Ionophore Feed Additives

<table>
<thead>
<tr>
<th>Specific Agents</th>
<th>Major Species</th>
<th>Usual Time of Onset</th>
<th>Usual Duration (if survives)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monensin (Rumensin ®; Coban ®)</td>
<td>Most species</td>
<td>Hours to 2 days</td>
<td>Days to permanent damage; often lethal</td>
</tr>
<tr>
<td>Lasalocid (Bovatec ®; Avatec ®)</td>
<td></td>
<td></td>
<td>See Lasalocid section</td>
</tr>
</tbody>
</table>

- Monensin, lasalocid, salinomycin, narasin, and laidlomycin propionate are ionophore feed additives and/or coccidiostats.
  - Horses are often poisoned, but cattle and other species also are affected.
  - Clinical pathology changes, arrhythmias, and heart lesions are highly variable with ionophore toxicoses in the horse, even in lethally affected animals.
- Salinomycin is reportedly quite toxic to turkeys.
- Recently salinomycin-contaminated commercial food seems to have caused a large outbreak of ascending paralysis leading to respiratory paralysis and deaths in domestic cats.
  - Affected cats might also exhibit histologic evidence of myelin degeneration.
  - It is suspected that the drug may have been in gut contents of poultry incorporated in the diet.
**Monensin**  
(Rumensin®, Coban®)

<table>
<thead>
<tr>
<th>Major Species</th>
<th>Usual Time of Onset</th>
<th>Usual Duration (if survives)</th>
<th>Full Table for Organic Compounds that Affect the Heart</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most species</td>
<td>Hours to 2 days</td>
<td>Days to permanent damage; often lethal</td>
<td></td>
</tr>
</tbody>
</table>

**Sources**

- Produced by *Streptomyces* fungi.
- Feed additive used in food producing animals.
- Beef cattle.  
  Used to increase feed efficiency, control bloat, lactic acidosis, and to decrease the likelihood of acute bovine pulmonary emphysema and edema. Shifts volatile fatty acid production in rumen from acetic and butyric acids to propionic acid.
- Poultry.  
  Coccidiostat.
- Research - To study movement of ions across cell membranes.
- Available forms - Premix, (Rumensin®, Coban®), intermediate mix, and ready to feed (final ration intended rates are 5 - 30 g/ton of feed).
- Not approved for sheep, swine, dairy cattle, or horses.

![Molecular structure of monensin](image)

**Toxicity**

**Single dose oral LD<sub>50</sub> in various species**

<table>
<thead>
<tr>
<th>Species</th>
<th>LD&lt;sub&gt;50&lt;/sub&gt; (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Horse (most susceptible)</td>
<td>1 - 2</td>
</tr>
<tr>
<td>Sheep</td>
<td>11.9</td>
</tr>
<tr>
<td>Swine (approximate minimum lethal dose = 7 mg/kg)</td>
<td>16.8</td>
</tr>
<tr>
<td>Dog</td>
<td>&gt; 20</td>
</tr>
<tr>
<td>Cattle</td>
<td>22 - 80 (varies)</td>
</tr>
<tr>
<td>Goat</td>
<td>26.4</td>
</tr>
<tr>
<td>Chicken (most resistant)</td>
<td>200</td>
</tr>
</tbody>
</table>

- Conditions surrounding exposure.  
  - Improper mixing, settling (especially in liquid supplements).
  - Exposure of therapeutic doses for food animals to susceptible species.
  - Concentrate, intermediate mix may poison any of the species.

**Absorption, Distribution, Metabolism and Excretion (ADME)**

- Absorption from GI tract is rapid.
- Rapidly metabolized by liver P450 enzymes in a significant first-pass effect - metabolites excreted via biliary system and feces.
- Inhibition of P450 by macrolide antibiotics from fermentation media (after removal of most of the drug) in the feed of cattle.
apparently decreased hepatic detoxification of monensin and thus resulted in monensin toxicosis.

- No urinary excretion.
- Does not accumulate in heart or skeletal muscles.
- Small fraction of ingested amount enters systemic circulation.

**Mechanism of Action**

- Lipid soluble, transports monovalent cations preferentially across cell membranes. It is very potent in transporting Na⁺ across lipid membranes.
- Proton exchange for sodium, leading to acidosis and potassium loss.
- High intracellular sodium leads to secondary intracellular calcium overload.
- This leads to mitochondrial swelling, catecholamine release, and increased myocardial cell and diaphragm cell contractility.
- Finally, all of this leads to:
  - Early positive inotropy.
  - Later negative inotropy and contracture.
- Results include skeletal muscle and cardiac muscle dysfunction.
- Some renal and gastrointestinal effects.

**Signs**

- Vary slightly with species.
- Latent period varies with species and other host factors (age, diet, etc.) as well as dose ingested.
- Signs appear within 12 hours to up to 72 hours.
  - Anorexia, ataxia, diarrhea, sudden death-seen in most all species affected.
  - Sublethally affected animals may linger 8 days and recover.
  - Delayed deaths may occur long after the acute exposure and apparent recovery (cardiac fibrosis). Permanent cardiac damage is possible in sublethal cases.
  - Respiratory dyspnea.
  - Signs of general cardiovascular collapse, weakness, decreased exercise tolerance, cyanosis, recumbency and death.
  - Depression, ataxia, stiffness.
  - Shock.
  - Loose watery diarrhea - Colic in the horse (secondary floral changes/ rumenitis in cattle).
- Myoglobinuria - Sheep, swine and dogs.
- Renal tubular damage - Equine.
- Colic, sweating, sudden death, delayed deaths all seen in equine.
- EKG changes in the horse occur in some animals and may include marked S-T segment depression, atrial fibrillation, paroxysmal atrial tachycardia, and multiple ventricular extrasystoles of multifocal origin. Post-recovery EKG alterations may reflect cardiac fibrosis.
- EKG alterations in cattle in some cases include prolongation of Q-T interval and QRS complex, 1st degree heart block, occasional premature atrial beats, and increases in T wave amplitude.
- Death may occur during an acute toxic episode or weeks thereafter.

**Clinical Pathology**

- Hemoconcentration, shock - reflects cardiac - skeletal muscle damage.
- Calcium, sodium seldom altered.
- Elevated CPK, LDH, and AST.

**Lesions**

- Equine: Cardiac pathology (almost entirely).
  - Edema.
  - Pericardial and epicardial hemorrhages - generalized tigroid appearance to heart (pale streaking).
  - Sanguinous effusions in body cavities.
  - Histologic lesions of myocardial necrosis and secondary lesions associated with heart failure.
- Bovine: Similar to horse - cardiac pathology.
  - Rumenitis - mild.
  - Some skeletal muscle damage - myoglobinuria.
- Ovine: Mainly skeletal muscle lesions.
• Pale streaks in skeletal muscle; histologically evident skeletal muscle necrosis.
• Pulmonary edema.
• Few cardiac lesions.
• Diffuse gastrointestinal hemorrhages.
• Porcine: Mainly skeletal muscle lesions.
  • Bilateral, symmetrical, white dry areas of skeletal muscle.
  • Difficult to detect cardiac lesions in swine.
    When seen localized to left atrium only.
  • Severe myoglobinurias.
• Poultry:
  • Congestion of head, neck, liver, and lungs.
  • Sanguinous tracheal exudate.
  • Myocardial enlargement and pallor.
  • Hydropericardium.

 Diagnosis

• Appropriate signs and postmortem lesions, EKG abnormalities.
  History of exposure.
• Rice hulls are often used as a carrier for monensin, lasalocid, and other feed-additive ionophores. Feed microscopy can, therefore, help suggest whether ionophore assays of feed are likely to be of value.
  • Analysis of feed samples, stomach/rumen contents (many labs will not test for ionophore antibiotics).
  • Tissue samples (e.g., liver, kidney) not very effective for detecting poisoning: Half-life of monensin is too short.

 Treatment

• May be extended and involved.
• Poor prognosis if cardiac related signs are present due to possibility of permanent cardiac damage or just sudden death.
• Early cases: prevent further exposure, activated charcoal and a saline cathartic (if no diarrhea already present).
• Minimize stress.
• Life support - no specific antidote.
  • Fluids - large volumes for shock, bicarbonate as needed to correct acidosis.
  • Vitamin E/Selenium may help in swine perhaps in other species; more data needed.
  • Correct diagnosed cardiac irregularities if warranted. Avoid cardiac glycosides.
  • Routine treatment of rumenitis in cattle.
• Residue considerations.
  • Monensin does not accumulate in bovine tissues therefore no tolerance levels are set by FDA in this species - check with local officials.
  • Monensin is not cleared for use in egg laying birds.
  • Not used in dairy cattle.

 Differential Diagnosis

White muscle disease, white snakeroot poisoning, lasalocid toxicosis, Taxus spp.
Lasalocid
(Bovatec ®; Avatec ®)

Sources

- Polyether antibiotic, ionophore.
- Produced by *Streptomyces* fungi.
- Feed additive for cattle rations to improve feed efficiency and rate of gain.
- Approved for prevention of coccidiosis in sheep.
- Anticoccidial agent in poultry rations.
- Available forms: Bovatec ® 68 Medicated Premix (68 gm of lasalocid/lb of premix).
- One lb of premix is added to 2,000 lb of feed to produce feed containing 34 mg/lb of mixed feed.
- Avatec ® Medicated Premix.

Molecular structure of lasalocid

Toxicity

<table>
<thead>
<tr>
<th>Species</th>
<th>Acute LD50 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poultry</td>
<td>71.5</td>
</tr>
<tr>
<td>Mouse</td>
<td>146.0</td>
</tr>
<tr>
<td>Adult rat</td>
<td>122.0</td>
</tr>
<tr>
<td>Rabbit</td>
<td>40.0</td>
</tr>
<tr>
<td>Horse</td>
<td>21.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Species</th>
<th>Toxic Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cattle</td>
<td>A single oral dose of 100 - 125 mg/kg produced death in 6 - 10 days in 2 cattle.</td>
</tr>
<tr>
<td>Sheep</td>
<td>Toxic in a single oral dose of 12 mg/kg BW or 6 daily oral doses of 8 mg/kg BW.</td>
</tr>
<tr>
<td>Swine</td>
<td>Fed 58 mg/kg BW, death occurred in 1 day</td>
</tr>
<tr>
<td>Donkey</td>
<td>57.5 mg/kg caused death in 1 donkey. &quot;All donkeys&quot; given 47.5 mg/kg survived.</td>
</tr>
<tr>
<td>Canine</td>
<td>20 - 30 mg/kg (varies)</td>
</tr>
</tbody>
</table>

Mechanism of Action

- Believed to be due to ionophoric properties. Lasalocid transports monovalent cations preferentially and it also transports catecholamines.
- Ion selectivity: transports Ca⁺ > Mg⁺ (among divalent cations) and K⁺ > Na⁺ (among monovalent cations).

Absorption, Distribution, Metabolism and Excretion (ADME)

- See Monensin.
- Reduced lasalocid metabolism by chloramphenicol, an inhibitor of P450 enzymes was associated with delayed neurotoxicity in broilers.
Clinical Signs

- Similar to monensin.
- Cattle.
  - At a single oral dose of 10 - 25 mg/kg, cattle were anorectic for 3 days.
  - A single oral dose of 25 mg/kg resulted in depression and anorexia with diarrhea occurring from 2 - 5 days postdosing. At 50 mg/kg, slight muscular tremors in the flank were also noted starting 6 - 9 hours postdosing. In addition, animals had increased rates of respiration. Doses above this resulted in similar, though more severe, clinical signs. At 125 mg/kg, death occurred on day 10 (6).
- Horses.
  - Horses given over 18 mg/kg showed reduced activity, ataxia, paresis, and complete or partial anorexia. Clinical signs lasted 2 - 8 days in animals given sublethal doses (5).
- Swine.
  - Above 35 mg/kg has produced transient muscular weakness (1).
- Other species.
  - Not reported.
- Dogs experience paresis or paralysis with retention of the ability to wag the tail and move the eyes. In the late stages of the toxicosis, death results from apparent respiratory paralysis.

Clinical Pathology

- Cattle - Increased CPK, LDH, SD.
- Horses - Increased glucose, phosphorus, total bilirubin, LDH. Of these, total bilirubin is likely to be the most consistently observed abnormality.
- Other species - Not reported.

Lesions

- Equine - Congested lungs, hyperemic kidneys, petechial hemorrhages to epicardium.
- Cattle - Myocardial and skeletal muscle vacuolation; myocardial contraction bands.
- Sheep - Necrosis more severe in skeletal than cardiac muscle.
- Deer - Myocardial necrosis.
- Lesions in dogs were so mild as to be difficult to distinguish from normal.
- Other species - Not reported.

Diagnosis

- Rice hulls are often used as a carrier for lasalocid, monensin, and other feed-additive ionophores, as well as vitamin and mineral supplements. Therefore, feed microscopy can help suggest whether ionophore assays are likely to be of value.
- Suspect feed or rumen/stomach contents can be analyzed for lasalocid.
- Low tissue levels, like monensin. No withdrawal period needed for cattle, chickens, or sheep fed at recommended levels.

Treatment

- See Monensin. No specific antidote.
- Activated charcoal, intravenous fluids, supportive care.
Cotton (Gossypium spp.), Cottonseed, and Gossypol

Gossypol (Gossypium spp. - cotton plants) - Members of the Malvaceae.

Images

- Cotton, Gossypium spp. - Google Image Search. - To view this image in full size go to the IVIS website at www.ivis.org.

Sources

- Cottonseed, cottonseed meal, and cottonseed cake are high protein materials used in animal feeds. Cottonseed contains about 20% protein and 20% oil. The meal made from it contains about 40% protein and 7% or less oil. Cottonseeds contain a polyphenolic binaphthalene pigment called gossypol in the glands of the seeds which appear as tiny black spots. Most gossypol is removed during processing of the seeds. Several commercial processes have proven less than trustworthy in producing cottonseed meal of consistently low gossypol content.
- The toxic substance in cottonseed, gossypol, is present only in the pigment glands which are retained in the seed after decortication (hull removal). Pigment glands of this type are present only in cottonseed and a few closely related plants of the Malvaceae. The pigment glands contain approximately 50% gossypol, which accounts for 2 - 5% of the weight of the seed and is comprised of 3 isomeric forms. Gossypol is also associated with 2 other pigments, gossypurpurin and gossyverdurin; the latter being more toxic than gossypol itself and possibly responsible in part for the finding that gossypol content may not always account for the entire spectrum of effects occurring in cottonseed related toxicosis. The gossypol content of cottonseed varies considerably with the strain of cottonseed, the location in which it is grown, the particular climatic conditions that year, and on the extraction procedure.
- The pigment glands may be removed from the seed by flotation. Alternatively the gossypol may be inactivated by heating but this procedure results in binding of the gossypol to lysine which reduces the nutritive value of the protein present. The cellulose walls of the pigment glands are quite tough and although gossypol is soluble in a number of solvents and reactive with a variety of compounds, it is not extractable nor does it react in most milling or rolling processes unless the glands are first ruptured. This is accomplished by the addition of water which ruptures the seams of the seeds.
- With the traditional cottonseed-oil extraction, the seed is heated to relatively high temperatures for comparatively long periods of time before mechanical pressing to expel the oil. During this cooking, the majority of the pigment glands are ruptured and their contents released into the meal. Free (toxic) gossypol is inactivated (bound) to form a nontoxic molecule in time by reactions which occur in the meal spontaneously or during the milling process. The amount of free gossypol present in the meal is dependent upon the degree to which the glands have ruptured and the degree of subsequent inactivation of the gossypol.
- With care and attention to moisture content during cooking, commercial press extraction meals can attain a constant free gossypol average of near 0.02%.
- Delinted cottonseed, sometimes referred to as "delinted cotton" or "whole cotton", may be made by treating cottonseed with sulfuric acid. This treatment may impart a yellow color to the dark seeds. Delinted cottonseed is sometimes added to cattle diets.

Fate and Mechanisms of Action

- Gossypol is highly lipid soluble. Primarily eliminated via feces; minor amount leaves as a conjugate in the urine. In rats, gossypol is relatively slowly eliminated: 97% is eliminated in 19 days.
- Cottonseed meal associated impairment of growth and hypoprothrombinemia may be, in part, attributable to inhibition of protein synthesis. Anemia may result from the chelation of iron to gossypol. Gossypol also binds to proteins and amino acids rendering them unavailable during the digestive process. It has also been suggested that gossypol may interfere with oxidative processes and prevent the release of oxygen by hemoglobin.
- It is believed that the major effects of gossypol on the liver are secondary to heart failure.
- Undecorticated cottonseed meal or cottonseed cake contains up to 25% indigestible fiber which may cause trouble from intestinal impaction. Cottonseed meal is so low in vitamin A that a deficiency may occur in animals unless adequately supplemented. Cattle with blindness, ataxia, swollen joints and anorexia may sometimes respond to vitamin A.
- Gossypol has been demonstrated to inhibit testicular lactic dehydrogenase (LDH) enzymes via a competitive inhibition of a cofactor required for LDH activation. Gossypol has been investigated as a possible human male contraceptive agent.

\[
\text{LDH} \quad \text{Lactate} + \text{NAD}^+ \rightarrow \text{Pyruvate} + \text{NADH} + \text{H}^+ \\
\text{LDH function}
\]

- Gossypol accumulates in the liver and inhibits glutathione S-transferase (may therefore decrease detoxification of other xenobiotics).

**Toxicity**

The acute toxicity of gossypol is low with the LD50 being on the order of 5 gm/kg. However, the ingestion of small amounts over long periods of time leads to illness and death.

**Susceptible Species**

- The horse is relatively resistant, but, in general, monogastrics are usually readily poisoned.
- Dogs and swine are affected by gossypol and rabbits and guinea pigs are also quite sensitive.
- Ruminants are not usually very susceptible except young calves before the rumen is fully functional. In fact, adult ruminants have been known to consume significant quantities of cottonseed meal containing free gossypol without effect. The resistance of adult ruminants has been attributed to the binding of gossypol to soluble proteins in the rumen to form a nontoxic molecule which resists subsequent digestion. When young Holstein and Jersey calves were fed cottonseed meal from birth, the Holsteins were much more sensitive and the signs and lesions were similar to those occurring in swine.
- **Broiler Diets** - Tolerance to gossypol may be affected by age and strain of birds, level of dietary protein, iron salts, and alkaline materials. Lysine and methionine are the two amino acids that are most likely to be marginal in cottonseed meal (CSM)-containing broiler rations. Broiler performance is not affected by dietary-free gossypol levels up to 100 to 150 ppm (0.010 - 0.015%). Levels up to approximately 400 ppm (0.04%) may be fed successfully if ferrous sulfate is added at 1:1 iron to free gossypol weight ratio.
- Experimental results showed that laying hens could tolerate free gossypol at up to 440 mg/kg diet without any significant adverse effect on egg production, egg weight, feed intake, and feed conversion efficiency. Supplementation of diets containing free gossypol with FeSO4 did not improve egg production, egg weight, and feed conversion efficiency. Free gossypol at 140 mg/kg feed had no effect on color of egg yolk or egg white in fresh eggs but caused discoloration in eggs stored for 1 month or longer. FeSO4 at 120 or 240 mg/kg feed increased the tolerance to free gossypol to 280 mg/kg feed and slightly decreased the occurrence of discoloration in stored eggs.
- In hens rate of egg production, egg weight, interior egg quality and feed intake were not significantly depressed by diets with free gossypol up to 200 mg/kg. But more than 50 mg/kg produced an increasing number of objectionable olive-colored yolks. The addition of ferrous sulfate at iron:gossypol ratios 4:1 and 8:1 was fairly effective in eliminating the number of objectionable eggs when free gossypol concentrations were as high as 100 mg/kg, but iron was less effective at higher gossypol intakes.
- Chickens were fed diets containing different concentrations of free gossypol and iron sulfate for 17 days. In some trials, chickens were given gossypol 0 or 980 mg/kg diet and Fe at 1,000, 1,500, 2,000, or 3,000 mg/kg. It was concluded that growing chickens can tolerate free gossypol at up to 590 mg/kg without any significant adverse effect on body weight gain, feed intake or feed conversion efficiency. FeSO4 at 120 or 240 mg/kg feed increased the tolerance to free gossypol to 280 mg/kg feed and slightly decreased the occurrence of discoloration in stored eggs.
- **Layers** - Excessive gossypol has been shown to affect weight gain, feed intake and efficiency, mortality, egg production, weight, quality, and hatchability. Dark discoloration of egg yolks presents a serious economic problem and results from an interaction between gossypol and iron in the yolks. Actual egg production, however, is not affected by dietary-free gossypol at up to 200 ppm (0.02%). Dietary concentrations of free gossypol up to 40 to 50 ppm may be fed without consequential egg yolk discoloration. When higher levels of free gossypol are fed (up to 150 ppm), protection against yolk discoloration can be provided by supplementing with iron in a 4:1 weight ratio to gossypol.

**Signs**

- Gossypol has a cumulative effect. Poisoning usually appears abruptly, but signs tend to begin after the animals have been on cottonseed meal for 4 weeks to as much as a year.
Clinical signs in growing pigs receiving low concentrations of gossypol include inappetence, weight loss, and poor feed conversion. Larger amounts cause weakness, dyspnea, emaciation, generalized edema and death. Generally death occurs 2 - 6 days after the onset, but on occasion the signs may persist for a month before death. The most prominent signs in affected swine are respiratory and include dyspnea, gasping or thumping, and occasionally there may be froth or bloody froth at the mouth. The rate of gain is somewhat inconsistently affected. Emaciation and weakness may appear with other signs, but feed intake is sometimes maintained until shortly before death. Cyanosis may be noted immediately prior to death. Dogs very sensitive to antifertility effects. Antifertility effects in swine not determined. Some people become hypokalemic. Poultry, which are of intermediate sensitivity, develop weight loss, anorexia, decreased hatchability, discolored egg yolks and whites and abnormal texture of the egg whites. (See Susceptible Species section above.)

Lesions

Gross lesions consist of widespread congestion and edema, the result in significant measure of progressive congestive heart failure. Large quantities of straw-colored fluid are usually present in the peritoneal, pericardial, and thoracic cavities. The ventral body wall, lungs, kidneys, mesenteric l.n. and other organs are sometimes congested and/or swollen. The lungs are edematous and there is usually foam in the trachea and sometimes pneumonia is present. Irritation or ulceration of the gastrointestinal tract may occur when gossypol is present at high concentrations. The liver appears congested and may be somewhat degenerative, however, severe changes are often present histologically. In many lobules most hepatocytes are lost leaving a thin zone of intact cells in the periphery with replacement of the lost cells by hemorrhage. Areas of the skeletal muscle appear white and the heart is edematous, flabby, dilated, and on histologic section, areas of necrosis are present. In long standing cases, regenerative hypertrophy may be present.

Diagnosis and Differential Diagnoses

Quantification of free gossypol in the feed and characteristic lesions. Differentials - Hepatosis dietetica, mulberry heart disease (selenium deficiency), coal tar poisoning (phenolics), selenium toxicity, monensin, lasalocid poisoning.

Treatment

Management of gossypol toxicosis may be comprised of efforts to alleviate pulmonary edema and congestive heart failure. Withdrawal of cottonseed from the diet is indicated as is supplementation with vitamin A. If unaffected animals in the group are to continue on cottonseed containing diets, supplementation with vitamin A, iron, lysine and protein are recommended.

Prevention

The toxicity of gossypol may be almost completely neutralized by the addition of iron, in the form of ferrous sulfate to the diet at a rate of 1 part iron to 1 part gossypol. The relative efficacy of dietary iron in an effort to limit adverse effects of gossypol on poultry are discussed under Susceptible Species above. Nevertheless, for unspecified reasons, this method has not been widely accepted. At a consistent average gossypol concentration of 0.02%, swine rations may safely contain up to 25% cottonseed meal. Generally, for swine and poultry, the concentration of gossypol in the diet must be less than 0.01% to be safe. According to Kingsbury, a general rule, based on the usual concentration in commercial meal, is that cottonseed meal may be added to swine feeds at a level of 9% without danger. High protein intake is protective against the effects of gossypol. Deaths in swine were produced at a free gossypol concentration of 0.02% in the diet when the protein content of the ration was 15%; however, when the protein content of the ration was 30%, no deaths occurred even when the diet contained 0.03% gossypol.
### Additional Toxicants

<table>
<thead>
<tr>
<th>Specific Agents</th>
<th>Major Species</th>
<th>Usual Time of Onset</th>
<th>Usual Duration (if survives)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea and other non-protein nitrogen sources</td>
<td>(See Toxicants with Mixed Effects on the CNS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Xylazine</td>
<td>Most species</td>
<td>Minutes to hours</td>
<td>Hours; rarely lethal</td>
</tr>
<tr>
<td>Amitraz</td>
<td>(See Toxicants that Cause CNS Depression)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caffeine and other methylxanthines</td>
<td>(See Toxicants Associated with Central Nervous Stimulation or Seizures)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tricyclic Antidepressants</td>
<td>(See Toxicants with Mixed Effects on the Nervous System)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cocaine</td>
<td>(See Toxicants Associated with Stimulation or Seizures)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diphenamyl methyl sulfate (Diathal ®) and Anesthetics</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Blister Beetles</td>
<td>(See Toxicants that Affect the Kidneys)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclopiazonic acid (Mycotoxin) (rare)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Citreoviridin (Mycotoxin) (rare)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Moniliformin (Mycotoxin) (toxicoses may be rare, but further research seems to be warranted on potential occurrence)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Batrachotoxin in poison dart frogs</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

- Blister Beetles (See Toxicants that Affect the Kidneys)
- Urea (See Toxicants with Mixed Effects on the CNS)
- Tricyclic Antidepressants (See Toxicants with Mixed Effects on the Nervous System)
- Cocaine (See Toxicants Associated with Stimulation or Seizures)
- Diphenamyl methyl sulfate (Diathal ®) and Anesthetics
- Cyclopiazonic acid (Mycotoxin) (Unlikely)
- Citreoviridin (Mycotoxin) (Unlikely)
- Moniliformin (Mycotoxin)
- Amitraz (See Toxicants that Cause CNS Depression)
- Xylazine (See Diagnosis and Management Section, under Emetics)

### References

**Cyanide**


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