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## Toxicants Associated with Stimulation or Seizures (9-Aug-1999)

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**Cyclodiene Organochlorine Insecticides and Lindane**

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**Chocolate, Caffeine, and other Methylxanthines**

**Nitrofuran Toxicosis**

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**4-Methyl-Imidazole**

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**Cocaine Toxicosis**

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***Cicuta* spp. - Water Hemlocks**

***Corydalis caseana* - Fitweed**

**Milkweeds (*Asclepias*)**

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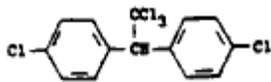
## Diphenyl Aliphatic and Miscellaneous Organochlorine Insecticides

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants Associated with Stimulation or Seizures
All Species	Minutes to chronic	Hours to days; often lethal	

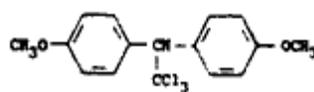
Organochlorine insecticides (OCs) are chlorinated hydrocarbon insecticides. These compounds appear to share the same mechanism with regard to neurotoxicity.

### Sources

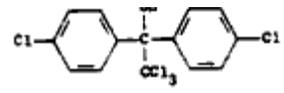
- DDT type (diphenyl aliphatic) - includes DDT, methoxychlor, perthane, and dicofol
  - Methoxychlor used a lot, including products for use around gardens, animals.
- Miscellaneous (mirex, kepone, paradichlorobenzene).
- Paradichlorobenzene.
  - An organochlorine of comparatively low toxicity, but does cause poisoning! Neurologic system toxicity similar to other members of this group. Also, metabolized to a phenolic and is hepatotoxic.
  - In moth crystals, cakes, deodorant block used in diaper pails, closets, restrooms, and in other moth products occasionally including moth balls. (Not same as naphthalene; the most common compound in moth balls).



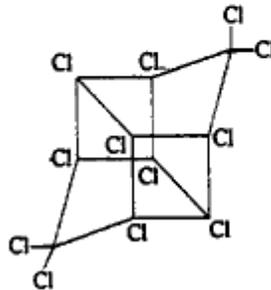
DDT



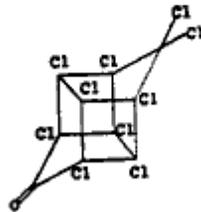
Methoxychlor



Dicofol



Mirex



Kepone



Paradichlorobenzene

### Mechanism of Action of DDT Type Organochlorine Insecticides

- Peripheral nerves and brain:
  - Slows down the turning off of the Na<sup>+</sup> influx and inhibits the turning on of the K<sup>+</sup> outflux; results in more of each cation inside the nerve than normal. Therefore, the inside of nerve membrane is more positive (partially depolarized)-which decreases the threshold for another action potential to occur. Sensory nerves are more readily affected by DDT than are motor nerves.
  - EEG shows a diffuse low amplitude, fast frequency pattern due to partial depolarization of neurons.
  - Methoxychlor, perthane, dicofol are similar to DDT in structure and mechanism.
  - Methoxychlor has estrogenic effects in rats. Enhances female sexual behavior but reduces fertility (1,3).
  - Methoxychlor is readily metabolized and excreted.
  - Mirex and kepone may have the same neurotoxic mechanism as DDT; however, mirex may also inhibit the postsynaptic binding of GABA.

### Toxicity and Signs of DDT Type Toxicoses

- All of these agents mainly cause tremors, salivation, ataxia, depression and sometimes vomiting. Seizures may occur in cats at low doses or in other species with very high doses. LD50s in most species tend to be relatively high. Absorption variable. Typically very fat soluble.
- DDT: unique aspects.
  - Banned in the US in 1972. Still used in some parts of the "developing world".
  - Potent mixed-function oxidase inducer as are its metabolites.
  - Egg shell thinning - birds of prey especially aquatic predators (e.g., bald eagles, ospreys, brown pelicans).
  - O'P'DDD (synonymous with TDE) and especially DDE are persistent metabolites in environment and in body.
  - O'P'DDD - causes thinning of the adrenal cortex in the dog; therefore used to treat Cushing's disease in the dog. Excessive use can cause Addisonian crisis. Potential problem in DDT exposed dogs.
  - See also later - DDT and Metabolites: Reproductive Effects and Effects on the adrenal gland (includes estrogenic activity).
  - LD50 rat (oral) for DDT 113 - 2500 mg/kg, rat (iv) 47 mg/kg.
  - Note in humans: toxic signs at 10 mg/kg (oral).
  - Paradichlorobenzene.
    - LD50 oral: mouse - 3.2 g/kg, rat - 2.5 g/kg, rabbit - 2.8 g/kg.

## Residues

- In addition to acute toxicoses - a primary concern, with regard to the more persistent organochlorines and their metabolites, is residues in the fats of meat and milk. Tendency to store in fat is a function of the rate of metabolism and excretion.
- Since organochlorines were used extensively in agriculture, they are often found in storage or as residues in soil on farms, near feed mills, etc., and can find their way into farm animals, usually via feed.
- Methoxychlor - eliminated fairly rapidly but still had a 30-day withdrawal at one time. More rapid dechlorination and especially oxidation versus DDT.
- DDT - concern regarding cancer, possibly unfounded. Potent mixed function oxidase inducer. DDE, DDT persistent in fat.
- For residue concerns monitor:
  - Milk fat; values may approximate body fat concentrations.
  - Fat biopsy. In cattle, fat may be taken from the tailhead, neck, and scrotum of steers. Prefer to avoid perirenal fat even at necropsy unless other fat is unavailable.
  - Can use experimentally derived data for a particular organochlorine to calculate time needed for a known concentration in body fat to fall below actionable level. **Note:** logical to consult with a veterinary toxicologist when trying to address recommendations for contaminated food animals.
  - Biological magnification--concentration in lipids of successive predators. Can sometimes result in chronic or acute (lethal) toxicoses. Most likely when aquatic systems are involved because: **1)** food chains are longer permitting a greater number of bioconcentrations and **2)** lipid soluble compounds are readily acquired from the environment especially sediments and the surface microlayer of natural waters. These compounds are washed into streams but are poorly soluble in the water column. Sediment concentrations should be checked.
  - Paradichlorobenzene is well absorbed, undergoes glucuronide or sulfate conjugation, and is eliminated over a period of days via the urine and bile.

## Diagnosis of Acute Toxicoses

- History of exposure, appropriate clinical signs.
- Brain analysis important for diagnosis of acute toxicosis:
  - Submit half a brain frozen (for organochlorine and other analyses and virology).
  - Other half fixed for histopathology to rule out infectious (encephalitides), degenerative, or neoplastic diseases.
- To determine sources, it may be appropriate to submit specimens for analysis such as:
  - Feed.
  - Suspect insecticidal formulation - granules, liquid, old containers, etc.
  - Gastrointestinal tract contents.
  - Hair (live animal) or skin (dead animal).
  - Liver.
- Fat or milk fat are the preferred samples to assess residue contamination.
- It is essential to avoid any cross contamination: e.g., from source material to animal or milk; or from skin or stomach contents to brain, etc.

## Treatment for Acute Toxicosis

- Dermal exposure - bathe with detergent - avoid human exposure by the use of heavy-gauge rubber gloves.
- Recent oral exposure - emetic (small animals and possibly swine) (only if presented very early), and not if any likelihood of seizures is apparent: must avoid aspiration of stomach contents into lungs (as discussed with strychnine previously), lavage. Usually use activated charcoal, saline cathartic.
- Monitor liver function.
- Usually seizure control is necessary for 24 hours or so, sometimes may need to medicate for longer periods of time. Suggested drug for initial control is diazepam (dogs) or, if it fails (or for other species), phenobarbital or pentobarbital. For prolonged CNS stimulation, the drug of choice is phenobarbital which may also stimulate mixed function oxidase activity to shorten half-life.

## Decontamination of Residue-Contaminated Livestock

- Identify source and terminate exposure - **essential**.
- Determine value of animals and duration of pasturing/feeding to achieve decontamination. Assess value of animals minus costs of decontamination versus other options. Consider costs including feed, labor, biopsy, analysis, killing and burial of highly contaminated individuals and purchase of additional animals.
- If animals must be destroyed, burial or other disposal should be approved by regulatory officials before euthanasia.
- Lactating animals tend to more rapidly eliminate insecticide residues due in part to losses in milk fat.
- Young animals sometimes metabolize/excrete significant amounts and, because of growth, dilute the residues and may therefore (sometimes) not require specific detoxification procedures.
- Placing fattened animals on pasture, so that they lean out, helps to hasten removal of the organochlorine insecticide from body fat stores. If residues are extremely high in fat, may need to monitor for neurologic effects as body fat residues are mobilized.
- The use of agents to promote metabolism or excretion such as phenobarbital, mineral oil, or repeated activated charcoal for the purposes of lowering residues in fat or milk fat are generally ineffective and not worthwhile.

## Gross Lesions

Large doses may sometimes cause centrilobular necrosis of the liver and smaller doses cause liver enlargement (consistent with many inducers of cytochrome P-450).

## Key Features

- Mechanism of action-increased Na<sup>+</sup> influx, decreased K<sup>+</sup> efflux, and partial depolarization, tremors, sometimes seizures.
- Cats more sensitive.
- Acute toxicoses, analyze brain, stomach contents, feces, and suspected source.
- Detoxification, pentobarbital or diazepam for seizures.
- Residue problems (not a significant problem with methoxychlor).
- Biological magnification, egg shell thinning especially aquatic raptors with DDT, DDE exposure.
- Residues: terminate exposure, analysis of milk fat or fat biopsy, determine if should detoxify or cull contaminated animals.

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## Cyclodiene Organochlorine Insecticides and Lindane

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants Associated with Stimulation or Seizures
All species	Minutes to chronic	Hours to days; often lethal	

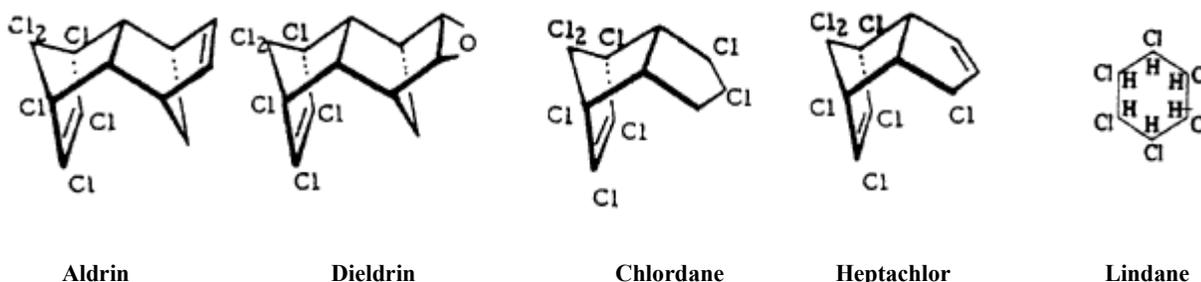
Organochlorine insecticides (OCs) are chlorinated hydrocarbon insecticides.

**Sources** Cyclodiene type: aldrin, dieldrin, chlordane, endrin, heptachlor, "active constituent" of toxaphene.

- Chlordane, heptachlor, aldrin used for termites.
- Aldrin used to be used for corn root worm.
- Endrin at least in past used in "Rid-a-bird".
- Relay toxicosis possible (documented with endrin).
- Toxaphene used to be made for animal dips, other uses.
  - Mixed isomers of chlorinated camphene containing 67 - 69% chlorine.
  - High toxicity of the cyclodiene compound 8-octachloroborane makes a very important contribution to insecticidal activity and, therefore, is referred to as the "active constituent" of toxaphene.

**Note** - Lindane is also called BHC, an abbreviation for the gamma isomer of benzene hexachloride which is a misnomer. Lindane is really hexachlorocyclohexane and must not be confused with HCB. HCB is hexachlorobenzene (true aromatic ring), which was used as a fungicide and is also a significant environmental pollutant because of its extreme persistence and biological magnification, as with many but not all of the organochlorine insecticides.

Lindane. Toxicosis is common in cats and dogs. It was never approved for cats, it is used for dogs (fleas, ticks, sarcoptic mange), also for people (Kwell) (for scabies).



**Toxicity** (See Osweiler et al., Clinical and Diagnostic Veterinary Toxicology; 1985.)

- These cause more seizure activity and are more acutely toxic (lower LD<sub>50</sub>s) than the DDT type organochlorines.
- LD<sub>50</sub> endrin (cats) 3 - 6 mg/kg.

#### **Mechanism of Neurotoxic Action of Cyclodiene Type OC Toxicoses**

- Act by competitive inhibition of the binding of GABA at its receptor - GABA is a more widely used inhibitory transmitter in the CNS than glycine.
- Note the effects of GABA are facilitated by benzodiazepines (such as Valium) and these drugs may therefore be of major benefit in treatment.
- EEG patterns - dieldrin - high amplitude - slow frequency.
- Metabolism in body and environment.
  - Aldrin-dieldrin.
  - Heptachlor - heptachlor epoxide.
  - Dieldrin and heptachlor epoxide are persistent in the body and the environment.
  - It is believed that lindane may also increase threshold by inhibiting GABA-stimulated Cl<sup>-</sup> uptake into the neuron (2).
  - Lindane may have an antiestrogenic mechanism.

#### **Signs of Cyclodiene Type OC Toxicoses**

- Hypersalivation, vomiting.
- Tremors, ataxia.
- Excitation or less often depression.
- Seizures, pivoting on one foot, fall over backwards.
- Possible liver failure.

#### **Signs of Lindane Toxicoses**

- Tremors.
- Excitement or depression.
- Seizures.
- Possible cardiac arrhythmia or cardiac arrest reported in rats.
- Idiosyncratic reaction involving bone marrow depression reported in human beings exposed to lindane. Rare reports of fatal lindane-induced aplastic anemia in humans.
- Some lindane isomers are hepatotoxic and hepatocarcinogenic.

## Residues

- In addition to acute toxicoses - a primary concern, with regard to the more persistent organochlorines and their metabolites, is residues in the fats of meat and milk.
- Toxaphene - comprised of chlorinated camphor extract (from pine), therefore many compounds are present. Most are rapidly eliminated. Animal uses recently banned.
- Several cyclodienes appear to be weakly mutagenic but may act as significant tumor promoters especially with regard to estrogen-responsive tumors (See section on other Estrogenic Toxicants). Most of the compounds are persistent in fat.
- For residue concerns monitor:
  - Milk fat; values may approximate body fat concentrations.
  - Fat biopsy. In cattle, fat may be taken from the tailhead, neck, and scrotum of steers. Prefer to avoid perirenal fat even at necropsy when other fat is obtainable.
  - Can use experimentally derived data for a particular organochlorine to calculate time needed for a known concentration in body fat to fall below actionable level. **Note:** logical to consult with a veterinary toxicologist when addressing persistent residue problems in food animals.
  - Biological magnification - concentration in lipids of successive predators. Can result in chronic or acute (lethal) toxicoses (see DDT above).

## Diagnosis and Treatment of Acute Toxicoses

- See Diphenyl Aliphatic Organochlorine.
- Recovery may be complete after 3 - 6 hours to a few days of treatment.

## Decontamination of Residue Contaminated Livestock

See Diphenyl Aliphatic Organochlorine.

## Key Features

- Mechanism of action: inhibition of GABA causes seizures.
- Acute toxicoses: analyze brain, stomach contents, feces, source.
- Residue problems (fewer problems with toxaphene).
- Biological magnification.
- Diazepam, detoxification, phenobarbital, or pentobarbital for seizures.
- Residues: terminate exposure, analysis of milk fat or fat biopsy, determine if should detoxify or cull contaminated animals.

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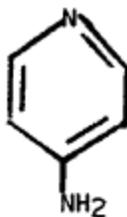
## 4-Aminopyridine

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants Associated with Stimulation or Seizures
All species, especially target birds	Minutes	Hours; potentially lethal	

## Sources

- Avitrol.
  - Bird control agent - usually used in corn - so corn present in GI tract.
  - Baits contain 0.5 - 3.0% of 4-aminopyridine.
  - Also available in concentrated (25 - 50%) form cut with powdered sugar.
- Drug form of 4-aminopyridine is used to antagonize the effects of botulinus toxin or pancuronium bromide. In

Europe, used clinically in humans as an antagonist to d-tubocurare. Effective reverser of xylazine sedation and ketamine/xylazine anesthesia in many species (2,3,4). Recently shown to be effective experimentally to antagonize the effects of two sodium channel blocking toxin, saxitoxin (in red-tide-associated paralytic shellfish poisoning as well as in some neurotoxic blooms of freshwater blue-green algae) and tetrodotoxin (toxin in puffer fish and some toxic newts).



**4-aminopyridine**

### **Susceptible Species**

- Frequently presented are pigeons, starlings - that fly abnormally, squawk, exhibit involuntary muscle contractions; birds crash, deaths - some with broken necks; skull fractures, etc.
- Sometimes the intent is to poison a few - frighten off rest of birds. In other instances the intent is to kill off entire flock.
- Mammals - of similar sensitivity, poisoning infrequently occurs in dogs, horses and others.

### **Toxicity**

- LD50 approximately 20 mg/kg in rats, less in dogs (3.7 mg/kg) and birds.
- LD50 dose of 0.5% bait for a 25 kg dog would be 100 mg of 4-aminopyridine or 20 gm of bait.
- Two Quarterhorses that ingested approximately 3 mg/kg exhibited excitability, profuse sweating, convulsions, and death in 2 hours.

### **Mechanism**

- Blocks potassium channels, thereby decreasing the efflux of potassium following an action potential.
- May enhance cholinergic transmission by causing increased release of acetylcholine and other neurotransmitters.
- High doses may elevate cardiac action potential plateau and depress diastolic depolarization.

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

- Can also be absorbed through the skin to reach toxic concentrations.
- Excreted in the urine.
- Rapidly detoxified in the liver.
- No relay toxicosis reported - flesh of the poisoned animal is not considered toxic but GI tract still contains the active ingredient.

## Signs

- Mammals
  - Hyperexcitability.
  - Salivation.
  - Tremors.
  - Incoordination.
  - Clonic-tonic seizures.
  - Cardiac arrhythmias, tachycardia, increased systolic arterial blood pressure or respiratory arrest.
  - Death.
  - Liver enzymes may be elevated, metabolic acidosis may occur.
  - At doses near the LD<sub>50</sub>, initial effects are usually noted in 10 - 15 minutes and death occurs 15 minutes to 4 hours later.
- Horses - sweat profusely, convulse, rapid 3rd eyelid flutter.
- Birds.
  - Disorientation.
  - Seizures.
  - Vocalization.
- Man.
  - Metabolic acidosis is a prominent feature.

## Diagnosis

- Analysis of stomach contents - consistently get positive results in poisoned animals. Urine and liver may be worth analyzing as well.
- Rapid onset of effects.
- Rapid onset of rigor after death.

## Differential Diagnosis

Organochlorine insecticide, acute lead, strychnine, metaldehyde, methylxanthine, tremorgenic mycotoxin, nicotine, and amphetamine poisoning.

## Treatment

- Emesis if presented before onset of clinical signs. Gastric or rumen lavage or enterogastric lavage if the emetic is contraindicated or if it fails.
- Activated charcoal and saline cathartic.
- Pancuronium bromide (curare-related drug) antagonizes the effect of 4-aminopyridine and has been (very carefully) used to control seizures in man. Endotracheal intubation should precede administration in case of induction of respiratory paralysis.
- diazepam or phenytoin has also been recommended for seizure control.
- Propranolol (dog, 0.04 - 0.05 mg/kg, IV, slowly) has been recommended for tachyarrhythmias.
- Horses - heavy sedation with xylazine has provided nearly complete relief from excitement and muscle tremors.

## Key Features

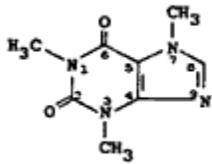
- Avitrol - corn.
  - Birds present in large numbers (especially pigeons) most often poisoned (target species).
  - Enhanced cholinergic transmission, muscle contractions, excitation, tremors, seizures, arrhythmias.
  - Analyze stomach contents.
  - diazepam, phenytoin or curariform drugs (intubate, artificial respiration as needed), propranolol as needed.
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## Chocolate, Caffeine, and other Methylxanthines

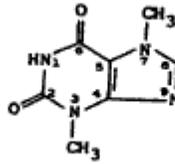
Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants Associated with Stimulation or Seizures
All species, esp. smaller dogs	Minutes to hours	Hours; potentially lethal	

### Sources

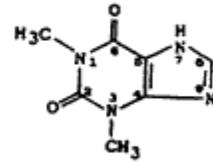
- Most poisonings from methylxanthines occur as a result of chocolate ingestion of dogs.
- Baking chocolate is especially toxic.
- Chocolate toxicoses especially at holidays: Valentine's day, Easter, Halloween, and Christmas.
- Cocoa bean hulls or waste used as bedding for animals has caused toxicosis primarily in horses.
- Second most prevalent poisoning from these agents is a result of caffeine tablets ingested by dogs (often tablets contain 100 mg each).
- Caffeine present in many over the counter medications.
- Caffeine used to hype race horses.
- Theophylline tablets or elixirs used as human or veterinary medication.
  - Readily passed in the milk of exposed lactating animals.



Caffeine



Theobromine



Theophylline

Amounts of Methylxanthines in Chocolate		
	Caffeine	Theobromine
Milk chocolate (1 oz)	6 mg	44 - 56 mg
Hot cocoa (6 oz cup)	5 mg	75 mg
Baking chocolate (1 oz unsweetened)	35 - 47 mg	393 mg
Sweet cocoa (1 oz 35% unsweetened)	20 mg	130 mg
Dark sweet chocolate (1 oz)	21 mg	134 mg
Semi-sweet chocolate (1 oz)	22 mg	138 mg
White chocolate (1 oz)	0.85 mg	0.2 mg
Oreo cookies (1)	2.4 mg	15 mg

- The theobromine content of cocoa beans is 1 - 2% and that of the hulls are 0.5 - 0.85%
- "Tootsie Rolls" contain 20 mg (caffeine and theobromine) per ounce. Bite sized "Tootsie Rolls" weigh 0.23 ounces

Equivalency of Formulations of Theophylline Derivatives and Salts Compared with Parent Theophylline		
Formulation or Salt	Trade Name	Percent Theophylline
Theophylline base and theophylline elixir	Various	100%
Theophylline monohydrate	-	90%
Theophylline ethylenediamine (aminophylline)	Various	78 - 86%
Choline theophylline (oxtriphylline)	Choledyl (Parke-Davis)	65%
Theophylline sodium glycinate (Sandoz)	Synophylate (Central Pharm.)	50%
Theophylline calcium salicylate	Quadrinal (Knoll)	48%

Comparative Pharmacokinetics of Theophylline*					
Species	Peak Concentration after Oral Administration (hours)	Elimination Half-Life (hours)	Volume of Distribution (L/kg)	Percent Bioavailability	Recommended Theophylline Dose
Humans	0.5 - 2.0	9.0	0.5	96%	4 mg/kg every 6 hours
Dogs	1.5	5.7	0.82	91%	9 mg/kg every 6 - 8 hours
Cats	1.5	7.8	0.46	96%	4 mg/kg every 8 - 12 hours

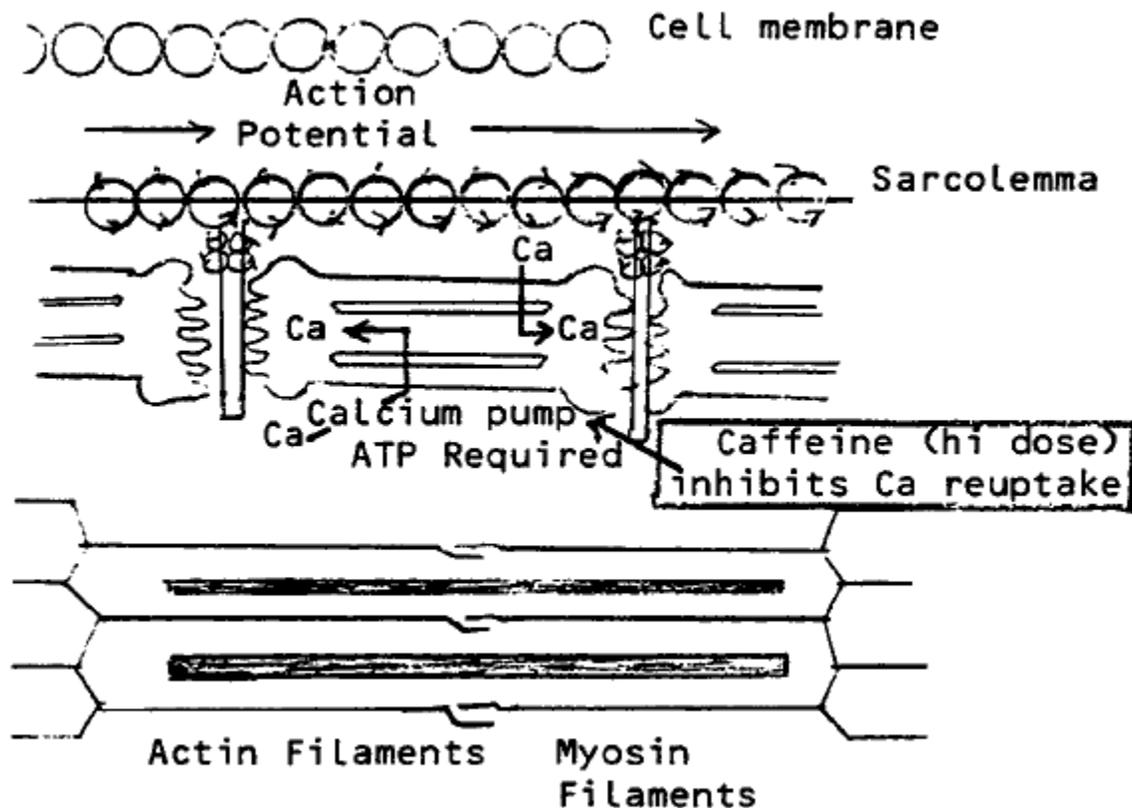
\*This table documents regular release formulations of theophylline.

## Mechanisms

Gaps in information exist with regard to the relationships between mechanisms of action *in vivo* and those identified in studies performed *in vitro*.

## Effects

- *Greatest sensitivity (definite clinical relevance)*: competitive antagonism of cellular adenosine receptors. Inhibition of adenosine receptors is likely to account for the behavioral effects and some of the other physiologic effects at therapeutic levels of exposure of methylxanthines. Inhibition at adenosine receptors is also presumably involved in effects noted at toxic doses. Adenosine receptors are linked through guanine nucleotide-binding regulatory proteins (G proteins) to adenylyl cyclase and to other effector systems. One adenosine mediated effector which is thought to function independent of adenylyl cyclase is a type of K<sup>+</sup> channel in cardiac (atrial) tissue. Inhibition of adenosine receptors causes CNS stimulation, constriction of some blood vessels, and tachycardia.
- *Intermediate sensitivity (definite clinical relevance)*: inhibition of calcium sequestration due to methylxanthine induced inhibition of Ca<sup>++</sup> reuptake. The net effect is increased free Ca<sup>++</sup> and associated increases in contractility of skeletal and cardiac muscle.
- *Least sensitivity (uncertain clinical relevance)*: inhibition of phosphodiesterase. Although historically regarded as of intermediate sensitivity (less sensitive than inhibition at adenosine receptors and more sensitive than reduced reuptake of Ca<sup>++</sup>), it is now less clear. It appears that concentrations capable of inhibiting phosphodiesterase sufficient to increase cyclic AMP concentrations are unlikely to be seen *in vivo* except, perhaps, after massive overdoses of methylxanthines. Increases in cyclic GMP are somewhat more likely to occur *in vivo* than are increases in cyclic AMP.
- *Other effect - (clinical importance unclear)*: Competition for benzodiazepine receptors in the brain.



**Excitation-contraction coupling in the muscle, showing an action potential that causes release of calcium ions from the sarcoplasmic reticulum and then reuptake of the calcium ions by a calcium pump.**

### Toxicity

- Similar in different species: dogs affected most due to eating habits. Theophylline LD<sub>50</sub> in dogs 300 mg/kg, cats 700 mg/kg. Caffeine and theobromine LD<sub>50</sub>'s in the dog are 140 mg/kg and 250 - 500 mg/kg, respectively.
- Animals that are more sensitive than average may die at less than LD<sub>50</sub> doses. Therefore, less than 2 ounces milk chocolate/kg bw or 10% this amount of baking chocolate could comprise a lethal dose.

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

- Absorption rapid after oral or parenteral administration.
- Parenteral administration does not prevent the development of some clinical signs of toxicoses, e.g., vomiting. GI signs are, at least in part, a result of plasma concentrations of methylxanthines.
- Enterohepatic recirculation after excretion in bile.
- Liver microsomal enzymes promote the metabolism of caffeine. The compounds also undergo N-demethylation and phase II conjugation reactions.
- Also eliminated in the urine.
- Very little parent methylxanthine compound is passed in the feces.
- Half-life of theobromine in dogs is comparatively long (17.5 hours) which also predisposes the species to chocolate toxicoses.
- Half-life of caffeine in dogs is 4.5 hours.

## Signs

- Vomiting (common initial sign), diarrhea, diuresis, restlessness, hyperactivity, tachycardia, PVCs, tachypnea, ataxia, tremors, seizures, weakness, coma, cyanosis, hypertension. May "bounce" when picked up and dropped a few inches onto feet.
- Possible hyperthermia, dehydration.
- Diuresis and vomiting may coincide with hypokalemia.
- Death from cardiac arrhythmias or respiratory failure.
- Horses exhibit anorexia, diarrhea, violent excitement and death.
- Teratogenesis: all 3 methylxanthines are teratogenic in laboratory animals.

## Diagnosis

- Exposure, clinical signs.
- Submit frozen plasma, urine, stomach contents (frozen).

## Lesions

- No specific lesions.

## Treatment

- Avoid erythromycin, corticosteroids (they interfere with excretion of methylxanthines).
- Monitor EKG: Do not use lidocaine in the cat! **Note:** in other species for ventricular-origin tachyarrhythmias use lidocaine (1 - 2 mg/kg IV until effect, 40 - 60 mg/kg/minute infusion rate to effect to maintain); if it fails, metoprolol (Lopressor®; Betaloc®) injection is preferred over propranolol - since metoprolol does not slow renal excretion of methylxanthines as propranolol can.
  - Metoprolol may be difficult to purchase. Suggested starting dose for injectable form of either metoprolol or propranolol is 0.04 - 0.06 mg/kg, which can be repeated tid and increased if needed. The rate of administration should not exceed 1 mg/2 minutes IV.
  - $\beta$  blockers can cause decrease in cardiac output and hypotension; monitor EKG.
- For bradycardia (less prevalent) use atropine at 0.04 - 0.08 mg/kg IM or SC (avoid doses causing gut stasis in cattle and horses).
- Artificial respiration if needed.
- If presented before signs, emetic; later use activated charcoal and a saline cathartic whether or not emetic was given. Repeated oral doses of activated charcoal are of additional benefit in shortening half-life (of serum theophylline).
- After signs-if vomiting is controlled, activated charcoal is given and repeated every 3 hours for up to 72 hours; saline cathartic (first 2 treatments only) or, for massive overdose, enterogastric lavage then leave activated charcoal in tract.
- diazepam for seizures; if that fails use phenobarbital and, if needed, pentobarbital.
- Catheterize urinary bladder to prevent reabsorption from urine in the bladder; fluids may also enhance excretion somewhat and counteract circulatory impairment.
- Cannot ion trap and peritoneal dialysis is ineffective.
- Crosses placenta and also excreted in milk: young may be affected (stimulated); also teratogenic in lab animals, therefore, of concern in humans as well.

## Key Features

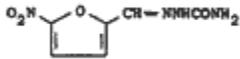
- Chocolate in dogs, caffeine tabs, cocoa bean hulls and wastes in large animals.
  - Central, peripheral and muscular mechanisms of action.
  - GI effects, PVCs, tachycardia, stimulation, tremors, seizures, coma, arrhythmias, respiratory failure, cyanosis.
  - Avoid erythromycin, corticosteroids.
  - Evacuate GI tract, activated charcoal with osmotic or saline cathartic twice at 3-hour intervals. Repeat activated charcoal every 3 hours for up to 72 hours.
  - Catheterize bladder.
  - diazepam or phenobarbital or pentobarbital, lidocaine, metoprolol or propranolol for tachyarrhythmias; atropine for bradyarrhythmias.
-

## Nitrofuran Toxicosis

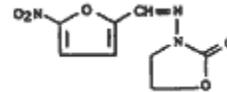
Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants Associated with Stimulation or Seizures
All species, esp. cattle, poultry	Hours to weeks	Days; often lethal	

### Sources

- Incriminated nitrofurans include: nitrofurazone, nitrofurantoin, and furazolidone. Toxicoses associated with overexposure.
- Toxicosis is apparently infrequently recognized.
- Used as a feed additive for swine and poultry. Not labeled for use in cattle.



**Nitrofurazone**



**Furazolidone**

### Mechanism

- May be related to inhibition of energy metabolism. Increases occur in pyruvate and lactate. May also inhibit enzymes responsible for the oxidation of succinate, lactate, and glycerol.
- Furazolidone antagonizes the utilization of thiamine in poultry.

### Signs

<b>Ducks</b>	Growth retardation, ascites, cardiomyopathy.
<b>Chicks</b>	Depression or hyperexcitability with convulsions, rapid onset. Deaths may follow.
<b>Chickens</b>	Delayed onset of egg production and reduced hatchability. Abnormal posture and loss of balance. Weight loss.
<b>Turkeys</b>	Cardiomyopathy, increased death losses.
<b>Bovine</b>	Depression of weight gain. Arched backs, tremors, circling and convulsions. Hyperirritability, running "fits". May see weakness, ataxia, and paralysis. Onset may be after several days on the medication.
<b>Horses</b>	Inappetance
<b>Swine</b>	Ataxia, especially in the rear; trailing of the rear limbs. Alternatively, hypermetria of the rear legs may occur. Signs aggravated by excitement. Lateral recumbency and paddling. Recovery after 3 days on clean feed.
<b>Goats</b>	Hyperexcitability, tail wagging, chewing, circling, salivation, diarrhea, colic, anorexia.

### Diagnosis

Difficult. Feed analysis may be possible but are often difficult to obtain, standards will likely have to be obtained by the laboratory (from the manufacturer).

### Pathology

- Goats treated with furazolidone.
- Slight congestion in brain, liver, kidneys.
- Histopathological findings included fatty changes in kidney tubules, fatty changes, and centrilobular necrosis of hepatocytes and dilation of sinusoids (venous congestion).

- Congestion in white matter of cerebellum and scattered vacuoles around nerve sheaths.
- Clinical pathological changes included increase in serum ammonia, urea, creatinine, potassium, and SDH activity; hypocalcemia.

### Treatment

- Terminate exposure and supportive or symptomatic therapy.
- Thiamine may have some benefit (goats).

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## Dicentra cucullaria - Dutchman's Breeches and other *Dicentra* spp.

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants Associated with Stimulation or Seizures
Herbivores	Minutes to hours	Minutes to hours; poisoning is rare	

### Images

- Dutchman's Breeches, *Dicentra cucullaria* - Google Image Search - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

### Description

- Small, somewhat parsley-like plant, soft growth. Flowers, source of the common name, white or pink with yellow tips.
- Related plant, squirrel corn, has underground corn-like tubers, not toxic, according to some sources; other sources say this and other related species should be regarded as toxic.
- Do not confuse with *Thamnosia texana*, a plant of the southwest USA, also known as Dutchman's breeches.

### Habitat

- Eastern half of the USA, grows in the midwest.
- Fatal poisoning reported in mountains of Virginia.
- Wooded areas, moist open areas in open woods.
- Other species southern USA and westward to California.
- Green and may be plentiful before other forage is abundant in the spring.

### Toxic Principle

Isoquinoline alkaloids.

### Toxicity

Danger of poisoning appears to be much less by the middle of May; high altitude hazard may persist as late as June.

### Susceptible Species

- Cattle may be much more sensitive than sheep.
- Infrequent cause of poisoning overall.

## Signs

- Trembling, running back and forth with the head held high.
- Salivation.
- Vomiting, including vomiting of rumen contents.
- Abdominal pain.
- Possible dyspnea.
- Trembling becomes continuous.
- Prostration.
- Convulsions and opisthotonus.
- Acute course.
- Rarely fatal.
- Recovery from poisoning is rapid.

## Lesions

Nonspecific.

## Treatment

- May recover in a few hours without treatment.
- Appropriate to administer activated charcoal and, if hydration is adequate or after it is restored, to use a saline cathartic as well.
- activated charcoal may be mixed in feed if just exposed and asymptomatic or minimally affected (early in course).
- Symptomatic and supportive care.
- Supplemental feeding may reduce consumption to subtoxic amounts.

## Prevention

Prevent access to the plant.

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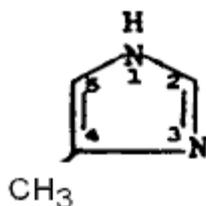
## 4-Methyl-Imidazole

(Bovine Bonker's Syndrome; Ammoniated Feed Syndrome)

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants Associated with Stimulation or Seizures
Herbivores, esp. ruminants	Minutes to days	Hours to days; often lethal	

## Sources

- 4-Methyl-imidazole (4-MI) is formed as a result of ammoniation of feeds in an attempt to increase the feed value of low and medium quality forages. A Maillard reaction occurs = a condensation of an amino group with a reducing sugar.
  - Ammoniated molasses.
  - Ammoniated higher quality forages such as forage sorghum, hybrid sudan, cereal grain, brome, fescue, alfalfa, wheat, and bermuda hays.
  - Ammoniated wheat straws, corn stalks, and corn silage are less often a problem, since they contain low levels of soluble sugars which are necessary for the formation of 4-MI.
  - Ammoniated straw is reportedly made more toxic as a result of heat build-up from wrapping treated bales in black plastic.
- Metabolites (not 4-methyl-imidazole itself but still toxic) in the milk of cows fed ammoniated forage or molasses.



**4-methyl-imidazole**

### Toxicosis

Fairly uncommon, not rare.

### Toxicity

- Pyrazines and imidazoles are formed as a result of the ammoniation of feeds.
- 4-MI is formed as a result of a nonenzymatic reaction (Maillard reaction) caused by the condensation of an amino group and a reducing compound (amino acid and reducing sugars).
- Pyrazines are considered to be nontoxic.
- 2-MI and 4-MI are known convulsant agents in mice; 4-MI is more potent than is 2-MI.
- Adult cattle, calves and other nursing animals [by virtue of the passage of active metabolites (not parent compound) in the milk] may all be poisoned.
- Occasionally, only calves affected. When calves were affected (and the cows nursing the calves acted normally), 40 - 120 ppm of 4-MI was found in incriminated forages. The threshold concentration for toxicosis, however, has not been established.

### Signs

- Onset: rapid or up to weeks after start on treated hay.
- Mouth chomping, salivation, impaired vision.
- Hyperexcitability, wild running, circling, seizures, death.
- Lactating cows may be more resistant than forage-eating calves (onset may occur after several days of feeding depending on concentration).
- Nursing calves may be affected even more rapidly (onset may occur within 2 days of the first feeding of the cows).

### Diagnosis

- Clinical signs, history of intake of appropriate ammoniated foodstuff; identification of 4-MI in significant amounts in ammoniated forage, molasses or complete ration.
- No lesions on postmortem.

### Treatment

- No treatment known.
  - Terminate exposure, symptomatic control of hyperexcitability if severe, seizure control (barbiturates or chloral hydrate).
  - Symptomatic and supportive care.
  - Try activated charcoal and a saline cathartic (no studies yet).
-

## Water Deprivation - Sodium Ion Toxicosis

(Could be called "water-deprivation-sodium toxicosis-water toxicosis")

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants Associated with Stimulation or Seizures
All species, esp. swine, cattle, poultry	Minutes to days	Hours to days; often lethal Permanent brain damage possible	

### Susceptible Species

- The problem of salt poisoning and water deprivation in swine occurs also in virtually all other species. Swine are the most sensitive of the domestic animals. Horses are next, while sheep are more resistant and cattle are intermediate in susceptibility. Lactating cows are less tolerant of excessive salts in the water or diet than are other cattle. Poultry are also commonly affected.
- Major problem in swine and poultry; most problems in ruminants occur in cattle in the western states.
- Dogs occasionally affected; serious toxicosis is rare.

### Sources and Conditions that Commonly Lead to Illness

#### Swine

- Salt is an essential nutrient. It is also added to the ration to either increase or decrease palatability. Normally 0.5 - 1% of ration.
- Primary problem is usually water deprivation.
  - Mechanical failure of waterers.
  - Neglect, overcrowding.
  - Medicated water unpalatable.
  - Animals fail to find water (new surroundings).
  - Frozen water.
- High salt intake increases water requirement which increases risk. Sources may include:
  - Sodium sulfonamides.
  - Poultry wet mash made with whey or brine.
  - High salt alone usually no problem unless fresh water restricted.
  - Toxic dose of sodium chloride quoted for cattle is 2.2 gms per kg of body weight. Diets containing 2% sodium chloride do not create problems unless water is restricted.
  - Sodium in water is more hazardous than in feed (water intake exceeds feed intake and no compensatory advantage to drinking more).
  - Salt used to control intake of protein block, mineral supplement, etc., esp. if animals unaccustomed.
  - Dogs sometimes eat rock salt, usually causes vomiting and not much else. Occasional concern: excessive use of salt as an emetic.
  - Gastroenteritis, diuresis; combine to cause dehydration which increases hazard of excess sodium.
- Aggravated by unlimited access to fresh water following water deprivation or following episode of high sodium intake (water toxicosis).

#### Cattle

- Acute form occurs when excessive amounts of salt are ingested causing an irritant gastroenteritis. Dehydration results and is aggravated by the increased osmotic pressure within the alimentary tract. Some salt is absorbed. Hemoconcentration and salt absorption cause increases in serum and CSF sodium concentrations. Can cause some CNS signs in addition to GI signs.
  - More likely in semiarid areas for several reasons: water supplies in lesser supply and easily dried up; lower humidity and higher temperatures tend to greatly increase water losses from the animals. Water supplied from natural springs and deep wells and water contaminated with run-off from oil well drilling may contain high levels of sodium chloride, calcium sulfate, and calcium carbonate. Any of these salts in water and especially calcium carbonate markedly reduce water consumption when cattle are first exposed to them.

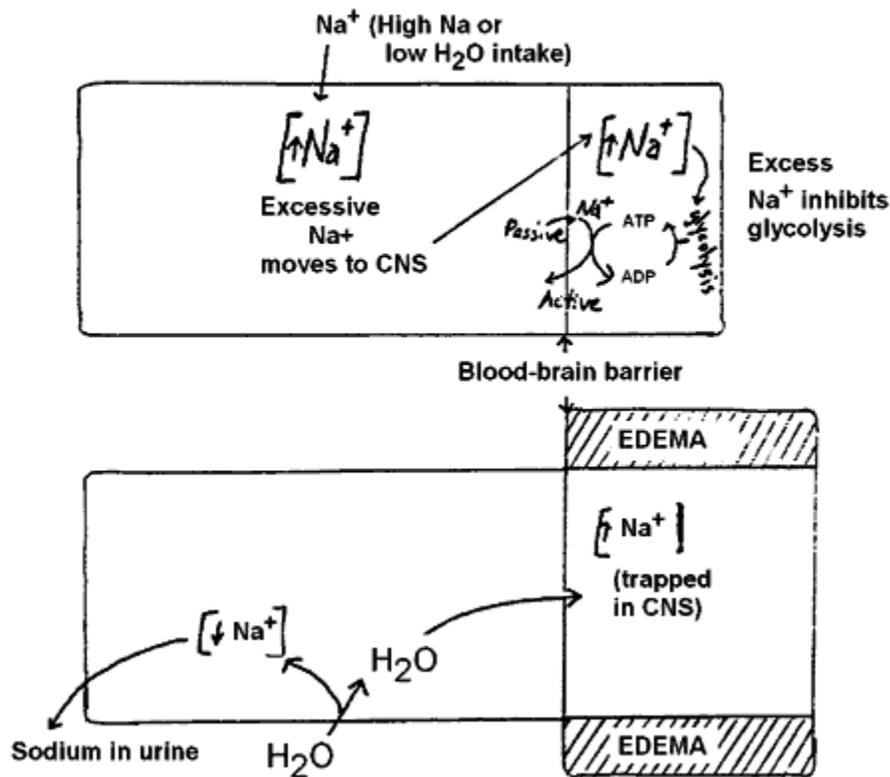
- Other causes: a sudden change from fresh water to salt water when animals are thirsty, and water accumulation in salt troughs during drought periods.
- Improperly mixed rations or attempts to limit protein supplement intake by "spiking" it with salt. Also, inadequate trough space increases the likelihood of gorging on concentrate, which may result in excessive sodium intake even with lower amounts of salt in the concentrate.
- Feeding urea can increase the likelihood of Na<sup>+</sup> toxicosis by elevating: 1) urinary output, 2) anhydremia, and 3) sodium concentrations in the brain.
- Lethal toxicosis in ruminants (especially cattle) is often associated with saline waters (especially on range) or other excessive exposure to a source of salt. Brine from oil well drilling.
- Sulfates can cause diarrhea and dehydration. Note sulfates used as saline cathartics.
- Saline waters that may be safe for cattle in the winter can be deadly in summer months.
- Total salt content of water is more important than any one salt. Total salts in water should not exceed 1.0% for cattle. Older references have suggested up to 1.5% total salts for nonlactating cattle.
- Fluorine and magnesium salts have a much greater adverse effect on the alimentary mucosa than does sodium.
- Water deprivation in the presence of normal sodium intake results in serious metabolic disturbances when cattle have lost 10% of their body water. Losses of 20 to 25% of body water are almost always fatal. Metabolic changes taking place in cattle deprived of water include:
  - Loss of weight due to reduction in tissue water and due to actual breakdown of body substance in an effort to furnish water for physiologic needs. First, fat and carbohydrate are used for this purpose and later protein.
  - Acid-base disturbances occur usually toward the acid side.
  - Obviously hemoconcentration occurs with associated polycythemia, increased plasma protein, and increased chloride and sodium.
  - Body temperature, pulse rate, and cardiac output all increase.
  - Nonprotein nitrogen increases presumably as a result of increased osmolarity of the blood resulting in decreased glomerular filtrate production and perhaps due to the increased protein catabolism mentioned above.
  - Drying out of mucous membranes, subcutaneous tissues and skin takes place.
  - Terminally, uremia, exhaustion, and collapse takes place.
- High salt consumption or water deprivation followed by unlimited access to water typically results in cerebral edema and neurological signs (water toxicosis).

### Toxicity

- Acute oral lethal doses.
  - Horse, cattle, swine: 2.2 g/kg.
  - Dog: 4 g/kg.
  - Sheep: 6 g/kg.
- Affected by salt concentration and availability of water.

### Mechanism (theory)

- Sodium is rapidly absorbed from gut, distributed throughout body.
- Normal animal.
  - Plasma Na<sup>+</sup> 135 - 155 meq/l (mean 143.3 ± 6.5).
  - CSF Na<sup>+</sup> 135 - 150 meq/l (mean 139.6 ± 5.2).
- Na<sup>+</sup> passively diffuses into CSF, but requires active transport to be removed from the CSF (energy required).
- With dehydration, high Na<sup>+</sup> in plasma diffuses into CSF; high Na<sup>+</sup> depresses glycolysis, therefore energy for active transport deprived. Na<sup>+</sup> accumulates in CSF.
- Rehydration with access to fresh water results in dilution and excretion (in urine) of excess sodium; plasma sodium returns to normal.
- Sodium trapped in CNS, attracts water due to osmotic gradient.
- Cerebral edema and resultant clinical signs.



Proposed mechanism of action

## Signs

- **Swine.** Nervous signs often include disorientation probably due to cerebral edema. (Signs described below are typical of a primary problem of water deprivation in swine.)
  - Thirst, colic, vomiting, diarrhea, pruritis, constipation (usually missed). Polyuria, late anuria.
  - Onset of nervous signs after 1 - 5 days of water restriction/deprivation.
  - Aimless wandering and circling, snout may twitch.
  - Head pushing, pivoting around one foot is common.
  - May not eat or drink.
  - Blindness, deafness, or at least nonresponsiveness in some animals.
  - Pigs dog-sit, tremor, jerk head back, fall over into clonic-tonic seizures with opisthotonos, paddling, death.
  - Morbidity varies due to salt intake, water availability, environmental conditions.
  - Mortality: averages 3 - 20%; about half of those with clinical signs die.
  - Rapid rehydration will cause more acute neurologic signs.
- **Poultry.** (Signs described are typical of a primary problem of water deprivation in poultry.)
  - Thirst, dyspnea, fluid discharge from beak, wet droppings.
  - Weakness or paralysis of hind limbs. No motor excitation.
- **Cattle.** The initial effects vary. Principle signs include weakness and dehydration. Severe water deprivation followed by access to water result in the following clinical signs in cattle:
  - Belligerent behavior.
  - Aggressiveness in getting to water supplies. This is mentioned because it makes it difficult to administer water gradually and is hard on water tanks.
  - Sucking in air as well as water with secondary bloat.
  - Incoordination.
  - Bellowing as if in severe pain.

- Fasciculation of fascial muscles.
- Ear twitching.
- Sticking the tongue out with the head outstretched as if painful in the pharyngeal area.
- Fence walking and aimless wandering.
- Some animals may have blindness, convulsive seizures followed by partial paralysis and knuckling of the fetlocks.
- Diarrhea, constipation.
- May appear normal but sometimes when approached take 3 - 4 steps and collapse pushing the muzzle into the ground.
- Animals have been known to drown in creeks unable to rise.
- Dairy cows may develop acetonemia.
- Some animals abort.
- Nursing calves are far less affected than adults by water deprivation. Waters high in salt can cause the opposite effect, that is cessation of milk production before damage to the cow is apparent.
- Sometimes hooves are sloughed.
- Those animals that develop knuckling of the fetlock joints may secondarily develop damage to the tendons, peripheral nerves, and associated tissues in spite of showing no evidence of pain.
- Some animals develop hemolysis, hemoglobinuria, and potentially anemia.
- Blindness, tonic-clonic convulsions, and terminal coma occur.
- When excessive salt intake is a primary factor in cattle, one can expect more gastroenteric signs due in part to the irritating effects of the salts. These include:
  - Anorexia.
  - Mucus in the feces.
  - Diarrhea.
  - Vomiting.
  - Death within 24 hours.
  - Additional signs may include constant polyuria and a nasal discharge.
- **Dogs.** Signs typical of ingestion of rock salt include:
  - Vomiting, gastrointestinal upset.

## Pathology

- **Swine.**
  - First 48 hours-eosinopenia, eosinophilic cuffs around vessels in cerebral cortex and adjacent meninges (eosinophilic meningoencephalitis).
  - Cerebral edema, early necrosis, malacia.
  - After 3 - 4 days-eosinophilic cuffs no longer present; see enlarged perivascular spaces left behind in some cases; eosinophils reappear in blood.
- **Cattle.**
  - No eosinophilic cuffs.
- Gross lesions in cattle with sodium ion poisoning, water deprivation, water intoxication may include:
  - Congested mucosae of the small intestine, omasum, and gall bladder.
  - Edematous lungs with moderate congestion.
  - Fluid feces.
  - Edema on ruminal surfaces associated with hemorrhage in the area adjacent to the gall bladder.
  - Edema around the major bile ducts.
  - Enlarged liver.
  - The brain appears firm, white, and swollen.
  - Polioencephalomalacia.
  - Decreased clotting of the blood postmortem (possible DIC).
  - May see leg lesions.
  - Often no gross postmortem findings.
  - Histopathologic findings include:
    - Dilation of mucosal and submucosal lymphatics in the duodenum.
    - Small foci of necrosis in the liver and renal medulla.
    - Leakage of eosinophilic material from glomeruli into Bowman's capsule.

- **Poultry.**
  - Edema of tissues.
  - Urate nephritis if saline water.

## Diagnosis

- History (if poor husbandry involved may be hard to get person to admit what happened).
- Serum and CSF Na<sup>+</sup> concentrations of over 160 meq/l. In water deprivation/ Na<sup>+</sup> ion toxicosis, CSF Na<sup>+</sup> usually exceeds serum Na<sup>+</sup>, unlike the situation in the normal animal.
  - Urine chloride increases and specific gravity decreases.
  - The PCV does not decrease much since water is apparently evenly distributed, at least in some cases, between plasma and RBCs.
- Brain (cerebrum) Na<sup>+</sup> usually exceeds 1800 ppm; often 2000 - 3000 ppm.
  - **Note:** If thorough rehydration has occurred and time has elapsed, the brain Na<sup>+</sup> may be normal. Also water deprivation and excessive serum and brain Na<sup>+</sup> concentrations may result from any other condition which prevents animals from drinking-includes other toxicoses, trauma, encephalitis, etc.
  - Ship half of brain to laboratory frozen (for analysis and virology).
  - Ship other half to the laboratory fixed in formalin.
  - Collect a complete set of tissues for toxicology and pathology in case the presumptive diagnosis is incorrect.

## Differential Diagnoses

Toxicosis due to lead, organochlorine, organophosphorus or carbamate insecticides, carbon monoxide, cyanide, metaldehyde, nicotine, and certain poisonous plants; as well as encephalitis, trauma, polioencephalomalacia, heat stroke, gut edema.

## Treatment

- Small amounts of water frequently (limit access), try to correct energy balance; i.e., hand feeding, symptomatic supportive care.
- Remove source of excess sodium if one is present.
- No largely successful therapy known. Natriuretic diuretics and anticonvulsants generally do not help.
- In extremely valuable animals or small animals the temporary use of hyperosmotic fluids (not hyperosmotic with excess sodium; instead use dextrose or other substance) may be worthwhile.
- In humans, treatment of sodium ion toxicosis/water deprivation/water intoxication with 50 - 100 ml of 5% saline has been used hourly until seizures are controlled. Monitoring to ensure that plasma sodium does not go too high is necessary. In two other human cases, therapy consisting of hypertonic glucose solutions containing physiologic quantities of balanced electrolytes IV has been effective treating dehydration and subsequent water intoxication. This course of action would appear to be more logical than treatment with saline solution.
- IV administration of dextrose and electrolytes was effective in saving some cattle after failure with water alone. Thus, hypertonic solutions (low in sodium) are recommended.

## Key Features

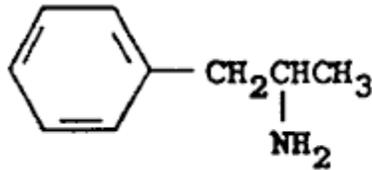
- Excess salt intake and deficient fresh water or just the latter.
  - Acute exposure: GI signs.
  - Swine - eosinophilic cuffs in brain, eosinophilia: both transient.
    - CNS signs, disoriented.
  - Cattle - no eosinophilic cuffs, may be belligerent, aggressive around water source, may drown after get to water; may damage soft tissues of legs.
  - Diagnosis - brain, CSF, and serum sodium; histopathology; rule out other causes.
  - Treatment - limited water intake, IV hypertonic solution (not NaCl). Supportive, symptomatic.
-

## Amphetamine Toxicosis

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants Associated with Stimulation or Seizures
Small animals, horses	Minutes	Hours to a day or so; potentially lethal	

### Sources

- Poisoning may be a result of exposure to illicit drugs and the caller may be reluctant to divulge the drug involved.
- Animal chewing up an owner's prescription bottle or eating spilled medication.
- Tablets often 5 - 10 mg each.



Amphetamine

### Toxicosis

- Uncommon, not rare.
- Estimated LD<sub>50</sub> 10 - 30 mg/kg.
- Deaths (man) reported following ingestions as low as 1.3 mg/kg of metamphetamine.

### Mechanism of Action

- Most important mechanism: stimulates catecholamine release centrally and from adrenals; stimulate cortical centers including cerebral cortex, medullary respiratory center, reticular activating system.
- Sympathomimetic compound-stimulates at sympathetic nerve endings greater stimulant activity than norepinephrine.
- Inhibits monoamine oxidase.

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

- Rapid absorption from GI tract.
- Enters CSF, CSF concentrations reported to be 80% of plasma concentrations.
- Elimination dependent on pH. Acidic pH shortens elimination half-life.

### Differential Diagnosis

Strychnine, organochlorine insecticide, methylxanthine, 4-aminopyridine, metaldehyde, other illicit drug toxicoses.

### Signs

- Similar cardiac and CNS effects to those seen in methylxanthine toxicosis.
- Seizures are infrequent, but can occur.
- Coma may sometimes be seen.
- Hypertension, hyperthermia, lactic acidosis, hypoglycemia.
- Mydriasis, tachycardia, hypertension, arrhythmias, occur in man; less commonly vomiting, diarrhea, dysuria, urinary retention.
- Renal failure secondary to rhabdomyolysis, dehydration sometimes reported.
- Hyperthermia, hyperventilation.

## Diagnosis

- Presence of tablets in vomitus or gastroenteric contents-confirm analytically if in doubt.
- Plasma concentrations of amphetamine, amphetamine in urine.

## Treatment

- Early before marked signs: emetic in SA, lavage if ineffective or later when animal is stimulated (after appropriate sedation). Activated charcoal and cathartic.
- Chlorpromazine (10 - 18 mg/kg IV) or haloperidol (1 mg/kg IV) given after administration of a lethal intravenous dose of amphetamine sulfate (10 mg/kg) increased survivability in dogs. Hyperthermia was also antagonized by chlorpromazine and haloperidol.
- Diazepam is effective (oral or IV administration) in man and therefore would probably be effective in dogs. Controls most of the undesirable CNS stimulatory effects.
- Barbiturates are probably adequate in other species, including the cat.
- If the body temperature becomes markedly elevated, it is probably wise to employ external cooling (ice, etc.).
- Amphetamine is a basic drug and its excretion can be enhanced by acidifying the urine. **Note:** there are precautions that are essential-acidification is **contraindicated** if the animal is in renal failure for any reason or if severe myoglobinuria from muscle damage is occurring.
- Ammonium chloride or ascorbic acid can be used in small animals to lower the urine pH to the range of 4.5 to 5.5.

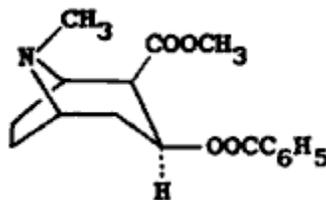
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## Cocaine Toxicosis

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants Associated with Stimulation or Seizures
Small animals	Minutes to hours	Hours; potentially lethal	

## Sources

- Natural alkaloid from coca (*Erythroxylon coca*).
- Used clinically in a 1 - 4% solution as an eye anesthetic or in 10 - 20% solution as a nasopharyngeal anesthetic. Requires special license.
- Poisoning may result from exposure to illicit drug. Exists as hydrochloride salt or as cocaine base, "crack"
- Note street cocaine is often impure, adulterants include sugar, local anesthetics, phencyclidine, etc.
- Cocaine look alikes commonly include sympathomimetics, e.g., phenyl propanolamine or ephedrine, caffeine, local anesthetics.



Cocaine

## Toxicosis

Uncommon.

## Toxicity

- Not well established.
- 20 mg capable of killing adult human.

## Mechanism of Action

- Local anesthetic effect is related to blocking fast Na<sup>+</sup> channel current.
- Powerful CNS stimulant effect is probably due to inhibition of reuptake of endogenous catecholamines, cocaine is the only local anesthetic with this effect.
- Stimulates dopaminergic neurotransmission by blocking the reuptake of dopamine.
- Pharmacologic effects include vasoconstriction, mydriasis, tachycardia, predisposition to seizures, arrhythmias are believed to be associated with activation of sympathetic system.
- Large doses cause direct cardiotoxicity.

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

- Rapidly absorbed from mucous membranes.
- Slightly delayed after oral ingestion.
- Enters milk and readily crosses the placenta.
- Metabolism not understood-plasma pseudocholinesterase and hepatic esterases involved.
- Nearly all is metabolized (only 5% is excreted unchanged in the urine). Other metabolites are eliminated via the urine.

## Clinical Signs

- Dogs-experimental IV administration (LD<sub>100</sub> = 39.5 mg/kg).
  - Hyperthermia. Also suspected as a cause of malignant hyperthermia.
  - Acidosis.
  - Tachycardia.
  - Seizures.
- Accidental poisoning clinical signs dogs and cats.
  - Hyperactivity, erratic behavior, depression, coma, seizures.
  - Vomiting, salivation.
  - Tachycardia.
  - Pulmonary edema, panting.
- The following clinical signs have been reported in human poisonings.
  - Initial tachycardia and hypertension followed by hypotension. Cardiac arrhythmias common.
  - Hyperpnea, respiratory arrest, pulmonary edema.
  - CNS stimulation, seizures.
  - Vomiting.

## Treatment

- Early, before clinical signs develop, emetic in small animals, followed by activated charcoal and cathartic. Gastric or enterogastric lavage may be required.
- Seizures if present may be controlled with diazepam.
- Cardiac tachyarrhythmias control-experimental pretreatment with high doses of propranolol (6 - 10 mg/kg IV) prevented development of tachycardia and hypertension. However, coronary vasoconstriction may be increased by propranolol. Because of the relatively short action of cocaine on the heart, usually, the short acting  $\beta_1$  selective blocker, esmolol, would be recommended with a half-life on the order of 10 minutes, repeated doses of esmolol may be needed. Another  $\beta_1$  selective blocker to consider using in these cases is atenolol. Its half-life is long, however, at 3 to 9 hours in the dog.
- Chlorpromazine (12 mg/kg IV) pretreatment decreased seizure activity, prevented acidosis, and prevented hyperthermia in dogs that received a lethal IV dose of cocaine. Possible benefit of chlorpromazine is through antidopaminergic effects. May lower seizure threshold. Also consider using if animal is extremely hyperthermic.
- Control hyperthermia by physical means.
- Diuresis, acidification are not effective.
- Fluid therapy if hypotension present.

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## Tremorgenic Mycotoxins and Various Staggers Syndromes

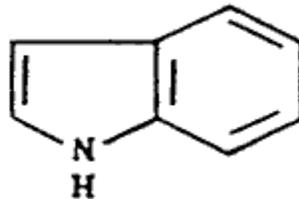
Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants Associated with Stimulation or Seizures
All species, esp. dogs, cattle	Minutes to days	One day to weeks; often lethal in dogs	

## Images

Bermuda Grass, *Cynodon dactylon* L. - Google Image Search - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

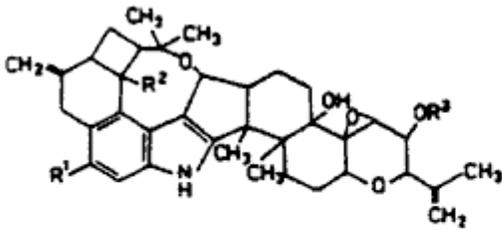
## Introduction

Tremorgens are mycotoxins (secondary fungal metabolites) which contain an indole moiety, presumably derived from tryptophan and which produce tremors or seizures in animals consuming toxic amounts of contaminated foodstuffs. There are at least five groups of tremorgens. The penitrem group, the paspalitrem group, the fumitremorgins group, the verruculogen group, and the tryptoquivaline group.

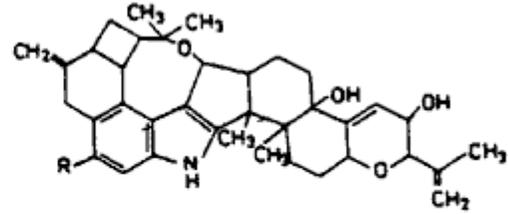


Indole

## Structures



Penitrem A,  $R^1 = Cl$ ,  $R^2 = OH$ ,  $R^3 = H$   
Penitrem B,  $R^1 = H$ ,  $R^2 = H$ ,  $R^3 = H$   
Penitrem E,  $R^1 = H$ ,  $R^2 = OH$ ,  $R^3 = H$   
Penitrem F,  $R^1 = Cl$ ,  $R^2 = H$ ,  $R^3 = H$   
25-O-Acetylpenitrem A,  $R^3 = AC$



Penitrem C,  $R = Cl$   
Penitrem D,  $R = H$

### 1. Penitrem A

Among the more common tremorgens are *Penicillium* mycotoxins, such as penitrem A. In older literature, this compound may appear as tremortin-A.

#### Sources of Penitrem A Include:

- Moldy refrigerated foods, cottage cheese, cream cheese.
- Moldy walnuts, especially English walnuts in Central to Northern California.
- Moldy peanuts.
- Moldy stored grains, mixed feeds.
- Penitrem A was initially isolated from *P. crustosum*, and so far, intense production has been limited to species of:
  - *P. crustosum*, *P. granulatum*, *P. cyclopium*, *P. palitans*, and *P. puperum*.

#### Susceptible Species

Include at least the following: bovine, ovine, equine, porcine, canine, rabbit, poultry, and several species of rodents.

#### Mechanisms

- Increases in resting potential, end plate potential, and duration of depolarization. Influence presynaptic transmitter release.
- Penitrem A facilitates transmission of impulses across the motor end plate.
- Also suggested that penitrem A inhibits glycine where it acts as a neurotransmitter in inhibitory neurons in the spinal cord.
- Verruculogens reduce brain GABA concentrations.

#### Toxicity of Penitrem A and Penitrem B

- Mice tremor at .25 mg/kg/bw of penitrem A.
- Mice tremor at 1.3 mg/kg/bw of penitrem B.
- LD50 penitrem A-1.05 mg/kg.
- LD50 penitrem B-5.84 mg/kg.
- Penitrem A is acid labile.

## Signs

- Tremors, seizures, and prostration.
- With low doses, fine muscle tremors occur; at high doses, convulsions and possible death may occur.
- Possible sequellae (seen in rats) are Parkinsonism-like signs that last up to 2 weeks.
- Polyuria may occur, possibly attributable to hyperglycemia.
- Dogs tremor from 2 - 4 hours to much longer until death during seizures, or may gradually return to normal over 1 - 2 days.

## Lesions

- No specific neurologic or muscle lesions. Trauma from seizures.
- Increased lactic dehydrogenase, creatinine phosphokinase, pyruvic acid, blood glucose.

## Diagnosis

- Differential diagnosis: in large animals, the syndrome is most similar to other mycotoxin-associated diseases such as paspalum (or Dallis grass) staggers, and Bermuda grass tremors (both believed to be due to tremorgens).
- For small animals, a bioassay may help in confirmation: 0.5 gram moldy food or stomach contents is emulsified in 2 ml of buffered saline. Mice are given 0.6 ml orally. Signs appear in 10 - 20 minutes and include: hyperirritability and muscle tremors. Over 2 - 3 hours, mice may have tonic-clonic seizures and opisthotonos alternating with depression and tremors. Some mice die, others recover over 24 hours.
- If standards are available, penitrem A is reportedly rapidly detected on thin-layer chromatography (TLC); when possible, submit suspected source to a laboratory which has standard.
- No specific lesions are seen at necropsy or on histopathology, secondary trauma is possible.

## Treatment

- For acute toxicosis, activated charcoal and a saline cathartic are recommended after the animal is appropriately sedated.
- Pentobarbital anesthesia has been advocated for control of seizures.
- Fluids and corticosteroids have been recommended for shock when present; and cold water baths for hyperthermia.
- Drugs that increase glycine in the CNS including mephenesin or nalorphine were shown to be able to abolish penitrem A tremors in mice.

## 2. Staggers Syndromes

### Introduction

- Staggers syndromes have different etiologies but similar clinical presentations. Syndromes include ryegrass staggers, paspalum (Dallis grass) staggers, Bermuda grass staggers, and corn staggers. Hyperexcitability and muscle tremors (which are enhanced by disturbing the animal) characterize the disease syndromes. Affected cattle have a stiff, stilted gait, ataxia, and may fall. A down animal may not get up unless left undisturbed for some time. Clinical signs include twitching of shoulder and flank muscles, head tremors, and an inability to stand or walk. Animals may become debilitated (limb injuries) and death from dehydration can occur.
- In all grass staggers syndromes, hazard increases with plant maturity and is greatest in later summer and fall particularly as a result of rainy, humid weather.

### Paspalum or Dallis Grass Staggers

#### Sources

- Paspalum staggers has been associated with Argentina Bahia grass and brown-seed paspalum in addition to Dallis grass (all *Paspalum* spp.).
- The syndrome has been associated with heavy ergot infection of Dallis grass heads. Both the sclerotial stage and the honeydew stage may induce the toxicosis.

- Dallis grass grows primarily from New Jersey south to Tennessee and Florida, west to Texas and California. Close grazing or mowing is recommended to prevent ingestion of ergot sclerotia in the mature seed heads. It is, however, also cut for hay.
- Paspalum staggers has been reported primarily in cattle and occasionally in sheep and horses in New Zealand, S. Africa, Australia, the USA, Portugal and Italy.
- *Claviceps paspali* grows on Dallis grass especially and generally produces little ergot alkaloid, but may produce significant tremorgens, namely paspalitremes.
- *Claviceps purpurea* generally produces ergot alkaloids  $\pm$  a small amount of tremorgen.

## Poisonous Principles

- Two of the tremorgens produced by *C. paspali* are paspalitremes A and B.
- Honeydew stage-toxicity.
  - Before the sclerotia are formed in the mature seed head, the infected flower heads are in the honeydew stage.
  - These may be up to 30 - 50% as toxic as the sclerotia.
- Lysergic acid related (ergot) alkaloids are present in low concentrations in ergotized Dallas grass, but these are apparently not responsible for the clinical neurology effects.
- Instead, the agents probably responsible are the tremorgens in the ergot sclerotia, which are roughly 1/30 as potent as penitrem A.
- When ergot alkaloids are administered with the tremorgens no difference is seen from animals receiving tremorgens alone.
- When the ergot sclerotia were force-fed to a 20 kg lamb at a high, 135 gm, single dose, it developed severe head and leg tremors the first day. The signs increased, and within 2 days the lamb was laterally recumbent, thrashing its limbs; and it died on the 3rd day.
- When 45 gm given daily for 3 days, a second lamb showed similar but less severe signs becoming recumbent on its sternum within 1 week of initial dosing. Over 2 weeks there was little change--tremors became severe and it was unable to stand. Its appetite remained good but its physical condition restricted its intake. It was assisted to and supported on its feet frequently during the 4th week at the end of which it was able to stand a few minutes. Thereafter, it gradually recovered over several weeks.
- When lambs were dosed over 6 - 8 consecutive days, mild head tremors were present at 24 hours after the 1st dose. Signs increased over 72 hours and incoordination of movements was noticeable after being driven. Responses were similar at 4 and 5 days. At 6 days, one showed severe tremors and rocked unsteadily on its feet and, therefore, they received no more ergot material. One lamb collapsed and thrashed about on the 7th day after a dog chased them.
- On days 8 - 12 all showed marked head and limb tremors and incoordinated limb movements when moved. When chased for a short distance, all developed short, stiff, leg movements, collapsed, and rolled on their sides. After several minutes on the ground, the lambs walked away unsteadily with hindquarters swaying and with general shaking of the body. From this state all the sheep made a gradual but complete recovery over 14 - 20 days.
- Cattle are more sensitive than sheep but recover faster. Cattle are also more prone to eat seed heads (includes sclerotia) while sheep favor the basal leafy material.
- When four steers were orally dosed with ergotized paspalum seed, head tremors became apparent within 24 hours. By 48 hours neck tremors and head nodding movements appeared. On the third day marked tremors of shoulders and hindquarter muscle groups were present. Incoordination, swaying, stumbling, and commonly collapse occurred. All signs increased when driven. On cessation of dosing, cattle got better each day. Recovery was complete in 4 - 6 days. Signs regressed in the reverse order of appearance. A dose of paspalum ergot greater than 1 gm/kg/day was enough to produce severe staggers in cattle.
- Lysergic acid alkaloids.
  - When sheep were given 3 mg D-lysergic acid hydroxyethylamide, the signs of Dallis grass staggers were not reproduced. Instead, the sheep almost immediately had lip licking movements and tail wagging, and they walked in a backwards direction. Frequently the hindquarters sagged somewhat, then the stance was corrected with a sudden jerk. No head or body tremors were seen but the respiratory rate was increased. The response reached a peak within 1 hour of injection and then declined until the sheep were normal within 5 hours. Thus, LSD effects are **not** those of Dallis grass staggers.

## Cattle and Sheep - Summary of Signs of Paspalum Staggers

- Tremors either confined to the head or extending over the whole body, and incoordination.
- Severely affected animals may show only mild tremors when undisturbed, but when forced to run quickly develop incoordination-marked tremors and temporary collapse.
- Cattle and sheep typically move their hind legs in unison.

## Ryegrass Staggers

- Ryegrass staggers is a significant problem affecting sheep, cattle, and sometimes horses in New Zealand, Australia, and possibly the Southeast USA.
- Toxicosis occurs primarily on perennial ryegrass (*Lolium perenne*) pastures that are eaten down low, and are dry. Sheep more commonly poisoned since they graze lower.
- Poisoning also associated with horses fed a pelleted ration that had perennial ryegrass hay presumably from Oregon as the primary ingredient.
- The organism now believed to produce the principal toxin that accounts for the signs of ryegrass staggers, lolitrem B, is produced by the endophytic fungus, *Acremonium lolii*.
- Previously suggested causes include Penitrem A and other tremorgens such as verruculogen and fumitremorgen B.
- *Aspergillus caespitosus* as well as *Penicillium piscarium* (isolated from a ryegrass pasture after a staggers episode in New Zealand) produced the latter two of these tremorgens.

## Clinical Signs and Lesions

- **Horse.**
  - Mild excitability, spastic ataxia, hypermetria, tetany (severe cases).
  - Elevated lumbosacral cerebral spinal fluid protein concentration 76 - 138 mg/dl. Normal values 70 mg/dl.
  - *Penicillium cyclopium* identified in ryegrass strain.
- Animals often appear normal at rest. When incited to move, stiff spastic gait, muscle spasms, occasionally tetanic seizures.
- Some animals with ryegrass staggers may have lesions in cerebellar purkinje cells.

## Corn Staggers

- May be seen with ingestion of corn silage.
- Especially associated with consumption (generally by cattle) of lodged (knocked down) corn.
- Spores of *A. flavus* and the tremorgen aflatrem have been implicated. It is likely that other *A. flavus*-produced toxins such as aflatoxins and cyclopiazonic acid may cause hepatic and digestive problems in some outbreaks.

## *Penicillium Martensii* on Crabgrass also Produces a Tremorgen

- This toxin causes trembles, spastic legs, and some blindness.
- A similar syndrome has been experimentally reproduced in mice.

**Note:** *Claviceps paspali*, *Aspergillus* sp. and *Penicillium* sp. are the principal organisms known to produce tremorgens at the present time.

## Key Features

- Moldy cheese, cream cheese, walnuts, refrigerator foods or occasionally grains
- Ergotized grain or Dallis grass, possible endophytic fungus in ryegrass.
- Fine muscle tremors, more severe tremors, hypermetria, excitation, seizures, deaths. Signs worse after stimulation. Hopping in large animals and with time weakness and paralysis.
- Signs may persist for days possibly up to weeks.
- Dallis grass staggers, cattle more sensitive.

- Signs in cattle usually disappear after 2 - 4 days on an uncontaminated diet.
- Treatment of acute toxicosis-terminate exposure and consider symptomatic and especially supportive care (herd feeding and watering may be essential); activated charcoal and saline cathartic.

### Bermuda Staggers (Bermuda Grass Tremors)

- First reported to affect cattle in 1951.
- Affects animals in large areas of the southern USA.
- Causative toxin(s) has **not** been identified.
- 3 syndromes have been associated with ingestion of Bermuda grass:
  1. Tremors and/or posterior paralysis that may be exercise-associated with consumption of hay.
  2. Hepatogenous photosensitization, icterus.
  3. Pulmonary edema and emphysema associated with consumption of green grass in spring.

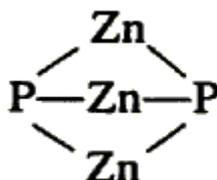
### Zinc Phosphide and Aluminum Phosphide

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants Associated with Stimulation or Seizures
<b>Zinc phosphide</b> (rodenticide)	All species, esp. dogs	Minutes to hours (neurologic or respiratory effects). Days (liver failure)	Neurologic signs: 1 to 2 days; often lethal Liver damage: days to permanent	
<b>Aluminum phosphide</b> (Fumigant)	All species	Minutes to hours (neurologic or respiratory effects). Days (liver failure)	Neurologic signs: 1 to 2 days; often lethal Liver damage: days to permanent	

### Sources

- Zinc phosphide is a dull, grayish-black powder used mainly as a rodenticide and for killing moles. Products: Zinc Phosphide, Kilrat, Rumutan.
- Zinc phosphide, or occasionally aluminum phosphide, may be used in baits of bread, buns, soaked wheat, damp rolled oats, or sugar at concentrations of 2 - 5%.
- Aluminum phosphide is used as a grain fumigant for insect and rodent control and in dusts for insect control.
- Zinc phosphide is unstable in water or acid, but is stable for about 2 weeks under average climatic conditions. Can be stable for long time periods if kept dry.
- Aluminum phosphide degrades more readily than zinc phosphide.
- Either compounds degrade to reactive (toxic) phosphine gas which accounts for much of the toxicity and smells like garlic or rotten fish.

### Zinc Phosphide



## Toxicity

- Lethal doses cattle, sheep, pigs, goats, dogs, cats between 20 - 50 mg/kg.
- Animals poisoned by feeding directly on bait or relay toxicosis associated with eating tissues of zinc phosphide-poisoned animals.

## Mechanism

- Food in the stomach increases HCl production which greatly increases the breakdown to toxic phosphine (PH<sub>3</sub>) gas which induces serious acute effects due to enteric and pulmonary irritation.  $Zn_3P_2 + 6H_2O \rightarrow 3Zn(OH)_2 + 2PH_3$ .
- CNS effects are due to an unknown mechanism but acidosis and hypocalcemia may occur.
- Both phosphine and intact zinc phosphide are absorbed from the GI tract. The phosphine is believed to cause the majority of acute signs, while the intact phosphide may cause hepatic and renal damage later.

## Signs

- Zinc phosphide causes emesis frequently in nonrodent species and, because of this effect, fatal poisoning is not a consistent sequel to ingestion. A few preparations have added tartar emetic to increase vomiting.
- Onset of clinical signs usually occurs from 15 minutes to 4 hours after ingestion, but may be delayed for up to 18 hours.
- Large doses may cause death within 3 - 5 hours.
- Severely affected animals rarely live longer than 48 hours.
- The vomitus of zinc phosphide-poisoned animals often contains dark blood.
- Dogs may show lateral recumbency with whole body tremors and salivation. May proceed into "running fits" and repeated jerking of the head. Terminal exhaustion may occur.
  - Anorexia, lethargy, and rapid deep breathing which often becomes wheezy or "clicky" sounding.
  - Abdominal pain, ataxia, weakness, and recumbency may follow.
  - Acidosis is prominent, and there may be hypocalcemia, terminal hypoxia, gasping, and struggling.
  - Hyperesthesia and sometimes seizures may be seen, and in some dogs these may closely resemble strychnine convulsions.
  - Hepatic and renal damage often may be detected 5 - 14 days later.
  - Acetylene (garlic, rotten fish) odor on breath.
- Abdominal pain, colic in horses, and bloat in cattle.

## Lesions

- Opening the stomach will reveal a characteristic acetylene odor and possibly evidence of gastritis (may be severe).
- Nonspecific postmortem findings.
- The lungs are often markedly congested and may have interlobular edema, pleural effusion, subpleural hemorrhages also noted.
- Acutely affected animals have extreme congestion of the liver and kidney.
- Myocardial degeneration sometimes may occur.
- Pale yellow mottling of liver may appear in subacute cases.
- On histopathology, there is fatty change and congestion of the liver and kidneys. Also, there may be renal tubular degeneration, hyaline change, and necrosis.

## Diagnosis

- Tentative diagnosis based on compatible clinical signs, an acetylene odor to the breath, and opportunity for or, better, evidence of exposure to zinc phosphide. Phosphine gas rapidly dissipates.
- Frozen vomitus or gastric lavage fluid may be submitted in an attempt to obtain confirmation (phosphine gas identified for zinc or aluminum phosphide analyses). Air-tight containers required, keep samples frozen.
- Rapid freezing (and care to maintain the frozen state in transit) of stomach contents, liver, and kidney increases the probability that laboratory analysis for phosphine gas may turn out to be worthwhile (be sure laboratory has

capability to run).

- With phosphine method, false negatives may be encountered.
- In some cases, concentrations of zinc in serum, liver, and kidney may be elevated but these assays are more difficult to interpret. Because of the use of zinc stearate to coat rubber, serum samples for analysis of zinc must be drawn in all glass or all plastic syringes (no rubber), and all glass or all plastic vials (no rubber stoppers) must be used for transport.

### Treatment

- The gastrointestinal contents should be evacuated by emesis in suitable species following administration of aluminum plus magnesium hydroxide gel (e.g., Maalox®) (Empirically recommended [rather than oral bicarbonate] to decrease phosphine release.). Activated charcoal orally, preferably mixed with sorbitol.
- Respiratory failure may necessitate administration of 100% humidified oxygen or possibly artificial respiration via a ventilator with positive and expiratory pressure (PEEP).
- Metabolic acidosis is corrected by IV administration of sodium bicarbonate (slow, in fluids).
- Fluids may be administered IV and corticosteroids may be needed to help alleviate shock.
- B-vitamins and dextrose may be used for possible hepatic injury along with appropriate dietary therapy.
- Seizures may be controlled with diazepam or, if it fails, phenobarbital or, if it fails, anesthesia induced with pentobarbital.

### Key Features

- Zinc or aluminum phosphide exposure.
- Rodenticide, fumigant, occasionally insecticide.
- Phosphine release-cause of acute effects, acetylene (fish, garlic) odor.
- Gastrointestinal upset.
- Respiratory and/or neurologic signs.
- Delayed liver or kidney failure.
- Diagnosis-difficult, try GI tract contents (freeze rapidly, ship in air-tight container), serum.
- Treatment: aluminum or magnesium hydroxide gel, evacuate GI tract, adsorbent, supportive, and symptomatic.

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## Cicuta spp. - Water Hemlocks

*Cicuta maculata*, *Cicuta douglasii*

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants Associated with Stimulation or Seizures
Herbivores, esp. ruminants, swine	Minutes	Hours; often lethal	

### Images

- Spotted Water-hemlock, *Cicuta maculata* - Google Image Search - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -
- Spotted Water-hemlock, *Cicuta maculata* - U.S. G.S. Northern Prairie Wildlife Research Center. - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

### Description

- Native perennial herb.
- 2 - 10 feet tall.
- Stem stout, hollow, often purple streaked.
- Base of stem hollow below ground with horizontal plates crossing hollow central cavity. Contains highly poisonous

resinous material.

- Leaves alternate, sheath stem.
  - 2 - 3 times pinnately compound.
- Flowers small white in compound umbles.
- Technical details used to separate from harmless genera like *Angelica* and *Osmorhiza*. (Consult with plant taxonomists-weed specialists, etc.)

### Habitat

- Wet, rich soil.
- Along ditches, low meadows, flood plains, swampy areas, stream beds, marshes.
- 8 species in USA; *C. maculata* most important in eastern half of country.

### Toxic Principle and Toxicity

- Cicutoxin-a long-chain highly unsaturated diol (C<sub>17</sub>H<sub>22</sub>O<sub>2</sub>).
  - Thick, yellow liquid with a carrot-like odor (also smells like raw parsnips). Especially in roots and base of stem (tubers) at or below ground surface. Tubers are toxic all year.
  - Young leaves are nearly as toxic as roots, but mature leaves in summer and autumn have been consumed causing no problem. Animals tolerate low amounts without displaying clinical signs.
  - Among the most toxic plants in USA.
- 2 oz of tubers can kill a sheep. 8 - 10 oz of mature plant can kill a cow.

### Susceptible Species

- Livestock and humans.
  - Especially from eating tubers, base of stem, young leaves.
    - Tubers and liquid containing cicutoxin therein may be consumed, especially when eating lower stems early in the year when the soil is moist and soft.
- Cattle.
  - Toxicosis reported from eating plant or drinking water in puddles with trampled plant material present.
  - Usually not a problem in hay unless roots are included (unlikely).

### Signs

- Cattle, sheep, other species affected: swine less often affected, possibly due to vomiting.
- Rapid onset-begins 30 minutes after ingestion; death within 45 - 60 minutes of ingestion.
- Peracute, violent course.
- Salivation.
- Muscle twitching.
- Chomping of jaws.
- Grinding of teeth.
- Appear painful.
- Muscle spasms.
- Convulsions.
- May be knocked off feet by seizures.
- Then running fits and convulsions continue.
- Coma.
- Death due to respiratory paralysis.
- In poisoned human beings, electroencephalographic abnormalities and occasional anxiety neurosis persisted at 3 month after exposure.

## Lesions

- Are preventable with treatment of poisoned animals (possible due to exertion and hypoxia).
- In untreated animals include: skeletal and myocardial degeneration.

## Clinical Pathology

Elevated muscle enzymes (LDH, AST, CK) may occur (variable).

## Treatment

- Usually too late.
- Usually if animal lives 2 hours, it is likely to survive.
- Control spasms, seizures with sodium pentobarbital.
- Assist (artificial) respiration if necessary and possible.
- Activated charcoal and saline cathartic if hydration near normal; if not give adequate fluids then give saline cathartic.

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## *Corydalis caseana* - Fitweed

*C. aurea* - Golden Corydalis

*C. sempervirens* - Pale Corydalis

*C. flavula*

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants Associated with Stimulation or Seizures
Herbivores, esp. sheep	Minutes	Hours to 2 days; potentially lethal	

**Family** - Fumariaceae (Fumitory Family)

## Description

Biennial or weak perennial, succulent, bushy, spreading branches, grows up to 3 feet tall, fleshy top root, pinnately decompose leaves. Fragrant, up to 3 inches long racemes of creamy white, spurred flowers, each about 3/4 inches long at ends of branches. Flowers may be tipped with purple.

## Habitat

- *C. caseana*  
Sierra Nevada Mountains of California. Shaded canyons in summer ranges; moist places along streams and near water between 1600 and 2200 meter elevations.
- *C. aurea*  
Eastern North America and Rocky Mountains. Open woods and recent clearings on stony, calcareous soils; disturbed areas, along streams, sandy soil.
- *C. sempervirens*  
Northern USA and parts of Canada. Open woods, recent clearings, burned-over areas and rocky banks.
- Poisonings primarily in mountains of Rocky Mountain region and Virginia.

## Toxic Principles

Isoquinoline alkaloids.

## **Susceptible Species**

Sheep seem to relish the plant, cattle sometimes also affected. Sheep are apparently more susceptible than cattle and horses.

## **Toxicity**

- Considerable quantities must be consumed: 5% of the animal's weight is potentially lethal to sheep and 2% may produce clinical toxicosis.
- Plant rarely abundant.
- Plant is toxic in all stages of growth; summer (July to September) most dangerous months.

## **Signs**

- **Sheep.**
  - Rapid onset.
  - Rapid breathing and increased heart rate.
  - Ataxia and fall into clonic seizures, which occur intermittently.
  - Animals weaken and respiration and cardiovascular functions become depressed.
  - Twitching of facial muscles, running fits.
  - Sharp external stimulus during seizures may provoke sudden rigidity.
  - Scouring is common.
  - Dyspnea in some.
  - Bleating and other vocalization is common.
  - Characteristic biting (chewing) movements.
  - After several convulsions, death may occur (usually in less than 24 hours).
  - Affected animals may make a rapid, uneventful recovery.

## **Lesions**

Nonspecific.

## **Treatment**

- Remove access to plant.
- Activated charcoal and if hydration is adequate or restored to near normal, a saline cathartic may be administered.
- Symptomatic and supportive care.

## **Prevention**

Supplemental feeding may reduce consumption to subtoxic amounts.

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## Milkweeds (*Asclepias*)

*Asclepias subverticulata* and *A. fascicularis* - whorled milkweeds.

*A. eriocarpa* - a broad leaf milkweed of California.

*A. syriaca* - common milkweed.

*A. incarnata* - swamp milkweed.

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants Associated with Stimulation or Seizures
Herbivores, esp. sheep	Minutes to hours	Hours to days; potentially lethal	

## Images

- Swamp Milkweed, *Asclepias incarnata* L. - Google Image Search - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -
- Swamp Milkweed, *Asclepias incarnata* L. - U.S. G.S. Northern Prairie Wildlife Research Center. - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -
- Common Milkweed, *Asclepias syriaca* L. - Google Image Search - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -
- Common Milkweed, *Asclepias syriaca* L. - U.S. G.S. Northern Prairie Wildlife Research Center. - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -
- Eastern Whorled Milkweed, *Asclepias verticillata* L. - Google Image Search - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -
- Eastern Whorled Milkweed, *Asclepias verticillata* L. - U.S. G.S. Northern Prairie Wildlife Research Center. - To view this image in full size go to the IVIS website at [www.ivis.org](http://www.ivis.org) . -

## Description

- Native perennial herbs.
- Sap milky, hence the name milkweed.
- **Note** - Other common poisonous plants with milky sap include the *Euphorbia* spp. (spurges) and *Apocynum* spp. (dogbane). **Note** - not all plants with milky sap are poisonous.
- Leaves opposite or whorled.
- Numerous seeds with tufts of silk in tear drop shaped pods.
- May be free standing or vines may cling to fences.
- Broad leaf and narrow leaf varieties exist. Whorled milkweeds have narrow leaves. Narrow leafed milkweeds tend to be of higher toxicity.
- Flower color varies with species. Most flowers are white, some purple, others range from white to red or orange.
- Become more common as a result of heavy grazing.
- Some are more common on sandy soils.
- Especially in western Midwest, Rocky Mountain areas, and southwestern California and Baja.

## Toxic Principle

- A "**resinoid**" exists at least in the tops of the plants which has been named galitoxin. "Resinoid" is defined as a substance resembling a **resin**. A resin is defined as a solid or semisolid organic substance of vegetable or synthetic origin that is insoluble in water but readily dissolves in alcohol, ether, and volatile oils.
- Toxic dose almost same as lethal dose.
- Taste less objectionable when dried, but toxic principle is retained.
- Roots and shoots are also toxic.
- Some western species contain cardenolides (cardioglycosides). Cardenolides are the main cause of fatalities.

## Toxicity

<i>Asclepias</i> spp.	Common Name	% Body Weight of Green Plant causing Fatalities
<i>A. labriformis</i>	Labriform milkweed	0.05 - 0.20
<i>A. fascicularis</i>	Whorled milkweed	.20
<i>A. latifolia</i>	Broadleaf milkweed	1.00

## Poisoning

- Only when good forage is inadequate.
- Frost decreases toxicity.

## Signs

- Sheep affected most; occasionally in horses, cattle, goats, fowl.
- Natural cases of milkweed poisoning, animals are usually found dead or in lateral recumbency within 24 hours of consuming a toxic quantity of the plant.
- Clinical signs can develop within 2 hours of ingestion and can continue for hours or days.
- Pulse initially slow and strong then rapid and weak.
- Hyperthermia, bloat.
- Whorled milkweeds (*A. subverticullata* and *A. fascicularis*) produce CNS signs.
  - Convulsions - usually preceded by severe depression, weakness, muscle tremors, ataxia, dyspnea.
  - Convulsions that occur are tetanic in nature, repeatedly occur.
  - Coma.
  - Elevated temperature.
  - Death due to respiratory failure, tachyarrhythmias.
  - Congestion - internal organs - CNS.
- *A. eriocarpa* - one type of broad leaf milkweed - dry soils - California.
  - GI signs; gastroenteritis, bloat in ruminants, crop impaction in birds.
  - Subnormal temperature.
  - Prostration.
- Cardiac glycoside containing milkweeds may cause digestive tract upset followed by bradyarrhythmias and/or tachyarrhythmias.

## Pathology

- No specific lesions.
- Congestion of lungs, liver, kidney frequent. Mild to severe hemorrhagic gastroenteritis with broadleaf varieties.

## Treatment

- Activated charcoal. Rumenotomy beneficial in early stages of poisoning.
  - Symptomatic - control seizures.
    - Assist respiration.
    - Good diet.
  - If signs of cardioglycoside toxicosis exist manage as cardioglycoside overdose (see toxins affecting the heart).
  - Chloral hydrate reportedly is effective in relaxing sheep in the convulsive stages and allows time for recovery.
-

## Oligomeris - Desert Spike

*Oligomeris linifolia* - Desert Spike - (Mignonette Family)

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants Associated with Stimulation or Seizures
Cattle	Days to weeks	Unknown; potentially lethal	

### Description

Annual, cool season (fall and winter), herb.

### Habitat

- Native to the Rio Grande Valley and Trans Pecos area of Texas and on to California, including Northern Mexico, low elevations.
- Poisoning may be more common in years of high rainfall, which seems to promote the growth of this plant.

### Susceptible Species

Poisoning has been documented in cattle.

### Toxicity

Low levels fed for 1 month caused mild depression and only very slight weight loss. At 5 - 20 g/kg fed for 26 days, marked "CNS signs" and 19% weight loss occurred. At 5 - 10 g/kg fed for 25 days, severe "CNS signs", seizures and 20% weight loss occurred. At 10 - 18 g/kg fed for 11 1/2 days, with the higher amounts being fed the last few days, severe CNS signs, mania, stupor, and pulmonary emphysema were seen.

### Signs

- Mild depression
- Salivation
- Ear twitching or exaggerated frequency of ear movement
- Blinking
- Increased tail movement
- Tremors
- Continual walking
- Stimulated appearance
- Apparent hallucinations
- Facial spasms
- Epileptiform seizures
- May see mild increase in glucose and increase in CPK
- Walk into walls
- Weakness
- Recumbency
- Stupor
- Nystagmus
- Dyspnea
- Death
- Goose-stepping
- Wide stance
- Chewing fits

### Lesions

No gross or histologic lesions.

### Treatment

- Rumen lavage has been demonstrated to be of major benefit in alleviating and shortening the duration of toxicosis.
- Activated charcoal is recommended when lavage is impractical (as often is the case).
- Tube feeding can make a major difference in the survival rate as well.

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