysuria, urinary frequency and urgency, penile discharge, abdominal and back pain, a generalized "hot" sensation, sleepiness, skin rash and desquamation, a sweet taste and anorexia. Symptoms persisted for 2-8 weeks after exposure was terminated.[24] In a single case, methemoglobinemia was reported.[25]

Chlordimeform is not a cholinesterase inhibitor.

Confirmation of Poisoning

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

Treatment

1. Decontaminate skin thoroughly with soap and water, as outlined in **Chapter 3, *General Principles***. Decontaminate eyes by irrigating exposed eyes with copious amounts of clean water or saline for at least 15 minutes. Remove contact lenses if present prior to irrigation. If irritation persists after irrigation, send patient for specialized medical treatment in a healthcare facility.

2. If chlordimeform has been ingested no more than an hour prior to treatment consider gastrointestinal decontamination as outlined in **Chapter 3**. Patients are at risk for fluid loss and subsequent electrolyte disturbances; young children are especially susceptible. Monitor fluid balance, electrolytes and acid base status closely.

3. Patients exposed should have serial urinalyses for protein and red cells to detect injury to the urinary tract. Resolution of hematuria ordinarily can be expected in 2-8 weeks. Relief from other symptoms usually can be expected earlier.

CHLOROBENZILATE

Chlorobenzilate is a chlorinated hydrocarbon acaricide, usually formulated as an emulsion or wettable powder for application in orchards. All U.S. registrations have been canceled.

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 derivatives. Based on observation of dosed animals, extreme absorbed doses may cause diarrhea, tachypnea, tremors, ataxia and muscle weakness.[26]

Limited human acute poisoning data are available. A case of toxic encephalopathy in a male following unprotected pesticide application in a field for 14 days at 10 hours per day has been reported. His symptoms included muscle pain, weakness, fever and mental status changes, progressing to a tonic-clonic seizure. He recovered without apparent sequelae within 6 days. Treatment included respiratory support and seizure management.[27]

Chlorobenzilate is not a cholinesterase inhibitor.

Fluorides
COMMERCIAL PRODUCTS

Cryolite

Kryocide

HIGHLIGHTS

Most cases of poisoning today are sources other than insecticides

Highly toxic sodium fluoride and sodium fluosilicate products no longer registered for use

SIGNS & SYMPTOMS

Hypocalcemia with possible tetany

Cardiac arrhythmia, shock

Possible CNS impacts

TREATMENT

Skin, eye, possible GI decontamination

May require intensive care treatment

Treat hypocalcemia with calcium gluconate or calcium chloride

Treatment of Chlorobenzilate Poisoning

1. Decontaminate the skin with soap and water as outlined in the **Chapter 3, *General Principles***. Treat eye contamination by irrigating exposed eyes with copious amounts of clean water or saline for at least 15 minutes. Remove contact lenses, if present, prior to irrigation. If irritation persists after irrigation, send patient for specialized medical treatment in a healthcare facility.

2. If a large amount of chlorobenzilate was ingested within a few hours prior to treatment, consider gastrointestinal decontamination as outlined in **Chapter 3**.

3. Treat seizures as outlined in **Chapter 3**.

CYHEXATIN

All U.S. registrations of this chemical have been canceled.

Toxicology

Tricyclohexyl tin hydroxide is formulated as a 50% wettable powder for control of mites on ornamentals, hops, nut trees and some fruit trees. It is moderately irritating, particularly to the eyes. While information on the systemic toxicity of this specific tin compound is lacking, it should probably be assumed that cyhexatin can be absorbed to some extent across the skin, and that substantial absorbed doses would cause nervous system injury (see organotin compounds on page 154 in **Chapter 16, *Fungicides***).

Treatment

1. Promptly decontaminate skin by washing with soap and water and decontaminate eyes by irrigating with clean water or saline for at least 15 minutes. Remove contact lenses, if present, prior to irrigation.

2. Manage poisonings by ingestion on the assumption that cyhexatin is toxic, even though rodent LD_{50} values are fairly high and no human poisonings have been reported in the medical literature. Management should be as with other organotin compounds (see page 154 in **Chapter 16, *Fungicides***).

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. No commercial products are available at this time.

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. Commercial products containing sodium fluosilicate are no longer registered for use.

Sodium fluoaluminate (sodium aluminofluoride, 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 man.

Most cases of fluoride poisoning now are related to hydrofluoric acid, sulfur fluoride or excess fluorosis from sources other than insecticides, such as well water and toothpaste. Hydrofluoric acid is an important industrial toxicant but is not used as a pesticide. The clinical symptoms from hydrofluoric acid poisoning are essentially the same as described below for fluoride pesticides and are related to the fluoride ion's effects on potassium, calcium and magnesium.[28] Fluoroacetate is discussed in **Chapter 18**, ***Rodenticides***. Sulfuryl fluoride is discussed in **Chapter 17**, ***Fumigants***.

Toxicology

Sodium fluoride and **sodium fluosilicate** used as insecticides present a serious hazard to humans because of high inherent toxicity and the possibility that children crawling on floors of treated dwellings will ingest the material. They are both used in the water fluoridation process, which is more likely to be a source of exposure than the insecticide. In a series of 87 pediatric cases of fluoride poisoning reported to a poison center, only one child had ingested an insecticide. Of note, that child was also the only fatality in the case series.[29]

Fluorides are readily and quickly absorbed from the GI tract with near complete bioavailability.[30,31] Plasma fluoride levels peak at around 30 minutes following ingestion. Fluoride is also distributed to the bone and saliva.[31,32] Excretion is chiefly in the urine. Within the first 24 hours of intoxication, renal clearance of fluoride from the blood is rapid. However, patients continue to excrete large amounts of fluoride for several days. The fluoride ion binds calcium and magnesium, leading to life-threatening cardiac toxicity in severe cases. Children are at relatively greater risk because of their smaller body mass compared to adults in relation to the amount ingested.[33]

Signs and Symptoms of Poisoning

The toxic effects of fluoride in mammals are multiple and may be life threatening. The primary effects from fluoride result from an inhibition of critical intracellular enzymes and the direct effect on ionized calcium in extra-cellular fluid. The absorbed fluoride ion reduces extracellular fluid concentrations of calcium and magnesium. Hypocalcemia commonly occurs, sometimes severe enough to result in tetany or cardiac toxicity leading death.[29,34,35,36,37]

While sodium fluoride supplementation is available in the form of liquid drops, there is a rather narrow therapeutic range; chronic, mild fluorosis is present with an intake of 0.1 mg/kg/day. Most evidence of minor skeletal fluorosis will disappear as the fluoride supplementation is stopped, except for the teeth mottling.[38] Acutely toxic dosages usually start at about 3-10 mg/kg, with GI symptoms being the first to develop.[29,39] Ingested fluoride is transformed in the stomach to hydrofluoric acid, which has a corrosive effect on the epithelial lining of the gastrointestinal tract. Thirst, abdominal pain, vomiting and diarrhea are usual symptoms. Hemorrhagic gastroenteritis, ulceration, erosions and edema are commons signs.[40]

Cardiac arrhythmia and shock are often prominent features of severe poisoning. Hypotension and severe arrhythmia including ventricular fibrillation may also occur.[37,41] These probably result from combinations of effects of fluid and electrolyte disturbances including hypocalcemia,[29,34,35,36,37] hyperkalemia[41] and direct actions of fluoride on heart and vascular tissues. Fluoride may directly affect the central nervous system resulting in headache, muscle weakness, stupor, convulsions and coma.[33,34,37] Respiratory failure and ventricular arrhythmias are common causes of death.[33,37]

Confirmation of Poisoning

A population drinking water with a concentration of 1 mg per liter will have a plasma inorganic fluoride concentration between 0.01-0.03 mg per liter[34] and rarely above 0.10 milligram per liter. In fatal cases of poisoning, plasma levels of 3.5 mg per liter and higher have been recorded, although survival has been reported in patients with levels as high as 14 mg per liter.[34,37] While not specific for fluoride poisoning, a low serum calcium level can be helpful in making the diagnosis.[29]

Treatment

1. Decontaminate the skin with soap and water as outlined in **Chapter 3, *General Principles***. Treat eye contamination by irrigating exposed eyes with copious amounts of clean water or saline for at least 15 minutes. Remove contact lenses, if present, prior to irrigation. If irritation persists after irrigation, send patient for specialized medical treatment in a health carefacility.

2. If sodium fluoride or sodium fluosilicate has been ingested, consider gastric decontamination as outlined in **Chapter 3**. It should be noted that activated charcoal will not bind the fluoride ion.

3. Severe complications such as hypotension, shock, cardia arrhythymia or cyanosis should be treated in an intensive care setting. Monitor serum electrolytes (sodium, potassium, ionized calcium, magnesium, fluoride and bicarbonate) and correct as needed. Calcium and magnesium replacement are of primary consideration.[29,36]

   If the victim is fully alert and the amount ingested is less than 8 mg/kg of fluoride, consider giving the victim milk.[29] Milk provides 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.[37] There are no data on the optimum amounts to be administered.

4. If hypocalcemia is demonstrated, or if it appears likely that a significant amount of fluoride has been absorbed, aggressive calcium repletion may be required. Give 10 mL of 10% calcium gluconate intravenously slowly and repeat as necessary to keep the calcium in the normal or supranormal range:

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. Repeat dosage as needed.***

Severe cases may require use of 10% calcium chloride:

Dosage of Calcium Chloride

- ***Adults and children over 12 years: 5 to 10 mL (500 to 1,000 mg) intravenously over 1 to 5 minutes; may repeat after 10 minutes.***
- ***Children under 12 years: 0.2 to 0.3 mL/kg (20 to 30 mg/kg) per dose, up to a maximum single dose of 5 mL (500 mg) intravenously over 5 to 10 minutes, repeated up to four times or until serum calcium increases.***

These patients should be managed in the intensive care setting.

5. If hypomagnesaemia is present, administer magnesium sulfate.
6. Consider hemodialysis, as it may be beneficial in patients with significant toxicity.[37]
7. Refer patients with evidence of burns in their oral cavity for surgical evaluation and endoscopy, since these compounds can cause severe burns to the esophagus and stomach.
8. If a very large amount of sodium fluoaluminate (Cryolite) has been ingested, although it is much less toxic than other fluorides, measure serum calcium to ensure that hypocalcemia has not occurred. If it has, intravenous calcium may be required (see 4 above).

HALOAROMATIC SUBSTITUTED UREA INSECTICIDES

Haloaromatic substituted urea compounds control insects by impairing chitin deposition in the larval exoskeleton. They are formulated in wettable powders, oil dispersible concentrate and granules for use in agriculture and forestry and in settings where fly populations tend to be large, such as feedlots. **Diflubenzuron** is the most commonly used product in this class, and most human data are based on this active ingredient.

Toxicology

There is limited absorption of **haloaromatic substituted urea compounds** across the skin and intestinal lining of mammals, after which enzymatic hydrolysis and excretion rapidly eliminate the pesticide from tissues. Irritant effects are not reported and systemic toxicity is low. Based on animal studies, methemoglobinemia is a risk from the metabolite of diflubenzuron (4-chloroaniline).[65,66] There has been a report of occupational exposure to 4-chloroaniline that resulted in methemoglobinemia, although it is not clear that the source of 4-chloroaniline was diflubenzuron.[67]

Treatment

1. Decontaminate the skin with soap and water as outlined in **Chapter 3, *General Principles.*** Treat eye contamination by irrigating exposed eyes with copious

amounts of clean water or saline for at least 15 minutes. Remove contact lenses, if present, prior to irrigation. If irritation persists after irrigation, obtain specialized medical treatment in a healthcare facility. Sensitization reactions may require steroid therapy.

2. If large amounts of propargite have been ingested and the patient is seen within an hour, consider gastrointestinal decontamination as discussed in **Chapter 3, *General Principles***.

3. If methemoglobinemia is severe (>30%), or the patient is cyanotic, administer methylene blue.

Dosage of Methylene Blue

- ***Adults and children: 1-2 mg/kg of 1% methylene blue, slow IV, in symptomatic patients. Additional doses may be required, given as a slow IV push over a few minutes, every 4 hours as needed. (It is formulated as a 1% solution with 1 mL containing 10 mg of methylene blue.)***

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 briquettes, sprays, foggers, soluble concentrate, suspension concentrate and baits.

Toxicology

Methoprene is neither an irritant nor a sensitizer in humans or laboratory animals. Systemic toxicity in laboratory animals is very low. No human poisonings or adverse reactions in exposed workers have been reported.

Treatment

1. Wash contaminated skin with soap and water. Treat eye exposures by irrigating exposed eyes with copious amounts of clean water or saline for at least 15 minutes. Remove contact lenses, if present, prior to irrigation. If irritation persists after irrigation, send patient to a healthcare facility for further medical attention.

2. If a very large amount of methoprene has been ingested, consider GI decontamination as outlined in **Chapter 3, *General Principles***.

N-PHENYLPYRAZONE INSECTICIDES

Fipronil is a broad-spectrum n-phenylpyrazole insecticide first registered by the U.S. Environmental Protection Agency in 1996. It is used for pests on agricultural crops and for lawn treatments. It is also commonly used for ant and cockroach control in the form of bait stations and as a topical application to domestic animals for flea and tick control.

Toxicology

Fipronil's mechanism of action is by inhibition of GABA-gated chloride channels. This inhibits passage of chloride ions, thus producing hyperexcitability. This effect is similar to the mechanism of action for the organochlorine insecticides, the difference being that fipronil acts only on the $GABA_A$ channels, while organochlorines inhibit both the $GABA_A$ and $GABA_C$ channels.[42,43,44]

Fipronil is well absorbed by the GI tract in its parent form. It is rapidly metabolized to a sulfone compound. This metabolite is toxicologically active like the parent compound. It also binds to the same GABA receptors as fipronil, but at a much higher affinity.[45]

Animal studies demonstrate that fipronil has a selectively higher toxicity for insects than mammals, mostly attributed to a much more selective affinity for insect $GABA_A$ channels than vertebrate $GABA_A$ channels.[43,45]

Signs and Symptoms of Poisoning

Despite the higher selective affinity for insects, there have been some reports of acute human toxicity. Patients may present with nausea and vomiting within several hours of ingestion. These appear to be self limiting, and no long-term gastrointestinal effects have been reported.[46] Consistent with the fact that the central nervous system is the primary target of fipronil, neurological symptoms have been the most commonly observed health effects.[46,47,48] Neurologic symptoms have been confirmed in cases of human poisoning following ingestion. Patients may present with altered mental status.[47] In severe cases, unconsciousness and generalized tonic-clonic seizures may also occur.[47,48,49] Most episodes of seizures or altered mental status appeared to be self limiting and have resolved within hours.[46,47]

One study analyzed pesticide surveillance data from 2001-2007, where 103 acute illnesses were identified with fipronil exposures in 11 states. The annual number of reported cases was shown to increase over time. The findings showed that the great majority of cases demonstrated mild clinical effects or short duration, thus confirming some of the previous observations. The reported effects in this study included conjunctivitis, headache, dizziness, nausea, vomiting, abdominal pain, oropharyngeal pain, cough, sweating, sensory impairment, weakness, drowsiness, agitation and seizure.[48] Of note, pet-care products were related to more than one-third of cases and accounted for the majority of childhood cases (64%).

There are no data available for signs and symptoms of chronic or subacute poisoning or exposure. However, the study of pesticide surveillance data also suggests that with occupational exposure, there is greater likelihood of repeated exposure to higher concentrations, thereby resulting in more severe effects.[48]

Confirmation of Poisoning

The parent compound can be measured in plasma and in urine, although the test is not widely available in most hospitals. Levels reported with acute symptomatic human poisoning have been recorded as 1,600 µg/L–3,740 µg/L.[46] The levels peaked by approximately 3-4 hours following ingestion. Reported levels of the sulfone metabolite were not available.

Treatment

1. Provide supportive care, as there is no specific antidote.

N-Phenylpyrazones

COMMERCIAL PRODUCTS

Fipronil
(brand names include, but are not limited to Maxforce, Over'nOut!, Frontline, Frontline Topspot, Combat, Chipco Choice)

HIGHLIGHTS

Inhibits $GABA_A$ channels

Well absorbed by GI tract

SIGNS & SYMPTOMS

Nausea, vomiting

CNS impacts

Unconsciousness, seizures

TREATMENT

Supportive care

GI decontamination

Control seizures with benzodiazepines

Control extreme agitation with lorazepam or propofol

Neonicotinoids
HIGHLIGHTS

Introduced in U.S. market in 1990s

Large (11-15%) and growing market share

Developed by modifying nicotine

Displace ACh from nAChRs

SIGNS & SYMPTOMS

Resembles acute nicotine poisoning

Usually ingestion or inhalation

Disorientation, confusion, agitation, headache, drowsiness, dizziness, weakness, tremor, unconsciousness

GI symptoms (vomiting, sore throat, nausea, diarrhea, abdominal pain) may be from formulation solvent

Respiratory toxicity can also occur

TREATMENT

Supportive treatment

Consider GI decontamination

Control extreme agitation with lorazepam or propofol

Consider IC setting for patients with mental status changes or severe poisoning

2. Send patients with significant mental status changes to an intensive care setting. At least initially, they are better managed there.

3. Use GI decontamination within the guidelines outlined in **Chapter 3, *General Principles***. There are insufficient data on the efficacy of activated charcoal.

4. Control seizures as early as possible with benzodiazepines.[46]

5. Control extreme agitation with lorazepam or propofol.

NEONICOTINOID INSECTICIDES

Neonicotinoids are a relatively new class of insecticides, developed in the mid 1980s and introduced in the U.S. market in the early 1990s. They are quickly growing in widespread use and were recently noted to have 11%-15% U.S. market share of insecticide use.[50] They are well absorbed into plants and consequently are used in agriculture for piercing-sucking insects such as aphids and other crop-damaging insects. They are also used for flea control on domestic pets. They act fairly selectively on insects, with comparably less acute toxicity to mammals. As noted below, however, they are not free from human toxicity. Imidacloprid is the most widely used insecticide in this class, while most others have limited use in the commercial U.S. market. Reported clinical toxicity in humans is rare. However, increasing use of this insecticide and its potential toxicity among humans warrants a heightened awareness about these compounds and their toxicity.

In one report of two fatal intoxications with **imidacloprid**, the diagnosis was made post mortem by liquid chromatography/mass spectrometric quantification of insecticide. No clinical descriptions of symptoms were available, as both patients were found dead.

Toxicology

Similar to synthetic pyrethroids being derived from naturally occurring pyrethrins, **neonicotinoids** were developed by modifying nicotine. Modifications include the **nitromethylene, nitroimine** or **cyanoimine** groups, which provide better activity and stability than nicotine. They are not very effective as contact insecticides but rather derive their effectiveness by being absorbed into the plant and migrating to the growing plant tip. They then affect insects that attempt to pierce the plant.

The toxicology of the neonicotinoids and special chemistry of the selective affinity of these insecticides is discussed in great detail in two recent reviews.[50,51] They act on nicotinic acetylcholine receptors (nAChRs) by displacing acetylcholine (ACh) from the receptor. Compared to other insecticides, most notably the organophosphate class, the neonicotinoids exhibit a relatively more selective affinity towards insect nAChRs than mammalian nAChRs.[50]

The acute oral LD_{50} in rats of the neonicotinoids varies from 182 mg/kg (acetamiprid) to 2,400 mg/kg (dinotefuran). At an LD_{50} of >5,000 mg/kg, clothianidin appears to be an outlier of this group.[50] While all neonicotinoids appear to selectively target insect nAChRs, imidacloprid and others that specifically contain the nitroimine group − thiamethoxam, clothianidin and dinotefuran − have a significantly higher affinity for the insect target site.[51] Of this subgroup, imidacloprid has the lowest rat LD_{50} and by far the highest market share. Thiamethoxam on the other hand, while having a high LD_{50}, has a much lower NOAEL than imidacloprid and is considered a likely human carcinogen.[50]

Neonicotinoids
COMMERCIAL PRODUCTS

acetamiprid

clothianidin

dinotefuran

imidacloprid
(brand names include, but are not limited to Merit, Admire, Provado, Gaucho, Imicide, Premise, Advantage),

thiacloprid

thiamethoxam

Mammalian toxicity is thought to be centrally mediated. Toxic effects are similar to that of nicotine. Vertebrate alpha-4-Beta-2 nAChRs are the primary target. Prolonged or chronic exposures will up-regulate the receptors without changing receptor affinity. Perhaps most notably, the neonicotinoids also have some responses outside the target nAChRs. Following binding to the nAChR, the protein kinase cascade may be activated, which could decrease neurologic functions. Some also have an analgesic effect similar to that of nicotine.[50]

In vitro studies of human intestinal cells find that imidacloprid is well absorbed. These pesticides are relatively highly soluble in water, and most are excreted unchanged by the kidney. Most do undergo significant metabolism in insects, and the same occurs in mammals. However, the process in mammals is slow and likely an insignificant part of their elimination process in humans. One notable metabolic process of imidacloprid is reduction by the P450 system in humans to a nitroso derivative. In animal studies conducted in mice this metabolic byproduct enters the brain.[52] It is not known whether this byproduct or the active ingredient may be responsible for toxic effects.[50]

Signs and Symptoms of Poisoning

Human data are currently limited to several reports of clinical poisoning, at least some of which have led to death, as confirmed by autopsy.[53,54,55,56] Toxic effects bear some resemblance to those of acute nicotine poisoning except for GI corrosive injuries, which may be related to solvent effects.[52] Human poisoning appears most likely following ingestion or inhalation. Most clinical effects are based on excessive nicotinic stimulation. Patients have presented with disorientation, confusion and agitation − severe enough to require sedation − headache, drowsiness, dizziness, weakness, tremor and, in some situations, loss of consciousness.[53,54,55] No seizures have been reported, and chronic residual neuropsychiatric effects have not been studied.

In a series of 68 patients, gastrointestinal effects following oral ingestion of an imidacloprid formulation were the most commonly reported and included vomiting, sore throat, nausea, diarrhea and abdominal pain.[57] Following ingestion, ulceration was noted in the posterior pharynx, esophagus and stomach. It was not clear if the effects were due to the toxicity of the active ingredient or the accompanying solvent. There is evidence that a solvent found in some formulations, N-methyl pyrrolide (NMP), has a severe irritant effect.[56] This emphasizes the importance of identifying and understanding the effects of inert ingredients in any pesticide exposure. Unfortunately, identification of such ingredients is usually difficult as they are not disclosed on the label and it is necessary to contact the formulator directly to determine which inert ingredients are in the formulation.

Toxicity to the respiratory system can also occur. Signs and symptoms include labored breathing, chest tightness, dyspnea, hypoxia and aspiration pneumonia. In severe cases, respiratory failure has ensued, requiring mechanical ventilation.[57,58,59]

Rhabdomyolysis may occur in severe poisoning; with creatine phosphokinase levels being reported as high as 1,200 U/L. Renal function and serum electrolytes were normal in this case. Patients will usually present with tachycardia due to nicotinic receptor over-stimulation of the autonomic nervous system.[53]

Cardiovascular effects include tachycardia, bradycardia, hypertension, hypotension and palpitations.[55] One case of fatal arrhythmia has been reported in which the patient presented within hours of ingesting 200 mL of imidacloprid. She initially had sinus tachycardia that rapidly progressed to ventricular tachycardia and subsequently ventricular fibrillation. At the time of presentation, this patient was noted to have a normal cardiac enzyme panel. Primary coronary artery disease could not be completely ruled out because of several coronary risk factors.[55]

Confirmation of Poisoning

Imidacloprid can be detected by liquid chromatography/mass spectroscopy, which was used to identify the cause of death in two patients found dead with no obvious initial cause.[60] However, the test is not widely available, and there are insufficient data on toxic levels to predict severity of toxicity.

Treatment

1. Provide supportive treatment, as there is no specific antidote for neonicotinoid poisoning. Patients with significant mental status changes should ideally be managed in the intensive care setting, at least initially.
2. Use GI decontamination within the guidelines previously outlined in **Chapter 3, *General Principles***.
3. Control extreme agitation with lorazepam or propofol.
4. Consider cardiac monitoring, especially in patients with risk factors for coronary artery disease.
5. In a severe poisoning, send patient to an intensive care setting for respiratory support.

PROPARGITE

Formulations are wettable powders and emulsifiable concentrates. Propargite is an acaricide with residual action.

Toxicology

Propargite exhibits very little systemic toxicity in animals. No systemic poisonings have been reported in humans. However, many workers having dermal contact with this acaricide, especially during the summer months, have experienced skin irritation and some have had documented positive skin testing.[61,62] Eye irritation has also occurred.[61] For this reason, stringent measures should be taken to prevent inhalation or any skin or eye contamination by propargite. Epidemiological studies have related this pesticide to an increased risk for cancer.[63,64] This is discussed in **Chapter 21**, ***Chronic Effects***.

Confirmation of Poisoning

There is no readily available method for detecting absorption of propargite.

Treatment

1. Decontaminate the skin with soap and water as outlined in **Chapter 3, *General Principles***. Treat eye contamination by irrigating exposed eyes with copious amounts of clean water or saline for at least 15 minutes. Remove contact lenses, if present, prior to irrigation. If irritation persists after irrigation, specialized medical treatment in a healthcare facility should be obtained. Sensitization reactions may require steroid therapy.
2. If large amounts of propargite have been ingested and the patient is seen within an hour, consider gastrointestinal decontamination as discussed in **Chapter 3**.

SULFUR

Elemental sulfur is an acaricide and fungicide widely used on orchard, ornamental, vineyard, vegetable, grain and other crops. It is prepared as dust in various particle sizes and applied as such, or 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.[68] 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.[69]

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

Treatment

1. Remove skin contamination by washing with soap and water as outlined in **Chapter 3, *General Principles***. Treat contamination of the eyes by irrigating exposed eyes with clean saline or water for at least 15 minutes. If present, remove contact lenses prior to irrigation. If eye irritation persists after irrigation, obtain specialized treatment in a healthcare facility.

2. Unless an extraordinary amount of sulfur (several grams) has been ingested shortly prior to treatment, there is probably no need for gastrointestinal decontamination. Absorbability of sulfur on activated charcoal has not been tested.

3. Administer oral or intravenous glucose and/or electrolyte solutions as appropriate if diarrhea is severe. The most serious consequence of sulfur ingestion is likely to be that of catharsis, resulting in dehydration and electrolyte depletion, particularly in children.

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COMMERCIAL PRODUCTS

Many commercial products are produced by many manufacturers. It is one of the agents approved by USDA for use by organic growers.

HIGHLIGHTS

Widely used organic acaricide/fungicide

SIGNS & SYMPTOMS

Skin/eye/respiratory irritant

TREATMENT

Decontaminate skin and eyes

Oral or IV glucose/ electrolytes if diarrhea is severe

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