Phenylpropanolamine
Phenylpropanolamine (PPA, Proin®) is a sympathomimetic agent used in veterinary medicine for controlling urinary incontinence in dogs. Signs can be seen at therapeutic doses in some dogs and serious signs appear at doses above 20 mg/kg. Signs include tachycardia, hypertension, panting, excitement/hyperesthesia, piloerection, tremors, and seizures. Reflex bradycardia may occur secondary to the hypertension. Signs normally start within 30-90 minutes and may continue up to 48 hours, depending on dose.

Emesis may be induced if the ingestion was within 10-15 minutes. Activated charcoal should be given if possible. Heart rate and blood pressure should be closely monitored. Nitroprusside or other pressor agents can be used to manage hypertension. Atropine is contraindicated in the management of bradycardia as it will worsen the hypertension. Phenothiazines may be used to control hyperesthesia and excitement. Animals should be put on IV fluids to promote excretion, protect renal function and help with thermoregulation. As with other stimulants, cyproheptadine may be given if signs of serotonin syndrome develop.

Chewable NSAIDs
Chewable NSAIDs are commonly ingested by both dogs and cats. They inhibit prostaglandin synthesis by blocking the conversion of arachidonic acid to various prostaglandins. NSAIDs decrease secretion of the protective mucous layer in the stomach and small intestine and cause vasoconstriction in gastric mucosa. They also inhibit renal blood flow, glomerular filtration rate, tubular ion transport, renin release and water homeostasis. NSAIDs may also affect platelet aggregation and possibly hepatic function. Serious hepatotoxicosis is more commonly seen with chronic dosing. The absorption of NSAIDs are rapid and plasma half life will vary with the medication. Half lives are generally longer in the cat and they are considered to be more sensitive to the adverse effects. Most NSAIDs are metabolized in the liver and undergo enterohepatic recirculation before being excreted in the urine. Geriatric animals and neonates, as well as animals with acute renal insufficiency, liver disease and hypoalbuminemia are at higher risk of toxicosis. Administration of NSAIDs combination with glucocorticoids, salicylates, or other NSAIDS could potentiate the adverse effects of these drugs.

Emesis can be performed in the asymptomatic animal. Activated charcoal adsorbs NSAIDs and may need to be repeated (enterohepatic recirculation). GI protectants are very important. A combination of misoprostol, H2 blockers, sucralfate and omeprazole can be used to manage and/or prevent gastric ulcers. Animals should be started on IV fluids at twice maintenance for 48 hours (or more) if renal failure is expected. Monitor BUN, creatinine, and urine specific
gravity (baseline level, 24, 48, and 72 h). Acid-base disturbances are rare and usually transient. Dialysis may be necessary if unresponsive oliguric or anuric renal failure develops.

Fluids, whole blood, inotropic agents, and electrolytes should be given to control hypotension and hemorrhage, maintain renal function, and correct electrolyte abnormalities. Assisted ventilation and supplemental oxygen may be required if animal is comatose. Seizures should be treated with diazepam. Prognosis is good if the animal is treated promptly and appropriately. Gastrointestinal ulceration usually responds to therapy. Acute renal insufficiency resulting from ibuprofen administration has been considered reversible, but development of papillary necrosis is generally considered irreversible.

**Carprofen**: Dogs can develop GI ulcers at 20 mg/kg and acute renal failure at 40 mg/kg. Cats develop ulcers at 4 mg/kg and ARF at 8 mg/kg.

**Deracoxib**: Dogs can develop GI ulcers at 15 mg/kg and acute renal failure at 30 mg/kg.

**Pimobendan (Vetmedin®)**
Pimobendan is a selective phosphodiesterase (PDE) III inhibitor with positive inotropic/vasodilator (“inodilator”) effects. Pimobendan and its metabolite UD-CG 212 have a dual effect. They increase sensitivity to calcium in cardiac muscle which has a positive inotropic effect. They also increase cAMP levels resulting in vasodilation. Pimobendan is used for management of congestive heart failure in dogs due to AV valvular insufficiency or dilated cardiomyopathy. The therapeutic dose of pimobendan is 0.5 mg/kg divided BID and peak plasma levels are reached within 1-4 hours. The drug and its active metabolite have a short half life and not detectable in the plasma at 4 and 8 hours, respectively, after dosing. Overdose effects can include hypotension and tachycardia, with vomiting seen at any dose. Symptomatic care includes IV fluids to control hypotension. If no response, pressor agents can be used.

**Methionine**
Methionine is an essential amino acid often found in veterinary urinary acidifiers. Because the formulation is often very palatable, animals may ingest these medications in great quantity. Animals with underlying hepatic insufficiency are at greater risk. Doses greater than 300 mg/kg can cause clinical signs. Signs of toxicity include ataxia, depression, lethargy, salivation, vomiting, metabolic acidosis and hepatic encephalopathy- type signs (restlessness, circling, seizures, aggression, blindness, coma). Deaths are rare. Recent evidence suggests the homocysteine metabolites produced in the liver and other organs are the cause of the CNS effects. If large amounts are ingested, emesis and activated charcoal should be implemented. Monitor acid-base status. Cats can develop methemoglobinemia and Heinz-body hemolytic anemia (more commonly seen with chronic dosing). Signs can last for up to 24 hours. The prognosis is excellent if clinical signs are managed.

**Avermectins**
Avermectins include ivermectin, milbemycin, selamectin, doramectin, abamectin and moxidectin. In nematodes and arthropods, avermectins bind to glutamate-gated chloride channels causing hyperpolarization by enhancing the movement of chloride ions into the cell. This results in paralysis. In mammals, avermectins cause CNS effects by potentiating the release and binding of GABA in the central nervous system. Doses of ivermectin and moxidectin in heartworm medications are safe for even MDR1 (ABCB1) deficient dogs (Collie-type breeds, Australian Shepherds, etc). Problems arise when owners are giving large amounts to treat dermatologic disorders or giving the equine product to their pets. In general, young animals are considered more sensitive to the effect of avermectins due to a less developed blood brain barrier. Ivermectin is well absorbed orally and the half life in the non-sensitive dog is as long as 2-3 days. Enterohepatic recirculation is suspected based on the long half life and extent of fecal excretion (98%) of ivermectin. With the 'non-sensitive' breeds of dogs signs may be seen at 2000 mcg/kg, but only 150 mcg/kg is needed in the 'sensitive' breeds to cause signs. Cats have demonstrated clinical signs at the "therapeutic dose" of 200 mcg/kg. Moxidectin is a semi-synthetic avermectin that is much more lipid soluble than ivermectin. Therapeutic levels of moxidectin have been measured 30 minutes post oral exposure. Moxidectin has a wide margin of safety in dogs when given orally. Doses of up to 300 times the therapeutic dose (300 mcg/kg) resulted in little to no side effects. Most problems are encountered when dogs ingest horse dewormer.

The most common clinical signs of avermectin toxicosis include: depression, weakness, recumbency, ataxia, and coma. Other reported signs include tremors, seizures, transient blindness, bradycardia, and hyperthermia. If the exposure has just occurred and the animal is asymptomatic, induce vomiting (if an oral overdose) or consider surgical debridement if given SQ and can localize injection site in massive overdoses. If the animal is symptomatic, treatment is mostly supportive care and repeated dosages of activated charcoal. Activated charcoal/cathartic should be given q 8-12 hours (sorbitol 70% -cathartic of choice) until normal. Intralipids can be given; however, efficacy is greater with moxidectin due to its higher lipid solubility. Treatment can take days to several weeks. Supportive care is very important (fluids, parenteral nutrition, frequent turning, etc.). Physostigmine can be given, but it is not an antidote. Physostigmine has a very short beneficial effect (arousal for 30-90 minutes) and should only be used in severely non-responsive dogs (not recommended for cats). The recommended dose is 0.05 mg/kg IM or IV (very slow, over 5 minutes). Prognosis depends on the speed of onset of clinical signs: the faster the onset, the worse the prognosis.

**Spinosad**

Spinosad is a tetracyclic macrolide anti-parasitic. It can cause vomiting and ataxia; however, if spinosad is given in conjunction with high dose ivermectin, avermectin toxicosis can develop.

**Piperazine**

Piperazine is an over the counter anthelmintic (roundworms only). The therapeutic dose for dogs and cats is 45-110 mg/kg PO. Signs can occur at therapeutic doses. The most common
signs include vomiting, ataxia and tremors. Signs start within the first 24 hours and can last for several days. Animals should be kept in a dark quiet area with fluid support.

**Amitraz**
Amitraz is a centrally acting alpha adrenergic agonist with some peripheral alpha 1 and alpha 2 activity. It can be found in some veterinary dips (Mitaban®, Taktic®) and tick collars (Preventic®). Amitraz has low dermal absorption, but rapid oral absorption. Clinical signs include sedation, ataxia, vomiting, ileus, bradycardia and hypotension. Hyperglycemia can occur due to suppression of insulin release. Cats and young animals are at increased risk. Clinical signs can be reversed with α-2 antagonists (yohimbine or atipamezole). Treatment also includes a bath if the exposure was dermal. If a collar is ingested, emesis, bulking the diet or endoscopy can be attempted.

**Permethrin and other concentrated pyrethrins**
Permethrin is a synthetic type I pyrethrins. Permethrin is found in shampoos, dips, foggers, spot-ons, and sprays. Permethrins appear to be relatively safe in dogs. Smaller dogs seem to have a greater risk of toxicity and skin hypersensitivity reactions to the spot-ons. Skin reactions can be treated with bathing +/- antihistamines or steroids. Cats are more sensitive to the toxicity of pyrethrins. The low concentration products (sprays, foggers) contain 0.05-0.1% of permethrin and do not seem to cause the signs that the concentrated (45-65% permethrin) spot-ons do. Permethrin toxicity usually occurs when the owner applies the dog product to the cat; however, cats which actively groom or engage in close physical contact with recently treated dogs may also be at risk of toxic exposure. Clinical signs of permethrin toxicity in cats include hypersalivation, depression, muscle tremors, vomiting, anorexia, seizures, and possibly death. Onset of clinical signs is usually within a few hours of exposure but may be delayed up to 24 hours. The severity of clinical signs varies with each individual. Treatment recommendations include bathing with liquid dish washing detergent and controlling the tremors. Methocarbamol works best to control the tremors. If no injectable methocarbamol is available, the oral form may be dissolved in water and given rectally. If the cat is actively seizing, barbiturates or inhalent anesthesia may need to be used. Permethrins appear to have no direct action on the liver or kidneys, but fluids may be needed to help protect kidneys from myoglobin break-down products in actively tremoring cats. Prognosis for mildly tremoring cats is usually good, but treatment may last 24-48 hours.

**Essential oils: D-limonene, maleleuca, pennyroyal**
Essential oils have been used for flea control. D-limonene is a derivative of citrus pulp. This essential oil has minimal to moderate efficacy to control fleas. If diluted properly, this product has a high margin of safety. Application of the undiluted product can cause skin and oral irritation, lethargy, vomiting, salivation, ataxia and muscle tremors. Essential oils can penetrate the skin and cause peripheral vasodilation leading to hypotension and hypothermia. Melaleuca oil is an essential oil from the Australian tea-tree, *Melaleuca alternifolia*. It does have antibacterial and antifungal properties but the efficacy of this agent to repel or kill fleas has not
been established. Inappropriate application of products not intended for topical use may result in ataxia, weakness, tremors and depression. Pennyroyal oil is derived from the leaves and flowers of the pennyroyal, squaw mint, or mosquito plants. Pennyroyal oil contains a volatile compound called pulegone, which is responsible for the toxic effects of the plants. The effectiveness of pennyroyal oil to kill fleas is unknown; however, toxicity has been reported. Exposure to pennyroyal oil may induce depression, vomiting, hepatic necrosis, diarrhea, epistaxis, seizures, and death.

Toxicity is dose-related and the possibility of severe signs is more likely if the pure oil is applied to the pet. Cats appear to be more sensitive than dogs to any of the essential oils. Treatment recommendations include bathing with liquid dish washing detergent, activated charcoal with cathartic, pain control if needed, body temperature regulation and fluids. Most essential oils have long half lives (days) due to enterohepatic recirculation.

**Metronidazole**

Metronidazole is a synthetic antibacterial and antiprotozoal agent. Signs can be seen with both chronic dosing and acute overdoses. It has been postulated, but not proven, that the neurotoxicity described during metronidazole therapy is related to conversion by gut flora to a neurotoxic thiamine analog. Signs of intoxication associated with metronidazole in dogs and cats include ataxia and nystagmus most commonly. Seizures, tremors, lethargy/depression, vomiting and hypermetria have also been reported. Signs can begin within 1-3 hours with an acute overdose. Treatment includes discontinuation of the medication (if applicable) and administering diazepam. Diazepam seems to decrease the treatment time needed for these cases to resolve. Neurologic symptoms may require days to weeks before resolving.