Toxicology of Newer Insecticides in Small Animals

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KEYWORDS

- Insecticides • Toxicity • Insect growth regulators • Spinosads
- Organophosphates/carbamates • Pyrethrins/pyrethroids
- Fipronil • Sulfluramid • Hydramethylnon

In the broadest definition, a pesticide (from fly swatters to chemicals) is a substance used to eliminate a pest. A pest can be insects, mice or other animals, weeds, fungi, or microorganisms like bacteria and viruses. An ideal pesticide would be specific to, safer, and highly efficacious in eliminating the target pest. Humans, domestic animals, wildlife, and the environment would have minimal to no impact. This ideal pesticide would have a short half-life and break down into nontoxic components. It would be inexpensive and easy to apply. The ideal pesticide has not yet been discovered.

However, although not perfect, newer insecticides are significantly safer. These insecticides are able to target physiologic differences between insects and mammals, resulting in greater mammalian safety. This chapter briefly reviews toxicity information of both older insecticides, like organophosphates (OPs), carbamates, pyrethrins, and pyrethroids, as well as some newer insecticides.

ORGANOPHOSPHATES AND CARBAMATES

OPs and carbamates are used to control insect and nematode infestations. They are available as sprays, pour-ons, oral anthelmentics, baits, collars, dips, dusts, granules and foggers.[1] OPs and carbamates competitively inhibit acetylcholinesterase (AChE) by binding to its esteric site.[2] With AChE bound, acetylcholine (ACh) accumulates at nerve junctions in muscles, glands, and the central nervous system (CNS). The excessive ACh causes excessive stimulation of smooth muscle and glandular secretions. At skeletal muscle junctions, the excessive ACh is partly stimulatory (fasciculations) and partly inhibitory (muscle weakness).

After binding, the bonds of some compounds actually strengthen with time, known as aging. This "aging" renders the enzyme unusable (covalent bonding). Inhibition of

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Table 1 Common AChE inhibitors (OPs and carbamates)	
Highly toxic	
LD_{50} <50 mg/kg	aldicarb, coumaphos,[a] disulfoton, famphur, methomyl, parathion, phorate, terbufos
Moderately toxic	
LD_{50} 50–1000 mg/kg	acephate, carbaryl, chlorpyrifos,[a] diazinon, phosmet, propoxur, trichlorfon[a]
Low toxicity	
LD_{50} >1000 mg/kg	dichlorvos,[a] dimethoate, malathion, fenthion,[a] temephos, tetrachlorvinphos

[a] Compounds that have caused clinical neuropathy in humans.
Data from Hayes WJ Jr. Pesticides studied in man. Baltimore (MD): Williams & Wilkins; 1982. p. 284–435.

AChE by OPs tends to be irreversible, while inhibition by carbamates is reversible.[3] Recovery of AChE activity after irreversible binding occurs only through the synthesis of new enzymes.[3]

OPs and carbamates are quickly absorbed after dermal, oral, and inhalation exposures.[1] Clinical signs of toxicosis can occur in minutes to hours of exposure, depending on the dose, route, and toxicity of the compound. OPs and carbamates distribute quickly in the body. Most, with the exception of chlorinated OPs (ie, chlorpyrifos), do not accumulate in fat. OPs and carbamates are hydrolyzed in the body. The toxicity and duration of clinical signs depend on treatment, dose, compound, and species of animal (**Table 1**).[4] Cats are considered more susceptible to AChE inhibitors than are dogs in general.[5] Very young, very old, and debilitated animals are also more susceptible.

OPs and carbamates produce muscarinic, nicotinic, and CNS signs. The muscarinic signs include the "SLUDDE" signs (salivation, lacrimation, urination, defecation, dyspnea, emesis) as well as miosis and bradycardia. Dyspnea is due to increased bronchial secretions. Sympathetic stimulation can override the muscarinic signs and result in mydriasis and tachycardia.[4] The nicotinic effects include muscle tremors, fasiculations, weakness, ataxia, and paresis progressing to paralysis.[6] The CNS signs are characterized by hyperactivity, ataxia, seizures, and coma.[6] CNS signs usually occur with high doses or from the highly toxic compounds. Death is due to respiratory failure or cardiac arrest.[6]

OP-induced delayed neuropathy (OPIDN) in animals is characterized by hindlimb ataxia, hypermetria, and proprioceptive deficits. Clinical signs of delayed neuropathy usually begin 2 to 3 weeks after exposure and are thought to be due to phosphorylation of neurotoxic esterase (not from inhibition of AChE).[4] Acute pancreatitis (protracted vomiting, diarrhea that can often be hemorrhagic, increased pancreatic enzymes) can follow OP exposure, due to ACh release from pancreatic nerves and prolonged hyperstimulation of pancreatic acinar cells.[4] The species that are more sensitive to the delayed neurotoxic effects of organophosphorus esters accumulate the esters more rapidly and eliminate them more slowly (chickens > cats > rodents).[7]

If OP/carbamate poisoning is suspected from the clinical signs, a test dose of atropine can be given. Take the baseline heart rate and then administer a preanesthetic dose of atropine sulfate (0.02 mg/kg) IV. If the heart rate increases and the pupils dilate, look

elsewhere for the cause of the signs as it takes roughly 10 times the preanesthetic dose (0.2 mg/kg) to resolve clinical signs caused by OP/carbamate insecticides.[4]

AChE activity can be measured in serum, plasma, or whole blood. Whole blood is preferred as in most animal species 80% or more of the total blood AChE activity is in the red blood cells (RBCs). AChE activity varies widely among species of animals, but generally an AChE activity that is less than 50% of normal indicates significant exposure, while an AChE activity less than 25% of normal plus the presence of characteristic clinical signs (SLUDDE, nicotinic signs) indicates toxicosis.[4] After death, AChE activity can be checked in the brain or eye (retina). As AChE activity varies among the regions of the brain, one half of the brain or whole eye (frozen or chilled) should be submitted for testing.[8] Blood and brain AChE does not always correlate well with the severity of clinical signs.[8] Animals that die rapidly may not have depressed (brain or blood) AChE activity. Carbamates are reversible inhibitors of AChE and the results may be normal even when characteristic clinical signs of toxicosis are present. A definitive diagnosis can be reached by finding an anticholinesterase insecticide in the tissue or body fluids (gastrointestinal [GI] tract, liver, skin, blood, etc), presence of clinical signs, and significantly depressed cholinesterase activity (OPs). AChE activity can remain depressed for 6 to 8 weeks with an OP exposure.

If the animal is asymptomatic, decontamination can include emesis (if oral ingestion) and administration of activated charcoal.[4] Due to the quick onset of seizures with the highly toxic AChE inhibitors, do not recommend inducing emesis at home. With dermal exposures to OPs and carbamates, wash the animal with liquid dish detergent and water. Wear gloves and ensure adequate ventilation.

If symptomatic, stabilize the animal and control seizures (diazepam, barbiturates) before proceeding. Oxygen and/or endotracheal intubation may be needed in small animals. A high dose of atropine sulfate (0.2 mg/kg) is given to control the muscarinic signs (SLUDDE). Give one-fourth of the initial dose IV and the rest IM or SQ. Atropine will not reverse nicotinic effects (muscular weakness, etc) or CNS effects (seizures). Atropine blocks the effects of accumulated ACh at the synapse and should be repeated as needed to control bradycardia and increased bronchial secretions.[4] Glycopyrrolate may also be used to control the muscarinic signs (0.01–0.02 mg/kg IV).

Oximes are used to reverse the neuromuscular blockade and nicotinic signs. Oximes should be given as soon as possible because they cannot reverse binding once aging has occurred. Pralidoxime chloride (2-PAM; Protopam) is the most common oxime used to treat OP toxicosis in the United States (20 mg/kg IM or IV bid; continue until nicotinic signs are present. Discontinue after 3 or 4 treatments if no response or if you see aggravation of nicotinic signs). Oximes are not used during carbamate intoxications. Diphenhydramine may also help to combat muscle weakness and tremors, although the usefulness of this treatment has not been established.[5] The prognosis depends on the type of OP/carbamate involved, exposure amount (dose), and treatment measures. Prognosis is considered good unless the animal shows signs of respiratory distress (increased pulmonary secretions, respiratory paralysis)r or seizures.

PYRETHRINS/PYRETHROIDS

Pyrethrins are botanical insecticides obtained from *Chrysanthemum cinerariaefolium*. Pyrethrums are plant-derived (natural) while pyrethroids are synthetic analogs of pyrethrins and have been modified to remain stable in sunlight. Pyrethroids are divided into type I, which do not contain a cyano group, and type II, which contain an alpha cyano group (**Table 2**). Etofenprox is a nonester pyrethroid-like insecticide. Pyrethrins/pyrethroids are often formulated with insect growth regulators

Table 2 The two types of pyrethroids	
Type I	allethrin, bifenthrin, bioresmethrin, permethrin, phenothrin, resmethrin, sumithrin, tefluthrin, tetramethrin
Type II	cyfluthrin, cyhalothrin, cypermethrin, cyphenothrin, deltamethrin, fenpropathrin, fenvalerate, flucythrinate, flumethrin, fluvalinate, tralomethrin

(methoprene), synergists, solvents (petroleum distillates, acetone), and other carriers (isopropanol). In some situations, the inert ingredients may cause more adverse effects than the insecticide.[9] Pyrethroids cause a rapid "knockdown" of insects, but because pyrethroids are rapidly metabolized, some insects may recover. Synergists such as pipernyl butoxide or MGK-264 are frequently added to the products to increase toxicity to insects.[9,10]

Pyrethroids modulate gating kinetics by slowing the closing of sodium gates. Type II pyrethroids cause a longer duration of the sodium current in the axon than type I pyrethroids and pyrethrins. Thus, type 1 pyrethroids tend to cause tremors and seizures. Type II pyrethroids cause depolarizing conduction blocks with weakness and paralysis. Type II pyrethroids are considered more toxic than type I. Paresthesia is thought to result from direct action on sensory nerve endings. Pyrethrins/pyrethroids can be absorbed dermally, orally, and via inhalation. In animals, dermal absorption is limited due to intradermal metabolism. Pyrethrins/roids are highly lipophilic and distribution to tissues (fat, CNS, peripheral nervous system) is rapid. They are also quickly metabolized and eliminated primarily through the urine. The actual kinetics varies with the specific agent.[9,11] Pyrethroids are generally considered safe when used per label directions. Oral LD_{50} varies with specific agents. Cats are especially sensitive to concentrated pyrethrins/pyrethroids available in monthly spot-ons (permethrin, phenothrin, etc), although individual sensitivity exists. Some cats are sensitive enough that casual contact with a dog treated with a spot-on containing concentrated permethrin (45%–65% permethrin) can cause clinical signs.

Paresthesia is common in all species of animal following dermal application. Paresthesia includes ear twitching, paw and/or tail flicking, hiding, hyperexcitability, and hyperesthesia. Many topical sprays are formulated with isopropyl alcohol and heavy application can result in clinical signs resembling alcohol toxicity (sedation, lethargy, and ataxia). Presence of alcohol in the formulation also frequently causes a taste reaction (drooling, foaming, excessive licking motions, and vomiting).[9,10]

Concentrated pyrethroids (monthly spot-ons) are most likely to cause toxicity, especially in cats. Clinical signs of pyrethrin/pyrethroidstoxicity in cats include paresthesia, generalized tremors, shaking, ataxia, drooling, seizures, and death. Rarely, myoglobinuria will develop (most likely due to shaking/tremors) resulting in acute renal failure. Dogs typically develop signs of paresthesia (shaking of legs, mild muscle fasciculation, rubbing of application site, agitation, nervousness) after dermal application.[9,12] When ingested, granular bifenthrin products designed for lawn use appear to result in vomiting, diarrhea, ataxia, tremors and sometimes seizures in dogs (ASPCA APCC, unpublished data, 2011).

Taste reactions are treated with a taste treat such as milk or tuna. For dermal exposures to spot-ons, bathing multiple times with a liquid dishwashing liquid is important. Paresthesia to spot-ons may be treated by rubbing vitamin E oil on the application area. Corn or olive oil may be used as well. Tremoring or seizing animals should be stabilized before bathing. Methocarbamol (50 mg/kg IV; repeat as needed;

maximum dose 330 mg/kg/d) works well for controlling tremors. Diazepam can be tried in mild cases. For severe tremors or seizures, a constant rate infusion (CRI) of propofol, barbiturates, or gas anesthesia can also be used. Body temperature should be closely monitored. Many cats present hyperthermic due to muscle activity, but after bathing and stabilization, the temperature will drop. IV fluids are recommended. IV lipid emulsion therapy (see article elsewhere in this issue) is has been suggested for resolving severe tremors and seizures from permethrin toxicosis. Some clinicians claim that cats treated with lipid emulsions typically show faster recoveries (ASPCA APCC, unpublished data, 2011).

AVERMECTINS

For details, see article by Merola and Eubig elsewhere in this issue.

IMIDACLOPRID

Imidacloprid was the first neonicotinoid insecticide registered for use. It is approved as a topical spot-on for dogs and numerous products for agricultural and yard use.[13] Imidacloprid mimics the action of ACh in insects; however, imidacloprid is not degraded by AChE. Imidacloprid binds to the postsynaptic nicotinic ACh receptor. This results in persistent activation, preventing impulse transmission and a buildup of ACh. This leads to hyperexcitation, convulsions, paralysis, and insect death. The binding affinity of imidacloprid at the nicotinic receptors in mammals is much less compared to binding affinity in insects. Imidacloprid is most effective against insects with large numbers of nicotinergic ACh receptors. Thus, fleas are susceptible to imidacloprid but ticks are not.[14,15] It has been hypothesized that there are 2 binding sites, based on a rat study, with different affinities for imidacloprid. Based on the study, imidacloprid has both agonistic and antagonistic effects on nicotinic ACh receptor channels.[15]

Imidacloprid is absorbed rapidly and almost completely from the GI tract. It is metabolized in the liver to 6-chloronicotinic acid, an active metabolite. Imidacloprid is widely distributed to tissues but does not accumulate and has poor penetration of the blood-brain barrier, contributing to mammalian safety. Elimination is primarily via urine (70%–80%) and feces (20%–30%). Dermal exposures have practically no systemic absorption. Imidacloprid is spread across the skin via translocation. The product is found in hair follicles and shed with hair and sebum.[13,14]

Dermal hypersensitivity to topical products may occur. Erythema, pruritic, and alopecia may be noted at the application site. Oral ingestions of topical preparations can cause drooling or vomiting. Oral ulcers and gastritis have been seen in cats dosed orally.[14] Large ingestions of agricultural or yard use products, although rare, may result in clinical signs similar to nicotine toxicosis. These signs may include lethargy, drooling, vomiting, diarrhea, ataxia, and muscle weakness.[13]

Imidacloprid has a wide margin of safety. In safety studies, topical applications at 50 mg/kg did not cause adverse effects; the NOEL (no effect level) 1-year feeding study in dogs was 41 mg/kg. Imidacloprid is labeled for use in pregnant animals. Topical products have been labeled for puppies and kittens as young as 7 weeks.[14,16]

Treatment for dermal hypersensitivity includes bathing with a liquid dishwashing detergent or follicle flushing shampoo. In cases with severe pruritis, antihistamines or corticosteroids may be required. Most oral exposures can be treated by diluting with milk or water. Most cases of vomiting will be self-limiting. If massive ingestions occur, treatment for clinical signs is symptomatic and supportive; no specific antidote exists.

NITENPYRAM

Nitenpyram is an insecticide in the neonicotinic class. Nitenpyram is an over-the-counter tablet developed as an oral adult flea insecticide. Nitenpyram is considered safe for pregnant and lactating animals. Nitenpyram works systemically and fleas begin to die within 30 minutes. Off-label use includes treating maggot infestations.[17] The mechanism of action is similar to other neonicotinic insecticides (imidacloprid). Neonicotinic insecticides have little to no binding to vertebrate peripheral ACh receptors.[18]

Nitenpyram is rapidly and almost completely absorbed. The peak plasma level is 1.21 hours for dogs and 0.63 hour for cats. The half-life is 2.8 hours in the dog and 7.7 hours in the cat. Nitenpyram has almost no tissue accumulation. It is primarily eliminated via the urine unchanged (94%).[18]

Nitenpyram has a wide margin of safety. Adult dogs and cats were dosed up to 10 times a therapeutic dose daily for 1 month without adverse effects.[19] Cats receiving 125 mg/kg (125 times therapeutic dose) did exhibit hypersalivation, lethargy, vomiting, and tachypnea. These clinical signs typically developed within 2 hours of treatment and resolved within 24 hours.[17,19]

Reported clinical signs are generally associated with the flea die-off and are not related to the medication. Reported signs include pruritis, hyperesthesia, hyperactivity, panting, agitation, excessive grooming, trembling, and ataxia. Signs are usually self-limiting and resolve without any treatment.[17]

FIPRONIL

Fipronil is a phenylpyrazole insecticide. Fipronil is approved as a spot-on or spray as well as ant and roach baits and seed and soil treatments.[20] Fipronil binds to GABA receptors of insects and blocks chloride passages (GABA antagonist). GABA receptors normally have an inhibitory effect but the net result of fipronil is stimulation of the nervous system and, ultimately, insect death. Fipronil has significantly less binding affinity for mammalian GABA receptors because of differences in receptor configuration.[14, 21]

Fipronil does not readily penetrate the skin, although it is lipid soluble. When applied topically, it is found on the hair shaft and in the stratum corneum and epidermis and accumulates in the sebaceous glands.[14] Orally, fipronil is absorbed slowly. It distributes to a number of tissues, including the GI tract, adrenal glands, and abdominal fat. Fipronil is metabolized by the liver and excreted in the feces and urine.[14]

Fipronil may cause dermal hypersensitivity-type reaction in sensitive animals. Erythema, pruritis, irritation, and alopecia at the application site are the most commonly noted signs from topical exposures. Many of these reactions may be related to the carriers. Typically, dermal hypersensitivity will develop within hours to a couple of days of application and last 24 to 48 hours. Oral ingestions may cause taste reactions (hypersalivation, foaming, gagging), retching, and vomiting. Gastritis has been reported after ingestion of spot-on products and is most likely related to carriers rather than the fipronil. Rarely, in cases of massive ingestions, ataxia, tremors, and seizures are possible. Extralabel use of fipronil on rabbits is known to cause severe and potentially fatal seizures.[14,20]

Fipronil has a wide margin of safety in laboratory animals. There is no reported LD_{50} for dogs and cats. The oral LD_{50} in rats and mice is 97 and 95 mg/kg, respectively. Dogs appear to be more sensitive than cats to fipronil.[20]

Treatment for dermal hypersensitivity includes bathing with a liquid dishwashing detergent by 48 hours after the topical application. Antihistamines and steroids may be used if pruritis is present. After oral exposures, taste reactions are treated by

diluting with milk or water. If significant vomiting or gastritis is present, antiemetics and GI protectants may be needed. Fluids and other supportive care should be started, and tremoring or seizing animals should receive methocarbamol, diazepam, or barbiturates as needed.[14]

BORATES

Borate compounds used as insecticides include boric acid, sodium tetraborate pentahydrate, boric acid, disodium octaborate tetrahydrate, and sodium metaborate.[22,23] Borates are generally considered to be cytotoxic to all cells and are irritating to mucous membranes.[24] The mechanisms of the systemic effects of borates are not known.[23]

Borates are rapidly absorbed through mucous membranes, abraded skin, and the GI tract. Borates are not absorbed across intact skin.[22,24] Boric acid is found in all tissues, except the brain, within 30 minutes after oral exposure.[24] Peak CNS concentration occurs within 3 hours.[24] Borates are concentrated in the kidney and excreted without change.[22,24] Preexisting renal disease may slow excretion and increase toxicity. The half-life in dogs is 12 hours.[22]

The most common signs seen in dogs and cats after oral ingestion of borates are vomiting, lethargy, hypersalivation, and anorexia (ASPCA APCC, unpublished data, 2011). Renal failure and seizures are reported in the literature but are rarely seen in small animals due to the small amounts involved. The signs occur within a few hours after exposure and last a couple of hours. No deaths or serious systemic toxic effects were found in dogs given 1.54 to 6.51 g/kg of borax or 1 to 3.09 g/kg of boric acid orally.[24] Young animals are likely more susceptible than adults to the toxic effects.

Treatment is symptomatic and supportive. Activated charcoal poorly binds to boric acid (30 g of charcoal is required to adsorb 380 mg of boric acid).[25] Antiemetics or GI protectants may be given. Fluid diuresis should be started if a large exposure occurs. Animal studies suggested that the use of *N*-acetylcysteine chelation therapy may increase the excretion of boron and reverse boron-induced oliguria.[22]

HYDRAMETHYLNON

Hydramethylnon is a trifluoromethyl aminohydrazone. It is the only member in this class of insecticide. Hydramethylnon is used to control ants, cockroaches, and termites. It is often used in single bait stations (ant and roach motels) or granular products, especially for fire ants. Hydramethylnon works by inhibiting the electron transport system, thus blocking the production of ATP. This decreases mitochondrial oxygen consumption. The slow disruption in energy metabolism and loss of ATP result in inactivity, paralysis, and insect death. The mechanism of action is similar to that of sulfluramid and rotenone.[14] Hydramethylon is poorly absorbed. More than 95% is excreted unchanged in the feces. Material absorbed is slowly metabolized. In rats, 72% was eliminated in 24 hours and 92% in 9 days.[14]

Hydramethylnon has a wide margin of safety in animals. Orally, it is considered only slightly toxic. Rat oral LD_{50} ranges from 1100 to 1300 mg/kg. The dermal LD_{50} in rabbits is greater than 5000 mg/kg. In 26-week feeding studies in dogs, 3 mg/kg increased liver weights and liver:body weight ratios; 90-day studies in dogs at 6 mg/kg/d caused decreased feed consumption, decreased body weight, and testicular atrophy.[14]

It is rare for any significant clinical signs to develop. Most cases cause only mild gagging or vomiting. In cases where the dose consumed is greater than 90 mg/kg, mild ataxia or tremors may be seen. There is a risk for foreign body obstruction if large

pieces of plastic from bait traps are swallowed. Decontamination is required only in large ingestions. Clinical signs are generally self-limiting. Symptomatic and supportive care should be administered as needed.

SPINOSAD

Spinosad is found as granules or sprays for agricultural and lawn use and chewable tablets for dogs to kill fleas.[26] A spot-on containing spinetoram, a related compound, is available for use on cats to kill fleas. Spinosad is a tetracyclic macrolide. It is a combination of spinosyn A and spinosyn D.[26] Spinosyns are produced from the naturally occurring bacterium *Saccharopolyspora spinosa*, an aerobic, nonantibiotic actinomycete. Spinosad activates nicotinic ACh receptors. Treated insects develop involuntary muscle contractions and tremors. Continued hyperexcitation results in prostration, paralysis, and flea death. Spinosad is not known to interact with the binding sites of other nictotinic or GABAergic insecticides (imidacloprid, nitenpyram, fipronil, mibemycin, etc). Spinosad is more selective for insect versus vertebrate nicotinic AChRs.[26]

Spinosad is quickly absorbed after oral ingestion and peak blood concentrations occur within 1 to 6 hours depending on the dose.[27] Spinosad is well distributed throughout the body with the highest concentrations found in fat, liver, kidneys, and lymph nodes.[27] Spinosad is biotransformed with glutathione conjugates and eliminated in the feces (70%–90%) via the bile.[28] Most of the radiolabeled agent is excreted within 24 hours. Elimination from the thyroid is much slower and can result in higher concentrations in the thyroid as compared to other tissues. The half-life of spinosad is 25 to 42 hours.[28]

Canine daily doses of 100 mg/kg for 10 consecutive days (16.7 times the maximum recommended monthly dose) caused vomiting and transient mild elevations in ALT.[26] Phospholipidosis (vacuolation) of the lymphoid tissue was seen in all dogs.[26] Cats dosed at 80 to 120 mg/kg experienced vomiting.[26]

The most common adverse clinical effects seen after ingestion are vomiting and lethargy. These signs usually begin within a few hours of exposure.[26] Ataxia, inactiveness, anorexia, diarrhea, and tremors have also been reported. Concurrent administration of spinosad to animals receiving high doses of ivermectin therapy (eg, demodicosis doses) can result in mild to moderate ivermectin toxicity.[26] It is recommended that dogs receiving extralabel doses of ivermectin not receive concurrent treatment with spinosad.[26] In an overdose situation, induction of emesis and administration of activated charcoal are rarely needed. Most treatment is symptomatic and supportive and includes managing vomiting and diarrhea.

INDOXACARB

Indoxacarb is found in insect baits (ant and roach) for home use and granules and liquids for agricultural use.[29] Recently, a spot-on containing indoxacarb has been introduced for use on dogs and cats. Indoxacarb acts by blocking sodium channels in the nervous system of insects. It is an oxadiazine insecticide despite its name.[30]

Indoxacarb is metabolized in the liver and excreted in both the feces and urine.[31] Most of the dose was excreted within 96 hours. The oral NOEL in dogs is 40 ppm (1.1 mg/kg/d).[32] The most common clinical signs seen in dogs and cats are vomiting, lethargy, diarrhea, and anorexia (ASPCA APCC, unpublished data, 2011). There is one case of a human developing methemoglobinemia after a massive ingestion of indoxacarb (suicide attempt).[33] Treatment is symptomatic and supportive. Due to a

low concentration of indoxacarb present in most ant and roach baits, ingestion only requires monitoring for signs of stomach upset.

SULFLURAMID

Sulfluramid (*N*-ethyl perfluoroctanesulfonamide) is in the chemical class of fluorinated sulfonamides. Sulfluramid is used in ant and roach baits and is impregnated into cardboard to control termites. It is considered a stomach poison.

Sulfluramid is lipid soluble. However, rat studies did not show any tissue accumulation. Cytochrome P450 metabolism produces the deethylated metabolite, perfluorooctane sulfonamide (desethylsulfluramid). The metabolite is a potent oxidative uncoupler and inhibits mitochondrial respiration. Disruption of energy metabolism, and thus the loss of ATP, results in lethargy, paralysis, and death. Based on rat studies, elimination is 56% respiratory, 25% fecal. and 8% urine. The parent compound is about 80% eliminated within 72 hours, while desethylsulfluramid has a half-life of 10.8 days.[34,35]

Sulfluramid has a wide range of safety in vertebrates. The oral LD_{50} in rats varies between 500 and 5000 mg/kg.[26] The most commonly reported clinical sign is mild vomiting. Plastic ingestion in dogs has a risk for foreign body obstruction. High doses in dogs caused transient arrest of spermatogenesis.[36] Treatment is symptomatic and supportive. Manage vomiting with anitiemetics if needed. Most exposures result in self-limiting clinical signs and do not require any treatment.

Environmentally, recent research is looking at long-term exposure to perfluorinated hydrocarbons as suppressants of humoral immunity.[37] The Environmental Protection Agency is phasing out sulfluramid-containing products, primarily due to the long half-life in the environment and potential for reproductive effects. These products are to be phased out by 2016.[38]

ESSENTIAL OILS

Essential oils are produced by plants. The oils are a mixture of terpenes (complex hydrocarbons) and other chemicals. Essential oils give plants their characteristic odors. They vary widely in toxicity. Although the oils have a number of uses, some are used as natural flea and tick treatments on pets (**Table 3** lists the common essential oils used for flea treatments).

Essential oils are rapidly absorbed orally and dermally. Oils are typically metabolized in the liver by glucuronide and glycine conjugates. Cytochrome P-450 enzyme

Table 3
Common essential oils used for flea treatments

Common Name and Source of Essential Oil	Specific Clinical Signs
Citrus sp (oranges, limes, grapefruit) D-Limonene/linalool	Cats: scrotal dermatitis, profound hypotension (undiluted dips) Rare: immune-mediated dermatopathies (TENS)
Melaleuca alternifolia (tea tree)	Transient hind limb paresis (spot-on), hepatotoxicity
Mentha pulegium Pennyroyal oil, pulegone	Hepatotoxicity
Peppermint, clove, cinnamon, lemongrass, thyme (commercial sprays and spot-ons)	Agitation, tremors, seizures, rarely death

Data from Refs.[40,49–52]

systems in the liver can be induced with repeated exposure to some essential oils. Cats appear to be relatively more sensitive to the effects of essential oil than dogs. Essential oils and their metabolities are primarily eliminated in the urine.[39,40]

The most common clinical signs after dermal exposure include ataxia, muscle weakness, and behavioral abnormalities. Oral ingestions can cause vomiting, diarrhea, and CNS depression. Essential oils can cause aspiration pneumonia if inhaled. Mortality has been reported following the use of melaluca oil in cats (see **Table 3** for clinical signs of specific oils in addition to these common signs).[39,40]

All species of animals may be susceptible to essential oils. Animals with preexisting liver disease have an increased risk of toxicosis. The LD_{50} of essential oils varies widely but typically falls between 2 and 5 g/kg body weight. Mixing oils with organic solvents such as alcohols or the presence of irritated and reddened skin can potentially increase absorption of essential oils resulting in toxicity.[41] The specific mechanism of action is not established.

Dermal exposures require bathing with a liquid dishwashing detergent. Emesis, in most cases, is contraindicated since a risk of aspiration pneumonia exists. Activated charcoal can be given if a large ingestion has occurred. Baseline blood work should be obtained as some oils will cause hepatic damage and acid-base and electrolyte abnormalities. Body temperature should be monitored and corrected as needed. Intravenous fluids can help maintain pressure and hydration status and also aids in renal elimination. Monitor cardiac and respiratory functions as needed. Seizures and tremors usually respond well to diazepam or methocarbamol. Aspiration pneumonia may require oxygen and broad-spectrum antibiotics. Hepatic damage usually responds to good supportive care. The use of SAM-e or milk thistle may be helpful.[40]

LUFENURON

Lufenuron is available as an oral suspension for cats, an injectable for cats, and an oral tablet for dogs. It is approved for use in dogs and cats 6 weeks of age and older for the control of flea populations. It has also been used off label for control of dermatophytosis. Lufenuron, a benzoylphenylurea dierivative, is a chitin synthesis inhibitor.[42] By stopping polymerization and deposition of chitin, it prevents the eggs from developing into adults.

Only about 40% of an oral dose of lufenuron is absorbed in the small intestine.[42] Absorption is enhanced if administered with a fatty meal. Lufenuron is stored in fat and is slowly redistributed back into the circulation. Lufenuron is not metabolized but excreted unchanged into the bile and eliminated in the feces.

Dogs dosed at 30 times the therapeutic dose for 10 months did not develop and signs of toxicosis.[42] Cats tolerate oral dosages of up to 17 times the therapeutic dose with no adverse effects.[42] Cats do require a substantially higher oral dosage per kilogram than do dogs for equivalent efficacy.

Adverse signs seen after ingestion include vomiting, lethargy, and diarrhea. Injection site pain and swelling can occur in cats. Do not give the injectable product to dogs as they will develop a severe local reaction.[42] Most signs are self-limiting, and treatment, if needed, is symptomatic and supportive.

METHOPRENE

Methoprene is available as suspensions, emulsifiable and soluble concentrates, briquettes, sprays, foggers, baits, and spot-ons. Methoprene is labeled for flea control in dogs and cats, aquatic mosquito control, crop pest control, and home pest control.[43] Methoprene is a juvenile hormone analog. While juvenile hormone

concentrations remain high, the insect remains in the same stage and cannot molt.[44] Methoprene is also absorbed by the female flea and affects her ovaries, providing an immediate inhibitory effect.[44]

Methoprene can be absorbed both orally and dermally. It is rapidly excreted, mostly in the urine and feces.[43] Sufficient methoprene is excreted unchanged that the concentration in feces is sufficient to kill some larvae that breed in dung.[45]

Methoprene is considered relatively safe in mammals. The dog oral LD_{50} is greater than 5 g/kg.[43] Younger animals are more susceptible to adverse effects (lethargy, ataxia, rarely tremors) after oral dosing.[43] Oral exposures can cause drooling, vomiting, and lethargy and rarely ataxia or tremors. The ataxia appears within 2 to 8 hours post administration and lasts 6 to 12 hours (ASPCA APCC, unpublished data, 2011). Usually no treatment is necessary if animal has ingested small amount. Local dermal hypersensitivity reactions (redness, itching, rubbing) can be seen in some animals. Most of the symptomatic animals recover without treatment. If the animal is ataxic, prevent further stimulation (provide a quiet and dark environment). Methocarbamol may help with muscle tremors.

PYRIPROXYFEN

Pyriproxyfen is used for insect control on pets, in the home, and on agricultural crops. It is available as a spray, fogger, collar, mousse, shampoo, granule, spot-on, powder, and liquid.[46] Pyriproxyfen is a pyridine-based non-neurotoxic carbamate that does not inhibit cholinesterase. It is an insect juvenile hormone analog. It is both ovicidal and larvicidal.

Pyriproxyfen is quickly absorbed and peak levels are reached in 2 to 8 hours after ingestion.[47] It is metabolized in the liver and excreted mainly in the feces.[44] The oral NOEL in dogs is 100 mg/kg/d for 1 year.[48] Hypersalivation and self-limiting vomiting may be seen with ingestion. Most animals will not need treatment.

SUMMARY

Insecticidal poisoning has become less common in small animal patients as the newer available insecticides are more specific in their mechanisms and target mostly insects, not mammals. This has made many of the newer pesticides safer for use on dogs and cats compared to some of the highly toxic OPs and carbamates available earlier. Serious toxicity problems can still occur, especially with inappropriate use of permethrin-containing spot-ons in cats.

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