With the new EPA regulations the types of rodenticides seen in practice are changing. Bromethalin is on the upswing along with the non-second generation anticoagulants.

**Anticoagulants**

Anticoagulants in use as rodenticides today are almost all second-generation derivatives. They inhibit the activity of vitamin K epoxide reductase, which converts vitamin K epoxide to the active reduced form. This reduced vitamin K is crucial to activation of clotting factors II, VII, IX, and X.

Any exposure > 0.02 mg/kg of a second generation anticoagulant requires treatment and evaluation. Emesis can be induced if ingestion has occurred within the last 4 hours. If little or no bait is recovered, administration of activated charcoal is next. Another option is to institute Vitamin K1 therapy (2.5-5 mg/kg/day) or monitor PT tests. Because the body has several days’ worth of active Vitamin K stored in the liver (the site of the re-activation activity), there is a delayed onset of effect on blood clotting after ingestion of an anticoagulant. Factor VII has the shortest half-life, so we can get the earliest valid estimate of effect by checking the prothrombin time (PT). The PT is expected to elevate within 24-48 hours post ingestion.

Early signs of anticoagulant toxicosis are vague, and depend on the site of a bleed. Lethargy, non-productive cough, intermittent lameness, mild anemia, or even sudden collapse can be seen. Petechiae and ecchymoses are more often seen later in the course of illness, after the platelet numbers have been depleted in smaller bleeds. Diagnosis is based on signs, history of possible exposure, and coagulation studies.

If the animal is actively bleeding, start vitamin K1 and give clotting factors via a whole blood transfusion, fresh frozen plasma, or fresh plasma. Minimize physical activity throughout therapy.

**Bromethalin**

Bromethalin is a neurotoxin that uncouples oxidative phosphorylation in CNS mitochondria. This results in lack of adequate ATP concentration and insufficient energy for maintaining Na⁺-K⁺ ion channel pumps. Loss of pump activity results in cerebral and spinal cord edema and a demyelination injury to long nerves.

Bromethalin is rapidly absorbed from GI tract. Cats are far more sensitive to this agent than are dogs. Dogs seem to have both a low-dose and a high-dose syndrome. With lower doses signs may not appear for 72-96 hours, and include hind limb ataxia and paresis, decreased proprioception, loss of deep pain response, vocalizations, patella hyper-reflexia, CNS depression progressing to coma, vomiting, and fine muscle tremors. At or above the mean lethal dose, signs can begin within 12-24 hours and include severe tremors, hyperthermia, extreme hyperexcitability, running fits, hyperesthesia and seizures.

Treatment of clinical signs is directed to controlling cerebral edema, and is mostly frustrating and non-productive. Mannitol, corticosteroids and diazepam may be used. Animals with sub-lethal doses will require good nursing care.

**Cholecalciferol**

Cholecalciferol is a Vitamin D₃ analog. It alters calcium metabolism in the body, increasing intestinal absorption and renal tubular reabsorption of calcium and stimulating bone resorption. Clinical signs of intoxication usually develop within 12-36 hours. Early signs include lethargy, weakness, anorexia, polydipsia, polyuria, and vomiting, often with blood. Biochemical alterations include hyperphosphatemia within 12 hours and hypercalcemia within 24 hours of exposure and azotemia (both renal and pre-renal). The elevated calcium levels result in calcification of many tissues, notable renal tubules and walls of blood vessels. The elevated calcium also has a direct effect on kidney function, sometimes causing acute renal failure even without mineralization.

Diagnosis of toxicosis is based on history of exposure, clinical signs, serum chemistries and urinalysis. Run baseline chemistries as soon as possible after a known exposure. Pursue GI decontamination if within several hours of ingestion, or if there is evidence of ingestion (chewed box) at unknown time but a still asymptomatic animal. Multiple doses of activated charcoal and cholestyramine can help decrease absorption.

Treatment is aimed at lowering the serum calcium and phosphorus levels, preventing a rise in these values if still normal, and stopping further calcium mobilization from the bones. IV normal saline at twice maintenance, prednisone and furosemide all enhance calcuiuria. Monitor serum calcium, phosphorus, BUN and creatinine daily to judge effectiveness of therapy. If calcium levels are rising despite calciuresis, best choice is pamidronate (Aredia™). Unlike salmon calcitonin, it needs to be given only once, with a repeat dose possibly at about 5-7 days. It acts at the level of the osteoclast and is deposited in the bone itself. Once the pamidronate has been administered, it is important to taper the initial treatments (prednisone, furosemide) and decrease the rate of fluid administration.
Continue to monitor calcium, phosphorus, and kidney values during this time. End of therapy will be marked by a return to normal of kidney values and the decrease of calcium x phosphorus levels (in mg/dl).

**Zinc phosphide**

Zinc phosphide is an old rodenticide posing as a new one. The phosphide salts are unstable in an acid environment. At gastric pH they degrade rapidly to form phosphine gas. Phosphine gas, when inhaled, results in acute non-cardiogenic pulmonary edema. When absorbed systemically, it is thought to block cytochrome C oxidase, leading to formation of highly reactive oxygen compounds. It is these reactive compounds which cause most of the tissue injury, most severe damage is in tissues with the highest oxygen demand – brain, lungs, liver and kidney.

Lethal doses for cattle, sheep, pigs, goats, dogs, and cats range between 20-50 mg/kg. For a 55 pound (25 kg) dog, that would be between 10 grams (0.35 ounce) and 25 grams (just under an ounce) of 5% bait. Severely poisoned animals may die in 3-5 hours. Those who survive longer than 48 hours have a pretty good chance.

Initial signs may vary by species, as well as by the dose. Onset of signs is normally between 15 minutes to 4 hours post ingestion. Vomiting, often with blood, is common. Dogs may show lateral recumbency with whole body tremors and salivation. Other signs may include anorexia and lethargy. Rapid deep breathing may signal the onset of the pulmonary changes. Abdominal pain, ataxia, and weakness leading to recumbency may follow. Hyperesthesis and seizures may develop that resemble the signs of strychnine toxocosis.

Metabolic acidemia ensues. Other biochemical changes may include depressed serum calcium and magnesium. If there is survival beyond 48 hours an elevated blood urea is common. Hepatic and renal damage often may be detected 5-14 days later.

Initial decontamination is tempered by the wish to keep the stomach pH as high as possible to prevent the formation of phosphine gas. If there has been no spontaneous vomiting, it may be better to induce emesis with apomorphine rather than hydrogen peroxide. Giving food, commonly done in order to improve gastric emptying and the response to peroxide, will trigger release of gastric acid and increase the rate of production of phosphine. If you are going to perform gastric lavage, add an alkalizing component like a magnesium and aluminum hydroxide gel to your lavage liquid. Also consider mixing into your activated charcoal preparation.

Supportive care includes IV fluids to maintain blood pressure renal perfusion, and gastroprotectants. Seizures may respond to diazepam, or may require barbiturates or full anesthesia. Since the most severe injury is probably due to action of the oxygen radicals, use of an antioxidant may be useful – consider vitamin C or n-acetylcysteine.

Caution: Phosphine gas released from vomitus or stomach washings can cause significant illness in veterinary personnel assisting animal. Phosphine has been describes as having a spoiled fish or garlic odor. It is detectable at 1-3 ppm in air; maximum allowed in air in occupational situations is 0.3 ppm, so if you can smell it, you are being exposed to a concentration that can be harmful.
Common Household Hazards

Tina Wismer, DVM, DABT, DABVT
ASPCA Animal Poison Control Center
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“The good”

Desiccants
Desiccant packs are included as moisture absorbents. They are found in shoeboxes, electronics, medications and food. Silica gel, one of the most common desiccants, is a white powder or a lustrous granule. Silica gel comes in paper packets or plastic cylinders. Packages of silica gel are attractive to pets because of the rustling noise, and the packages are easy to bat around. Most ingestions will not cause clinical signs, although a mild gastrointestinal upset may occur. If a large amount is ingested, there is potential for osmotic diarrhea occurring. Ingestion of the intact packet may cause a gastrointestinal obstruction.

Food products often contain desiccants composed of iron. Deli meats, pepperoni, etc. are likely to have this type of desiccant. The iron content can range from 30-60%. Once the iron has oxidized, the resulting compound (iron oxide) is inert and non-toxic. Vomiting is very common.

Ant and roach baits
Ant and roach baits are common objects found in households. They are also referred to as hotels, traps, or stations. The insecticides used most commonly in these baits are sulfuramid, fipronil, avermectin, boric acid, and hydramethylnon, all of which are of low mammalian toxicity and present in very low concentrations within the baits. The baits also contain inert ingredients such as peanut butter, breadcrumbs, fats and sugar to attract the insects; these agents are also sometimes attractive to pets. Exposures of pets to these types of ant baits usually do not require decontamination or treatment.

Birth control pills
Birth control pills generally come in 28 tablet packs with 21 hormone tablets (estrogen +/- progesterone) and 7 placebo tablets. Most hormone pills contain 0.035 mg of estrogen or less. In general, estrogen doses of less than 1 mg/kg are not of concern. At higher doses, bone marrow suppression may be seen.

Non-ionic and anionic detergents
Non-ionic and anionic detergents are found in a wide variety of household products, including body soaps, shampoos, dishwashing detergents, various household cleaners, etc. These products are gastrointestinal and ocular irritants with few to no systemic effects. Clinical signs consist of hypersalivation, vomiting, and diarrhea, and are generally mild and self-limiting, although ingestion of large quantities may result in more severe vomiting (+/- blood) requiring veterinary intervention.

Toilet water (tank drop-Ins)
Tank "drop in" products typically contain anionic/nonionic detergents, cationic detergents, bleach, and/or acids. However, when a tank "drop in" cleaning product is used in a toilet, the actual concentration of the cleaner is very low in the bowl. With dilution by the bowl water, the cleaning agent is just a gastric irritant. Common signs seen with ingestion include mild vomiting.

Glow-in-the-dark sticks and jewelry
Glow-in-the-dark items (glo-sticks, necklaces) are popular novelty items that are sold at fairs, carnivals, novelty stores and skating arenas. The primary luminescent agent in these types of products is dibutyl phthalate (n-butyl phthalate), an oily liquid that is also used as a plasticizer and insect repellent. Dibutyl phthalate is of low toxicity (LD50 >8000 mg/kg in rats) so serious problems are unlikely. Even though the extremely unpleasant taste of dibutyl phthalate may limit exposure, some very dramatic signs may be seen. Signs generally occur within seconds of the pet biting into the item. Compared to dogs, cats tend to have a much more exaggerated reaction to the taste of dibutyl phthalate. Cats may display proful salivation and foaming, with occasional retching and/or vomiting. In all cases, signs are generally self-limiting and should resolve once the pet gets the taste of the product out of their mouth. The exposure is managed by diluting the taste of the dibutyl phthalate using milk or highly palatable food (e.g. canned tuna). Any chemical that has gotten on skin or fur should be bathed or wiped off to prevent re-exposure when the animal grooms themselves; taking the pet into a darkened room will aid in identifying the luminescent chemical on the skin or coat.

“The bad”

Acids
Products containing acids include cleaning agents (e.g. toilet bowl cleaners), anti-rust compounds, etching compounds, automotive batteries, and pool sanitizers. The relative toxicity of an acid is related to its concentration and decreases with dilution. Acids produce localized coagulative necrosis of tissue and generally produce immediate pain upon exposure, which helps to limit ingestion. In most cases, clinical signs occur almost immediately upon exposure. Oral exposure results in oral pain, vocalization, dysphagia, vomiting (+/- blood), abdominal pain, and irritation or ulceration of oral and/or esophageal mucosa. Lesions often appear milky white to gray initially, then gradually turn black. Esophageal lesions are less common than with alkaline products. With high levels of exposure, gastric ulceration is also possible. Dermal exposure results in dermal irritation or ulceration, accompanied by intense local pain.
Inhalation of acid fumes may result in dyspnea, pulmonary edema, tracheobronchitis or pneumonitis. Ocular exposure may result in corneal erosion or ulceration.

Attempts to chemically neutralize with a weak alkali are contraindicated, as this may stimulate an exothermic reaction that will exacerbate tissue injury. Treatment of oral exposure includes immediate dilution with water or milk. Gastric lavage and induction of emesis are contraindicated due to the risk of increasing corrosive injury. Activated charcoal is ineffective for caustic agents and should not be used. Treatment of oral lesions is symptomatic, and should include antibiotics to prevent infection; pain management (opioids), sucralfate slurries to treat oral, esophageal or gastric ulcers; intravenous fluids to maintain hydration; and provision for nutritional support (e.g. gastrostomy tube). Dermal exposures should be treated with copious flushing with clear water for 15 minutes. For ocular exposures, eyes should be flushed with room temperature water or sterile saline solution for 15 minutes. Fluorescein staining of the eyes should be performed, and corneal erosion or ulceration should be treated as needed. Animals with significant respiratory signs (coughing, dyspnea, etc.) should be monitored for a minimum of 24 hours for the development of pulmonary edema. Supplemental oxygen or other respiratory supportive care should be used as needed.

**Alkalis**

Alkali products include sodium or potassium hydroxide, ammonium hydroxide, sodium or potassium hydroxide, and potassium permanganate. Common sources of alkaline products include drain openers, automatic dishwasher detergents, alkaline batteries, toilet bowl cleaners, swimming pool products and radiator cleaning agents. Agents with pH greater than 11 should be considered to be capable of causing significant corrosive injury. Alkaline agents penetrate local tissue rapidly and deeply, causing liquefactive necrosis. Unlike acidic products, very little pain may be evident upon initial contact with an alkaline product, which may encourage further contact and ultimately result in more extensive exposures.

Clinical signs may not develop immediately, and it may require up to 12 hours for the full extent of tissue damage to become apparent. Acute signs are similar to acid ingestions but may also include significant hyperthermia (>104°F). Esophageal and/or pharyngeal ulceration may occur. Treatment is the same as with acid exposures, emesis should NOT be induced and activated charcoal should not be given. Evidence of oral discomfort and inflammation generally develop within 2 to 4 hours, although the full extent of injury may not be evident until 12 hours post exposure. Esophageal lesions may take weeks to heal and there is risk of stricture formation, leading to impairment of esophageal function.

**Cationic detergents**

Cationic detergents are contained in fabric softeners, some potpourri oils, hair mousse, algaecides, germicides and sanitizers. Cationic detergents are more toxic than non-ionic/anionic detergents and can cause extensive systemic and local effects at levels as low as 2% or less. Local tissue injury caused by cationic detergents resembles that seen with exposure to alkaline products (see Alkali section). In addition, cationic detergents can cause systemic toxicity including CNS depression, coma, seizures, hypotension, muscular weakness and fasciculations, collapse, pulmonary edema, and metabolic acidosis; the mechanism of these signs is not known. Treatment of local exposure is similar to that for alkaline products (see Alkali section). Systemic signs should be treated symptomatically (i.e. fluids for hypotension, diazepam for seizures, etc.).

**Pennies**

Pennies minted since 1983 contain 99.2% zinc and 0.8% copper, making ingested pennies a rich source of zinc. Other potential sources of zinc include hardware such as screws, bolts, nuts, etc., all of which may contain varying amounts of zinc. In the stomach, gastric acids leach the zinc from its source, and the ionized zinc is readily absorbed into the circulation, where it causes intravascular hemolysis.

The most common clinical signs of penny ingestion are vomiting, depression, anorexia, hemoglobinuria, diarrhea, weakness, collapse and icterus. Secondarily, acute renal failure may develop. Clinical laboratory abnormalities will be suggestive of hemolysis (elevated bilirubin, hemoglobinemia, hemoglobinuria, regenerative anemia) and may also indicate the development of kidney failure. Serum zinc levels may be obtained—blood should be collected in all plastic syringes (no rubber grommets) and shipped in Royal blue top vacutainers to minimize contamination with exogenous zinc. Radiography of the abdomen may reveal the presence of coins or other “hardware” within the stomach.

Treatment for recently ingested pennies would include induction of vomiting. Activated charcoal is not indicated, as it is of little benefit in binding metals. Removal of zinc-containing foreign bodies via endoscopy or gastrotomy/enterotomy may be required. Treatment for symptomatic animals should include blood replacement therapy as needed, intravenous fluids, and other supportive care. The use of chelators may not be necessary in cases where prompt removal of the zinc source is accomplished. If chelation therapy is instituted, careful monitoring of renal parameters is important for the duration of therapy.

**Polyurethane adhesives**

Isocyanate glues (Gorilla Glue®, Elmer’s ProBond Polyurethane Adhesive®) are expanding wood glues that have been associated with gastric foreign bodies (FB) in dogs. These products contain isocyanates. When ingested (chewing a 2 oz bottle of adhesive has been sufficient) the adhesive polymerizes into a large, friable FB that can form a cast of the gastric lumen. The adhesive is hygroscopic, absorbing water from the stomach as it expands and the warm body temperature may also play a role in expansion. Dogs
licking small amounts off of the floor or ingesting paper towels soaked with the product generally had mild, transient GI signs but no FB. Attempts to dilute recently ingested glues with food or liquids have not prevented FB development. Do not induce emesis due to risk of expanding FB in esophagus. Radiographs can be performed to determine the presence of a FB in the stomach (looks like kibble). Sometimes the FB is large enough to palpate. Evidence of a foreign body has been seen as early as 4 hours post-ingestion, but radiographs at 24 hours post-ingestion are likely to be more reliable. If present, the FB will require surgical removal.

“The tasty” Chocolate

There are a wide variety of chocolate and cocoa products to which pets may be exposed, including candies, cakes, cookies, brownies, and cocoa bean mulches. The active (toxic) agents in chocolate are methylxanthines, specifically theobromine and caffeine. Methylxanthines stimulate the CNS, act on the kidney to stimulate diuresis, and increase the contractility of cardiac and skeletal muscle. The relative amounts of theobromine and caffeine will vary with the form of the chocolate (see table).

The LD₅₀’s of theobromine and caffeine are 100-300 mg/kg, but severe and life threatening clinical signs may be seen at levels far below these doses. Mild signs have been seen with theobromine levels of 20 mg/kg, moderate signs have been seen at 40-50 mg/kg, and seizures have occurred at 60 mg/kg. Clinical signs occur within 6-12 hours of ingestion. Initial signs include polydipsia, bloating, vomiting, diarrhea, and restlessness. Signs progress to hyperactivity, polyuria, ataxia, tremors, seizures, tachycardia, PVC’s, tachypnea, cyanosis, hypertension, hyperthermia, and coma. Death is generally due to cardiac arrhythmias or respiratory failure. Because of the high fat content of many chocolate products, pancreatitis is a potential sequela.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Milligrams per ounce</th>
<th>Theobromine</th>
<th>Caffeine</th>
</tr>
</thead>
<tbody>
<tr>
<td>White Chocolate</td>
<td>0.25</td>
<td>0.85</td>
<td></td>
</tr>
<tr>
<td>Milk Chocolate</td>
<td>58</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Semi-sweet Chocolate chips</td>
<td>138</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Baker’s Chocolate (unsweetened)</td>
<td>393</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>Dry cocoa powder</td>
<td>737</td>
<td>70</td>
<td></td>
</tr>
</tbody>
</table>

Management of chocolate ingestion includes decontamination via emesis. Activated charcoal may be given in some instances. Intravenous fluids at twice maintenance levels will help maintain diuresis and enhance urinary excretion. Because caffeine can be reabsorbed from the bladder, placement of a urinary catheter is recommended. Cardiac status should be monitored via EKG and arrhythmias treated as needed; propranolol reportedly delays renal excretion of methylxanthines, so metoprolol is the beta-blocker of choice. Seizures may be controlled with diazepam or a barbiturate. In severe cases, clinical signs may persist up to 72 hours.

Bread dough

Raw bread dough made with yeast poses mechanical and biochemical threats to animals ingesting it. The warm, moist gastric environment stimulates yeast growth, resulting in expansion of the dough mass, resulting in gastric distention, which if severe, can result in respiratory and vascular compromise. Perhaps more significant is the release of alcohol from yeast fermentation, resulting in profound metabolic acidosis, CNS depression and death. Early clinical signs may include unproductive attempts at emesis, abdominal distention, and depression. As alcohol intoxication develops, the animal becomes ataxic and disoriented. Eventually, profound CNS depression, weakness, recumbency, coma, hypothermia may occur. Management of exposure includes decontamination and treatment for alcohol toxicosis. Because emesis is often unsuccessful, gastric lavage with ice water may be needed.

Moldy food (tremorgenic mycotoxins)

Tremorgenic mycotoxins produced by molds on foods are a relatively common, and possibly under-diagnosed, cause of tremors and seizures in pet animals. Because of their relatively indiscriminate appetites, dogs tend to be most commonly exposed to tremorgens. These toxins are produced from a variety of fungi that grow on practically any food, including dairy products, grains, nuts, and legumes; compost piles may also provide a source of tremorgens.

Clinical signs include fine muscle tremors that may rapidly progress to more severe tremors and seizures. Death generally occurs in the first 2 to 4 hours and is usually secondary to respiratory compromise, metabolic acidosis or hyperthermia. Other signs that may be seen include vomiting (common) hyperactivity, depression, coma, behavior alterations, tachycardia, and pulmonary edema. Asymptomatic animals exposed to moldy foods should be decontaminated via emesis or lavage followed by activated charcoal and cathartic. In symptomatic animals, control of severe tremors or seizures has priority over decontamination. Seizures may respond to diazepam, tremors respond best to methocarbamol (Robaxin®; 55-220 mg/kg IV to effect). Supportive care should include intravenous fluids, thermoregulation, and correction of electrolyte and acid-base abnormalities. In severe cases, signs may persist for several days, and residual fine muscle tremors may take a week or more to fully resolve. Testing of stomach content, suspect foods, or vomitus for tremorgens is available through the Animal Health Diagnostic Laboratory, Michigan State University (517-355-0281).
Macadamia nuts
Macadamia nuts are cultivated from Macadamia integrifolia trees commonly found in Hawaii and Australia. After ingesting macadamia nuts, dogs develop weakness, depression, vomiting, ataxia, tremors, transient paresis, and hyperthermia. The mechanism of macadamia nut toxicosis in dogs is not known. Signs develop within 12 hours and most dogs return to normal with minimal care within 48 hours. Clinical signs are reported at ingestions as low as 2.4 g/kg body weight. Treatment of clinical signs includes fluids and thermoregulation. Prognosis of macadamia nut intoxication is good.

Xylitol
Xylitol is a sugar alcohol. It is used in sugar-free products such as gums and candies as well as for baking. It doesn’t cause significant increases in blood glucose or insulin in humans. However, in dogs, xylitol causes a rapid, dose-dependent insulin release followed by potentially significant hypoglycemia. Signs can include vomiting, weakness, ataxia, depression, hypokalemia, seizures, and coma. Some dogs have developed liver dysfunction or failure following ingestion of xylitol although the mechanism of action is unknown.

Treatment of xylitol ingestion by dogs should include emesis, if asymptomatic. A dog can show signs of hypoglycemia in as few as 30 minutes. Activated charcoal does not bind xylitol. Frequent small meals or oral sugar supplementation may be used to manage dogs not showing signs. If clinical signs of hypoglycemia develop, a bolus of IV dextrose followed by a dextrose CRI should be used to control moderate to severe hypoglycemia. Hypokalemia, likely secondary to insulin-induced movement of potassium into cells, should be treated if significant. Treatment should continue until blood glucose normalizes. Liver enzymes should be monitored for 24 hours.
Prevent toxicant absorption
Decontamination should be instituted only after the animal has been fully stabilized. If there could be possible legal action, seal with tape and initial/date sample. It is important to maintain records of chain of custody of samples (vomitus, carcass, etc.).

Ocular exposure
Ocular exposures may cause irritation or corrosion of the ocular tissues depending on the substance, the concentration, the exposure time and the sensitivity of the patient. With any ocular exposure, the eyes should be flushed repeatedly with tepid water or saline solution for a minimum of 20-30 minutes. An eyedropper may be used for smaller patients. With a larger patient, fill a plastic cup and slowly pour over the ocular area, or a medicinal syringe may be used. Patients may be given a mild sedative prior to flushing if needed and if the health of the patient will allow. If not sedated, the patient should be allowed to rest at regular intervals during the flushing to minimize stress. Fluorescein staining should be performed after flushing and repeated at 12 – 24 hours post-exposure to check for corneal ulceration. Treatment with lubricant ointments should follow staining, and topical medications applied as indicated.

Dermal exposure
Dermal exposures may occur to a large variety of substances including petroleum products, pesticides and insecticides, corrosive or irritating materials and substances that are sticky (tar, asphalt, sap and glue). Removal of dermal substances may be less stressful if the patient is sedated. Sedatives should only be used if the health of the patient will allow. If not sedated, the patient should be allowed to rest at regular intervals during the bathing to minimize stress.

Bathing
For dogs and cats, bathing in a mild liquid dishwashing detergent (e.g. Dawn) and warm water is recommended. Baths may need to be repeated to completely remove the toxicant. Afterwards, the animal should be rinsed well with warm water and towel dried to prevent chilling. These patients should be kept in a warm environment away from drafts until completely dry. Dermal substances can be removed from very small animals such as birds, reptiles or rodents by misting with room temperature water in a warm environment. Misting should continue until the product can no longer be detected on the coat or feathers by odor or touch. If misting is insufficient at removing the product, a liquid dishwashing detergent (e.g. Dawn) should be diluted in the misting bottle and applied, making sure to avoid the eyes. After removal of the substance, the animal should be rinsed via misting with clear water until all soap is removed. With heavy exposures, the animals may be bathed with liquid dishwashing detergent and rinsed well, with care taken not to over-stress the animal. After misting or bathing, the animal should be wiped with a dry towel and kept in a warm environment away from drafts until completely dry.

Sticky substances
When dealing with sticky substances (e.g. gum, glue traps, tar, etc), the use of solvents should be avoided as solvents may cause dermal irritation or burns. To remove sticky substances from mammals, trim the fur to remove as much of the substance as possible. Then work a small amount of vegetable oil, mineral oil, mayonnaise or peanut butter through the rest of the substance until it breaks down into "gummy balls". Afterwards, wash with liquid dishwashing detergent as described above. For birds, do not trim the feathers, just utilize vegetable oil, mayonnaise or peanut butter and then bathe.

Oral exposure
Dilution
Dilution with milk, water, or liquid from water-packed tuna fish is recommended in cases of ingestion of corrosive or irritant products, exposure to toad secretions, or taste reactions due to topically applied products (e.g. “foaming kitties” following flea spray application). Dilution with milk may also aid in relief of oral discomfort secondary to chewing on plants that contain insoluble calcium oxalates in their leaves (e.g. Philodendron spp.). For birds and reptiles, juicy fruits and vegetables can be fed to accomplish dilution.

Emesis
Emetics generally empty 40-60% of the stomach contents and are assumed to be more beneficial than gastric lavage. Dogs, cats, ferrets, and potbellied pigs are examples of animals that can vomit. Emetics should not be used in rodents, rabbits, birds, horses, and ruminants. Induction of emesis is contraindicated with ingestion of corrosive agents or hydrocarbons. Pre-existing conditions (e.g. seizure disorders, severe dyspnea) may also cause use of an emetic to be contraindicated. Emesis should not be attempted if the animal...
has already vomited or is exhibiting significant clinical signs. Potential complications from emesis induction may include aspiration, persistent gastritis, and transient bradycardia (due to vagal stimulation).

Emesis is most productive if performed within 2-3 hours post-ingestion. In some cases, such as ingestion of chocolate, large numbers of sugar-coated tablets, grain-based rodenticides, or plant material, emesis may be effective even after 2-3 hours due to formation of boluses of product in the stomach (chocolate, tablets) or delay in gastric emptying (grain-based products, plants). Feeding the animal a small meal prior to inducing vomiting can increase chances of an adequate emesis.

Three percent (3%) hydrogen peroxide is a preferred emetic, especially if emesis is to be induced at home by the owner. Peroxide is readily available (needs to be “fizzy,” not flat), easy to administer, and often highly effective, especially in dogs. The dosage is 1 teaspoonful/5 lbs body weight, not to exceed 3 tablespoons. Vomiting usually occurs within 10-15 minutes and the dose can be repeated once if not initially successful. In the process of foaming (which triggers the vomiting) the peroxide is converted to water and oxygen, so if no vomiting occurs there is no concern about adverse effects from the retained peroxide. Overdosing with hydrogen peroxide should be avoided, as it may result in gastritis that may take days to resolve.

Apomorphine hydrochloride may also be utilized as an emetic in dogs. The recommended dosage is 0.04 mg/kg IV, SQ. Reversal of the CNS depression from apomorphine may be accomplished through the use of naloxone. An alternative route of administration is to instill apomorphine conjunctivally. The eye should be rinsed well after the animal has vomited. Anecdotally, the latter method results in less CNS depression than injection. Xylazine or dexmedetomidine can be used as an emetic in cats. It will cause significant hypotension, bradycardia and CNS depression, but these effects can be reversed with yohimbine or atipamezole.

Other emetics have been used including salt, liquid dishwashing liquid, syrup of ipecac and powdered mustard. Salt that is not vomited up may result in hypernatremia, causing severe neurological derangements. Syrup of ipecac generally has a delay in onset of action of up to 40 minutes in dogs and if not vomited up can cause myocardial depression and hypotension; the FDA has withdrawn ipecac as an emetic for human use due to questions of efficacy and safety. Powdered mustard does not appear to be an effective emetic in dogs or cats.

**Adsorbents**

Activated charcoal adsorbs toxicants and facilitates excretion via the feces by capturing the toxicant molecules in its micro-porous matrix. Activated charcoal is available in powder, liquid, gel and capsule forms. Activated charcoal capsules are not uniformly broken down in the GI tract of animals, and many will pass through the digestive tract intact. For this reason, if capsules are to be given, they must be cut open and the charcoal from multiple capsules pooled and then mixed with liquid to be administered. Activated charcoal tablets used for breath freshening or “anti-gas” are not appropriate forms of charcoal for decontamination.

Activated charcoal is contraindicated in animals that have ingested caustic materials. Chemicals that are not effectively adsorbed by activated charcoal include ethanol, methanol, fertilizer, fluoride, petroleum distillates, most heavy metals, iodides, nitrates, nitrites, sodium chloride, and chlorate.

The recommended dose of activated charcoal for all species of animals is 1-3 gms/kg body weight. Repeated doses of activated charcoal every 4-8 hours at half the original dose may be indicated when enterohemepatic recirculation of the toxicant is known to occur, or if ingestion of sustained release medications has occurred. See precautions regarding electrolyte disturbances under Cathartics below.

Kaolin-Pectin (Kaopectate) has also been recommended as an adsorbent in some instances. Kaolin is a form of clay (hydrated aluminum silicate) and pectin is a purified carbohydrate derived from fruits. Unfortunately, many of these kaolin-pectin products have recently been reformulated to contain salicylates, which makes their use in small animals less desirable. Another clay, bentonite (colloidal hydrated silica) has been used historically, but in most instances activated charcoal is a superior absorbent to the clays.

**Cathartics**

Cathartics enhance elimination of substances, including activated charcoal, by moving them through the gastrointestinal tract. Without cathartics, the toxicant bound by activated charcoal can eventually be released and absorbed by the GI tract. Cathartics are not to be used if the animal has diarrhea or is dehydrated. There are saline, osmotic and bulk cathartics.

**Caution:** Saline and osmotic cathartics may result in electrolyte disturbances (most notably hypernatremia) if overdosed or used in small, dehydrated or debilitated animals. Occasionally, hypernatremia may develop in animals with no apparent predisposition. Animals developing tremors, fasciculation, disorientation or other neurologic signs within 1-3 hours of receiving activated charcoal should have their electrolytes evaluated.

Bulk cathartics can be utilized in mammals and birds. One such cathartic is psyllium (Metamucil®). The dose for dogs and cats is 1 teaspoonful mixed with food every 12 – 24 hours. Psyllium is dosed in birds as follows: mix ½ teaspoon with 60 ml of baby food and give via a dosing syringe or eyedropper. Boiled white rice or unspiced, canned pumpkin may also be used in cats and dogs. Dilute peanut butter, fruit or vegetables can be utilized in birds and reptiles. Timothy hay can be utilized in rabbits.

Osmotic cathartics, like sorbitol, pull electrolyte-free water into the gastrointestinal tract. Sorbitol is commonly combined with activated charcoal in prepared products. The dose is 3ml/kg. Osmotic cathartics can be utilized in mammals, birds and reptiles.
Saline cathartics include sodium sulfate (Glauber's salts) and magnesium sulfate (Epsom salts). Saline cathartics act by stimulating gastrointestinal motility. The dose is 250 mg/kg mixed in water or activated charcoal. Saline cathartics should not be used in birds or reptiles.

**Enemas**
Enemas can be helpful when elimination of toxicants from the lower gastrointestinal tract is desired. The general technique is to use plain warm water or slightly soapy warm water. Enemas are not recommended for birds. In reptiles, enemas may be useful since ingested materials often lag for prolonged periods in the colon.

**Lavage**
**Gastric lavage** is used in mammals to remove recently ingested toxicants. Gastric lavage should not be used to remove caustic substances or hydrocarbons. Rabbits have very thin stomachs wall so use great caution when performing gastric lavage in this species. Gastric lavage is generally considered to be less effective than emesis in removing toxicants from the stomach, but may be indicated in cases where induction of emesis has been ineffective or is not possible (e.g. seizing animals). General anesthesia must be maintained when performing gastric lavage. A cuffed endotracheal tube should be in place to prevent aspiration. Body temperature water or physiologic saline (preferred for small patients) should be instilled via gastric tube at 10 ml/kg BWT. Use only gravity to instill and to drain the liquid, repeat until lavage fluid runs clear. Inclining the patient head-down at 20-degree angle will facilitate fluid removal, and use of large bore tubes and multiple flushes may yield better success. Body temperature should be monitored closely, as animals may become hypothermic even when body temperature water has been used. Potential complications from gastric lavage may include gastric or esophageal perforation, aspiration, and hypothermia.

**Enterogastric lavage** is sometimes recommended when potentially lethal oral exposure has occurred and there is need for evacuation of more than just the stomach. Gastric lavage is performed as directed above and an enema administered. A pre-anesthetic dose of atropine (0.02 mg/kg), if not already given for anesthesia and not contraindicated, may aid in intestinal relaxation and prevent abdominal distention. With the stomach tube left in place, the enema tube is attached to a water faucet and digital pressure around the rectal orifice is used to seal the tube in place. Low pressure, body temperature water is allowed to slowly fill the intestinal tract until water flows from the stomach tube; gently massaging the intestines may via abdominal palpation may enhance the water passage. Once the water from the stomach tube flows clear, the process is complete. Potential complications from this procedure include intestinal rupture, profound hypothermia, and gastroenteritis.

**Gastrotomy** may be indicated for agents that will not readily pass through the gastrointestinal tract on their own. This may include ingestion of pennies and iron supplements (both of which tend to adhere to gastric mucosa), raw yeast bread dough, expandable polyurethane wood glues, lead objects, and ingestion of large amounts of toxic plant material, pill vials or medication tubes.

**Crop lavage** is used in birds to remove recently ingested toxicants. Frightened and fractious birds should be anesthetized prior to crop lavage. An endotracheal tube should be placed to prevent aspiration. The crop should be flushed gently with warm saline and aspirated. This should be repeated 3 – 4 times. Crop lavage should not be performed in cases of caustic or petroleum distillate ingestion.

**Miscellaneous**
For patients with cheek pouches (e.g. many rodents), the cheek pouches should be emptied in cases of oral exposure to a toxicant.

**Intralipids**
Intralipids are lipid emulsions. Lipid emulsions are commonly used as a fat component for parenteral nutrition. While more studies are needed, lipid therapy is very exciting new treatment for lipid soluble toxicoses. Lipid use is based on human research investigating bupivacaine overdoses. The possible mechanism for lipid rescue is that the lipids bind to the fat soluble toxin (“lipid sink”) and bound toxin is inactive.

Liposyn, or any other 20% lipid solution, can be given through a peripheral catheter and is relatively inexpensive. A bolus of 1.5 ml/kg is given (over 1 minute if cardiac arrest, slower otherwise), followed by 0.25 ml/kg/min for 30-60 minutes. This is repeated in four hours if the serum is clear. Lipid therapy can hasten recovery time in some cases.

There are possible complications to lipid therapy: significant lipemia, pancreatitis, transiently increased liver enzymes, volume overload and lipids can also remove antidotes and other therapies.

**Cholestyramine**
Cholestyramine is an anion exchange resin available by prescription only. It is used to lower cholesterol in patients who have not responded to normal therapies. Cholestyramine has been used in human medicine to aid in the treatment of toxicoses (amiodarone, digoxin, chlordane, methotrexate, piroxicam, vitamin D, warfarin, blue-green algae, indomethacin). It binds with bile acids in the intestine, preventing their reabsorption. This stops enterohepatic recirculation. Cholestyramine is not absorbed out of the digestive tract, so it has no systemic effects, but constipation and mild liver enzyme elevation may be seen. The dose is 0.3 – 1 g/kg TID for
several days (depends on toxin ingested). For our patients, the powder should be given or mixed with canned food. Cholestyramine is cost effective with a price around $50-80 for 240g.

**Inhalation exposure**

“Decontamination” of animals exposed to inhaled toxicants primarily involves removing them from the source of the inhalant and administering oxygen as needed. Depending on the type of inhalant (e.g. smoke, chlorine gas, etc.), monitoring for up to 24 hours for the development of noncardiogenic pulmonary edema is recommended.

**Ancillary support**

General supportive care includes maintaining hydration, ensuring adequate urine output, monitoring of respiratory, cardiac and neurologic status, and managing clinical signs as they develop. Recumbent or comatose animals require careful monitoring and thermoregulation. Gastrointestinal protectants or anti-emetics may be required (e.g. NSAID overdosages). Management of secondary hepatic or renal injury is imperative.
**Intoxications of Marijuana and New Cannabinoid Products**

**Tina Wismer, DVM, DABT, DABVT**
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**Marijuana**

Over the past few years there has been an increase in the number of marijuana intoxicated pets presented to veterinary clinics. It is unknown if this is truly an increase in cases, if people are more willing to seek veterinary care due to changing attitudes about marijuana or if more potent forms of marijuana are prompting pet owners to seek medical attention.

Marijuana (Cannabis sativa) is used both recreationally and medicinally by people. It is thought to be the most commonly used illegal substance worldwide, with nearly half the population in the United States reporting at least one time use. Marijuana has been used as an anti-emetic, analgesic, anticonvulsant, muscle relaxant, appetite stimulant and to decrease intra-ocular pressure in glaucoma. Currently in the United States, there are 25 states that legally allow cannabis for medical use and four states (Alaska, Colorado, Oregon, Washington) and the District of Columbia, have legalized small amount of cannabis for recreational use by adults age 21 years of age and older. However, it is still a Schedule I controlled substance under the US Controlled Substances Act.

The main toxic principle of marijuana is a resin called tetrahydrocannabinol (THC), but the plant contains over 60 cannabinoids and cannabiol. The amount of these resins will vary with plant variety, sex of plant, "sensemilla" more toxic, geographic location, and growing season. THC acts via stimulation of cannabinoid receptors throughout the body. Cannabinoid receptors found in the pain pathways of the brain and spinal cord mediate its analgesic effects. The antiemetic properties are thought to be secondary to the effect of cannabinoid receptors within the central nervous system. d-9-THC also affects dopaminergic, cholinergic, noradrenergic, serotonergic, and GABA sites. There are 2 main cannabinoid receptors, CB1 and CB2. CB1 receptors, primarily found in the CNS, are associated with psychoactive effects, and peripheral CB2 receptors are associated with the immune system, responsible for the immunomodulatory effects of cannabinoids.

In the past, most pet exposures to marijuana were ingestions of plant material from baggies or joints. This has changed and now edibles (cookies, brownies, etc.) and concentrates (oils, waxes, shatters) have become more popular. Through selective breeding, THC levels have become higher than ever. The University of Mississippi Potency Monitoring Project has reported that THC levels have more than doubled over the last 25 years. THC levels in plant material ranges from 1-8%, extracts 28%, and hash oil up to 50%. Another change has been the increase in marijuana butter based edibles. THC butter is made by heating marijuana in butter to extract the lipophilic THC. This butter is then used to make the baked goods. While both dogs and cats willing ingest plant material, dogs are the most likely to consume edibles. Many of the edibles also incorporate chocolate and this can increase the toxicity.

Another issue with THC containing products is quality control. In one study, 75 products were evaluated to determine the amount of cannabidiol and THC found in the various products. The results indicated that 17% of products were accurately labeled, 23% were under labeled and 60% were over labeled with respect to THC content.

The most common clinical signs after ingesting marijuana are ataxia, lethargy, and urinary incontinence. However, about 25% of patients may present stimulated instead. Hyperesthesia and disorientation are also frequently seen along with bradycardia, hypothermia, mydriasis, and tremors. Animals that get into concentrates or THC butter products may become comatose and hypotensive. Clinical signs can be seen as soon as 30 minutes after oral ingestion and may last up to 72 hours.

Urine drug screening tests have not been validated for use in dogs. Most over-the-counter urine drug tests will give a false negative result for marijuana (THC) in dog urine. This is thought to be due to different metabolites produced by dogs when compared to humans (8-OH-Δ9-THC produced by dogs vs 11-OH-Δ9-THC in humans). These different metabolites may also explain the urinary incontinence that is seen in dogs and not in other species.

As marijuana is an anti-emetic, inducing emesis may not be successful but can be tried with recent (< 30 minutes) oral exposures if the animal is asymptomatic. Activated charcoal is generally not needed. Intravenous fluid administration should be started and adjusted if dehydration or hypotension develops. Diazepam or low dose acepromazine (if normotensive) can be used for agitated patients. Monitor blood glucose levels in young animals. Many cases with plant material ingestion can be managed at home with confinement and monitoring the ability to ambulate. Monitor blood glucose levels in young animals. Many cases with plant material ingestion can be managed at home with hydration or multiple dose charcoal in the management of marijuana toxicosis. THC is highly protein bound (97% to 99%) and has a large volume of distribution (10 L/kg, with high lipophilicity), and thus dialysis or hemoperfusion have no theoretical benefit.
Toxicity is dose-related, however, there is a wide-range of variability among individuals. Patients with hepatic impairment may be more sensitive. A lethal dose has not been established in dogs or cats, but it only takes a small amount to cause clinical signs. Fortunately death is rare. There are published reports of two dog deaths after ingesting edibles and a 12-week-old ferret after ingesting plant material. If appropriate treatment is implemented, the prognosis is good and no permanent effects should be anticipated.

**Synthetic cannabinoids**

Synthetic marijuana, or more precisely synthetic cannabinoids, are chemicals synthesized in laboratories and mimic the effects of delta-9-tetrahydrocannabinol (THC), the main psychoactive ingredient in marijuana. They may also be called cannabinoid receptor agonists or tetrahydrocannabinol (THC) homologs. These compounds are not structurally related to classic cannabinoids or THC. However, they primarily interact with the CB1 receptors within the CNS, resulting in cannabis-like effects. Synthetic cannabinoids have shown a higher binding affinity for receptors than THC. They have been divided into 7 major groups based on their chemical structure:

- Naphthoylindoles (e.g. JWH-018, JWH-073 and JWH-398)
- Naphthylmethylindoles
- Naphthoylpyrroles
- Naphthylmethylindenes
- Phenylacetylindoles (i.e. benzoylindoles, e.g. JWH-250)
- Cyclohexylphenols (e.g. CP 47,497 and homologues of CP 47,497)
- Classical cannabinoids (e.g. HU-210)

These compounds are sprayed on plant material and sold as potpourri or herbal incense labeled "not for human consumption." These products are often referred to as “herbal highs” or “legal highs” because of their hazy legal status and purported natural herbal make-up. They may also be sold as a liquid for use in e-cigarette type vaporizers. These products are available through the internet, gas stations, liquor stores, and head shops (see Table 1 for common brand names).

These compounds first began appearing in Europe in 2004 and have since come to the United States. Their original use was as a research tool to investigate analgesic and anti-inflammatory properties of cannabinoids but without the psychotropic effects. These substances have no accepted medical use in the United States.

There have been over 40 different synthetic cannabinoids identified and classified as Schedule 1 controlled substances by the DEA. This makes it it illegal to manufacture, distribute, possess, import, or export these cannabinoids. As the older generations of synthetic cannabinoids are made illegal, new ones take their place. These ‘new synthetic cannabinoids’ may use the same or similar product labels while having a higher intensity or longer-lasting high putting the user at more risk. Other contributing factors to synthetic cannabinoid toxicosis include potential unidentified contaminants (eg, sympathomimetics), or bath-to-bath variability of an individual THC homolog among products. The specific composition of these products is constantly changing as individual chemical constituents are banned. In addition, there is very little known regarding the herbal mixtures used as the delivery vehicle; the herbs themselves may also have additive psychoactive properties.

Use of synthetic cannabinoid receptor agonists has been associated with adverse psychiatric, cardiovascular, renal, pulmonary, and neurologic effects in humans. Clinical signs in dogs are similar to traditional marijuana exposures: ataxia, lethargy, hypothermia, bradycardia, vomiting, urinary incontinence, hyperesthesia, mydriasis and disorientation. However, cardiac signs appear to be more prevalent and seizures have been reported. One fluorinated synthetic cannabinoid (XLR-11) has been associated with AKI in humans.

Treatment for synthetic cannabinoids is the same as for marijuana. Monitor respiratory function, heart rate, blood pressure and body temperature. In severe cases, intralipids may be helpful. No specific CBC or chemistry profile abnormalities are expected.

The toxic dose is variable, depending on the specific THC homolog. The duration of effects can be shorter or longer than THC when smoked, but there is no kinetic information about ingestion of these products.

So why would a person chose synthetic cannabinoids over the real thing? In many cases it has to do with drug testing. The typical screening tests on blood and urine samples will be false negative. This is due to a difference in metabolites. However, some private labs have now developed tests to detect the metabolites of certain cannabinoids in blood or urine.

**Cannabinoids**

Cannabinoids (CBDs) do not have the psychoactive properties of THC and have been suggested for pain control and appetite stimulation in pets. CB2 selective agonists have been shown to be effective in the treatment of pain, various inflammatory diseases, and osteoporosis in humans. CBD even has anticonvulsant-activity. At this point more research is needed in this area. There is no known appropriate dose for pets and the ASPCA Animal Poison Control Center has had dogs develop the same signs as THC ingestion after ingesting CBD only products (quality control?).
**Salvia divinorum**

Salvia is a plant in the mint family that has been used historically for religious rituals and herbal healing. Salvia contains salvinorin A which is hallucinogenic. In a double blind, placebo-controlled trial, healthy humans experienced hallucinations without a significant change in HR or BP. In humans with inhalation exposures, hallucinations occur within seconds and may last for 30 minutes. There is some absorption through the oral mucosa, but hallucinogenic effects are not seen after oral ingestion. Salvia is not scheduled by the DEA but some states have restrictions. ASPCA APCC data shows dogs exposed to *Salvia divinorum* develop signs similar to THC (anxiety, ataxia, bradycardia, hyperthermia, nausea, panting, sedate, urinary incontinence).

### Table 1. Common names of synthetic cannabinoid products

<table>
<thead>
<tr>
<th>Spice</th>
<th>K2</th>
<th>Skunk</th>
<th>Moon Rocks</th>
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<td>Golden Leaf XXX</td>
<td>Blaze</td>
<td>Red x Dawn</td>
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<td>Yucatan</td>
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<td>Crazy Clown</td>
<td>Mojo</td>
<td>Black Mamba</td>
<td>Black Voodoo</td>
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<td>Scooby Snax</td>
<td>Bizzaro</td>
<td>Silver</td>
<td>Aroma</td>
<td>Genie</td>
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</tbody>
</table>

**References**

Toxicity of Human Medications
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Aspirin
Aspirin (acetylsalicylic acid, ASA) is the salicylate ester of acetic acid and is a weak acid derived from phenol. It is available as tablets and capsules (65, 81, 325, and 500 mg), powders, effervescent tablets and oral liquid preparations. Aspirin reduces pain and inflammation by reducing prostaglandin and thromboxane synthesis through inhibition of cyclooxygenase. At very high doses, aspirin and other salicylates uncouple oxidative phosphorylation leading to decreased ATP production. Salicylates also affect platelet aggregation.

Aspirin is rapidly absorbed from the stomach and proximal small intestine. Aspirin is metabolized in the liver and excreted through the urine. The elimination half-life increases with the dose. Cats are deficient in glucuronyl transferase and have prolonged excretion due to decreased metabolism. Elimination is also slower in neonates and geriatric animals.

Signs may include vomiting (+/- blood), hyperpnea, respiratory alkalosis, metabolic acidosis, gastric hemorrhage, central lobular liver necrosis, and bleeding diathesis. Fever and seizures may be seen due to the uncoupling of oxidative phosphorylation. Renal insufficiency is uncommon with salicylate toxicoses.

Emesis can be performed in the asymptomatic animal, unless contraindicated. Activated charcoal adsorbs aspirin and repeated doses may be used with large ingestions. A cathartic should be used, unless the animal is dehydrated or has diarrhea. Liver values, glucose, acid base status and electrolytes should be monitored. Maintain hydration and start GI protectants (sucralfate, H2 blockers, +/- misoprostol, +/- omeprazole). Gastric protectants should be continued for 5 - 7 days, longer in the symptomatic patient. Antiemetics should be used to control vomiting. Alkalization of the urine results in ion trapping of salicylate in the kidney tubule and increases its secretion. Ion trapping should only be used in cases where the acid base balance can be monitored. Assisted ventilation and supplemental oxygen may be required if the animal is comatose. Seizures should be treated with diazepam. Fluids, whole blood, and electrolytes may be needed to control hypotension and hemorrhage, manage acute bleeding ulcers, and correct electrolyte abnormalities. Acid base imbalances should be corrected. Hyperpyrexia should be treated conservatively as aggressive cooling (ice baths or cold water enemas) may result in hypothermia. Prognosis is good if the animal is treated promptly and appropriately. The development of hepatic necrosis is considered to have a poor prognosis. With hepatic damage, treatment may need to be continued for weeks.

Other salicylates
Salicylates are found in many products. Bismuth subsalicylate (Pepto-Bismol®, Kaopectate®) contains 9 mg of salicylate in 1 ml (2 tablespoons = 325 mg aspirin). Topically applied salicylates (arthritis, psoriasis, teething, wart removal) can be absorbed through the skin and cause systemic problems. Oil of wintergreen is used as a flavoring for candy and contains approximately 98% methyl salicylate.

Acetaminophen
Acetaminophen (Tylenol®, non-aspirin pain reliever, APAP) is a synthetic non-opiate derivative of p-aminophenol. Acetaminophen is rapidly and almost completely absorbed from the GI tract. Peak plasma levels are seen at 10-60 minutes (60-120 min for extended release). Two major conjugation pathways are used to metabolize APAP by most species (P-450 metabolism followed by glucuronidation or sulfation). APAP-induced hepatotoxicity is due to the formation of the oxidative metabolite, N-acetyl-para-benzoquinoneimine (NAPQI). Glutathione can conjugate and neutralize NAPQI, but when glutathione stores are depleted, NAPQI binds to sulfhydryl groups on the hepatic cell membrane and damages the lipid layer. Another metabolite, PAP (para-aminophenol), appears to be responsible for methemoglobinemia and Heinz body formation.

Methemoglobin values increase within 2-4 hours, followed by Heinz body formation. Clinical signs include depression, icterus, vomiting, hypothermia, methemoglobinemia, facial or paw edema, death, dyspnea, and hepatic necrosis. Liver necrosis is less common in cats than in dogs. Clinical signs of methemoglobinemia may last 3-4 days. Hepatic injury may not resolve for several weeks. Early decontamination is most beneficial. Emesis is usually unrewarding. Activated charcoal adsorbs APAP and a cathartic should also be used, unless the animal is dehydrated or has diarrhea. Monitor liver values and for the presence of methemoglobinemia. ALT, AST and bilirubin may rise within 24 hours after ingestion and peak within 48 to 72 hours.

Symptomatic patients need initial stabilization, including oxygen if dyspneic. Treatment involves replenishing the glutathione stores and converting methemoglobin back to hemoglobin. N-acetylcysteine (Mucomyst®, NAC) is a precursor in the synthesis of glutathione and can be oxidized to organic sulfate providing sulfhydryl groups that bind with APAP metabolites to enhance elimination. An initial oral loading dose of 140 mg/kg (dilute to 5% in dextrose or sterile water) is given, followed by 70 mg/kg PO QID for 7 treatments, or longer if still symptomatic. Fluid therapy is used to correct dehydration and for maintenance needs, not for

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diuresis. Whole blood transfusion may be necessary to increase oxygen carrying capacity, but cats must be monitored for volume overload. Ascorbic acid provides a reserve system for the reduction of methemoglobin back to hemoglobin; however, ascorbic acid has questionable efficacy and may irritate the stomach. Cimetidine is an inhibitor of cytochrome p-450 oxidation system but takes several days to become effective and should be avoided in cats. It has now been demonstrated that cimetidine blocks one of the only pathways that cats have to convert methemoglobin back to hemoglobin. For hepatic injury, s-adenosylmethionine (SAMe, Denosyl-SD4®) at 20 mg/kg/day shows a positive effect for treatment of APAP toxicosis. Prognosis is good if the animal is treated promptly. Animals with severe signs of methemoglobinemia or with hepatic damage have poor to guarded prognosis.

**Ibuprofen**

Ibuprofen (Motrin®, Advil®, etc.) is a nonsteroidal anti-inflammatory agent. Ibuprofen inhibits prostaglandin synthesis by blocking the conversion of arachidonic acid to various prostaglandins. Ibuprofen decreases secretion of the protective mucous layer in the stomach and small intestine and causes vasoconstriction in gastric mucosa. Ibuprofen inhibits renal blood flow, glomerular filtration rate, tubular ion transport, renin release and water homeostasis. Ibuprofen may also affect platelet aggregation and possibly hepatic function. Serious hepatotoxicosis is not a common problem with ibuprofen. Absorption of ibuprofen is rapid (0.1 to 1.5 h). Plasma half-life in the dog has been reported to be 2-2.5 hours, but the elimination half-life is considerably longer. Ibuprofen is metabolized in the liver and undergoes significant enterohepatic recirculation before being excreted in the urine. The onset of GI upset is generally within the first 2-6 hours after ingestion, with GI hemorrhage and ulceration occurring 12 hours to 4 days post ingestion. Renal failure often occurs within the first 12 hours after massive exposure to an NSAID but may be delayed for 3-5 days.

Emesis can be performed in the asymptomatic animal. Activated charcoal adsorbs ibuprofen and a cathartic should also be used, unless the animal is dehydrated or has diarrhea. 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 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. 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. 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.

**Opioids and opiates**

There are many opioids and opiates used in human and veterinary medicine. Opioids and opiates are synthetic or natural compounds derived from the opium poppy, *Papaver somniferum*, and are generally classified (agonist or partial agonist) by their ability to exert effects at the different opioid receptors (mu, kappa, delta, sigma). Partial agonists are agonists at one (or more receptors) and antagonists at others. Opioids act centrally to elevate the pain threshold and to alter the psychological response to pain. Most of the clinically used opioids exert effect at the mu receptor (mu: subtype mediates analgesic effects, mu: mediates respiratory depression).

Opioids are well absorbed from the GI tract, but bioavailability is variable as some opioids have a large first pass effect (i.e. fentanyl). These opioids are administered in other manners (CRI, buccal, transdermal) to reach therapeutic blood levels. Metabolism varies, but opioids generally undergo hepatic metabolism (conjugation, hydrolysis, oxidation, glucuronidation, or dealkylation). This glucuronidation may account for the sensitivity of cats (who are deficient in glucuronyl-S-transferase) to opioids.

In dogs, CNS signs include depression, ataxia, and seizures. Respiratory depression, vomiting, bradycardia, and hypotension may be seen. Cats may show excitatory behavior and urinary retention. Detection of opioids can be made from urine or serum samples. Treatment in an asymptomatic animal may include emesis if the ingestion is recent. Activated charcoal with cathartic should be administered and the patient monitored for up to 12 hours. If the animal becomes symptomatic, naloxone (0.1-0.2 mg/kg IV, IN, IM or SQ) can be administered. As the duration of action of naloxone is much shorter than that of the opioids, repeat dosages may be necessary. Partial agonists/antagonists (i.e. butorphanol) may be used to partially reverse pure agonists if no naloxone is available. Monitor temperature, cardiac function and blood gases. Treatment times will vary with the half life of the opioid. If respiratory and cardiovascular function can be maintained then prognosis is good. For those cases that are seizing, prognosis is guarded.
<table>
<thead>
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<th>DRUG</th>
<th>ACTIVITY</th>
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(P = partial)

Fentanyl

Fentanyl suckers, lozenges and transdermal patches are becoming more frequently used in both human and veterinary medicine. The lozenges or suckers contain fentanyl citrate in a sucrose and liquid glucose base and are attractive to animals. The patches have poor absorption from the GI tract, but can be absorbed transmucosally while the animals are chewing on them. Signs are similar to other opioids with depression, bradycardia, hypotension, weakness, and pallor predominating. Treatment is as for other opioids.

Selective serotonin reuptake inhibitors (SSRIs)

Selective serotonin reuptake inhibitors (SSRIs) all differ structurally, but have the same ability to inhibit presynaptic neuronal reuptake of serotonin. Drugs in this class include fluoxetine (Prozac®), paroxetine (Paxil®), sertraline (Zoloft®), fluvoxamine (Luvox®), citalopram (Celexa®) and escitalopram (Lexapro®). They have little to no effect on non-serotonin neurotransmitters and thus have less anticholinergic, sedative and cardiovascular side effects than other types of antidepressants. The most common signs of overdose are depression, vomiting, anorexia, ataxia, muscle tremors, arrhythmia (tachycardia and bradycardia are possible), and hypertension. The term serotonin syndrome has been used to describe multiple signs associated with severe SSRI toxicosis, including agitation, tremors, tachycardia, and hyperthermia. Other less common signs include diarrhea, salivation, mydriasis, seizures, nystagmus, and coma.

Emesis should only be attempted with recent exposures, assuming that the patient is asymptomatic. Gastric lavage may be considered if large numbers of pills were ingested. Activated charcoal with a cathartic should be administered and may be effective several hours after exposure. Treatment consists of monitoring vital signs closely, controlling clinical signs and providing appropriate supportive care. Diuresis does not enhance excretion because SSRIs are highly protein bound, but fluid therapy should be considered to help support blood pressure and maintain renal function. Diazepam can be used to control seizures and treatment of CNS signs may also help in the control of some of the other signs such as tachycardia, hypertension, and hyperthermia. Propranolol may be used to counter tachycardia. Cyproheptadine, in addition to being an antihistamine and an appetite stimulant, is a non-selective serotonin reuptake inhibitor. Chlorpromazine or acepromazine can be used in addition to cyproheptadine to treat agitation.

Venlafaxine

Venlafaxine (Effexor®) is a bicyclic antidepressant; it is a potent serotonin and noradrenaline reuptake inhibitor as well as a weak dopamine reuptake inhibitor. It is available as both an immediate release and extended release medication. While it is rare for cats to willingly ingest medications, cats and dogs seem to readily eat venlafaxine. Mydriasis, vomiting, tachypnea, tachycardia, ataxia and agitation are the most common signs. Treatment would consist of emesis in asymptomatic individuals. Activated charcoal can be administered with a repeated dose in 4-6 hours if an extended release formulation was involved. Heart rate and blood pressure should be monitored. Acetophenazine may be used for the agitation, and cyproheptadine may be useful in antagonizing the serotonin effects.

With ingestion of the extended release medication, cats can be symptomatic for up to 72 hours. Venlafaxine is lipid soluble, so intralipids can be used to decrease plasma levels and decrease treatment time. Liposyn, or any other 20% lipid solution can be given through a peripheral catheter. A bolus of 1.5 ml/kg is given, followed by 0.25 ml/kg/min for 30-60 minutes. This is repeated in four hours if the serum is clear. As an aside, venlafaxine will cause a false positive reaction for PCP on the OTC urine drug tests.

Amphetamines and related compounds

Amphetamines can be found in both prescription ADHD and weight loss medications (Ritalin®, Adderall®, Vyvanse®, Concerta®), as well as illicit substances (methamphetamine, crack). Pseudoephedrine is found in cold and allergy medications. Amphetamines and pseudoephedrine are sympathomimetic alkaloids. They stimulate alpha- and beta-adrenergic receptors, causing the release of endogenous catecholamines at synapses in the brain and heart. This stimulation causes peripheral vasoconstriction and cardiac stimulation resulting in hypertension, tachycardia, ataxia, agitation, tremors, and seizures.

Asymptomatic animals may have emesis induced and activated charcoal administered. Fluid therapy is important to enhance elimination and maintain CV stability. Agitation, hyperactivity, and tremors tend to respond best to phenothiazines. Diazepam can worsen dysphoria. Because part of the syndrome is related to serotonin excess, cyproheptadine has been used to manage some of the CNS effects. If tachycardia persists, propranolol may be used. Signs may last up to 48-72 hrs in severe cases.

Albuterol
Albuterol (Proventil®, Ventolin®) is a synthetic sympathomimetic amine with primarily beta-2 receptor agonist properties. It is used most commonly for the treatment of asthma. Albuterol binds to beta-2 receptors on the surface of the smooth muscle cells in many different tissues as well as in skeletal muscle, liver and cardiac tissue. Binding to the receptor initiates the conversion of ATP to cyclic AMP, which mediates a variety of intercellular responses resulting in smooth muscle relaxation, increased skeletal muscle contractility and an intracellular shift of potassium. Overdoses of albuterol may lead to effects of beta-1 stimulation, including increased inotropic and chronotropic effects on the heart.

Dogs are usually exposed by chewing on inhalers but there are also solutions, syrups, powders, tablets, and extended release tablets available. When inhalers are punctured, dogs get an inhalation plus an oral exposure. This leads to a quick onset of signs and prolonged duration signs. When inhaled, signs can begin in five minutes. Ingestions usually have a lag time of 30 minutes before clinical signs start. In dogs, signs generally resolve within 12 hours except for certain individuals who may experience signs for up to 48 hours. The most common signs seen are tachycardia, vomiting, depression, tachypnea, hyperactivity, muscle tremors, hypokalemia, and weakness. Rarely, death has been reported.

Decontamination is not advised for inhaler, solution or syrup exposure due to rapid absorption and onset of actions. Emesis (if within minutes of ingestion) and activated charcoal advised with tablet ingestion only (especially extended relief tablets). Vital signs, heart rate and rhythm, and serum potassium levels should be monitored closely for at least the first 12 hours post-exposure and longer if clinical signs persist.

Propranolol or other non-selective beta blockers should be administered if heart rates greater than 160 to 180 bpm are observed. Propranolol slows the heart rate, has direct myocardial depressant effects and helps normalize serum potassium levels. Potassium may be supplemented as needed and should be considered if serum potassium levels fall below 2.5 mEq/l. Animals with known or underlying cardiac disease may be at risk for decompensation and sudden death. Agitation can be treated with diazepam or low dose acepromazine. Prognosis in most cases is very good.

Imidazoline decongestants
Naphazoline (Clear Eyes), tetrahydrozoline, oxymetazoline (Afrin), and xylometazoline (Neo-Synephrine) are imidazoline decongestants. They are vasoconstrictors used for the symptomatic relief of rhinitis, sinusitis, or conjunctival inflammation. Imidazolines are sympathomimetic agents with primary effect on alpha-adrenergic receptors. There is little if any effect on beta-adrenergic receptors. Overdose or intoxication from oral ingestion or excessive topical administration can result in severe drowsiness with diaphoresis, hypotension or shock, bradycardia, respiratory depression, and coma.

Imidazoline decongestants are readily absorbed via the gastrointestinal tract. Most cases result when a dog punctures or chews a container and ingests the contents. Signs of intoxication may include (with decreasing frequency): vomiting, bradycardia, cardiac arrhythmias, poor capillary refill time, hypotension or hypertension, panting, upper respiratory sounds, depression/weakness/drowsiness, nervousness, hyperactivity and shaking. These signs are expected to be present within 30 minutes to 4 hours post exposure.

Emesis is generally not practical due to very rapid absorption and onset of clinical signs. Monitor heart rate and level of alertness. If no signs within 3-4 hours, do not expect to see any. Assess heart rate, rhythm and blood pressure and consider EKG if indicated. Administer intravenous fluids. If there is a significant decrease in heart rate, give atropine at a pre-anesthetic dose. Atropine may not raise the heart rate, but its use was followed by a significant rise in blood pressure. Give diazepam if significant nervous effects (apprehension, anxiousness, shaking) are present. If signs persist for several hours, assess serum electrolytes (potassium, sodium, chloride) and correct them as needed. Since this is an alpha-adrenergic agent, it is reasonable to consider using an alpha antagonist like yohimbine or atipamezole to reverse the hypotension and bradycardia.
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
Pimobendan (Vetmedin®) 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 give 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.). Phystostigmine can be given, but it is not an antidote. Phystostigmine 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 macrolides anti-parasitic. It can cause vomiting and ataxia, however, if spinosad is given in conjuction 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 pyrethrin. 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 pyrethroids. 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 inhalant 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 breakdown products in actively tremoring cats. Prognosis for mildly tremoring cats is usually good, but treatment may last 24-48 hours.

Essential oils
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.
Baclofen

Baclofen is a centrally acting skeletal muscle relaxant that mimics γ-aminobutyric acid (GABA) within the spinal cord and causes a flaccid paralysis of skeletal muscles. At oral therapeutic levels, baclofen has virtually no CNS effects due to its poor ability to cross the blood brain barrier, but in overdose situations, CNS effects are common. The most common clinical signs of toxicosis are vomiting, ataxia and vocalization/disorientation, but the most life threatening signs are dyspnea, respiratory arrest and seizures. Dyspnea and respiratory arrest are secondary to paralysis of the diaphragm and intercostal muscles.

The onset of clinical signs varies in dogs with signs occurring anywhere from 15 minutes to 7 hours post exposure (average of 1.9 hr). Duration of clinical signs vary from several hours to several days. Signs can continue long after serum baclofen levels have returned to normal due to the slow clearance from the CNS. Dog doses as low as 1.3 mg/kg can cause vomiting, depression and vocalizing. There are no established lethal doses in animals, but per the APCC data base, deaths in dogs have occurred at doses as low as 8 mg/kg.

Due to the rapid onset of clinical signs, emesis should be considered in only the asymptomatic, recently exposed patient. Gastric lavage may be considered with large ingestions, but care must be taken to ensure that anesthesia does not compound CNS depression. Short acting induction agents such as propofol followed by inhalent anesthesia with a protected airway is preferred. All asymptomatic cases should receive activated charcoal with a cathartic. Avoid magnesium-based cathartics (Epsom salts), as they may worsen CNS depression. Exposed animals should be monitored for 12 hours for development of clinical signs.

Ventilatory support is a prime concern and endotracheal intubation and positive pressure mechanical ventilatory support may be needed for an extended time in severe cases. Diazepam is the drug of choice for centrally acting skeletal muscle relaxant induced seizures. Propofol or isoflurane may be considered in cases that are refractory to diazepam. Long acting barbiturates or other agents that produce profound or prolonged CNS depression should be used with care. Cyproheptadine (1.1 mg/kg PO or rectally) has been used successfully to reduce the vocalization/disorientation seen in some animals. Fluid diuresis is used to enhance elimination and maintain blood pressure. Intralipids have been used successfully in early intoxications. The use of CNS respiratory stimulants are of questionable value and experimental studies have failed to consistently produce positive outcomes when flumazenil was used and have potential to cause serious adverse effects (seizures). Prognosis is variable, and can depend on the availability of ventilatory support for depressed patients. Prognosis is more guarded if seizures develop.

Calcium channel blockers (CCB)

Calcium channel blockers (verapamil, diltiazem, nifedipine, etc.) slow the activity of the SA pacemaker as well as conduction through the AV node. They also cause frequency-dependent channel blockade in the AV node so that it is effective in slowing supraventricular arrhythmias. Calcium channel blockers reduce total peripheral resistance, blood pressure, and cardiac afterload. They can also cause negative inotropic effects, but this is rarely of clinical significance.

Calcium channel blockers have a low margin of safety, causing hypotension and dysrhythmias. Bradycardia and AV nodal depression are the most common dysrhythmias, although others are possible. Hyperglycemia, hyperkalemia, hypokalemia, and hypocalcemia are possible. Due to a rapid onset of signs, the induction of emesis may not be appropriate. Standard decontamination practices should be performed in cases of significant exposure. Any dose exceeding the therapeutic dose should be monitored for cardiovascular signs. Fluid replacement and calcium chloride administration may help correct blood pressure and conduction abnormalities. Calcium gluconate (1 ml/10 kg of 10% solution) may be less effective than calcium chloride but can be used. Monitor for hypercalcemia if calcium is supplemented. Atropine and isoproterenol may be used for bradyarrhythmias and may be more effective following calcium administration. If hypotension persists, norepinephrine, neosynephrine, dopamine, dobutamine, or amrinone are recommended. Insulin and dextrose infusions in a canine model improved survival following verapamil overdose. The newest treatment is intralipids. Prognosis is dependent on dosage and response to therapy. Noncardiogenic pulmonary edema has been reported in cases of massive overdose.

Digoxin

Digoxin is a digitalis glycoside that can be found in elixers (0.05 and 0.15 mg/ml), tablets (0. 125, 0.25 and 0.5 mg) and capsules (0.05, 0.1 and 0.2 mg). Digitalis-like compounds (cardiac glycosides) are also found in several plants: oleander (Nerium oleander), foxglove (Digitalis purpurea), Kalanchoe sp. and lily-of-the-Valley (Convallaria majalis). These compounds inhibit the myocardial cell membrane Na-K ATPase pump. This inhibition results in increased intracellular sodium concentrations. The sodium must exit by exchanging with extracellular calcium. The sarcoplasmic reticulum binds the excess calcium and uses it to increase contractility. Digitalis is used in the treatment of congestive heart failure, atrial fibrillation or flutter and supraventricular tachycardias.
5-Fluorouracil (5-FU) is in the antimetabolite class of antineoplastic agents. The topical creams and solutions (Efudex, Fluoroplex, Adrucil) are extremely toxic if ingested. 5-FU destroys rapidly dividing cells, causing severe vomiting and GI irritation. It is likely ingestions especially in patients with underlying disease and risk factors. The drug, inactivating it. It is expensive however and several vials may be needed for treatment. Prognosis is guarded with large ingestions especially in patients with underlying disease and risk factors.

5-Fluorouracil (5-FU) is in the antimetabolite class of antineoplastic agents. The topical creams and solutions (Efudex, Fluoroplex, Adrucil) are extremely toxic if ingested. 5-FU destroys rapidly dividing cells, causing severe vomiting and GI irritation. It is likely converted to fluorocitrate affecting the Krebs cycle and causing seizures similar to fluoroacetate. If given enough time (5-20 days) and if the animal survives, it could destroy bone marrow stem cells resulting in leukopenia which can progress to a pancytopenia. This may be due to the 5-FU metabolite, FdUMP, not readily diffusing across cell membranes as 5-FU does, leading to delayed clearance from the bone marrow.

The onset of clinical signs usually occurs within 0.5 to 5 hours following ingestion. 5-FU rapidly distributes to the total body water and it is absorbed by all cells. In dogs that survived, signs lasted from 18 hours to 14 days. The minimum lethal oral dose for the dog is 20 mg/kg, but signs of toxicity are seen as low as 8.6 mg/kg. Often signs begin with vomiting (with or without blood) and progress to tremors and seizures within a few hours. The vomiting isn't always seen before seizures, nor are seizures seen in every case. Seizures may require care for more than 24 hours. Emesis, activated charcoal and cathartic can be started if the animal is asymptomatic and the ingestion was recent (less than 1 hour). Seizures and tremors are rarely controlled with diazepam. Pentobarbital, phenobarbital, gas anesthetics (isoflurane), and propofol have been used successfully. GI protectants and antiemetics should be started. IV fluids, thermoregulation, antibiotics, and pain control are very important parts of the therapy. If animals live through the severe vomiting and seizures, WBC's could start to decline in 5-20 days. Filgrastim (Neupogen) may be given for neutropenia (5-6 mg/kg SQ). Prognosis is guarded to poor once signs occur. Sixty-four percent of dogs ingesting 5-FU die or are euthanized.

5-hydroxytryptophan (5-HTP, griffonia seed extract) is a precursor of serotonin. 5-HTP is available over-the-counter and is used to treat a variety of disorders including obesity, depression, anxiety, insomnia, PMS, and compulsive gambling. Overdoses of 5 HTP induce "serotonin syndrome" due to overstimulation of serotonin receptors in nervous system, gastrointestinal tract, cardiovascular and respiratory systems.

In dogs the most common clinical signs include: vomiting, diarrhea, seizures, hyperthermia, hyperesthesia, depression, mydriasis, vocalization, death, blindness, hypersalivation, dysnea, ataxia/paresis, disorientation, hyperreflexia, and coma. Signs are similar, but vary in severity, whether 5-HTP or other serotonergic drugs such as SSRIs or MAOIs are ingested. Treatment of serotonin syndrome is largely symptomatic and supportive. Inducing vomiting is not recommended if clinical signs are present because of the increased risk of aspiration. Seizures and agitation generally respond to diazepam or phenothiazines (the drug of choice in humans), and barbiturates can be used in refractory cases. Because hyperthermia is a significant concern, cooling measures should be instituted. Diuresis does not enhance excretion, but intravenous fluids should be administered to support the cardiovascular system, aid in thermoregulation, and maintain renal blood flow. The use of cyproheptadine, a nonselective serotonin
antagonist, has shown to be a helpful adjunct in managing serotonin syndrome in animals. Cyproheptadine may be administered at a dose of 1.1 mg/kg PO (dogs) or 2-4 mg PO (cats). In cases where the oral route is not feasible (e.g. severe vomiting), cyproheptadine may be crushed and mixed with saline to be instilled rectally. Propranolol also has some serotonin blocking effect, and may be of benefit if animals are tachycardic. Metabolic acidosis may occur and can be corrected with sodium bicarbonate as indicated by blood gas analysis. Symptomatic care to control vomiting, abdominal pain, or other signs can be instituted as needed.

**Cholecalciferol**

Cholecalciferol is a Vitamin D₃ analog. It can be found in rodenticides, oral vitamins and dermal preparations for psoriasis (Dovonex®). Cholecalciferol alters calcium metabolism in the body, increasing intestinal absorption and renal tubular reabsorption of calcium and stimulating bone resorption. Clinical signs of intoxication usually develop within 12-36 hours. Early signs include lethargy, weakness, anorexia, polydipsia, polyuria, and vomiting, often with blood. Biochemical alterations include hyperphosphatemia within 12 hours and hypercalcemia within 24 hours of exposure and azotemia (both renal and pre-renal). The elevated calcium levels result in calcification of many tissues, notable renal tubules and walls of blood vessels. The elevated calcium also has a direct effect on kidney function, sometimes causing acute renal failure even without mineralizations.

Diagnosis of toxicosis is based on history of exposure, clinical signs, serum chemistries and urinalysis. Run baseline chemistries as soon as possible after a known exposure. Pursue GI decontamination if within several hours of ingestion, or if there is evidence of ingestion (chewed box) at unknown time but a still asymptomatic animal. Decontamination consists of multiple doses of activated charcoal and possibly cholestyramine. Cholestyramine is an anion exchange resin available by prescription only. It is used as an adjunctive therapy for the lowering of serum cholesterol in patients with primary hypercholesterolemia who have not responded to diet or other measures alone. Cholestyramine is also indicated for use in the relief of pruritus associated with partial biliary obstruction. It has also been used to aid in the treatment of toxicoses in humans (amiodarone, digitoxin, chlordane, methotrexate, piroxicam, pfiesteria toxin, thyroid, Vitamin D, warfarin, blue-green algae, indomethacin).

Cholestyramine binds with bile acids in the intestine, preventing their reabsorption and producing an insoluble complex, which is excreted in the feces. Cholestyramine has been shown to decrease the toxicity of indomethacin in the dog. Animals are dosed at 0.3 – 1 g/kg TID for several days (depends on toxin ingested). The powder should be given before feeding if possible or mixed with canned food. Cholestyramine is not absorbed out of the digestive tract, so it has no systemic effects other than possible constipation. If giving with activated charcoal, alternate q 4 hours.

Treatment for cholecalciferol is aimed at lowering the serum calcium and phosphorus levels if elevated, preventing a rise in these values if still normal, and stopping further calcium mobilization from the bones. IV normal saline at twice maintenance, prednisone and furosemide all enhance calciuria. Monitor serum calcium, phosphorus, BUN and creatinine daily to judge effectiveness of therapy. If calcium levels are rising despite calciuresis, best choice is pamidronate (Aredia™). Unlike salmon calcitonin, it needs to be given only once, with a repeat dose possibly at about 5-7 days. It acts at the level of the osteoclast and is deposited in the bone itself. Dose is 60-90 mg (about 1.3 mg/kg) mixed in 500-700 ml saline and given slowly over 2-4 hours. The advantage is that it works quickly in a majority of dogs and cats. Once the pamidronate has been administered, it is important to taper the initial treatments (prednisone, furosemide) and decrease the rate of fluid administration. Continue to monitor calcium, phosphorus, and kidney values during this time. End of therapy will be marked by a return to normal of kidney values and the decrease of calcium and phosphorus levels.

**Strychnine**

Strychnine is derived from the tree, *Strychnos-nux vomica*. It is frequently used in malicious poisonings. The approximate lethal dose in dogs is about 0.75 mg/kg. One-quarter ounce (7 gram) of bait has estimated 35 mg of strychnine, enough to kill a hundred-pound dog. Strychnine acts by competitively and reversibly antagonizing glycine at postsynaptic neuron sites in the spinal cord and medula. Glycine is an inhibitory neurotransmitter, so this results in unchecked reflex stimulation. More powerful extensors predominate, resulting in rigidity.

Signs begin within 10-120 minutes, usually without vomiting. There is anxiety and stiffness, followed rapidly by violent tetanic seizures. Sound or touch can elicit these spells, but external stimuli are not necessary to trigger them. There is a classic saw horse stance and a strained facial grimace. Death results from anoxia, as periods between rigidity decrease. The primary goal of treatment is to prevent asphyxiation. General anesthesia (pentobarbital, inhalents, propofol) will allow control of the airway and you can perform gastric or enterogastric lavage, followed by AC. IV fluids and forced diuresis enhance elimination. If severe tachycardia continues after the muscle activity is controlled, consider propranolol.

**Zinc phosphide**

Zinc phosphide is an old rodenticide posing as a new one. The phosphide salts are unstable in an acid environment. At gastric pH they degrade rapidly to form phosphine gas. Phosphine gas, when inhaled, results in acute non-cardiogenic pulmonary edema. When absorbed systemically, it is thought to block cytochrome C oxidase, leading to formation of highly reactive oxygen compounds. It is...
these reactive compounds which cause most of the tissue injury, most severe damage is in tissues with the highest oxygen demand – brain, lungs, liver and kidney.

Lethal doses for cattle, sheep, pigs, goats, dogs, and cats range between 20-50 mg/kg. For a 55 pound (25 kg) dog, that would be between 10 grams (0.35 ounce) and 25 grams (just under an ounce) of 5% bait. Severely poisoned animals may die in 3-5 hours. Those who survive longer than 48 hours have a pretty good chance.

Initial signs may vary by species, as well as by the dose. Onset of signs is normally between 15 minutes to 4 hours post ingestion. Vomiting, often with blood, is common. Dogs may show lateral recumbency with whole body tremors and salivation. Other signs may include anorexia and lethargy. Rapid deep breathing may signal the onset of the pulmonary changes. Abdominal pain, ataxia, and weakness leading to recumbency may follow. Hyperesthesia and seizures may develop that resemble the signs of strychnine toxocosis.

Metabolic acidemia ensues. Other biochemical changes may include depressed serum calcium and magnesium. If there is survival beyond 48 hours an elevated blood urea is common. Hepatic and renal damage often may be detected 5-14 days later.

Initial decontamination is tempered by the wish to keep the stomach pH as high as possible to prevent the formation of phosphine gas. If there has been no spontaneous vomiting, it may be better to induce emesis with apomorphine rather than hydrogen peroxide. Giving food, commonly done in order to improve gastric emptying and the response to peroxide, will trigger release of gastric acid and increase the rate of production of phosphine. If you are going to perform gastric lavage, add an alkalizing component like a magnesium and aluminum hydroxide gel to your lavage liquid. Also consider mixing into your activated charcoal preparation.

Supportive care includes IV fluids to maintain blood pressure renal perfusion, and gastroprotectants. Seizures may respond to diazepam, or may require barbiturates or full anesthesia. Since the most severe injury is probably due to action of the oxygen radicals, use of an antioxidant may be useful – consider vitamin C or n-acetylcysteine.

Caution: Phosphine gas released from vomitus or stomach washings can cause significant illness in veterinary personnel assisting animal. Phosphine has been describes as having a spoiled fish or garlic odor. It is detectable at 1-3 ppm in air; maximum allowed in air in occupational situations is 0.3 ppm, so if you can smell it, you are being exposed to a concentration that can be harmful.
Pesticides

**Cholecalciferol** is a Vitamin D₃ analog. It alters calcium metabolism in the body, increasing intestinal absorption and renal tubular reabsorption of calcium and stimulating bone resorption. Clinical signs of intoxication usually develop within 12-36 hours. Early signs include lethargy, weakness, anorexia, polydipsia, polyuria, and vomiting, often with blood. Biochemical alterations include hyperphosphatemia within 12 hours and hypercalcemia within 24 hours of exposure and azotemia (both renal and pre-renal). The elevated calcium levels result in calcification of many tissues, notable renal tubules and walls of blood vessels. The elevated calcium also has a direct effect on kidney function, sometimes causing acute renal failure even without mineralizations.

**Ethylene glycol** (EG) is present in automotive radiator antifreeze, brake fluids, aircraft deicers, condensers, heat exchangers, home solar units and portable basketball goal post bases. Ethylene glycol may also be used to winterize toilets in RVs and summer homes in colder latitudes. Cats, rabbits and humans are the most sensitive to EG, with dogs, cattle, pigs and rodents having an intermediate sensitivity. It is important to remember that EG is a potent alcohol and many of the signs of toxicosis will relate to severe alcohol intoxication. Because of the different mechanisms involved in EG toxicosis, clinical signs frequently change throughout the course of the toxicosis. It is sometimes easier to break the clinical signs into 3 different stages, although considerable overlap between these stages may be seen and some animals will not experience each stage; death can occur at any stage. The stages are 1) neurologic—the initial inebriation due to the effects of alcohol on the CNS, 2) cardiopulmonary—due to severe acidosis and electrolyte disturbances, and 3) renal—due to renal tubular injury from calcium oxalate crystals. Treatment of EG toxicosis must be timely and aggressive. Failure to institute appropriate therapy within the first several hours may result in irreversible renal damage or death of the animal.

**Phenol** (carbolic acid, hydroxybenzene, oxybenzene) is a hydrolyzed form of benzene. Phenols are used for their antiseptic and local anesthetic properties. Dilute phenol solutions (0.1-4.5%) are found in sore-throat lozenges, throat sprays, gargles, gels, ointments, and lotions as a local anesthetic. Phenol destroys the outer layers of skin and is sometimes used as a chemical peel. Phenol is readily absorbed following inhalation, oral and dermal exposure. In dilute solutions, phenol is an irritant and inflammation may be seen at the site of absorption. In concentrations of 5% or more, phenol rapidly denatures all proteins with which it comes into contact. Dermal application of phenol can also cause systemic signs. Large doses can lead to muscle tremors, seizures, coma and death. Mortality associated with dermal exposure to phenol is greatly influenced by the surface area exposed as well as the concentration of the applied solution. Cats are more sensitive to phenol because of their limited glucuronide transferase activity. Oral phenol exposure in animals causes panting, profuse vomiting, diarrhea, salivation, and ataxia, which may progress to gastric ulcers, muscle fasciculations, and methemoglobinemia. Urinalysis abnormalities include albinuria, hematuria, green/black color, and the presence of casts.

**Pine oil** (arizole, oleum abietis, unipine, yarmor) is a component of many household cleaners and disinfectants. Pine-scented formulations contain small amounts of pine oil and have minimal toxicity compared with pure pine oil. Oral and dermal absorption of pine oil is considered to be poor. Pine oils are irritating to the mucous membranes, producing erythema of the oropharynx, mouth, and skin. Ingestion of pine oil may cause vomiting, CNS depression, tachycardia, nephritis, and fever. Less commonly seen signs include diarrhea, hypotension, bradycardia, ataxia, coma, renal failure, and myoglobinuria following large ingestions. Pulmonary toxicity may be caused by either aspiration, or chemical pneumonitis resulting from absorption of pine oil from the GI tract with subsequent deposition in the lung. Cats are deficient in certain types of glucuronyl transferase activity, making them more susceptible than other species to pine oil toxicoses. A cat that ingested about 100 ml of Pinesol® (20% pine oil, 10.9% isopropanol) developed severe depression, ataxia, unresponsive pupils, and died. Autopsy revealed pulmonary edema, acute centriflobular hepatic necrosis, and total renal cortical necrosis.

**Pharmaceuticals**

**Nonsteroidal anti-inflammatory drugs** (NSAIDs) inhibit prostaglandin synthesis by blocking the conversion of arachidonic acid to various prostaglandins. Decreased prostaglandins mean decreased pain but also decreased secretion of the protective mucous layer in the stomach and small intestine and vasoconstriction in gastric mucosa. NSAIDs inhibit renal blood flow, glomerular filtration rate, tubular ion transport, renin release and water homeostasis. NSAIDs have a narrow margin of safety. GI ulcers and renal failure can be seen after an acute ingestion. Cats are thought to be twice as sensitive as dogs due to their limited glucuronyl-conjugating capacity.

There are many other renal toxic pharmaceuticals including: **sulfonamides**, **tetracyclines**, **amphotericin B**, **cisplatin** and most of the heavy metal **chelators**. **Alpha lipoic acid** is a neutraceutical that can also cause renal failure.
Metals

**Arsenic** can be found in some fungicides, herbicides, pesticides and ashes from chromated copper arsenate (CCA) treated lumber. Arsenic interferes with a variety of enzyme systems within the body, resulting in disruption of cellular homeostasis that can result in peracute death within hours of exposure. Arsenic is readily absorbed via ingestion and has a predilection for skin, nails, hooves, feathers, sweat glands and hair. Bloody vomiting and/or diarrhea due to extensive necrosis and hemorrhage of the gastrointestinal tract characterize acute arsenic toxicosis. Damage to capillary endothelium results in fluid and blood leakage, hypovolemia, dehydration, hypotension and shock. Cardiac arrhythmias, pulmonary edema and multi-organ failure secondary to acute cardiovascular collapse are possible. Later signs may include lethargy, anorexia, fever, polyuria progressing to anuria, tremor, hypothermia, stupor and death. Treatment of arsenic toxicosis entails removal of the arsenic source, symptomatic care and, potentially, chelation with British Anti-Lewisite (BAL).

**Mercurial salts** are present in elemental, inorganic and organic forms. Inorganic mercury compounds have been used historically in diuretics, antibacterials, antiseptics, ointments, laxatives, and antisyphilitic agents. Mercury ions bind to sulfhydryl groups and also have an affinity for phosphoryl, carboxyl, amide and amine groups. This impairs the structure and function of key proteins and enzymes, and alters receptor affinities and cellular metabolism. Inorganic mercury salts are corrosive and nephrotoxic following ingestion. Salivation, abdominal pain, watery bloody diarrhea, proteinuria, and acute renal failure may occur and potentially fatal hypovolemic shock may result. Perform chelation in symptomatic patients (DMSA, BAL, d-penicillamine).

Plants

**Grapes/raisins** (Vitis sp.) can cause renal failure in dogs. At this time the mechanism of action and toxic principle are unknown. Histopathologic examination has shown proximal renal tubular degeneration or necrosis with the basement membrane remaining intact. The distal convoluted tubules are usually less frequently and less severely affected. Some dogs are exposed and never develop signs and some only develop mild GI signs and recover. Vomiting usually begins within 6 hours of ingesting the grapes/raisins. BUN and creatinine begin to elevate in 12-18 hours. Dogs developing severe oliguria or anuria generally were poorly responsive to attempts to increase urine production (mixed results with peritoneal and hemodialysis). If renal values are normal at 48 hours, the animal can be weaned off fluids and sent home.

**True lilies** of the *Lilium* and *Hemerocallis* genera (Easter lilies, tiger lilies, day lilies, etc.) can cause acute renal failure in cats. The water soluble toxic principle is unknown. Even minor exposures (bite on a leaf, ingestion of pollen) may result in toxicosis, so all feline exposures to lilies should be considered potentially life-threatening. It should be noted that not all plants with “lily” in the name are true lilies. Cats often begin vomiting within a few hours after exposure. Within 24 to 72 hours of ingestion, oliguric to anuric renal failure develops, accompanied by depression, anorexia, and dehydration. Elevations in BUN, creatinine, P and K⁺ are detectable as early as 12 hours post ingestion. Creatinine elevations may be especially high. Abundant casts, proteinuria, glucosuria, and isosthenuria are usually detectable on urinalysis within 24 hours of ingestion, reflecting lily-induced damage to renal tubular cells. In severe cases, death or euthanasia due to acute renal failure generally occurs within 3 to 6 days of ingestion.

**Cortinarius sp.** mushrooms contain orellanine, a nephrotoxic compound. These bright rust-brown or orange-brown mushrooms occur throughout the U.S. and Canada. Orellanine is not destroyed by drying or cooking. It inhibits alkaline phosphatase which in turn interrupts the production of ATP. Lesions are limited to the kidney (tubulointerstitial nephritis). There can be a latent period of 36 hours to 20 days before the onset of symptoms in people. Anorexia, vomiting, diarrhea, PU/PD, lethargy, and muscle pain can be followed by oliguric or anuric renal failure. Due to the long lag time, GI decontamination is limited. Monitor for renal failure, hypotension, arrhythmias, respiratory depression, hypoglycemia, electrolyte disturbances, and hypoxia. Forced diuresis should NOT be done because it may increase renal damage. Peritoneal dialysis and kidney transplants are performed in humans. Outcome is based on the amount of toxin ingested, but a great deal of variability exists. A shorter latent period correlates with a poorer prognosis.

**Mycotoxins**

**Ochratoxin** A (OA) is a potent nephrotoxin produced by several species of *Aspergillus* and *Penicillium* molds. Monogastric species are much more sensitive to ochratoxins than ruminants. Ochratoxosis is usually associated with the feeding of contaminated barley, but wheat, oats, corn, beans, peanuts, hay, and green coffee beans have tested positive. OA is a competitive inhibitor of protein synthesis, induces lipid peroxidation and interferes with carbohydrate metabolism. OA causes degeneration of proximal renal tubules and bile duct proliferation. OA can be tested for in feed, liver or kidney and metabolites can be found in milk or urine. Treatment is symptomatic and supportive.

**Citrinin** is another mycotoxin that can cause renal tubular necrosis. It is commonly found with ochratoxins. Most grains including wheat, oats, barley and corn can be affected. Within a few hours, protein, and glutathione (GSH) tissue levels are decreased and the respiratory capacity (uptake of O₂) and the metabolic enzyme succinic dehydrogenase are inhibited. Treatment is symptomatic and supportive.
Miscellaneous
Any toxin that causes hemoglobinuria (pit viper venom, onions/garlic, brown recluse spiders, zinc) can cause hemolysis. Free hemoglobin is toxic to the kidney. Hemoglobinuria can induce acute tubular necrosis through the formation of hemoglobin casts. IV fluids should be started to combat hypovolemia and protect the kidneys. Toxin cause tremors/seizures can lead to myoglobinuria (see Why so agitated? notes). Myoglobin, a monomer containing a heme molecule similar to hemoglobin, when excreted in the urine can precipitate, causing tubular obstruction and acute kidney injury.
Why So Yellow?
Liver Toxicants
Tina Wismer, DVM, DABT, DABVT
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Household and Industrial

**Xylitol** is a sugar alcohol. It is used in sugar-free products such as gums and candies as well as for baking. It doesn’t cause significant increases in blood glucose or insulin in humans. However, in dogs, xylitol causes a rapid, dose-dependent insulin release followed by potentially significant hypoglycemia. Signs can include vomiting, weakness, ataxia, depression, hypokalemia, seizures, and coma. Some dogs have developed liver dysfunction or failure following ingestion of xylitol although the mechanism has not been established.

Pharmaceutical

**Acetaminophen** (Tylenol®, non-aspirin pain reliever, APAP) is a synthetic non-opiate derivative of p-aminophenol. APAP acts primarily in the CNS to increase the pain threshold and may also inhibit chemical mediators that sensitize the pain receptors to mechanical or chemical stimulation. The antipyretic activity of APAP is achieved by blocking the effects of endogenous pyrogens by inhibiting prostaglandin synthesis. Two major conjugation pathways are used to metabolize APAP by most species (P-450 metabolism followed by glucuronidation or sulfation). Acetaminophen-induced hepatotoxicity and nephrotoxicity is due to the formation of the oxidative metabolite, N-acetyl-para-benzoquinoneimine (NAPQI). Glutathione can conjugate and neutralize NAPQI, but when glutathione stores are depleted, NAPQI binds to sulfhydryl groups on the hepatic cell membrane and damages the lipid layer. NAPQI causes severe oxidative stress to RBCs leading to methemoglobinemia and Heinz body formation. Methemoglobin values increase within 2-4 hours, followed by Heinz body formation. Clinical signs include depression, weakness, hyperventilation, icterus, vomiting, methemoglobinemia, hypothermia, facial or paw edema, death, cyanosis, dyspnea, and hepatic necrosis. Liver necrosis is less common in cats than in dogs. Clinical signs of methemoglobinemia may last 3-4 days. Hepatic injury may not resolve for several weeks.

**Aspirin** (acetylsalicylic acid, ASA) is the salicylate ester of acetic acid and is a weak acid derived from phenol. Aspirin reduces pain and inflammation by reducing prostaglandin and thromboxane synthesis through inhibition of cyclooxygenase. At very high doses, aspirin and other salicylates uncouple oxidative phosphorylation leading to decreased ATP production. Salicylates also affect platelet aggregation. Signs may include vomiting (+/- blood), hyperpnea, respiratory alkalosis, metabolic acidosis, gastric hemorrhage, central lobular liver necrosis, and bleeding diathesis. Fever and seizures may be seen due to the uncoupling of oxidative phosphorylation.

**Ketoconazole** is a broad-spectrum imidazole antifungal agent that alters the permeability of the cell membrane and inhibits intracellular enzymes of susceptible fungi. Adverse events following therapeutic doses may include hypertension, nausea and vomiting, liver toxicity, skin eruptions, and adrenal suppression. Hepatitis, hepatocellular necrosis, icterus, and fatal hepatic failure have been reported.

**NSAID** hepatotoxicity can be seen with any NSAID and is thought to be an immune mediated reaction. Most cases are reversible with supportive care.

Metals

**Iron** is an essential mineral that is important in oxygen delivery to tissues, enzymatic processes, and oxidative metabolism within the body. Accidental overdosing of iron supplements may cause acute iron toxicosis, characterized by corrosive gastroenteritis and hepatic injury. Iron absorption from the gastrointestinal tract is highly regulated by the body. Iron is carried in the blood by a protein called transferrin, which conveys the iron to the liver where it is transferred to ferritin. In the liver, iron is either utilized or stored in small amounts as ferritin or as in larger amounts as hemosiderin. When the level of iron exceeds the amount of protein available to bind it, free iron causes oxidative injury to hepatocytes. This hepatic injury may be massive and severe, as in the case of an acute massive iron overdose, or it may be chronic and fulminating, resulting in cirrhosis of the liver over time. Clinical signs of acute iron toxicosis include bloody vomiting and/or diarrhea, abdominal pain, weakness, shock, collapse and death due to shock or anemia. Animals that survive may subsequently develop signs of acute hepatic failure such as lethargy, anorexia icterus, fatty stools, and coagulopathy.

**Copper** is an essential dietary mineral in mammals and a variety of copper compounds are used in manufacturing, medicine, agriculture, and welding (anthelmintics, algaeicides, fungicides, wood preservatives, livestock footbaths). Copper accumulates in hepatocytes, where it damages lysosomal membranes, resulting in release of copper and lysosomal hydrolases into the cytoplasm. In Bedlington terriers, an autosomal recessive genetic defect is responsible for the sequestration of copper within the liver. The result is chronic-active hepatocellular necrosis, ultimately resulting in fibrosis and macronodular regeneration. Young dogs may show
episodic lethargy, anorexia, and vomiting indicative of active liver disease. Older dogs (> 6 y) may show icterus, weight loss, anorexia, vomiting/diarrhea, hepatonecephalopathy, ascites, and coagulopathy (i.e. end-stage liver disease). West Highland white terriers, Skye terriers, Doberman pinschers, and keeshonds are breeds in which high hepatic copper levels have been found in both animals with normal livers and those with significant hepatic injury. It is not unknown whether the sequestration of copper is the cause of hepatic injury, or whether the copper levels are a consequence of some other disease process.

**Plants**

**Amatoxins** are found in some of the Amanita, Galerina and Leptiola sp. of mushrooms. These mushrooms have a wide distribution throughout the U.S.. Amanitins inhibit nuclear RNA polymerase II, interfering with DNA and RNA transcription, thus inhibiting ribosomal protein synthesis. Cells with high metabolic rates (hepatocytes, intestinal crypt cells) are most sensitive. There are three phases in amatoxicosis. A latent phase of approximately 6-24 hours is followed by a gastrointestinal phase with abdominal pain, vomiting and diarrhea. This phase usually lasts 2-3 days. The hepatic phase begins 36-48 hours after ingestion. Jaundice progresses to fulminate hepatitis with hepatic coma, coagulopathies and anuria. Many humans have required liver transplantation following ingestion of amatoxin-containing mushrooms.

**Blue green algae** (cyanobacteria) can be found in many lakes, ponds and rivers throughout the world. Toxic blooms are seen following warm, sunny weather. Toxic blooms are seen more frequently in ponds that get runoff from heavily fertilized fields or from feed lots or pastures bearing significant numbers of animals. Steady winds often propel toxic algae to the shoreline where animals are exposed. The most important toxin-producing genera of fresh and brackish water blue-green algae are Microcystis, Anabaena, Oscillatoria, Aphanizomenon, Nodularia, and Nostoc. The primary toxic effects of blue-green algae in animals include acute hepatotoxicoses, paracutaneous neurotoxicoses, and gastrointestinal disturbances. Microcystis, Oscillatoria, Nodularia, and less often Anabaena may produce hepatotoxins called microcystins. Microcystins cause disorganization of the actin filaments of the hepatic cytoskeleton, leading to cellular collapse. Clinical signs in animals with hepatotoxicoses include weakness, stupor, prolonged capillary refill time, pallor of mucous membranes, bloody diarrhea, and cardiovascular collapse. Clinical signs are usually observed within 12 hours after exposure. Death may occur within a few hours to a few days, depending upon the amount ingested and the toxicity of the bloom. Death often is preceded by coma, muscle tremors, and seizures. Death usually results from intrahepatic hemorrhage and hypovolemic shock and/or acute liver failure.

**Sago palms** (*Cycas* and *Macrozamia* sp.) are ornamental plants found in tropical to subtropical climates, but they can also be grown as houseplants. There are three toxins in cycads. Cycasin is thought to be responsible for the hepatic and gastrointestinal signs. Sago palms also contain two neurotoxins (B-methlamino-L-alanine and an unidentified toxin). The seeds contain the highest amount of cycasin, but the entire plant is toxic. Cycasin causes centrolobular and midzonal coagulative hepatic necrosis along with GI hemorrhage. GI signs begin within a day and laboratory values (ALT, bilirubin, Alk Phos) become abnormal in 24-48 hrs. The most common signs are vomiting (+/- blood), depression, diarrhea, anorexia, and seizures. Mortality rate is about 30%.

**Mycotoxins**

**Aflatoxins** are mycotoxins produced by *Aspergillus flavus, Penicillium* spp. and possibly other fungi. The most commonly affected crops are corn, peanuts, and cottonseed, but rice, sweet potatoes, wheat, oats, barley, millet, sesame, sorghum, cacao beans, almonds and other nuts can be affected. Aflatoxin metabolites bind with cellular components including nucleic acids, organelles and regulatory proteins thereby disrupting normal cellular processes. Signs of acute toxicity include anorexia, lethargy, vomiting, bloody diarrhea, weakness, and seizures. Liver failure, oliguria, and DIC often result in death within a few days.

**Fumonisin** is most noted for causing equine leukoencephalomalacia (blind staggers, moldy corn poisoning), but it can affect all species. Fumonisin is produced by *Fusarium verticillioides* which grows primarily on corn. Fumonisins are structurally similar to sphingosine a constituent of sphingolipids. Fumonisins inhibit sphingolipid biosynthesis and liver damage may be a consequence of derangements in cell membranes and disruption of normal regulatory mechanisms within cells due to the accumulation of sphinganine. Treatment is symptomatic and supportive.