

SAVING PETS' LIVES, 24 HOURS A DAY, 7 DAYS A WEEK

**PET POISON HELPLINE**


**Veterinary Pet Insurance** **Nationwide** is on your side

## Interesting Cases from the Toxicology Archives

or cases that I've known and loved

May 12, 2015

**Robert H. Poppenga, DVM, PhD, DABVT**  
California Animal Health and Food Safety Laboratory System  
SVM, University of California at Davis, Davis, CA



**UC DAVIS**  
VETERINARY MEDICINE  
California Animal Health and Food Safety Laboratory System  
www.petpoisonhelpline.com | 3600 American Blvd. W., #725 Bloomington, MN 55431 | Pet Poison Helpline 02015

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### Did you know?

- > The amount spent by pet owners to treat common toxicities...
- > Compare 2012 and 2013 data...

|                               |                | 2012      | 2013      |
|-------------------------------|----------------|-----------|-----------|
| <b>Rodenticide Toxicities</b> | Submitted Fees | \$203,314 | \$210,553 |
|                               | Cost per pet   | \$394     | \$425     |
| <b>Poisonous Plants</b>       | Submitted Fees | \$389,320 | \$538,336 |
|                               | Cost per pet   | \$507     | \$565     |

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### VPI® and Pet Poison Helpline® working together

- > Shared mission in highlighting the importance of preparing for accidents and poisonings in small animals
- > Addressing the cost of veterinary care
  - > VPI covers the \$49 Pet Poison Helpline fee when a pet is brought in to your hospital for care
- > Enabling best medicine
  - > Pet owners with VPI pet insurance spend 60% more on veterinary care than those without pet insurance

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## Routine Samples for Toxicologic Testing

- Antemortem
  - Whole blood/serum
  - Urine
  - Vomitus/lavage material
- Postmortem
  - GI contents
  - Liver
  - Kidney
  - Brain
  - Eyeball
  - Other – consult with laboratory!
- Environmental
  - Source material
  - Feed – must be representative!
  - Plants/mushrooms



Collect a complete set of samples in sufficient amounts!  
Keep samples refrigerated or frozen.



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- Diagnostic veterinary toxicology is a symbiotic relationship between the veterinary toxicologist and analytical chemist.
- Sophisticated analytical systems are available that are very sensitive, accurate, and *expensive*.
- There is no "one" analytical system or single analytical method that can test for every potential toxicant.
- The availability of mass spectral libraries of toxicants allows for "unknown" screening.



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**oops!**

- Biggest mistake – too little sample amount!
- The kinetics of a given toxicant and timing of sample collection following exposure can help determine an appropriate sample type for submission:
  - Some chemicals can be too rapidly metabolized to readily detect
    - Xylitol
  - Some chemicals are very lipophilic so samples with a high fat content are ideal
    - Bromethalin and its toxic metabolite desmethylbromethalin
  - Some chemicals are harder to find antemortem than postmortem
    - SGAR persist for weeks in liver tissue but not in serum/plasmas/blood
  - It is possible to detect THC metabolites in urine for several days after an exposure.



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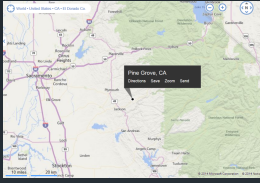

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**Case 1**

- 13-week-old Boxer puppy, ~ 5 kg
- Pine Grove, CA (Sierra Foothills)
- Presented to Sacramento area veterinary referral clinic with acute hepatic and renal failure within 24 hours of being fed Wellness Well Bites Beef and Turkey Recipe soft and chewy treats.
- Treatment was instituted but the dog died of "multiple organ failure".


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Beef, Turkey, Ground Brown Rice, Oatmeal, Vegetable Glycerin, Guar Gum, Cane Molasses, Carrots, Salt, Natural Smoke Flavor, Garlic, Blueberries, Flaxseed, Sweet Potatoes, Apples, Phosphoric Acid (a natural acidifier), Sorbic Acid (a preservative), and Mixed Tocopherols (a natural preservative).




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**Gross Postmortem**

- Moderate autolysis
- Generalized pallor and yellow tinge to body organs and fat
- Slightly firm liver, pale and yellow-tinged
- Stomach, intestines, mesentary – diffusely edematous
- Melena
- Pulmonary edema
- Heart – diffusely and severely pale




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### Histopathology

- Massive acute hepatic necrosis
- Marked intestinal crypt necrosis/cryptitis
- Severe, bilateral acute tubular necrosis
- Pulmonary edema
- Segmental acute neuronal necrosis



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### Differential

- ?
- ?
- ?
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What is the number one reason for pet food recalls?



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### Tests

- Salmonella PCR and confirmation culture: lung, liver, spleen, mesenteric lymph node and feces
- Fecal examination: no parasite eggs detected
- Canine distemper virus IHC: negative
- Toxicology
  - Microcystins (LA, LR, RR, and YR) on stomach contents
  - -amanitin on kidney



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Wide distribution in the U.S.

*A. phalloides*

*A. ocreata*

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Fungi of the genus *Amanita*

A B C

Hallen H E et al. PNAS. 2007;104:19097-19101

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- Extremely toxic: -amanitin IV LD<sub>50</sub> in dogs of 0.1 mg/kg (oral LD<sub>50</sub>s generally < 1 mg/kg)
- Use the transport system for bile acids to reach hepatocytes.
  - Na<sup>+</sup> - taurocholate cotransporter polypeptide (Ntcp)
- Enterohepatic cycling maintains high intra-hepatocyte concentrations.
- No known metabolism.
- 80 to 90% is eliminated via kidneys.
- Relatively short plasma t<sub>1/2</sub>.
- Detected in plasma, urine and kidney/liver samples up to 36 h, 72 h and 22 d, respectively, post-exposure.

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- Bind eukaryotic DNA-dependent RNA polymerase II (RNAP II) which inhibits RNA elongation essential for transcription.

Protein Synthesis **STOP**

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## Clinical Disease

- Classically:
  - Long asymptomatic incubation delay following ingestion - 6 to 12 hours
  - Gastrointestinal phase – 12 to 24 hours
    - Diarrhea, vomiting, abdominal pain and dehydration
  - Hepatotoxic phase – 24 to 48 hours
    - liver damage and coagulopathy
  - Hepato-renal phase – hemorrhage, convulsions, fulminant hepatic failure, coma and death

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Protecting and Promoting Your Health

Home | Food | Drugs | Medical Devices | Radiation-Emitting Products | Vaccines, Blood & Biologics | **Animal & Veterinary** | Cosmetics | Tobacco Products

**Animal & Veterinary**

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**Pet Food**

**I am looking for**

- Animal Food
- Pet Food
- Animal Drugs
- Unapproved Animal Drugs
- Substance Use of Admixtures

**Reporting Problems**

- Recalls
- How to Report a Pet Food Complaint
- How to Report a Livestock Food Complaint
- Veterinary Adverse Event
- Veterinary Reporting
- Veterinary Adverse Event Reporting for Manufacturers

**Navigate the Animal & Veterinary Section**

Development & Approval Process  
New Animal Drug Applications, Electronic Submissions, User Fees, Genetic Engineering, Minor Use/Minor Species, Abbreviations, Food Additive Petitions

Resources for the Animal Health Literacy, Information for Consumers and Veterinarians  
Safety & Health

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## Diagnostic Approach

- Possible criminal case
- Need for excellent documentation
- Always good idea to conduct thorough post-mortem examination
- General toxicology screening possible when dealing with unknowns
  - Sample testing priority



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## Methomyl

- Methomyl is an N-methyl carbamate insecticide currently registered for use on a wide variety of sites including field, vegetable, and orchard crops, and on turf (sod farms only).
- Methomyl is generally a restricted use pesticide [based on percent active ingredient] and there are currently no homeowner uses. However, certain low percentage AI formulations are not designated as restricted use and can be used around livestock quarters, commercial premises and refuse containers.
  - Some uses are being canceled or reduced in 2015
- EPA Toxicity Class 1
  - Rodent oral LD<sub>50</sub>s of 10 to 24 mg/kg
  - Inhalation of dust or aerosol potentially serious



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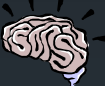
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## MOTA



- Inhibition of cholinesterase enzymes
  - Acetylcholinesterase ("true" cholinesterase)
  - Samples of choice: red blood cells and 1/2 brain



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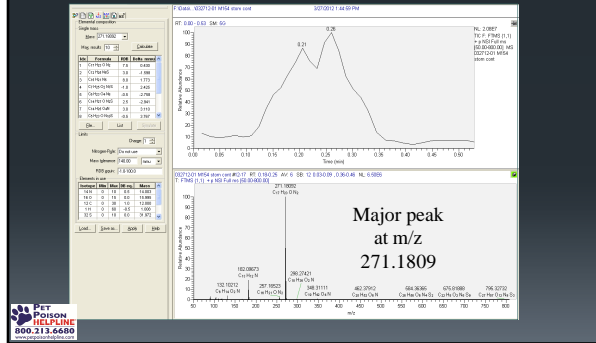
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### Result of DART Analysis




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### Doxylamine



- Antihistamine sedative used as a nighttime sleep aid: Unisom Sleep Gels®; Sleep Aid®; Nighttime Sleep Aid®
  - 25 or 50 mg formulations
- Also used in combination with antitussives and decongestants for relief of cold and cough symptoms.
- Adverse effects: CNS depression, dizziness, lassitude, disturbed coordination, muscular weakness, paradoxical excitement reported in some patients, particularly children (restlessness, insomnia, tremors, euphoria, nervousness, delirium, palpitation, and seizures), and anticholinergic effects.

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### OTC On-Site Urine Drug Tests



- Designed for human urine
- Cheap!
  - \$10-35/test in stores
  - cheaper online
- Easy to find!
  - Target, Wal-Mart, CVS
- Fast!
  - 2-5 min
- Available for 1-12 drugs
  - THC, amphetamines, barbiturates, benzos, cocaine, MDMA, methamphetamine, morphine, PCP, opiates, methadone, TCAs.

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
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
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Table 2  
Selected False Positives Reported in UDS<sup>2,3,6</sup>

| Substance                       | False Positives   |
|---------------------------------|---|
| Alcohol                         | Isopropyl alcohol   |
| Amphetamine/<br>methamphetamine | Amantadine, brompheniramine, bupropion, chlorpromazine, desipramine, dexroamphetamine, ephedrine, isometheptene, labetalol, methylene dioxymethamphetamine, methylphenidate, phenemine, phenylephrine, phenylpropanolamine, promethazine, pseudoephedrine, ranitidine, selegiline, thioridazine, trazodone, trimethobenzamide, trimipramine |
| Barbiturates                    | Fenoprofen, ibuprofen, naproxen   |
| Benzodiazepines                 | Oxaprozin, sertraline   |
| Cannabinoids                    | Dronabinol, efavirenz, fenoprofen, ibuprofen, naproxen, pantoprazole  |
| Opiates                         | Dextromethorphan, diphenhydramine, gatifloxacin, ofloxacin, rifampin, verapamil   |
| <b>Methadone</b>                | Clomipramine, clemizolazine, diphenhydramine, <b>doxylamine</b> , quetiapine, thioridazine, verapamil   |
| Phencyclidine                   | Dextromethorphan, diphenhydramine, doxylamine, ibuprofen, imipramine, ketamine, meprobamate, mescalazine, thioridazine, tramadol, venlafaxine   |



Doxylamine



Methadone

Abbreviation: UDS, urine drug screen.

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## Case 4

- "Kefi" (3 year-old, 15 kg, F, Duck Tolling Retriever) and her 1 year-old 13 kg daughter "Teal" were presented to the ES after having ingested ~ 60 capsules of Leptopril and 16 tablets of Lexapro sometime within the last 4 hours.
- Both dogs were hyperexcitable, panting, tachycardic, tremoring, hyperthermic (104 to 105° F), and salivating. Kefi's signs were less severe than Teal's.



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- Used for the treatment of major depressive disorder and generalized anxiety disorder.
- A SSRI – pharmacologic effect is likely due to potentiation of serotonin activity within the CNS.
- Extensively metabolized by the liver.
- Signs of overdose include convulsions, coma, dizziness, hypotension, insomnia, nausea, vomiting, sinus tachycardia, somnolence, and ECG changes (including QT prolongation).




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**Selected Topics: Toxicology**


**COMPARISON OF TOXICITY OF ACUTE OVERDOSES WITH CITALOPRAM AND ESCITALOPRAM**

David D. Hagan, M.D.,<sup>1</sup> Richard D. Hagan, M.D.,<sup>2</sup> Richard F. Clark, M.D.,<sup>3</sup> William A. Miller, M.D.,<sup>4</sup> and John T. Wineschitz, M.D.<sup>5</sup>

**Table 2. Dose-Outcome Relationship**

| Outcome      | Mean Dose ± SD (mg) | Median Dose (mg) | Range    | p-Value* |
|--------------|---------------------|------------------|----------|----------|
| Escitalopram |                     |                  |          |          |
| No effect    | 164.7 ± 177.7       | 100              | 5-1400   | 0.008†   |
| Minor        | 216.1 ± 241.2       | 150              | 5-1600   |          |
| Moderate     | 354.8 ± 449.3       | 160              | 10-1800  |          |
| Major        | 300                 | N/A              | N/A      |          |
| Citalopram   |                     |                  |          | < 0.001† |
| No effect    | 321.9 ± 275.9       | 280              | 5-1200   |          |
| Minor        | 433.6 ± 364.3       | 300              | 20-2000  |          |
| Moderate     | 658.2 ± 561.2       | 470              | 20-2400  |          |
| Major        | 1031.4 ± 564.7      | 600              | 500-2000 |          |

\* Kruskal-Wallis one-way analysis of variance on Ranks (Dunn's method).  
† Comparing all outcomes for the specific drug.




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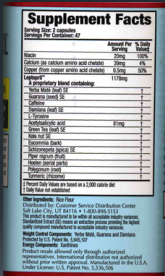

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### Question

- Can you perform an exposure assessment for the Leptipri® product?

1. Yes
2. No
3. Yes and No


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- Initial treatment focused on controlling CNS signs and muscle tremors.
- Dogs did not respond to multiple doses of diazepam. CRIs of propofol were not entirely effective. Symptoms were finally controlled with barbiturates. Methocarbamol and esmolol were also administered.
- AC was given PO to "Kefi"
- "Teal" was never stabilized and exhibited supraventricular tachycardia, ventricular tachycardia, and cardiac arrest. Dog died ~ 7 hours post-presentation.
- "Kefi" underwent hemodialysis with significant improvement noted; discharged ~ 36 hours after presentation.



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### Case 5



- Charlie, an 18 month old M Labradoodle weighing approximately 22.7 kg body weight was referred to a veterinary specialty clinic with acute renal failure. There was a two day history of anorexia and vomiting, with severe azotemia noted by referring veterinarian. The dog was anuric and remained anuric for 24 hours despite IVF and diuretics. The dog was euthanized due to deteriorating condition.
- Owner noted that they found a gel packet in between the couch that had been chewed with little of the contents remaining.



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## Toxicology Results

- + for ethylene glycol (~ 440 ppm)
- + for diethylene glycol (~ 230,000 ppm or 23%)



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■ No calcium oxalate crystalluria was noted.



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## Ciphering



- Toxicity of EG
  - Minimum lethal dose of EG for dogs is approximately 6.6 ml of undiluted EG per kg body weight.
  - Undiluted antifreeze is ~ 95% EG
  - Assume specific gravity ~ = water (1 gram EG = 1 gram water)
  - 6.6 ml EG ~ = 6.6 grams or 6,600 mg EG
  - Gel contained 440 ppm EG, or 440 mg/L or ; it would take ingestion of 15 liters of gel per kg body weight to reach the minimal lethal dose.
  - $6,600 \text{ mg} \div 440 \text{ mg/L} = 15 \text{ L}$



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## Toxicity of diethylene glycol

- A potentially lethal dose of DEG for people is ~ 1 ml/kg.
- 1 ml ~ = 1 gram DEG
- Lethal dose = 1000 mg/kg
- DEG was present in the gel at 23% or 230,000 ppm or 230,000 mg/L or 230 mg/ml
- Therefore a potentially toxic dose of DEG would require ingestion of ~ 4.34 ml/kg of the gel.
- 22.7 kg dog would only have to ingest ~ 98.6 ml of the gel to reach a potentially lethal human dose.




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OCCOCCO

OCCO

## Diethylene glycol

- Long history of intoxication of people
- Clinical manifestations in people typically begin with abdominal pain, nausea, and vomiting followed by metabolic acidosis, acute renal failure, and progressive mental status depression over several days.
- Uncertain if adverse effects are caused by parent DEG or metabolite.
- Interestingly, in contrast to ethylene glycol exposure, diethylene glycol intoxication is not associated with the formation of calcium oxalate crystalluria.
- Based upon limited evidence it is reasonable to initiate fomepizole (or ethanol) and hemodialysis EARLY.




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The screenshot shows the United States Consumer Product Safety Commission website. The main heading is "California Innovations Expands Recall of Freezer Gel Packs Due to Ingestion Hazard". The recall date is listed as JUNE 07, 2012. The product is identified as "Freezer Gel Packs". The recall is categorized as a "Classwide Recall". The website also provides information on how to report a problem and how to get a replacement.




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## Case 6

- Turkey vulture fell from tree at 9 AM and vomited 4X.
- Uncoordinated, couldn't fly away.
- 5th vulture presented to wildlife rehabilitation center with similar presentation.
- Vomit was tested.




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**marinij.com**  
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### State confirms Marin turkey vultures unintentionally poisoned by euthanasia drug

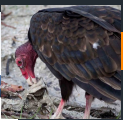
By Megan Hansen, *Marin Independent Journal*

POSTED: 02/20/15, 9:32 PM PST | UPDATED: ON 02/21/2015 | # COMMENTS

State and local wildlife officials are asking Marin residents to make sure deceased pets and livestock are properly disposed of as turkey vultures have recently been poisoned by a euthanasia drug.

California Department of Fish and Wildlife officials confirmed Friday that six turkey vultures treated by WildCare, a wildlife rehabilitation center in San Rafael, from July to October of last year were poisoned after ingesting pentobarbital — a barbiturate used to euthanize animals such as dogs, livestock and horses.

Stella McMillin, senior environmental scientist at the California Department of Fish and Wildlife, said WildCare submitted samples of the birds' stomach contents to the California Animal Health and Food Safety Laboratory at the University of California at Davis for testing. Once the drug was identified, state wildlife officials tried to determine where the birds were getting sick.





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Steve Magner / ISEWS




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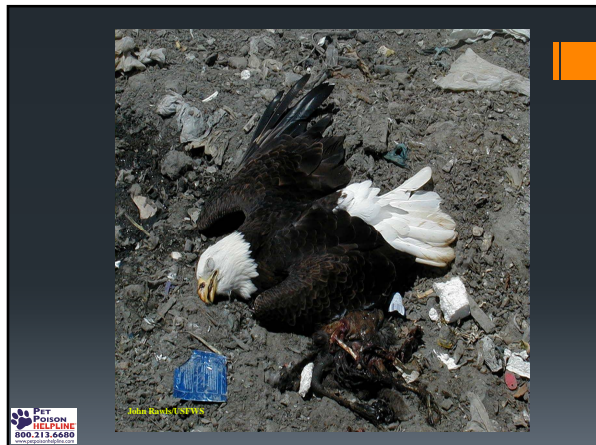
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### Barbiturate Factoids

- Can persist in euthanized carcasses for months to years depending on environmental conditions.
- Accidental poisoning of wildlife can result in criminal penalties.
- Barbiturates activate inhibitory GABA<sub>A</sub> receptors and inhibit excitatory glutamate receptors.
- Death is most often due to hypoxia and hypothermia.

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**Thank you for attending!**

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2. **I attended the webinar but wasn't the person who logged in. Can I still get interactive CE credit?** Yes. Send your name and email address to [info@petpoisonhelpline.com](mailto:info@petpoisonhelpline.com) by **1pm central time on May 13, 2015** (strict deadline).
3. **Can I watch the recorded webinar online for CE credit?** Yes. You can receive non-interactive CE credit. Go to the "For Vets" page on our website, [www.petpoisonhelpline.com](http://www.petpoisonhelpline.com) for more info.

Comments? Questions? Email us! [info@petpoisonhelpline.com](mailto:info@petpoisonhelpline.com)

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