

Toxicology

**All substances are
poisonous; there is none
that is not a poison. The
right dose differentiates
a Poison and a Remedy**

Philippus Aureolus Theophrastus
Bombastus von Hohenheim

“Paracelsus” 1493 – 1541



PESTICIDES

Definition: Agents (Physical, chemical or biological) designed to kill pests that interfere with the comfort, health or economic well-being of man animal alike. Recorded use of compounds in the control of pests goes back to 1000 BC, when sulfur was used for such purpose.

Groups of Pesticides

Insecticides, Herbicides, Fungicides, Rodenticides, and Others (more effective and safe)

Based on production: Herbicides > Insecticides > Fungicides > Rodenticides > others.

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HERBICIDES: Pages 50 – 59

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Rodenticides – Historical Development

Year	Pesticides
1000 BC	Sulfur used by Greeks
900	Arsenicals used by Chinese
1763	Nicotine as crude tobacco used as insecticide
Pre 1800	Arsenic/Lead
1800's	First use of Pyrethrins in Asia First use of retinoids
Early 1900s	Thallium sulfate/Phosphorus
Late 1940s	Fluroacetacetate (1080)/ANTU/Dicoumarol/Warfarin
Early 1950s	Diphacinone/Norbromide
1850s (early post)	Strychnine/Ricin
1939	Inscticidal property of DDT discovered – P Muller
1940-50	Development of Organochlorine insecticides
1944	Parathion synthesis
1950's	Development of carbamate insecticides
1963	First formamidine pesticide synthesis - Chlordimeform
1970's	Modern Pyrethroids development.
1976	Pyriminil (vacor)/Brodifacoum
Pre 2000	Cholecalciferol/Bromethalin

Since then there have been continued development of more effective pesticides. Currently in use today are > 600 pesticides, constituting 15,000 compounds in 3,500 formulations.

RODENTICIDES

Widely used by pest control operators and the public.

One of the most common causes of animal poisoning, with the majority attributable to anticoagulant baits.

Relative incidence rates: Dogs > cats > livestock > horses

Generally non-selective.

Secondary poisoning or relay toxicity may occur with some rodenticides (e.g., fluoroacetate and strychnine).

SOME COMMON RODENTICIDES

Anticoagulants (Warfarin and second generation compounds)

Cholecalciferol

Bromethalin

Strychnine

1080

Thallium

ANTU

Zinc Phosphide

COMMON CLINICAL SIGNS (PRESENT [+] OR ABSENT [-]) ASSOCIATED WITH RODENTICIDE POISONING IN COMPANION ANIMALS

Clinical Sign	Anticoagulant	Cholecalciferol	Bromethalin	Strychnine
Seizures	rare	rare	+	+
Hypercalcemia	-	+	-	-
Hemorrhage	+	+	-	-
Coagulopathy	+	-	-	-
Paralysis	rare	-	+	-
Onset	Delayed	Delayed	Delayed	Acute

Clinical Sign	1080	Thallium	ANTU	Zinc phosphide
Seizures	+	rare	-	+
Pulmonary edema	-	-	+	+
Skin lesions	-	+	-	-
Liver ± renal involvement	-	+	-	+
Onset	Acute	Acute to chronic	Acute	Acute

Anticoagulant Rodenticides

Source and Chemistry

Numerous types of anticoagulant rodenticides. All share a common mechanism of action. Anticoagulants are also classified as either first- or second- generation by their ability to kill warfarin-resistant rodents.

First-generation anticoagulants:

Warfarin (Final® and others). Warfarin was the first marketed anticoagulant and therefore became the best known and most widely used. Relatively limited sales today, due to the availability of more potent anticoagulants and the emergence of warfarin-resistant rodents (**3-(alpha-acetylbenzyl)-4-hydroxycoumarin**).

Pindone (Pival®, Pivalyn®, others). Pindone is also one of the early anticoagulants which is still available for use in commensal rodent control.
(**2-pivalyl-1, 3-indandione**)

Chlorophacinone (Drat®, Mouse Out®, RoZol®, others) Diphacinone (RoKill®, Ramik®, Ditrac®, others). Chlorophacinone and diphacinone are similar in potency and are significantly more toxic than the anticoagulant compounds developed earlier. Consequently, they are formulated at lower concentrations.

Second-generation anticoagulants:

Brodifacoum (d-Con Mouse Prufe II®, Enforcer®, Talon®, Havoc®, others). **Brodifacoum** is the most potent rodenticide currently available for commensal rodents. It is available in **0.005% pellet formulations and in wax blocks**. A related rodenticide is **Difenacoum** which is registered by the US EPA but appears to be used more widely in Europe.

3-[3-(4'bromo[1,1'-biphenyl]-4-yl)-1,2,3,4,-tetrahydro-1-naphalenyl]-4-hydroxy-2H-1-benzophyran-2-one

Bromadiolone (Just One Bite®, Rat Arrest®, Maki®, Contrac®, others). It is available in 0.005% pellet formulations and in wax blocks.

Difethialone (Generation®, D-cease®, Hombre®). This is a newer antiticoagulant in the market. **Limited information available on its toxicity.** It appears to be as toxic or may be slightly more toxic than brodifacoum.

Absorption, Distribution, Metabolism, and Excretion

- 1) GI absorption is generally high (> 90%)
- 2) Highly (> 95%) protein bound (albumin)
- 3) Liver metabolism
- 4) Renal excretion
- 5) Plasma $T_{1/2}$ 20-24h in dog (warfarin). Longer $T_{1/2}$ with other second generation anticoagulant rodenticides (e.g., mean $T_{1/2}$ of 6 +/- 4h in dogs).

Toxicity:

Potential hazard to all species of mammals and birds.

Chronic low level exposures also result in the development of toxicity.

Animals that may be more susceptible to the development of toxicity include Hypo-prothrombinemic juveniles, and patients with deficient clotting factor production due to liver failure or gastrointestinal malabsorption syndromes.

Concurrent administration of highly protein bound drugs (e.g., phenylbutazone, aspirin) or other disease states (e.g., chronic renal disease) may also predispose the patient to the development of toxicity.

Risk of relay toxicity is considered moderate to high with second generation anticoagulants.

Toxicity of Common Anticoagulant Rodenticides

Species	Agent	Single dose (mg/kg)	Multiple doses
Cat	Warfarin	5-50	1 mg/kg, 5 days
	Diphacinone	15	
	Brodifacoum	25	
Dog	Warfarin	5-50	5 mg/kg, 5 - 15 days
	Diphacinone	3	
	Brodifacoum	0.25-3.6	
Pig	Warfarin	3	0.05 mg/kg, 7 days
	Diphacinone	150	
	Brodifacoum	0.5-2.0	

Mechanism of Action:

Interfere with the **vitamin K epoxide reductase** enzyme. This enzyme is required for the reversion of **inactive vitamin K₁ to its active quinone form**. Ultimately results in **decreased vitamin K- dependent clotting factor (factors II, VII, IX, X) levels and vitamin K₁ itself**.

Pesticides – Anticoagulant Rodenticides

Clotting Factors	T1/2
11	41h
V11	6.2h**
1X	13.9h
X	16.5h

** Diagnostic

Clinical Signs:

Hemorrhaging in K-dependent coagulation factors occur at rates that approximate the coagulation factors half-lives (e.g., 6 - 41h; dog).

Slows the extrinsic/intrinsic, and common clotting pathways.

The severity and duration of the resultant coagulopathy is primarily dependent upon the specific anticoagulant ingested. **Warfarin anticoagulant rodenticides will depress clotting factor amounts for 7-10 days while chlorophacinone, diphacinone, and brodifacoum and other second generation products depress activity for 3-4 weeks.**

Animals remain asymptomatic until depletion of active clotting factors occurs, therefore **clinical signs generally do not develop until 1-2 days post ingestion.**

Common clinical signs include depression, vomiting, anorexia, ataxia, diarrhea, hemorrhage, melena, weakness and dyspnea. Many cases of anticoagulant poisoning are subacute in nature, and animals may be presented with pale mucous membranes, anemia, dyspnea, weakness, hematemesis, epistaxis, or bloody feces. Other clinical signs may include hemorrhage into body cavities, hematuria, scleral or subconjunctival hemorrhage, bruising or external bleeding, and shock. Sudden deaths may occur as the result of hemorrhage into the pericardium, thorax, mediastinum, abdomen or cranium.

Diagnosis:

Depends upon a history of exposure, development of compatible clinical signs, and laboratory confirmation. Specimens obtained at postmortem for detection of anticoagulants should include stomach contents, liver or unclotted blood (the preferred specimen), and kidney.

A positive therapeutic response to vitamin K₁ therapy may be supportive.

Clinical Pathology:

Decreased packed cell volume (PCV)

Prolonged bleeding from venipuncture or injection sites, delayed whole blood clotting time (WBCT), increased activated clotting times (ACT, often elevated 2-10-fold), as well as prolonged activated prothrombin time (PT, often elevated 2-6-fold), one-stage prothrombin time (OSPT), or activated partial thromboplastin (APTT, often elevated 2-4-fold) time. Since factor VII has the shortest half-life (6.2 hours), the use of the PT test is the most sensitive tool in early diagnosis. The measurement of PT times at 1 and 3 days after exposure is therefore recommended to monitor an animal for the development of a coagulopathy.

Platelet count: normal or marginally low. Fibrin degradation products: normal.

Elevated levels of the carboxylated forms of the vitamin K dependent coagulation factors (PIVKA)

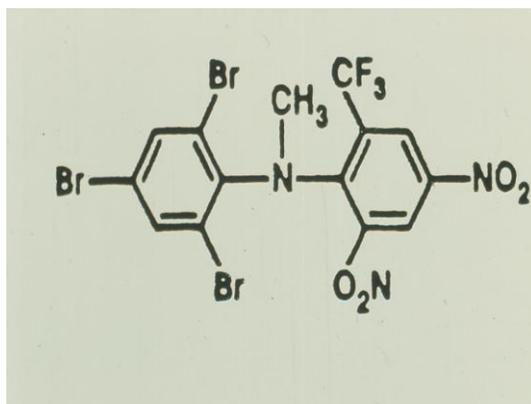
Treatment:

Vitamin K₁ (phytonadione). Vitamin K₁ requires 6-12 hours for effect. Vitamin K₁ may be administered by the intravenous (IV - may result in anaphylactoid reactions), intramuscular (IM - may aggravate hemorrhage), subcutaneous (SC - may see slow absorption), or oral routes (PO), oral dosing is preferred. Occasionally animals may require more extended therapy duration (e.g., additional 2-4 weeks).

Vitamin K₁ Therapy (Dogs, cats, pigs)		
Rodenticide	Dose (mg/kg)	Duration
Warfarin	1-2	10-14 d
Fumarin, pindone, valone	1-2	4-6 d
Diphacinone, Chlorphacinone, Bromadiolone	3-5	3-4 wk
Brodifacoum	3-5	3-4 wk

Transfusion of whole blood or fresh plasma (if not anemic). In all cases of significant exposures to an anticoagulant, follow-up determinations of PT times at 2-3 days after cessation of vitamin K therapy would be indicated.

Bromethalin



Source and Chemistry:

Bromethalin is a single-dose rodenticide that causes central nervous system depression and paralysis, leading to death in 2 to 4 days. Trade names include Vengeance[®], Assault[®], Trounce[®], and others. Bromethalin-based rodenticides are pelleted (often tan colored) grain-based products that contain 0.75 - 1.5 ounces (21 - 42 gram) of bait in paper "place pack" envelopes.

Chemical name: N-methyl-2,4-dinitro-N-(2,4,6-tribromophenyl)-6-(trifluoromethyl) benzenamine

Toxicity:

Reported LD₅₀s for technical grade bromethalin include: 1.8 mg/kg in the cat, 4.7 mg/kg in the dog, 13 mg/kg in rabbits, and > 500 mg/kg in the guinea pigs.

Minimum toxic doses of bromethalin baits: 1.67 grams/kg (dog) and 0.30 grams/kg (cat).

Minimal lethal doses of bromethalin baits are 2.5 grams/kg (dog) and 0.45 grams/kg (cat).

Bromethalin-based baits acute oral LD₅₀s are 3.65 grams/kg (dog) and 1.1 grams/kg (cat).

Relay (secondary) toxicity may occur.

Mechanism of Action:

Courtesy of Prof. Cecil Brownie

Bromethalin uncouples oxidative phosphorylation resulting in a lack of adequate ATP concentrations, so that insufficient energy is available for Na⁺ - K⁺ ion channel pumps resulting in the development of cerebral edema.

Absorption, Distribution, Metabolism, and Excretion:

Rapidly absorbed from the gastrointestinal tract, with peak plasma concentrations occurring ~ 4-hr after ingestion.

Excretion however, is slow and a plasma half-life of 5.6 days has been reported.

Bromethalin is N-demethylated by the liver to a more toxic metabolite (desmethylbromethalin).

Clinical Signs:

Animals that ingest oral doses of bromethalin at or above the LD₅₀ generally develop clinical signs within 24 hours. Bromethalin ingestion at these higher oral doses often produces an acute syndrome that is characterized by severe muscle tremors, hyperthermia, extreme hyper-excitability, and focal motor and generalized seizures.

Lower oral dose of bromethalin (less than an LD₅₀ of bait) produces a toxic syndrome with a slower onset of clinical signs (e.g., 24 - 86 hours). This syndrome is characterized by the development of hindlimb ataxia and/or paresis and/or central nervous system depression, extensor rigidity, and opisthotonus, anisocoria, seizures, tremors, coma, and mydriasis.

Diagnosis:

The diagnosis of bromethalin poisoning is dependent upon the presence of an exposure history to a potentially toxic dose of a bromethalin-based rodenticide and the subsequent development of appropriate clinical signs within an appropriate time-frame.

Chemical confirmation of bromethalin residues is not widely available, and may have limited clinical utility in cases in which a delay in presentation (i.e., the chronic syndrome) occurs.

Treatment:

Prevention of absorption in recently poisoned animals with emetics, repeated administrations of activated charcoal, and saline or osmotic cathartics. Dexamethasone and osmotic diuretics have been reported to be effective.

Cholecalciferol



Source and Chemistry

Cholecalciferol (Vitamin D₃, 9, 10-Seocholesta-5,7,10(19)-trein-3 betaol) rodenticides have been marketed under the brand names Quintox[®], Rampage[®], Ortho Rat-B-Gone[®], and Ortho Mouse-B-Gone[®]. Baits typically contain 0.075% cholecalciferol.

Ingestion of **antipsoriasis** creams containing **calcipotriol**, a congener of **1, 25-dihydroxyvitamin D₃** has become a common source of vitamin D toxicosis in **dogs**. Ingestion of other types of vitamin D-containing medications is also a potential source of exposure.

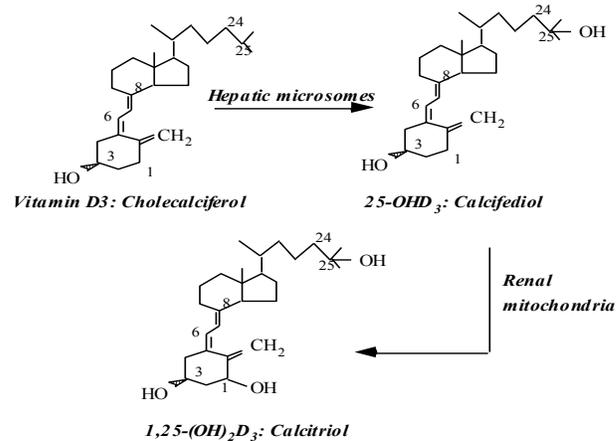
Toxicity:

An acute oral LD₅₀ of cholecalciferol as the 100% technical material in dogs was reported to be 88 mg/kg body weight.

A rodenticide bait was lethal to dogs experimentally at an oral dose of 10 mg of cholecalciferol/kg body weight. Toxicity in dogs following the ingestion of 1 gram of bait per pound body weight (2 mg cholecalciferol/kg body weight) have been reported. Note that 2mg cholecalciferol/kg body weight = 80,000 U/kg body weight. Animals with preexisting kidney disease may be predisposed to toxicity.

Metabolism:

Cholecalciferol is fat soluble and is absorbed through chylomicrons into the lymphatic system. Cholecalciferol is metabolized by the liver to 25-hydroxycholecalciferol (25-OH-D₃), which is the major circulating metabolite during vitamin D excess. Further metabolism of 25-OH-D₃ occurs in the kidney where calcitriol (1,25-(OH)₂-D₃) is produced. Cholecalciferol and 25-hydroxycholecalciferol have limited biological activity; calcitriol is the most potent cholecalciferol metabolite in terms of enhancing bone resorption and intestinal calcium transport.



Mechanism of Action:

Cholecalciferol and other vitamin D metabolites increase intestinal absorption of calcium, stimulate bone resorption, and increase the renal tubular reabsorption of calcium.

Clinical Signs:

The most common clinical signs include vomiting, depression, anorexia, polydipsia, polyuria and diarrhea. Gastrointestinal and pulmonary hemorrhage sometimes occur as an apparent result of dystrophic calcification, and should not lead to a misdiagnosis of anticoagulant rodenticide toxicity.

Courtesy of Prof. Cecil Brownie

Clinical signs generally develop within 12-36 hours of ingestion of cholecalciferol.

Clinical Pathology:

Hypercalcemia (serum calcium > 12 mg/dl), and associated dystrophic calcification.

Hyperproteinemia, hyperphosphatemia and azotemia can occur.

Urinalyses may reveal hyposthenuria (U_{spg} 1.001-1.007), proteinuria, and glucosuria. Urine sediment examination occasionally reveals leukocytes, erythrocytes, and casts in variable numbers; metabolic acidosis.

Pathology:

Gross lesions in dogs poisoned with cholecalciferol based rodenticides may include diffuse hemorrhage in the gastric mucosa, duodenum, and jejunum.

Microscopic lesions may include necrosis and mineralization of the myocardium and of the arterial intima.

Mineralization of glomerular capillary walls, renal cortical tubular basement membranes, Bowman's capsules, and stomach has been described.

Diagnosis:

The diagnosis of a cholecalciferol rodenticide poisoning depends upon a history of a potentially toxic level of exposure, appropriate clinical signs, and the development of hypercalcemia.

Hyperphosphatemia and hypercalcemia tend to develop within 12 and 24 hours, respectively, after the ingestion of a cholecalciferol based rodenticide.

Mineralization may be appreciated radiographically.

Elevated serum concentrations of cholecalciferol and its primary metabolites, 25-hydroxycholecalciferol, 24,25-dihydroxy-cholecalciferol and/or 1,25-dihydroxycholecalciferol, may also support a diagnosis.

Total kidney calcium concentrations may be elevated when compared to normal animals.

Baseline serum calcium determinations are recommended for all cases of potentially toxic ingestion. These serve as basis for comparison with subsequent time points. The initial calcium values obtained are likely to be within the normal range (even when potentially lethal doses are consumed) for up to several hours after ingestion.

Treatment:

Treatment goals include –

- 1). Detoxification of the gastrointestinal tract to decrease cholecalciferol absorption via administration of an emetic and activated charcoal with a saline or osmotic cathartic
- 2). Correcting fluid and electrolyte imbalances.
- 3). Initiation of specific therapies that will prevent or reduce the hypercalcemic state:
 - Calciuresis with IV 0.9 % sodium chloride
 - Furosemide at 2-5 mg/kg every 8-12 hours
 - Oral prednisone at 2 mg/kg every 12 hours
 - Salmon calcitonin sq at 4-6 IU/kg every 2 to 3 hours until serum calcium levels stabilize
- 4). Rarely, seizure control, treatment of arrhythmias, and other symptomatic therapies may be required.

Following significant exposures, serum calcium and BUN should be determined at 1, 2, and 3 day's post-exposure. If hypercalcemia (serum calcium > 12 mg/dl) is present or the animal is symptomatic, then further diuresis and additional therapies may be indicated.

Vitamin D-induced hypercalcemia often persists for several weeks requiring long term management.

After the serum calcium is stabilized within the normal range, maintenance therapy consisting of furosemide orally at 2-4.5 mg/kg every 8-12 hour and oral prednisone at 2 mg/kg every 12 hour.

Calcitonin is the recommended drug for treatment of cholecalciferol-induced hypercalcemia. Calcitonin by itself is ineffective for treatment of cholecalciferol-induced hypercalcemia and is always accompanied by aggressive fluid, diuretic, and corticosteroid administration. The half-life of calcitonin is short (3 to 4 hours); therefore, multiple daily injections must be given for 2 to 3 weeks to maintain blood calcium levels within the physiologic range. Prolonged calcitonin administration is associated with undesirable adverse effects including vomiting and anorexia. Decreased responsiveness has also been reported in humans.

Pamidronate is a potentially useful antidote against cholecalciferol toxicity in dogs. Pamidronate (aminohydroxy-propylidene biphosphonate) and clodronate are bisphosphonates - a new class of inhibitors of bone resorption. In a recent experimental

study (Rumbeiha et al., AJVR 61: 9-13, 2000), cholecalciferol-poisoned Beagle dogs were treated at 1 and 4 days after cholecalciferol ingestion with intravenous infusions of either 1.3 mg or 2.0 mg of pamidronate/kg in 0.9% saline (150 ml total volume given during a 2-hr period). Treated dogs demonstrated decreased serum calcium levels and improved renal function when compared to animals given saline alone.

Strychnine

Source and Chemistry

Strychnine is a colorless crystal or white bitter tasting indole alkaloid powder extracted from the seeds of the plants *Strychnos nux-vomica* and *Strychnos ignatii*. Strychnine was first used in medicine (e.g., *Nux vomica*) and as an animal poison since the sixteenth century.

Pesticidal applications: rat control.

Many commercially available baits are pelleted and are dyed either bright green or red.

Preparations containing less than 0.5% strychnine are approved for subsoil use against burrowing rodents (restricted use pesticide).

Continues to remain as a potential cause of toxicosis particularly in dogs.

Absorption, Distribution, Metabolism, and Excretion:

Oral exposure is common and vomiting often does not occur, stomach contents may contain high levels of strychnine. Strychnine appears to be readily absorbed from the intestinal tract

Excretion is accomplished in urine (5-20% unchanged) and through secretion into the stomach.

Strychnine is ionized in acidic media ($pK_1 = 6.0$, $pK_2 = 11.7$). Therefore, strychnine should be highly ionized in the stomach and not readily absorbed. Ion trapping of strychnine occurs in the acid conditions of the stomach and urinary excretion may be enhanced by acidification of the urine.

Highest concentrations of strychnine are found in blood, liver and kidney.

Hepatic microsomal enzymes metabolize strychnine.

Mechanism of Action:

Strychnine reversibly antagonizes the action of glycine in the spinal cord and medulla. Net effect is reduced action of inhibitory postsynaptic neurons.

The physiologic effect of strychnine is uncontrolled reflex activity. All striated muscle groups are affected, but the relatively more powerful extensors predominate to produce symmetrical and generalized rigidity and tonic seizures. Sublethal convulsant doses of strychnine may elevate blood pressure, heart rate and right ventricular pressure in dogs.

Toxicity:

Strychnine is a highly toxic compound to most domestic animals.

Species	Approximate oral lethal dose
Bovine	0.5 mg/kg
Equine	0.5 mg/kg
Porcine	0.5-1.0 mg/kg
Canine	0.75 mg/kg
Feline	2.0 mg/kg
Fowl	5.0 mg/kg
Rat	3.0 mg/kg

Relay (secondary) toxicity may occur.

Clinical Signs:

Clinical signs of strychnine poisoning appear within ten minutes to two hours after ingestion of the poison.

Early signs: apprehension, nervousness, tenseness, and stiffness.

Violent tetanic seizures may appear spontaneously or be initiated by stimuli such as touch, sound, or a sudden bright light.

There is extreme and overpowering extensor rigidity causing the animal to assume a "saw horse" stance. The legs and body are stiff, the neck arched, ears erect, and the lips are pulled back from the teeth. Duration of a tetanic convulsion may vary from a few seconds to a minute or more. Intermittent periods of relaxation are observed but become less frequent.

Convulsive seizures become more frequent and death eventually occurs from exhaustion or anoxia during a tetanic seizure. The entire syndrome, if untreated, is often less than 1 to 2 hr.

Pathology:

Rigor mortis occurs rapidly after death.

Courtesy of Prof. Cecil Brownie

No gross or microscopic lesions (e.g., neurons, axons, or myelin sheath) characteristic of strychnine poisoning can be consistently detected.

Diagnosis:

Tentative diagnosis is usually based on history of ingestion, characteristic clinical signs, and lack of lesions.

Characteristically, the stomach of strychnine-poisoned animals is filled with food or bait that has not been completely digested.

Samples for analysis should include stomach contents, liver, kidney, urine, and central nervous system. In addition, bait or vomitus should be kept for analysis. Most chemical confirmations of strychnine poisoning are from stomach contents or liver. Concentrations of strychnine in dogs dying of acute poisoning ranged from 0 to 52 ppm in liver and from 0 to 12,800 ppm in stomach contents.

Treatment:

Of prime concern in strychnine poisoning is prevention of asphyxia.

Morphine should be avoided, due to possibility of respiratory depression.

Ketamine should also be avoided, since it has motor stimulant effects in the brain.

Oral detoxification: Induce vomiting (e.g., apomorphine) if animals are not hyperesthetic or convulsive.

Activated charcoal very effective (pretreatment with diazepam may be required).

In anesthetized animals, gastric lavage could be used.

Forced diuresis (5 % mannitol in 0.9 % sodium chloride administered at the rate of 6.6 ml/kg/hour) and acidification of the urine with ammonium chloride (132 mg/kg, PO) may enhance excretion of strychnine. Forced diuresis with acidification has had limited benefit in many cases.

Facilities for positive pressure pulmonary ventilation, oxygen administration, and warm quiet conditions should be readily available.

Control seizures *e.g.*, diazepam (2-5 mg/kg, IV) is the drug of choice although pentobarbital may be required.

Resolution of signs generally occurs within 1-2 days

Zinc Phosphide

Source:

Zinc phosphide (Zn_3P_2) has been available commercially for rodent control since 1930.

Zinc phosphide, or occasionally aluminum phosphide, is employed in baits of bread, bran mash, soaked wheat, damp rolled oats, or sugar at concentrations of from 2 to 5 percent.

Zinc phosphide is a dull, grayish black powder, insoluble in water and having a faint acetylene odor in atmospheric air.

Toxicity:

Most animals and poultry can be poisoned by 40 mg/kg depending upon the pH in the stomach.

Oral LD_{50} of zinc phosphide in rats is 40.5 mg/kg body weight.

A dose of 40 mg/kg zinc phosphide administered to a dog by gelatin capsule induced onset of convulsive seizures seven hours after administration, and the animal expired within thirty minutes after the onset of convulsions. Dogs fed zinc phosphide in amounts of 300 mg/kg can survive if the toxicant is given on an empty stomach. Feeding dogs a normal ration stimulates gastric HCl secretion and greatly increases their susceptibility to zinc phosphide.

Some commercial products contain tartar emetic to stimulate vomiting as a protective measure in non-target species. Zinc phosphide itself has a strong tendency to induce emesis in nonrodent animals, and it does not consistently cause fatal poisoning when accidentally ingested.

Mechanism of Action:

Liberates phosphine gas upon acid hydrolysis in the stomach.

CNS effects are due to an unknown mechanism of action.

Clinical Signs:

Onset of poisoning is rapid, usually within fifteen minutes to four hours after ingestion of a toxic amount of zinc phosphide. Death from large doses is usually within three to five hours, and animals rarely survive longer than 24-48 hr. In some instances onset of clinical signs may be delayed as long as 12-18 hr after ingestion.

Early signs: anorexia, lethargy, vomiting, tachypnea, and abdominal pain. Ataxia, weakness, and recumbency follow. There may be terminal hypoxia, gasping for breath, and struggling. Also, hyperesthesia, "running fits," and seizures can be seen. Metabolic acidosis can occur.

Pulmonary edema. Liver and/or kidney failure may occur.

Pathology:

There is marked congestion of the lungs and interlobular edema in some cases. Pleural effusion and sub-pleural hemorrhages may be seen. Myocardial degeneration may occur.

The liver and kidney are extremely congested in acute cases. Renal tubular degeneration, hyaline change, and necrosis may occur, gastritis. The freshly opened stomach has a characteristic odor of acetylene.

Diagnosis:

History of exposure to zinc phosphide, accompanied by rapid death characterized by dyspnea, vomiting, pulmonary edema, and visceral congestion suggests zinc phosphide poisoning.

Chemical detection of zinc phosphide in stomach contents or gastric lavage is possible.

Zinc levels in blood, liver, and kidney may be elevated.

Treatment:

Correct acidosis and hypocalcemia

If detected early, emesis should be induced. Activated charcoal.

Breakdown of zinc phosphide to phosphine may be retarded by gastric lavage with aluminum or magnesium hydroxide gel.

MINOR RODENTICIDES

Alpha—Naphthyl Thiourea (ANTU)

Alpha-naphthyl thiourea (ANTU) is used exclusively as a rodenticide.

Rodents are very susceptible to ANTU toxicity (rat oral LD₅₀ 6-7 mg/kg).

Dogs, cats, and swine are the most susceptible domestic animals. Mature and aged dogs are more susceptible than young ones. The single oral lethal dose in the mature dog is recorded to be between 10 and 50 mg/kg body weight. In young dogs the single lethal dose is 85-100 mg/kg.

ANTU causes pulmonary edema.

Treatment

Symptomatic and supportive.

Phosphorus

Phosphorus is used little today because better, safer rodenticides are available. The characteristic odor is described as garlic-like.

Lethal dose in most species 1-2 mg/kg.

Clinical Signs:

Phase I: Initial signs occur within hours of ingestion and characterized by gastrointestinal, abdominal and circulatory signs: vomiting ± blood, cardiac arrhythmias, no diarrhea, shock cyanosis, incoordination and coma may develop with death occurring before the second and third phases appear.

Phase II: an interim or latent phase (1-3 days after ingestion) in which apparent recovery occurs.

Phase III: recurrence of severe clinical signs characterized by vomiting and occasionally hematemesis, icterus and hepatic failure and central nervous system dysfunction. Hypoprothrombinemia and a tendency to bleeding especially from gingiva, stomach, intestine or kidney. Hypoglycemia may be severe and liver enzymes are elevated. Oliguria can develop attended by a rise in blood urea nitrogen and other parameters associated with renal tubular damage. Urinalysis

Courtesy of Prof. Cecil Brownie

reveals albuminuria, hematuria and increased concentrations of amino acids. Phosphorus content of the blood is generally normal.

Treatment:

Symptomatic and supportive.

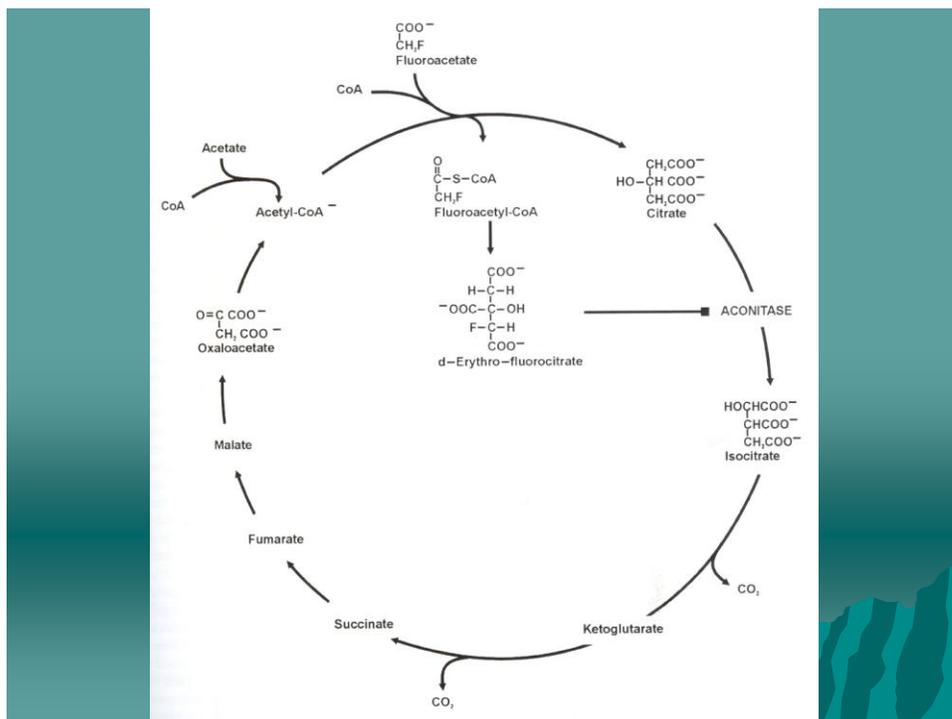
Sodium Monofluoroacetate (compound 1080)

Sources:

The primary use of fluoroacetate is to control predators. In the United States, fluoroacetate compounds are mixed with a black dye (nigrosine) and are available only to licensed exterminators.

Dogs are very susceptible and as little as 0.05 mg/kg may be lethal.

Undergoes synthesis to fluorocitrate which then acts to inhibit the enzyme aconitase in the Krebs or tricarboxylic acid cycle resulting in a buildup of citrate and inhibition of cellular respiration.



Convulsions may be prominent or cardiac effects may be dominant. In all species there is a characteristic latent period of from 0.5-2h after ingestion of 1080. When signs commence, the onset is acute and the course rapid and usually violent.

Treatment:

Symptomatic and supportive (Decontaminate the GI tract and seizure control).

Thallium

Pesticide use prohibited since 1965.

The LD₅₀ for most species is in the range of 10-15 mg/kg.

Thallium will accumulate in the body ---> chronic toxicity.

Rapidly absorbed from the GI tract.

Excreted both in the urine and in the feces but is only slowly removed from the body.

Interferes with oxidative phosphorylation.

Clinical Signs:

Acute Form: 1-4 days of ingestion: severe gastric irritation, vomiting, severe hemorrhagic diarrhea, abdominal pain and anorexia. Lingual ulcers have been reported in cats. In the acute form the dog or cat may die from the severe gastritis, depression and renal damage within three to six days. In the acute form motor paralysis and trembling may occur.

Sub-acute Form: 2-7 days of ingestion: mild gastric distress with prominent skin changes. There is a reddening of the skin and early pustular formation. This usually begins on the ears and nose and then will proceed to involve the axillary region, ventral abdomen and torso. Marked reddening of the oral membranes and to a lesser extent the skin.

Chronic Form: 7-10 days of ingestion: loss of hair and the drying and scaling of the skin.

Courtesy of Prof. Cecil Brownie

Pathology:

Severe hemorrhagic gastroenteritis

Fatty degeneration and necrosis of the liver, and congestion and hemorrhage of the spleen, heart and kidneys may be observed.

Hyperkeratosis, parakeratosis, hyperemia and some hyalinization of the skin.

Diagnosis:

Mixed GI and skin effects

Detection of thallium in the urine or tissues.

Treatment:

Symptomatic and supportive. Forced potassium diuresis.

Decontamination of GI tract (emetics, activated charcoal)

Prussian Blue

INSECTICIDES

Syndrome – Toxic response

Acute: Organophosphates/Carbamates
Pyrethrins/Pyrethroids
Arsenic
Organo-chlorine

Chronic: Delayed neuropathy with some Organophosphates and among some animal and birds species

Residues:
Organo-chlorines (DDT, Mirex, and others)

Organophosphorus (OP) and Carbamate Insecticides

Source and Chemistry

The most prevalent and toxic chemical warfare agents are potent organophosphorus compounds (soman, sarin, tabun). These compounds are not used as insecticides. Carbamate insecticides, are derivatives of carbamic acid are used for similar surface applications. The original carbamate, physostigmine, is a plant alkaloid, derived from the "ordeal bean."

Animal poisonings from organophosphorus (e.g., Asuntol, chlorpyrifos, dichlorvos)/carbamate (e.g. aldicarb, methomyl, propoxur, carbaryl, carbofuran) insecticides commonly result from their deliberate dermal application or accidental ingestion. Most of these insecticides are applied to surfaces of plants, animals, soils, or household, floors, etc. Others are systemics (e.g., Spot-On[®]) that are absorbed via any route by plants or animals and then distributed through the organism on which the insect pest feeds.

An important source of toxicity in the cat results from the inappropriate use of chlorpyrifos-based products used for the control of fleas and other ectoparasites. Flea control formulations available for domestic animals that contain chlorpyrifos include dips, sprays (polymer-based), and collars. However, except for flea collars, chlorpyrifos is not approved for use on cats. The inappropriate use of chlorpyrifos-based products on cats results in a significant number of poisoning

cases each year. Chlorpyrifos and Diazinon based formulations have been withdrawn from sale in the US in 2000 and 2004 respectively.

Environmental contamination: Concern varies with the specific Compound and their route of exposure. Whereas the carbamates (except for aldicarb in ground water and on vegetables) are less of a concern environmentally the organophosphorus insecticides tend to be much less persistent than the organochlorine insecticides.

Generic Name	Trade Names
Acephate	Orthene, Asataf, Pillarhene, Kitron, Aimthane, Ortran, Ortho 12420, Ortril, Chrevron RE 12420, and Orthene 755
Chlorpyrifos	Brodan, Detmol UA, Dowco 179, Dursban, Eradex, Lorsban, Piridane, Stipend
Coumaphos	Agridip, Asunthol, Meldane, Muscatox, Umbethion, Co-Ral, Asuntol, Bay 21, Baymix, Dilice, Resistox, Suntol, Negashunt
Diazinon	Knox Out, Spectracide and Basudin
Dimethoate	Cekuthoate, Chimigor 40, Cygon 400, Daphene, De-Fend, Demos NF, Devigon, Dimate 267, Dimet, Dimethoat Tech 95%, Dimethopgen, Ferkethion, Fostion MM, Perfekthion, Rogodan, Rogodial, Rogor, Roxion, Sevigor, Trimetion

Absorption, Distribution, Metabolism, and Excretion:

Exposures – oral, ophthalmic, respiratory and dermal routes

Generally lipophilic compounds and are well absorbed, widely distributed, accumulate in fat, liver metabolized, and excreted as metabolites in urine.

Organophosphates – Some OPs (especially those with a -P=S moiety, e.g., parathion) require metabolic activation, forming Oxons which irreversibly phosphorylate cholinesterase, becoming more toxic over a longer duration due to aging OP-Acetylcholinesterase complex rather than the new enzyme (Acetylcholinesterase) synthesis.

Carbamates- Inhibit cholinesterase enzyme “carbamylation” ester. Complexation is labile, reversible and of a shorter duration of action.

Toxicity:

Wide variation depending on dose and compound involved - Characterized in the case of OPs as highly toxic (e.g. parathion), intermediate toxicity (e.g. coumaphos) or low toxicity (e.g. fenthion); and in the case of Carbamates as extremely toxic (e.g. aldicarb, methomyl), highly toxic (e.g. propoxur, aminocarb) or moderate toxicity (e.g. carbaryl).

LD₅₀ Chlorpyrifos in the cat is between 10 and 40 mg/kg. Some cats may develop severe clinical signs following exposures to even smaller doses especially if chronically exposed.

Mechanism of Action:

Competitive inhibitors of cholinesterase enzymes (Acetylcholinesterase or true Cholinesterase and Pseudo-cholinesterase or plasma cholinesterase) activity

Acetylcholinesterase – present in RBC membrane

Pseudo-cholinesterase – present in plasma, liver, pancreas and CNS.

Acetylcholine (ACH) is the mediator at junctions including those between preganglionic and postganglionic neurons in both the parasympathetic and sympathetic nervous system, smooth muscles or glands, motor nerves and skeletal muscles, and some neuron to neuron junctions in the CNS.

Acetylcholinesterase (ACHE) is the enzyme that rapidly hydrolyzes ACH at these locations. Actual physiological purposes of the enzymes located in blood are unknown.

Clinical Signs:

Organophosphorus and carbamate insecticides are potent inhibitors of acetylcholinesterase in mammals and produce three categories of effects namely: **muscarinic** (salivation, lacrimation, bronchial secretion, vomiting, diarrhea), **nicotinic** (tremors, respiratory paralysis), and **CNS** (seizures, miosis, hyperactivity).

Death is usually due to one or more of the following effects: increased respiratory tract secretions and bronchiolar constriction with hypoxia aggravated by bradycardia; respiratory depression from nicotinic stimulation to the point of paralysis; and respiratory paralysis from CNS depression due to central effects of the insecticide (may be the primary cause of respiratory-failure in some species).

Horses--colic, abdominal pain, salivation, severe diarrhea (often watery), dehydration.

Chlorpyrifos toxicosis in cats and bulls. The classical syndrome of OP poisoning characterized by salivation, lacrimation, urination, and defecation ("SLUD") is rarely observed in cats or bulls except following acute oral exposure. More typically, animals are presented following a delayed onset of 1 to 5 days after dermal exposure. Clinical signs in cats (and bulls to some extent) may include depression, ataxia, tremors (generally involving the head, neck, and back), behavior changes (personality change, aggression), hyperactivity, and hyperesthesia, as well as miosis or mydriasis. Other signs include anorexia, salivation, vomiting, diarrhea, tachypnea, and dyspnea. Tachypnea, and dyspnea result from excessive bronchoconstriction and hypersecretion and may be life-threatening in overly stressed cats. Clinical signs commonly persist for several weeks in topically dosed cats and bulls. This duration may be the result of prolonged cholinesterase inhibition and debilitation that results in hypokalemia. Although not specific for chlorpyrifos toxicosis, electromyographic (EMG) abnormalities reported to occur in chlorpyrifos-poisoned cats include prolonged insertion activity, fibrillation potentials, positive sharp waves, and high-frequency discharges consistent with a neuropathy or neuromyopathy. Electromyographic changes are most severe in the pelvic limbs.

Interestingly, in addition to the acute effects of organophosphorus insecticides, some compounds (e.g. phosphoramidates, phosphonates) are associated with the rare development of organophosphate induced delayed neuropathy (OPIDN), characterized by central-peripheral distal axonopathy ("dying back polyneuropathy"). For example, in addition to its acute effects, experimental chlorpyrifos toxicosis has also associated with the development of OPIDN. Although controversial, the postulated mechanism of action in the development of OPIDN involves the phosphorylation and aging of a second class of esterase, neuropathy target esterase (NTE). In the cat, this neuropathy is characterized by a central-peripheral distal axonopathy ("dying back polyneuropathy"). The appearance of clinical signs is delayed for up to 2 to 3 weeks after exposure. This syndrome is rarely encountered clinically, but when it occurs it is characterized by ataxia (waddling gait), hind-limb hypermetria, depressed conscious proprioception, weakness, and an ascending paralysis.

Diagnosis:

A diagnosis is based upon a history of exposure, development of appropriate clinical signs, and chemical analysis of stomach contents and tissues (available at most diagnostic laboratories).

Test try dose of atropine: a pre-anesthetic dose of atropine and, if normal atropinization occurs (normal extent and duration of rapid heart rate, dry mouth and mydriasis), it tends to rule out poisoning from a cholinesterase inhibitor.

Pathology: Nonspecific. Salivation, Bronchial secretion or pulmonary edema. Occasional hemorrhages in gastrointestinal tract serosa and mucosa.

Determination of reduced cholinesterase activity (< 50% normal activity) in blood, brain, and retinal tissues is highly supportive of a diagnosis. Depending on the diagnostic laboratory's preference, whole blood samples (collected in the appropriate anticoagulant), serum, plasma, or brain tissue (one hemisphere) should be frozen and shipped on ice.

Reduced whole blood cholinesterase activity may suggest exposure to an organophosphate or carbamate and, although, not a conclusive test, should be performed on animals presented alive. In most species, whole blood cholinesterase is considerably less sensitive than pseudocholinesterase. Therefore, depression of the activity of whole blood cholinesterase is more indicative of serious exposure or toxicosis than plasma pseudocholinesterase. Conversely, plasma pseudocholinesterase is a more sensitive test for detecting exposure than whole blood cholinesterase. It is possible to have no plasma cholinesterase activity detected in animals exposed to therapeutic (parasitocidal) amounts of OPs. In most species, the red blood cells contribute the major fraction of the activity in total blood cholinesterase. In most instances, the whole blood cholinesterase values of poisoned animals fall below 25% of control values. Feline whole blood cholinesterase activity is comprised primarily of pseudocholinesterases that are extremely sensitive to inhibition by organophosphorus and carbamate insecticides. Therefore, reduced cholinesterase activity may suggest exposure but may be difficult to use prognostically. Blood cholinesterase activity may not be representative of CNS cholinesterase activity in a symptomatic animal (false negative).

Because the incubation time allows for decarbamylation, the **MICHEL METHOD** of cholinesterase analysis may give false negative (false normal)

Courtesy of Prof. Cecil Brownie

values for carbamate toxicoses. Effects of various insecticides on whole blood acetylcholinesterase (AChE) activity (incubation temperature and times).

Insecticides	Whole blood AChE	
	37C; 5 min	37C; 60 min
Organophosphorus	Decreased	Decreased
Carbamates	Decreased	Normal
Pyrethrin and pyrethroids	Normal	Normal
Organochlorines	Normal	Normal
Rotenone	Normal	Normal
d-Limonene and linalool	Normal	Normal

Tissues of internal organs usually do not yield detectable residues of organophosphate or carbamate compounds even in seriously poisoned animals. Stomach or rumen contents are often important in confirming diagnoses after oral exposure because the insecticides are most often detected in these samples (ship frozen).

Differential Diagnoses:

Insecticides that are commonly used for the control of ectoparasites on companion animals include organophosphorous, carbamates, pyrethrins, pyrethroids, organochlorines, d-limonene, d-linoolol, rotenone, pennyroyal oil, and amitraz. Of these insecticides, organophosphorous, carbamates, pyrethrins, pyrethroids, and citrus oil derivatives (d-limonene and d-linoolol) may induce central nervous system depression. Organophosphorous, carbamates, pyrethrins, pyrethroids, rotenone, and organochlorine insecticide toxicoses commonly result in muscle tremors and central nervous system stimulation.

Clinical Pathology:

Measurement of whole blood, brain, or retinal acetylcholinesterase activity is diagnostically useful in cases in which an exposure to an organophosphorus or carbamate insecticide may have occurred

Hypokalemia and elevation of serum creatine kinase activity has also been reported in chlorpyrifos-poisoned cats.

Treatment:

Decontamination: Very early, emetics (only for very recent exposures; never when contraindicated and constant monitoring will not be undertaken). Activated charcoal (always use for any recent oral exposure) administered with appropriate precautions to avoid aspiration. Thoroughly bathe with detergent all animals exposed topically taking care to avoid exposure of human skin.

Atropine sulfate (0.1-0.2 mg/kg, intramuscular or intravenous, repeated as needed) is antidotal, and can be used to control salivation and bronchial secretions (muscarinic effects). Atropine will not control muscle tremors (nicotinic). The initial dose of atropine should be divided, with one quarter given intravenously and the remainder given either subcutaneously or intramuscularly. Since long-term atropine therapy may be required, one should use the lowest dose that alleviates the dyspnea and bradycardia. The reversal of excessive salivation may serve as a useful clinical marker of effective atropinization. Do not attempt to monitor atropinization using pupil size, since this is an unreliable indicator in cats and other animals. The dose of atropine should be decreased or discontinued if tachycardia, gastrointestinal stasis, severe behavioral changes (e.g., delirium), or hyperthermia develop. Lower doses of atropine are required in horses to avoid a possibly lethal atropine-induced colic. May want to avoid atropine sulfate altogether in horses due to gut stasis, (except with life-threatening pulmonary or cardiac effects). When used in horses, atropine is added to fluids and administered IV while auscultating the abdomen. Administration is stopped prior to a reduction (to less than normal) in gastrointestinal sounds. Some rabbits have atropinase and may require higher dosing, begin at 1.0 mg/kg but may need to increase to 10 mg/kg. In all cases, subsequent doses of atropine should depend on the reappearance and severity of clinical signs.

Enzyme reactivators act on the organophosphorus insecticide-acetylcholinesterase complex to free the enzyme and restore normal function. These agents are only effective if covalent binding of the organophosphorus insecticide to acetylcholinesterase (aging) has not yet occurred. Aging involves the cholinesterase inhibitor-bound enzyme, and usually occurs within 24 hours of the initial binding of the insecticide to the enzyme. Even with an extended postexposure interval and possibility of aging, enzyme reactivators may still be useful. Skin and subcutaneous fat may serve as a depository for some insecticides (e.g., chlorpyrifos) following topical exposure, redistribution from this depot results in continued enzyme exposure to the insecticide with subsequent aging.

The newly formed, but not aged enzyme-insecticide complex, is the site of action for the enzyme reactivators.

Of the enzyme reactivators, pralidoxime chloride (Protopam chloride, Wyeth-Ayerst Laboratories, Philadelphia, PA) has received the widest clinical use. Pralidoxime chloride is given (20 mg/kg, IM, repeated every 12 hr), to relieve tremors and other nicotinic signs and should be continued until these signs are abolished or until additional prolonged benefit (lasting more than a day) is no longer observed. Cattle and horses can be dosed at 10-20 mg/kg. Pralidoxime chloride is generally of low toxicity; however, overdoses can cause tachycardia and cardiac arrhythmias. Not effective for carbamate insecticide toxicosis.

Aggressive symptomatic and supportive care (hypokalemia is common in chlorpyrifos-poisoned cats; oral potassium supplementation may be required) and maintenance of caloric intake and hydration status. Artificial respiration may be needed to counteract respiratory paralysis. It is essential to avoid hypoxia. Seizures may be controlled with diazepam or barbiturate anticonvulsants. Systemic acidosis may complicate OP poisoning. Sodium bicarbonate administered at an initial dose of 5 mg/kg IV can be used to correct acidosis. Subsequent 1-3 mEq/kg IV doses may be required. Monitor acid base status. Animals should be monitored for the development of chemical pneumonitis due to secondary aspiration of hydrocarbon solvents if such formulations are ingested; and for aspiration of gastric contents. Stress may cause secondary clinical problems, e.g., hemobartonella, reported in OP-poisoned cats.

It is critical that further exposures to organophosphorus and carbamate insecticides be avoided until the animal is fully recovery. Exposure to another acetylcholinesterase inhibitor should not be allowed until 4 to 6 weeks after the initial exposure. It is unknown whether prior organophosphorus or carbamate insecticide exposure increases the sensitivity of animals to other classes of nonacetylcholinesterase-inhibiting insecticides.

Organochlorine Insecticides

Source and Chemistry

Animal exposures to organochlorine insecticides (e.g., lindane, endrin, DDT) continue to result in serious neuro-toxicoses.

DDT type (diphenyl aliphatic)--includes DDT, methoxychlor, perthane, and dicofol. Methoxychlor used a lot, including products for use around gardens, animals.

Miscellaneous (lindane, mirex, kepone, paradichlorobenzene).

Lindane (hexachlorocyclohexane) is used in some veterinary insecticidal dips and shampoos. Lindane toxicosis is most commonly the result of the overuse of lindane-based insecticides on dogs or its inappropriate use on cats. Lindane toxicosis is common in cats and dogs. Never approved for cats, used for dogs (fleas, ticks, sarcoptic mange), also people (Qwell; for scabies). Some lindane isomers are hepatocarcinogenic.

Cyclodiene type: aldrin, dieldrin, chlordane, endrin, heptachlor, "active constituent" of toxaphene. Chlordane, heptachlor, aldrin used for termites. Aldrin used to be used for corn root worm. Endrin has been used as an avicide, and toxicosis in the cat can result from secondary poisoning from ingestion of endrin-poisoned birds. Endrin at least in past used in "Rid-a-bird." Toxaphene used to be made for animal dips, other uses.

Paradichlorobenzene (moth crystals, cakes, deodorant block used in diaper pales, closets, rest rooms, and in other moth products occasionally including moth balls; note: not the same as naphthalene; the most common compound in moth balls). Of comparatively low toxicity, but does cause poisoning! Neurologic system toxicity similar to other members of this group.

Absorption, Distribution, Metabolism, and Excretion:

Absorption variable. Typically very fat soluble.

Lindane like other organochlorine insecticides is very lipophilic, is rapidly absorbed, and tends to develop high fat and brain tissue concentrations. As lindane and other organochlorine insecticides are very lipophilic, they are rapidly absorbed, and tend to develop high fat and brain tissue concentrations. Paradichlorobenzene metabolized to a phenolic and is

hepatotoxic. Aldrin is metabolized to dieldrin in the body and environment. Heptachlor is metabolized to heptachlor epoxide. Dieldrin and heptachlor epoxide are persistent in the body and the environment.

Toxicity:

LD50s in most species tend to be relatively high. Cyclodiene insecticides cause more seizure activity and are more acutely toxic (lower LD50s) than the DDT type organochlorines. LD50 endrin (cats) 3-6 mg/kg.

Lindane toxicosis is most commonly seen in cats (although dogs are sensitive) and often follows the deliberate application of the product by the owner. The minimal oral lethal dose for lindane in most species ranges from 5 to 25 mg/kg.

DDT: LD50 rat (oral) 113-2500 mg/kg, rat (iv) 47 mg/kg

DDT: unique aspects. Banned in 1972. DDT and its metabolites are potent mixed-function oxidase inducers. Egg shell thinning--birds of prey especially aquatic predators (e.g., bald eagles). O'P'DDD (synonymous with TDE) and especially DDE are persistent metabolites in environment and body. O'P'DDD--causes thinning of the adrenal cortex in the dog; therefore used to treat Cushing's disease in the dog. Excessive use on dogs can cause Addisonian crisis.

Mechanism of Action:

Methoxychlor, mirex, kepone, lindane, perthane, dicofol are similar to DDT in structure and mechanism. Slows down the turning off of the Na^+ influx and inhibits the turning on of the K^+ outflux; results in more of each cation inside the nerve than normal. Therefore, the inside of nerve membrane is more positive (partially depolarized) which decreases the threshold for another action potential to occur. Sensory nerves are more readily affected by DDT (and similar agents) than are motor nerves. EEG shows a diffuse low amplitude, fast frequency pattern due to partial depolarization of neurons.

Cyclodiene insecticides act by competitive inhibition of the binding of GABA at its receptor. GABA is a more widely used inhibitory transmitter in the CNS than glycine. Note the effects of GABA are facilitated by benzodiazepines (such as Valium) and these drugs may therefore be of major benefit in treatment. Lindane may also affect the GABA-receptor-ionophore complex.

Clinical Signs:

All of these agents mainly cause tremors, salivation, ataxia, depression and sometimes vomiting. Seizures may occur in cats at low doses or in other species with very high doses.

Clinical signs of lindane toxicosis generally develop within 24 hours of exposure.

Clinical signs may be progressive or explosive in nature, and commonly include excitation, depression, tremors, clonic-tonic seizures, hyperactivity, ataxia, circling, salivation, hyperthermia, and coma.

Electroencephalographic changes can include increased low amplitude-fast frequency and spike activities.

Liver damage is occasionally observed several days after exposure.

Diagnosis:

History of exposure, appropriate clinical signs.

Pathology:

Liver damage is occasionally observed several days after exposure. There is usually no histologic lesions in the brain or spinal cord.

Chemical analyses:

Brain analysis important for diagnosis of acute toxicosis; submit ½ brain frozen (for organochlorine and other analyses and virology). Other 1/2 should be fixed for histopathology to rule out infectious (encephalitides), degenerative, or neoplastic diseases.

To determine sources, it may be appropriate to submit specimens for analysis such as: feed; suspect insecticidal formulation (e.g., granules, liquid, old containers, etc); gastrointestinal tract contents; hair (live animal) or skin (dead animal) Liver, fat, and milk fat are the preferred samples to assess residue contamination. It is essential to avoid any cross contamination: e.g., from source material to animal or milk, from skin or stomach contents to brain, etc.

Clinical Pathology:

Increased liver enzymes, azotemia occasionally observed

Treatment:

With dermal exposures bathe with detergent--avoid human exposure by the use of heavy-gauge rubber gloves.

Recent oral exposure--emetic (small animals and possibly swine) (only if presented very early), and not if any likelihood of seizures is apparent: must avoid aspiration of stomach contents into lungs (as discussed with strychnine previously), lavage. Usually use activated charcoal, saline cathartic.

Monitor liver function.

Seizure control is usually necessary for 24 hours or so, sometimes may need to medicate for longer periods of time. Suggested drug for initial control is diazepam (dogs) or, if it fails (or for other species), phenobarbital or pentobarbital. For prolonged CNS stimulation, the drug of choice is phenobarbital which may also stimulate mixed function oxidase activity to shorten half-life.

Residues:

In addition to acute toxicoses residues in the fats of meat and milk are a primary concern.

The tendency of organochlorine insecticides to store in fat is a function of the rate of metabolism and excretion. Biological magnification is the concentration of an agent in the lipids of successive predators. Can sometimes result in chronic or acute (lethal) toxicoses. Most likely when aquatic systems are involved because: 1) food chains are longer permitting a greater number of bioconcentrations and 2) lipid soluble compounds are readily acquired from the environment especially sediments and the surface micro-layer of natural waters. These compounds are washed into streams but are poorly soluble in the water column.

Methoxychlor is eliminated fairly rapidly but still had a 30-day withdrawal at one time.

More rapid dechlorination and especially oxidation versus DDT.

DDT once had concern regarding cancer (e.g., human breast cancer) may possibly be unfounded. Potent mixed function oxidase inducer. DDE, DDT persistent in fat.

In general: For residue concerns monitor: Milk fat; values may approximate body fat concentrations. Fat biopsy. In cattle, fat may be taken from the tailhead, neck, and scrotum of steers. Prefer to avoid perirenal fat even at necropsy unless other fat is unavailable. Can use experimentally

derived data for a particular organochlorine to calculate time needed for a known concentration in body fat to fall below actionable level. Note: logical to consult with a veterinary toxicologist when trying to address recommendations for contaminated food animals.

Decontamination of Residue-Contaminated Livestock:

Essential to identify source and terminate exposure. Determine the value of animals and the duration of pasturing/feeding to achieve decontamination. Assess value of animals minus costs of decontamination vs. other options. Consider all costs including feed, labor, biopsy, chemical analysis, killing and burial of highly contaminated individuals and purchase of additional animals. If animals must be destroyed, burial or other disposal should be approved by regulatory officials before euthanasia.

Lactating animals tend to more rapidly eliminate insecticide residues due in part to losses in milk fat. Young animals sometimes metabolize/excrete significant amounts and, because of growth, dilute the residues and may therefore (sometimes) not require specific detoxification procedures.

Placing fattened animals on pasture, so that they lean out, helps to hasten removal of the organochlorine insecticide from body fat stores. If residues are extremely high in fat, may need to monitor for neurologic effects as body fat residues are mobilized.

The use of agents to promote metabolism or excretion such as phenobarbital, mineral oil, or repeated activated charcoal for the purposes of lowering residues in fat or milk fat are generally ineffective and not worthwhile.

Pyrethrin and Pyrethroid Insecticides

Source and Chemistry

Pyrethrin and pyrethroid insecticides are contained in a variety of insecticidal formulations. Pyrethrins and pyrethroids are classified on the basis of their neurophysiologic and toxicologic effects and chemical structure. Due to their increasing use on dogs and cats, pyrethrin and pyrethroid toxicoses have become more commonplace.

The pyrethrins are natural insecticidal esters of chrysanthemic acid and pyrethric acid, and are obtained by extracting dried pyrethrum flowers (e.g., *Chrysanthemum cinerariifolium*). Pyrethrins are natural insecticides and include pyrethrin I and II, jasmolin I and II, cinerin I and II.

Pyrethroids (e.g. allethrin, tetramethrin, deltamethrin, fenvalerate) are synthetic insecticides having greater chemical stability versus natural pyrethrins.

One product (Hartz Blockade[®]) contains a pyrethroid (fenvalerate) and the insect repellent N,N-diethyl-m-toluamide (DEET).

Absorption, Distribution, Metabolism, and Excretion:

Rapid hydrolysis in the gastrointestinal tract and liver metabolism. Pyrethrins and pyrethroids are highly lipophilic and undergo rapid absorption and distribution following topical application. Orally administered pyrethrins and some pyrethroids may undergo enterohepatic recirculation.

Toxicity:

Pyrethrin and pyrethroid insecticides are considered among the safest classes of insecticides available. For example, rat oral LD₅₀ values range from 128 mg/kg for deltamethrin to 4640 mg/kg for tetramethrin. The low oral toxicity of pyrethroids is in contrast to a much higher degree of toxicity (LD₅₀'s < 10 mg/kg) following parenteral administration.

The introduction of the alpha cyano moiety found in some pyrethroids generally results in an increase in toxicity to both insects and mammals.

The low acute oral toxicity of these insecticides is due in part to their rapid hydrolysis in the digestive tract and metabolism by liver microsomal esterases.

Synergists (e.g., piperonyl butoxide, and N-octyl-bicycloheptene dicarboxiimide [MGK 264]) are combined with pyrethrins and pyrethroids to enhance their insecticidal activity and may enhance mammalian toxicity as well.

Mechanism of Action:

No one mechanism of action seems to account for all of the clinical signs observed in mammals associated with the various types of pyrethrin and pyrethroid insecticide toxicoses. Toxicologic mechanisms of action of these insecticides include interference with sodium channels, enhanced sodium ion conductance, and post-synaptic gamma aminobutyric acid (GABA) receptor-chloride ionophore complex blockade.

Clinical Signs:

Most of our knowledge regarding the syndromes associated with pyrethrin and pyrethroid insecticide toxicosis occurs from experimental studies that utilize rodents. Type I pyrethroid poisoning in mice and rats produces a syndrome, referred to as tremor or T syndrome, which is characterized by tremors, prostration, and altered startle reflexes. Type II pyrethroid poisoning in mice and rats causes ataxia, convulsions, hyperactivity, choreoathetosis, and profuse salivation, and is referred to as the choreoathetosis/salivation or CS syndrome. All pyrethroids that contain the alpha cyano phenoxybenzyl alcohol moiety (type II) produce the CS syndrome, however, the CS syndrome is not exclusively produced by these alpha cyano-containing pyrethroids, there are certain type I pyrethroids which also cause the CS syndrome. Moreover, subsequent investigations have not found this classification (type I = T syndrome; type II = CS syndrome) to be all inclusive; some compounds produce a combination of the two syndromes leading to a tremor, hypersalivation syndrome (TS syndrome). Furthermore, different stereoisomeric forms (e.g. cis vs. trans isomers) of a given pyrethroid can produce different syndromes.

The development and severity of clinical signs have been shown to be proportional to the concentration of a given pyrethroid in nervous tissues.

Pyrethrin or pyrethroid toxicosis generally develops within hours of exposure, but may be delayed if a result of prolonged exposure from dermal absorption or grooming.

Clinical signs of pyrethrin and pyrethroid insecticide toxicosis in cats and dogs include tremors, increased salivation, ataxia, vomiting, depression, hyperexcitability or hyperactivity, seizures, dyspnea and death. In general, the development of pyrethrin/pyrethroid toxicosis develops within hours of exposure, but may be delayed as a result of prolonged exposure from dermal absorption or grooming.

In sub-lethally exposed animals, the syndrome is considered reversible, with most animals recovering within 72 hours.

Diagnosis:

A presumptive diagnosis of pyrethrin/pyrethroid poisoning is based upon a history of a potentially toxic level of exposure to a pyrethrin or pyrethroid containing insecticide, and the timely development of appropriate clinical signs.

No specific diagnostic test or histopathologic changes exists for the confirmation of pyrethrin or pyrethroid toxicosis. The use of chemical analysis of pyrethrin or pyrethroid residues on the skin or in the gastrointestinal tract of exposed animals may be used to confirm topical or oral exposure to this class of insecticide. Often tissue (especially brain) concentrations of pyrethroids may help to support a tentative diagnosis of pyrethrin poisoning, however, direct correlations between tissue residues and severity of clinical signs (including death) have not been determined for domestic animals.

Differential Diagnoses:

A list of differential diagnoses for pyrethrin and pyrethroid toxicosis should include other seizure or tremor producing neurotoxicants or disease states, and other neurotoxic insecticide toxicoses (e.g., those from organophosphorus, carbamate, and organochlorine insecticides). The determination of whole blood or brain acetylcholinesterase activity can be used to rule out an exposure to a toxic level of an organophosphorus or carbamate insecticide.

Treatment:

Treatment for pyrethrin and pyrethroid toxicosis primarily involves basic life support, seizure control when needed, and prevention of further absorption of the insecticide. The most severe clinical sign of toxicosis is seizure, and if untreated may result in the death of the animal.

The following treatment recommendations for acute pyrethrin/pyrethroid poisonings have been made: a) institution of life-saving symptomatic therapy as needed, b) anticonvulsant therapy using diazepam or as a second choice phenobarbital, c) bathing the animal with a mild liquid dish detergent or shampoo to decrease further dermal absorption (when appropriate), d) oral administration of activated charcoal and a saline or osmotic cathartic to interrupt possible enterohepatic recirculation, and to decrease gastrointestinal absorption if oral

exposure has occurred (e.g. ingestion of dip, grooming), e) administration of atropine to alleviate some clinical signs (if severe, e.g. diarrhea, salivation), and f) other symptomatic and supportive therapy as needed.

The protective effect of diazepam is thought to be due to its interactions with the GABA-benzodiazepine receptor. Due to the presumed extrapyramidal stimulation from pyrethrins and pyrethroids, the use of phenothiazine tranquilizers is considered to be contraindicated.

Citrus Oil Extracts (e.g., d-limonene)

Source and Chemistry

Crude citrus oil extracts have been formulated into preparations labelled for use on pets, "to control itching due to" (in tiny letters), "fleas, ticks, and lice," (in giant letters). This was an attempt to avoid EPA safety testing by avoidance of an insecticidal claim on the label. These should not be confused with formulations containing purified d-limonene another citrus derived agent.

d-Limonene has also been used as a wetting and dispersing agent, as a food flavor, and as a fragrance in various detergents.

A third citrus derivative, linalool, is now on the market alone (in dip solutions) and in a spray product in combination with d-limonene and the mixed function oxidase inhibitor, piperonyl butoxide.

Absorption, Distribution, Metabolism, and Excretion:

When applied topically, at least some of the compound(s) is (are) absorbed through the skin which probably accounts for some of the systemic effects. With regard to the absorbed fraction of linalool, a major portion is conjugated in the liver to form a glucuronide or sulfate conjugate with significant excretion in the urine (a total of 55% of administered radiolabel from linalool is excreted in the urine in one form or another). Some linalool undergoes enterohepatic recycling. Orally administered linalool is rapidly absorbed. Approximately 25% of orally administered linalool is eliminated by metabolism to CO₂.

Toxicity:

Rat oral LD₅₀ s 2790 mg/kg.

Toxicosis resulting from citrus oil extracts is most likely in cats. Cats died at the recommended concentrations of the preparation containing crude citrus oil.

Courtesy of Prof. Cecil Brownie

Cats are, however, highly tolerant of d-limonene. For example, cats treated with 15 times the recommended concentration in the final dip solution survived with no supportive or detoxification treatment. The cats treated at this level did, however, display marked, although temporary signs of toxicosis.

Mechanism of Action:

The mechanism of action of these agents is not thoroughly understood. There is evidence of both centrally and peripherally acting vasodilation. Prolonged vascular effects of linalool appear to be related to nervous system mechanism of action.

Clinical Signs:

Cats treated with excessive amounts of citrus-based insecticides tend to display ataxia, central nervous system depression (or generalized paralysis), and at least in the case of d-limonene, profound hypothermia when exposed to high rates of exposure. Cats exposed to crude citrus oil products may die after a period of central nervous system depression. Cats given excessive exposure to the-spray containing linalool, d-limonene and piperonyl butoxide were recumbent for up to 6 days after topical application.

With topical exposure to d-limonene alone, recovery in healthy cats should be expected within 6-12 hours.

The only lesion likely to be observed in excessively treated cats is scrotal and associated (self-trauma-induced) perineal dermatitis in male cats.

Diagnosis:

History of toxic exposure with development of appropriate signs. Do not ignore the possibility of other more toxic agents being used on or around the cat and causing the toxic syndrome (i.e., other insecticides or various other toxicants used in the home or on the animal).

Treatment:

Bathing in a liquid dish detergent solution is recommended to remove any significant residual insecticide. Keep the animal warm but well ventilated. Other therapy is symptomatic and supportive. Atropine is NOT indicated.

Amitraz (Francodex, Mitaban, Mitac, Mitacur, Ovasyn, Preventic, Taktic, Triatox, Zema)

A formamidine derivative insecticide (used as an acaricide and immiticide)
Available – various forms (powders, collars, sprays, dips, and topicals) and concentrations

Exposures – collar ingestion, products misuse

Clinical signs – route of exposures and dose:

Topical – transient sedation lasting 48-72h.

Oral – more severe signs (depression, head pressing, ataxia, seizures, coma, ileus, diarrhea, vomiting, hyper-salivation, polyuria, hypothermia, bradycardia, hyper- or hypotension. and mydriasis.

Mechanism of action:

A diamide topical parasitticide – (mechanism of action is poorly understood

1⁰ a CNS α_2 -adrenergic agonist and a weak monoamine oxidase inhibitor
And a mild serotonin and antiplatelet effect

Pharmacokinetics/Absorption, Distribution, Metabolism, and Excretion:

Pharmacologic action in animal is not well known but (follows closely to that of human patients).

Rapid oral absorption (signs develop within 30 mins. - 2 hours)

Dermal absorption – minimal (some animals show clinical signs of toxicity when dipped in amitraz)

Concentrations in tissues bile > liver > eye > intestines

Liver metabolized to active and inactive metabolites

Metabolites excretion - 1⁰ urine with some fecal excretion

Toxicity:

LD₅₀ PO dogs (100 mg/kg

4 mg/kg/day PO (90 days) Beagles – CNS depression, ataxia, hypothermia, hyperglycemia, and increased pulse rates. No deaths reported.

Toxicity – amitraz-impregnated collars reported in all species studied

Systems affected:

CNS – depression, ataxia, coma, seizures

GI – bloat or ileus 2⁰ to anticholinergic-like effects, hyper-salivation, vomiting, diarrhea

Cardiovascular – hypertension or hypotension, bradycardia 2⁰ to alpha₂-adrenergic receptor activity.

Endocrine/Metabolic – hyperglycemia, presumably by inhibiting insulin release; hypothermia or hyperthermia

Respiratory – respiratory depression due to depression of the respiratory center of the brain.

Ophthalmic – mydriasis, due to alpha₂-adrenergic receptor activity

Renal/urologic – polyuria may result at higher overdoses due to ADH suppression

Hemic/lymphatic/immune – DIC 2⁰ to severe hyperthermia from prolonged seizures/tremors.

Signalment/history:

All breeds of dogs are affected. Toy breeds reported to be more susceptible to the CNS effects

Cats (very sensitive) to toxicosis, developing signs at much lower doses

Horses are very sensitive to toxicoses.

Risk factors:

Contraindicated for canine patients <4 months of age

Geriatric and debilitated animals (toxicity even at normal doses)

Not suitable for patients with seizure disorders (potentially lower the seizure threshold)

Interactions with drugs, nutrients or environment:

Corticosteroids (other immune-suppressing drugs)

MAOI (Selegiline) and those with MAOI-type activity

Tricyclic anti-depressants (amitriptyline, clomipramine)

SSRIs (fluoxetine and fluvoxamine)

Atypical antipsychotic agent

Anesthetic drugs with known adrenergic activity (Xylazine or medetomidine)

Cats ingesting amitraz should not have emesis induced with Xylazine due to risks of severe CNS depression with 2⁰ aspiration pneumonia.

Clinical signs:

Clinical signs (onset) within 30 mins. – 2h post ingestion (may be delayed for up to 10-12h)

Present – CNS depression, tremors, ataxia, and GI signs (hyper-salivation and bloat); hypothermia or hyperthermia may also be present.

Some seizing or in patient with a history of having seizure. Often with mydriatic

Duration of clinical signs (quite long 3-7 days) without the use of reversal drugs.

Differential Diagnosis:

Toxicities: 5-HTP, Atypical antipsychotic agents, benzodiazepines, imidazolin, methionine, Tremorgenic mycotoxins, nicotine, SSRIs, TCAs.

1^o or 2^o neurologic disease

1^o metabolic diseases (renal, hepatic, hypoglycemia)

Diagnosis:

Baseline chemistry (CBC, renal values)

ECG and blood pressure monitoring (bradycardia and hypotension)

Monitor frequent blood glucose levels (diabetic patients in particular)

Pathological findings – nothing specific of significance

Treatment:

Detoxification

Emesis is not recommended for animals showing clinical sign

Asymptomatic - Early ingestion stage, not an aspiration risk; administer activated one dose charcoal with cathartic

Patient stable on topical exposure, decontaminate with dish detergent and warm water

Remove ingested pieces of collar (surgery, endoscopy)

Monitor TPR

Medications/antidotes – none specifically available. alpha₂-adrenergic antagonists (broad range of safety, multiple administrations due to short half-life) may help.

Antipamezole (Antisedan) 50ug/kg IM or Yohimbine 0.1mg/kg IV to reverse severe sedation and bradycardia

Crystalloid IV fluid to maintain hydration and treat hypotension. Diuresis does NOT speed elimination. Lingering hypotension, might include additional therapy (colloid like Hetastarch and/or vasopressin therapy).

Tremor/seizures – treat with diazepam (valium) or barbiturates at ye lowest effective dose (prevents severe sedation)

Diazepam 0.1-0.25 mg/kg, IV to effect PRN

Phenobarbital 2-4 mg/kg, IV to effect PRN

Protracted vomiting – antiemetic therapy

Ondasetron 0.1-0.2 mg/kg SQ, IV, q 8-12h.

Maropitant 1 mg/kg SQ q 24h.

Metoclopramide 0.2-0.5 mg/kg SQ, IMq 8-12h.

Precautions: Do not use Xylazine or medetomidine as emetic agents in amitraz exposed patients. Do not treat atropine to treat bradycardia in these patients (exacerbate hypertension and gastrointestinal stasis)

Considerations: Endoscopic or surgical removal of amitraz-containing collar

Possible complications: Extended tremors/seizures duration – myoglobinuric renal failure and DIC

**Prognosis – generally good with early detection and treatment. Patients showing CNS signs generally have poor prognosis
Poor prognosis in equid developing ileus secondary to amitraz toxicosis.**

Boric Acid

Source and Chemistry:

Roach and ant poisons, which are often > ~5% boric acid (often called ortho-boric acid), comprise the most common source causing toxicosis in small animals. Sodium borate (borax) is used in cleaning clothing in washing machines. Sodium perborate, which decomposes to form hydrogen peroxide and sodium borate, is found in denture cleansers. Whether sodium borate breaks down to boric acid is unknown.

Absorption, Distribution, Metabolism, and Excretion:

Soluble borates are absorbed from the gastrointestinal tract. Concentrated in the kidney before excretion; probably related to the fact that the kidney is the organ that is most damaged. Renal excretion is comparatively slow.

Toxicity:

Boric acid--oral LD₅₀ in the rat is 2.68 g/kg to 4.08 g/kg. Borate oral LD₅₀ in the rat ranges from 4.5-4.98 g/kg. One gram of boric acid = 1.55 g Borax. Sodium borate = 21.50% boron.

Mechanism of Action:

Exact mechanism is unknown; generally cytotoxic to all cells.

Clinical Signs:

Vomiting, diarrhea, anorexia. Muscle weakness and ataxia, possible hyperpyrexia. Seizures possible, tremors may be seen prior to seizures if they occur. Depression and lethargy. Oliguria or anuria, possibly hematuria, and albuminuria. Erythematous skin eruptions develop in humans (and pet monkeys) which may become generalized; may have a "boiled lobster" appearance. Metabolic acidosis may occur.

Lesions may include gastroenteritis, nephrosis, fatty degeneration of kidneys, hepatic damage, fatty degeneration of liver, possible cerebral edema.

Diagnosis:

Appropriate clinical signs and/or lesions with a history of sufficient exposure. A bench chemistry test is available for detecting boric acid in urine. Oliguria, anuria, proteinuria, casts and red blood cells. Chronic poisoning can occur.

Treatment:

For recent exposure, an emetic has been recommended or if contraindicated, gastric lavage is suggested, either approach is followed by activated charcoal administration. Symptomatic, plus fluid diuresis and peritoneal dialysis or

Courtesy of Prof. Cecil Brownie

exchange transfusions. Peritoneal dialysis has been shown to be effective in reducing blood levels of boric acid in human poisoning. Should seizures occur in dogs, diazepam is recommended.

Rotenone

Source and Chemistry:

Rotenone-based insecticides are occasionally used on companion animals. Rotenone is a natural insecticide derived from the root of the *Derris* plant.

Toxicity:

Rotenone is moderately toxic with acute oral LD50s in laboratory rodents ranging from 13 to 130 mg/kg.

Mechanism of Action:

Rotenone is a highly potent mitochondrial poison, effectively blocking the NADH dehydrogenase system.

Clinical Signs:

Clinical signs of rotenone toxicosis may include vomiting, central nervous System depression, muscle tremors, seizures, dyspnea, and death.

Diagnosis:

History of exposure with development of appropriate signs.

Treatment:

Oral decontamination (emetics in asymptomatic animal, activated charcoal). Symptomatic and supportive therapy.

Fipronil (Frontline®)

Source and Chemistry:

Fipronil is a phenylpyrazole insecticide which was introduced to the United States for use in animal health, indoor pest control, and commercial turf in 1996. Products containing fipronil include: granular turf products, pet care flea and tick sprays, pet care flea and tick topical solutions, roach and ant baits.

Frontline Spray Treatment contains 0.29 percent of the active ingredient, fipronil, and is labeled for control of fleas and ticks on dogs, puppies, cats and kittens.

Frontline Top Spot for Cats and Frontline Top Spot for Dogs contain 9.7 percent fipronil and are labeled for the same use as Frontline Spray Treatment but are applied with a pre-measured pipette applicator to a single area of skin between the pet's shoulder blades. Frontline Spray Treatment label directions state that "Approximately 1 to 2 Pumps per pound of the animal's body weight will be required." Each pump delivers ~1.5 milliliter (ml) of Frontline Spray Treatment.

Toxicity:

The technical product (96.5% fipronil) has a high order of toxicity with respect to ingestion and inhalation in the rat, but appears to be less toxic via skin absorption.

Absorption, Distribution, Metabolism, and Excretion:

The major route of fipronil excretion in rats is via feces. Excretion in the feces ranges from 45-75% of the administered dose, while excretion in urine ranges from 5-25%.

Mechanism of Action:

Fipronil disrupts normal nerve function. The insecticidal action involves blocking the lambda-aminobutyric acid (GABA)-gated chloride channel with much greater sensitivity of this target in insects than in mammals.

Clinical Signs:

Fipronil may cause mild irritation to the eyes and slight skin irritation. It does not sensitize the skin.

Courtesy of Prof. Cecil Brownie

Signs of toxicity in rats include reduced feed consumption, anuria, increased excitability, and seizures.

Technical fipronil caused a number of toxicological effects in chronic animal studies at relatively low doses. Clinical signs of neurotoxicity were reported in rats and dogs at doses as low as 0.07 and 1.0 milligrams per kilogram body weight per day (mg/kg/day), respectively. Clinical signs of neurotoxicity were also reported in a 21-day dermal exposure study in rabbits at a dose of 10 mg/kg/day, indicating that neurotoxicity can result from dermal exposures.

Diagnosis and Treatment:

History of exposure with development of appropriate signs.

Oral decontamination (emetics in asymptomatic animal, activated charcoal).

Symptomatic and supportive therapy.

Insect Growth Regulators

A number of insect growth regulators have been developed for use on domestic animals. Products include:

Advantage (imidacloprid 9.1%)

Program (lufenuron)

Sentinel (milbemycin + lufenuron)

Diflubenzuron (chitin inhibitor like lufenuron),

Pyriproxyfen

Fenoxycarb

Nylar

Methoprene

Insect growth regulators are juvenile hormone analogs (resemble the natural growth factor found in the flea) that work by interfering with egg development and molting from various life stages of the flea. The two most commonly available IGRs are methoprene (Precor®) and fenoxycarb. IGRs are found in sprays, foggers, and flea collars. They may be used on the pet or applied to the environment. An advantage of the IGRs is their high margin of safety. These are products that would be among the most safe for application in a household with infants or other people intolerant to insecticides.

Insect development inhibitors work by interfering with a particular aspect of development. Most of these products interfere with the synthesis of chitin, a

protein necessary for maturation and function of the flea exoskeleton. Chitin inhibitors include lufenuron, pyriproxyfen, and cyromazine.

Imidacloprid

Imidacloprid works by binding to the insect's nicotinic receptor sites on the postsynaptic neuron, thus disrupting normal nerve transmission. Imidacloprid has both multiple agonist and antagonist effects on the neuronal nicotinic acetylcholine receptor-channels. Imidacloprid is selectively toxic to specific insect species. Even though all insects and mammals have nicotinic receptors in the postsynaptic nerve region, certain insect species have a larger proportion of nicotinic acetylcholine receptors to which imidacloprid binds. Mammals and other organisms have larger proportion of muscarinic receptors, or other types of nicotinic receptors, and these receptors do not bind imidacloprid effectively. Imidacloprid is found in a variety of commercial insecticides. Imidacloprid based insecticide formulations are available as dustable powder, granular, seed dressing (flowable slurry concentrate), soluble concentrate, suspension concentrate, and wettable powder. The products Admire, Condifor, Gaucho, Premier, Premise, Provado, and Marathon all contain imidacloprid as the active ingredient. Imidacloprid is moderately toxic. The oral dose of technical grade imidacloprid that resulted in mortality to half of the test animals (LD_{50}) is 450 mg/kg body weight in rats, and 131 mg/kg in mice. The 24-hour dermal LD_{50} in rats is $>5,000$ mg/kg. It is considered non-irritating to eyes and skin (rabbits), and non-sensitizing to skin (guinea pigs). Clinical signs of poisoning would be expected to be similar to nicotinic signs and symptoms, including fatigue, twitching, cramps, and muscle weakness including the muscles necessary for breathing. Some granular formulations may contain clays as inert ingredients that may act as eye irritants.

Methoprene (Altosid, Apex, Diacon, Dianex, Kabat, Minex, Pharorid, Precor, ZR-515).

Methoprene is classified by the U.S. Environmental Protection Agency (EPA) for general use as both an insecticide and a growth regulator. Methoprene is referred to as an insect growth regulator because it interferes with the maturation stages through which an insect goes: from egg, larvae, and pupa, to adult. Methoprene is relatively non-toxic when ingested or inhaled and slightly toxic by dermal absorption. No overt signs of poisoning have been reported in incidents involving

accidental human exposure to methoprene. The oral LD₅₀ for methoprene in rats is greater than 34,600 milligrams per kilogram (mg/kg). The oral LD₅₀ for methoprene in dogs is between 5,000 and 10,000 mg/kg. The dermal LD₅₀ for methoprene in rabbits is between 3,038 - 10,250 mg/kg. In mammals, methoprene is rapidly and completely broken down and excreted, mostly in the urine and feces. Methoprene is excreted unchanged in cattle feces in amounts that are sufficient to kill some fly larvae that breed in dung

Herbicides

A large group of diverse compounds (plants are target species affected): Arsenicals, Atrazine – photosynthesis inhibitor; Bipiryridyl derivatives (paraquat, diquat) – disrupt cell membranes, Chlorophenoxy acids (2,4-D, 2,4,5-T) – plant growth regulators, Glyphosate (roundup) – plant amino-acid synthesis inhibitor, etc.

In general, toxicoses are reported in dogs, cattle and horses.

Characterized by clinical signs which are:

Non-specific gastrointestinal (all)

Tremors, muscular twitching, myotonia (ex. 2,4-D)

Respiratory >> pulmonary fibrosis and death (paraquat).

In some cases their mechanism (s) of action have been ascertained -uncoupler of oxidative phosphorylation (Chlorophenoxy acids) or
When metabolized (as is the case for paraquat, they form free radical >> damage lung parenchyma (paraquat).

Chlorophenoxy Herbicides (2,4-D, MCPP, SILVEX, 2,4,5-T)

Sources

Phenoxyacetic acid (chlorinated) derivatives, such as 2,4-D (2,4-dichlorophenoxyacetic acid), 2,4,5-T (2,4,5-trichlorophenoxyacetic acid), silvex, MCPP, MCPA, and others may possibly be involved.

2,4,5-T was contaminated with very toxic chlorinated dibenzodioxins, especially 2,3,7,8 tetrachlorodibenzodioxin, but these are not encountered in 2,4-D.

Dibenzodioxins were the toxic contaminant found in the defoliant Agent Orange, which was a 50/50 combination of 2,4-D and 2,4,5-T.

Toxicity:

In theory 2,4-D should not cause toxicoses in dogs which only have contact with it via lawns treated with the herbicide, when it is used at recommended rates. Whether there is a segment of the canine population that is exceedingly susceptible is unknown.

2,4-D

LD₅₀ dog 100 mg/kg (oral). Lethal to dogs at 25 mg/kg/day for 6 days.

Oral LD₅₀ rat 375-1,200 mg/kg.

Toxicity observed in calves at 200 mg/kg, swine 100 mg/kg.

2,4,5-T

Oral LD₅₀ dog approximately 100 mg/kg.

Oral LD₅₀ rat 500 mg/kg, guinea pigs 381 mg/kg.

MCPA

Oral LD₅₀ rat 612-1,200 mg/kg.

Dicamba (a benzoic acid herbicide with some toxic effects similar to the phenoxy herbicides)

Oral LD₅₀ rat 757-1414 mg/kg.

Mechanism of Action:

2,4-D has a direct effect on muscle membranes causing increased irritability and rigidity followed by paralysis.

Absorption, Distribution, Metabolism, and Excretion:

2,4-D salts or esters are readily released in the gastric acid and rapidly absorbed due to protonation (addition of hydrogen ion) of the free anion in the gastric acid. Most of the herbicide is excreted in the urine as the unchanged acid. 2,4,5-T may undergo enterohepatic circulation. Dogs are predisposed as compared to other species possibly due to their poor ability to excrete organic acids in the urine. In practice, also seem to eat inordinate amounts of phenoxy-herbicide treated grass.

Clinical Signs:

Dogs: Often the only signs seen in the field from moderately toxic doses of phenoxy herbicides are related to gastrointestinal effects including vomiting, diarrhea (occasionally bloody). With serious toxicosis as more often occurs after exposure to concentrates or pools of sprays, or when dogs are present and heavily exposed during spraying, muscular effects may predominate including a hesitancy to move, rigidity of skeletal muscles, ataxia, and weakness especially in the rear legs. Clearly neurologic signs including seizures, clonic spasms, opisthotonus, and coma occur only with highly toxic doses. The most sensitive effect of 2,4-D toxicosis in the dog is found by use of the electromyogram. Greatly increased insertional activity (harmonic response upon insertion of the needle electrode) occurs at lower doses. At much higher doses, nerve degeneration which is at least partially reversible may also occur. This may be largely a result of damage to the nerve at the neuromuscular junction. Additional effects, which may occasionally occur in dogs, include oral ulcers, small intestine mucosal damage, renal tubular degeneration, and focal hepatic necrosis.

Ruminants: Clinical signs include anorexia, depression, bloat, rumen atony, weakness, and diarrhea. Oral mucosal ulceration may be noted. Congestion of kidney, hyperemia of lymph nodes, and congested friable liver may be seen on postmortem examination. Rumen stasis commonly observed.

Swine: Display diarrhea, ataxia, depression, vomiting, and weakness.

Phenoxyherbicides may cause an increased palatability of some types of poisonous plants due to abnormal plant carbohydrate metabolism. Phenoxy herbicides can also increase the concentration of nitrates and cyanogenic glycosides in some plants.

Clinical Pathology:

Elevation of CPK, SGOT, LDH.

Treatment:

Usually there is an oral exposure from drinking or eating the herbicide or from eating heavily treated grass. Grooming of 2,4-D from the body by the animal may prolong exposure. The use of activated charcoal and a saline cathartic for very

recent exposures is indicated, along with a bath in a detergent. Ion-trapping of 2,4-D may enhance the removal from the tissues and promote its excretion in the urine. Fluids containing 1-2 mEq/kg bicarbonate are therefore indicated, if normal renal function is present. A bland diet and good nursing care should be provided. Most animals should be expected to make an uneventful recovery.

Dinitrophenol and Related Herbicides

Sources

Various dinitro derivatives of cresol and phenol are used as insecticides acaricides, fungicides, and herbicides (nonselective biocides). They are applied in sufficient amounts to wet the target organism for contact action. Included in these compounds are: dinitrophenol (2,4-dinitrophenol, an insecticide and acaricide, fungicide which is phytotoxic to green plants); dinoseb (2-sec-butyl-4,6-dinitrophenol; DNBP, Dinitro[®], Basanite[®], Dow General Weed Killer[®], and several other products used as a herbicide, dessicant or dormant fruit spray; withdrawn by US EPA in October, 1986); DNOC (dinitrocresol); DNAP (Dinosam[®], a rarely encountered herbicide); and 5 DN-III, a discontinued product. Animals may be seriously exposed from entering treated fields, etc. or by contact with concentrated forms of these pesticides.

Toxicity:

The LD₅₀ Of dinitrophenol in the rat is 0.027-0.10 mg/kg. The acute oral and dermal LD₅₀ of dinoseb in the rat is 20-40 mg/kg. The acute oral LD₅₀ of DNOC in the rat is 20-50 mg/kg. Dinitrophenol is about twice as toxic as disophenol on a single dose basis, but is less toxic on a repeated basis, indicating that it is not as cumulative as disophenol.

Absorption, Distribution, Metabolism, and Excretion:

Generally well absorbed from gastrointestinal tract and skin.

Courtesy of Prof. Cecil Brownie

Mechanism of action:

Uncouples oxidative phosphorylation resulting in a lack of adequate ATP concentrations, so that insufficient energy is available for $\text{Na}^+ - \text{K}^+$ ion channel pumps ----> development of cerebral edema.

Clinical Signs:

Muscle tremors, hyperexcitable, hyperthermia, tachypnea, miotic pupils, ataxia, weakness, seizures.

Diagnosis:

History of toxic exposure with development of appropriate clinical signs. Analysis of pesticide residue on skin or in gastrointestinal tract.

Treatment:

Oral and dermal decontamination;

Symptomatic and supportive

Control seizures

Control hyperthermia (cold water baths)

Fluid therapy

Atropine is contraindicated ----> increased hyperthermia

Gramoxone (Cepupat, Dextron X, Dextrone, Herbaxon, Paraquat)

Source

A non-selective contact herbicide (selective pulmonary toxicant in animals)

Oral absorption – rapid but incomplete (5%-10%) and dose dependent

Inhalation/dermal absorption (2^0 to chronic exposure), reaction is less severe reaction.

Peak plasma concentration (75 minutes)

Distribution 4 h post exposure (lungs 10X higher than other selective sites.

4-10 days post exposure lung concentration 30-80X higher than plasma concentration

Courtesy of Prof. Cecil Brownie

Comparative toxicity: Dogs 25-50 mg/kg; Cats 40-50 mg/kg; Pigs/Sheep and Ruminants 25-75 mg/kg; Rats 100 mg/kg; Turkeys 290 mg/kg.

Signalment/History:

No breed, sex or age predilection (toxic to all mammals). . Dogs most frequently affected (more likely to ingest)

Owner works in pesticide industry, recent spraying activity, Agricultural area, observed ingestion of finding bates intended for dogs

Metabolism/Excretion:

Extensive cyclic oxidation-reduction reactions in sequestering tissues – excreted largely unchanged (urine). Active excretion (renal tubular cells at higher concentration than creatinine (initially), kidney damage worsens T1/2 increases from <12h to > 12h.

Clinical signs:

Chronic / subacute exposure (anorexia, depression, diarrhea) observed in 7 days or so, progress to pulmonary fibrosis and progressive respiratory distress over several weeks and death. Multi-systems involvement (GI, respiratory, cardiovascular, renal, neurological, and skin).

Day 1: Caustic injury – vomiting; GI erosion and hemorrhage, hypovolemia and acute pulmonary edema.

Days 1-3: Preferential distributional distribution to lungs kidney and liver.

Day4 and beyond – Progressive pulmonary fibrosis, respiratory failure and death.

Mechanism:

Absorption >> transported to Alveolar Cells >> metabolic activation in presence of oxygen >> free radical intermediates and hydrogen peroxide formation >> lipid peroxidation >> damaged alveolar cells >> impaired lung functions >> cells (fibrotic) proliferation >> death from hypoxia.

Selectively accumulates in lung alveolar cells (type 1 and type 2; clara cells; as well as renal proximal tubular epithelium

Differential Diagnosis:

GI disease (pancreatitis, parvovirus), **heavy metal** (lead, zinc inorganic arsenic, or mercury), or **zinc phosphide** ingestion; 1^o cardiac disease; 1^o or 2^o pulmonary disease (Canine distemper in puppies, Toxoplasmosis, Asthma (Siamese cats), Pneumocystis carinii; Pulmonary interstitial fibrosis (West highland white terrier).

Diagnosis:

Dithionate spot test – paraquat detection in tissues (rapid diagnosis)

Serum paraquat levels - most predictive of severity and prognosis (levels quickly undetectable. Urine analysis up to 48h post ingestion. Stomach contents, vomitus, tissues, and organs; chest radiographs (1-3 days post-ingestion) – observe changes due to severity of pulmonary changes.

Pathological findings: Gross pulmonary congestion, bullous, emphysema, hemorrhage, bronchodilation, or atelectasis

Microscopic: Alveolar necrosis (Type 11 pneumocytes denuding alveolar basement membrane with severe pulmonary edema and/or fibroplasias.

Gastrointestinal and pulmonary signs suggestive of exposure to hydrocarbon solvents.

Absence of neurologic effects – a rule out for hydrocarbon solvents.

Respiratory signs – slow and progressive.

Treatment:

Detoxification:

Early intervention post exposure a must. Emesis or gastric lavage (< 1h post ingestion)

Symptomatic and supportive care at best

Activated charcoal is preferred for GI decontamination. Fuller's earth, bentonite or clay soil along with saline cathartic may decrease absorption

No known specific antidote.

Riboflavin, ascorbic acid, superoxide dismutase, and N-acetylcysteine seem promising.

Long-term corticosteroids

Oxygen therapy is contraindicated (oxidant damage).

Poor prognosis - Death.

Glyphosate (Roundup)

Sources:

Glyphosate is a broad-spectrum, non-selective systemic herbicide. It is useful on essentially all annual and perennial plants including grasses, sedges, broad-leaved weeds and woody plants. It can be used on non-cropland and among a great variety of crops. Glyphosate is usually formulated as an isopropylamine salt. While it can be described as an organophosphorus compound, glyphosate is not an organophosphate ester but a phosphanoglycine, and it does not inhibit cholinesterase activity.

Tradenames include Roundup, Rodeo, and Pondmaster. It may be used in formulations with other herbicides.

Toxicity:

Glyphosate is a moderately toxic herbicide and carries the signal word WARNING on the label. Even though the LD₅₀ values show the compound to be relatively non-toxic it can cause significant eye irritation.

The toxicity of the technical product (glyphosate) and the formulated product (Roundup) is nearly the same. The acute oral LD₅₀ in the rat is 5,600 mg/kg. Other oral LD₅₀ values for glyphosate are 1,538 to greater than 10,000 mg/kg for mice, rabbits, and goats.

Technical material was fed to rats and dogs at dietary levels of 200, 600, and 2000 ppm for 90 days. No significant differences from control animals were observed in mean body weight, food consumption, behavioral reactions, mortality, hematology, blood chemistry, or urinalyses. There were no relevant gross or histopathologic changes.

Absorption, Distribution, Metabolism, and Excretion:

Glyphosate is poorly absorbed from the digestive tract and is largely excreted unchanged by mammals. Ten days after treatment there were only minute amounts in the tissues of rats fed glyphosate for three weeks.

Cows, chickens, and pigs fed small amounts had undetectable levels (less than 0.05 ppm) in muscle tissue and fat. Levels in milk and eggs were also undetectable (less than 0.025 ppm). Nearly all glyphosate residues were rapidly eliminated by fish that had been exposed for 10 to 14 days once these fish were transferred to glyphosate-free water. Glyphosate has no significant potential to accumulate in animal tissues.

Treatment:

Symptomatic and supportive

Pendimethalin

Sources:

Pendimethalin is a selective herbicide used to control most annual grasses and certain broadleaf weeds in field corn, potatoes, rice, cotton, soybeans, tobacco, peanuts and sunflowers. It is used both pre-emergence, that is before weed seeds have sprouted, and early post-emergence. Incorporated into the soil by cultivation or irrigation is recommended within 7 days following application. Pendimethalin is available as emulsifiable concentrate, wettable powder or dispersible granule formulations.

Some trade names include AC 92553, Accotab, Go-Go-San, Herbadox, Penoxalin, Prowl, Sipaxol, Stomp and Way-Up.

Mechanism of pesticidal action: Pendimethalin inhibits plant cell division and cell elongation.

Toxicity:

The oral LD₅₀ for technical pendimethalin in rats is greater than 5000 mg/kg. The dermal LD₅₀ for technical pendimethalin in rabbits is greater than 2000 mg/kg. Increases in alkaline phosphatase level and liver weight were produced in dogs fed 50 and 200 mg/kg for 2 years. Pendimethalin is very toxic to fish (96-hour fish toxicity: 0.199 ppm for bluegill sunfish (highly toxic) and 0.138 ppm for rainbow trout) and aquatic invertebrates; however, due to its high partitioning coefficients, pendimethalin will not likely be mobile in soil.

Absorption, Distribution, Metabolism, and Excretion:

By 24 hours after the administration of 37 mg/kg of radio-labeled pendimethalin to rats, 90.3% of the dose was recovered in the feces and urine. After 96 hours, 95.8% of the dose was recovered in the urine (20.9%) and feces (74.9%). When a lower dose was administered (7.3 mg/kg), 99.8% was recovered in the urine (21.8%) and feces (78.0%) after 12 hours. After 96 hours, residues were less than 0.3 ppm in all body tissues except fat, which had 0.9 ppm. This study indicates that ingested pendimethalin is largely unabsorbed by the bloodstream and excreted through the feces.

Treatment:

Oral and dermal decontamination; Symptomatic and supportive

Miscellaneous Pesticides

Metaldehyde

Source and Chemistry:

Metaldehyde toxicosis is most commonly the result of the ingestion of metaldehyde-based (usually 3.5%) molluscicides.

Absorption, Distribution, Metabolism, and Excretion

Well absorbed from gastrointestinal tract.

Toxicity

The approximate lethal dose of metaldehyde ranges from 100 to 360 mg/kg.

Mechanism of Action

The mechanism of action of metaldehyde is unknown. Metaldehyde ingestion can produce systemic acidosis. Decreases in brain serotonin, gamma amino butyric acid (GABA), and noradrenalin occurs in metaldehyde poisoned animals.

Clinical Signs:

Clinical signs of metaldehyde toxicosis often develop within 3 hours of ingestion, and commonly include tachycardia, salivation, tremors, vomiting, hyperesthesia, seizures, hyperthermia, diarrhea, and depression. Seizures are typically more continuous than that observed during strychnine toxicosis. Death from respiratory failure may develop from 4 to 24 hours after exposure. Delayed deaths due to liver failure may also occur 3 to 4 days following ingestion.

Diagnosis:

Nonspecific histologic lesions in the liver, kidney, gastrointestinal tract, lungs, and heart may be observed. Chemical analysis of frozen stomach contents, liver, and urine is available at some diagnostic laboratories.

Clinical Pathology:

Metabolic acidosis.

Treatment:

In addition to anticonvulsants and activated charcoal administration, fluid therapy to control acidosis is also recommended.

4-Aminopyridine (Avitrol®)

Source and Chemistry:

Based on its potential hazard to fish and nontarget birds, some or all uses of 4-Aminopyridine formulations are classified by the U.S. EPA as a Restricted Use Pesticide that may be purchased and used only by certified applicators. Corn baits containing 4-aminopyridine are used for the control of starlings, pigeons, and other birds (avicide). Birds often exhibit involuntary muscle contractions; birds may crash with deaths resulting from broken necks, skull fractures, etc. Baits contain 0.5-3.0% of 4-aminopyridine. Also available in concentrated (25-50%) form cut with powdered sugar. Drug form of 4-aminopyridine is used to antagonize the effects of botulinus toxin or pancuronium bromide.

Absorption, Distribution, Metabolism, and Excretion:

Can be absorbed through the skin to reach toxic concentrations. Excreted in the urine. Rapidly detoxified in the liver. The flesh of the poisoned animal is not considered toxic but GI tract still contains the active ingredient so relay toxicosis is possible, although rarely reported.

Toxicity:

4-Aminopyridine is highly toxic to animals with an approximate oral LD₅₀ of 20 and 3.7 mg/kg in the rat and dog, respectively. Two horses that ingested approximately 3 mg/kg exhibited excitability, profuse sweating, convulsions, and death in 2 hours.

Mechanism of Action:

Enhances cholinergic transmission by causing increased re-release of acetylcholine and other neurotransmitters. Also blocks the potassium ion current of repolarization following an action potential. High doses may elevate cardiac action potential plateau and depress diastolic depolarization.

Clinical Signs:

Clinical signs observed in 4-aminopyridine poisoned animals often develop within several hours of ingestion, and commonly include hyperexcitability, cardiac arrhythmias, tachycardia, salivation, tremors, sweating (horses), ataxia, seizures, increased systolic arterial blood pressure or respiratory arrest. Death from respiratory failure may develop within four hours of exposure. At doses near the LD₅₀, initial effects are usually noted in 10-15 minutes and death occurs 15 minutes to 4 hours later. Liver enzymes may be elevated, metabolic acidosis may occur.

Diagnosis:

Chemical analysis of frozen stomach contents, liver, and urine is available at some diagnostic laboratories. Differential diagnoses may include organochlorine insecticide, acute lead, strychnine, metaldehyde, methylxanthine, tremorgenic mycotoxin, nicotine, and amphetamine poisoning.

Treatment:

Although no specific antidotal therapy exists, anticonvulsants and activated charcoal administration are recommended. Pancuronium bromide has been used in the management of seizures in human patients poisoned with 4-aminopyridine. Endotracheal intubation should precede administration in case of induction of respiratory paralysis. Diazepam or phenytoin has also been recommended for seizure control. Propranolol (dog, 0.04-0.05 mg/kg, IV, slowly) has been recommended for tachyarrhythmias. Horses--heavy sedation with xylazine has provided nearly complete relief from excitement and muscle tremors.