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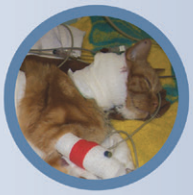
FELINE TOXICOLOGICAL EMERGENCIES

When to suspect and what to do

Tobias Grave and Amanda Boag

Practical relevance Confirmed or suspected intoxications with a wide variety of agents represent a small but important group of feline emergency cases. Generally it is thought that toxicities are less common in cats compared with dogs, with a higher proportion relating to dermal as opposed to oral exposure.



Clinical challenges Once toxicity is suspected or diagnosed, it must be recognised that treatment regimes may need modification compared with those established for dogs. Different drugs or different dosages may be warranted and the choice of available drugs may be reduced.

Evidence base This review draws on published studies, case reports and clinical experience to summarise key features of the general management of the intoxicated feline patient before describing some of the more serious and common intoxications in more detail.

Audience The focus throughout the review is on the peculiarities of feline metabolism and how they may impact on presentation and treatment. The aim is to assist companion animal and feline practitioners, who are in the frontline when it comes to managing these emergency cases.

THE UNIQUENESS OF THE CAT

The toxicological emergencies seen most commonly in cats reflect in part their unique metabolism; specifically, the susceptibility of their red cells to oxidative injury and their reduced hepatic capacity for certain key metabolic processes such as glucuronidation contribute to the severity and frequency of certain intoxications. Feline behavioural characteristics of intensive grooming, the ability to access secluded areas through small access points and their investigative nature may additionally influence the toxins to which they are most commonly exposed.

TABLE 1 Common intoxications in cats: enquiry and fatality data provided by the UK's Veterinary Poisons Information Service (VPIS) for 2009

Toxin/source of toxin	Number of enquiries received by VPIS in 2009	Number of fatal cases reported to VPIS in 2009
Ethylene glycol	59	26
Permethrin	233	22
Unknown agent	128	17
Lilium species	260	4
Neem oil/margosa oil	58	4
Paracetamol	60	3
Luminous/fluorescent necklace/bracelet	78	–
Fipronil	63	–
Benzalkonium chloride	60	–
White spirit	60	–
Praziquantel	56	–

NB This data must be interpreted in the knowledge that there is no mandatory reporting scheme in the UK and no mandatory subscription to the VPIS

Regardless of the likely underlying diagnosis, empirical therapy should be instituted as a matter of urgency, and should be ongoing as the diagnostic evaluation is completed.

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GENERAL MANAGEMENT OF THE INTOXICATED CAT

Triage and initial stabilisation

The initial triage and primary survey of the patient presenting with suspected intoxication should follow the same well-established principles that apply during the initial assessment of all potentially unstable patients. Specifically, the clinician should evaluate for life-threatening abnormalities using the ABC (airway, breathing, circulation) approach, and this should be followed by a major body systems evaluation. The cardiovascular, respiratory and neurological systems should be assessed in the knowledge that the range and severity of possible abnormalities in these body systems is very variable, dependent on the toxin. Regardless of the likely underlying diagnosis, empirical therapy for any abnormalities found should be instituted as a matter of urgency and should be ongoing as the rest of the diagnostic evaluation is completed.

Cardiovascular system

Assessment of perfusion should include evaluation of heart rate, pulse quality, mucous membrane colour and capillary refill time, as well as mentation and body temperature. A complete review of the feline response to hypoperfusion is beyond the scope of this article but it should be remembered that cats with severe shock of any aetiology tend to show inappropriate bradycardia (heart rate in the range 100–140 bpm) and hypothermia as well as poor pulse quality, pale mucous membranes and a prolonged capillary refill time.[1,2] If the patient is thought either to be hypovolaemic secondary to intravascular fluid loss (eg, vomiting) or to be exhibiting relative hypovolaemia secondary to vasodilation (eg, severe acidosis), intravenous fluid therapy should be instigated.

Fluid therapy plans must be tailored to the individual patient. Given the cat's propensity to exhibit fluid overload and develop respiratory signs in response to aggressive fluid therapy, multiple small incremental boluses (eg, 10 ml/kg isotonic crystalloid over 30 mins) are recommended. The patient should be carefully monitored, both to ensure resolution of the signs of poor perfusion and to limit the risk of inadvertent intravascular volume overload.

Respiratory system

Assessment of the respiratory system should include ensuring the airway is patent and evaluating respiratory rate and effort. In patients with intoxication, vomiting coupled with mental depression constitutes a risk for airway obstruction that should be urgently addressed by suctioning and endotracheal intubation if necessary. Dyspnoea may also be due to aspiration pneumonia or, less commonly, to direct effects of the toxin on the respiratory system. All dyspnoeic patients should receive oxygen supplementation as a matter of urgency. Intubation and positive pressure ventilation may be necessary on rare occasions.

Neurological status

Many intoxicated patients show neurological signs including mental depression/obtundation and/or seizures. Patients with seizures should receive urgent treatment to control the signs. Diazepam (0.5 mg/kg IV) is typically the first-line treatment but, if it is unsuccessful in controlling the signs, other drugs such as barbiturates or propofol constant rate infusions should be used without delay. Importantly, a minimum database should also be obtained as a matter of urgency to rule out metabolic causes for the seizures, such as hypoglycaemia.

Minimum database

The minimum database should include packed cell volume/total solids (PCV/TS), blood glucose, blood urea nitrogen, electrolytes and, ideally, venous acid–base status. This facilitates detection of potentially life-threatening problems such as acidosis, hypocalcaemia, hypoglycaemia and hyperkalaemia.

Following the major body systems assessment and institution of any necessary empirical therapy, a full physical examination should be performed. It is strongly recommended that in all animals where toxicity is suspected a minimum database is obtained shortly after admission (see left). This helps with the creation of a prioritised differential diagnosis list and acts as a baseline against which future progression can be judged.

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Addressing subsequent goals of therapy

Beyond any initial empirical treatment used to stabilise the major body systems, therapy needs to address a number of subsequent goals that are common to all intoxicated patients (see right).

Goals of therapy

Efforts should be made to:

- **Prevent further absorption of the toxin** (dermal and gastrointestinal decontamination)
- **Enhance elimination of the toxin** (emesis, gastric lavage, adsorbents/cathartics, dialysis)
- **Administer antidotal therapy** (if possible)
- **Provide ongoing supportive care** (targeted to the individual patient's signs)

Dermal decontamination

Some life-threatening emergencies in cats are induced by direct absorption or by oral ingestion of a toxin (due to grooming) after dermal exposure. Timely removal of any excess material from the haircoat and skin can prevent further absorption. It is helpful to have at least two people on hand, one to hold the cat and one to perform the dermal decontamination, which can include brushing and/or bathing. During bathing, both should wear gloves or other available protective wear. The water temperature needs to be as close as possible to normal body temperature. Prolonged rinsing after bathing might be necessary but hypothermia must be avoided. The patient should be actively dried. Clipping of long-haired cats may aid the process.

Gastrointestinal decontamination (emesis)

In patients with suspected oral toxin ingestion, the induction of emesis is recommended at the earliest possible opportunity, unless one of the below contraindications applies. Note that if the substance was ingested more than 4–6 h prior to presentation, induction of emesis may be attempted, but is less likely to be effective as much of the toxin may already have been absorbed or have passed into the small intestine.

In the cat, the most reliable emetic agent is considered to be the α_2-adrenergic agonist, xylazine, administered at 0.44 mg/kg IM. Due to physiological differences, xylazine is a more potent emetic in cats than in dogs.[4] In our experience it is more effective if the stomach contains some food at the time of induction of emesis and feeding a small amount of food prior to induction should be considered. Care should be taken to monitor for unwanted sedative effects, of which the most important are bradycardia, respiratory depression and the potential to exacerbate any pre-existing hypotension.

The use of apomorphine in cats is controversial. This D2-dopamine receptor agonist is a less potent emetic in cats than in dogs and has the potential for inducing behavioural effects.[4]

Sodium carbonate (washing soda) crystals and hydrogen peroxide have also been reported to be effective emetics in cats. The dose of both is empirical (eg, 1–3 ml/kg hydrogen peroxide not to exceed 10 ml). Ideally, both should be administered under veterinary supervision as there is the potential for adverse effects – notably a caustic effect with washing soda, and foaming and risk of aspiration with hydrogen peroxide. Syrup of ipecac, an agent used for inducing emesis in children in some countries, is not recommended due to its potential to cause cardiotoxic effects.

Contraindications to the induction of emesis

The patient has severe CNS depression

Protective airway reflexes may be impaired in these patients and induction of vomiting is associated with a real risk of aspiration pneumonia.

The ingested substance is caustic, acidic or petroleum-based

Mucosal irritation and trauma, with subsequent stricture formation, is a possible sequela when caustic or acidic substances are passing through the oesophagus.[3] Petroleum-based substances are not as irritable to the oesophageal mucosa, but are potentially more prone to being aspirated due to their viscosity.[3]

Gastric lavage

Gastric lavage is a common procedure in human and veterinary medicine for evacuating gastric contents after recent toxin exposure.

When performing gastric lavage in cats, the patient should be anaesthetised and a cuffed endotracheal tube placed. The cuff on the tube should be fully inflated to reduce the risk of aspiration of any lavage fluid. The patient should be positioned in right lateral recumbency with the head slightly below the level of the thorax/stomach. A tube with a multi-fenestrated end should be pre-measured from the oral cavity to the last rib and the length should be marked with a pen or tape. The tube

should be of the largest bore available that will pass through the cat's oesophagus; this makes for a more efficient procedure, with larger amounts of stomach contents being removed per unit of time. After careful advancement of the tube into the stomach up to the mark, its correct positioning should be confirmed by direct visualisation of the tube passing the larynx into the oesophagus and/or by detecting 'bubbling sounds' within the stomach while blowing small amounts of air into the tube. Radiographs are rarely necessary but could be taken to confirm placement if there is any concern.

Small amounts of warm water (5–10 ml/kg) are then instilled into and retrieved from the same tube until the water returning from the stomach is clear and free of stomach contents. Following the procedure, the oral cavity should be examined and the oropharynx suctioned prior to recovering the cat from anaesthesia and extubation. When removing the tube it should be kinked to avoid leakage of extraneous fluid into the patient.

When is gastric lavage appropriate?

The advantages of gastric lavage (rapid removal of gastric contents and the administration of adsorbents in uncooperative patients) have to be weighed against the disadvantages (requirement for general anaesthesia, risk of aspiration, potential for oesophageal trauma). Dependent on the toxin, gastric lavage should be considered if the patient has a history of recent ingestion, the induction of emesis is contraindicated or unsuccessful and/or survey radiographs show the presence of gastric contents.

Administration of adsorbent/catharsis

Following gastrointestinal decontamination, it is recommended that an adsorbent is administered to reduce further gastrointestinal absorption. The most frequently used adsorbent is activated charcoal. Charcoal is 'activated' by treating it with steam, oxygen and acids at high temperatures, which makes the material very porous, resulting in a very high surface binding capacity. Activated charcoal is, therefore, highly efficient at adsorbing a wide variety of materials – although there are some notable exceptions (eg, ethylene glycol [EG] and other alcoholic substances). Doses of 2–5 g/kg PO are recommended, which can be given as a slurry of 1 g in 5 ml of water.

Activated charcoal should be used with caution in the vomiting patient due to the risk of aspiration.

Sorbitol is commonly used alongside adsorbents as a cathartic agent. The recommended dose is 3 mg/kg or 1–2 ml/kg of a 70% solution PO. Combinations of a cathartic and activated charcoal are commercially available and might be the most efficient way to bind and eliminate many toxins. The cathartic reduces the transit time of the saturated activated charcoal and therefore the danger of desorption and reabsorption. Sorbitol (3 mg/kg) can also be manually mixed with the activated charcoal.

Antidotes

Antidotes are available for only a small number of specific toxins. Even then, in some instances they may not be available in a timely fashion or their use may be limited by expense. In the majority of intoxicated feline patients, antidotes are a less important part of treatment than diligent, thorough supportive care. Where antidotes are recommended for specific common intoxications in cats they are mentioned below in the relevant sections on the individual toxins.

Supportive care

Following initial stabilisation and gastrointestinal decontamination, most cats will need and benefit from ongoing supportive care. Fluid diuresis is a useful tool for promoting excretion of many toxins and is also recommended in situations where a toxin is suspected but not confirmed. Isotonic replacement crystalloid fluids should be used and the fluid rate should be adjusted so that the urine output reaches at least 2 ml/kg/h. If a urinary catheter is not placed, incontinence pads or nappies can be used to absorb the urine and can be weighed. The difference in wet to dry weight provides a crude measure of the volume of urine produced.

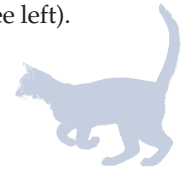
Other ongoing care should include, but not be limited to, support of normothermia, support of the respiratory and neurological systems, treatment of any metabolic problems identified and, if the patient remains hospitalised for more than 24 h, consideration of nutritional requirements.

Patients should be carefully monitored – with the precise monitoring chosen tailored to the patient's presenting signs and progression, and an assessment of the likelihood and nature of possible complications (see left).

Ongoing monitoring

Regular physical examination, with a focus on the major body systems and temperature, remains the most important monitoring technique but this may be supplemented by additional tools. Dependent on the nature of the toxin and its effect on the patient, the following should all be considered: arterial blood pressure measurement via Doppler ultrasonic or oscillometric methods, central venous pressure, continuous ECG, pulse oximetry, and in-house blood work including PCV, TS, blood glucose, electrolytes and acid–base status. Some or all of these monitoring tools may be used every 2–6 h in the critically ill feline patient, with the frequency of monitoring being reduced as the patient's signs improve.

In the majority of intoxicated feline patients, antidotes are a less important part of treatment than diligent, thorough supportive care.



The popularity and widespread occurrence of lily plants, combined with the potent nature of the toxin and the investigative character of cats, makes lily poisoning a significant concern in veterinary emergency practice.

MANAGEMENT OF SPECIFIC TOXICITIES

Lily intoxication

Acute renal failure in cats caused by ingestion of plant parts of the family Liliaceae was first described in 1989 by the Animal Poison Control Center (APCC) in the USA. Since then an increasing number of reports have emerged that underline the severity of this intoxication.[5–7] Although only certain kinds of lilies have featured in published reports to date (Table 2), it is currently advisable to consider all *Lilium* and *Hemerocallis* species as potentially being toxic to cats (Fig 1).[8]

Lilium species may be found both outdoors and as house plants. All vegetative parts of the plant have shown potential toxicity to cats, including the pollen – in one report, ingestion of less than half a leaf led to severe toxicosis.[9] Aqueous extracts from both flowers and leaves induce typical signs of lily intoxication in cats, with the extract from flowers being more potent than that from the leaves.[10] The popularity and widespread occurrence of lily plants, combined with the potent nature of the toxin and the investigative character of cats, makes lily poisoning a significant concern in veterinary emergency practice.

TABLE 2 Some lily species known to be toxic in cats

Common name	Latin name
Easter lily	*Lilium longiflorum*
Tiger lily	*Lilium lancifolium*
Rubrum (oriental) lily	*Lilium speciosum*
Hybrid lilies	*Lilium* species hybrids
Daylilies	*Hemerocallis* species

FIG 1 Some supermarkets have started to alert pet owners to the toxicological potential of lilies. *Courtesy of Richard Irvine*

Mechanism of toxicity

Although it is well recognised that lily toxicity leads to acute renal failure, the agent responsible and the precise mechanism of toxicity is currently unknown. Pathologically, the principal feature is acute tubular necrosis, which is especially prominent within the proximal tubules of the kidney. Casts, cellular debris and oxalate crystals have all been documented within the tubules. The finding of oxalate crystals is remarkable as lilies have not been shown to contain any oxalates. It has been speculated that their accumulation may be due to the reduced capacity for endogenous oxalate excretion in affected animals.

Although the mortality rate is high, histopathology results in some individuals demonstrate the presence of mitotic figures within the tubules and an intact basement membrane. This may indicate a potential for functional recovery of affected renal tubules if supportive care can be provided for a sufficient period of time.[7]

Clinical signs and diagnosis

The initial signs of intoxication develop shortly after ingestion and predominantly reflect gastrointestinal irritation. Vomiting, anorexia and depression are often the first signs noticed by the owner and occur within 2 h of ingestion. In some affected individuals the severity of vomiting decreases after 12 h and owners may feel the animal is improving. More typically, anorexia and depression continue to be evident.

Within 24–96 h of ingestion, renal failure develops and the animal shows signs consistent with this, including dehydration, uraemic breath and enlarged painful kidneys.[6,10] Urine production is variable at this stage. If urinalysis is performed early in the course of the intoxication, it may reveal signs of acute renal tubular injury before the development of azotaemia. Isosthenuria, glucosuria (without concurrent hyperglycaemia), proteinuria and the presence of cylinduria should elicit a suspicion of lily intoxication. Routine serum biochemical panels will reveal a worsening azotaemia. It has been reported that the serum creatinine level may be disproportionately elevated in comparison with the blood urea nitrogen (BUN) level.[9] The reason for this is currently unknown and it does not seem to be a consistent finding. In contrast to EG poisoning, total calcium levels are usually normal.

Lily toxicity – treatment and prognosis

As the toxic agent and mechanism of toxicity is unknown there is no specific antidote available. If a patient is presented with a known history (observation) of lily ingestion, gastrointestinal and/or dermal decontamination is warranted (see earlier discussion). Once renal failure has developed, treatment is based on symptomatic and supportive care.

Intravenous fluid therapy with a replacement electrolyte solution should focus on correction of hypovolaemia and dehydration, and initiation and maintenance of diuresis. Fluid therapy rates must be tailored to the individual patient and should ideally be adjusted after establishing fluid ins-and-outs with the use of a closed urinary collection system.

In addition to fluid therapy, anuric or oliguric patients may require further medical treatments (eg, furosemide, mannitol) to promote diuresis. Careful attention must be paid to managing electrolyte and acid–base complications, especially hyperkalaemia and metabolic acidosis. If an adequate urinary output cannot be established, dialysis should be considered (Fig 2).[11]

The prognosis may be good if the cat is presented immediately following ingestion and decontamination can be carried out successfully. In one case report, a cat survived after developing renal failure and receiving intensive therapy including haemodialysis.[12] Generally, however, even if advanced therapeutic options are available, the prognosis is grave once renal failure has developed.[13]

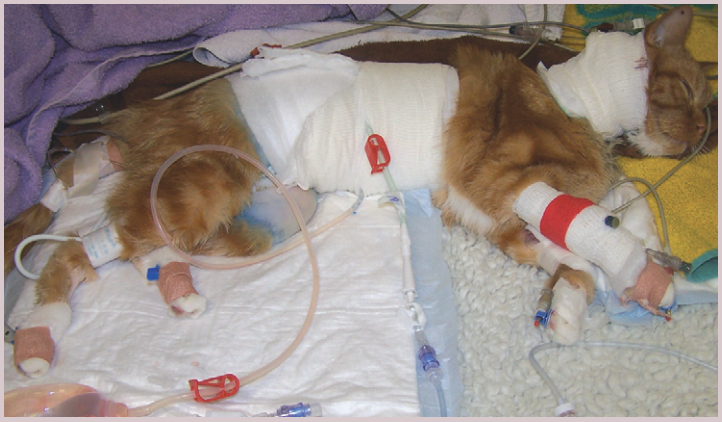
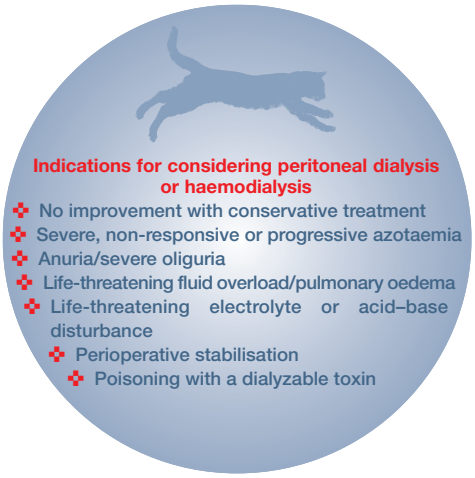


FIG 2 Feline patient undergoing peritoneal dialysis for presumed lily toxicity

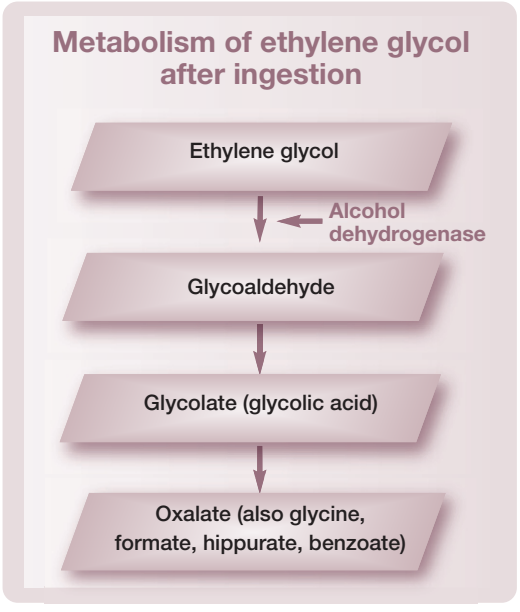


Pancreatitis has been suspected as a concurrent problem in some affected cats, although evidence that this may be a sequela of lily intoxication is weak.[10] At present it should only be considered as a possible additional complication.

Ethylene glycol intoxication

Ethylene glycol is a relatively common toxicant and poses a severe risk for cats due to the highly toxic nature of its metabolites.[14] Most cats are exposed to EG via ingestion of antifreeze (which contains up to 95% EG); one US study found a slight increase in exposure during the months of March to May.[15] The sweet (and ostensibly enjoyable) taste of antifreeze, its rapid absorption through the gastric mucosa and the small volume required for a lethal dose all combine to make this a particularly deadly toxin. The lethal dose for cats is at least three times lower than that for dogs (approximately 1.5 ml/kg versus 4.4–6.6 ml/kg, respectively).[16]

Lack of public awareness of the potential dangers of EG to animals may account for its relative accessibility. The severity of intoxication is dose dependent, but EG is nevertheless associated with one of the highest mortality rates of all intoxicants in cats.[17]



The sweet (and ostensibly enjoyable) taste of antifreeze, its rapid absorption through the gastric mucosa and the small volume required for a lethal dose all combine to make ethylene glycol a particularly deadly toxin.

Mechanism of toxicity

Peak plasma concentrations of EG are attained within 2–3 h of ingestion and the half-life in plasma is only 3 h. Ethylene glycol itself is only mildly toxic but is rapidly metabolised to more toxic metabolites (see box on page 854). These metabolites can then persist for several days within the body.[18] The metabolism of glycolate is the rate-limiting step, and so high levels of both EG and glycolate can be found in the urine.[19]

Ethylene glycol and glycoaldehyde are considered to be principally responsible for the initial CNS signs, both as a direct action of the toxin plus concurrent hyperosmolality. All metabolites seem to be cytotoxic to the renal tubular epithelium, causing the destruction of intracellular organelles, although glycolate is thought to be the main contributor to the life-threatening nephrotoxic effects. Additionally, calcium binds with oxalate to form calcium oxalate crystals, a process that consistently leads to crystalluria (Fig 3).

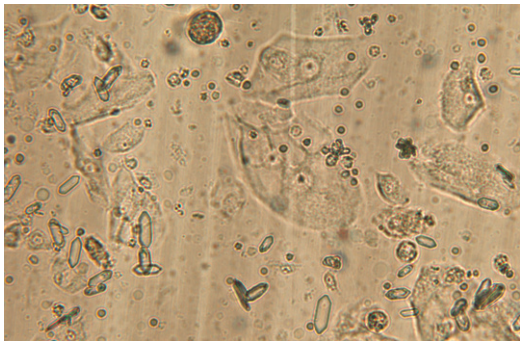


FIG 3 Needle-shaped monohydrate calcium oxalate crystals, epithelial cells and cellular debris in the urine of a cat with EG toxicity. *Courtesy of Dr Karen Lisa Hulme-Moir*

Clinical signs and diagnosis

Untreated, EG toxicity classically progresses through three stages:

✣ **Stage 1** starts within 30 mins of ingestion and can last up to 12 h. The signs principally relate to the CNS and resemble alcohol intoxication. Nausea, vomiting, depression, incoordination and ataxia are the predominant features, whereas with more severe

Tips for early detection of ethylene glycol intoxication

Collect a thorough history
Any free-roaming cat with an acute onset of CNS signs (looking 'drunk') and/or polyuria should raise a suspicion of EG intoxication. Polydipsia may not be present.

Perform urinalysis and look for calcium oxalate crystalluria
Both monohydrates and dihydrates might be seen, but monohydrates are considered to be more specific. Do not confuse with hippuric acid crystals. A negative result does not rule out EG intoxication.

Wood's lamp examination
Potentially, fluorescence within urine, originating from stains added to antifreeze formulations, may be detectable; but only up to 6 h after ingestion and a negative result does not rule out EG toxicity. The oral cavity, face, paws and vomitus can also be examined.

Haematology
Hyperphosphataemia without azotaemia might be attributable to the phosphate rust inhibitors within antifreeze formulations. Approximately 50% of patients develop hypocalcaemia due to chelation of calcium by oxalic acid. Approximately 50% of patients develop hyperglycaemia (thought to be due to inhibition of glucose metabolism, increased epinephrine/corticosteroids, uraemia).

Echocardiographic examination
Assess for the presence of a prolonged Q–T segment, which (in the absence of hypothermia) might indicate hypocalcaemia.

Renal ultrasonography
The so-called 'renal medullary rim sign' (hyperechogenicity of the corticomedullary junction) may be visible on renal ultrasound examination, surrounded by the 'halo sign' (hypoechogenicity parallel to the rim sign).

Ethylene glycol toxicity – treatment and prognosis

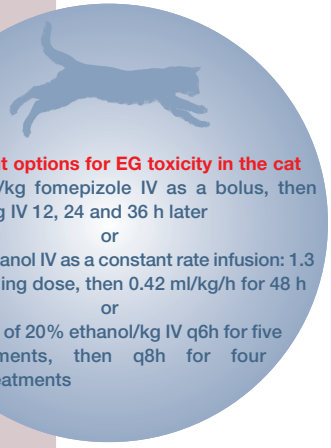
Early recognition and aggressive treatment are key to the successful management of EG intoxication. Treatment within 6 h of ingestion has the best prospects of influencing outcome. It is within this period that the chance of disrupting the formation of toxic metabolites is greatest. Theoretically, decontamination strategies (discussed earlier) could be helpful, but practically the beneficial effects of emetics, gastric lavage and adsorbents are limited due to the rapid systemic absorption of EG.[18]

Disruption of the metabolic pathways is achieved by inhibition of alcohol dehydrogenase (ADH) activity using either ethanol or fomepizole (4-methyl-1H-pyrazole). Ethanol is structurally similar to EG and binds competitively and with a higher affinity for ADH than EG. It is, however, not transformed into toxic metabolites by the body.

Treatment with ethanol is not without risks. With high-dose injections, CNS depression and respiratory arrest can develop. Administration via continuous rate infusion may help to reduce the severity of these negative effects. Furthermore, ethanol itself contributes to hyperosmolarity, osmotic diuresis and metabolic acidosis by increasing the conversion of pyruvate to lactate.[20] When using this treatment strategy, intensive monitoring must be in place to maintain optimal supportive care.

More recently, fomepizole has been shown to be a more promising treatment, with fewer side effects.[21] It is a direct, as opposed to a competitive, ADH inhibitor and although initial results from studies investigating the potential use of fomepizole in cats were not promising, dosages were extrapolated from studies in dogs. Further research indicated that feline ADH might be less sensitive to the inhibitory effects of fomepizole than canine ADH. A subsequent study showed advantages regarding outcome and safety of higher dosed fomepizole over ethanol treatment.[21]

Factors that influence the prognosis include the amount of toxin ingested and, most importantly, the time that elapses between ingestion and the initiation of treatment. If EG toxicity is recognised at an early stage and appropriate aggressive treatment is instituted, the prognosis is moderate. However, for patients that develop anuric renal failure, the prognosis is grave unless peritoneal or haemodialysis is available. Renal transplantation might be considered where accessible.



Treatment options for EG toxicity in the cat

- 125 mg/kg fomepizole IV as a bolus, then 31.25 mg/kg IV 12, 24 and 36 h later

or

- 20% ethanol IV as a constant rate infusion: 1.3 ml/kg loading dose, then 0.42 ml/kg/h for 48 h

or

- 5 ml of 20% ethanol/kg IV q6h for five treatments, then q8h for four treatments

intoxications seizures and coma might be present. Treatment is more likely to be successful if it is initiated at this stage.

- **Stage 2** spans approximately the next 12 h (ie, 12–24 h after ingestion). It is characterised by clinical signs associated with worsening acute renal failure including anorexia, vomiting, diarrhoea and gastrointestinal ulceration. Serum BUN and creatinine start to rise.
- **Stage 3** occurs after approximately 24 h, with the development of oliguria and progression to anuric renal failure.

Reliable tests to detect EG (utilising gas chromatography) are not readily accessible and are expensive. Less cost-prohibitive test kits are generally considered to be relatively insensitive, especially for cats, and may have limited availability outside the USA. If a confirmed diagnosis is required, it is recommended that contact is made with a local human toxicology laboratory to enquire about its testing capabilities.

Blood work reveals a high anion gap metabolic acidosis, the increased anion gap being due to the presence of the many negatively charged metabolites (see right). The increase in the anion gap can be seen within 3 h of EG ingestion, peaks at 6 h and stays high for approximately 48 h. Urine specific gravity might be decreased, but in the early stages might be above the isosthenuric range.

Ionised hypocalcaemia may be seen. Although increasingly veterinary surgeons have the ability to measure ionised calcium in-house, the astute clinician may suspect ionised hypocalcaemia by identification of a prolonged Q–T segment on an echocardiogram (ECG). Body temperature should always be measured in these patients as significant hypothermia is a differential diagnosis for prolonged Q–T.

Demonstrating urine fluorescence with a Wood's lamp may also be an aid to diagnosis. Fluorescent stains are frequently added to antifreeze substances to allow mechanics to detect any leaks within a vehicle's cooling system or radiator. The cat's paws and face should be examined using a Wood's lamp as some cats might walk through antifreeze and then ingest the substance by licking it off their paws.

Calculation of the anion gap

$([Na^+]+[K^+]) - ([Cl^-]+[HCO_3^-])$ (units mEq/l)

Normal values in the cat (which have been extrapolated from the dog) are considered to be 10–27 mEq/l

Pyrethroid intoxication frequently follows inappropriate application of spot-on formulations intended for use in dogs. Some cats may even be affected by close contact with dogs treated with a spot-on formulation.

Pyrethrins and pyrethroids

Pyrethrins and pyrethroids are insecticides that are sold for the treatment of flea and tick infestation. Pyrethrins are natural substances extracted from *Chrysanthemum* species; the term pyrethroid describes similar, synthetically manufactured molecules produced with the aim of increasing the photostability of this group of drugs. Although it might be expected that pyrethrins would be relatively safe to use for ectoparasite control, given the differences between mammals and insects, cats are frequently presented as an emergency to the veterinary practitioner showing clinical signs after pyrethrin exposure.[22]

Between 1988 and 2006, the Veterinary Poisons Information Service in the UK received 1306 enquiries relating to permethrin exposure. Of those enquiries, 49.8% related to spot-on formulations, of which 80.9% involved cats.[23] Intoxication frequently follows inappropriate application of spot-on formulations intended for use in dogs, and some cats may even be affected by close contact with dogs treated with a spot-on formulation.[24] The toxic dose for pyrethrin and pyrethroids is currently unknown, but based on cases reported to the APCC, 1 ml of 45% permethrin applied dermally to a 4.5 kg cat can result in life-threatening toxicosis.[25] In the UK, spot-on preparations for dogs can contain up to 74.4% permethrin.[23]

There are a number of reasons why cats may be particularly susceptible to intoxication with pyrethrins and pyrethroids. Their rela-

Pyrethrin and pyrethroid toxicity – treatment and prognosis

Dermal decontamination should be instituted at the earliest possible opportunity. Bathing of the patient is generally indicated and the use of a hand- or dishwashing detergent might enhance the cleaning process.[26] Hypothermia may potentiate the effect of pyrethroids on ion-channel activity and, therefore, bathing the patient with cold water and/or prolonged sedation should be avoided. Conversely, bathing in water that is too warm might enhance resorption through the skin due to hyperaemia and should also be avoided. The patient should be actively dried and, if transport to a veterinary facility is delayed, owners can be advised to wrap it in a warm towel. Valentine showed a potential positive effect of activated charcoal even after dermal exposure.[29] This may be due to the existence of some enterohepatic recirculation of the toxic agent. The risk of administering activated charcoal to these patients must, however, be carefully weighed against the potential benefit.

Once clinical signs are present, treatment should focus on control of the muscle tremors and/or seizures. Benzodiazepines are typically insufficient to control signs in severe intoxications, and may also be responsible for paradoxical exacerbation of neurological signs.[24] Methocarbamol (Robaxin-V; Fort Dodge) is a peripherally acting muscle relaxant that is recommended for control of severe muscle tremors. Its use is limited by lack of availability of the intravenous preparation outside the USA. Where available it may be administered as multiple boluses or a continuous rate infusion; the recommended dose is 55–220 mg/kg IV and doses should not exceed 330 mg/kg/day. Where methocarbamol is not available, or where it is suspected that the animal has seizures as well as muscle tremors, a constant rate infusion of propofol (0.1–0.4 mg/kg/min) may be used. The duration of propofol infusion in cats should ideally be limited to approximately 12 h due to its ability to induce red cell oxidative injury in this species. Phenobarbital is another drug that may be used; however, it should be noted that, even when given intravenously, its onset of action is in the order of 20–30 mins, making it less useful for control in the patient with acute seizures. Pentobarbitone may be used but its current lack of availability in a sterile form is a limitation. Whatever drug is chosen, it is not usually necessary to eliminate all muscle activity and an appropriate balance between an improvement in clinical signs and potential side effects of the sedative drug must be sought.

In the face of hypersalivation, the use of atropine is often considered but is not recommended as it may produce further CNS stimulation. A potential positive benefit of atropine administration is helping to distinguish between suspected pyrethroid and carbamate intoxication. (Low doses of atropine should not alleviate any signs in the carbamate-intoxicated patient.)

For mildly affected cases the prognosis is good and there are unlikely to be any long term effects. For more severely affected cases, survival rates can also be good but only if patients receive early aggressive management and continuous supportive care; unfortunately, some will be euthanased or die due to the severity of their signs. If prolonged seizure activity cannot be suppressed, irreversible brain damage can occur, but with successful treatment, long term clinical signs seem to be absent.[30]

Typically recovery takes approximately 2–3 days, but there is a wide range between individual cases (3 h to 7 days).[23] As successful treatment may require intensive support, with all the associated expense, clearly the problem is best avoided where possible. Educating owners as to the potential severity of signs that can follow exposure of cats to some canine flea products is an important part of achieving this goal.

1 ml of 45% permethrin applied dermally to a 4.5 kg cat can result in life-threatening toxicosis.

tively high surface area to weight ratio means that, with topical application, smaller individuals tend to receive higher doses on a mg/kg basis. Furthermore, pyrethroids are excreted following either oxidation or glucuronidation and the reduced capacity for glucuronidation in the cat can contribute to the accumulation of metabolites and a less efficient detoxification process.[26] Finally, other substances added to the formulation might utilise the capacity of detoxification enzymes, further prolonging exposure.

Mechanism of toxicity

After application of a spot-on emulsion, the lipophilic pyrethroids are quickly absorbed through the skin into the systemic circulation. Their absorption is also rapid after oral intake and even inhalation. Pyrethroids principally affect the peripheral and central nervous system. They reversibly alter the function of sodium channels within the axon in such a way that it prolongs their conductance and leads to repetitive firing of the nerve fibre. This effect is enhanced by low temperatures. Due to their lipophilic properties, pyrethrins pass easily through the blood–brain barrier and can induce CNS signs, including seizures. There is evidence of accumulation of pyrethroids within neural tissue even when blood levels are low.

Clinical signs and diagnosis

Clinical signs are normally noticed immediately after exposure, but can be delayed for up to 72 h.[27] In mild intoxications, paraesthesia induced by direct contact with the substance may result in paw flicking, ear twitching and uncontrolled contractions of the cutaneous trunk muscles. Grooming of a contaminated body area can result in hypersalivation and vomiting. Severe muscle tremors, seizures and/or depression are normally seen only in severe intoxications.[23] In one study, the most common clinical signs were tremors/muscle fasciculations (86%), twitches (41%), hyperaesthesia (41%), seizures (33%), pyrexia (29%), ptyalism (24%), ataxia (24%), mydriasis (19%) and temporary blindness (12%).[28]

Laboratory detection of pyrethrins/pyrethroids is not readily available and haematology, biochemistry and other findings might be normal. One of the principal differential diagnoses is organophosphate/carbamate toxicosis. Where available, measurement of cholinesterase levels may be helpful in distinguishing between the two groups of toxins – with levels being unremarkable in pyrethrin/pyrethroid toxicity and most likely decreased in organophosphate toxicity.

Paracetamol intoxication

Paracetamol (acetaminophen in the US) is a popular human antipyretic and analgesic drug that is available in a vast array of formulations.[31,32] Feline intoxications are not uncommon, most occurring secondarily to owner administration. Paracetamol has been used at therapeutic dosages in dogs, but due to specific differences in feline physiology, the ingestion of even small amounts poses a substantial risk for the cat.[33] It should, therefore, never be administered as a therapeutic agent to cats.

Mechanism of toxicity

Paracetamol is rapidly absorbed from the gastrointestinal tract and widely distributed throughout the body. As in EG intoxication, it is not the paracetamol itself that is responsible for the toxic effects, but its metabolite, N-acetyl-p-benzoquinoneimine (NAPQI). After absorption of paracetamol, the majority (90%) is excreted as non-toxic metabolites following glucuronidation or sulfation. As cats have a low level of the enzyme glucuronyl transferase, the glucuronidation pathway is soon saturated and any remaining paracetamol is processed within the P450 system, producing the toxic NAPQI.

As a free radical, NAPQI can lead to substantial oxidative cell damage. Initially, the effects of NAPQI can be limited by its conjugation with endogenous glutathione. However, as glutathione stores become depleted, toxicity occurs and methaemoglobinaemia can develop. Heinz body formation may also occur as the ferrous group of the haem molecule is oxidised to a ferric group. These oxidised haem-sulfhydryl groups form disulfide bonds between globin chains leading to a structural deformation and potentially denaturation of these globins. Their subsequent precipitation is responsible for the increased formation of Heinz bodies (Fig 4).

Cats are particularly susceptible to red cell oxidative damage as they have eight sulfhydryl groups per haemoglobin tetramer, compared with the four found in humans and dogs. Additionally, the different structural anatomy of the feline spleen is partially responsible for a decreased ability to recognise and remove red blood cells with Heinz bodies, thus increasing the circulation time of these dysfunctional cells.

Paracetamol has been used at therapeutic dosages in dogs, but due to specific differences in feline physiology, the ingestion of even small amounts poses a substantial risk for the cat.

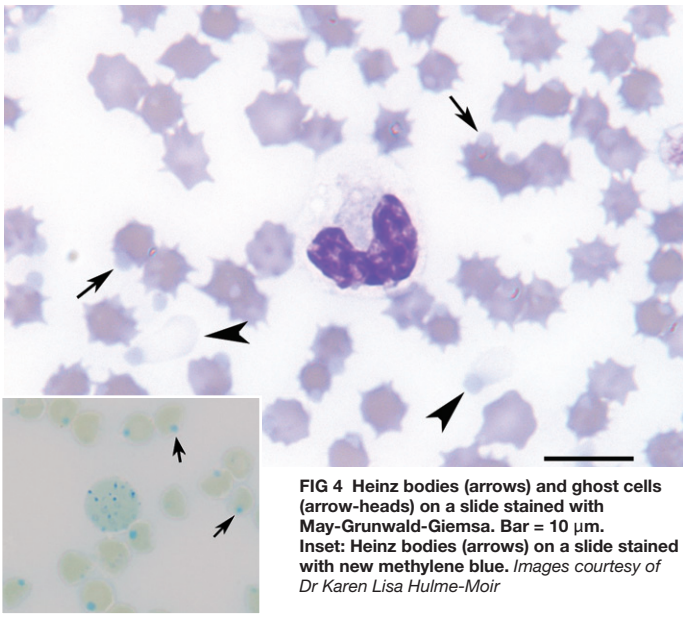


FIG 4 Heinz bodies (arrows) and ghost cells (arrow-heads) on a slide stained with May-Grunwald-Giemsa. Bar = 10 µm. Inset: Heinz bodies (arrows) on a slide stained with new methylene blue. *Images courtesy of Dr Karen Lisa Hulme-Moir*

Clinical signs and diagnosis

Cats may show clinical signs of depression, anorexia, hypersalivation and vomiting after ingestion of as little as 10 mg/kg paracetamol.[34] Signs may develop within 4 h of ingestion or may be delayed for up to 24 h. Between 24 and 72 h, some cats develop facial oedema, with the paws and forelimbs occasionally being affected as well. This is thought to be the consequence of increased vascular permeability and vasculitis.

Patients normally develop pigmenturia (methaemoglobinuria) and signs associated with haemolysis/methaemoglobinaemia, including tachypnoea and chocolate-coloured or icteric mucous membranes, and abdominal pain. The chocolate-coloured discoloration of the mucous membranes is due to the presence of methaemoglobin. As this form of haemoglobin exhibits a different light absorption to both oxy- and deoxyhaemoglobin, pulse oximetry is not a useful way of evaluating oxygen-carrying capacity in these patients. Pulse oximetry typically shows a consistent value of around 85%, although the actual oxygen saturation may be much lower. Co-oximetry is a more accurate way of detecting methaemoglobinaemia, but is not routinely available in most veterinary practices.

Biochemistry usually shows elevated aspartate transaminase (AST) levels. Signs of hepatotoxicity, as seen in dogs, are normally only observed at a later stage of the disease process or in severe intoxications. Severely affected cats rarely live long enough to develop significant hepatotoxic signs.

Paracetamol toxicity – treatment and prognosis

If ingestion occurred over an hour before presentation, induction of emesis might be ineffective. The administration of activated charcoal is, however, usually valuable as it adsorbs paracetamol efficiently.

Aggressive supportive care, to ensure tissue oxygen delivery is maintained, is the cornerstone of stabilisation in the severely affected patient. Oxygen administration, a blood transfusion and/or Oxyglobin (OPK Biotech) administration may be necessary and should be tailored to the cat's clinical signs.

Several specific treatments may also be instituted, all of which aim to reduce oxidative damage:

- N-Acetylcysteine may be administered as an additional source of glutathione. A loading dose of 140 mg/kg PO or IV is followed by 70 mg/kg PO or IV q4h for five to seven treatments. Oral administration can be challenging due to its bitter taste and the use of a gastric tube might be necessary.
- S-Adenosylmethionine (SAMe) has been shown to protect cat erythrocytes from oxidative injury in a feline experimental model of paracetamol toxicity.[34] SAMe was administered at 180 mg PO q12h for 3 days and then at 90 mg PO q12h for 14 days.
- Methylene blue has been successfully used in certain settings in humans to counteract methaemoglobinaemia, but has not been as successful in cats. One study showed that methylene blue and N-acetylcysteine together were not much more effective than N-acetylcysteine alone.[10]
- Ascorbic acid has also been discussed in human medicine as a potential means of promoting the reduction of methaemoglobin back to haemoglobin, but its effect is thought to be insufficient to be clinically useful.
- Cimetidine may be of benefit due to its inhibitory effect on the P450 enzyme system, thereby reducing the production of NAPQI. Evidence to support its use is lacking and the dosages necessary to achieve this effect might be too high to be useful clinically.[35]

The prognosis is dependent on the severity of intoxication. Clinically the ability to predict outcome accurately after initial treatment is challenging, complicated by the fact that feline metabolic capacity and, hence, vulnerability to the toxin is variable. Nevertheless, to maximise the prognosis, early and aggressive treatment should be instituted.[32]

KEY POINTS

- Due to their distinctive physiology, the toxicological spectrum exhibited by cats differs to that of dogs.
- Although toxicological emergencies are relatively less common in cats compared with dogs, they nonetheless pose a challenge for the veterinary practitioner.
- Establishing a diagnosis can be demanding, especially if the ingestion of a specific toxin has not been witnessed. Nevertheless, a complete history, a thorough physical examination and further diagnostic tests are helpful in establishing an initial treatment plan.
- Even if the underlying toxicant is not identified, immediate stabilisation and aggressive therapy must be initiated so that the patient has the best chance of a positive outcome.

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References

1 Boag AK, Hughes D. Assessment and treatment of perfusion abnormalities in the emergency patient. *Vet Clin North Am Small Anim Pract* 2005; **35:** 319–42.
2 Mazzaferro EM. Complications of fluid therapy. *Vet Clin North Am Small Anim Pract* 2008; **38:** 607–19.
3 Hackett T. Emergency approach to intoxications. *Clin Tech Small Anim Pract* 2000; **15:** 82–87.
4 Page SW, Maddison JE. Principles of clinical pharmacology. In: Maddison J, Page S, Church D, eds. Small animal clinical pharmacology. 2nd edn. Philadelphia: Elsevier, 2008: 18.
5 Hall JO. Nephrotoxicity of Easter lily (*Lilium longiflorum*) when ingested by the cat [abstract]. *J Vet Intern Med* 1992; **6:** 121.
6 Brady M, Janovitz E. Nephrotoxicosis in a cat following ingestion of Asiatic hybrid lily (*Lilium sp*). *J Vet Diagn Invest* 2000; **12:** 566–68.
7 Langston CE. Acute renal failure caused by lily ingestion in six cats. *J Am Vet Med Assoc* 2002; **220:** 49–52.
8 Tefft K. Lily nephrotoxicosis in cats. *Compend Contin Educ Pract Vet* 2004; **26:** 149–56.
9 Volmer P. Easter lily toxicosis in cats. *Vet Med* 1999; **94:** 331.
10 Rumbeiha W, Francis J, Fitzgerald S, et al. A comprehensive study of Easter lily poisoning in cats. *J Vet Diagn Invest* 2004; **16:** 527–41.
11 Cowgill LD, Francey T. Hemodialysis. In: Dibartola SP, ed. Fluid therapy in small animal practice. 3rd edn. Philadelphia: WB Saunders, 2006: 650–77.
12 Berg RI, Francey T, Segev G. Resolution of acute kidney injury in a cat after lily (*Lilium lancifolium*) intoxication. *J Vet Intern Med* 2007; **21:** 857–59.
13 Gulledge L. Acute renal failure in a cat secondary to tiger lily (*Lily tigrinum*) toxicity. *Feline Pract* 1997; **25:** 38–39.
14 Grauer G, Thrall M. Ethylene glycol (antifreeze) poisoning in the dog and cat. *J Am Anim Hosp Assoc* 1982; **18:** 492–97.
15 Khan SA SM, Trammel HL, Hansen SR, Knight MW. Ethylene glycol exposures managed by the ASPCA National Animal Poison Control Center from July 1995 to December 1997. *Vet Hum Toxicol* 1999; **41:** 403–6.
16 Thrall M, Connally H, Grauer G, Hamar D. Ethylene glycol. In: Peterson ME, Talcott PA, eds. Small animal toxicology. 2nd edn. St Louis: Elsevier Saunders, 2006: 703.
17 Thrall M, Grauer G, Dial S. Antifreeze poisoning. In: Bonagura J, Kirk R, eds. Kirk's Current Veterinary Therapy XII. Philadelphia: Saunders, 1995: 232.
18 Davis DP, Bramwell KJ, Hamilton RS, Williams SR. Ethylene glycol poisoning: case report of a record-high level and a review. *J Emerg Med* 1997; **15:** 653–67.
19 Clay KL, Murphy RC. On the metabolic acidosis of ethylene glycol intoxication. *Toxicol Appl Pharmacol* 1977; **39:** 39–49.
20 Dial S, Thrall M, Hamar D. Comparison of ethanol and 4-methylpyrazole as therapies for ethylene glycol intoxication in the cat. *Am J Vet Res* 1994; **55:** 1771–82.
21 Connally H, Thrall M, Hamar D. Safety and efficacy of high-dose fomepizole compared with ethanol as therapy for ethylene glycol intoxication in cats. *J Vet Emerg Crit Care* 2010; **20:** 191–206.
22 Volmer P, Khan S. Warning against use of some permethrin products in cats. *J Am Vet Med Assoc* 1998; 213: 800–1.
23 Sutton NM, Bates N, Campbell A. Clinical effects and outcome of feline permethrin spot-on poisonings reported to the Veterinary Poisons Information Service (VPIS), London. *J Feline Med Surg* 2007; **9:** 335–39.
24 Martin A, Campbell A. Permethrin toxicity in cats. *Vet Rec* 2000; **147:** 639.
25 Hansen S. Pyrethrins and pyrethroids. In: Peterson M, Talcott P, eds. Small animal toxicology. 2nd edn. St Louis: Saunders Elsevier, 2006: 1004.
26 Whittem T. Pyrethrin and pyrethroid insecticide intoxication in cats. *Compend Contin Educ Pract Vet* 1995; **17:** 489–92.
27 Merola V, Dunayer E. The 10 most common toxicoses in cats. *Vet Med* 2006; **101:** 339–42.
28 Boland LA, Angles JM. Feline permethrin toxicity: retrospective study of 42 cases. *J Feline Med Surg* 2010; **12:** 61–71.
29 Valentine W. Toxicology of selected pesticides, drugs, and chemicals. Pyrethrin and pyrethroid insecticides. *Vet Clin North Am Small Anim Pract* 1990; **20:** 375–82.
30 Richardson JA. Permethrin spot-on toxicoses in cats. *J Vet Emerg Crit Care* 2000; **10:** 103–6.
31 Richardson JA. Management of acetaminophen and ibuprofen toxicoses in dogs and cats. *J Vet Emerg Crit Care* 2000; **10:** 285–91.
32 Aronson LR, Drobatz K. Acetaminophen toxicosis in 17 cats. *J Vet Emerg Crit Care* 1996; **6:** 65–69.
33 Plumb D. Veterinary drug handbook. Ames: Iowa State University Press, 1999.
34 Webb C, Twedt DC, Fettman. S-adenosylmethionine (SAMe) in a feline acetaminophen model of oxidative injury. *J Feline Med Surg* 2003: **5:** 69–75.
35 Slattery J, McRorie T, Reynolds R. Lack of effect of cimetidine on acetaminophen disposition in humans. *Clin Pharmacol Ther* 1989; **46:** 591–97.