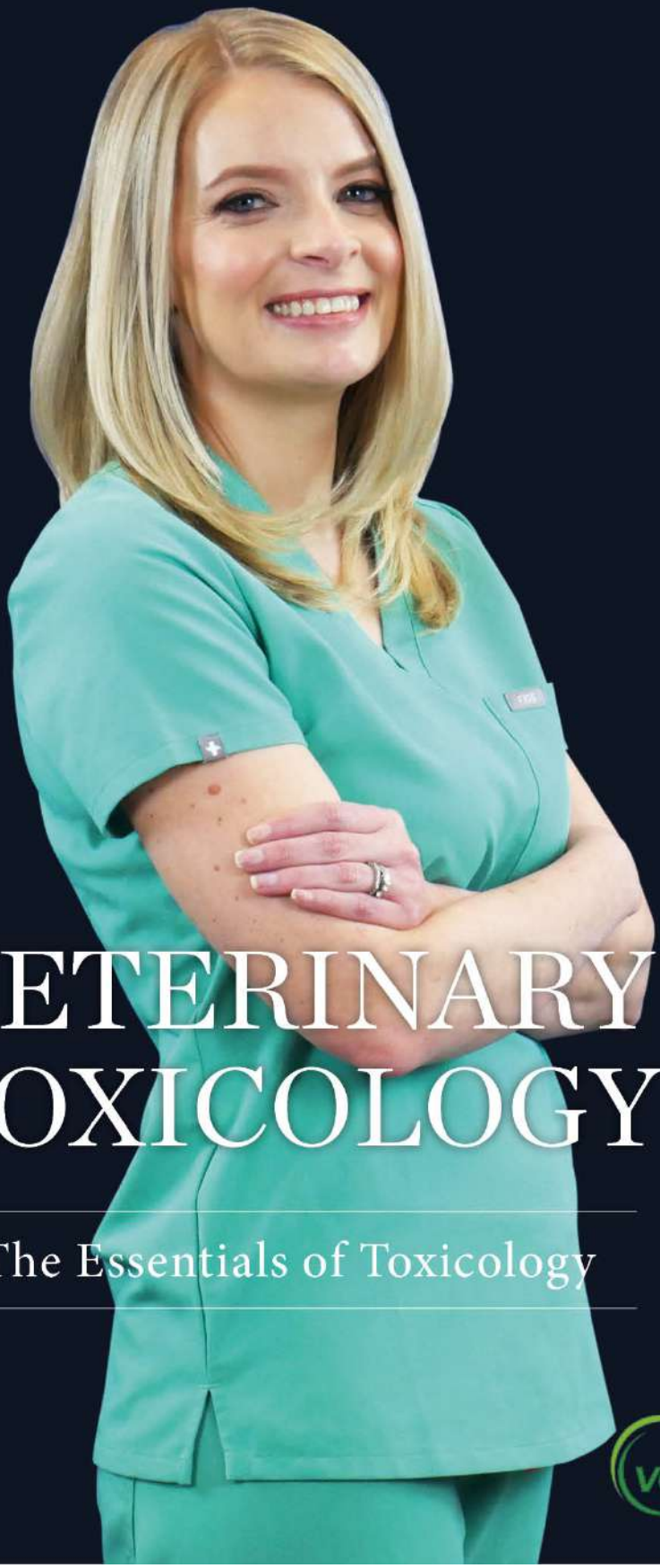
DR. CAREY HEMMELGARN



VETERINARY TOXICOLOGY

The Essentials of Toxicology

Vet Candy

vetoquinol
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CLEVOR®

(ropinirole ophthalmic solution)
30 mg/mL
For ophthalmic use in dogs only

Single use dropper

BRIEF SUMMARY: Before using CLEVOR® (ropinirole ophthalmic solution), please consult the product insert, a summary of which follows:

CAUTION:
Federal law restricts this drug to use by or on the order of a licensed veterinarian.

INDICATION:
For induction of vomiting in dogs.

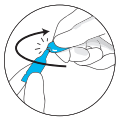
DOSAGE AND ADMINISTRATION:
This product should be administered by veterinary personnel.

Dosing Instructions:
Administer the appropriate number of eye drops topically according to Table 1. The number of eye drops administered corresponding to body weight results in a target dose of 3.75 mg/m^2 (dose band 2.7 - 5.4 mg/m^2). If the dog does not vomit within 20 minutes of the first dose, then a second dose may be administered.

Table 1. Dose Administration

Body weight in kilograms	Body weight in pounds	Total number of eye drops	Example admini-stration
1.8 - 5	4 - 11.1	1	1 drop into either left or right eye
5.1 - 10	11.2 - 22.1	2	1 drop each eye
10.1 - 20	22.2 - 44.1	3	2 drops in one eye and 1 drop in the other eye
20.1 - 35	44.2 - 77.2	4	2 drops in each eye
35.1 - 60	77.3 - 132.3	6	An initial dose of 2 drops in each eye, followed 2 minutes later by 1 drop in each eye
60.1 - 100	132.4 - 220.5	8	An initial dose of 2 drops in each eye, followed 2 minutes later by 2 drops in each eye

Dose Administration:



- Wear gloves and protective eye wear when handling or administering this product to prevent accidental exposure.
- Open the dropper by twisting off the tail.

- Keep the dog's head steady in a slightly upright position.
- Hold the dropper in an upright position without touching the eye.
- Rest your finger on the forehead of your dog to maintain the distance between the dropper and the eye.
- Squeeze the prescribed number of drops in to the eye(s).

- CLEVOR is a single use dropper and is light sensitive.
- After administration, with gloves on, return the dropper to the aluminum pouch and place in the carton.

- If the dog does not vomit, a second dose can be given 20 minutes after administration of the first dose.
- This second dose is the same number of drops as the first dose.
- Thirty minutes after opening, with gloves on, dispose of dropper, aluminum pouch, and carton.

Refer to the **Animal Safety Warnings** section for treatment of protracted vomiting.

CONTRAINDICATIONS:
Do not use in dogs with central nervous system depression or seizures.
Do not use in cases of ingestion of sharp foreign objects, corrosive agents (acids or alkalis), volatile substances or organic solvents.
Do not use in cases with corneal ulceration, ocular irritation, or ocular injury.
Do not use when there is a known sensitivity to ropinirole or the inactive ingredients.

WARNINGS:
Human Safety Warnings:
Not for use in humans. Keep out of reach of children.

Wear gloves and protective eye wear when handling or administering this product to prevent accidental exposure. In case of accidental eye, oral or skin exposure, flush with water. If wearing contact lenses, eyes should be rinsed first, then remove contact lenses and continue rinsing. Remove contaminated clothing. Ropinirole is a dopamine agonist. **Seek medical attention if accidental exposure occurs and show the package insert or label to the physician.** Exposure to this drug may cause adverse reactions such as headache, nausea, vomiting, dizziness, orthostatic hypotension, and sleepiness. Avoid contact with the product if pregnant, planning to become pregnant, or breast-feeding, as exposure has been shown to have adverse effects on embryo-fetal development based on rodent studies.

Animal Safety Warnings:
This product should be administered by veterinary personnel.
Dogs should be monitored for CLEVOR-associated clinical signs, including protracted vomiting, salivation, muscle tremors, evidence of abdominal discomfort, lethargy, transient tachycardia, transient decrease in blood pressure and signs of ocular irritation, including conjunctival hyperemia, mild blepharospasm, and protrusion of the third eyelid. These clinical signs are related to the pharmacological action of ropinirole. To stop protracted vomiting, administer metoclopramide (dopamine D2 antagonist) at a dose of 0.5 mg/kg intravenously (IV) or subcutaneously (SQ). Metoclopramide also decreases the prevalence of most CLEVOR-associated clinical signs.

PRECAUTIONS:
The safe use of CLEVOR has not been evaluated in dogs with cardiac disease or cardiovascular compromise. CLEVOR can cause transient tachycardia and transient decreased systolic blood pressure.
The safe use of CLEVOR has not been evaluated in dogs with hepatic impairment. CLEVOR is metabolized by the liver.
The safe use of CLEVOR has not been evaluated in dogs younger than 4.5 months of age and weight less than 4 pounds.
The safe use of CLEVOR has not been evaluated in dogs that are pregnant, lactating, or intended for breeding.

ADVERSE REACTIONS:
Safety was evaluated during a field study that enrolled 132 dogs (100 in the CLEVOR group and 32 in the vehicle control group). CLEVOR was administered as drops into the eyes at the dose as directed by the dosing table (see **DOSAGE AND ADMINISTRATION**). The following table shows the number of dogs exhibiting ocular, systemic, and clinical pathology adverse reactions.

Table 2: Adverse Reactions Reported During the Study (all dogs)

Organ System	Adverse Reaction	CLEVOR (N=100)	Vehicle control (N=32)
Ocular	Conjunctival hyperemia[a]	51 (51%)	6 (19%)
	Protrusion of the third eyelid[a]	38 (38%)	1 (3%)
	Conjunctival discharge[a]	30 (30%)	1 (3%)
	Blephar-ospasm[a]	19 (19%)	0
	Conjunctival swelling[a]	3 (3%)	0
	Scratching/rubbing of eyes[a]	4 (4%)	0
	Corneal ulceration	1 (1%)	0
	Corneal fluorescein uptake without corneal ulceration	1 (1%)	0
Systemic	Lethargy	41 (41%)	0
	Tachycardia (>160 beats per minute)[a,b]	14 (14%)	0
	Vomiting duration longer than one hour	8 (8%)	0
	Salivation	3 (3%)	1 (3%)
	Trembling	3 (3%)	0
	Diarrhea or soft stool	2 (2%)	1 (3%)
	Anxious	1 (1%)	0
	Borborygmi	1 (1%)	0
Clinical Pathology	Crystalluria[c]	13 (20%)	3 (15%)
	Pyuria[c]	12 (18%)	3 (15%)
	Increased liver enzymes[d]	3 (3%)	0
	Decreased blood glucose	2 (2%)	0
	Increased prothrombin time	1 (1%)	0

[a] Assessment performed 30 minutes after dose administration
[b] Tachycardia resolved for most dogs within 4 hours after dose administration
[c] Urinalysis results were reported for only 86 dogs (66 administered CLEVOR and 20 control)
[d] All three dogs had elevated alanine aminotransferase. Additionally, one of the dogs also had an elevated aspartate aminotransferase and another of the dogs also had an elevated alkaline phosphatase and total bilirubin.
Note: If any animal experienced the event more than once, only the first occurrence was tabulated.

To report suspected adverse events call 1(800) 835-9496, for technical assistance or to obtain a copy of the SDS, contact Vetoquinol USA, Inc. at 1 (800) 267-5707 or www.vetoquinolusa.com.

For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at www.fda.gov/reportanimalae.

CLEVOR is a trademark of Orion Corporation

Manufactured by:
Orion Corporation

Distributed by:
Vetoquinol USA, Inc.
Ft. Worth, TX (USA) 76137
1 (800) 267-5707
www.vetoquinolusa.com

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BASIC TOXICOLOGY PRINCIPLES AND TERMINOLOGY

For a basic understanding of toxicology, there are few key topics that are helpful to know.

First, what is toxicology? Toxicology is the science and study of how substances affect an organism. Toxicology may be completely different from one species to the next; some substances may be toxic to one population of a species but fine for another subset. A substance may be toxic in a neonate but safe for an adult.

The dose is defined as the amount of a drug or toxicant that an individual receives or is exposed to. Dosage is the most important factor in toxicity. Some substances require large amounts of exposure to show toxicity; for others, even the smallest amount can cause very severe consequences.

The toxicity is the degree to which a substance can induce harm. An acute toxicity is a single or short-term exposure that causes harmful effects. In contrast, subchronic toxicity means exposure to a substance for more than one year but less than a lifetime that can cause negative effects. Chronic toxicity is a substance causing harm over an extended period, through either repeated or chronic exposure.

Toxins can be further defined as local toxins, where the effect is seen only at the site of contact, and systemic toxins, where effects may be seen distant from exposed sites. Some toxins will have both local and systemic signs.

LD_{50} describes the median lethal dose; 50% of a test population dies after exposure to this substance. This is a number that can be helpful when calculating the dosage of an individual patient, but we can often see clinical signs before the LD_{50} has been reached. Also, some patients will be more sensitive to a toxin than others.

Bioavailability refers to the proportion of a drug or other substance that enters the circulation when introduced into the body and can then have an effect. Substances with high bioavailability are close to 100%, so the entire dose reaches circulation.

Lipid-soluble substances have a high affinity for adipose or lipid tissues and therefore do not stay in the vascular compartment for a long time.

Pharmacokinetics is the study of the bodily absorption, distribution, metabolism, and excretion of a substance. Four main factors make up the pharmacokinetics of a substance; the acronym to remember is ADME:

- **Absorption**- This depends on the route of administration and exposure.

- **Distribution**- This is the process of a substance entering systemic circulation and the peripheral tissue. Drugs with a high volume of distribution have a low concentration in the circulating bloodstream but high concentrations in tissue. Drugs with low volume of distribution are the opposite—a large amount in the bloodstream but limited amounts in the tissue. Distribution is also affected by whether a substance is highly vs. minimally protein-binding.

- **Metabolism**- This depends on the main organ metabolizing the substance. If a patient has an underlying condition affecting the metabolizing organ, the substance can last longer in the system, potentially causing a longer period of toxicity, or it could harm that organ further. The half-life is used to describe metabolism; the half-life is the time for 50% of the original concentration of a substance to be metabolized. For example, if the initial dose was 500 mg of substance X, and two hours later, the concentration is 250 mg, then the half-life of this substance is two hours. Toxin metabolism can also differ between species. a perfect example of this is cats' decreased glucuronidation ability, which plays a big part in acetaminophen toxicity. Cats have this limited ability, but dogs and people are better able to metabolize acetaminophen.

- **Excretion**- The kidneys normally excrete toxins, but that can vary based on the particular toxin. Underlying kidney disease can delay excretion and therefore prolong toxicity. Also, some substances can go through enterohepatic recirculation, being excreted through the biliary tract but then reabsorbed in the intestines and going through the whole process again.

We may not have all this information for every substance and every species. In these cases, we need to extrapolate from the available data and make the best, most educated recommendations. Poison control centers have large databases that tabulate information and have access to human poison control and toxicity data. Important questions to ask a poison control veterinarian:

- Would intravenous lipid emulsion therapy be helpful in this toxicity?
- Would intermittent hemodialysis or hemoperfusion be helpful?
- What is the worst-case scenario? Do you need to refer to a 24-hour facility after initial decontamination for round-the-clock care and monitoring?
- Is mechanical ventilation a possibility?

Some patients come into the hospital, and there is clear information about the toxin and the dose, such as a dog who ate the half-pound of dark chocolate chips that were on the counter one hour ago and was previously healthy. Not every case, however, is this straightforward.

Important information to get from triage history of suspected toxicity:

- What is the likelihood of toxicity? Was it witnessed? Is there zero chance of toxin ingestion?
- What are the possible toxins to which the animal might have been exposed?
  - Household medications, both human and veterinary
  - Chemicals in the house
  - Recreational drugs
  - Recent rodenticide or pesticide treatment at home
- What is the timeframe for exposure?
- What is anyone's best guess as to the dosage of exposure? Always calculate based on worst-case scenario.
- Are there underlying/previous health problems?
- Is the animal currently on any medications? Look for adverse drug reactions.
- Have any treatments been instituted at home?

TRIAGING A PATIENT SUSPECTED OF TOXICITY AND DECONTAMINATION OPTIONS

After getting a triage history and having an idea of possible toxicity, the next step is to evaluate the patient. This includes a complete physical exam. Using the ABCs can be a helpful starting point, especially if your patient is critical.

- **Airway-** Evaluate the airway; look for any signs of stridor/stertor/choking that could indicate a problem with the upper airway. Evaluate the neurological status of the patient; if a gag reflex is present, that is very important. Some toxins can cause severe neurological derangements, leaving the patient comatose with no gag reflex. In these cases, the patient needs to be intubated with a cuffed endotracheal tube to secure an airway. These patients also need IV vascular access, one-on-one monitoring by a skilled technician and advanced cardiovascular monitoring, including ECG, SpO2, EtCO2, and Doppler blood pressure.

- **Breathing-** Breathing can be assessed by visually looking at the patient; are they tachypneic, dyspneic, cyanotic, at risk for exhaustion? They may have abnormal lung sounds on thoracic auscultation. Other ways of assessing their breathing can be through monitoring, including SpO2 and EtCO2. In addition, blood gas analysis can give an idea of oxygen/ventilation status. Hypercapnia (PaCO2 >45 mmHg) can be an indicator of hypoventilation. In these cases, intubating and providing supplemental oxygen won't be enough; assisted ventilation is needed. Patients that have hypoxemia (PaO2 <65 mmHg) need to have supplemental oxygen provided. If they improve enough with up to 40% oxygen, then mechanical ventilation is needed to get them up to 100%.

- **Circulation-** Circulation can be assessed by evaluating a patient's perfusion—evaluating their mucous membrane color, capillary refill time, femoral pulses, and extremity temperatures. If a patient has poor perfusion, then their distal extremities can be cooler than their core. Some patients with toxin exposure will present with hypovolemic shock—pale mucous membranes, tachycardia (more common in dogs), bradycardia (more common in cats), cold extremities, and dull mentation. Some patients may have volume deficits due to fluid loss (vomiting/diarrhea) before arriving at the clinic. Hypovolemic shock can be confirmed with additional diagnostics such as blood pressure and lactate measurements. Hyperlactatemia is very common in hypovolemic shock and can be used as a serial measuring tool to evaluate response to treatment.

- Patients with evidence of hypovolemic shock should have an IV catheter placed, and bolus therapy of crystalloid fluids should be initiated. Starting dose in canine patients should be 10–20 mL/kg, reassess vitals/bloodwork, and repeat if needed. Cats are more sensitive to fluids, and initial bolus rates are more conservative at 5–10 mL/kg.

- If response to fluids is not achieving normotension, vasopressor therapy should be considered. Norepinephrine and dopamine are considered first-line vasopressor agents.

Some toxins can also cause cardiovascular abnormalities such as tachycardia or bradycardia that prevent normal perfusion. Performing an ECG and checking blood pressure is important in toxicity patients.

- If tachycardia is thought to be secondary to toxicity, then further characterizing the arrhythmia is important in treatment.

    - For sinus tachycardia, as is seen with chocolate toxicity, initial treatment would be a beta-blocker such as propranolol.

    - If ventricular tachycardia is seen, then an initial bolus of lidocaine to assess for response would be recommended. Cats are much more sensitive to lidocaine and need smaller doses; use with caution.

- If bradycardia is noted, it should be further characterized on an ECG.

    - If atrial standstill is noted, electrolytes should be checked. Make sure hyperkalemia is not present, as that would change treatment.
    - If sinus bradycardia is noted, then a dose of atropine or glycopyrrolate should be tried.

Additional concerns that could be encountered during triage of a toxicity patient are seizure activity and/or hyperthermia. In these patients, an IV catheter should be placed, and initial bloodwork should be performed. This bloodwork is looking for hypoglycemia, anemia, or other electrolyte abnormalities. If initial bloodwork is relatively normal, a dose of midazolam or diazepam should be given to stop seizure activity and start active cooling. Active cooling should include fluid therapy (as long as there is no concern for cardiac disease), cool towels placed over the patient, fans to improve evaporation for heat dissipation, and frequent temperature monitoring. Active cooling should be stopped at 103.5 to prevent hypothermia. If a patient's seizures continue through midazolam/diazepam and the electrolytes (blood glucose/potassium) are normal, then a loading dose of Keppra® IV should be started. Additional anticonvulsants are needed in some cases, and phenobarbital would be the next step. In patients that are having tremors instead of active seizures, then methocarbamol would be a good starting point to evaluate response.

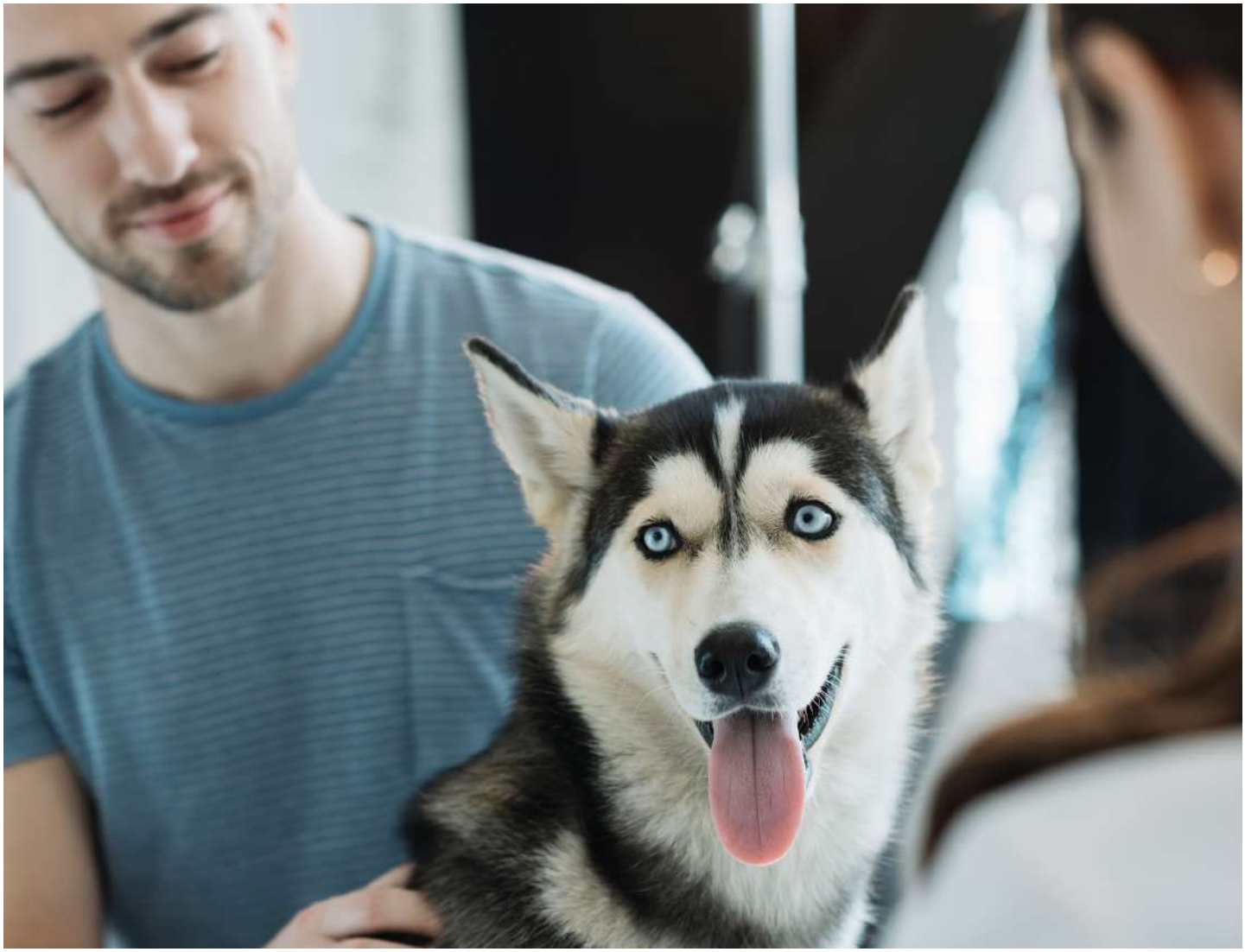
Once a patient is stable in cardiovascular terms, decontamination should be considered; each patient is unique, and each toxin is unique. Emesis should be considered if the

toxin was ingested within two hours of presentation or, if it is a toxin with a high level of toxicity, up to a few hours post-ingestion, in hope of removing any that might still be in the stomach. Emesis should not be induced in patients who have consumed a strong alkali or acid due to corrosive injury. A patient also needs to be neurologically appropriate with a gag reflex to induce vomiting; this is to minimize the risk of aspiration. If a patient is at all neurologically impaired, emesis should not be attempted. If a pet has consumed zinc or aluminum phosphide rodenticide, emesis should be done in a well-ventilated area, and caution should be taken, as this rodenticide creates phosphine gas in the stomach, which causes human injury.

One way to induce emesis is with apomorphine. With a dose of 0.02 mg/kg to 0.04 mg/kg IV, the dog should vomit within 15 minutes of the injection. There are also apomorphine tablets that can be dissolved in saline and then given in the subconjunctival sac. Hydrogen peroxide can also induce vomiting in dogs, but it carries higher risks. There is a risk of aspiration, as dogs will not willingly ingest hydrogen peroxide. Hydrogen peroxide has also been shown to cause gastroduodenal ulceration after administration. A study comparing gastroduodenal ulcerations in a study population of dogs showed that all dogs had gastric ulcerative lesions, and some had duodenal lesions, whereas none of the dogs that received apomorphine had these ulcerative changes.[1] A study comparing apomorphine to hydrogen peroxide showed a higher success rate with apomorphine (94%); the hydrogen peroxide had a 90% success rate.[2] Due to the risks of aspiration during administration and gastric/duodenal ulcerations, inducing emesis with hydrogen peroxide is not readily recommended.

The U.S. Food and Drug Administration's Center for Veterinary Medicine has approved Clevor® (ropinirole ophthalmic solution) for inducing vomiting in dogs. Clevor is a dopamine agonist that is administered by drops in the dog's eye.

Some examples of when a veterinarian may want to induce vomiting in dogs include when the dog has eaten something that may be poisonous or that can't pass through the intestinal tract, and that can be safely vomited as determined by a veterinarian. Clevor® is available by prescription only, as the drug should only be administered by veterinary personnel because professional expertise is required to ensure safe use of the drug, assess the animal patient for contraindications associated with the induction of vomiting, and monitor any possible adverse reactions.



The effectiveness of Clevor® was demonstrated in a clinical field study in which it was administered to 100 client-owned dogs to induce vomiting of the last meal the dogs ate (no harmful objects or toxins were given to the dogs). The study demonstrated that Clevor® is effective for the induction of vomiting in dogs, as 95 percent of dogs treated with Clevor® vomited within 30 minutes. Eighty-six percent of dogs in the Clevor® group vomited after the first dose, and 14 percent needed a second dose 20 minutes after the first dose was administered. Half of the dogs vomited within 10 minutes, with 3 minutes being the fastest.

Common side effects after using Clevor® may include transient mild or moderate hyperemia of the eye, ocular discharge, protrusion of the 3rd eyelid and blepharospasm, transient mild lethargy, and increased heart rate. All Clevor®-related observations resolved within 6 hours post-dosing.

Clevor® is available as a carton of 5 droppers that are individually wrapped in aluminum foil packaging. Each prefilled dropper contains 0.3 mL. The shelf life of unopened droppers is 2 years from the time of manufacture. Once opened, a dropper should be discarded after 30 minutes of opening.

Options to induce vomiting in cats include:

- Dexmedetomidine
- Xylazine
- Hydromorphone

Dexmedetomidine more consistently induced vomiting in cats (81%) compared with xylazine, which only produced emesis about 40–60% of the time in a study population of cats. The median dose of dexmedetomidine that was used successfully was 7 mcg/kg given IM or IV. The most common adverse effect noted after either of these medications was sedation.

One study compared hydromorphine with dexmedetomidine to induce emesis in cats and found a higher percentage of cats vomited after hydromorphine (75%), compared to 58% with dexmedetomidine. Less sedation was noted after hydromorphine, and less bradycardia was noted. Hyperthermia was noted in some cats after hydromorphine but it was self-limiting[4]

Once emesis has been induced in cases when it is recommended and safe, further decontamination methods can be discussed. Activated charcoal is commonly recommended, depending on the toxin, due to its ability to absorb toxins so they can move through the GI tract without being absorbed and then safely eliminated. Sorbitol in charcoal formulations acts as cathartic to speed up GI transit, and with multiple doses can cause marked diarrhea. Cathartic containing doses should be given only once, and then subsequent doses should not have sorbitol. Activated charcoal can be mixed with a small volume of food if the patient will eat it readily. Otherwise, they can be syringe-fed their dose, but extreme caution must be observed to prevent aspiration of charcoal. Other options would be inducing anesthesia, securing the airway with a cuffed endotracheal tube, passing a gastric tube, and instilling charcoal directly into the gastric lumen. This is not commonly performed. Activated charcoal can cause hypernatremia, and electrolytes should always be rechecked before subsequent doses and skipped if hypernatremia is noted. Also, if a patient is showing neurological signs unexpectedly at any point, then electrolytes should be checked. Repeat doses of non-sorbitol-containing charcoal are often needed in toxins that undergo enterohepatic recirculation.

With some toxins, gastric lavage is indicated. One particular circumstance for this is uncooked bread dough or products containing yeast. These products will ferment in the stomach, causing marked gastric distention, which can lead to GDV; also, fermentation creates ethanol, which can cause neurological signs and hypoglycemia. In these cases, gastric lavage is recommended to remove the dough and stop the fermentation process. Gastric lavage involves general anesthesia, the airway protected with a cuffed endotracheal tube, and then a gastric tube being passed into the stomach. The stomach is then lavaged with water or, in the case of dough ingestion, ice water using a siphon technique. The procedure can be stopped when minimal material is being returned and the lavage fluid is relatively clear.

With ingestion of acids or alkali, poison control commonly recommends diluting the toxin with water or milk. Occasionally an anti-inflammatory dose of corticosteroids may be recommended.

Dermal toxin decontamination should focus on early removal of the substance from the skin. Bathing with a mild soap such as Dawn dish soap is the most common recommendation. If the toxin is caustic, owners and/or veterinary staff should take precautions to avoid their own dermal exposure. Bathing can be repeated until residue or odor is reduced or eliminated. Take caution bathing neurological patients and monitor for hypothermia. If it is a sticky substance, using oils such as butter, vegetable or mineral oil, or peanut butter to reduce the residue can be used. Bathing afterwards is fine. Powders or dusts should be brushed off or vacuumed off before bathing.

After any possible exposure to ocular toxins, the eyes should be flushed for 20–30 minutes with tepid water or sterile saline. Sedation may be needed for this process. Soaking up the toxin with a towel or gauze to prevent dermal exposure is recommended. Avoid high-pressure eye flushing. After flushing, evaluation for corneal abrasions/ulcerations is recommended. If ocular chemical burns are noted, lubricating eye ointments should be started. Avoid corticosteroids.

> **“BATHING CAN BE REPEATED UNTIL RESIDUE OR ODOR IS REDUCED OR ELIMINATED.”**

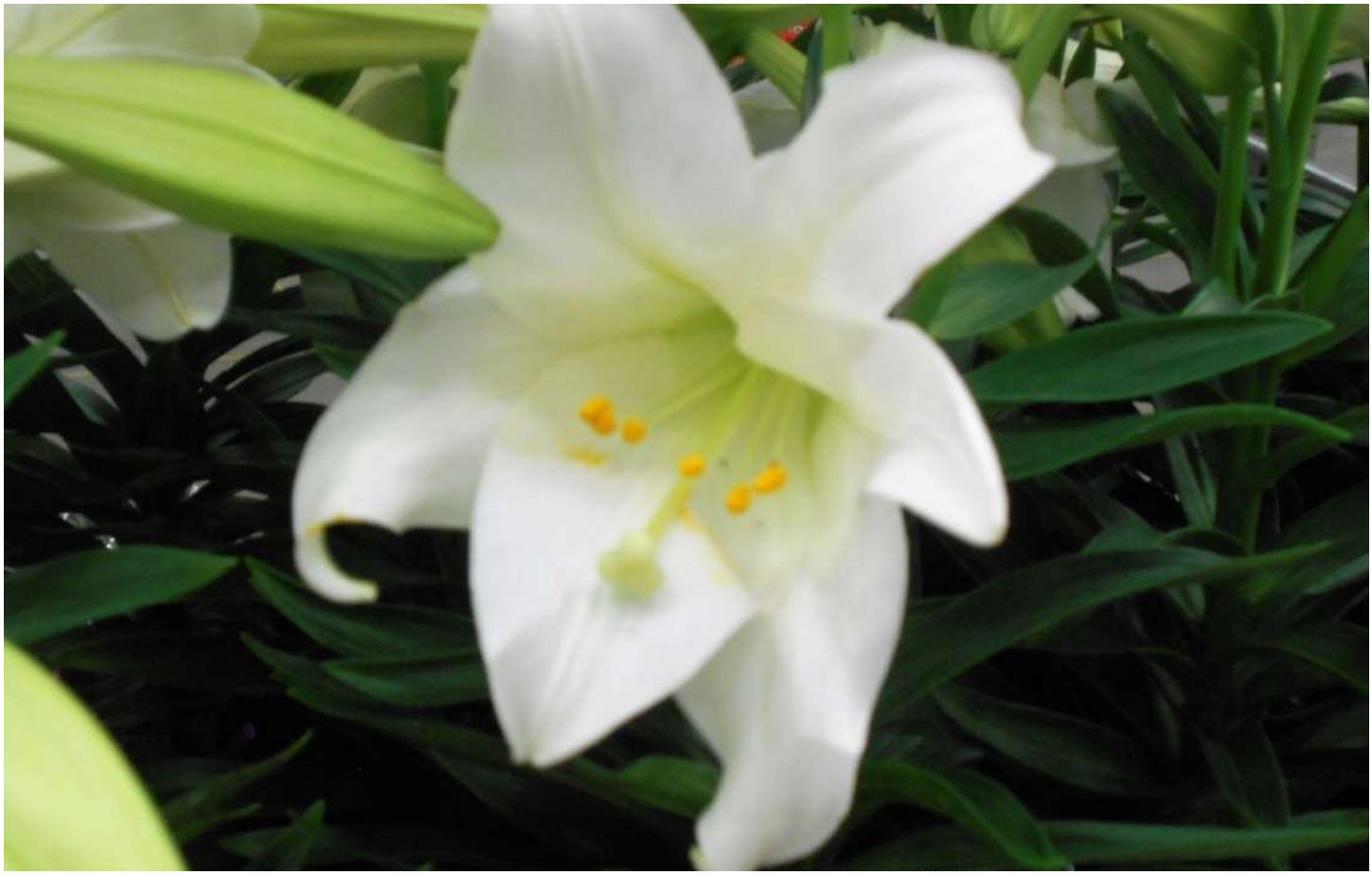
POISONOUS PLANTS

There are many plants that can be found inside and outside the home that can be toxic to pets. After possible exposure, the best resource is the *ASPCA toxic plant list*, which provides pictures and is the most comprehensive list. We are going to go through some of the more common toxic plants.

Lilies are the classic toxic plant. This includes Lilium and Hemerocallis species, which fall into the Liliaceae family. They are toxic to cats and nontoxic to dogs and horses. The toxic principle is unknown, unfortunately, and all parts of the plants are nephrotoxic to cats. If cats have pollen on their faces or paws, they should be bathed to remove the toxin and to prevent re-exposure. If they ate pieces of the plant, emesis should be induced. Toxicity can be seen within hours of ingestion. Most classic clinical signs include vomiting, hypersalivation, anorexia, and depression. Initial management of toxicity include obtaining baseline renal values, placing an IV catheter, starting IV fluid diuresis, and monitoring renal values every 24 hours for the first 72 hours post-exposure. At any point, if rising azotemia or anuria is noted, transferring to a facility that has hemodialysis capabilities is recommended. The prognosis is better if treatment is initiated immediately, before azotemia or anuria occur.

Sago palm toxicity has been more prevalent in the recent years, as they have appeared in grocery stores and in houses where they previously were not. Cycads, which include sago palms, are toxic to humans, dogs, cats, and horses. There have been many cases of cycad toxicity in people and livestock that have eaten these plants. Chronic exposure to cycad products has been linked to the development of amyotrophic lateral sclerosis and Parkinsonism-dementia complex in people, mainly in the subtropic regions where these plants are common. There are three toxins in the cycad plants:

- Azoxyglycosides with a toxic metabolite methylazoxymethanol (MAM)
- B-methylamino-l-alanine (BMAA)
- An unidentified high-molecular-weight compound



The seeds contain the highest concentration of toxins, but they can be seen through the whole plant. Toxicity is seen most commonly in spring and summer but can be year-round if plants are inside. The most common clinical signs can occur as early as 15 minutes after ingestion and up to three days after exposure. The most common initial clinical signs are severe gastrointestinal symptoms—vomiting, diarrhea, abdominal pain, and melena or hematochezia. As the disease progresses, signs of liver failure will be present, including icterus, coagulopathies, and neurological signs. Bloodwork shows elevations of liver values, coagulation values, thrombocytopenia, hypocholesterolemia, hypoglycemia, and hypoalbuminemia. No definitive testing is available; diagnosis is presumptive based on possible exposure.

Decontamination is warranted if the animal is presented soon after ingestion; inducing emesis or gastric lavage is a consideration due to the high level of toxicity. Activated charcoal can be considered due to the enterohepatic recirculation that can be seen with this toxicity. Treat clinical signs with IV fluids, anti-nausea medication, gastroprotectants, liver protectant medication (n-acetylcysteine), plasma transfusions, vitamin K1, and antibiotics to help with bacterial translocation. Prognosis is guarded pending clinical signs and response to treatment; some papers have noted a 50% chance of survival.

Rhododendrons, including rosebays and azaleas, are toxic to cats, dogs, livestock, and horses. Rhododendron belongs to the Ericaceae family, and the toxic component of the plant is the grayanotoxin. All parts of the plant contain the toxin, and toxicity can be seen with ingestion of as little as 0.2% of body weight. Initial clinical signs are located mostly in the gastrointestinal tract with vomiting, diarrhea, inappetence, hypersalivation, and abdominal pain. Neurological and muscular signs can be seen because grayanotoxin interferes with muscle and nerve function. Cardiac problems can be noted due to cardiac muscle weakness. Treatment is mainly supportive; no antidote is known. Prognosis is highly dependent on the severity of clinical signs.

Oleander, also known as rose laurel, can be toxic to dogs, cats, livestock, and horses. The toxins found in this plant are cardiac glycosides, which can be found in all parts of the plant. The red-flowered oleanders are more toxic than the white varieties. The cardiac glycosides inhibit the cellular membrane sodium-potassium (NA-K-ATPase enzyme system) pump, which causes depletion of intracellular potassium and increases serum potassium. This causes bradycardia and can eventually lead to full atrial standstill and death. Clinical signs can include vomiting, arrhythmias, weakness/collapse, dyspnea, and mydriasis. Confirmatory diagnosis would be detection of cardiac glycosides in serum/urine. Treatment includes emesis if ingestion has been recent and activated charcoal to slow absorption. If hyperkalemia is noted, then treatment with IV fluids, albuterol, dextrose/insulin, and supportive care are advisable. Calcium gluconate should be avoided, as this can potentiate cardiac glycosides. Treatment with digoxin-specific antibodies has been effective in humans with oleander toxicity.

Castor bean plants are also known as castor oil plants, higuerilla, palma Christi, mole bean plants, and African wonder trees. They are toxic to animals and humans. The toxic chemical in the plant is ricinoleic acid, which is found in the highest concentration in the seeds. Ricin is absorbed from the intestinal tract and is metabolized in the liver. Afterwards, it is absorbed into cells and inhibits ribosomal protein synthesis. Symptoms include gastrointestinal signs, muscle weakness, cardiovascular collapse, hepatic failure, and Multiple organ dysfunction syndrome. Treatment involves early decontamination, activated charcoal administration, and supportive therapy with IV fluids and gastrointestinal support. Vitamin C therapy has been reported to be helpful.

Kalanchoe is also known as mother-in-law plant, devil's backbone, chandelier plant, and mother of millions. Kalanchoe, like oleander, contains cardiac glycosides as the toxic principle. Toxicity is mainly in the summer, when the flowers contain the highest concentration of the glycosides compared with the stems and leaves. The glycosides present in kalanchoe are a group of bufadienolide compounds including bryotoxins, bryophyllins, and bersalgenins. These compounds work in a similar way to digitalis and inhibit the Na-K-ATPase enzyme system, causing cardiotoxic hyperkalemia. The initial clinical signs after ingestion are usually gastrointestinal, but as time progresses, weakness, bradycardia, and cardiovascular collapse can be seen. In some dogs, neurological signs have been reported, but this is seen more commonly in livestock that have chronic exposure. No definitive test for identification is present. Decontamination is important. Treatment is supportive for gastrointestinal signs. Treatment for hyperkalemia and arrhythmias is necessary if present. This would include IV fluids, albuterol, dextrose/insulin, and digoxin-specific antibodies.

Yew is also known as Japanese yew. The toxin principle is taxine, which is a group of toxic alkaloids. All parts of the green plant are toxic, the most toxic being the leaves in the winter. Dried leaves can also be toxic. Many clinical signs can be seen with toxicity, including gastrointestinal signs, muscle tremors, ataxia, cardiovascular collapse, bradycardia, seizures, and/or dyspnea. Yew toxicity can be toxic based on severity of clinical signs. Treatment is supportive based on clinical signs, and atropine can be given to combat bradycardia. There is no definitive diagnostic tool to identify yew toxicity.

Tulips can be toxic to dogs and cats. The toxins, mainly located in the bulb, are called Tulipalin A and B. Clinical signs of toxicity include gastrointestinal signs—vomiting, diarrhea, inappetence, and hypersalivation. Treatment is based on clinical signs.

Poinsettia is toxic to dogs and cats. This plant contains an irritating sap that causes irritation to the mouth and stomach with generally mild gastrointestinal signs. Treatment is supportive.

Aloe vera are plants are in the family Liliaceae and can be toxic to dogs and cats. The two toxic substances in the plant are saponins and anthraquinones. Clinical signs are usually vomiting, diarrhea, and lethargy; usually mild signs are noted. Treatment is supportive.

COMMON HOUSEHOLD HAZARDS

There are many household products that can be toxic to pets. Any possible toxin should be locked up and put out of pets' reach.

Ant baits are a common household product that pets are exposed to. Most of these products are in plastic or cardboard boxes; the ants crawl in and eat the toxin. These are generally considered safe, but mild gastrointestinal signs can be seen with some ingestions. If the casing is ingested, an intestinal obstruction is a possibility.

Cockroach bait traps are similar to ant bait traps. They tend to be benign if pets ingest the contents, though mild GI irritation is possible. The outer casing can cause obstruction if the entire trap is ingested.

Silica gel packets or other types of desiccant and oxygen-absorbing packets may look scary because they are commonly labeled "do not ingest." Luckily, they are non-toxic to humans and pets. If a large amount is ingested, there may be mild gastrointestinal signs. If large quantities are ingested, the silica could cause an obstruction in the GI tract.

Laundry detergent pods have posed a new threat of toxicity over the last few years. They are brightly colored and small, and both these qualities can make them seem like a toy or something to chew on. If ingested, they can cause severe gastrointestinal upset but can also cause irritation to the upper airway. They can also be aspirated, causing severe chemical pneumonia. Treatment is supportive for GI signs; if pneumonia is suspected, they may need supplemental oxygen, antibiotics, and in advanced cases, potentially mechanical ventilation. Pet owners should be educated on this toxin and make sure the pods are always out of pets' reach.

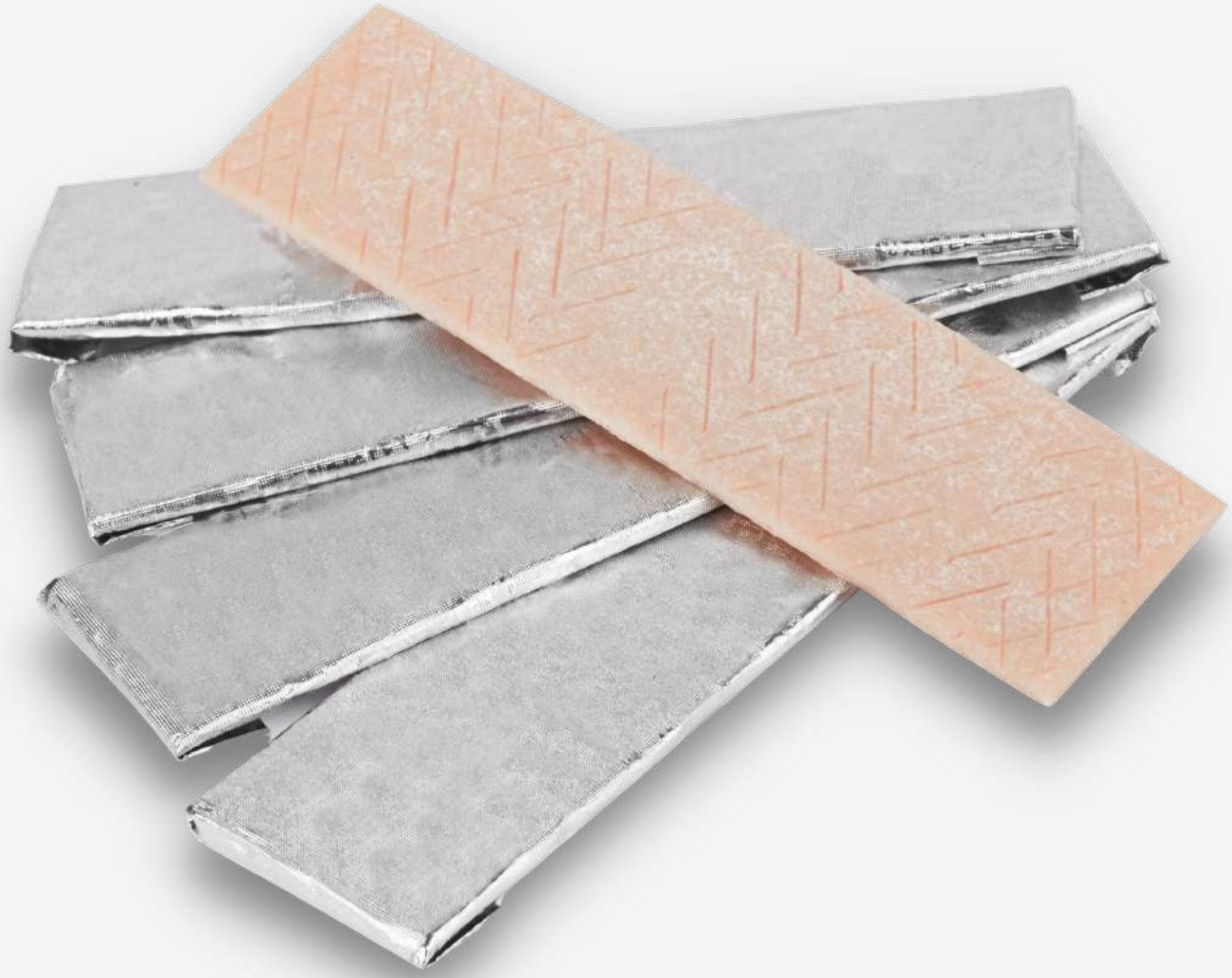
Gorilla glue and other adhesive products can cause serious injuries to pets. These include any adhesives that contain diisocyanates, which makes them flexible but expandible as they dry. The pets eat the liquid adhesive, but in the stomach, the liquid will expand as it would to fill a crack or hole. Radiographs are very classic for this toxicity, and unfortunately the only treatment option is surgery to remove the ball of dried adhesive from the stomach. Emesis should not be induced, as the expansion happens quickly. Also, limiting water intake after ingestion can be helpful to prevent further expansion. This can be fatal if surgery is not pursued.

Cleaning products are commonly found around the house, and many can be toxic to pets. One of them is bleach, which can cause esophageal and gastric irritation if ingested. Cats might walk through bleach and then have chemical burns on

their feet. Pets with oral/esophageal and gastric ulcers should be treated supportively with gastroprotectants and IV fluids if they are dehydrated or not eating. If the oral ulcerations are severe enough, occasionally esophageal feeding tubes need to be placed for them to get nutrition until they are eating consistently.

Dryer sheets might seem like a harmless household product, but they can cause significant toxicity in pets. Dryer sheets contain cationic detergents. If pets chew on new or unused sheets, they can develop oral/esophageal ulcers, drooling, vomiting, and fever. Veterinary care is often needed depending on the severity of clinical signs and ulcerations. If whole sheets are ingested, they could cause intestinal obstruction.

Toilet bowl cleaner, whether liquid or tablets, is toxic. Toilet water that has been treated with chemicals tends to cause mild GI signs if any clinical signs are noted. Luckily, the volume of water in the toilet and frequent flushing helps to dilute the chemicals to a low level. If the pet eats an actual tablet or the undiluted liquid, more significant ulcerations and GI signs may be noted.



Xylitol is a sugar substitute commonly used in human food products. It is harmless in people and cats but causes life threatening toxicity in dogs. Peak levels can be seen in a dog's blood stream within 30 minutes of ingestion. In dogs, the insulin levels are 2.5–7 times higher than when the same volume of dextrose is consumed. The elevated insulin level leads to profound hypoglycemia, which is usually the first clinical sign noted with this toxicity. The delayed toxicity of xylitol is hepatic necrosis.

Xylitol toxicity is dose-dependent. Ingestion of >0.1 g/kg creates risk of hypoglycemia; dogs that ingest >0.5 g/kg are at risk for hepatic necrosis and acute liver failure. The exact dose may not be known, or the amount could be proprietary to the company. Poison control can often extrapolate some idea of xylitol concentration for each product. If xylitol is not listed as the first ingredient on gum packaging, assume 0.3 g/piece of gum. One cup of xylitol is approximately 190 g when calculating concentration in bake goods. Dogs that develop hypoglycemia will often also develop hypokalemia and hypophosphatemia due to intracellular shift into cells due to increased insulin. Hyperphosphatemia has been associated with xylitol ingestion and in people is linked with increased mortality in acute liver failure (not xylitol-related in people).

Early emesis is important to prevent further absorption, although peak serum levels may already be present. Activated charcoal is not recommended for xylitol toxicity unless a massive dose was ingested. Dogs that are already hypoglycemic at presentation or that ingested >0.1 g/kg should be admitted to the hospital for an IV catheter, dextrose bolus if hypoglycemic, and hourly blood glucose monitoring. Dextrose supplementation in crystalloid fluids is recommended especially if patient ingested a hepatotoxic dose. Baseline bloodwork (including liver values) should be checked at presentation and every 24 hours for 72 hours. Liver protectants such as N-acetylcysteine, S-adenosylmethionine, silymarin, and vitamin E should be started in patients at risk for hepatotoxicity. If hepatic failure is suspected or coagulopathy is noted, coagulation testing should be pursued and fresh frozen plasma given if indicated.

Homemade play dough contains a large amount of salt; if ingested, it can cause salt poisoning. Initial clinical signs include excessive thirst, vomiting, diarrhea, neurological signs, tremors, and seizures. Treatment involves IV catheter, IV fluids, anti-emetics, and serial monitoring of sodium levels and adjusting IV fluids of different tonicity until hypernatremia is achieved. Sodium levels should not be corrected faster than 0.5 mEq/L/hr.

Coins—although infrequently consumed—are foreign bodies commonly seen in puppies. Sometimes the ingestion is witnessed, and sometimes they are found on radiographs when evaluating GI signs. If coins are noted on radiographs, endoscopy is recommended. Pennies are the most concerning of coins to ingest, as pennies minted after 1982 are mainly made of zinc, which the stomach acid breaks down, causing zinc toxicity in pets. Zinc toxicity can cause immune-mediated hemolytic anemia. Removal of the penny is important to prevent further zinc toxicity. In advanced

disease, in addition to removal of coins, packed red blood cell transfusions may be necessary. In some cases, chelation and immunosuppressants are necessary.

Allium species (onions, garlic, chives, and leeks) can cause Heinz body anemia in dogs and cats when ingested in large enough quantities. Cats and Japanese dog breeds (akita, shiba inu) tend to be more sensitive to this toxicity compared to other dogs. Ingestions of 0.5% of body weight can potentially cause toxicity. Clinical signs include vomiting, lethargy, pale mucous membranes, tachypnea/dyspnea, and rarely, hypoglycemia. Treatment is decontamination if ingestion was recent and activated charcoal administration. If the patient is clinical for anemia, packed red blood cell transfusion is needed. Provide dextrose support if hypoglycemia is present.

Raw dough expands in the warm stomach cavity when ingested. It can expand enough to cause vomiting, gastric dilation, and gastric dilation volvulus. In addition to the expansion, fermentation can occur, producing ethanol. The ethanol can get into the blood stream, causing alcohol toxicity and hypoglycemia. Clinical signs include vomiting, abdominal distention, weakness, lethargy, ataxia, seizure, and/or respiratory depression. Emesis is rarely successful due to rapid expansion. Treatment involves ice-water gastric lavage to stop fermentation and remove the dough. Gastric lavage involves general anesthesia, intubation with a cuffed endotracheal tube, passing a gastric tube, and lavaging/siphoning with ice water. This should be continued until most of the dough has been retrieved and the lavage water is clear. Hypoglycemia should be treated with dextrose boluses and dextrose CRI if necessary. If the patient is already showing signs of intoxication, monitoring for hypoventilation is important.

Grapes and raisins: The toxic principle for these fruits is now thought to be tartaric acid. All grape/raisin ingestion should be considered toxic. Emesis is recommended to retrieve as many fruits as possible. Some resources recommend activated charcoal if all the fruit is not retrieved. Baseline renal values should be obtained, and then IV fluid diuresis for a minimum of 48 hours is recommended. Clinical signs can include vomiting, diarrhea, inappetence, lethargy, and ataxia.

Batteries can contain alkaline or acidic material. The most common batteries (9-volt, D, C, AA, AAA) are alkaline dry cell batteries, which contain potassium hydroxide or sodium hydroxide. If the alkaline substances leak and are exposed to the mouth, esophagus, or stomach, liquefaction necrosis can occur, causing deep ulcers that can be full thickness. Disc-shaped batteries can cause electric current to pass to the tissues and cause current-induced necrosis. Lithium button-type batteries are the most dangerous and can cause the most severe injuries. A thorough oral exam should be completed on any pets who could have eaten batteries; sometimes black debris can be seen in the mouth if the batteries have been punctured. The mouth should be thoroughly lavaged with water to minimize contact time. If a battery is present in the stomach or GI tract, it should be removed as soon as possible to minimize further damage. Gastroprotectants and ulcer management is necessary.

Magnets: When a solo magnet is ingested, emesis may be successful. If multiple magnets are ingested, they can stick to each other across gastric/intestinal loops and cause pressure necrosis, leading to perforation. Endoscopy is an option if the magnets are all in the stomach, but if there are multiple magnets in the intestinal tract, surgery is needed.

RODENTICIDES: ANTICOAGULANTS, BROMETHALIN, CHOLECALCIFEROL, AND PHOSPHIDES

There are four main categories of rodenticides, based on their mechanism of action. In 2008, the US EPA issued a decision to prohibit second-generation anticoagulant rodenticide in residential sites. This changed the rodenticide exposure seen in pets. The four categories are:

- Anticoagulant rodenticide
- Bromethalin
- Cholecalciferol
- Phosphides

Decontamination is the same for all four rodenticides. Emesis should be induced if the ingestion was recent. If it has been greater than two hours since ingestion, however, emesis may not be useful. Activated charcoal is recommended post-emesis to minimize further exposure. If the type of rodenticide is known, then treatment recommendations should be followed for that type of rodenticide and based on the quantity that could have been ingested. If the type is unknown, then the animal needs to be treated for all four types of rodenticide.

Anticoagulant rodenticides are divided into groups based on how long they stay in an animal's system. First-generation is fourteen days—those are warfarin, coumafuryl, and pindone. Bromadiolone lasts for twenty-one days, and second-generation anticoagulants can last up to four weeks. The second-generation anticoagulants include brodifacoum, chlorophacinone, difenacoum, difethialone, diphenadione, and valone. Anticoagulant rodenticides work to inhibit production of clotting factors II, VII, IX, and X by inhibiting vitamin K1 epoxide reductase. The first clotting factor affected is factor VII because it has the shortest half-life, and if a coagulopathy is going to be seen, it will be within 36 and 72 hours of ingestion. If a patient has recently ingested anticoagulant rodenticide, emesis and activated charcoal should be given, and the patient should be started on vitamin K1 orally for 30 days, then have coagulation checked 48 hours after last dose (day 32 after ingestion). Coagulation

testing should not be done at presentation if a pet has just ingested the rodenticide. If a patient presents with hemorrhage/coagulopathy, and rodenticide is a possibility, further testing should be completed. The patient should have coagulation testing done, particularly PT (prothrombin) to see if it is prolonged and consistent with rodenticide toxicity. Pending the patient's stability, packed red blood cell transfusion may be needed if markedly anemic and symptomatic for anemia. If patient is not anemic or symptomatic but has prolonged clotting times (>1.5 times normal) then fresh frozen plasma transfusion is indicated. Coagulopathy should be corrected before doing advanced procedures such as thoracocentesis for pleural effusion. These patients also need to be started on oral or injectable vitamin K1 therapy for 30 days and rechecked 48 hours after the last dose.

Bromethalin is a neurotoxin rodenticide. Its mechanism of action affects the mitochondria in the liver and brain. It causes decreased ATP production, which causes sodium and potassium pumps to fail and leads to intracellular sodium buildup. This leads to cellular death and associated edema. There is no antidote for this toxicity, so early emesis and decontamination with activated charcoal is important. Median lethal dose per Pet Poison Hotline for dogs is 2.38–3.65 mg/kg with minimum lethal dose of 2.5 mg/kg. Cats are more susceptible and need a lower dose for clinical signs; median lethal dose in cats is 0.54 mg/kg. Clinical signs can occur within 2 to 24 hours after ingestion with signs including ataxia, depression, hyperesthesia, seizures, and coma. Some dogs that get into sublethal doses can have delayed onset of clinical signs; it can take days after ingestion for signs to appear and then progress for 1–2 weeks after ingestion. Some pets can develop delayed paralysis, a coma-like state that can take weeks for recovery. Treatment involves early emesis and decontamination with multiple doses of activated charcoal. If clinical signs appear, treatment is supportive with IV fluids, anti-seizure medication, corticosteroids to help with cellular edema, and mannitol for intracranial hypertension. Prognosis is poor once neurological signs are present and progressive.

Cholecalciferol (vitamin D3) has become more popular as anticoagulant rodenticides are phased out. Cholecalciferol is involved in calcium hemostasis in the body. When this rodenticide is ingested, it causes unregulated calcium absorption for the GI tract and bone storage. This leads to marked hypercalcemia and hyperphosphatemia. These electrolyte changes lead to acute kidney failure and soft tissue mineralization within days after ingestion. Clinical signs include depression, weakness, anorexia, vomiting, increased thirst/urination, and dehydration. Bloodwork will show elevated calcium, phosphorus, and azotemia. Treatment involves inducing emesis if ingestion was recent and activated charcoal administration afterwards. A toxic dose is as little as 50 mcg/kg. If clinical signs are present, treatment involves IV fluids, anti-emetics, corticosteroids, loop diuretics, and bisphosphonates as clinically indicated. Prognosis is good with early treatment before hypercalcemia and azotemia have occurred but guarded to poor if these are already present.

Phosphide rodenticides are rare. When zinc phosphide is ingested, it interacts with gastric acid and creates phosphine gas, which is toxic. Phosphine gas is absorbed across the gastric mucosa and distributed throughout the body but has the most concentrated toxic effect on tissues with high oxygen demand such as the brain, lungs, liver, kidneys, and CNS. Clinical signs can occur hours after ingestion, including profuse vomiting, depression, abnormal mentation, lethargy, tachypnea, and tachycardia. Care should be taken when inducing emesis in a patient that could have eaten zinc phosphide bait, as the gas can be toxic to veterinary professionals. This should be performed in an open, well-ventilated space. Treatment is supportive for clinical signs. Prognosis is good if a patient is asymptomatic 8–12 hours after ingestion. Prognosis is variable depending on the severity of clinical signs.

HUMAN MEDICATIONS

Anti-inflammatory pain medications are very common in households but are also, unfortunately, given to pets for pain relief. Non-steroidal anti-inflammatory medications are a common toxicity in veterinary medicine. NSAIDS are rapidly absorbed into the system, and animals can start exhibiting signs within hours of ingestion. NSAIDS are highly protein-bound to albumin, but the unbound fraction is the only active form. They are mainly metabolized in the liver and excreted in the urine. Due to high protein binding, they tend to have a low volume of distribution. The main mechanism of action involves inhibition of prostaglandin production. Salicylates inhibit the enzyme COX, which helps in the synthesis of prostaglandins. There are two isoenzymes of COX, COX-1 and COX-2; COX-1 is involved in the more physiological processes in the body including renal blood flow and is found mainly in the stomach, kidneys, endothelium, and platelets. COX-2 is the inducible form and is responsible for the production of inflammatory mediators. The COX pathway aids in production of prostaglandins; PG helps with inflammation, GI with mucosa health and renal blood flow. The GI tract and kidneys are the most vulnerable organs to NSAID toxicity. Prostaglandins help with vasodilation to regulate renal blood flow; inhibition of prostaglandins can lead to decreased blood flow to the kidneys and an ischemic injury.

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Treatment for toxicity is very similar for all NSAIDS. The first goal should be early decontamination by inducing emesis and administering activated charcoal. Enterohepatic recirculation is important with NSAIDS, and multiple doses of activated charcoal are recommended but only the first with sorbitol. GI ulcers are a possibility, and GI protectants such as H2 blockers—cimetidine, famotidine, ranitidine—or proton pump inhibitors such as omeprazole or pantoprazole are recommended. Sucralfate is helpful to coat the stomach. Misoprostol, which is a prostaglandin analog, is recommended. Administer antiemetic if vomiting or nausea is noted. IV fluids are incredibly helpful in NSAID toxicity and should be continued for 48-96 hours depending on the particular NSAID. If the dose is large enough, hepatic toxicity can be seen, and liver protectants like SAMe are recommended in these patients. In extremely large doses, neurological signs such as seizures have been noted; anticonvulsants should be used to manage seizures and mannitol/hypertonic saline if intracranial hypertension is noted. In large ingestions, hemoperfusion and hemodialysis may be recommended; ask poison control if the patient is a candidate when discussing the case. Kidney and liver values should be checked at presentation and then daily for 3-5 days.

Particular NSAIDS

- Ibuprofen: Cats are more sensitive to ibuprofen toxicity than dogs. This is thought to be secondary to reduced glucuronidation ability.
- Carprofen: Selectively inhibits COX-2 over COX-1, but at large doses this doesn't apply.
- Grapiprant: A non-COX-inhibitor that works by blocking EP4 receptors, which is thought to be the main medicator of pain and inflammation in dogs with arthritis. Galliprant is a sulfa drug, so use caution in sulfa-sensitive dogs/breeds; rule of thumb is black and tan dogs.

Acetaminophen is a synthetic non-opiate pain medication that is a derivative of the p-aminophenol family. Compared to NSAIDS, acetaminophen is poorly protein-bound and has a large volume of distribution. It is metabolized in the liver and small amounts in the kidneys. It is excreted through the bile. Acetaminophen is metabolized by glucuronidation and sulfation. If the body is unable to use these pathways, such as in a cat due to decreased glucuronidation ability, it causes N-acetyl-p-benzo-quinone imine (NAPQI) to accumulate, which is toxic. NAPQI causes red blood cell damage, renal injuries, and liver injury. RBC damage is secondary to oxidative injuries, which cause methemoglobin and Heinz body formation. Clinical signs include tachypnea, dyspnea, cyanosis, vomiting, weakness, and face/paw edema, and it can be fatal. Hematuria may be noted. Methemoglobinemia can be diagnosed crudely by putting a drop of blood on a paper towel. Blood with methemoglobin will turn brown instead of red; quantitative oximetry can be used. If ingestion is recent, decontamination with emesis and activated charcoal is recommended. If symptomatic, then oxygen support and n-acetylcysteine administration. N-acetylcysteine binds NAPQI and helps to speed up elimination. Cimetidine, n-acetylcysteine, and ascorbic acid (vitamin C) together have been shown to improve prognosis. Cimetidine is a H2-receptor antagonist that inhibits P450 and reduces metabolism of acetaminophen to NAPQI. Methylene blue injection has been proposed but has higher risks than other proposed treatments.

Albuterol inhalers are an oddly common toxicity for dogs. Dogs chew on the cases and can puncture the canister. Unfortunately, this is a serious toxicity. Albuterol is a beta agonist that has positive inotropic and chronotropic effects on the heart; it can also cause arrhythmias, rapid breathing, tremors, and seizures. The initial puncture can cause thermal burns to the inside of the mouth. The more profound signs of toxicity are hypokalemia secondary to intracellular movement of potassium. Decontamination isn't an option because it is an inhaled gas. Treatment involves IV fluids, potassium supplementation, and frequent electrolyte monitoring, as well as treatment of tachycardias/hypertension if present. Anticonvulsants should be administered if seizures are noted. Hypophosphatemia may also be seen secondary to intracellular shifting.

Antidepressant toxicity[6] is a rising toxicity due to the prevalence of the medications in households. The most common antidepressants fall into three categories: tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and selective serotonin reuptake inhibitors (SSRIs).

- Tricyclic antidepressants act by blocking the reuptake of norepinephrine and serotonin at the neurons. They are rapidly absorbed into the system with high protein binding. Emesis is recommended if the ingestion has been recent, but if >30 minutes, it will most likely already be absorbed. Charcoal administration is helpful post-ingestion. Clinical signs include tachycardia, vomiting, mydriasis, hypotension, dyspnea, seizures, coma, and death. Treatment is symptomatic for clinical signs; IV lipid emulsion has been shown to help in TCA overdoses.

- Monoamine oxidase inhibitors act by increasing levels of epinephrine, norepinephrine, dopamine, and serotonin in the CNS. Clinical signs are hypotension or hypertension, arrhythmias, depression, agitation, seizures, respiratory distress, coma, and death. Signs can be seen within 2 hours of ingestion, up to 12 hours. Decontamination is recommended with activated charcoal afterwards. Treatment is supportive based on clinical signs. Intralipids can be useful in MAOI toxicity.

- Serotonin reuptake inhibitors work by inhibiting presynaptic neuronal reuptake of serotonin. They are absorbed rapidly in the system and are highly protein bound. Clinical signs are lethargy or agitation, vomiting, ataxia, tremors, seizures, and tachycardia. Decontamination and activated charcoal are recommended. Treatment is supportive, and intralipids can help. Serotonin syndrome is a possibility with overdoses of SSRIs; clinical signs are similar to toxicity, treatment is supportive, and cyproheptadine (a serotonin antagonist) has been recommended in treatment.

Baclofen is a muscle relaxant that is commonly used in human medicine. Baclofen mimics GABA in the spinal cord and helps to reduce muscle spasms. Baclofen is rapidly absorbed from the GI tract, and peak levels are seen within 2–3 hours post-ingestion. Clinical signs include vomiting, ataxia, dyspnea, respiratory depression, seizures, and respiratory arrest. Decontamination is important as long as the patient isn't showing clinical signs. Activated charcoal is recommended if it can be safely administered. IV fluids and lipid therapy can be helpful. If a patient is having significant respiratory signs, including dyspnea, hypoventilation, or muscle fatigue, mechanical ventilation is needed. Hemodialysis with mechanical ventilation has been reported to help in severe cases of baclofen toxicity.

Birth control pills' ingredients vary between brands; contact poison control to confirm the contents. Mild GI signs are a possibility, and if the whole packaging is consumed then GI obstruction is possible. If massive ingestions are noted, bone marrow suppression secondary to estrogen toxicity is a possibility; the animal would normally need to ingest a >1 mg/kg total dose.

ADHD medications include Adderall® (amphetamine dextroamphetamine), which is the most common, but other generic or similar combinations of medications are available. These can be immediate and sustained release formulas. Clinical signs include hyperactivity, hyperthermia, tachycardia, tachypnea, mydriasis, tremors, seizures, and coma. Diagnosis is made by exposure; illicit drug urine screening will show up positive for amphetamines. Treatment is supportive with IV fluids, sedatives, anti-arrhythmic medications, and anti-seizure medications. Prognosis is usually good with early treatment.

Nicotine can be a routine household product, and ingestion is common. The most common exposure is to nicotine gum, chewing tobacco, and nicotine vape pens. Clinical signs include hyperactivity, tremors, drooling, vomiting, hypertension, tachycardia, respiratory depression, coma, and death. Treatment is supportive with IV fluids and anti-arrhythmia medications.

Illicit recreational drugs can be household products, and unfortunately, ingestion is common.

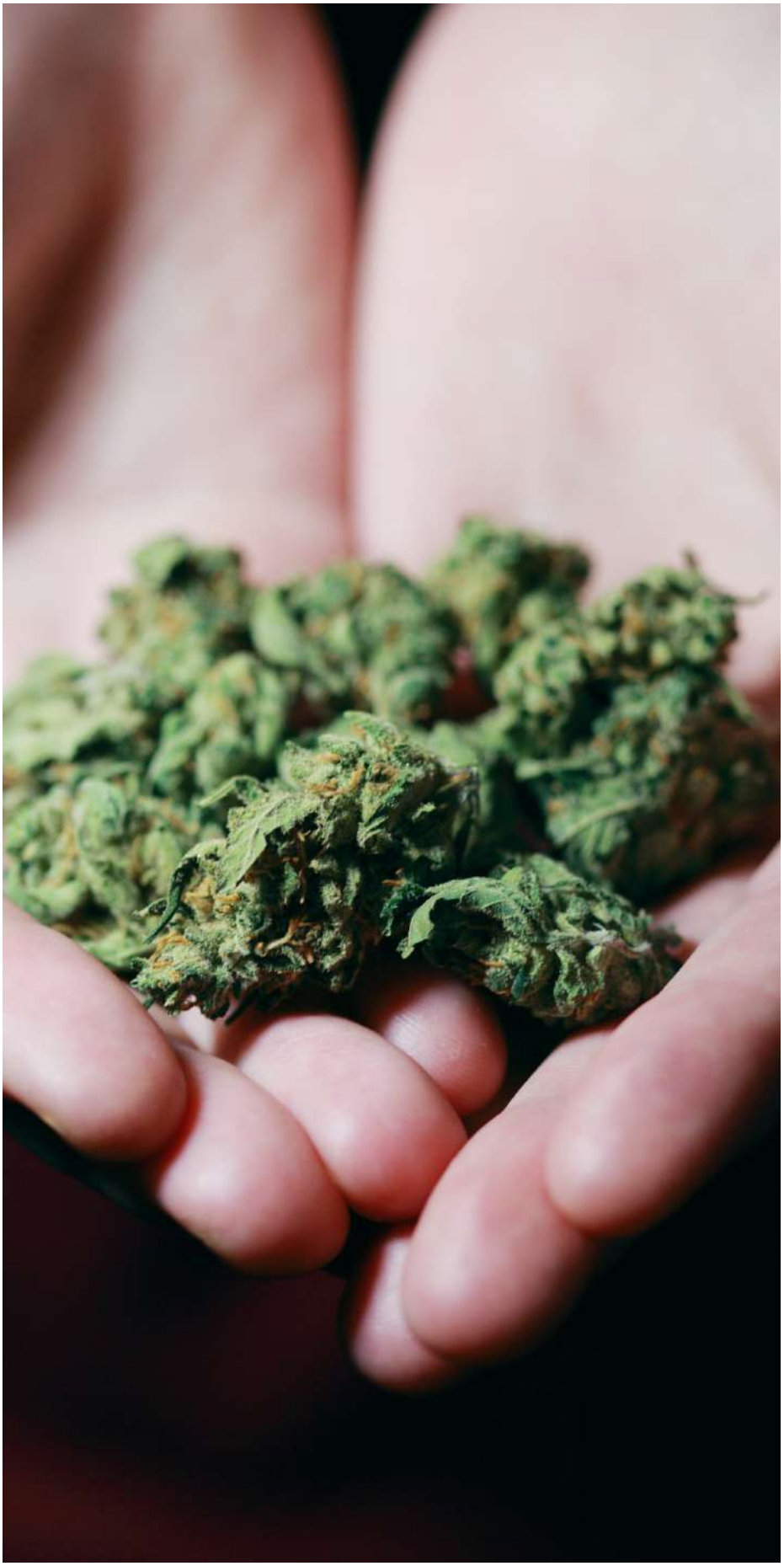
- Marijuana is by far the most common illicit drug toxicity seen in the ER clinics. Clinical signs are quick after ingestion; these include vomiting, depression, hyperesthesia, mydriasis, bradycardia, and urine dribbling. In large overdoses, stupor, respiratory depression, tremors, and seizures can be seen. Decontamination is recommended if early and there are no clinical signs. Treatment is supportive with IV fluids and antiemetics; lipid therapy has questionable response.

- Cocaine is rapidly absorbed in the system after ingestion. CNS stimulation is the systemic action of this drug. Clinical signs include hyperactivity, restlessness, vomiting, bradycardia, then tachycardia, seizures, hypertension, hyperthermia, and death. Hypoglycemia is seen. Decontamination is asymptomatic, activated charcoal if it can be safely administered. Diagnosis can be made by illicit drug urine testing. Treatment is supportive for clinical signs.

- Amphetamine toxicity treatment is as discussed previously for ADHD medications.

- Opiates include opium-derived drugs, semi-synthetic drugs, and totally synthetic opioids. Clinical signs include hypersalivation, vomiting, depression, bradycardia, hypotension, hypoventilation, increased urination/defecation, seizures, and coma. Decontamination is recommended if asymptomatic. Treatment is supportive, with mechanical ventilation if respiratory depression is profound. Naloxone can be used as a reversal agent, and repeat doses can be administered if needed.

- Benzodiazepines can be prescription or recreational. Clinical signs include sedation, ataxia, weakness, lethargy, nausea, respiratory depression, and bradycardia. Decontaminate early if possible. Treatment is supportive and flumazenil can work as a reversal agent.



INSECTICIDES, MOLLUSCICIDES, AND PEST CONTROL

Insecticides may be prescribed medications that, when given to the wrong pet or consumed in large doses, can cause toxicity.

Permethrin is a chemical that is used for small-animal flea control. This medication binds to sodium channels on nerves and affects conduction. Permethrin can be absorbed orally or topically across the skin barrier. They are metabolized in the liver and excreted in the urine. Permethrins are safe in dogs and have a low risk of toxicity if given at appropriate doses. Small dogs are at risk of toxicity if given large-dog doses or they inadvertently ingest a large amount. Cats are much more sensitive to permethrins, and permethrins should not be used in cats for flea control. Cats' intolerance stems from their decreased ability for glucuronidation. Most commonly toxicity in cats is seen when a dog product is placed on a cat or a cat is in close contact with dogs that have this spot-on therapy and ingest the permethrin. Clinical signs include muscle tremors, seizures, hypersalivation, hyperthermia, vomiting, and depression. Decontamination is recommended if a topical product has been applied. Treatment is IV fluids, methocarbamol for tremors, anticonvulsants, and IV lipid emulsion therapy.

Fipronil is a phenylpyrazole insecticide that is the main ingredient in Frontline® topicals and sprays; it can also be found in some roach traps. Fipronil works by binding to GABA receptors and blocking chloride channels. Fipronil in pets is not systemically absorbed and is instead absorbed in the sebaceous glands and released in the follicular ducts. Toxicity is low in this product when used appropriately. Safety studies have shown that doses up to 5 times the recommended dose do not cause signs of toxicity. Hypersensitivity locally on the skin has been reported with appropriate topical doses; respond with supportive treatment. Fipronil can cause seizures in rabbits when used off label.

Imidacloprid is an insecticide that is used for flea control in cats and dogs, most commonly used in the product Advantage®. It works by preventing acetylcholine from binding and results in paralysis of the insect. Imidacloprid is a safe insecticide when administered appropriately; oral administration can cause vomiting and hypersalivation. Signs of toxicity, if they were to occur, include lethargy, tremors, and muscle weakness.

Selamectin is a semi-synthetic avermectin that is the main ingredient in the product Revolution®. This is safe for dogs and cats; it has been tested and is also safe for collies and MDR mutation pets and heartworm-positive dogs and cats. If given orally, hypersalivation and vomiting may occur. Diarrhea 24 hours after administration has been noted in some pets.

Ivermectin is a mixture of 22,23-dihydroavermectin B1a and B1b, which is produced from fungus Streptomyces avermitilis and can be used in dogs, cats, livestock, and horses. Toxicity with ivermectin can be seen with overdoses or with dogs that have a mutation in their MDR1 gene. Dogs with this mutation are highly sensitive to ivermectin and can exhibit toxicity when it is administered at higher than the heartworm preventative dose of 0.006 mg/kg to 0.024 mg/kg. Dogs with MDR1 mutation can show signs of toxicity with doses as low as 0.2 mg/kg. Toxicity is often seen in farm dogs that ingest horse/cow dewormer in large doses but can also be seen with inadvertent administration, either orally or injectable. Clinical signs are depression, ataxia, hyperesthesia, hypersalivation, seizures, respiratory depression, coma, and death. Absent menace reflex is classic with ivermectin toxicity. Diagnosis is based on exposure and can be detected in blood and tissue levels. Treatment is symptomatic; lipid therapy can be very helpful. In severe cases, mechanical ventilation and hemoperfusion is recommended. Recovery can be prolonged with clinical signs lasting for days to weeks.

Chlorinated hydrocarbon compounds are used as insecticides and can cause toxicity in cases of exposure in small animals. Benzene hexachloride has been used as an insecticide in large animals and in dogs but is highly toxic in cats. Chlorinated hydrocarbons are general CNS stimulants. Clinical signs include neuromuscular tremors and convulsions. The tremors usually start in the face and extend caudally. Diagnosis is based on exposure or blood/tissue levels. Activated charcoal can be helpful to minimize exposure. Treatment is supportive; sedatives may be needed based on excitation. Phenobarbital may slow clearance.

Organophosphate toxicity has been less frequent, as this type of insecticide is being phased out due to its high toxicity. Pets exposed to organophosphates will have classic SLUDDE signs (salivation, lacrimation, urination, defecation, dyspnea, and emesis). Bradycardia may also be noted. Large doses can also cause neurological signs such as tremors, seizures, coma, and death. Clinical signs can progress for days to weeks, depending upon product and dose. Decontamination is recommended if ingestion was recent. Treatment is supportive. Atropine can be given as an antidote; it is recommended to give ¼ of initial dose (0.1–0.2 mg/kg IV) and then the rest IM or SQ. Pralidoxime chloride (2-PAM) can be used, which releases acetylcholine and can improve signs.

Metaldehyde is a cyclic polymer of acetaldehyde which is the active ingredient in molluscicides that control slugs and snails. Metaldehyde is metabolized in the stomach to acetaldehyde. Enterohepatic recirculation occurs with this toxin. Metaldehyde reduces GABA concentration in the CNS, causing excitation. Clinical signs include muscle tremors, hyperexcitability, hyperthermia, tachycardia, and progressive metabolic acidosis. Seizures and coma are end stage. Diagnosis is made by exposure history or blood/tissue levels, but no easy bedside test exists. Decontaminate if detected early and before clinical signs. Activated charcoal can help to eliminate enterohepatic recirculation. Treatment is supportive for clinical signs present, IV fluids, managing hyperthermia, and methocarbamol. Xylazine helps in horses with clinical signs.

Strychnine is an indole alkaloid obtained from seeds of Strychnos nux-vomica and Strychnos ignatii. Dried seeds are used to make powders, extracts, and solutions containing strychnine. This is mainly labeled for use as a buried pesticide for burrowing rodents. Malicious poisoning has been seen in small animals with this toxin. Clinical signs include tremors, vomiting, ataxia, hyperthermia, hyperesthesia, and seizures. Strychnine is a competitive and reversible inhibitor of glycine, which is an inhibitory neurotransmitter. This toxicity causes stimulation of motor neurons, causing generalized rigidity and tonic-clonic seizures. Diagnosis is by exposure or blood/tissue levels. Decontamination is important early post-ingestion. Treatment is managing seizures with methocarbamol, diazepam, and oftentimes propofol bolus or CRI is needed. Mechanical ventilation may be needed depending on respiratory depression and level of consciousness.

OUTDOOR HAZARDS

Ethylene glycol (antifreeze) toxicity is seasonally common around the country. Ethylene glycol is odorless and sweet, which leads to its ingestion by some pets. It is a small molecule that is absorbed across the GI tract rapidly after ingestion. It is metabolized in the liver by the alcohol dehydrogenase pathway to the following metabolites: glycolaldehyde , glycolic acid, glyoxylic acid, oxalic acid, and formic acid. These metabolites are then excreted in the urine. The metabolites' break-down products are what causes the toxicity in pets. Cats and people are much more sensitive to ethylene glycol than dogs, but it is toxic and can be lethal in all exposed. In cats, the toxic dose is reported to be as low as 1.5 mL/kg. In dogs, it has been reported to be approximately 6 mL/kg. The toxic metabolites cause severe metabolic acidosis, which is responsible for the clinical signs seen in the initial stages. Calcium oxalic acid forms complexes which deposit in the renal tubules, which results in calcium oxalate (monohydrate) to deposit in the tubules and causes edema in the kidneys.

Clinical signs are divided into phases:

- Phase 1 is within the first 12 hours post-ingestion. This phase is predominately gastrointestinal and CNS signs, including vomiting, ataxia, depression, and muscle fasciculations.
- Phase 2 is 12–24 hours post-ingestion. Cardio-pulmonary-clinical signs in this phase are secondary to the severe metabolic acidosis secondary to the toxic metabolites. Tachycardia, tachypnea, and dyspnea can be seen.
- Phase 3 is 24 hours post-ingestion and is characterized by renal failure.

Diagnosis is made by possible exposure. Ethylene glycol will fluoresce with a black light, so if an exposure was possible, you can try to fluoresce the paws and face to see if any residue is found. Laboratory changes can help in the diagnosis and possible exposure to ethylene glycol. There are benchtop clinic tests that can detect ethylene glycol levels above 50 mg/dL in pets. This is above the toxic dose in cats, so some cats may not test positive on the hospital tests but still have been exposed and could show signs of toxicity.

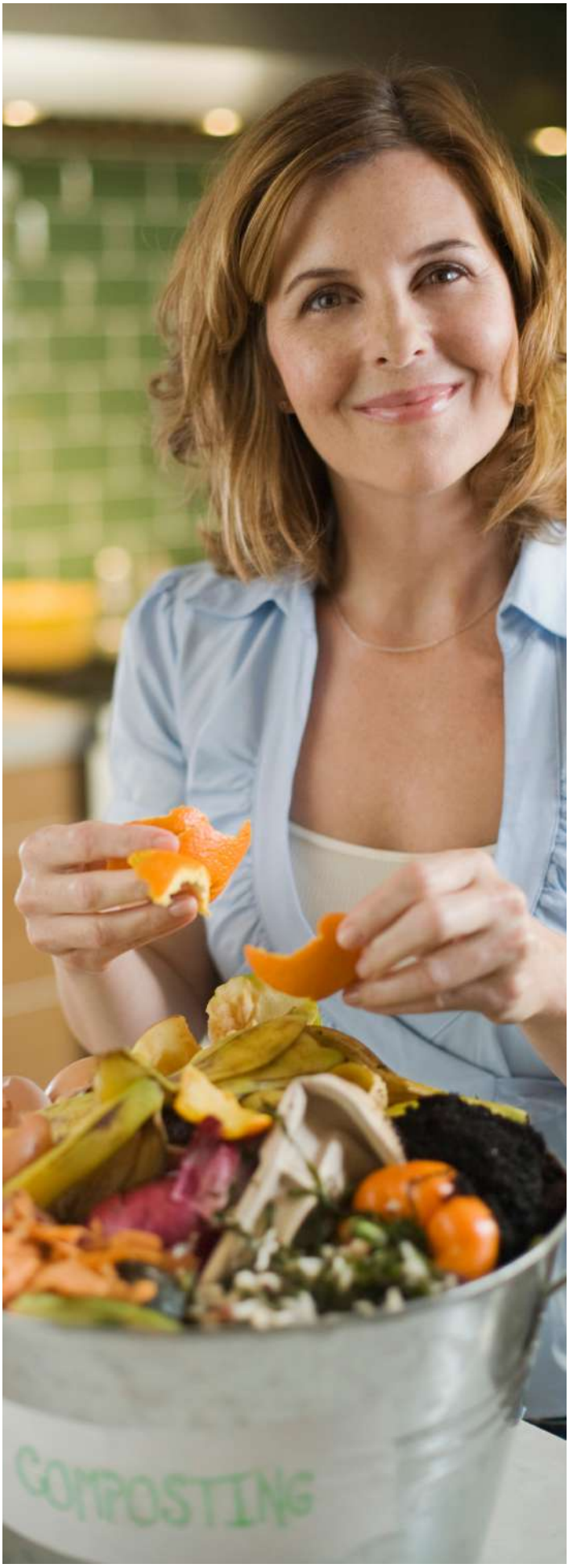
Other key changes to blood that can be seen with ethylene glycol toxicity include:

- Metabolic acidosis- Usually very profound, this can be seen within an hour of ingestion.
- Elevated serum osmolality- This can also be seen very early after ingestion.
- Isosthenuria (USG of 1.008–1.012)- This can be seen within 3 hours of ingestion; cats may not follow these rules.
- Calcium oxalate crystalluria- Can be seen as early as 3 hours post-ingestion in cats and 6 hours post-ingestion in dogs.
- Azotemia- This is noted later after ingestion, 12 hours in cats and 24–48 hours in dogs; this can also be secondary to dehydration.
- Hyperphosphatemia
- Hyperkalemia
- Hypocalcemia- Secondary to calcium oxalate crystal formation.

The earlier the presentation and diagnosis, the better the prognosis. Emesis and activated charcoal may have limited value due to rapid absorption. If ingestion is known or confirmed, the best recommendation is immediate referral to hospital with hemodialysis, even before renal failure is noted. If hemodialysis is not an option, treatment is aimed at reducing the breakdown of ethylene glycol to the toxic metabolites. Fomepizole (Antizol®) can be used in treatment of ethylene glycol because it is a competitive alcohol dehydrogenase inhibitor. Another option is treatment with ethanol, which has a higher affinity for the alcohol dehydrogenase than ethylene glycol. It would preferentially bind and metabolize ethanol compared to ethylene glycol. Treatment also involves supportive care with IV fluids, gastroprotectants, anti-emetics and serial monitoring of bloodwork. If renal failure is already present at treatment, prognosis is very poor and will most likely be fatal.

Herbicides help to combat unwanted outdoor plants and tend to have low toxicity in pets. The most common reason for herbicide toxicity in small animals is exposure to large quantities in poorly sealed containers. Clinical signs are usually acute GI signs of vomiting, diarrhea, lethargy, and hypersalivation. Chronic exposure and toxicity are seen more in large animals. Treatment is supportive for clinical signs. Ideally, if ingestion is certain and the product information is known, poison control should be contacted to discuss further treatment and considerations.

Compost is another household toxin that can have multiple levels of toxicity. Compost can contain toxic human food such as grapes/raisins, garlic, onions, chocolate, coffee, and many others. It can contain toxic plants. Also, when food is composting, mold can form and develop tremorgenic mycotoxins. History of compost ingestion is helpful in the diagnosis. Treatment is symptomatic based on clinical signs. If tremors are noted, methocarbamol is the first-line treatment.



Cocoa bean mulch is a newer product that has been showing up more frequently as a toxicity, mainly in dogs. This mulch is made from discarded hulls or shells of cocoa beans. When outside in the sun, it can smell like chocolate and can be appealing to some dogs. During the processing of the mulch, most of the methylxanthine is removed, but theobromine and caffeine are still present. Clinical signs are the same as those expected with chocolate toxicity—vomiting, diarrhea, hyperactivity, tachycardia, tremors, and possible seizures. Emesis is recommended if ingestion was recent, followed with activated charcoal if it can be safely administered. Treatment is IV fluids, anti-emetics, and beta blockers if tachycardia is profound. Sedation with acepromazine may be needed, and frequent walks are advisable, as the toxic compounds can be reabsorbed in the bladder and recirculated. Prognosis is good with treatment.

Mushroom toxicity in small animals is most commonly a dog-only toxicity. It is rare that cats would be foraging in the backyard, eating random mushrooms, whereas this is a dog specialty. Mushrooms can be hard to identify, and often pet owners do not know which mushrooms are in their yards or which were ingested. The main categories of mushroom toxicity are:

- Hepatotoxic mushrooms- The most common mushrooms that fall into this category are Amanita, with common names like death cap or death angel.
- Neurotoxic or hallucinogenic mushrooms- These are psilocybin, hydrazine, and isoxazole mushrooms.
- Gastrointestinal mushrooms- This is the largest group of mushrooms, with most causing only mild GI signs, although muscarinic mushrooms fall into this category, and they can cause significant vomiting/diarrhea and SLUDDE signs (salivation, lacrimation, urination, diarrhea, dyspnea, and emesis).
- Nephrotoxic mushrooms- Cortinarius species of mushrooms fall into this category. There have been human cases of nephrotoxicity but no documented dog or cat cases.

Amanita mushrooms' toxic principles are cyclopeptides, the three of them being amatoxins, phallotoxins, and virotoxins. These toxins are rapidly absorbed from the GI tract and can also go through enterohepatic recirculation. Clinical signs may be delayed for hours after ingestion. There are three phases to cyclopeptide toxicity:

- Gastroenteritis is the first phase, marked by vomiting, bloody diarrhea, marked dehydration, salivation, and abdominal pain. This phase can last for about 24 hours.
- Elevated ALT is the secondary phase, which is usually seen 12–24 hours after ingestion.
- The hepatorenal phase can be seen 3–4 days after ingestion. During this time, elevated liver and renal values are noted. Hypoglycemia, coagulopathies, and neurological dysfunction with hepatic encephalopathy can be seen. Most patients will pass away within 3–7 days after ingestion.

Treatment is focused on early decontamination with emesis and activated charcoal administration. Treatment is supportive based on clinical signs. Penicillin G has been proposed for use as it can displace amatoxins from protein binding sites and allows for earlier excretion. N-acetylcysteine is used as a hepatic protectant.

The most common neurotoxic mushrooms are from the Gyromitra species, which contain hydrazine compounds as the toxic principle, with the most known about gyromitrin. Gyromitrin is hydrolyzed in the GI tract to monomethylhydrazine, which initially causes GI signs but then progresses to CNS signs. Clinical signs are anxiety, restlessness, and seizures. Treatment involves decontamination and supportive care. Pyridoxine infusions have been recommended as an antidote for this type of toxin.

Muscarinic mushrooms contain muscarine, which causes postganglionic parasympathetic effects that are found in members of the Inocybe and Clitocybe genera of mushroom. Clinical signs are seen within hours of ingestion and are mainly characterized by SLUDDE signs—salivation, lacrimation, urination, defecation, dyspnea, and emesis. Treatment involves early decontamination, symptomatic supportive care, and atropine to reverse muscarinic signs observed.

Hallucinogenic mushrooms have LSD-like properties secondary to two main toxins: psilocybin and psilocin. Common clinical signs include hyperactivity, aggression, disorientation, weakness, hyperesthesia, seizures, and hyperthermia. Treatment involves decontamination and symptomatic supportive care. Sedatives may be needed to prevent self-harm.

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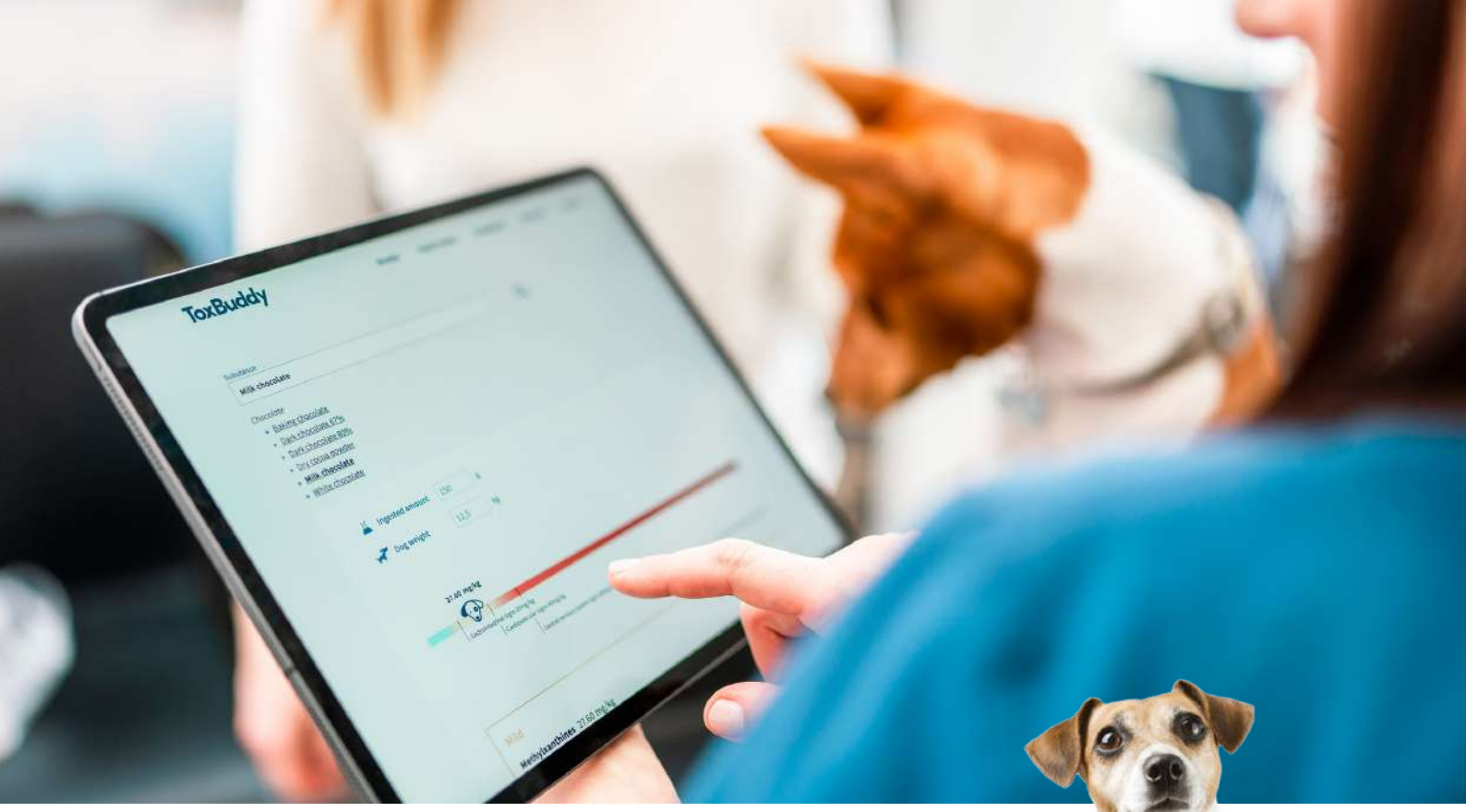

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DR. CAREY HEMMELGARN

Dr. Hemmelgarn is the co-founder of Intensivets, an online veterinary education platform. As an experienced criticalist, Dr. Hemmelgarn is currently working in Brooklyn, New York at Blue Pearl Veterinary Partners..

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