Chapter Sections

Astragalus and Oxytropis - Locoweeds
Hexachlorophene
Bromethalin
Vacor
Deet
Methionine
Carbon Disulfide (CS₂)
Persea Americana - Avocado
Aesculus - Buckeye and Horsechestnut
Convolvulus (Morning Glory)
Mushrooms - General
Mushrooms - Hallucinogenic Indoles
Additional Toxicants

Astragalus and Oxytropis - Locoweeds

Astragalus spp. - Locoweed, poison vetch, wooly locoweed, crazyweed, Texas loco, Emory milkvetch, red stemmed peavine, other milkvetch (several).
Astragalus miser - Timber milkvetch
Oxytropis spp. - Locoweed, crazyweed, Lambert's crazyweed, white loco.

<table>
<thead>
<tr>
<th>Major Species</th>
<th>Usual Time of Onset</th>
<th>Usual Duration (if survives)</th>
<th>Full Table for Toxicants with Mixed Effects on the Central Nervous System (Part II)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sheep, horses, cattle, other herbivores</td>
<td>Weeks</td>
<td>Months, persistent to permanent damage is common; often lethal</td>
<td></td>
</tr>
</tbody>
</table>

White Locoweed, "Rattleweed", *Oxytropis Lambertii* - Google Image Search. - To view this image in full size go to the IVIS website at www.ivis.org.

Crazyweed, *Oxytropis Lambertii* - Google Image Search. - To view this image in full size go to the IVIS website at www.ivis.org.

*Oxytropis besseyi* - Google Image Search. - To view this image in full size go to the IVIS website at www.ivis.org.

Family - Leguminosae or Pea family

Description

- *Astragalus* and *Oxytropis*.
  - Legumes, erect or prostrate herbaceous perennials. Usually hairy, alternate pinnately divided leaves.
  - *Astragalus* spp.
    - Usually perennial herbs, growing in clumps, with pinnately compound leaves; flowers are pea-like, clustered in the axils of the leaves; white, blue or purple; fruits short or long pods, often inflated. Leaves arise from above nodes.
  - *Oxytropis* spp.
    - Like *Astragalus* except leaves are present from the ground up (no above-ground nodes). Leguminous flowers have characteristic pointed keel, which distinguishes them from *Astragalus*.

Habitat

- *Astragalus* spp.
  - Poisoning occurs from the plains westward, especially in central to westward rangelands; from forest to desert.
- *Oxytropis* spp.
  - In western grasslands or in grass among open stands of trees.

Susceptible Species and Toxicity

- Perhaps the most economically significant genera of poisonous plants in the USA.
- Poisoning, which is common in western states, occurs in sheep, cattle, horses, and occasionally wild herbivores.
- Lethal dose 3-nitro-1 propanol to cattle is about 57 mg/kg.

Responses to Various Groups of Locoweeds Based on the Toxic Principles Present

I. There is a large group of nontoxic species: e.g., *Astragalus nuttallianus* (SW US) and *A. cicer* have been used as forage plants.

II. A large group (over 200 species) ranges from Mexico to Canada and includes some plants in the Eastern United States, which contain 3-nitropropanol or 3-nitropropionic acid. Miseroxin as it occurs in *A. miser* is also present. It is a glycoside of 3-nitropropanol or 3-nitropropionic acid. Miseroxin is metabolized to the highly toxic 3-nitro-1-propanol in the digestive tract of ruminants. The 3-nitro compounds in the rumen break down into 2 fractions, inorganic nitrite and a 3-carbon side chain. Nitrite oxidizes hemoglobin to produce methemoglobinemia. When cattle were fed a lethal dose of plants containing 3-nitro-1-propanol, production of methemoglobin was prevented by methylene blue administration, however, the animals still died. Thus, nitrite contributed to the syndrome but was not the sole cause of death. The 3-nitropropionic acid is more slowly absorbed from the GI tract. As plants mature and dry, they decrease in toxicity until they are nontoxic when they are dry.

Miserotoxins (glycosides which, upon hydrolysis, yield 3-nitropropanol or 3-nitropropionic acid).

These plants cause poisoning in cattle, horses, and sheep. Included in the clinical signs are pulmonary emphysema, which especially affects sheep; and demyelination of the posterior spinal cord, to which cattle are especially sensitive. The latter results in goose
stepping, weaving, and interference between the hindlimbs causing clicking of the dew claws when walking (condition called cracker heels). Other signs of toxicosis due to 3-nitro compounds (primarily in cattle) include: weakness; knuckling of the fetlocks, goosestepping; respiratory distress and roaring, cyanosis; difficulty arising; sudden ccolapse; may drag hindquarters. Sometimes the 3-nitro compounds can release nitrite, which oxidizes hemoglobin to form methemoglobin. Cyanosis and tachypnea may result; e.g., *A. emoryanus* (emory milkvetch), *A. canadensis*, *A. miser*, and *A. tetrapterus*. Cattle appear more sensitive than sheep.

If a lethal dose of plant has been consumed, the animal will die in 4 - 25 hours. Sudden exertion may cause death in either chronic or acute poisoning. Signs of chronic poisoning are related to the effects on the respiratory tract and the CNS. If affected animals are removed from access to the plant and given good feed, they may make an apparent clinical recovery but may die later if stressed.

### III. The selenium indicator plants, of which there are approximately 25, are associated with acute and chronic poisoning.

A. Acute poisoning is rare and is associated with range conditions in which animals are introduced to a new area and simply consume selenium indicator plants at too high a rate of intake. As in other forms of acute selenium poisoning, respiratory failure, pulmonary edema, and shock may cause death within 1 day. Diarrhea and fever may also precede death.

B. Chronic poisoning is of two subtypes:

1. The first is so-called "alkali disease" and occurs after ingestion of seleniferous grasses and selenium accumulators over a long time. The responsible locoweeds may be selenium accumulators and not necessarily selenium indicator plants. Alkali disease is apparently genuine selenium poisoning and is characterized by long hooves, separation of the coronary band, rough hair or loss of the tail and/or mane. The greatest economic loss in alkali disease is diminished reproduction which can often occur without other signs. Although alkali disease affects cattle, sheep and horses, the major reproductive failures occur in the ruminants. Sudden death sometimes occurs in alkali disease of sheep.

2. The second form of chronic poisoning by the selenium accumulating species of locoweeds, blind staggers, is possibly not due to the selenium in these plants. Blind staggers affects cattle and occasionally sheep, but not horses. It has been suggested that blind staggers is really a form of polioencephalomalacia, or is possibly a variant form of "true locoism".

IV. True locoism, which affects all livestock, is the result of ingestion of the indolizidine alkaloid, swainsonine or swainsonine N-oxide. Locoism is characterized by emaciation, habituation, proprioception deficits, slow, staggering gait, decreased libido, abortion (can approach 100%), small, weak young, and birth defects, especially bent legs. Impaired function of the liver, pancreas, thyroid, and parathyroid glands contribute to weight loss of locoed animals. Decreased lacrimation and retinal cell vacuolation results in impaired vision. Immunosuppression (decreased T lymphocyte function) has been observed with experimental feeding of locoweed to sheep.

![Swainsonine Diagram](image)

Swainsonine is an alkaloid which inhibits alpha-mannosidase with increase in oligosaccharides inside lysosomes (histolysosomal swelling and vacuolization is prominent). Onset of toxicosis occurs after at least 2 weeks and usually after chronic exposure. Swainsonine gets its name from another legume, the Australian "darling pea", *Swainsona* spp., which also contains this alkaloid and which causes a syndrome similar to that induced by locoweeds. Horses are especially sensitive to locoism and, once exposed, may be more sensitive to the production of toxic effects and habituation than prior to exposure (this is termed sensitization). Habituation may be manifested by ingestion of all plant parts. This may include eating soil containing the roots of locoweed after other parts of the plants have been grazed. Often significantly poisoned horses may become belligerent and CNS dysfunction may render them useless or dangerous to their owners. The indolizidine alkaloids are passed in milk and calves develop cytoplasmic vacuolation, which may account for unthriftness.

V. Groups of cattle grazing locoweed (*O. serius*) at high altitude and experiencing "true locoism" sometimes also display an increased incidence of right heart failure ("highmountain disease"). The toxic principle causing this latter syndrome has not been defined.

### Mechanisms

- Understood (in part only):
  - Methemoglobinemia (Part of II. above).
  - Nitrites oxidize iron (Fe^{2+}) in hemoglobin to form methemoglobin (Fe^{3+}) which cannot carry oxygen.
  - Some nitro compounds are also capable of complexing with ferrous hemoglobin (Fe^{2+}) in blood to produce methemoglobin directly.
  - Swainsonine (cause of true locoism) (See IV. above).
• Inhibits α -mannosidase.
  • Result is mannosidosis, which is an accumulation of mannose-rich oligosaccharides in vacuoles within neurons, renal tubules, liver, placenta, lymphocytes, etc. (lesion in lymphocytes in peripheral blood is used diagnostically).
  • Abortion occurs after death of the fetus in association with heart failure.

Lesions

• "3-nitro" related diseases (See II. above).
  • Gross.
    • Acute nonspecific pulmonary congestion, cyanosis.
    • Chronic hepatic congestion and swelling.
    • Pulmonary emphysema and pneumonia.
    • Excessive cerebrospinal fluid.
    • Ulceration near the cardia of the abomasum in ruminants.
  • Histology.
    • Chronic pulmonary emphysema, edema, fibrosis.
    • Wallerian degeneration (dying back neuropathy with demyelination) of the spinal cord and peripheral nerves.
  • Acute selenium poisoning (See III.A. above).
  • Pulmonary congestion and edema (see Toxicants that Affect the Respiratory System).
  • Chronic selenium toxicosis (See III.B.1. above).
    • Rough hair coat, loss of mane or tail.
    • Erosions of joints of long bones.
    • Emaciation.
    • Possible cracking and/or irregular hoof growth.
  • True locoism (See IV. above).
    • Vacuolization of neurons, renal cortical tubular epithelial cells, hepatocytes, pancreas. Vacuolization of renal tubules appears 4 days after feeding of locoweeds. By day 32 in an experimental study, almost all tissues showed vacuolization. Vacuolization is reversible.
    • Enlarged thyroid glands.
    • Emaciation.
    • Retinal damage (vacuolation) and vacuolar degeneration in the lacrimal gland may occur, the latter leading to a "dull eye"
    • Delayed placentation in ewes, cytoplasmic vacuoles in the placenta.
    • Abortion, small, weak lambs.
    • In rams: reduced spermatogenesis; vacuolation of spermatogonia, epithelium of the epididymus and seminal vesicles.
      • E.M.
      • Mild myelin degeneration (with local fluid accumulation) and axonal degeneration with "axonal spheroids" in many areas of the CNS.
      • Enlargement of lysosomes.
      • Mitochondrial swelling and degeneration (later).
  • Congestive heart failure (See V. above).
    • Right ventricular enlargement.

Treatment

• Withdraw from source of plant. Due to habituation this is essential, especially in true locoism. Supplemental feeding in such cases may fail, and therefore it is desirable to move the animals to a clean range.
• Mild cases generally resolve in 1 - 2 weeks. Patients with chronic locoism with long-standing clinical signs generally do not recover.
• Splinting of contraction deformities may be of considerable value in some neonates. Many mildly to moderately deformed lambs respond spontaneously.
• Animals with acute selenium poisoning should not be stressed. Handle minimally, consider feeding activated charcoal and a low dose of a saline cathartic initially. If necessary treat for pulmonary edema.
• Animals with acute methemoglobinemia may respond somewhat to methylene blue, but this generally has not ensured survival due to the other effects of the "3-nitro compounds".
• No specific treatment has been identified for other syndromes.
**Stemless loco weed** (*Aragallus lambertii*): a, Flowering plant; b, seed pods; c, cross section of seed pods - all one-third natural size.

**Wooly loco weed** (*Astragalus mollissimus*): a, whole plant; b, section of pod - both one-third natural size.

**Blue Loco** (*Astragalus lentiginosus var. diphysus*).
White Loco, or "Rattleweed" (*Oxytropis Lamberti*).
Hexachlorophene

Sources

- Phisohex (3% emulsion).
- Surgical scrubs containing hexachlorophene (such as Surgicen®, Bilevon®, Dermadex®, and Exofene®) may have been withdrawn from the market as they are no longer listed in the PDR).
- Plant bacteriacide.
- Soil and foliar fungicide (Seribak®).
- Cosmetics-regulated to contain less than 0.1%.

Hexachlorophene

Toxicity

- Dogs and swine are especially susceptible, but cattle and other species may also be poisoned. Neonates appear most susceptible.
- Used to be OTC and used to be in bar soaps.
- Poisoning now infrequent. Most medical products containing > 0.75% hexachlorophene are available to lay persons only by prescription.
- Estimated lethal (total) dose (humans): 2 - 10 grams.
- LD₅₀ (rat): 60 mg/kg.
- MLD (dog): 40 mg/kg.

Mechanism of Action

 Uncouples oxidative phosphorylation at very high doses (like nitrophenol, certain chlorophenols and certain other compounds) may therefore cause hyperthermia.

Absorption, Distribution, Metabolism and Excretion (ADME)

Rapidly absorbed from skin and GI tract. Metabolized by liver.

Signs

- CNS (predominant signs) signs depend on dose, and are apparently related to uncoupling of phosphorylation in the CNS resulting in myelin damage and secondary axonal degeneration.
  - High doses.
    - Usually after massive oral exposure--fatal outcome.
    - Twitching, whining, chewing.
    - Increasingly severe tonic-clonic convulsions.
    - Opisthotonus.
    - Coma, death.
    - Fever can be seen at very high doses.
  - In acute cases may also see: excitation, hypermetria, walking backwards, diarrhea, head shaking, deafness, anorexia, lethargy, stilted gait, outward rotation of rear legs, salivation, death may be due to respiratory failure.

<table>
<thead>
<tr>
<th>Major Species</th>
<th>Usual Time of Onset</th>
<th>Usual Duration (if survives)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All species, esp. dogs</td>
<td>Hours to weeks</td>
<td>Several days to permanent damage; often lethal</td>
</tr>
</tbody>
</table>

Full Table for Toxicants with Mixed Effects on the Central Nervous System (Part II)
Intermediate degrees of exposure.
- Increasingly severe muscle tremors when standing.
- Ataxia especially in rear.
- Lower doses-chronic exposure.
  - Blindness, dilated pupils, decreased or absent pupillary light reflexes.
- Additional signs reported (man).
  - Bradycardia, cardiorespiratory arrest, hypotension, depression, nausea, vomiting, and diarrhea commonly occur as early signs of toxicity.

Lesions
- Renal tubular necrosis.
- Hepatic congestion, fatty degeneration of liver.
- Gastroenteritis.
- Cerebral edema-vacuolar degeneration of the white matter of the brain (spongy change) and spinal cord (due to splitting of myelin).
- When blindness is present, there is often demyelination of optic nerve and/or severe meningitis present.

Diagnosis
- Signs, history of exposure.
- Tremors may not be relieved entirely by barbiturates.
- Hypocalcemia may be present.
- Hexachlorophene analysis of:
  - Feces
  - Blood
  - Liver
  - Stomach contents
- Appropriate lesions, especially histologic lesions.

Treatment
- Oral exposure.
  - Evacuate GI tract: emetic, only for very recent exposure, if still alert (no contraindications), or lavage (instill activated charcoal) for acute exposure.
  - Recent exposures: give activated charcoal and a saline cathartic. Repeat oral activated charcoal doses (every 2 - 6 hours) may enhance total body clearance and elimination. Do not repeat if loss of motility (auscultate for bowel sounds) has occurred.
- Topical exposure.
  - Bathe-do not use alcohol to remove: disperses hexachlorophene.
- Any route of exposure.
  - Mannitol and dexamethasone for cerebral edema.
  - Calcium if hypocalcemic.
  - Seizure control with diazepam (Valium) or phenobarbital or pentobarbital (if the other drugs fail to control seizures).
Bromethalin

**Sources**

- Bromethalin is marketed as a single feeding rodenticide active against anticoagulant resistant rodents. Rodent deaths are delayed for 3 - 5 days, and no bait shyness is reported.
- Available in 2 oz or smaller throw packs containing 0.01% bromethalin (5.7 mg active ingredient per pack). Assault Mouse and Rat Place Pack (Purina), Vengeance (Velsicol).
- Chemical class: diphenylamine.

![Bromethalin](image)

**Toxicity**

- Clinical signs including depression, ataxia, and depressed hindlimb conscious proprioception were observed at an oral dose of 1.67 mg/kg.
- The lowest observed lethal dose of the bromethalin-containing rodenticide was 2.5 mg/kg (= 25 grams bait/kg).
- The estimated LD₅₀ of bromethalin when in bait material was 3.65 mg of active ingredient/kg.

<table>
<thead>
<tr>
<th>Species</th>
<th>Oral LD₅₀ (mg/kg) of technical grade material (i.e., not in bait)</th>
<th>Approximate minimum toxic dose of bait (g/kg)</th>
<th>Approximate minimum lethal dose of bait (g/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>House</td>
<td>6.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mouse</td>
<td>2.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norway Rat</td>
<td>4.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dog</td>
<td>5.0</td>
<td>16.7</td>
<td>25</td>
</tr>
<tr>
<td>Cat</td>
<td>1.8</td>
<td>3.0</td>
<td>4.5</td>
</tr>
<tr>
<td>Monkey</td>
<td>13.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rabbit</td>
<td>&gt; 100.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guinea Pig</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Note** - Cats are more than 3 times as sensitive as dogs. One package could therefore be lethal to a cat.
- Relay toxicosis has not been observed in experimental studies. However, there may be reason for concern in cats based upon reported field experiments.
Mechanism of Action

Bromethalin and its N-demethylated desmethyl bromethalin metabolite are uncouplers of oxidative phosphorylation in central nervous system mitochondria. This may result in diminished Na+/K+ ATPase activity and lowered ATP and subsequent fluid buildup due to inability to maintain osmotic gradients. Fluid buildup is manifested by fluid-filled vacuoles between myelin sheaths. Vacuole formation reportedly may result in increased cerebral spinal fluid pressure and increased pressure on nerve axons. There is decreased nerve impulse conduction, paralysis, and possibly death due to respiratory paralysis.

Clinical Signs

- **Note** - Bromethalin toxicosis may mimic a number of neurologic disorders!
- Lower dosages (1.67 - 2.5 mg/kg) of bromethalin given to dogs generally caused tremors, mild to severe depression, ataxia, vomiting, and lateral recumbency. To illustrate the lower dose syndrome, one dog, which was given bromethalin at an oral dose of 2.5 mg/kg, developed hindlimb weakness and ataxia 70 hours after ingestion. By 92 hours postingestion, the dog appeared depressed, experienced generalized muscle tremors, and had depressed hindlimb conscious proprioception. The animal continued to display mild muscle tremors, ataxia, depression, and weakness for an additional 10 days, after which time it recovered. Another dog which was given 2.5 mg/kg of bromethalin remained asymptomatic until 86 hours postingestion, at which time it developed vomiting. By 90 hours postingestion, the animal displayed fine muscle tremors of the head and neck, severe depression, symmetrical miosis, hindlimb paresis, loss of hindlimb conscious proprioception, and dyspnea. The animal ultimately lost hindlimb deep pain response and died approximately 120 hours after dosing.

- Cats given 0.5 mg/kg bromethalin developed a similar syndrome of progressive depression, ataxia, abdominal swelling, focal motor seizures, vocalization, and respiratory depression.

- Dogs which were given higher oral dosages (at or above the LD50 of bromethalin) generally developed clinical signs within 4 - 36 hours of dosing. As the oral dose of bromethalin increased (5.0 - 6.25 mg/kg), the toxin syndrome was characterized by hypereexcitability, severe muscle tremors, occasional running fits characterized by rapid circling, focal motor and generalized seizures, hindlimb hyperreflexia, mild to severe depression, and death. Less frequently observed clinical signs included marked sinus arrhythmias, anorexia, cervical neck pain, loss of forelimb conscious proprioception, and cyanosis. Interestingly, a large number of animals stopped barking after the administration of bromethalin, and the loss of bark generally preceded (1 - 2 hours) the development of other clinical signs.

- At higher bromethalin dosages, paralyzed animals occasionally displayed abnormal postures (e.g., Schiff-Sherrington, forelimb extensor rigidity), abdominal pain, resting and/or variable (positional) nystagmus, and anisocoria. Animals which developed the convulsing syndrome required rapid anticonvulsant therapy to abolish seizure clusters. Animals at higher bromethalin dosages which did not exhibit the convulsant syndrome subsequently developed the paralytic syndrome. Postdosing ophthalmologic examinations were normal in all examined animals. Ingestion of an oral dose larger than the LD50 usually results in onset of clinical signs within 24 hours (4).

- Acute clinical signs (dose greater than the LD50 consumed) in target (rodent) animals include tremors, prostration, clonic convulsions, hypothermia, and death. Chronic signs include lethargy, hindlimb weakness, loss of muscle tone, and paresis to paralysis.

Electrophysiology

Postdosing EEG abnormalities were observed in clinically affected animals given oral doses of bromethalin ranging from 1.67 - 6.25 mg/kg. The EEGs of these affected animals were generally characterized by voltage depression and/or excessive slow wave activity. Some dogs developed abnormal EEG patterns characterized by seizure activity (occasionally strobe induced), spike and spike-wave activity, excessive slow wave activity, and voltage depression in various combinations at different times postdosing. Nerve conduction velocities and electromyograms remained within normal limits.

Clinical Pathology

- A significant increase in entry CSF pressure was observed in dogs following the ingestion of 6.25 mg/kg bromethalin. Animals given bromethalin had a mean entry CSF pressure of 122.0 ± 33.256 mm CSF. Entry CSF pressure was measured from 15 - 63 hours after animals were given bromethalin.

- Examination of the cerebrospinal fluid (CSF) from these bromethalin-dosed animals revealed specific gravities of 1.006 - 1.008, 10 mg of protein/dl, and 0 - 3 cells/ml. Cytologic examination of the CSF revealed primarily macrophages and occasional ependymal cells. One individual's (63 hours postdosing) CSF cytology revealed 60% neutrophils, 40% macrophages, and occasional eosinophils which were considered consistent with an inflammatory process. A marked elevation in entry CSF pressure (184 mm CSF) was also observed 64 hours postdosing in one animal given 5.0 mg of bromethalin/kg during the preliminary study.

- Bromethalin or desmethyl brown ethylene can be identified in kidney, liver, fat, and brain tissues. Careful tissue handling is necessary, however, since the compounds rapidly photodegrade (4).
Lesions and Diagnosis

- Mild cerebral edema.
- Lesions observed in dogs and target (rodent) animals include vacuolation and edema of the cerebellum. "Spongy" appearance to the cerebellum is seen. Swelling of the brain and spinal cord occurs.
- Electron microscopy reveals appearance of vacuoles, edema, and splitting of the myelin sheaths.
- Frozen liver, kidney, and brain may be analyzed using gas chromatography with an electron capture detector to confirm exposure.

Treatment

- In animals significantly exposed (e.g., 10% of an LD50 or more), an emetic should be given early on.
- Repeated oral administration of a superactivated charcoal/sorbitol mixture (4 doses, q 12 hours) was the only effective therapy for bromethalin toxicosis in the dog.
- The use of corticosteroids (2 mg/kg, q 6 hours, IV), mannitol (250 mg-1 g/kg, IV, QID-SID), and furosemide (2.5 mg/kg, 96 hours, SQ, IV) were ineffective at reversing the toxic syndrome (paralysis, depression) once clinical signs developed.
- Therapy designed to abolish seizures is indicated. This would include phenobarbital (administered at 5 - 10 mg/kg, IV, to effect) or diazepam (5 - 10 mg, IV, as needed).

Vacor

<table>
<thead>
<tr>
<th>Major Species</th>
<th>Usual Time of Onset</th>
<th>Usual Duration (if survives)</th>
<th>Full Table for Toxicants with Mixed Effects on the Central Nervous System (Part II)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dogs, cats, horses</td>
<td>Hours to few days</td>
<td>Hours to several days; may be lethal esp. to cats</td>
<td></td>
</tr>
</tbody>
</table>

Synonyms

- N-3-pyridylmethyl-N'-p-nitrophenyl urea (PNU)
- RH-787 (RH: Rohm and Haas Company, Philadelphia)

Sources

- Vacor Rat-Killer, DLP-787 2% Bait, DLP-787 10% tracking powder.
- Rodenticide introduced in the 1970s, Vacor was sold as a 39 g bait packet with 2% active ingredient.
- Has subsequently been withdrawn and is now rarely encountered.

Structure

![Structure of Vacor](image)

Toxicity

- LD50 cat 62 mg/kg.
- LD50 rat 4.5 mg/kg.
- LD50 monkey 1200 - 2000 mg/kg.
- LD50 human estimated at 5 mg/kg.
- Horses poisoned by 0.25 - 0.5 kg of 2% Vacor bait.
Mechanism of Action

- Interferes with nicotinamide: thought to depress intracellular NAD levels.
- May produce several clinical syndromes including peripheral neuropathy, encephalopathy, and diabetes mellitus.

Clinical Signs

- The following initial clinical signs have been reported in human poisonings: weakness, abdominal pain, nausea, vomiting, and hypotension.
- Later clinical signs in humans include sensory and motor peripheral neuropathy, cardiac arrhythmias, tremors, ataxia, and diabetic-type keto-acidosis (diabetes mellitus).
- Clinical signs in human poisonings begin within 1 - 48 hours of ingestion. Signs vary depending on dose and individual susceptibility.
- Diabetes mellitus was a consistent sequelae in human survivors. It developed from 4 hours to 7 days postingestion and in some cases required insulin therapy.
- Autonomic dysfunction is also a consistent finding in surviving humans: includes urinary bladder atony, hypotension, and gastrointestinal hypomotility. Variable onset from 4 hours to 4 days.
- Clinical signs in dogs included vomiting, blindness (2 days postingestion), and temporary glycosuria.
- In poisoned horses, muscle tremors, mydriasis, sweating, colic, ataxia, weakness, anorexia, and temporary glycosuria have been described.
- "Fishy" urine odor described in poisoned cats and horses.
- Fatalities have not been reported in domestic species.

Pathology and Clinical Pathology

- Lesions may include erosions, ulcers, or perforations in the esophagus, stomach, small bowel, or colon.
- Clinical pathological findings in affected humans include glycosuria, hyperglycemia, ketosis, elevated serum lipase and serum amylase.
- Clinical pathological changes in the horse include hyperglycemia, CPK, SGOT, and alkaline phosphatase, as well as hemoconcentration.

Diagnosis

- Exposure to a toxic dose and appropriate clinical, clinical pathologic, and perhaps pathologic findings.
- Analysis of urine and tissue for Vacor and metabolites, amino Vacor, and acetamide Vacor (may be difficult to obtain tissue and urine analysis).

Treatment

- Emetic if recent exposure, and no contraindications exist.
- Activated charcoal and cathartic.
- Since gastrointestinal hypomotility can occur, lavage/emesis may be warranted up to 12 hours postingestion.
- Nicotinamide administration has been demonstrated to be an effective antidote in rats.
- Human success with nicotinamide has been variable; possibly due to delay in therapy (generally ineffective if \( \geq 1 \) hour delay has occurred), species differences, or dose effects.
- Symptomatic and supportive therapy.
- Monitor blood glucose for the development of diabetes mellitus. Generally insulin responsive.
Deet

<table>
<thead>
<tr>
<th>Major Species</th>
<th>Usual Time of Onset</th>
<th>Usual Duration (if survives)</th>
<th>Full Table for Toxicants with Mixed Effects on the Central Nervous System (Part II)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dogs, cats</td>
<td>Hours</td>
<td>Hours to a few days; poisonings are infrequent; deaths rare, possible interactions with pyrethroids</td>
<td></td>
</tr>
</tbody>
</table>

**Synonym**

N-N-diethyltoluamide

**Sources**

- DEET or diethyl toluamide is found in insect repellents—such as Off®, Deep Woods Off®, Cutter's, and other brands including some forms of DMT-50 (50% DEET, a veterinary product). Poisoning may occur during warm months, as a result of owner's treatment of pets in attempts to lessen insect bites. Dogs and especially cats are affected.
- DEET was combined with fenvalerate in the Hartz Blockade products.

![Deet](image)

**Mechanism**

Unknown, a "neuropathy" has been suggested in heavily exposed humans.

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

- Rapid skin absorption. From 19 - 48% of the applied dose of DEET is absorbed within 6 hours in experimentally treated guinea pigs.
- Accumulation of DEET in the skin with persistence for long periods was seen in animals and humans.
- Rapid urinary excretion occurs: 70% excreted in first 24 hours as metabolites.
- Oxidized by hepatic microsomes.

**Toxicity**

- Oral LD₅₀ rat, 1 - 2 g/kg; dermal LD₅₀ rabbit, 3 g/kg.
- Enhances absorption of dermally applied chemicals.
- The ortho isomer of DEET is the most toxic followed by the meta- and para-isomers.

**Signs**

- Laboratory animal (rats, rabbits) studies have shown the following signs of systemic toxicity: depression, ataxia, dyspnea, seizures, tremors, and coma.
- DEET (when the only active ingredient) toxicosis has been infrequently observed in small animals. Clinical signs in dogs and cats with suspected DEET poisoning included vomiting, tremors, excitation, ataxia, and seizures.
- Clinical signs reported in human cases of DEET toxicosis included seizures in juvenile girls, sensory hyperesthesia, vomiting, diarrhea, nausea, ataxia, depression, and coma.
- Hepatopathy has also been reported in humans.
Treatment

- For topical exposure, bathe with detergent (liquid dish detergent or strong shampoo; repeat as needed to thoroughly remove.
- For oral exposure, emetics may be contraindicated, activated charcoal and a saline cathartic are recommended. When serious clinical signs are developing and the likelihood of continuing absorption from the digestive tract exists, enterogastric lavage is recommended.
- Symptomatic and supportive care.
- Control seizures with diazepam or barbiturates.

Methionine

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

Sources

- Methionine (d,l-methionine) is encountered primarily in medications dispensed as urinary acidifiers. Methioform, Methigel, Uracid, and numerous other brands including generics and combinations such as Methischolp, which combines methionine and choline. Methischol is used as a "lipotropic agent". Uroeze Fus is a combination product with methionine and ammonium chloride. Methionine is, of course, an essential amino acid.
- Most problems occur with Methioform because of its chewable formulation. Cats and dogs often ingest this product in large quantities.

\[
\begin{align*}
\text{COOH} \\
H_2N\overset{\text{C}}{\text{H}} \\
| \\
\text{CH}_2 \\
| \\
\text{S} \\
\text{CH}_3
\end{align*}
\]

**Methionine**

Toxicity

- LD50 mouse - 4,000 mg/kg.
- Acute administration of excessive amounts of methionine is believed to result in a metabolic acidosis.
- Animals with pre-existing liver disease (which may be chosen as patients to be medicated with lipotropic agents) are predisposed to toxicosis.

Absorption, Distribution, Metabolism and Excretion (ADME) and Mechanisms of Action

- Acidosis.
- Methionine is degraded by gut flora to a group of metabolites, collectively termed mercaptans (methanethiol, ethanethiol and dimethylsulfide). Dimethylsulfide is often present in the breath of cirrhotics and is considered responsible for the typical breath odor (which is called fetor hepaticus) in patients with hepatic failure. The formation of dimethylsulfide is one excretory route for
The toxicity of methionine is also related to its metabolism (in part by the gastrointestinal flora) to ammonia and other metabolites, since orally administered methionine produces hepatic encephalopathy while intravenously administered methionine does not. Moreover, methionine toxicosis may be alleviated by oral antibiotic therapy.

Methanethiol is probably the most toxic metabolite of methionine. It may produce coma alone, or in subcoma doses may act synergistically with ammonia and short chain fatty acids to induce encephalopathy.

Naturally, preexistent hepatic disease is an important factor in methionine induced hepatic encephalopathy. The longer hepatic disease has been present, the less methionine, methanethiol or ammonia is required to induce coma.

Portocaval shunt is one condition that predisposes animals to methionine-induced hepatic encephalopathy.

Signs

- After high doses in any animal, effects most often include ataxia, depression, lethargy and often vomiting.
- In patients with liver disease, signs may include hyperactivity and pacing which may begin within a few hours of the onset of methionine administration. Excessive salivation, disorientation and apparent inability to rest comfortably may be seen. Other signs may include: ataxia, circling, head pressing, aimless pacing, abnormal aggression, somnolence, blindness, seizures and stupor, leading to coma.
- Elevated blood ammonia levels are reported.
- Cats experimentally given 0.5 - 1 g/kg dl-methionine developed severe hemolytic anemia with increased Heinz body formation and increased methemoglobin concentrations.

Treatment

- For recent exposure in otherwise healthy patients:
  - Emetics may be used if not contraindicated.
  - activated charcoal and a saline cathartic may be used if significant ingestion has occurred.
  - Fluids and bicarbonate may also be indicated.
- In liver patients and hepatic encephalopathy, management is comprised of:
  - Cessation of the use of methionine.
  - Steps may be taken to lower blood ammonia concentrations as in hepatic encephalopathy.
  - Oral antibiotics such as neomycin may be of some value.
  - Medical treatment for hepatic encephalopathy may also include oral lactulose, saline enemas, thiamine, a low protein diet, and glucose.
- Monitor blood glucose for hypoglycemia and use 2.5 - 5.0% dextrose as needed.

Carbon Disulfide (CS₂)

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

Sources

- Carbon disulfide is a nonviscous, explosive liquid, which is freely miscible with carbon tetrachloride. When heated, carbon disulfide decomposes to form sulfur dioxide and carbon monoxide. Water may be used to extinguish fires.
- Chemically pure CS₂ has a sweetish, aromatic odor; however, industrial grade CS₂ may have a yellowish color and a rotten cabbage or radish odor.
- Carbon disulfide has been used as a fumigant for grains, and until recently was used in a 20% combination with carbon tetrachloride (CCl₄). CCl₄, which is now banned, was added in part because of its fire-retardant characteristics. Over a million gallons of this combination were used annually. The use of CS₂ as a fumigant is probably still the primary source of exposure to domestic animals and man.
- Carbon disulfide is also used as a soil fumigant, since it will reduce the germination of most seeds, and is a general insecticide.
- Carbon disulfide was used via stomach tube to kill bot larvae in horses at a dosage of 24 ml to a 1,000 lb horse; however, it is no longer the drug of choice. Colic often follows its use and CS₂ was always contraindicated in sick or debilitated horses as well as in mares during the last trimester.
- Carbon disulfide is also used as an industrial solvent.
Absorption, Distribution, Metabolism and Excretion (ADME)
Carbon disulfide is absorbed from all routes: dermal, oral, inhalation, and parenteral. The rate of absorption from the gastrointestinal tract is unknown, but clinical evidence suggests that the process is a rapid one. In the blood, CS₂ has an affinity for the red cells. As far as organs are concerned, initially absorbed CS₂ tends to accumulate in the liver followed by general body distribution, and then accumulation in the brain. Of absorbed CS₂, about 20 - 40% may be eliminated by the lungs, but a major fraction of the remainder appears to bind to body tissues.

Mechanisms of Action and Lesions
- CS₂ is highly reactive with nucleophilic substances including amino acids, catecholamines, steroid hormones and other compounds. The reaction of CS₂ with vitamin B₆ (pyridoxamine) to form pyridoxine dithiocarbamic acid results in the subsequent blockade of a number of pyridoxamine-dependent enzymes, especially transaminases and amino oxidases.
- The neurotoxic effects of carbon disulfide may be associated with the CS₂ reaction with tryptophan to produce tryptophan dithiocarbamate which is neurotoxic due to impairment of the formation and destruction of biogenic amines. For example, amino acid dithiocarbamates inhibit dopamine hydroxylase and block the formation of norepinephrine from dopamine.
- In addition, the reaction products of CS₂ with epinephrine and norepinephrine block monoamine oxidases. Dithiocarbamates chelate metals such as copper and zinc. These metals are necessary for proper neuronal function, and Cu and Zn supplementation produces a protective effect for induced neurotoxicity in rats.
- Carbon disulfide produces marked lesions in the blood vessels of the heart, retina and brain. These are believed to be due to interference with elastase-inhibiting factors in the plasma, and to a functional copper deficiency which together result in disruption of the elastic elements in the walls of arteries, aneurisms, and ruptured blood vessels. There is generalized destruction in the microcirculation of the brain.
- Peripheral and central nervous function are also disrupted by virtue of demyelination, vacuolization, and cellular death.
- Testosterone and adrenal steroid production are reduced by CS₂ exposure. Also, tyrosine dithiocarbamate may interfere with thyroid hormone production and/or receptor site activity.
- Biochemical lesions of copper or zinc deficiency may occur in CS₂ poisoning by virtue of the binding to these metals of endogenously produced dithiocarbamates.
- Carbon disulfide associated liver disease may result in thymine deficiency and derangement of thymine metabolism, leading to a generalized neuropathy which is preventable in part by treatment with thymine.
- The hepatotoxic effect of CS₂ is believed to be due to the conversion of the parent molecule to an active sulfur by the microsomes. By virtue of the subsequent reaction of the sulfur with the microsomes, cytochrome P-450 activity is lost. Mild fasting or pretreatment with phenobarbital markedly increases the hepatotoxicity of CS₂. Carbon disulfide also inhibits protein synthesis through the formation of amino dithiocarbamates, and in CS₂ poisoning there are reductions in both the total serum protein and in the albumin/globulin ratio. Hepatic lesions may include pale, swollen livers, with foamy vacuolation of the centrilobular hepatocytes and foci of hepatic necrosis.
- Dermal contact with CS₂ produces vesicles and severe burns (possibly full thickness) on the skin and degenerative changes in the nearby peripheral nerves.
- Eye exposure may also cause degeneration in the retina and optic nerve.

Clinical Signs
- Acute inhalation exposure produces signs similar to ether anesthesia.
- High doses may cause coughing, dyspnea and respiratory failure.
- After ingestion, vomiting is a common sign in monogastric animals. Colic in horses. Ataxia, abnormal reflexes and fine tremors occur. Large doses may result in excitement followed by muscular weakness, and possible blindness, coma, collapse, and death. High doses (4800 ppm) associated with delirium, hallucinations, convulsions, and coma in humans.
- In women, CS₂ has been associated with abortions, chronic metritis, sterility, amenorrhea and abnormal menstrual cycles. These may be attributable to disruption of neurohormonal endocrine balance. CS₂ also causes marked depression of libido in both males and females and, in humans, the adverse effects on reproductive performance are permanent.

Treatment
- activated charcoal and a saline cathartic should be given for recent ingestion.
- Exposed eyes should be washed with water for at least 15 minutes.
- Dermal exposure-bathe with liquid dish detergent repeatedly. Treat as for thermal burns.
- Treat respiratory signs symptomatically. Initiate O₂ therapy as needed.
- Treat seizures with diazepam (dogs) or if unresponsive with barbiturates.
- Intravenous urea at 0.5 - 1.5 gm/kg has been recommended to inactivate free carbon disulfide in the blood.
- Vitamin B₆ in large doses.
- Adrenergic drugs and stimulants, such as amphetamines, are contraindicated due to CS₂-associated inhibition of monoamine oxidase.
Persea Americana - Avocado

Images

- Avocado - *Persea Americana* - Google Image Search. - To view this image in full size go to the IVIS website at www.ivis.org . -

Habitat

Avocados are grown primarily in southern states, especially California and Florida. Several commercial varieties are produced.

Susceptible Species

Cattle, horses, goats, rabbits, canaries, and fish have been poisoned under natural conditions.

Toxicity

- Leaves, fruit, bark, and seeds have been reported toxic.
- Toxicity retained in leaves after drying.
- Not all varieties are equally toxic. Fuate and Nabal strains produced acute death in the rabbit while the Mexicola strain produced no clinical signs.

Signs and Lesions

- Mouse.
  - Mild to marked dyspnea prior to death. Cerebral, liver, and pulmonary hemorrhage, mild gastrointestinal hemorrhage.
- Rabbit.
  - Noninfectious mastitis; pulmonary congestion, acute death, within 24 hours.
- Cattle.
  - Noninfectious mastitis.
  - *Diplodia* spp. causes black discoloration (black spots) on over-ripe avocados and has been associated with tremors in exposed cattle.
- Dairy goat.
  - Noninfectious mastitis (elevated somatic cell counts noted); decreased milk production.
  - Subcutaneous edema in the neck and brisket area; acute death.
  - Depression, teeth grinding.
  - Elevated SGOT, LDH.
- Horse.
  - Noninfectious mastitis.
  - May be a cause of laryngeal edema.
  - Several field reports indicate a **clinical syndrome** (signs) somewhat similar to that observed in horses that have nigropallidal encephalomalacia caused by yellow star thistle, *Centauria solstitialis*.
- Cage Birds.
  - Respiratory distress, generalized congestion, hydropericardium, anasarca, and death.
  - Onset may be within 24 hours (usually after 12 hours or more) with death within 1 - 2 days of the time of exposure.

<table>
<thead>
<tr>
<th>Major Species</th>
<th>Usual Time of Onset</th>
<th>Usual Duration (if survives)</th>
<th>Full Table for Toxicants with Mixed Effects on the Central Nervous System (Part II)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurologic effects more likely in horses</td>
<td>Hours to chronic</td>
<td>Days to weeks; reversibility?</td>
<td></td>
</tr>
</tbody>
</table>
**Aesculus - Buckeye and Horsechestnut**

<table>
<thead>
<tr>
<th>Specific Agents</th>
<th>Major Species</th>
<th>Usual Time of Onset</th>
<th>Usual Duration (if survives)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Buckeye</strong> <em>(Aesculus glabra)</em></td>
<td>Herbivores</td>
<td>Hours to days</td>
<td>Hours to days; infrequently lethal</td>
</tr>
<tr>
<td><strong>Horse chestnut</strong> <em>(Aesculus hippocastanum)</em></td>
<td>Herbivores, poultry</td>
<td>Hours to days</td>
<td>Hours to days; infrequently lethal</td>
</tr>
</tbody>
</table>

**Images**


**Description**

- Trees or shrubs, flowers in cluster.
- Buckeye 5 - 9 leaflets, Horsechestnut 7 leaflets. These are opposite and palmately compound.
- Fruits are covered with a globular spine covered, leathery capsule which contains 1 - 3 large glossy, chocolate colored nuts with a white or tan scar. Spines on the capsules of some species are lost at maturity.

**Habitat**

Southern 2/3 of the Midwest and Old South, including eastern Texas, Missouri, Illinois, Indiana, Ohio. Woods and moist soils, river banks, etc.

**Toxic Principle**

Glycosides, especially a glycosidic saponin called aesculin and possibly a narcotic alkaloid.

**Note - Glycoside** is defined as a molecule containing a carbohydrate (sugar) moiety, particularly any such natural product in plants.

**Toxicity**

- Poisoning may occur in the spring, because *Aesculus* plants "leaf out" before most herbaceous plants have produced much forage. Also occurs from early fall to early winter.
- Bark, fruit and leaves are all toxic, however, young growth, sprouts and mature nuts are most dangerous. Do not confuse with edible chestnuts.
- Horse chestnut *(A. hippocastanum L.)* was more toxic to chicks and hamsters than was Ohio buckeye *(A. glabra, Willd).*
- Experimental study with yellow buckeye *(A. octandra Marsh)* nuts produced clinical signs in calves fed ground nuts at 0.5 - 1% bw. Severity of clinical signs appeared to be dose related.

**Signs**

- Cattle, sheep, hogs, chickens, and horses have been poisoned.
- Early signs include: vomiting, dullness, incoordination, staggering, hyperesthesia, and mydriasis. Colic may occur in horses, inflamed mucous membranes may be prominent.
- Subsequent signs: trembling of muscles, excitement or sluggishness, recumbency, paralysis, coma, convulsions, extensor rigidity, respiratory paralysis, and death. Despite neurologic signs, poisoned cattle displayed no apparent visual deficits or loss of menace response. Most were responsive until they had been down for a day or longer. Convulsions can be elicited by handling.
• Muscle incoordination, depression, paralysis, and coma noted in experimentally poisoned birds.
• Secondary complications including bloat, pulmonary aspiration, and musculoskeletal damage may contribute to death.

Lesions

• No lesions may be noted on postmortem examination.
• Congestion of the kidney, streaking of the renal cortex have been reported in field cases.
• Hepatic congestion, centrilobular vacuolization.

Diagnosis

• Clinical signs-hyperesthesia, myoclonus, recumbency.
• Finding plant material in GI contents.

Differential Diagnosis

Hypomagnesemic tetany, polioencephalomalacia, tetanus.

Treatment

• For recent exposures: activated charcoal with a saline carthartic.
• Demulcents, such as milk and egg may be given for irritated mucous membranes of the gastrointestinal tract.
• Fluids, electrolytes for losses.
• Other supportive, symptomatic therapy as indicated, control bloat, seizures.
• Rumenotomy may be required in severe cases.

---

**Convolvulus (Morning Glory)**

<table>
<thead>
<tr>
<th>Specific Agents</th>
<th>Major Species</th>
<th>Usual Time of Onset</th>
<th>Usual Duration (if survives)</th>
<th>Full Table for Toxicants with Mixed Effects on the Central Nervous System (Part II)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morning glory (Convolvulus)</td>
<td>All species, esp. dogs, cats</td>
<td>Hours</td>
<td>Up to 2 days; infrequently lethal</td>
<td></td>
</tr>
<tr>
<td>Ergot alkaloids in seed heads of small grains and grasses</td>
<td>Herbivores</td>
<td>Minutes to days</td>
<td>Days; sometimes lethal</td>
<td></td>
</tr>
</tbody>
</table>

---

Images

• Morning Glory, Convolvulus - Google Image Search - Google Image Search. - To view this image in full size go to the IVIS website at www.ivis.org . -

• Morning glory seeds may contain toxic concentrations of LSD and related alkaloids.
  • D-lysergic acid (ergine).
  • D-isolysergic acid.
  • D-lysergic acid methylcarbinolamide (ergonovine, an ergot alkaloid).
  • Certain clavine alkaloids.
• Hallucinogenic in people and may cause diarrhea.
Mushrooms - General

- Serious poisoning from mushrooms is apparently rarely encountered in veterinary medicine. There have been few documented reports of mushroom poisoning in the veterinary literature.
- Most mushroom poisonings in animals occur as a result of ingestion of wild mushrooms. Occasionally, small animals are poisoned as a result of ingestion of hallucinogenic "illicit" mushrooms.
- Ideally, cases of mushroom poisoning should be treated using the combined knowledge of a mycologist and a toxicologist. Rarely can this ideal be obtained. When possible, have the mushroom identified as quickly as possible by a competent mycologist. Consult with local university botany departments, botanical gardens, mycological societies or mushroom clubs for names of mycologists in your area.
- Even if a mycologist is available to identify the suspect mushroom, remember the adage: **Treat the patient not the mushroom** for the following reasons:
  - Many mushrooms contain several toxins in varying concentrations. These concentrations may vary from locality to locality, season to season, or even from individual to individual. Much of the confusion concerning poisoning from *Amanita muscaria* has occurred for this reason. Originally thought to contain only the cholinergic poison, muscarine (named for the mushroom), it was later found more often to contain other toxins with anticholinergic properties (opposite effect).
  - Poisonous and nonpoisonous mushrooms often grow side by side so that mixed collections are gathered and eaten. The mushroom that is brought for identification may not be the only one eaten.
  - Mushroom poisonings and poisons have not been well documented. Many mushrooms may be poisonous, but without case reports of poisoning, they are not a suspect. Also, many mushrooms are known to be poisonous, but the toxins have never been identified.
  - Mushrooms, like vegetables, may be contaminated with pesticides or other poisons.

**Poisonous Principles**

The toxins of major importance in North American mushrooms can be divided into the following classifications:

<table>
<thead>
<tr>
<th>Effect</th>
<th>Genera</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Toxins that cause cellular destruction:</td>
<td>Amanita, Galerina Gyromitra</td>
</tr>
<tr>
<td>I. Cyclopeptides</td>
<td></td>
</tr>
<tr>
<td>II. Monomethylhydrazine</td>
<td></td>
</tr>
<tr>
<td>B. Autonomic Nervous System effects:</td>
<td>Coprinus Clitocybe, Inocybe, <em>Amanita muscaria</em> (minority of strains), Boletus</td>
</tr>
<tr>
<td>III. Coprine poisoning</td>
<td></td>
</tr>
<tr>
<td>IV. Muscarinic effects</td>
<td></td>
</tr>
<tr>
<td>C. CNS effects:</td>
<td>Amanita muscaria (majority of strains), <em>A. panterina</em>, possibly some strains of <em>Panaeolus</em> Psilocybe, Panaeolus, Gymnopilus, Copelandia, Conocybe, Lactarius torminosus, Boletus satanus, Russula emetica, and Chlorophyllum molybdites</td>
</tr>
<tr>
<td>V. Ibotenic acid-muscimol (anticholinergic)</td>
<td></td>
</tr>
<tr>
<td>VI. Psilocybin, psilocin, baeocystin, norbaeocystin, indoles similar to LSD (d-lysergic acid)</td>
<td></td>
</tr>
<tr>
<td>D. Gastrointestinal irritants:</td>
<td>Agaricus, Amanita, Lepiota</td>
</tr>
<tr>
<td>VII. Unclassified GI irritants</td>
<td></td>
</tr>
</tbody>
</table>

Several specific mushroom poisoning syndromes are mentioned under the organ/systems affected.

**General Principles of Diagnosis**

- Mushroom poisoning evoked by the ingestion of a single toxic species is classified by time of onset of signs and by signs elicited.
- Short (< 6 hour) onset:
  - Rarely fatal.
  - Gastroenteric irritants.
    - Colic, diarrhea, vomiting.
    - Clinical signs generally resolve within 24 hours.
  - Muscarinic effects.
    - *Inocybe* and *Clitocybe*.
    - Parasympathetic activity—salivation, lacrimation, miosis.
• Therapy with atropine indicated.
• Hallucinogenic mushrooms.
  • Contain psilocybin or muscimol.
  • Can cause behavior changes, depression, ataxia, seizures, coma.
• Coprin poisoning.
  • Inky cap, Coprinus atramentarius.
  • Edible mushroom.
  • Amino acid coprine converted to 1-aminocyclopropanol, clinical problems associated with ingestion of alcohol (similar to disulfiram [Antabuse]).
• Delayed (> 6 hour) onset.
  • Clinical signs appear suddenly.
• Monomethylhydrazine.
  • Gyromitra (air dried mushrooms are edible).
  • G. esculenta = false morel.
  • Depression, abdominal pain.
  • Hemolytic episode in a dog-note in this animal, a 3-hour onset of signs (vomiting) was observed.
• Cyclopeptide poisoning.
  • Amanita and Galerina.
  • Amanita phalloides-most commonly encountered, seriously toxic mushroom.
  • Substantial latent period of 10 - 20 hours before onset.
  • Colic, diarrhea, vomiting.
  • Dried mushrooms and cooked mushrooms are still toxic.
  • Hepatotoxins.

Treatment

• Emesis is generally safe in mushroom poisonings unless the patient is extremely weak, seizuring, comatose or does not possess an intact gag reflex. Removal of a portion of the ingested mushrooms should be accomplished in all cases, either by emesis or lavage with a large gastric tube. Often profuse vomiting occurs spontaneously in many types of mushroom poisonings. Treat the patient individually.
• activated charcoal should be given after cessation of vomiting or lavage. A cathartic should be administered unless diarrhea has occurred.
• The mortality rate in humans with known mushroom poisonings is more than 50% if untreated; however, it is less than 5% with effective therapy.
• Save all emesis and stools as well as all specimens of mushrooms that come in with a patient in plastic bags in the refrigerator for identification. Do not freeze. Try to have specimens identified within 24 hours.
• Many of the mycetotoxins are not understood, therefore, it is best to avoid all but absolutely indicated drugs.

Mushrooms - Disulfiram (Antabuse) Like (Problems Occur in Ethanol Intoxicated Human Beings)

<table>
<thead>
<tr>
<th>Major Species</th>
<th>Usual Time of Onset</th>
<th>Usual Duration (if survives)</th>
<th>Full Table for Toxicants with Mixed Effects on the Central Nervous System (Part II)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dogs, herbivores</td>
<td>1 to 24 hours</td>
<td>Up to 2 to days; rarely lethal</td>
<td></td>
</tr>
</tbody>
</table>

Images

Fly amanita, Amanita Muscaria - Google Image Search. - To view this image in full size go to the IVIS website at www.ivis.org . -

Mushrooms

Coprinus atramentarius. Reports from Japan indicate Clitocybe claviceps (claviceps) causes a similar clinical syndrome, but no reports have come from other countries.

Pharmacology

Unknown disulfiram-like substances which inhibits normal activity of enzymes metabolizing ethanol in the human, such as aldehyde
dehydrogenase. Apparently only certain people, perhaps those with an enzyme deficiency, are affected.

**Clinical Effects in Humans**

**Signs**

Occur a short time after ingestion of alcohol if the mushroom has been eaten during the preceding eight hours by the susceptible individual. Flushing of the face and neck with throbbing distension of neck veins and a feeling of swelling and paresthesia in the hands and feet are followed by a metallic taste, tachycardia and often chest pains. Later, nausea and vomiting occur. In severe cases, visual disturbances, vertigo, weakness, confusion, postural hypotension and occasionally respiratory difficulties and shock occur.

**Range of Toxicity**

Recovery is usually spontaneous and complete.

**Mushrooms - Hallucinogenic Indoles**

<table>
<thead>
<tr>
<th>Major Species</th>
<th>Usual Time of Onset</th>
<th>Usual Duration (if survives)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dogs, herbivores</td>
<td>1 to 24 hours</td>
<td>Up to 2 to days; rarely lethal</td>
</tr>
</tbody>
</table>

**Images**

*Psilocybe baeocystis* - Google Image Search. - To view this image in full size go to the IVIS website at www.ivis.org . -
*Psilocybe semilanceata* - Google Image Search. - To view this image in full size go to the IVIS website at www.ivis.org . -
*Psilocybe cubensis* - Google Image Search. - To view this image in full size go to the IVIS website at www.ivis.org . -

**Mushrooms Containing Hallucinogenic Indoles Include:**

*Conocybe cyanopus, Gymnopilus spectabilis, possibly other Gymnopilus species, Panaeolus foenisecoo, Panaeolus suboalteatus, Psilocybe baeocystic, Psilocybe cyanes, Psilocybe cubensis, Psilocybe fimentaria, Psilocybe mexicana, Psilocybe pelliculosa, Psilocybe semilanceata, and Psilocybe silvatica.*

**Toxic Principle**

- Psilocybin, psilocin, baeocystin, norbaeocystin, and indoles similar to LSD (d-lysergic acid). Their effects are primarily central (hallucinogenic), but there are some peripheral effects, probably through the serotonin-norepinephrine pathways.
- "Street mushrooms" may be edible commercial mushrooms laced with LSD or other hallucinogenic compounds or other drugs which may give confusing clinical signs, etc.
- Indoles are thermostable, therefore cooking does not render these mushrooms nontoxic.

**Clinical Effects in Humans**

Within 30 - 60 minutes (occasionally as late as 3 hours) after ingestion of 5 - 15 mg of psilocybin (10 - 30 grams fresh weight of mushrooms) a hallucinogenic dysphoric state begins. The mood may be pleasant or apprehensive ("good" or "bad" trip). The patient's critical judgement is impaired, and performance ability is poor. He may experience unmotivated hyperkinetic compulsive movements and laughter, mydriasis, vertigo, ataxia and paresthesias may occur. Muscle weakness and drowsiness progressing to sleep end the episode which usually lasts only 6 hours. In children a high temperature (102 - 106º F) may develop with tonic-clonic convulsions, which are usually intermittent, and not precipitated by sudden sounds.

**Toxicity**

Fatality rate is probably less than 1%. One death in a six year old child who ate Psilocybe baeocystis has been reported.
Treatment

- Prevention of absorption:
  - Emesis should be initiated unless contraindications are apparent.
  - If contraindications to emesis exist, intubation should precede gastric lavage.
  - Activated charcoal at 5 - 10 times the estimated ingested dose or 2 grams/kg bw suspended in a water slurry.
  - Sodium or magnesium sulfate 250 - 500 mg/kg orally as a cathartic. Dilute in 5 - 10 times as much water before administration.
- Hyperpyrexia reported in children. Aspirin and acetaminophen should not be used. Tepid water sponging is the method of choice to reduce fever.
- Seizures in dogs should be treated initially with diazepam.
## Additional Toxicants

<table>
<thead>
<tr>
<th>Specific Agents</th>
<th>Major Species</th>
<th>Usual Time of Onset</th>
<th>Usual Duration (if survives)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethylene glycol</td>
<td>(See Toxicants that Cause Acidosis)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boric Acid</td>
<td>(See Toxicants that Affect the Kidneys, Metals and Inorganics)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fipronyl</td>
<td>Cats, dogs?</td>
<td>Unknown, hours?</td>
<td>Unknown</td>
</tr>
<tr>
<td>Phenothiazine tranquilizers</td>
<td>All animals</td>
<td>Minutes to hours</td>
<td>Hours to 2 days; infrequently lethal</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>All animals, esp. dogs and cats</td>
<td>Minutes to hours</td>
<td>Hours to 2 days; infrequently lethal</td>
</tr>
<tr>
<td>LSD (lysergic acid diethylamide)</td>
<td>All animals, esp. dogs and cats</td>
<td>Minutes to hours</td>
<td>Hours to 2 days; infrequently lethal</td>
</tr>
<tr>
<td>Japanese yew (Taxus)</td>
<td>Dogs</td>
<td>Minutes to hours</td>
<td>Days (very little data in dogs); often lethal. NOTE: cardiototoxic effect are predominant except in dogs</td>
</tr>
<tr>
<td>Mescal Bean (Sophora secundiflora)</td>
<td>All species, esp. sheep and cattle</td>
<td>Hours to days</td>
<td>Days up to 2 weeks; often lethal in poisoned cattle</td>
</tr>
<tr>
<td>Cocklebur (Xanthium strumarium)</td>
<td>Swine, herbivores, fowl</td>
<td>Few hours to 2 days</td>
<td>Days; often lethal</td>
</tr>
<tr>
<td>Buttercup (Ranunculus)</td>
<td>Herbivores, swine</td>
<td>Minutes to hours</td>
<td>Days to a week; infrequently lethal</td>
</tr>
<tr>
<td>Milkweed (Asclepias)</td>
<td>Herbivores</td>
<td>2 to 24 hours</td>
<td>Hours to days; most species infrequently lethal; but some species are more toxic</td>
</tr>
<tr>
<td>Hypomagnesemia (grass tetany; wheat, oats, bluegrass, alfalfa, cornstalks, others)</td>
<td>Herbivores esp. sheep</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Corynetoxins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Domoic acid (cause of amnesic shellfish poisoning)</td>
<td>Waterbirds, aquatic predators</td>
<td>Hours to days</td>
<td>Days to months; potentially lethal</td>
</tr>
<tr>
<td>Pfiesteria piscicida</td>
<td>Cats?, dogs?</td>
<td>Hours?</td>
<td>Persistent?</td>
</tr>
</tbody>
</table>

- Ethylene Glycol (See Toxicants Causing Acidosis)
- Hypomagnesemia (Grass Tetany) (Wheat, Oats, Bluegrass, Alfalfa, Cornstalks, Others)
- Boric Acid (See Toxicants that Affect the Kidneys, Metals and Inorganics)
- *Phenothiazine Tranquilizers
- LSD
- Mescal bean (Sophora secundiflora) (See Toxicants with Nicotinic Effects)
● Cocklebur (*Xanthium*) (See Poisonous Plants that Affect the Liver)

● Tall Buttercup (*Ranunculus*) (See Plants that Affect the Gastrointestinal Tract)


● Grass seed nematodes (e.g., toxin produced by the nematode *Anguina agrostis* in seed galls of various types of fescue, bluegrass, timothy, orchard grass, etc.) (See Galloway JH. Grass seed nematode poisoning in livestock. J Am Vet Med Assoc 1961; 139:1212-1214.)

### References

#### Lead Toxicosis


#### Mercury


#### Organotin Compounds


Feed Related Ammonia Poisonning

Pyrethrum (Pyrethrins) and Pyrethroids

Rotenone

Tricyclic Antidepressants

Fumonisins

**Centauria - Yellow Star Thistle and Russian Napweed**


**Astragalus and Oxytropis - Locoweeds**


**Hexachlorophene**


**Bromethalin**


**Vacor**


**Deet**


**Methionine**


**Carbon Disulfide**


**Persea Americana - Avocado**


**Aesculus - Buckeye and Horsechestnut**


**Mushrooms General**


**Additional toxicants**

4. Domoic acid - Ping Y, Ramsdell JS (1996) Brain Fos induction is a sensitive biomarker for the lowest observed neuroexcitative effects of domoic acid. Fundam Appl Toxicol 31:162-168

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