DANGEROUS TREAT
An influx of chocolate exposures is observed by APCC during the winter season because the agents are readily available to pets in the home. Examples of common forms of chocolate the APCC receives calls about include candy bars, snack mixes, brownies, cakes, cookies, and baking goods such as chocolate chips and cocoa powder.

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Winter Holiday Toxins

The winter holiday season holds an abundance of dangers for domestic pets that could result in toxicosis. This article will focus on exposures to chocolate, grapes and raisins, and homemade playdough in dogs. Plants that dogs and cats are commonly exposed to during the winter months will also be discussed.

MEET THE AUTHOR

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Carrie has been working as a certified veterinary technician at the ASPCA Animal Poison Control Center (APCC) since 2007. She obtained her associate's degree in veterinary technology from Parkland College in 2003 and her bachelor's degree in natural resources and environmental science from the University of Illinois in 2006. She worked for 2.5 years at a small animal clinic while in college and has assisted with several research projects in fish and wildlife ecology.

During her 10 years at the APCC, Carrie has gained a wealth of knowledge in the field of toxicology. She has been published in several peer-reviewed journals and is currently studying to become a board-certified toxicologist.

CHOCOLATE

The APCC received more calls about chocolate than any other agent in 2016, averaging over 41 cases per day. An influx of chocolate exposures is observed by APCC during the winter season because the agents are readily available to pets in the home. Examples of common forms of chocolate the APCC receives calls about are candy bars, snack mixes, chocolate desserts (brownies, cakes, and cookies), and baking goods such as chocolate chips and cocoa powder.

Chocolate contains 2 methylxanthines of toxicologic significance: theobromine and caffeine.[1] The concentration of these methylxanthines differs between products (**TABLE 1**). White chocolate has a very low concentration of methylxanthines and has low toxicologic significance. Milk chocolate, dark chocolate (semi-sweet chocolate), baking chocolate (unsweetened chocolate), and cocoa powder have much higher concentrations of methylxanthines, and exposures to these more commonly result in toxicosis.

Methylxanthine toxicosis causes stimulation of the cardiovascular and central nervous systems. The degree of toxicity is dose dependent. With low doses of chocolate, only mild gastrointestinal (GI) upset is observed. At cardiotoxic doses, more severe signs such as tachycardia, tachypnea, hyperthermia, cardiac arrhythmias, tremors, and seizures can develop. If exposure to chocolate is suspected or observed, an estimated dose of methylxanthines should be calculated. In an asymptomatic patient, this dose will determine whether decontamination or treatment is necessary (**BOX 1**).

Decontamination and Treatment

Decontamination through emesis is recommended in patients that have ingested >35 mg/kg of methylxanthines. Doses lower than this are not expected to cause serious clinical signs. With large exposures to chocolate that do not yield a toxic dose, emesis is recommended to prevent severe GI upset and to decrease the risk of pancreatitis. Emesis should be considered if the exposure occurred within the past 2 to 6 hours.[2]

Activated charcoal can help in preventing absorption of methylxanthines from the GI tract. However, charcoal can cause electrolyte changes and therefore is only recommended when a risk of severe toxicosis exists.

TABLE 1 Concentration of Methylxanthines in Different Types of Chocolate

TYPE OF CHOCOLATE	CONCENTRATION OF METHYLXANTHINES[a]
White chocolate	1 mg/oz
Milk chocolate	65 mg/oz
Dark chocolate	165 mg/oz
Baking chocolate	400 mg/oz
Unsweetened cocoa powder	800 mg/oz

[a]Amounts used by the APCC in calculating chocolate dose.

VITAL KNOWLEDGE

The APCC received more calls about chocolate than any other agent in 2016, averaging over 41 cases per day.

There is no antidote for chocolate toxicosis; therefore, treatment consists largely of supportive and symptomatic care.[2] Propranolol is recommended in treating moderate to severe tachycardia,[2] whereas muscle tremors can be managed with methocarbamol or diazepam.[2] Diazepam is also recommended for the management of seizure activity.[2] IV fluids are recommended to help increase excretion of methylxanthines,[2] and the bladder should be emptied regularly to prevent reabsorption of methylxanthines through the bladder wall.[2]

The prognosis for chocolate toxicosis is generally considered good with successful decontamination and veterinary intervention.[1] However, pets that present with seizures or tachyarrhythmias have a more guarded prognosis.[2]

GRAPES AND RAISINS

Exposures to grapes and raisins are especially common during the winter season because these items are used in many holiday recipes and meals.

Grapes, raisins, and zante currants belong to the genus *Vitis*, and ingestion can result in acute renal injury in

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BOX 1

Chocolate Dose Calculations

To calculate a dose of chocolate, 3 pieces of information are needed:

- The weight of the pet in kg
- The amount of the agent ingested in grams or ounces
- The estimated concentration of methylxanthines

Milk Chocolate
For example, consider a 15-kg dog that has ingested a 3.5-oz solid milk chocolate bar (solid meaning there are no nuts or fillings). Milk chocolate contains an estimated methylxanthine concentration of 65 mg/oz. To get the mg/kg dose of chocolate, the weight of the chocolate bar is multiplied by the concentration of methylxanthines, which is then divided by the pet's weight in kg.

3.5 oz × 65 mg/oz = 227.5 mg / 15 kg = 15.166 mg/kg

A 15-mg/kg dose of chocolate would be expected to cause only mild GI upset with a low risk of pancreatitis. No veterinary treatment would be required for this exposure.

Dark Chocolate
However, if this chocolate bar were made of dark chocolate, then the concentration of methylxanthines would be 165 mg/oz.

3.5 oz × 165 mg/oz = 577.5 mg / 15 kg = 38.5 mg/kg

A 38.5-mg/kg dose of chocolate is not cardiotoxic, but could cause moderate GI upset, polydipsia, pancreatitis, and mild agitation or hyperactivity. In an asymptomatic patient, emesis would be recommended. With successful emesis, further veterinary care would not be required.

Baking Chocolate
Some milk and dark chocolate bars show a percentage of cacao on the label, which is generally seen on the front of the bar and not in the ingredient list. Cacao is unsweetened (baking) chocolate. If this percentage is observed, then an extra calculation must be done to obtain the bar's estimated concentration of methylxanthines. A range of estimated concentrations exists, but the APCC uses those listed in **TABLE 1.** For example, if the label shows a 65% concentration of cacao, the APCC multiplies the percentage by 400 mg/oz.

0.65 × 400 mg/oz = 260 mg/oz

When substituted into the previous equation, the 15-kg dog that ingested a 3.5-oz dark chocolate bar containing 65% cacao has an estimated chocolate dose of 60.67 mg/kg.

3.5 oz x 260 mg/oz = 910 mg / 15 kg = 60.67 mg/kg

This dose is at a cardiotoxic level and can be expected to significantly stimulate the cardiovascular and central nervous systems. Hospitalization would be recommended.

Calculating a dose of chocolate can be challenging, especially if the agent involved is a baked good such as a chocolate cake or brownie. Looking at the ingredients in the agent will help determine what concentration of methylxanthines should be used in the dosage calculation. With purchased baked goods or box mixes, the ingredients are commonly printed on the label. If the baked good was made from scratch, ask the owner what ingredients were used in the recipe, the amounts of each ingredient, and the amount of the baked good yielded.

dogs.[3] The mechanism of action is unknown at this time. Although studies have evaluated these fruits for mycotoxins, pesticides, heavy metals, and vitamin D_3,[3] there have been no positive results for these nephrotoxins.

Not all dogs that ingest grapes or raisins develop acute renal injury. A dose-response relationship, common to other toxic agents, has not been observed with *Vitis* exposures.[4] Therefore, the severity of toxicosis does not depend on the amount of grapes or raisins ingested. Also, grape seed extract, grape juice, grape jelly, and wine have not been shown to cause *Vitis* toxicosis.[5]

Clinical signs may be delayed by several hours after the ingestion of *Vitis* species. Vomiting is common within the first 24 hours,[4,6] followed by diarrhea, anorexia, lethargy, and abdominal pain.[1,6] Oliguria or anuria may be observed days to weeks after the exposure as renal injury progresses.[1] Elevated creatinine, blood urea nitrogen, calcium, and phosphorus can be observed 24 hours

after ingestion,[6] whereas pathologic changes observed on blood chemistries may be delayed by several days.[1,6]

Decontamination and Treatment

Any exposure to grapes or raisins should be considered significant, and decontamination via emesis and activated charcoal is recommended. Grapes and raisins have a tendency to sit in the stomach for prolonged periods of time[6]; therefore, emesis can be induced in asymptomatic patients up to 6 hours after the exposure.[5]

Protection of the kidneys is critical with exposures to *Vitis* species. IV fluid diuresis is recommended for 48 to 72 hours.[6] A baseline blood chemistry should be obtained and rechecked every 12 hours for 72 hours to monitor renal function, and electrolytes should be monitored along with urinalysis. Furosemide, dopamine, or mannitol can be used to treat oliguria, while hemodialysis or peritoneal dialysis may be helpful in treating uremia.[1] The prognosis is considered poor for pets that develop weakness, ataxia, oliguria, or anuria.[1,6]

HOMEMADE PLAYDOUGH

Exposures to homemade playdough are not as common as exposures to chocolate or grapes and raisins. The ingestion of playdough, however, can result in rapid onset of a life-threatening toxicosis called *hypernatremia*, an excessive amount of sodium in the blood.

Onset of Hypernatremia

Homemade playdough, used to make salt ornaments and other holiday crafts, is made from dough consisting of flour, table salt (sodium chloride), and water. Other ingredients such as vegetable oil, cornstarch, and cream of tartar are also used in some recipes. Homemade playdough contains a high concentration of salt. Some dough formulations contain 8 g of salt per tablespoon of dough.[7] When the dough is ingested, an increase in sodium in the vasculature results in a fluid shift in the body, causing cellular dehydration and vascular expansion.[7]

Signs of salt toxicosis can be observed at a dose of 2 g of NaCl per kilogram of body weight, with the lethal dose at 4 g/kg.[7] A dog is considered to be hypernatremic when the serum sodium concentration is >156 mEq/L.[7] Clinical signs are commonly observed when the serum sodium concentration is >170 mEq/L.[7] Vomiting develops within the first 2 hours of ingestion,[5] followed by neurologic signs, including tremors and seizures.[8] Signs most commonly observed by the APCC include vomiting, anorexia, diarrhea, ataxia, polydipsia, trembling, weakness, tremors, and seizures.[5]

Decontamination and Treatment

The treatment for acute salt toxicosis includes decontamination, management of clinical signs, and lowering serum sodium levels. With recent exposures (<2 hours) and in patients that are asymptomatic, emesis is recommended. Baseline electrolytes should be obtained and frequently monitored. Asymptomatic patients with a normal serum sodium concentration should be allowed free access to water after emesis has been managed and monitored closely for clinical signs.

Patients that have clinical signs or elevations in serum sodium concentration should be started on IV fluids using a low-sodium fluid (D5W, 0.4% NaCl).[5] Warm-water enemas at a dose of 5 to 10 mL/kg can be used in addition to IV fluids.[5] A loop diuretic, such as furosemide, can be administered to aid in sodium excretion and to help prevent pulmonary edema caused by fluid overload.[5] Patients exhibiting mild to moderate clinical effects that receive timely and aggressive treatment generally have a favorable prognosis.[5] The prognosis is guarded in patients that have developed severe neurologic signs.[5]

PLANTS

There are several popular holiday plants that dogs and cats may have the opportunity to ingest during the winter season that may remain in the home several months.

They include:

- Christmas cactus
- Evergreen trees
- Holly
- Mistletoe
- Poinsettias
- Amaryllis
- Christmas kalanchoe

Exposures to Christmas cactus, evergreen trees, holly, mistletoe, and poinsettias commonly result in GI upset, but are unlikely to cause serious toxicosis. Amaryllis and Christmas kalanchoe can cause more serious signs, depending on the part of the plant

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TABLE 2 Plant Quick Reference[9,10]

COMMON NAME	LATIN NAME	CLINICAL SIGNS	COMMENTS
Amaryllis	*Hippeastrum* spp.	Vomiting, diarrhea, anorexia, hypersalivation, hypotension, sedation, and seizures	Mild to moderate GI upset with small exposures to the leaves, flowers, and bulb. Large exposures to the bulb increase the risk for more severe GI signs, as well as hypotension, sedation, and seizures.
Christmas cactus	*Schlumbergera truncata*	Vomiting, diarrhea, anorexia, and depression	Signs are expected to be mild and self-limiting. Minimal treatment is required.
Christmas kalanchoe	*Kalanchoe blossfeldiana*	Vomiting, depression, lethargy, diarrhea, weakness, dyspnea, anorexia, tachycardia, and vocalization	Flowers are the most toxic. Most exposures only cause GI signs.
Evergreen trees (firs, pines, and spruces)	*Abies, Pinus, Picea*	Vomiting, anorexia, abdominal pain, and depression	Exposure to tree water containing tree preservatives is not expected to cause serious toxicosis, but mild GI upset is possible. Water that is not frequently changed could grow bacteria or fungi over time, possibly resulting in gastroenteritis if ingested.
Holly	*Ilex aquifolium*	Hypersalivation, vomiting, anorexia, diarrhea, head shaking, and lip smacking	GI irritation is due to the saponins in the leaves and berries.
Mistletoe	*Phoradendron* spp	Vomiting, diarrhea, depression, hypotension	Hypotension is uncommon.
Poinsettia	*Euphorbia pulcherrima*	Vomiting, hypersalivation, diarrhea, and dermal irritation	Historically, toxicity has been greatly exaggerated.

the pet is exposed to and the amount of the plant ingested. **TABLE 2** lists the clinical signs that can be expected after ingestion of these plants. **TVN**

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About ASPCA

Toxicology Talk is written and reviewed by members of the American Society for the Prevention of Cruelty to Animals (ASPCA) Animal Poison Control Center (APCC). The mission of the APCC is to help animals exposed to potentially hazardous substances, which it does by providing 24-hour veterinary and diagnostic treatment recommendations from specially trained veterinary toxicologists. It also protects and improves animal lives by providing clinical toxicology training to veterinary toxicology residents, consulting services, and case data review.

The ASPCA APCC includes a full staff of veterinarians, including board-certified toxicologists, certified veterinary technicians, and veterinary assistants, and its state-of-the-art emergency call center routinely fields requests for help from all over the world, including South America, Europe, Asia, and the Pacific Islands.

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Indications

Control of pruritus associated with allergic dermatitis and control of atopic dermatitis in dogs at least 12 months of age.

Important Safety Information

Do not use APOQUEL in dogs less than 12 months of age or those with serious infections. APOQUEL may increase the chances of developing serious infections, and may cause existing parasitic skin infestations or pre-existing cancers to get worse. APOQUEL has not been tested in dogs receiving some medications including some commonly used to treat skin conditions such as corticosteroids and cyclosporines. Do not use in breeding, pregnant, or lactating dogs. Most common side effects are vomiting and diarrhea. APOQUEL has been used safely with many common medications including parasiticides, antibiotics and vaccines.

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For more information, please see Brief Summary of full Prescribing Information on reverse.

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3.6 mg 5.4 mg 16 mg

Brief Summary of Prescribing Information

For oral use in dogs only

Caution: Federal (USA) Law restricts this drug to use by or on the order of a licensed veterinarian.

Indications: Control of pruritus associated with allergic dermatitis and control of atopic dermatitis in dogs at least 12 months of age.

Dosage and Administration: The dose of APOQUEL (oclacitinib maleate) tablets is 0.18 to 0.27 mg oclacitinib/lb (0.4 to 0.6 mg oclacitinib/kg) body weight, administered orally, twice daily for up to 14 days, and then administered once daily for maintenance therapy. APOQUEL may be administered with or without food.

Dosing Chart

Weight Range (in lb)		Weight Range (in Kg)		Number of Tablets to be Administered		
Low	High	Low	High	3.6 mg Tablets	5.4 mg Tablets	16 mg Tablets
6.6	9.9	3.0	4.4	**0.5**	-	-
10.0	14.9	4.5	5.9	-	**0.5**	-
15.0	19.9	6.0	8.9	**1**	-	-
20.0	29.9	9.0	13.4	-	**1**	-
30.0	44.9	13.5	19.9	-	-	**0.5**
45.0	59.9	20.0	26.9	-	**2**	-
60.0	89.9	27.0	39.9	-	-	**1**
90.0	129.9	40.0	54.9	-	-	**1.5**
130.0	175.9	55.0	80.0	-	-	**2**

Warnings:
APOQUEL is not for use in dogs less than 12 months of age (see **Animal Safety**).
APOQUEL is not for use in dogs with serious infections.
APOQUEL may increase susceptibility to infection, including demodicosis, and exacerbate neoplastic conditions (see **Adverse Reactions** and **Animal Safety**).

Human Warnings:
This product is not for human use. Keep this and all drugs out of reach of children. For use in dogs only. Wash hands immediately after handling the tablets. In case of accidental eye contact, flush immediately with water or saline for at least 15 minutes and then seek medical attention. In case of accidental ingestion, seek medical attention immediately.

Precautions:
APOQUEL is not for use in breeding dogs, or pregnant or lactating bitches.
The use of APOQUEL has not been evaluated in combination with glucocorticoids, cyclosporine, or other systemic immunosuppressive agents.
Dogs receiving APOQUEL should be monitored for the development of infections, including demodicosis, and neoplasia.

Adverse Reactions:
Control of Atopic Dermatitis
In a masked field study to assess the effectiveness and safety of oclacitinib for the control of atopic dermatitis in dogs, 152 dogs treated with APOQUEL and 147 dogs treated with placebo (vehicle control) were evaluated for safety. The majority of dogs in the placebo group withdrew from the 112-day study by Day 16. Adverse reactions reported (and percent of dogs affected) during Days 0-16 included diarrhea (4.6% APOQUEL, 3.4% placebo), vomiting (3.9% APOQUEL, 4.1% placebo), anorexia (2.6% APOQUEL, 0% placebo), new cutaneous or subcutaneous lump (2.6% APOQUEL, 2.7% placebo), and lethargy (2.0% APOQUEL, 1.4% placebo). In most cases, diarrhea, vomiting, anorexia, and lethargy spontaneously resolved with continued dosing. Dogs on APOQUEL had decreased leukocytes (neutrophil, eosinophil, and monocyte counts) and serum globulin, and increased cholesterol and lipase compared to the placebo group but group means remained within the normal range. Mean lymphocyte counts were transiently increased at Day 14 in the APOQUEL group.

Dogs that withdrew from the masked field study could enter an unmasked study where all dogs received APOQUEL. Between the masked and unmasked study, 283 dogs received at least one dose of APOQUEL. Of these 283 dogs, two dogs were withdrawn from study due to suspected treatment-related adverse reactions: one dog that had an intense flare-up of dermatitis and severe secondary pyoderma after 19 days of APOQUEL administration, and one dog that developed generalized demodicosis after 28 days of APOQUEL administration. Two other dogs on APOQUEL were withdrawn from study due to suspected or confirmed malignant neoplasia and subsequently euthanized, including one dog that developed signs associated with a heart base mass after 21 days of APOQUEL administration, and one dog that developed a Grade III mast cell tumor after 60 days of APOQUEL administration. One of the 147 dogs in the placebo group developed a Grade I mast cell tumor and was withdrawn from the masked study. Additional dogs receiving APOQUEL were hospitalized for diagnosis and treatment of pneumonia (one dog), transient bloody vomiting and stool (one dog), and cystitis with urolithiasis (one dog).

In the 283 dogs that received APOQUEL, the following additional clinical signs were reported after beginning APOQUEL (percentage of dogs with at least one report of the clinical sign as a non-pre-existing finding): pyoderma (12.0%), non-specified dermal lumps (12.0%), otitis (9.9%), vomiting (9.2%), diarrhea (6.0%), histiocytoma (3.9%), cystitis (3.5%), anorexia (3.2%), lethargy (2.8%), yeast skin infections (2.5%), pododermatitis (2.5%), lipoma (2.1%), polydipsia (1.4%), lymphadenopathy (1.1%), nausea (1.1%), increased appetite (1.1%), aggression (1.1%), and weight loss (0.7).

Control of Pruritus Associated with Allergic Dermatitis
In a masked field study to assess the effectiveness and safety of oclacitinib for the control of pruritus associated with allergic dermatitis in dogs, 216 dogs treated with APOQUEL and 220 dogs treated with placebo (vehicle control) were evaluated for safety. During the 30-day study, there were no fatalities and no adverse reactions requiring hospital care. Adverse reactions reported (and percent of dogs affected) during Days 0-7 included diarrhea (2.3% APOQUEL, 0.9% placebo), vomiting (2.3% APOQUEL, 1.8% placebo), lethargy (1.8% APOQUEL, 1.4% placebo), anorexia (1.4% APOQUEL, 0% placebo), and polydipsia (1.4% APOQUEL, 0% placebo). In most of these cases, signs spontaneously resolved with continued dosing. Five APOQUEL group dogs were withdrawn from study because of: darkening areas of skin and fur (1 dog); diarrhea (1 dog); fever, lethargy and cystitis (1 dog); an inflamed footpad and vomiting (1 dog); and diarrhea, vomiting, and lethargy (1 dog). Dogs in the APOQUEL group had a slight decrease in mean white blood cell counts (neutrophil, eosinophil, and monocyte counts) that remained within the normal reference range. Mean lymphocyte count for dogs in the APOQUEL group increased at Day 7, but returned to pretreatment levels by study end without a break in APOQUEL administration. Serum cholesterol increased in 25% of APOQUEL group dogs, but mean cholesterol remained within the reference range.

Continuation Field Study
After completing APOQUEL field studies, 239 dogs enrolled in an unmasked (no placebo control), continuation therapy study receiving APOQUEL for an unrestricted period of time. Mean time on this study was 372 days (range 1 to 610 days). Of these 239 dogs, one dog developed demodicosis following 273 days of APOQUEL administration. One dog developed dermal pigmented viral plaques following 266 days of APOQUEL administration. One dog developed a moderately severe bronchopneumonia after 272 days of APOQUEL administration; this infection resolved with antimicrobial treatment and temporary discontinuation of APOQUEL. One dog was euthanized after developing abdominal ascites and pleural effusion of unknown etiology after 450 days of APOQUEL administration. Six dogs were euthanized because of suspected malignant neoplasms: including thoracic metastatic, abdominal metastatic, splenic, frontal sinus, and intracranial neoplasms, and transitional cell carcinoma after 17, 120, 175, 49, 141, and 286 days of APOQUEL administration, respectively. Two dogs each developed a Grade II mast cell tumor after 52 and 91 days of APOQUEL administration, respectively. One dog developed low grade B-cell lymphoma after 392 days of APOQUEL administration. Two dogs each developed an apocrine gland adenocarcinoma (one dermal, one anal sac) after approximately 210 and 320 days of APOQUEL administration, respectively. One dog developed a low grade oral spindle cell sarcoma after 320 days of APOQUEL administration.

To report suspected adverse events, for technical assistance or to obtain a copy of the MSDS, contact Zoetis Inc. at 1-888-963-8471 or www.zoetis.com.

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

Storage Conditions:
APOQUEL should be stored at controlled room temperature between 20° to 25°C (68° to 77°F) with excursions between 15° to 40°C (59° to 104°F).

How Supplied:
APOQUEL tablets contain 3.6 mg, 5.4 mg, or 16 mg of oclacitinib as oclacitinib maleate per tablet. Each strength tablets are packaged in 20 and 100 count bottles. Each tablet is scored and marked with AQ and either an S, M, or L that correspond to the different tablet strengths on both sides.

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February 2013 428007800A&P