Lead Toxicosis
(Plumbism)

<table>
<thead>
<tr>
<th>Major Species</th>
<th>Usual Time of Onset</th>
<th>Usual Duration (if survives)</th>
<th>Full Table for Toxicants with Mixed Effects on the Central Nervous System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most species, esp. dogs, horses, cattle, waterfowl.</td>
<td>Hours to months (pty)</td>
<td>Days to permanent damage; often lethal (pty)</td>
<td></td>
</tr>
<tr>
<td>Swine resistant.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Sources Usually Involved With Small Animals

- Lead paint, especially paint chips lost during remodelling. Lead is still commonly found in some artist's paints.
- Lead objects, esp. a concern with psittacine birds, dogs:
  - Toys, drapery weights, sinkers, solder, foil from top of wine bottles.
- Plumbing materials.
- Lead shot in tissues (usually does not cause lead toxicosis).
- Tile, linoleum.
- Improperly glazed bowls.
- Leaded gasoline (contains the organolead compound, tetraethyl lead, which is highly absorbed by all routes). Also burning of tetraethyl lead produces particulate lead in the exhaust of engines burning regular [leaded] gasoline. Leaded gasoline was banned years ago in the U.S.A., however, it is still in use in some countries.
- Soil near roads and urban buildings.
- Soil near lead smelters.
- Absorption of lead from soil presumably follows ingestion associated with grooming.

Sources Usually Involved With Large Animals

- Batteries in pastures, broken in feed mixers, etc.
- Roofing felt.
- Motor oil from engines that burn regular gasoline (no longer a likely source in the USA).
- Grease if it contains lead.
- Lead paint (licked from the walls of barns, in paint cans, etc.).
Lead smelters-effluent onto forage; also, some uptake by plants.
Lead mine tailings.
Note: With lead arsenate pesticides; signs and lesions of poisoning relate much more to arsenic than to lead.

Sources Water Fowl

Consumption of lead shot or lead sinkers.
Lead shot was recently banned for waterfowl but is still used for upland game. Lead shot availability to waterfowl via sediments depends in large measure on the nature of the substrate and the tendency for the pellets to penetrate into the deeper layers.

Susceptibility

Young more susceptible: absorb greater fraction of ingested amount.
Dogs, horses, cattle, and waterfowl are all poisoned comparatively often.
Horses may be even more sensitive than cattle.
Cats are probably of intermediate sensitivity but are infrequently poisoned.
Sheep are probably of intermediate sensitivity.
Swine, goats, and chickens are comparatively tolerant.

Toxicity

Toxicosis is usually due to acute exposure, but can result from repeated exposure with a gradually increased buildup of lead in the body.
Acute single lethal dose of lead ranged from 400 - 600 mg/kg in calves and 600 - 800 mg/kg in adults. Lead is toxic at 6 - 7 mg/kg when eaten daily by cattle.
Ingestion of 1 - 3 lead shotgun pellets can be lethal to waterfowl. Lead shot tends to remain in gizzard.

Absorption, Distribution, Metabolism and Excretion (ADME)

Most common route of exposure is oral ingestion of lead. However, inhaled lead particles are cleared by mucociliary action and then swallowed.
A small amount (1 - 2%) of the lead ingested is absorbed. Most of the remainder is excreted in feces as insoluble lead complexes.
A greater degree of absorption occurs in the young, especially when calcium deficient.
Absorption depends in part on the surface area, therefore finely divided lead as occurs in used motor oil is more toxic.
Lead crosses the placenta and can enter milk.
In cattle, ingested objects containing lead may settle and be retained in reticulum allowing absorption of lead over an extended period of time.
Inorganic lead is not absorbed through intact skin, but tetraethyl lead, as in regular (leaded) gasoline is readily absorbed.
Lead is slowly excreted in untreated animals; and is excreted predominately via the bile. Enterohepatic circulation not known. Urine excretion is minimal unless chelation therapy is administered.

Mechanisms and Clinical Pathologic Effects

Lead affects multiple tissues, especially the gastrointestinal tract and nervous system.
Interferes with thiol (-SH containing) enzymes.
Lead may replace zinc in some enzymes.
Cerebral edema and neuronal damage centrally, demyelination and reduced nerve conduction velocity peripherally.
At very high concentrations, lead may interfere with GABA mediation by lowering GABA concentrations at inhibitory interneuron junctions in the CNS.
At high concentrations inhibits these inhibitory interneurons.
Lead can cause anemia:
Increased red cell fragility.
Depression of bone marrow (several enzymes are affected).
Interferes with function of delta aminolevulinic acid (ALA) dehydratase (an enzyme functioning in heme synthesis), therefore, a large increase is seen in delta-ALA in the plasma and urine of lead poisoned animals. Other heavy metals, e.g., Zn, Cu, Hg, also depress this activity in circulating blood but not to the same degree as lead. Alcohol and possibly ethylene glycol can also depress this activity.
Lead also interferes with the incorporation of iron into the heme molecule via inhibition of heme synthetase. Therefore, one sees an increase in protoporphyrin.
- Inhibition of the enzyme nucleotidase is thought to be responsible for basophilic stippling and increased fragility of RBCs.
- Zinc protoporphyrin increases in lead poisoning. Apparently, the failure of heme synthetase to insert iron atoms leaves protoporphyrin free to chelate endogenous zinc atoms. This indicates a chronic metabolic effect of lead on newly produced RBCs. Zinc protoporphyrin will generally remain normal for first 1 - 2 weeks following lead exposure.
- With chronic or subchronic toxicosis may see nucleated red blood cells and increased numbers of cells with basophilic stippling present. This occurs most often in dogs and is often present in the face of normal or only slightly reduced red blood cell counts and hemoglobin concentrations. Basophilic stippling can be normal in ruminants and is therefore not considered to be a diagnostic feature.

**Mechanism of Action not completely understood**

**Signs**

- **Neurologic effects.**
  - Nervous system signs often predominate.
  - Blindness. Swelling of optic disk. Iridocyclitis.
  - EEGs indicative of increased irritability.
- Hysteria, chomping, seizures, muscle spasms, opisthotonus.
- Retardation in children, sometimes animals.
- Circling.
- Pushing against objects (head pressing).
- Ataxia.
- Cattle - rhythmic bobbing of the head, twitching of the ears, exaggerated blinking, fine muscle tremors, marked excitation or seizures (bad prognostic sign).
- Segmental demyelination interferes with nerve impulse conductance in peripheral nerves. Signs of peripheral nerve involvement are associated with chronic lead poisoning, can be important, especially in the horse. Motor nerves primarily affected with little sensory perception loss. Horse:
  - Paresis of lower lip, laryngeal paresis, pharyngeal paresis, and rectal sphincter paresis.
  - Regurgitation of water from nose when horse drinks.
- **Gastrointestinal tract.**
  - Mucosal damage, abdominal distress, tucked abdomen.
  - Anorexia, vomiting.
  - Constipation, then diarrhea, colic.
  - Cattle - rumen motility reduced or abolished, grinding of teeth.
- **Respiratory.**
  - Inspiratory dyspnea in horses occurs due to paralysis of recurrent laryngeal nerve, "roarers".
  - Death can occur from respiratory paralysis during convulsions.
- **Immune system.**
  - Somewhat immunosuppressive, even with amounts in the body insufficient to cause clinical effects.
- **Reproductive.**
  - Crosses placenta and affects fetus: can cause abortion, resorption, and sterility.
  - Some in milk, increased tendency of young animals (and people) to absorb lead.
- **Psittacine birds.**
  - Clinical signs often vague. Nonspecific gastrointestinal, renal, and neurologic dysfunction. Often acute onset.
  - Depression, weakness, anorexia, regurgitation, polyuria, greenish-black diarrhea, ataxia, headtift, blindness, circling, and convulsion have been reported.
  - Suspect if hemoglobinuria and CNS abnormalities are present.
- **Waterfowl signs.**
  - Clinical signs of toxicosis in wildlife are frequently not observed.
  - Animals are not provided with a sheltered existence and human monitoring.
  - Generally just see decreased numbers in an affected population.
  - May have increased predation, starvation, etc., in a sublethally poisoned population of waterfowl.

**Lesions**

- Lead objects, paint, or used motor oil in the gastrointestinal tract in some cases.
- Mild gastritis or enteritis.
- Esophageal dilatation in some dogs.
- Pale liver, possible to see evidence of centrilobular degeneration. May have acid-fast intranuclear inclusions in hepatocytes.
- Muscle may also be pale.
- Kidneys may be acutely hyperemic or hemorrhagic; with chronic toxicosis possible to see fibrosis. Do not rule out lead toxicosis because of the absence of renal lesions. Degeneration and necrosis and sometimes prominent, acid-fast intranuclear inclusions may occur in the renal tubular epithelial cells. It can cause a degree of renal failure, although this is not usually a primary finding.
- May see edema, swelling, increased prominence of vessels in the brain.
- Capillary damage in the CNS. Collapse of small arterioles.

**Diagnosis**

**Antemortem**

- Blood lead (whole blood: heparinized or EDTA tubes).
  - 0.6 ppm or greater is diagnostic (often 1 to 1.2 ppm).
  - 0.35 ppm or greater with signs and especially with confirmatory tests (such as delta ALA or fecal lead) is also diagnostic.
  - Lead is carried on the red cell, 90% of circulating lead is bound to erythrocytes. Therefore, serum lead is **not** routinely used and is not readily interpretable.
  - Blood lead concentrations are a valuable indicator of exposure but they do not indicate the length of exposure or total amount of lead deposited in the body. They do not correlate extremely well with the severity of clinical signs.
  - In chronic exposures (man), there can be a high percentage (approximately 30%) of false negatives.
Nucleated RBCs or basophilic stippling (in dogs, cat, horse) is suggestive but, if not present, does not rule out lead toxicosis.

X-ray abdomen or reticulum of ruminants when possible.
- Positive findings can help to rule in, negative X-ray findings do not rule out lead poisoning.
- X-ray epiphyseal plate.
- Infrequently see lead line, even in lead poisoned dogs.

Serum ALA dehydratase inhibition and erythrocyte protoporphyrin assays are highly sensitive tests for exposure to, and an indication of a possible effect of lead. They are not a substitute for blood lead assay which confirms the presence of the metal as a specific cause.

Urine increase in delta ALA. Not as reliable as serum ALA dehydratase activity.

Hair: shedding in animals decreases the value of lead analysis and hair is not as good an indicator of chronic exposure as in man.

Fecal lead: 35 ppm is suspect.

**Postmortem**

- Liver and kidney. Renal cortex more reliable to assay than liver because kidney stores more lead.
  - 1 - 10 ppm; usually when see 10 ppm call conclusive toxicosis, with other supportive findings present, toxicologists may consider somewhat lower concentrations to be diagnostic.
- Characteristic lesions.

**Differential Diagnosis**

- Dog, cat: rabies, distemper, hepatitis, other heavy metal toxicoses.

  | Ruminants | major DDx: | rabies, poliencephalomalacia, TEME, listeriosis. |
  | minor DDx: | hypomagnesemic tetany, nervous ketosis, hypovitaminosis A, nervous coccidiosis, mercury poisoning, meningitis, encephalitis, hepatoencephalopathy, organic insecticide poisoning. |

**Treatment**

- Locate source and prevent further exposure.
- Remove remaining lead from digestive tract.
  - Saline cathartic.
    - Sodium sulfate or magnesium sulfate (0.5 mg/kg in a 10% solution in H2O PO or by stomach tube).
    - Promotes evacuation, plus insoluble (poorly absorbable) lead sulfate is formed.
    - Gastric lavage (infrequently needed).
  - Surgery to remove large objects, particularly those not progressing through the GI tract.
    - X-ray to be sure removal was complete.
    - Rarely necessary to remove lead shot from tissue after gunshot, but if it is associated with high blood lead and clinical signs, and if other exposure has not occurred, removal may be needed.
  - Ingested lead paint or lead in motor oil, etc., is usually not evident on x-rays.
  - Flush and siphon lead pellets from gizzard or feed large amount of grit to expel pellets. Make sure proventriculus is not impacted.
  - Removal of lead sinkers from the digestive tract may be essential for survival of large waterfowl such as swans.
  - Some avian practitioners recommend feeding peanut butter in baby cereal to provide lubrication to aid in passage of lead foreign bodies.
  - Chelation therapy.
    - Chelation: Binding in a nonionized, soluble complex (a chelate) that is excretable in the urine.
    - Orally administered chelation agents may enhance absorption of metals when present at elevated concentrations in the GI tract. They are, therefore, used (by this route) only after the metal has left the digestive tract.
    - CaEDTA = Ca disodium EDTA = Ca disodium ethylene diamine tetraacetate = Ca disodium versenate. Must use calcium EDTA: Na EDTA chelates calcium and, therefore, high doses can cause hypocalcemia.
    - Since CaEDTA can cause gastrointestinal and renal toxicosis, it is used judiciously in courses of therapy.
    - Clinical signs of experimentally induced CaEDTA toxicosis include anorexia, depression, diarrhea, and vomiting. Pathologic changes include intestinal congestion and hemorrhage, necrosis of the intestinal epithelium. Toxicity may be related to chelation of trace elements.
      - **Note:** These clinical signs are similar to those reported for lead toxicosis in dog. Although less notable than in human patients, dogs and cattle may also experience necrotizing nephrosis in the proximal renal tubules, despite a normal BUN and creatinine. When present, renal signs tend to occur after the onset of gastrointestinal effects.
      - Zinc supplementation may reduce the gastrointestinal upset associated with CaEDTA therapy.
      - EDTA only slowly diffuses into the CNS. Does not penetrate red blood cells. Increases Pb excretion 20 - 50X. **Occasionally increases signs**, therefore, with severe toxicosis use BAL (British Anti-Lewisite, also called dimercaprol) first, then EDTA.
During second or subsequent courses of CaEDTA, it is a good idea to monitor urine Pb before and after CaEDTA to determine whether a large increase in urine lead occurs. If this occurs, it suggests that the lead may still be present at high concentrations in the tissues and therapy may need to be continued.

BAL removes lead directly from parenchymatous organs.

BAL - Reaches brain, recommended for small animals where severe CNS signs are present. Occasionally painful (is administered IM in oil).

BAL increases Pb excretion in urine, and especially via the bile, and removes Pb from red blood cells.

DMPS (2,3-dimercapto-1-propanesulfonic acid sodium salt) and DMSA mesodimercapto- succinic acid - Succimer® - a structural analog of BAL, show considerable promise as chelation agent. DMSA is available as a human product in 30 mg capsules. It is used in pet birds at 25 - 35 mg/kg PO BID 5 days a week for 3 - 5 weeks. DMSA appears to be a more rapid and effective chelator of lead, in birds, than Ca EDTA and is also less toxic (10).

Penicillamine is an orally administered chelation agent.

Penicillamine is sometimes used to follow up in-patient treatment as a home medication. One-week course or 2-week-long courses of penicillamine therapy separated by 1 week of rest.

In dogs, penicillamine is given at 10 - 15 mg/kg BID up to 55 mg/kg BID for 1 week or for 2 weeks (separated by 1 week interval). The drug should be given orally on an empty stomach. To minimize side effects such as anorexia, listlessness, and vomiting, the daily dose can be divided and given TID to QID. It should not be given to small animals with signs of vomiting, depression, anorexia, or marked neurological disorders. It is contraindicated when lead is still present in the gastrointestinal tract.

Penicillamine is often recommended in stubborn cases, where elevated blood lead persists.

Prior to metabolism, lead in tetraethyl lead (organic lead) is nonionic and therefore not accessible to chelation therapy.

Chelation Therapy Dosage Regimens.

Horse/cattle - CaEDTA (6.6% solution) at 0.5 ml/lb (73 mg CaEDTA/kg) using slow IV administration in divided doses 2 - 3 times per day for 3 - 5 days. If necessary to treat more than 5 days (based on clinical signs, urine lead), a 2-day rest period is provided before the second 5-day course of therapy.

Dog - CaEDTA at 100 mg/kg for 2 - 5 days. The daily dose is divided into four portions, administered SC after dilution to a concentration of 10 mg CaEDTA/ml of a 5% dextrose solution. Clinical improvement can occur in 24 - 48 hours. Do not exceed 5 days of continuous therapy or 2 grams as a single day's total dose because of potential nephrotoxicosis.

Psittacine birds - CaEDTA at 35 - 40 mg/kg undiluted IM twice daily for 5 days. Do not exceed 5 days of continuous therapy. Second course of therapy, if needed, is given after a 5 - 7 day waiting period. Seizures controlled with diazepam 0.5 - 1 mg/kg IM BID to TID as needed.

See DMSA above.

Thiamine.

Helps symptomatology, best documented in cattle. Given to cattle at 250 - 1000 mg (total dose) BID for 5 days.

Does not influence excretion - not a chelation agent.

Seizure control.

Barbiturates (prefer phenobarbital) or diazepam are recommended for seizures when present.

Cattle - phenobarbital up to 30 mg/kg IV (to effect) or chloral hydrate 50 - 70 mg/kg IV as a 5 - 7% solution.

Cerebral edema.

Dexamethasone (cattle, horse, 0.1 mg/kg IV, SC, or IM; dog, 1 - 2 mg/kg SC, IM, or IV) and/or mannitol (20% solution, 1 - 2 gm/kg slow IV) may be indicated for the treatment of cerebral edema, although based on speculation.

Since lead may be immunosuppressive, broad-spectrum antibiotics may be indicated to control secondary bacterial infections.

Prevention

Avoiding exposure is essential.

Clean up of contaminated soils sometimes can be followed by extraction and recycling of lead.

Immobilizing lead in soil with Ca(H2PO4) is somewhat effective, but this treatment tends to mobilize arsenic in the soil.

Adding organic material in soil tends to increase its ability to bind metals, including lead. The increase in binding capacity is limited because the organic material will tend to be degraded over time in the environment.

Altering the pH (alkalinizing) is another method being studied in efforts to immobilize lead in soil.

Key Features

Sources include paint (leaded), used motor oil, storage batteries, lead objects, lead shot, linoleum, etc.

Mixture of gastrointestinal (colic) effects and CNS (mixed signs), sometimes with effects on red blood cells.

Rare in cats; almost unheard of in swine.

Common in dogs and cattle, occasionally encountered in horses.

Dogs tend to experience the syndrome over several days.

Cattle may have sudden deaths after a rapid, brief course, or sometimes a prolonged toxicosis.
• Treatment.
  • Sulfate cathartic for precipitation in digestive tract; steps to remove objects.
  • Calcium EDTA, BAL, penicillamine.
  • Thiamine.
  • Control seizures if present.
  • Control secondary infections if present.

DIMERCAPROL
British Antilewisite (BAL)
(2,3-Dimercapto-1-propanol)

Lead Mono-BAL Complex
(Nonpolar)

PENICILLAMINE
D-Isomer is the Natural Form. Penicillamine is the Most Characteristic Degradation Product of Penicillin Antibiotics.

CALCIUM DISODIUM EDTATE
(Calcium Disodium Versenate) Metal Replaces Calcium
Mercury

Mercury is a growing concern in the environment. Mercury may be encountered as:

- Elemental mercury (Hg\(^0\); in the form of metallic mercury or Hg\(^0\) vapor).
- Mercury salts (also called inorganic mercury) such as mercuric chloride, mercuric oxide, etc.
- Organomercurial compounds (includes alkyl forms such as ethyl, methyl, propyl, dimethyl, etc., and aryl forms of mercury, such as phenylmercuric acetate).
- Mercury metal Hg\(^0\).
  - Liquid, volatile (many other mercury compounds are somewhat volatile as well).
  - Mercury circulates in the environment. Because of its volatility the earth continuously "degasses" mercury.
  - Thermometers.
  - Barometers.
  - Dental amalgum used for fillings.
  - Produced from other forms of mercury in aquatic sediments of the environment, but only under anaerobic conditions as sometimes occurs in aquatic sediments. Hg\(^0\) is not the major form in sediments.
  - A major source of mercury in the biosphere is mercury vapor produced by burning coal (and to a much lesser extent, other fossil fuels).
  - Metallic mercury is sometimes used in crude gold mining techniques employed in developing countries such as those surrounding the upper tributaries of the Amazon River. This use directly contaminates the local streams and the atmosphere.
- Mercury in manufactured formulations (several compounds; inorganic and organic). As compared to aryl organic mercury compounds, alkyl organics such as methyl or ethyl mercury tend to be more toxic, especially after repeated exposure. Inorganic mercury salts include monovalent mercurous compounds and divalent mercuric compounds.
  - Mildew proof or antifouling paints such as some types used on boat bottoms.
  - Batteries (some small batteries are high in mercury).
  - Fungicides (some are inorganic, many are organic compounds).
  - Fungicide treated seed grains used in feeds.
  - Highly toxic mercurial fungicides have been largely replaced by far less toxic nonmercurial or phenylmercurial fungicides.
- Mercury-containing medications.
  - Mercurial diuretics are similar in toxicity to mercury salts and are no longer used appreciably.
  - Phenylmercuric acetate--sometimes used in dermatology--topical application.
- Sewage sludge may be very high in mercury in some instances.
- Mercury in living organisms.
  - Methyl mercury and, to a lesser extent, ethyl mercury are primary concerns with regard to environmental forms of mercury. All forms of mercury are converted to these by anaerobic bacteria. Methyl mercury is the principle tissue residue form in eggs, regardless of the mercury compound ingested by a bird.
  - Aquatic organisms accumulate methyl mercury from polluted watersheds, bays, etc.
  - Methyl mercury can accumulate in eggs and animal tissues.
  - Dimethyl mercury is also produced in sediments. Like metallic mercury, dimethyl mercury is somewhat volatile and may therefore leave the aquatic ecosystem.

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

- Metallic mercury is fairly low in toxicity when ingested because of fairly low absorption, but poisoning can result if a sufficient amount is ingested (0.01% is absorbed through the GI tract) or when embedded in tissues (be careful not to break thermometers). Laboratory toxicoses are possible from inhalation of much more highly toxic, volatilized metallic mercury. Persons should avoid home-made barometers, etc. Goldminers in South America that burn off metallic mercury used in trapping the gold particles have experienced acute lung and kidney damage.
- Inorganic mercury compounds are absorbed from the lungs, but poorly through the skin and GI tract (7 - 15% absorption); mercury
salts can also bind to gut mucosa. Residues in liver, kidney, and plasma (50% is bound to albumin).

- Toxic dose inorganic mercury in horse is 8 - 10 grams. Chronic toxicity can be produced by ingestion of 0.4 mg/kg/day over a several- week period of time.

- Organic mercurials are absorbed via all routes including dermal.

- Alkyl mercury compounds (noncyclic, saturated hydrocarbon compounds) i.e., methyl and ethyl mercury are the most toxic forms of mercury. These compounds initially bind to erythrocytes, become distributed throughout body, and eventually bioaccumulate primarily in brain and to some extent in kidney and muscles. Methyl mercury has a high affinity for the brain and is attached to red blood cells (not much in plasma, therefore, only a small amount is available for hepatic excretion). Methyl mercury is present in eggs when other forms of mercury are ingested.

- Aryl mercurials such as phenyl mercury compounds are slightly less toxic than alkyl mercury compounds on a single dose basis and considerably less prone to bioaccumulate because of catabolism in the liver to free mercury ion with its subsequent excretion via the kidney and large intestine. Aryl mercurials tend to be somewhat less absorbable via the skin, such that some are used in topical medications.
  - Half-life of methyl mercury in cats in one study was reported as = 70 - 74 days.
  - Half-life of mercury in cats was reported in another study as 39 days.
  - Half-life of mercuric compounds is 60 days in man.
  - Half-life of methyl-mercury in humans is estimated at 44 days.

- Elimination - Inorganic Hg is eliminated primarily via the urine; organic mercury is eliminated mainly via the bile and feces, less than 10% appears in the urine.

  Note: Marine mammals and some other marine organisms may have extraordinarily high mercury concentrations. This is possible primarily because of formation of insoluble, 1:1 complexes of mercury and selenium intracellularly.

**Mechanism**

- Sulfhydryl groups of enzymes and other proteins are affected (bound to mercury). Hg readily forms covalent bonds with sulfur. Hg replaces H₂ (Note: 2 atoms) to form mercaptides: X-Hg-SR and Hg(SR)₂ (where R = a protein and S = an electronegative radical).

- Associated epithelial and neuron damage may explain some of the problems.
  - Gastrointestinal mucosal damage.
  - Skin lesions.
  - Renal tubular damage (especially with inorganic mercury).
  - Vascular and neuronal damage in the brain (especially with methyl mercury).
  - Blood-brain barrier can be disrupted with less than 1.0 ppm Hg ions in the brain.

- Both methyl mercury and Hg⁺⁺ can disrupt ion exchange across both voltage-gated and ligand-gated channels.

- Mercury may irreversibly inhibit voltage-gated K⁺ outcurrent in the early developing nervous system. This may help explain neurologic teratogenicity.

- Methyl mercury-induced neurotoxicity is believed to be the result of an increase in reactive oxygen species caused by a disruption of the mitochondrial electron transport chain. This increase in free radicals in turn depletes glutathione and mediates neuronal injury.

- Methyl mercury also inhibits ATP production and release of Ca⁺⁺ from mitochondria, resulting increased intracellular Ca⁺⁺ concentration, which leads to spontaneous depolarization and release of acetylcholine.

- Methyl mercury decreases uptake of choline by nerve terminals, so there is decreased synthesis of acetylcholine.

- In vitro, methyl mercury has been shown to disrupt microtubule assembly and cellular migration.

**Signs**

- Onset is usually after a period of several days or longer postexposure, although a more acute onset is possible. An acute syndrome can be seen with mercuric compounds due to the corrosive effects on the GI mucosa with resultant fluid and electrolyte loss.

- Neurologic, GI, renal, dermal effects.

**Cattle.**
- Stomatitis, salivation, loose teeth, gastroenteritis.
- Nasal discharge, bronchopneumonia, dyspnea.
- Dermatitis, pustules, skin ulceration, depilation, hyperkeratinization.
- Weakness, anorexia, emaciation, prostration, low total protein, low globulin, proteinuria (in severely affected).
- CNS depression, ataxia, stumbling, hyperesthesia, convulsions (rare).
- Epistaxis, hematuria, bloody feces, nonregenerative anemia.
- High fever, severe skin lesions, hemorrhage all give poor prognosis.

**Swine** - more commonly poisoned with Hg.
- Anorexia, weight loss, constipation, poor growth.
- Weakness, flaccid abdominal muscles.
- Gagging, vomiting.
- Fever.
- Thickened, scaly skin.
- Cyanosis.
- Blindness.
- Abnormal posture, staggering, stiffness, disorientation.
- Depression, tremors, paresis, paddling, coma.
- Excitation, chewing, but without prehension of food.
- Death often within 2 - 3 days of onset of major neurologic signs.
- At high doses: Gastrointestinal upset, tachycardia, CNS depression, cyanosis, hypothermia, dyspnea, coma and death within 1 day.

**Feline.**
- Sensitive to environmental mercury (especially methyl mercury in seafood); sentry of environmental/food contamination for humans.
- Paresis, rear leg rigidity, knuckling over at the carpus and/or tarsus, hypermetria, cerebellar ataxia, tremors, hypersalivation, sensory impairment, tonic-clonic, convulsions.
- Blindness, persistent vocalizing, paddling, coma, hyperthermia.
- Weakness, lateral recumbency.
- Vomiting, diarrhea.
- Skin pustules.
- Death.
- Cerebellar hypoplasia (mimics panleukopenia) and other teratogenic effects in kittens, deaths prior to 3 months of age.

**Birds.**
- Reduced hatchability, eggs without shells.

**General.**
- Pulmonary damage and associated clinical signs may predominate in cases of inhalation of toxic amounts of Hg°.

**Lesions**
- Renal: pale swollen kidneys; renal tubular damage especially affecting the proximal tubular epithelium (P3 segment); glomerulonephritis is possible with chronic exposure due to the antigen-antibody complex deposition.
- Hepatic: liver is pale and reduced in size; microscopic examination may reveal hydropic change.
- Digestive tract: possible necrotic pharyngitis, focal erosive or ulcerative gastritis; necrotic enteritis and typhlitis.
- Brain: no grossly evident brain lesions.
  - Cerebral precapillary arterioles exhibit fibrinoid degeneration especially in swine and cattle.
  - Cerebral laminar necrosis and myelin loss.
  - Cerebral granular layer atrophy and atrophy of calcarine and central cortices in cats; cerebellar hypoplasia and other teratogenic effects, poor survival in kittens.
- Peripheral nerves: myelin and axonal damage.
- Inhalation of mercury vapor may produce an acute, corrosive bronchitis and interstitial pneumonia.

**Diagnosis**
- Kidney (especially cortex) Hg usually 10 - 15 ppm or more. With time, Hg may decrease to a few ppm. Submit cortex and medulla.
- Much lower concentrations of mercury were associated with severe experimental methyl mercury poisoning in cats.
- Liver and brain are also worth analyzing for mercury (in addition to kidney).
- Gross and histologic lesions (send fixed specimens also).
- Test blood, plasma and urine antemortem, though false negatives are possible in urine as excretion is concentration and time dependent.
- Differential diagnoses: lead, thallium, phenylarsonic feed additive, and ethylene glycol toxicosis, encephalitis, polioencephalomalacia, hog cholera, and erysipelas.

**Treatment**
- Neurologic damage may be permanent (give appropriate prognosis before owner decides to treat).
- Keep in mind that meat from livestock can be a hazardous source of mercury for humans.
- Acute oral exposures:
  - Feed egg then use an emetic if not contraindicated.
  - Activated charcoal and saline cathartic.
  - Sodium thiosulfate orally also safe to bind Hg.
  - Cattle 30 grams orally in a 10% solution.
  - Scarlet Drench Powder, 10% sodium thiosulfate solution.
• **Seizures:**
  - Diazepam (0.2 - 2.0 mg/kg, IV, to effect) (dogs) or barbiturates (e.g., phenobarbital or, if it fails, pentobarbital) (most species).
  - Fluids and electrolytes for corrosive GI syndrome.
  - Support renal function.

• **Any acute mercury toxicosis:**
  - **Chelation therapy** in general is not very effective with the organic Hg compounds as only a small fraction is in the plasma and available for excretion.
  - D-penicillamine (15 - 50 mg/kg) orally, but only after gut is free of significant ingested mercury and only if renal function is present, otherwise is dangerous.
  - BAL British Antilewisite (dimercaprol) is not very effective after chronic exposure to organic mercurial compounds. It is contraindicated with organic mercurials as it will increase the brain concentration. BAL also contraindicated with preexistent liver or kidney damage.
    - BAL (in oil) injections may still be recommended for more acutely poisoned small animals (with inorganic mercury sources) although its efficacy is not well documented.
    - BAL - reportedly not highly effective in large animals or humans.
    - Nevertheless, the recommended dose for cattle is 3 mg/kg QID for 3 days, then BID for 10 days; for horses, 3 mg/kg every 4 hours for the first two days, QID on third day, BID for next 10 days (until recovery is complete).
    - When using BAL, it is recommended that one should alkalize the urine - helps maintain BAL mercury complex which may otherwise dissociate in acid urine and thereby damage renal tubules.
  - **DMSA and DMPS.** Mesodimercaptosuccinic acid (DMSA) and dimercaptopropane sulfonate (DMSA) are water-soluble analogs of BAL which are less toxic and have greater water solubility than BAL but have limited lipid solubility. They are effective when given orally. DMSA is preferred.
    - **Methyl Hg.** The methyl Hg content of kidney, brain, and liver in mice and guinea pigs was reduced with DMSA (DMPS was less effective in kidney, liver, and it was not effective in brain).
    - DMSA (e.g., Succimer®) was 4 times more effective than N-acetylpenicillamine in increasing urinary excretion of MeHg.
    - In the dog, the most effective method of mobilizing and excreting MeHg was extracorporeal complexing hemodialysis with DMSA. DMSA may confer a sulfur odor to the breath and urine.
    - With inorganic mercurials, DMSA > BAL > DMPS at increasing urinary excretion.

**Key Features**

• Fungicides, thermometers, barometers, antifouling paints, small batteries, mercury medication and methyl mercury in aquatic organisms from pollution.
  - GI, renal, dermal and CNS effects.
  - Diagnose by blood and urine Hg antemortem; and renal, brain, liver Hg concentrations and lesions (uncluding histo) postmortem.
  - Sodium thiosulfate, D-penicillamine, BAL, or especially DMSA supportive.
  - Relay toxicosis to man well documented from consumption of poisoned swine.

---

**Organotin Compounds**

<table>
<thead>
<tr>
<th>Major Species</th>
<th>Usual Time of Onset</th>
<th>Usual Duration (if survives)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All species</td>
<td>Hours to weeks</td>
<td>Days to permanent damage; potentially lethal</td>
</tr>
</tbody>
</table>

**Sources**

Some wood preservatives, antifouling marine paints, slime-control products used in paper mills, and various antifungal products have contained organotin compounds. Most such products have been withdrawn from the marketplace. Containers of the products may still be available. Also, wetland areas may contain persistent residues.

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

• Topical exposure and ingestion of organotin compounds may lead to toxicosis.
  - **Note:** Metallic tin is poorly absorbed and therefore low in toxicity.
  - The organotin compounds, trimethyl and triethyl tin, readily penetrate the nervous system.
Mechanism of Actions

- Organotins inhibit oxidative phosphorylation and the Na⁺/K⁺ pump. Some act by interfering with sulfhydryl groups of mitochondrial enzymes.
- Short-chain trialkyltins (trimethyl and triethyl tins) are neurotoxic:
  - Dialkyltins are hepatotoxic:
    - Cholangitis occurs in species with a common bile duct and pancreatic duct.
    - Tributyl tin can become hepatotoxic after conversion to dibutyl tin.
  - Trialkyl and trialkyl tins (propyl = 3 carbon and longer chain compounds) inhibit T-cell lymphocyte proliferation and thus are immunotoxic.
  - Alkyltins are often mutagens.
  - Larval and, to a lesser extent, older fish are sensitive to triphenyl tin. Developmental defects included.
- Skeletal malformations. There was also increased mortality.
- Disrupts myelin production in neonates.
- Decreases neurotransmitter concentrations.

Signs and Lesions

- Dialkyl and trialkyltins are potent neurotoxins. Like organomercurials and organolead compounds, a major site of action is the central nervous system.
- Signs may include depression, headaches, loss of libido, irritability, hyperactivity, aggression, weakness, paresis or paralysis.

Diagnosis

- Depends on detection of organotin compounds in source materials, stomach contents, and tissues.
- Initial screening for tin content with atomic absorption spectroscopy or inductively coupled spectroscopy may also be worthwhile.
- Nervous system lesions consistent with organotin poisoning may be noted on histopathologic studies.
- There is no specific treatment for organotin toxicosis. Prevention and limiting absorption are important approaches in preventing harm to animals.

Treatment

None specific - detoxification and support.

Feed Related Ammonia Poisoning

<table>
<thead>
<tr>
<th>Specific Agents</th>
<th>Major Species</th>
<th>Usual Time of Onset</th>
<th>Usual Duration (if survives)</th>
<th>Full Table for Toxicants with Mixed Effects on the Central Nervous System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quaternary ammonium disinfectants</td>
<td>Dogs</td>
<td>Minutes to hours</td>
<td>Hours; potentially lethal</td>
<td></td>
</tr>
<tr>
<td>(ingested)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ammonia toxicoses</td>
<td>Herbivores, esp.</td>
<td>Minutes to hours</td>
<td>Hours; often lethal</td>
<td></td>
</tr>
<tr>
<td>(urea and other sources of nonprotein</td>
<td>ruminants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>nitrogen)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Sources

- Urea, biuret and ammonium salts serve as sources of non-protein nitrogen (NPN) for ruminants. Toxicosis results from the associated build-up of ammonia in the animal.
The compounds may be used to furnish up to one-third of the nitrogen protein requirement of ruminant animals.

The major NPN source in use today is urea, which is commonly incorporated into feed supplements for mixing or blending, range blocks, range cubes, and molasses-NPN combinations.

Extensively used to supplement cattle feeds, although use has declined in recent years.

When used as a source of non-protein nitrogen for ruminants, urea is incorporated in rations in amounts not to exceed 1% of the total ration.

Biuret, when used as a source of non-protein nitrogen, should not exceed 3% of the total ration.

The improper mixing of the raw chemicals or supplements containing high concentrations of urea, biuret, and diammonium phosphate in feeds prepared for sheep and cattle has resulted in toxicosis and death.

Ammonium phosphates are used primarily as sources of phosphorus.

Ammonium salts may be used as expectorants or in the treatment of urolithiasis. The common dose of ammonium chloride as a means of reducing urolithiasis in cattle is 0.75 - 1.5 ounces per cow/day and 0.25 ounces per sheep/day.

Currently available nonprotein nitrogen (NPN) sources include urea, feed grade biuret, gelatinized starch-urea product, diammonium phosphate, ammonium phosphate solution, ammoniated rice hulls, ammoniated cottonseed meal, ammonium sulfate and mono-ammonium phosphate. Characteristics of representative compounds are shown in the following table:

<table>
<thead>
<tr>
<th>Compound</th>
<th>N %</th>
<th>P %</th>
<th>Protein Equivalent %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea-pure</td>
<td>46.7</td>
<td>0</td>
<td>292</td>
</tr>
<tr>
<td>Urea-feed grade</td>
<td>45.0</td>
<td>0</td>
<td>281</td>
</tr>
<tr>
<td>Biuret-pure</td>
<td>40.8</td>
<td>0</td>
<td>255</td>
</tr>
<tr>
<td>Biuret-feed grade</td>
<td>37.0</td>
<td>0</td>
<td>320</td>
</tr>
<tr>
<td>Monoammonium Phosphate</td>
<td>12.0</td>
<td>27.0</td>
<td>75</td>
</tr>
<tr>
<td>Phosphate</td>
<td>21.0</td>
<td>23.0</td>
<td>131</td>
</tr>
<tr>
<td>Diammonium Phosphate</td>
<td>21.0</td>
<td>0</td>
<td>131</td>
</tr>
<tr>
<td>Ammonium Sulfate</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

One part of urea is equivalent to 2.92 parts of protein and 1% protein is equivalent to 0.34% urea.

To calculate a toxic dose, urea and ammonium salts can be considered together, e.g.:

- Feed tag states that the feed contains 70% crude protein with 10% from soybean meal and the remaining 60% as protein equivalent from NPN sources. 60% x 0.34 = 20.4% urea content.
- One kg would contain 204 gm urea enough to poison a 200 - 400 kg animal if rapidly ingested.
- Dry and liquid fertilizers usually contain ammonia, ammonium salts, or urea and may be accidentally ingested.

Toxicity

- Most cases of toxicosis are associated with mistakes in mixing, or as a result of feeding supplements containing a high percentage of urea with disregard for the manufacturer's recommendation.
- All mammalian species are susceptible to ammonia poisoning.
- Horses, other monogastrics, and ruminants are all of similar susceptibility to poisoning by ammonium salts.
- Ingestion of 1.5 grams/kg of ammonium salts are lethal to monogastric animals.
- The toxicity of the other compounds is dependent on the rates of ammonia formation and absorption. Ruminants are susceptible to poisoning by all compounds used as a source of non-protein nitrogen.
- Because of hydrolysis of urea to ammonia by rumen microorganisms, ruminants are much more susceptible to urea than most monogastrics.
- Ruminants may show signs of mild toxicosis following ingestion of 0.3 - 0.5 grams of urea or ammonium salts/kg body weight. Doses of 0.5 - 1.5 g/kg of urea, urea phosphate, and ammonium salts may be lethal to cattle and sheep.
- Horses are of intermediate susceptibility to poisoning by urea. Doses of 4 grams/kg of urea and 1.4 grams/kg of ammonium salts may cause death in horses.
Predisposing Factors

- Several factors including fasting, low energy diets, high rumen pH, elevations of body temperature, dehydration, stress, disease, hepatic insufficiency, lack of natural protein sources, and failure to gradually adapt ruminants to diets containing NPN predispose the animal to urea toxicosis.
- Dietary intake should be carefully monitored during cold weather as the energy needs of the animal rise and cause increased consumption of concentrate mixtures containing NPN.
- Raw soybeans contain urease; but contrary to belief, feeding soybeans does not appear to increase the hazard associated with concurrent exposure to urea.

Mechanism

- The hydrolysis of urea (urealysis) in the rumen is outlined in the following reaction:

$2\text{NH}_3 + \text{CO}_2 \rightarrow \text{H}_2\text{N}--\text{C}--\text{NH}_2 + 2\text{H}_2\text{O}$

- Signs of toxicosis which follow the ingestion of NPN sources or ammonium salts occur as a result of the absorption of ammonia following its release in the digestive tract.
- The rate of release of ammonia from urea depends primarily upon the amount of NPN ingested, the amount of urease present in the rumen, and the pH of the rumen contents. At rumen pHs less than 6.2, the major fraction of the nitrogen released from urea exists as the charged ammonium ion (NH$_4^+$) which is highly water soluble and poorly absorbed. At pH 9.0, NH$_3$/NH$_4^+$ equals one and large amounts of ammonia are available for absorption.

- Rumen microorganisms have the ability to form amino acids by imitating carbohydrates. To accomplish this, they need a good supply of carbohydrate (a good diet of adequate energy content).
- When rumen flora microorganisms are overwhelmed by excess ammonia produced during urealysis, the ammonia dissipates in rumen fluids, takes on protons to form ammonium ions and thereby increases the pH. As the pH rises (and fewer hydrogen ions are available), the ammonium ions are no longer formed and the concentration of (uncharged) ammonia (NH$_3$) in rumen fluids and blood increases rapidly. At this time, the clinical signs of ammonia toxicosis become apparent.
- Absorbed ammonia is normally incorporated into the urea cycle and excreted as urea in the urine. The conversion of ammonia to urea (which is more water soluble and excretable) occurs in the liver, and elevation of blood ammonia represents a failure of the liver to convert the excess portal blood ammonia to urea. Hepatic failure produced by ligation of the hepatic artery causes a two- to three-fold
increase in the ammonia concentrations in muscle, brain and pancreas.

- Ammonia inhibits the Kreb's cycle and there is a compensatory increase in anaerobic glycolysis with resultant lactic-acidemia.
- High brain ammonia concentration interferes with cerebral energy metabolism and the sodium-potassium-ATPase pump.
- Hyperkalemia has been associated with lethal effects on the heart.

**Signs**

- Within 10 minutes to 4 hours following the ingestion of excess urea or other NPN sources, animals may exhibit frothy salivation, depression, hyperirritability, grinding of teeth, abdominal pain, increased defecation, and polyuria.
- Muscle tremors, incoordination, increased respiratory rate, and general weakness are commonly noted. Animals may appear blind.
- Bloat and regurgitation of rumen contents may occur, especially in sheep. Recumbency, hyperthermia, anuria, cyanosis, and convulsions are common terminal signs.
- The clinical course of the toxicosis is usually from 0.5 - 4 hours.
- Signs appear when rumen ammonia and blood ammonia concentrations exceed 80 mg/100 ml and 2 mg/100 ml, respectively.
- Hyperkalemia has been associated with lethal effects.

**Lesions**

- Postmortem examination may reveal few changes, but an odor of ammonia is often noted in rumen contents and tissues.
- Although there are no definitive lesions, pulmonary edema, petechial hemorrhages, and generalized congestion are common findings.
- Animals bloat rapidly, and carcasses seem to decompose more rapidly than normal.

**Diagnosis**

- Clinical signs and a history of acute illness following ingestion of urea or other NPN sources are important in establishing a presumptive diagnosis.
- Chemical analysis of suspect feeds, rumen fluid, and jugular whole blood or serum are requisite for a definitive diagnosis. Blood ammonia values ranging from 1 - 4 mg/100 ml and rumen ammonia values greater than 80 mg/100 ml are compatible with a diagnosis of ammonia toxicosis. Samples of blood and urine should be collected immediately after death and specimens should be frozen if tests cannot be done in 1 hour. Composite samples of rumen fluids should be obtained. When blood and rumen contents are not preserved properly, autolysis and proteolysis of rumen contents may raise NH3 concentrations 20 -50 mg/dl above those that existed at death, which may give false positive interpretations.
- The excess NPN is often found in the feed.
- Significant increases in the packed cell volume, blood ammonia, blood glucose, blood urea nitrogen, serum potassium and phosphorus, rumen pH, rumen ammonia and SGPT are noted during ammonia toxicoses. Blood pH and urine production are decreased.

**Differential Diagnosis**

- Several conditions including toxicosis from organochlorine or organophosphorus insecticides and cyanide, as well as protein or grain engorgement, enterotoxemia, meningitis, and encephalitis should be considered as possible alternatives to ammonia intoxication.
- Rumen pH values existing in various disorders serve as an aid in establishing a diagnosis.

<table>
<thead>
<tr>
<th>Rumen pH Values (Lloyd, 1973)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Condition</td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Urea poisoning</td>
</tr>
<tr>
<td>Protein engorgement</td>
</tr>
<tr>
<td>Fasting</td>
</tr>
</tbody>
</table>
A rumen pH of 4.0 - 7.6 is required for proper rumen motility.

**Treatment**

- Effective only if initiated early in the course of the toxicosis. Most effective when given within 20 - 30 minutes after the appearance of clinical signs.
- Recumbent animals almost never respond.
- The best treatment for cattle consists of administration of a combination of 5 - 10 gallons of cold water and a gallon of 5% acetic acid (or vinegar) by means of a stomach tube. The cold water reduces the temperature of the rumen and thus the rate of urease action. The acetic acid reduces the rumen pH and converts the readily absorbed ammonia present in ruminal fluids to the relative innocuous ammonium ion. The drop in rumen pH also slows urease activity. When performed on nonrecumbent animals showing tetany, recovery with return of normal rumen pH and fermentation occurs within 48 hours. Retreatment may be needed depending upon the response of the animals.
- Intravenous fluids should be administered to insure adequate urine flow.
- When bloat occurs, it should be relieved immediately.
- Some people suggest that rumen lavage via a rumenotomy incision or trochar may be superior to cold water/acetic acid.

**Key Features**

- Ingestion of a NPN source in excessive amounts or by unaccustomed animals or by animals on a low-energy ration.
- Ruminants most susceptible to urea; horses intermediate; all species affected by ammonia salts.
- NH₄⁺ innocuous but NH₃ from urea builds up causing most toxic effects.
- Rapid syndrome, polyuria, bloat, abdominal pain, tremors, incoordination.
- Diagnosis: Very high rumen pH, determine rumen and blood ammonia concentrations + analyze feed.
- Therapy comprised of relieving bloat, cold water and vinegar, fluids, control of severe neurologic signs enough to treat.
Pyrethrum (Pyrethrins) and Pyrethroids

**Sources**
- Pyrethrins are natural insecticides produced by certain exotic *Chrysanthemums* (sometimes called *Pyrethrum*) flowers, not by domestic horticultural varieties. Pyrethrum contains pyrethrins and cinerins.
- Pyrethroids are synthetic insecticides.
- Used in numerous formulations including aerosols, sprays, dusts, tags, dips, and shampoos. Some formulations include additional insecticides and/or insect repellants. Flea control products constitute the primary source of exposure leading to problems in small animals.

**Toxicity**
- Toxicity varies with the specific compound and route of administration involved.
- In general, introduction of an alpha cyano moiety (type II pyrethroids) results in an increase in toxicity.

<table>
<thead>
<tr>
<th>Major Species</th>
<th>Usual Time of Onset</th>
<th>Usual Duration (if survives)</th>
<th>Full Table for Toxicants with Mixed Effects on the Central Nervous System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cats, dogs</td>
<td>Minutes to hours</td>
<td>Hours (usually) to two days; rarely lethal</td>
<td></td>
</tr>
</tbody>
</table>

### Toxicity Table

<table>
<thead>
<tr>
<th>Rat LD50 (mg/kg)</th>
<th>Type I Compounds</th>
<th>Oral</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrethrin I</td>
<td>900</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allethrin</td>
<td>680</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetramethrin</td>
<td>4,640</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kadethrin</td>
<td>600</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resmethrin</td>
<td>100</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Phenothrin</td>
<td>10,000</td>
<td>&gt;300</td>
<td></td>
</tr>
<tr>
<td>Permethrin</td>
<td>2,000</td>
<td>&gt;135</td>
<td></td>
</tr>
<tr>
<td>Cismethrin</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bromophenothrin</td>
<td></td>
<td>&gt;30</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Rat LD50 (mg/kg)</th>
<th>Type II Compounds</th>
<th>Oral</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fenpropathrin</td>
<td>25</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Cypermethrin</td>
<td>500</td>
<td>6-9</td>
<td></td>
</tr>
<tr>
<td>Deltamethrin</td>
<td>31</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Fenvlerate</td>
<td>450</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Fluorocypophenothrin</td>
<td></td>
<td>5-7</td>
<td></td>
</tr>
<tr>
<td>Fluvalinate</td>
<td>1,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dowco 417</td>
<td>460</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flucythrinate</td>
<td>67</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bay-FCR</td>
<td>590</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Absorption, Distribution, Metabolism and Excretion (ADME)

- Rapid hydrolysis of ester linkage in digestive tract results in low oral toxicity.
- Most are rapidly metabolized by ester hydrolysis and via oxidation by liver microsomal enzymes.
- The resulting alcohol, phenol, or carboxylic acid metabolites are often conjugated with glycine, glucuronide, sulfate, and glucoside prior to excretion.
- Residues: follow label recommendations on withdrawal, usually not a problem.

Mechanism

- Pyrethrins and type I pyrethroids act on sodium ion channels; decreasing peak sodium conductance, prolonging the sodium conductance, and suppressing potassium conduction. These changes result in decreases in the amplitudes of action potentials and repetitive nerve discharges. Nerve conduction block can occur.
- Type II pyrethroids (contain a cyano group) also act on sodium ion channels which is thought to account for the sensory nerve stimulation associated with paresthesias in humans (and presumably other species). A depolarization of nerve membranes without repetitive discharges occurs with decreased action potential amplitudes.
- Type II pyrethroids are also believed to interfere with the binding of GABA and glutamic acid at their respective nervous system's receptor sites.
- Allethrin (and perhaps other pyrethroids) allosterically affects binding at the acetylcholine nicotinic receptor.
- Pyrethrins and pyrethroids also inhibit various adenosine triphosphatases including the calcium-ATPase and the calcium magnesium-ATPase in nervous tissues.
- Increased cerebellar concentrations of cyclic GMP (but not cyclic AMP) occur before the development of seizures in cypermethrin (and perhaps other pyrethroid)-poisoned rats. With in vitro exposure to cypermethrin, however, the cGMP concentration was unaltered. It is therefore believed that the increase in cGMP concentration is a secondary, rather than a primary, effect. Increased cerebellar cyclic GMP is sometimes seen with other agents causing seizures.
- Synergists-Addition of mixed function oxidase inhibitors, such as piperonyl butoxide, N-octyl bicycloheptene dicarboxiimide MGK264, sesame oil (and/or several others) enhances toxicity in insects and mammals by prolonging the life of the intact, active form of the insecticide in the body.
- In most cases at this time, the actual cause of clinical signs is unknown: possibly insecticide, synergist, or solvent. This is due to a lack of adequate toxicity testing.

Susceptible Species

- Small animal poisoning occurs principally in cats.
- Rodents.
- Fish are often extremely sensitive.

Signs

- Often associated with vigorous insecticide treatment of the animal.
- Possibly due in part to larger amounts of synergist(s) in the formulation.
- Effects on rodents classified into two syndromes: type I and type II syndromes which correlate with the chemical structures.
  - Type I syndrome: classical pyrethrins and type I pyrethroids (no alpha cyano group).
    - Increased sensitivity to stimuli, fine muscle tremors, whole body tremors, prostration.
  - Type II syndrome-alpha-cyano pyrethroids.
    - Salivation; rodents paw, burrow, writhe, and may display clonic seizures; possible paresthesia of skin.
- In cats and dogs, clinical signs associated with toxicosis from pyrethrins and type I or type II pyrethroids may include tremors, increased salivation, ataxia, vomiting, depression, increased body temperature, hyperexcitability or hyperactivity, seizures, dyspnea, and death.
- Clinical signs generally develop within hours of exposure, but may be delayed as a result of prolonged exposure from dermal absorption or grooming.
- Generally, sublethally exposed animals recover within 72 hours.

Lesions

- No specific gross lesions noted.
- Deaths generally rare.

Diagnosis
Based upon a history of a potentially toxic level of exposure to a pyrethrin or pyrethroid containing insecticide and the development of compatible signs.

- Rule out other insecticides, e.g., organophosphorus and/or carbamate compounds, in part by measuring acetylcholinesterase activity.
- Chemical analysis of pyrethrin/pyrethroid residues on skin of animal will confirm exposure. Tissue concentrations of pyrethrins/pyrethroids may support a tentative diagnosis of poisoning but diagnostically confirmatory concentrations in tissue are not yet established.

**Treatment**

- Topical exposure: bathe thoroughly with detergent.
- Recent oral exposure (within a few hours): (Early) emetics if not contraindicated; activated charcoal and saline cathartic.
- For severe CNS stimulation with seizures:
  - To treat pyrethroid toxicosis in dogs, try diazepam (0.2 - 2.0 mg/kg IV to effect). If this fails, parenteral phenobarbital is recommended. If it too fails, induction of anesthesia with pentobarbital may be necessary.
- Cats with severe tremors due to inappropriate use of concentrated permethrin often improve after IV administration of methocarbamol (Robaxin Vâ) at 55 - 220 mg/kg. Half the dose should be given rapidly but no faster than 2 ml/min. Administration should be discontinued briefly as the cat relaxes, then resumed until the desired effect is achieved. The maximum dose on the label (330 mg/kg) should not be exceeded. Initial treatment with diazepam or pentobarbital, or mask induction with isoflurane may be needed for control of seizures.
- Atropine can reduce some clinical signs (e.g., diarrhea, hypersalivation). However, in experimental studies with lethally poisoned laboratory animals, atropine minimized excessive salivation and diarrhea without affecting the observed LD50.
- Muscle relaxants, e.g., methocarbamol at 55 - 220 mg/kg IV at a rate not to exceed 200 mg/minute, may be of benefit.
- Phenothiazine tranquilizers are contraindicated.
- Symptomatic and supportive therapy.

---

**Rotenone**

<table>
<thead>
<tr>
<th>Major Species</th>
<th>Usual Time of Onset</th>
<th>Usual Duration (if survives)</th>
<th>Full Table for Toxicants with Mixed Effects on the Central Nervous System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cats, dogs, birds, fish, amphibians</td>
<td>Minutes to hours</td>
<td>Hours to days; infrequently lethal except in aquatic organisms and arthropods</td>
<td></td>
</tr>
</tbody>
</table>

**Sources**

- Derived from roots of the *Derris* and *Lonchocarpus* plant.
- Synonyms derrin, nicourine, and tubatoxin. (All these terms are rarely used.)
- Used historically in Malaya and South America to kill fish and for poison arrows.
- Insecticide.
- More toxic than pyrethrins.
- Formulated into products for use in gardens and on dogs and cats (dips, sprays, powders). Formulations include dusts of 0.75 - 1.5% concentration, emulsifiable concentrates, wettable powders of 5% concentration, solutions (up to 57%) and resins.
- Products may be synergized with piperonyl butoxide.

![](Rotenone.png)
Toxicity

- Highly toxic to birds and fish, may affect any species.
- Cats most often affected after deliberate use of rotenone containing products for ectoparasitism.
- Oral LD50s in laboratory animals range from 10 to 30 mg/kg.
- LD50 IP (mice) = 2.8 mg/kg.

Absorption, Distribution, Metabolism and Excretion (ADME)

- Rotenone is metabolized by liver, undergoes hydroxylation to form equally toxic rotenoids. Detoxification in liver by demethylation can also occur.

Mechanism

- Rotenone blocks NAD-flavin electron transport in respiratory metabolism which results in blockade of nerve conduction. Specifically, interferes with the electron transport process between flavoprotein and ubiquinone (coenzyme Q). Also blocks oxidation of NADH.

Signs

- Pharmacologic effect-anesthetic effect when in contact with nerve axon or mucous membrane.
- Oral exposure:
  - Gastric irritation.
  - Vomiting.
  - Poor absorption.
- Dermal exposure:
  - May cause problems in dogs; more often in cats.
  - Possible skin irritation and severe pulmonary irritation from inhalation of dust.
  - Signs may include vomiting, lethargy, tremors, stupor, clonic, repeated convulsions, respiratory failure, dyspnea and death.
  - Possible hypoglycemia.
  - Death occurred in a 6-month-old Persian cat apparently as a result of being dipped in a rotenone dip. **Note:** Long-haired cats may dermally absorb much more of any type of insecticide due to prolonged contact with the wet insecticide (whether prolonged volatilization and inhalation of vapors of some such compounds also contributes to systemic absorption is not certain but seems plausible).

Pathology

- Pulmonary congestion, gastrointestinal tract irritation.
- When chronically fed to rats or dogs, passive congestion of the liver with midzonal necrosis was observed.

Treatment

- Oral exposure: avoid fatty or oily foods as they enhance absorption.
- Minimize fraction absorbed: depending upon route of exposure and condition of patient (bathe with detergent, emetic, enterogastric lavage, activated charcoal, saline cathartic).
- Monitor blood glucose, administer glucose as needed. May not enhance survivability.
- Monitor acid-based status and, if necessary, correct metabolic acidosis with diluted bicarbonate (slow iv).
- Vitamin K3 (do not use in the horse) which activates a bypass of the rotenone sensitive site has been recommended based on theoretical (in vitro) rather than experimental (in vivo) grounds.
- If a solvent vehicle has been used, it may be necessary to manage as a petroleum hydrocarbon ingestion (see pulmonary toxicants).
- Supportive and symptomatic care.
Tricyclic Antidepressants

Chemical Structure

- Term tricyclic is derived from the 3-ring chemical structure of the central portion of the molecule.
- Tertiary amines exist within the tricyclic class.
- Amoxapin has a 4-ring structure but is classified as a tricyclic antidepressant (TCA) since it retains the classic 3-ring moiety.

Tricyclic Antidepressants and Trazodone

Sources

- Increasing use as antidepressants in human medicine.
- Represent most common life-threatening drug ingestion in human patients.
- Infrequently encountered in veterinary medicine, however accidental poisoning incidence is on the increase.

Toxicity

- In general, 15 - 20 mg/kg is thought to be potentially lethal in human patients.

Absorption, Distribution, Metabolism and Excretion (ADME)

- TCAs in therapeutic (human) doses are rapidly absorbed from the GI tract. Have high lipid solubility. Large ingestions may result in prolonged GI absorption due to anticholinergic effects and associated decrease in GI motility.
- Highly protein bound.
- Free TCA concentration can be decreased by alkalinization of serum.
- Primarily undergo liver metabolism: demethylation or hydroxylation followed by glucuronidation. Note this may be an important consideration in cats.
- Variable elimination half-lives from 10 - 81 hours.
Mechanism of Action

- Inhibition of biogenic amine (serotonin, norepinephrine) uptake centrally. Regulate it higher availability causes generalized CWS stimulation.
- H1 and H2 histamine receptor antagonists.
- Quinidine-like cardiac effects are the most life-threatening effects of TCA overdose (4).

Clinical Signs

- Humans.
  - Generally develop within hours of ingestion.
  - Primarily involve CNS, parasympathetic nervous system, and cardiovascular systems.
  - Tachycardia, CNS excitation (early), convulsions, coma, hypotension, arrhythmias, and cardiac arrest.
  - EKG alterations include prolonged QRS intervals which correlate with arrhythmias and seizure development. PR and QT prolongation. Sinus tachycardia common; but various arrhythmias possible.
- Dog.
  - Vomiting. Behavioral changes including disorientation, "anxiety®, and aggression have been reported. Severe depression to semicomatose status. Seizures have been observed.
  - Cardiac abnormalities include tachycardia, bradycardia, and arrhythmias.
  - Hypothermia, ataxia, weakness, tremors, and shock also occur.
  - Experimental studies in dog with amitryptyline resulted in increased heart rate and prolonged QRS duration. Ventricular tachyarrhythmias occurred in almost all dogs.
  - Progression of signs can be very rapid. Death may occur within 1 - 2 hours of ingestion if left untreated (4).

Treatment

- Due to general lack of information in the veterinary literature, the following treatment recommendations are based on current management of human patients.
- Maintain airway, support respiration.
- Gastric lavage with administration of activated charcoal and cathartic.
- Consider emetic only in recent exposure and only if animal is still alert. Generally, emesis is not recommended since seizures may occur abruptly.
- Repeated oral doses of activated charcoal every 2 - 3 hours may enhance elimination.
- Seizure control-try diazepam (Valium ) first. Long-acting anticonvulsants (phenobarbital) should be administered concurrently. Valium has been effective in poisoned dogs.
- Seizures can produce metabolic acidosis which enhances cardiotoxicity, therefore sodium bicarbonate (administered at 1 - 3 mEq/kg) is strongly indicated. Experimentally shown efficacious in poisoned dogs. Best to monitor acid base status.
- Phenytoin has been used with variable success in treating seizures and cardiac arrhythmias in human patients.
- Ventricular arrhythmias can also be managed with lidocaine in the dog. Quinidine sulfate, procainamide, and disopyramide are contraindicated in TCA poisonings.
- β blockers, e.g., propranolol, have had variable success in treating TCA cardiotoxicity. May be of some benefit in sinus tachycardias. However, β1 selective blockers such as metoprolol or esmolol may be preferred to avoid inadvertently causing bronchoconstriction.
- Hypotension should be corrected with fluid therapy.
- Symptomatic therapy.
- TCA management requires close patient monitoring for a minimum of 6 - 12 hours postingestion.
Fumonisins

Sources
- Fumonisins are mycotoxins produced by the fungus *Fusarium moniliforme* primarily in corn. Fumonisin B1 is generally the dominant toxin present.
- Worldwide distribution, primarily associated with feeding of corn or corn products.
- Corn screenings, taco plant sweepings, or whole shelled corn is often involved. The infested corn may appear grossly normal.
- The presence of *F. moniliforme* in corn is not diagnostic since nearly all corn in the USA is contaminated by this organism.
- Several climatic factors predispose to fungal growth and toxin production such as: midsummer drought, an early wet fall, fluctuating warm and cold temperatures, accompanied by an early frost and delayed harvests.
  - During a drought year (1989), fumonisin B1 was detected in Illinois corn at over 250 ppm.
  - In 1995, corn in Texas was found to contain fumonisin B1 at up to 100 ppm.

Susceptible Species
- Horses, ponies, and donkeys may develop leukoencephalomalacia and/or liver failure.
- Other species such as swine and rabbits may be poisoned by fumonisin-contaminated corn although the syndrome is different.
  - Swine develop pulmonary edema.
  - Rabbits may develop renal failure.

Mechanisms of Action
- Fumonisin B1 apparently causes its toxic effects, at least in part, by inhibiting the action of sphingosine N-acyltransferase, an enzyme involved in the conversion of sphinganine and sphingosine into sphingolipids.
- Sphingosine is an important second messenger in a range of cell types.
- Sphinganine can be very cytotoxic or can lead to cell proliferation and affect a wide variety of cellular systems. Inhibition of N-acyltransferase may cause increases in sphinganine concentration in tissues.
- Sphingolipids are important in regulation of cell growth, differentiation, and neoplastic transformation. Alteration in sphingolipid concentrations and functions, especially in the vasculature, also are believed to contribute to the major signs and lesions of fumonisin toxicosis.
- In horses with leukoencephalomalacia, regional brain tissue sphingolipid alterations were not evident which may suggest that the primary site of fumonisin action causing the "stroke-like" lesions may be the endothelial cells of the vasculature.
- Swine develop severe pulmonary edema in fumonisin toxicosis. It is theorized that, in this species, fumonisin causes damage to hepatocyte membranes causing release of membrane fragments to the circulation. These are trapped in the lung where they are engulfed by pulmonary intravascular macrophages which may release substances that activate neutrophils and alter capillary permeability resulting in pulmonary edema.
- Cardiac failure and pulmonary hypertension, due to pulmonary vasoconstriction, also may occur in swine, predisposing them to pulmonary edema.

Signs in Horses
- Poisoning in the USA most often occurs in late fall or early winter.
- Onset may occur as early as 7 days after a new batch of corn is first fed, but first signs are usually seen after 14 - 21 days; occasionally onset may be delayed 90 days or more.
- Outbreaks on the same farm affecting several horses are common; sometimes other local herds are also affected. Horses in various stages of the disease will often be present.
- In 1901 - 02, over 2,000 horses reportedly died in the USA as a result of leukoencephalomalacia; and in 1934 - 35, over 5,000 horses died as a result of this syndrome in Illinois alone.
- In a given outbreak, the overall morbidity is generally low, less than 25%; but mortality usually approaches 100% in affected animals.
- **Neurotoxic syndrome**: the clinical course is generally short with an acute onset of signs and deaths within 2 - 3 days. This syndrome is currently termed equine leukoencephalomalacia (ELEM), although historical names include blind staggers, cerebritis, leukoencephalitis, encephalomyelitis, cornstalk disease, moldy corn poisoning, foraging disease, and cerebrospinal meningitis.
  - The neurotoxic form progresses over hours (usually) to 4 - 5 days. Surviving horses may be encountered on occasion, and

<table>
<thead>
<tr>
<th>Major Species</th>
<th>Usual Time of Onset</th>
<th>Usual Duration (if survives)</th>
<th>Full Table for Toxicants with Mixed Effects on the Central Nervous System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Horses, and possibly rabbits may have neurologic effects</td>
<td>Several days to months</td>
<td>Permanent damage likely in horses that survive; often lethal</td>
<td></td>
</tr>
</tbody>
</table>
some such animals have permanent neurologic deficits.

- T,P,R are all normal, at least initially.
- Partial anorexia often occurs early in the course.
- Depression, ataxia, blindness, and hysteria are common.
- Head is often held low, especially when left alone.
- Reluctance to move and loss of equilibrium are noted in some horses when forced to walk.
- Anorexia progresses and coincides with glossopharyngeal paralysis, paralysis of the lips and tongue, and loss of the ability to grasp and chew food.
- Incoordination increases.
- Aimless walking, circling, and ataxia often occur.
- Head pressing, marked stupor, and hyperesthesia are common.
- Hyperexcitability, profuse sweating, delirium, mania, or convulsions are often present, especially terminally.
- Blindness is usually unilateral and often "progressive" when it occurs.
- Lateral recumbency often occurs, most often within 4 - 12 hours of onset.
- Convulsions.
- Acutely affected animals often progress through the manic and depressive stages of the syndrome within 4 - 12 hours of the onset and become recumbent and moribund.
- Death—may occur without previous signs being noted.

**Hepatotoxic syndrome:**

- With the hepatotoxic form, there are usually 5 - 10 days between the onset and death.
- Icterus is usually prominent in horses with hepatic degeneration. There may also be edema of the face and submandibular space and oral petechia. Elevated bilirubin, liver enzymes are typically present.
- Terminal diaphoresis, coma, and sometimes clonic convulsions may be noted, presumably due to hepatoencephalopathy.

**Signs in Swine**

- Decline in feed consumption is usually the first sign. If toxin consumption is significant, acute pulmonary edema and, often, death follows. Onset of pulmonary edema may be delayed for up to 7 days after feeding of fumonisin-contaminated feed is begun and typically deaths cease within 48 hours after withdrawal from contaminated feed.
- At low doses, slowly progressive liver disease may occur.

**Signs in Other Species**

- Poultry-poor performance, feed refusal, diarrhea, weakness, and high mortality may be noted.
- Rats-hepatic neoplasia.
- Rabbits—sudden renal failure.
- Human beings—esophageal cancer is suspected to be related to consumption of fumonisin-contaminated corn.

**Lesions: General**

- In all mammals studied to date hepatic lesions have been found.
- Effects on other organs vary among species (species-specific effects).

**Lesions in Horses**

- There are two syndromes in the horse that may appear independently or concurrently:
  1. The classical nervous form with liquefactive necrosis in the white matter (may occur as a result of low consumption over a long time).
  2. A primary hepatocellular disease with secondary hepatoencephalopathy (may occur due to consumption of large amount of affected corn over a short time).
- **Lesions of both types may be present** within the same animal or within the group.
- The liquefactive necrosis in the subcortical white matter is usually evident grossly; the surface of the brain may look normal, but the liquefaction may extend into or even through the cortex in some horses.
- The cavities are fluid-filled and there may be variable degrees of hemorrhage. Adjacent to these areas, the brain may have a greenish-yellow, granular appearance.
- Mild cases may exhibit only histologic lesions, consisting of a perivascular reaction, with infiltration of mononuclear and plasma cells and occasionally eosinophils; there may also be astrocytosis.
- The liver may be small and firm.
- Liver lobules tend to have a red center and a yellow periphery, resulting in an increased lobular pattern.
Histopathologic examination of the liver may reveal centrilobular necrosis, and moderate to marked periportal fibrosis. Gross lesions occasionally reported that involve other organs include congestion of the lungs, intestinal mucosa, and kidneys, as well as petechial hemorrhages on the epicardium.

Lesions in Swine

- Severe pulmonary edema and hydrothorax.
- Congestion of alveolar septa without hyperplasia or fibroplasia.
- Focal to massive pancreatic necrosis is sometimes noted with dissociation and rounding of acinar cells.
- Hepatocellular cytomegaly, disorganized hepatic cords, and early perilobular fibrosis have been reported.

Lesions in Other Species

- Rats-hepatic neoplasia, renal tubular nephrosis.
- Rabbits-acute proximal tubular necrosis.
- Broilers-multifocal hepatic necrosis, thinning of the thymic cortex.

Diagnosis

- History of ingestion of corn in diet.
- Culture for F. moniliforme can be somewhat supportive but is not diagnostic.
- Clinical signs and lesions.
- Characteristic liquefactive necrosis of white matter in the brain may be only histologically evident even in lethally affected horses.
- Detection of approximately 10 ppm fumonisin in horse feed or 50 ppm in swine feed.
  - Assays are now available at most veterinary diagnostic laboratories.
  - An ELISA-based screening test for fumonisin is sold by Neogen.

Treatment

- Isolate affected horses to prevent other horses from traumatizing them or vice versa.
- Be careful: horses may be dangerous (crazed).
- Thiamine may help—but is not a panacea. There are no data demonstrating a benefit from thiamine treatment.
- Activated charcoal at one pound per head and a saline cathartic for the first two days could be tried. There are no studies to illustrate whether or not it would be of any benefit. Most damage may have already occurred but if not tried, no benefit could be realized.
- Change of diet-avoid corn.
- Support, quiet surroundings, maintain hydration, etc.

Prevention

- For equine species, it has been recommended that the non-roughage portion of the diet contain less than 5 ppm fumonisin B1. This is a narrow margin of safety.
- For swine, it has been recommended that the total diet contain less than 10 ppm fumonisin B1. This is a narrow margin of safety
- For dairy cattle, no level has been recommended.
- For beef cattle, it has been recommended that the non-roughage portion of the diet contain no more than 50 ppm fumonisin B1.
- For poultry, it has been recommended that the total diet contain less than 50 ppm fumonisin B1.

Key Features

- F. moniliforme contaminated corn (almost always).
- Equids, outbreaks usually affect several horses over a period of days.
- Neurotoxic form-rapid death after sudden onset of bizarre neurologic deficits and behavioral effects.
- Hepatotoxic effect-more gradual: hepatoencephalopathy may result.
- Neurologic form: liquefactive necrosis, perivascular reaction on histopathologic examination.
- Liver may be small, firm, with an increased lobular pattern.
- Most horses die; those surviving usually have neurologic (brain) damage.
- Severe pulmonary edema with marked hydrothorax in swine.
- No known effective therapy.
Centauria - Yellow Star Thistle and Russian Napweed Cause of "Chewing Disease" of Horses

<table>
<thead>
<tr>
<th>Major Species</th>
<th>Usual Time of Onset</th>
<th>Usual Duration (if survives)</th>
<th>Full Table for Toxicants with Mixed Effects on the Central Nervous System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Horses</td>
<td>Days to months</td>
<td>Permanent damage often lethal</td>
<td></td>
</tr>
</tbody>
</table>

Images


Description

- Yellow Star Thistle (*Centauria solstitialis*).
  - Annual weed, branches from the base to about 1 foot in height.
  - Leaves densely covered with cottony hair.
  - Flowers-composite heads, terminal with ovoid spiny base and terminal spreading cluster of bright yellow florets, early stage looks like dandelion.
- Russian Napweed (*Centauria repens*).

Habitat

- Yellow Star Thistle.
  - Primarily western, especially the dry pastures of northern California, also spreading in northwestern states; rare if at all in South and East. Extremely costly to eliminate with herbicides.
- Russian Napweed (*Centauria repens*).
  - Western 1/2 of USA.

Toxic Principle - Unidentified

Dried plants are reportedly still toxic as cases of apparent toxicosis have occurred as a result of consuming hay containing the plant.

Toxicity

Some horses have grazed at least 110 days with no problem; others exhibit onset by 30 days, most from 30 - 90 days of grazing. Signs begin after consumption of several hundred pounds of these weeds.

Mechanism

- Signs are reportedly a result of hyperirritability of the CNS and loss of control (loss of neuronal connections) from the higher centers. The initial signs are believed to result from release of dopamine from nigrostriatal nerve endings and the later signs may be due to dopamine deficiency. Impairment of drinking and eating may be due to damage to neural areas supporting cranial nerves V, VII, and XII.
- Focal reflexes and sensations reportedly remain intact.

Usual Signs

- Hypertonicity of facial and lip muscles, upper lips are pulled over teeth, lower lip hangs, may traumatize lips.
- Tongue lolling.
- Horses perform chewing movements but are unable to obtain food or to swallow it.
- Mouth may be held open with the tongue protruding. However, the animal is able to withdraw the tongue and there is not a flaccid paralysis.
- Yawning.
- Head tossing.
- Chews food; then food drops out of mouth; food never gets to pharynx.
• May eventually "lose interest" in food.
• Also can't drink normally, may immerse head into water to the level of the pharynx so it can be swallowed.
• Sometimes signs are unilateral, but then progress.
• Death occurs as a result of starvation in most horses.
• Prognosis is uniformly poor.

Rare Signs

• Abnormal gait, incoordination, hypermetria, tremors, extreme depression.
• Dyspnea, inhalation of food, secondary gangrenous pneumonia.

Lesions

Nigropallidoencephalomalacia: areas of ischemic necrosis and malacia with gitter cells clearing necrotic debris in the substantia nigra, which is just posterior to the pituitary, and/or in the globus pallidus, which is at the base of the brain, in front of the optic chiasma. Most lesions are bilaterally symmetrical.

References

Lead Toxicosis


Mercury


Organotin Compounds

Feed Related Ammonia Poisoning

Pyrethrum (Pyrethrins) and Pyrethroids

Rotenone

Tricyclic Antidepressants

Fumonisins

Centauria - Yellow Star Thistle and Russian Napweed


Astragalus and Oxytropis - Locoweeds


Hexachlorophene


Bromethalin


Vacor


Deet


**Methionine**


**Carbon Disulfide**


**Persea Americana - Avocado**


**Aesculus - Buckeye and Horsechestnut**


**Mushrooms General**


All rights reserved. This document is available on-line at www.ivis.org. Document No. A2606.0899.