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Toxicants that Cause Central Nervous System Depression (9-Aug-1999)

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Chapter Sections

Eupatorium rugosum - White Snakeroot

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Cause Central Nervous System Depression
Cattle, horses, sheep, goats	Days to weeks	10 - 14 days in cattle; permanent heart damage in horses; often lethal in both species	

Synonyms - Richweed, white sanicle

Images

- White snakeroot (*Eupatorium rugosum*).. Knight A.P. and Walter R.G. (Eds.). A Guide to Plant Poisoning of Animals in North America. Ithaca: International Veterinary Information Service (www.ivis.org), 2003. - To view this image in full size go to the IVIS website at www.ivis.org . -
- Eupatorium rugosum - White Snakeroot.. Source: Cornell University, Poisonous Plants Informational Database (www.ansci.cornell.edu/plants/index.html). - To view this image in full size go to the IVIS website at www.ivis.org . -
- White Snakeroot, *Eupatorium rugosum* - Google Image Search. - To view this image in full size go to the IVIS website at www.ivis.org . -

Description

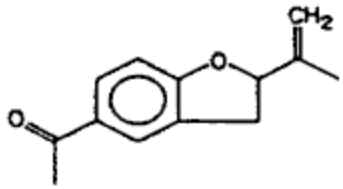
- An erect, herbaceous perennial with stiff, branched or unbranched stems, mostly 3 - 4 feet tall. Grows from a shallow mat of fibrous whitish roots. Leaves are opposite, 3 - 6 inches in length, with serrated margins, and 3 ribs. Leaves get larger as you move down the stem.
- Flowers are white, small, in composite heads of 10 - 30 flowers at the top of the plant. Although it is fairly easy to identify, similar nontoxic species of *Eupatorium* do exist, therefore, confirmed identification by a botanist is recommended.

Habitat

- Open-wooded, semi-shaded areas, especially common at the edge of the woods, from eastern North America westward to Minnesota and Texas.
- Most severe problems in southern Ohio, Indiana, and Illinois, as well as in eastern Missouri and North Carolina.

Toxic Principle

- The apparent toxic principle in white snakeroot has been given the trivial name, tremetol, and has been described as a fat soluble, high molecular weight alcohol.
- Crude tremetol, was later shown to be separable into a toxic ketone fraction (61%) (tested in goldfish) and a sterol fraction (39%), which was nontoxic. The ketone fraction was later separated into tremetone, dihydrotremetone, and hydroxytremetone. These may all be components of a fragile tremetol molecule, however, the identity of the toxic principle remains to be clarified. For the purposes of this course and state board exams, it should be assumed that tremetol is the toxic principle in white snakeroot.



Tremetone

Toxicity

- The toxic substance remains in the dried plant after frosts. The toxic principle is a cumulative poison and repeated exposure to small amounts results in intoxication.
- The toxin is secreted in the milk apparently far more rapidly than by any other route which can result in relay toxicosis to offspring or humans.
- No reliable test for the presence of tremetol is presently available.
- It generally stays green and succulent in dry weather and after the first frost, so that more consumption and more poisoning occurs at those times.
- Reported that ingestion of 1 - 10% of an animal's body weight of green plant may be lethal to cattle, sheep, and horses, whether ingested at 1 time or with smaller successive doses.

Susceptible Species

- Cattle, horses, and sheep are most commonly poisoned. Goats appear to be particularly sensitive.
- Suckling calves are especially at risk; at least in cattle, lactating animals are significantly protected. Thus in cattle, beef calves are most often affected.
- Nonlactating, grazing animals are also affected.
- "Milksickness" was a major problem in humans during the period of westward expansion, reportedly caused the death of Abraham Lincoln's mother. Pasteurization does not detoxify milk; but dilution in modern dairies apparently provides a large safety factor.

Signs and Effects

- In cattle:
    - Stiffness, apparent severe CNS depression, unsteadiness, ataxia, sternal recumbancy, anorexia, and weight loss. Animals develop tremors especially of the flank, neck, hind legs, and face which become more severe with exercise. Later complete relaxation without tremors, coma, and frequently death.
    - Occasionally constipation, salivation.
    - Syndrome persists for at least 10 - 14 days after removal from white snakeroot and weaning.
    - Ketoacidosis may be a major feature in some cases (acetone odor to breath and urine in some animals).
    - Deaths occur within 2 - 10 days.
- In horses:
    - Onset of clinical signs within 2 days to 3 weeks after ingestion (usually after at least several days of ingestion).
    - Congestive heart failure.
    - Stand with legs wide apart.
    - Swelling of ventral neck near thoracic inlet.
    - Jugular pulse, tachycardia.
    - EKG changes include increased rate, ST elevation, and variable QRS complexes, e.g., ventricular premature beats. Auscultable cardiac arrhythmias are often present.
    - Sweating, especially between rear legs.

- Tremors are inconsistently observed.
- Stumbling (in rear legs) when turned in some instances. Severe depression can occur.
- Hematuria may occur.
- Choke sometimes occurs.

Clinical Pathology

Horse, elevated CPK, SGOT, SGPT, and SAP.

Lesions

- In cattle:
  - Fatty liver, congestion and degenerative changes in liver. Hemorrhage of variable extent may be found in the heart and GI tract.
- In horses:
  - Myocardial degeneration, necrosis, and fibrosis. Straw-colored fluid in pericardial sac. Extensive pale areas of the subendocardium.
  - Ventral edema.
  - Centrilobular degeneration with mild necrosis and fatty changes, possibly due to cardiac insufficiency.

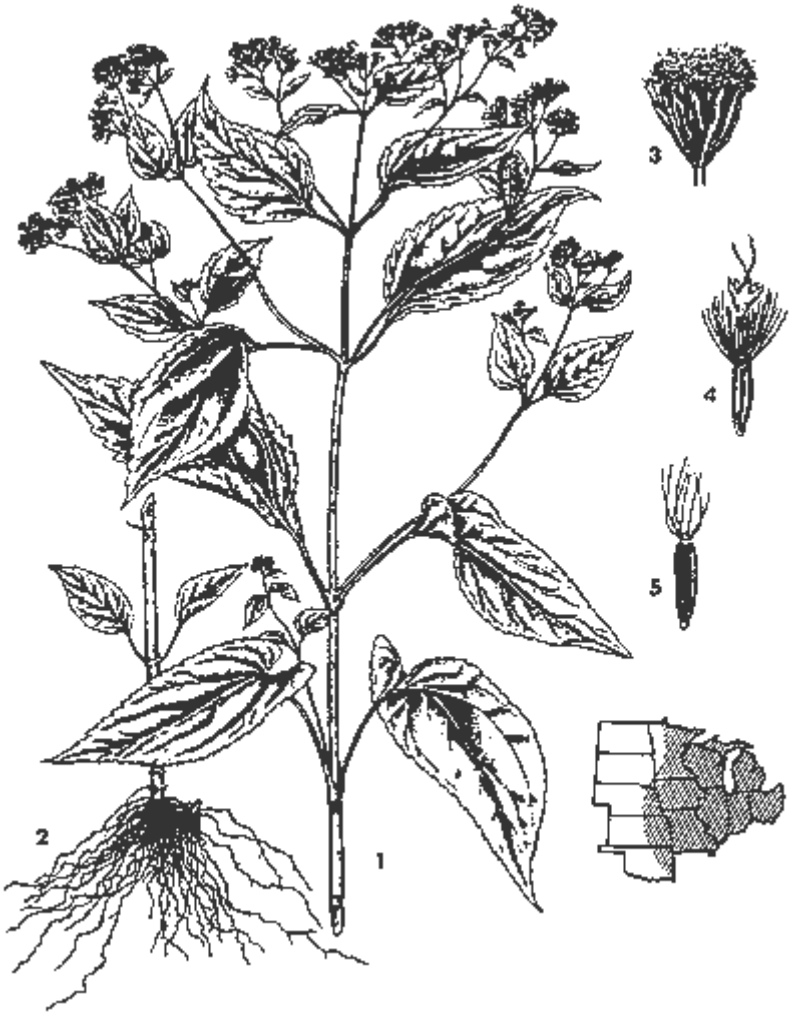
Diagnosis

- Characteristic clinical signs.
- History of exposure to white snakeroot.

Treatment

- No studies involving therapy are known to have been conducted.
- Treatment is therefore empirical.
- In cattle:
  - Activated charcoal and if hydration is adequate a saline cathartic. Dry bedding, good shelter, good nursing care. Provide feed and water in such a way that animals can consume them (i.e., put under animals nose if necessary). Consider need for fluids, B-vitamins, and tube feeding. Monitor for secondary infections, etc. May require treatment for ketosis. If possible, continue to milk animals to enhance excretion; dispose of milk.
- In horses:
  - Activated charcoal, saline cathartic. Monitor arrhythmias and EKG: treat symptomatically. May be left with severely scarred heart, and associated circulatory dysfunction. Fecal softeners.
  - Symptomatic and supportive therapy.

Composite Family, *Compositae*



White Snakeroot, *Eupatorium rugosum* houtt. **1**, upper part of plant; **2**, root; **3**, flower head; **4**, single flower; **5**, seed. **Perennial**, spreading by seeds and short rhizomes. **Roots** much branched and fibrous. **Stem** 1 to 3 feet (30 - 90 cm) tall, smooth, and branched near top. **Leaves** opposite, elliptical, thin, smooth, with toothed edges and slender petioles. **Flower heads** small, of white disk flowers only. **Seed** black, angular, about 1/8th inch (3 mm) long, with a tuft of white hairs. **Found** in hardwood timber areas, woodland, pastures, and waste places. It grows only in shaded areas. Contains a cumulative poison that causes the disease known as "trembles" in cattle and horses. Dairy products from animals that have eaten the plant are poisonous to man, causing "milk sickness", one of the main scourges of pioneers in the region.

Isocoma wrightii - Previously *Haplopappus* or *Aplopappus* - Rayless Goldenrod

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Cause Central Nervous System Depression
Herbivores, esp. goats	Days to weeks	Days to weeks; potentially lethal especially in goats	

Synonyms - Jimmyweed, burrow weed

Images

- Burrow weed (*Isocoma pluraflora*). (Courtesy of Dr. Robert Glock, Veterinary Diagnostic Laboratory, Tucson, Arizona). Knight A.P. and Walter R.G. (Eds.). A Guide to Plant Poisoning of Animals in North America. Ithaca: International Veterinary Information

Service (www.ivis.org), 2003. - To view this image in full size go to the IVIS website at www.ivis.org . -
- Rayless Goldenrod, *Isocoma wrightii* - Google Image Search. - To view this image in full size go to the IVIS website at www.ivis.org . -

Description

- An erect, bushy, unbranching, perennial shrub, that grows 2 - 4 feet tall.
- Leaves are alternate, linear and sticky, and the flowers are terminal and yellow.

Habitat

- Dry range lands of southern Colorado, western Texas, and most of northern Mexico and Arizona.
- Grows especially in river valleys and along drainage areas. Abundant along the Pecos River.

Susceptible Species and Poisonous Principle

Affects horses, cattle, sheep, and goats. Young are poisoned because the toxic substance, reportedly tremetol, is secreted in the milk. Severe losses have occurred in livestock; milk sickness in nursing animals and humans.

Toxicity

Ingestion of 1 - 1.5% of bw of *I. wrightii* during a 1 - 3 week period may cause toxicosis in cattle, sheep, and horses.

Clinical Signs

- Cattle.
    - The syndrome in cattle is similar to that which occurs in white snakeroot poisoning; however, the tremors that occur may be much more severe.
    - Rear limb weakness, knuckling of fetlocks, can progress to posterior paralysis.
    - Acetone odor on breath from ketosis.
    - Urinary incontinance and constipation.
    - Skeletal muscle damage may be extreme and elevations of CPK may be marked. Elevation of SGOT and LDH also occurs.
- Horse.
    - There is no documentation of heart muscle degeneration of horses as occurs in white snakeroot poisoning.

Lesions

- Centrilobular necrosis of liver.
- Congestion of brain and spinal cord.
- Congestion and fatty degeneration of liver and kidneys.

Diagnosis

- Clinical signs.
- History of exposure.

Isocoma wrightii. The narrow pointed leaves, the clusters of yellow flower heads at the tip of the branches, and the flower (enlarged, lower right) and fruit (enlarged, lower left) with its crown of bristles characterize this plant.

Opiates and Opioids

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Cause Central Nervous System Depression
Dogs, cats	Minutes to hours	Hours to 2 days	

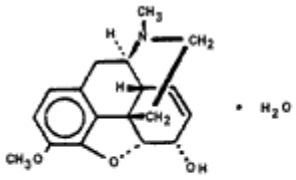
General Statements

- Rare cause of poisoning in dogs and cats.
- Dogs - Several agents used in dogs as analgesics; apomorphine used as an emetic.
- Cats - Extreme stimulation with some agents such as morphine-therefore not used except at a very much lower dose than in the dog. Apomorphine-no safe and reliable dose in cats established in spite of attempts to find one. Demerol (meperidine) is sometimes used in the cat as an analgesic at 2 - 4 mg/kg, IM, SC (not as an emetic).
- Morphine used in treatment of pulmonary edema (cardiogenic and neurogenic pulmonary edema); but not for use with pulmonary edema from chemical irritants.

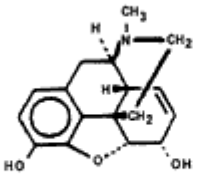
Sources

- Most opiates available in both oral and parenteral forms, both legally and illicitly.
- Morphine - Analgesic; some use as an emetic in dogs.

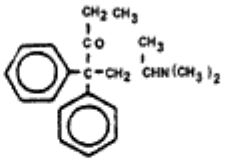
- Etorphine (M99), a derivative of the opium alkaloid thebaine, used for immobilization of wild-life and is 80 - 1000 times more analgesically potent than morphine. Diprenorphine M50 - 50 is an etorphine antagonist.
- Paregoric - Camphorated tincture of opium.



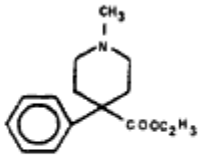
Codeine



Morphine



Methadone



Meperidine

Phenanthrene Derivatives **Diphenylheptane Derivatives** **Phenylpiperidine Derivatives**

Chemical Types

- Opiates are classified into three general groups based on chemical structures, namely:
    a. Phenathrene derivatives including morphine, codeine, and oxymorphone;
    b. Phenylpiperidine derivatives including meperidine and fentanyl; and
    c. Diphenylheptane derivatives of which methadone is the only commercially available forms.

Mechanism of Action

- Interact at opiate receptor sites in the CNS and other tissues. Several subtypes of opiate receptors have been described including m-receptor (pain centers CNS), a receptor (cerebral cortex), w receptor (limbic system, and the s receptor (CNS).
- Opiate interaction with receptor populations varies with each specific opiate agonist.
- Precise mechanism of action producing analgesia is not fully understood.
- Result in suppression of cough reflex, respiratory depression, behavioral changes, and CNS depression.
- Produce miosis, decrease GI motility by an unknown mechanism. Also result in increased urinary sphincter tone which can result in dysuria.
- Produce hypotension by causing peripheral vasodilation.

Absorption, Distribution, Metabolism and Excretion (ADME)

- Variable absorption following oral administration.
- Onset and duration of signs varies with each particular opiate.
- Cross placental barrier, can cause fetal depression.
- Primarily metabolized in the liver by glucuronidation (deficient in cats), hydrolysis, and oxidation; excretion of glucuronide derivative in the urine.

Common Opiates and Opioids - Key Differences

- Morphine - Limited penetration of the brain.
- Codeine - Weak action at opiate receptors; action may be due to conversion to morphine in the body.
- Heroin (diacetylmorphine) is rapidly hydrolyzed to monoacetylmorphine which is hydrolyzed to morphine. Heroin more readily penetrates the blood brain barrier as compared to morphine. Elimination same as morphine.

Predisposing Factors

- Increased susceptibility to respiratory depression in:
    - Old patients and neonates.
    - Hypothyroid patients.
    - Hypothermic animals.
    - Liver disease.
    - Patients with reduced blood volume.

- Contraindicated in head injury.
    - The narcotics may increase intracranial pressure plus increase the tendency for respiratory depression to occur.
- Contraindicated with seriously decreased respiratory depression from any cause.
- Hypotension may be aggravated by concurrent exposure to phenothiazine tranquilizers, monoamine oxidase inhibitors or tricyclic antidepressants.

Toxicity

- Lethal SC or IV doses morphine in dog 110 - 220 mg/kg.
- Meperidine (Demerol) can produce excitement and convulsions in the cat when administered at 20 - 30 mg/kg.
- Propoxyphene hydrochloride (Darvon) at 40 mg/kg PO in dogs produced tremors, salivation, ataxia, and vomiting. Lethal effects produced at 125 mg/kg.
- Pentazocine lactate (Talwin) administered at 6 - 10 mg/kg IM in the dog and 2.2 - 4.4 mg/kg IM in the horse produced ataxia, tremors, and convulsions.

Signs

- CNS depression, vomiting, ataxia, and respiratory depression are commonly observed.
- Coma, cyanosis, and poor perfusion are seen in later stages. Bradycardia and arrhythmias may occur.
- Miosis, but if severely hypoxic, mydriasis can occur. Mydriasis more commonly seen with meperidine overdoses in human patients.
- Hypothermia.
- Flaccidity of muscles.
- Convulsions occasionally seen.
- Pulmonary edema and pneumonia may also develop.
- Death due to respiratory failure, or later due to shock.

Diagnosis

- Clinical signs.
- History of exposure.
- Response to naloxone 0.01 - 0.02 mg/kg. If no improvement after 1 - 2 doses, reconsider the diagnosis.

Treatment

- Airway-assist respiration, or artificial respiration. O_2 therapy.
- Narcotic antagonist:
    - Duration of effect of antagonists is often less than that of the opioid. Antagonist must, therefore, be repeated to avoid subsequent severe depression. Antagonists, such as nallorphine or levallorphan may exert depressant effects, whereas nalloxone does not have this disadvantage.
    - Nalloxone, drug of choice, at 0.01 - 0.02 mg/kg is administered IV, IM, or SQ in the dog or cat.
- Oral exposure - Evacuate gastrointestinal tract, activated charcoal and saline cathartic.
- Gastric lavage and activated charcoal may be effective even many hours after ingestion since opiate-induced pylorospasm may be present.
- Nalozone has been reported to not prevent meperidine (Demerol) - induced seizures. Treatment with phenobarbital was successful in antagonizing lethal convulsive effects of meperidine.

Note

Opiate agonists are subject to control under the Federal Controlled Substances Act of 1970.

Cannabis sativa - Marijuana

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Cause Central Nervous System Depression
Dogs, rarely cats	Minutes to hours	One to 2 days; unlikely to be lethal	

Synonyms - Marijuana, hemp, pot, grass, Mary Jane, sensemilla.

Images

- Marijuana (*Cannabis sativa*) plant (Courtesy of Carol Salman, Fort Collins, Colorado). . Knight A.P. and Walter R.G. (Eds.). A Guide to Plant Poisoning of Animals in North America. Ithaca: International Veterinary Information Service (www.ivis.org), 2003. - To view this image in full size go to the IVIS website at www.ivis.org . -
- Marijuana showing typical leaf structure (*C. sativa*).. Knight A.P. and Walter R.G. (Eds.). A Guide to Plant Poisoning of Animals in North America. Ithaca: International Veterinary Information Service (www.ivis.org), 2003. - To view this image in full size go to the IVIS website at www.ivis.org . -
- Marijuana (*Cannabis sativa*).. Source: Cornell University, Poisonous Plants Informational Database (www.ansci.cornell.edu/plants/index.html). - To view this image in full size go to the IVIS website at www.ivis.org . -
- Marijuana, *Cannabis sativa* - Google Image Search. - To view this image in full size go to the IVIS website at www.ivis.org . -

Hashish is a concentrated, dried resinous form of marijuana that sometimes may contain other (added) drugs.

Description

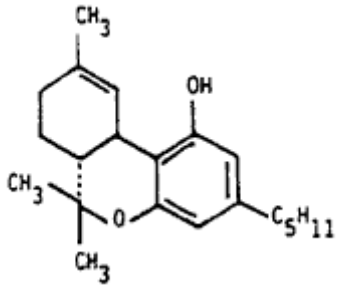
Marijuana is a tall, coarse annual herb in the hemp family; introduced from temperate Asia. The leaves are long-stalked and palmately divided into 3 - 7 narrow, pointed, toothed leaflets. Flowers are small, green, and clustered in the leaf axils. Male and female flowers are on separate plants. Flowers, leaves, and stems are covered with hairs which exude a sticky resin.

Habitat

It is a widely naturalized weed in temperate North America and is cultivated in warmer regions.

Toxic Principle

The toxins are various resins, mainly THC (tetrahydrocannabinol) and related compounds. Canabinoid is a C_{21} compound, carboxylic acid. Analogs include W^{9}-trans-tetrahydrocannabinol (WTHC), the most active constituent on the CNS in cannabis.



Structure of THC

Toxicity

- Not considered a poisonous plant if consumed fresh, becomes poisonous when damaged by drying, heating, smoking, and/or aging.
- The entire plant is toxic, especially the leaves, flowering parts, sap, and resinous secretions.
- The amount of resinoid in the various plant parts varies with plant variety, sex of plant (female plant, "sensemilla" more toxic), geographic location, and growing season.
- Toxic substances are highest in plants grown in warm climates or seasons.
- Poisoning may result from drinking the extract and chewing or smoking the plant parts. Effects of these plants have been known for

more than 2,000 years.
- Effect of marijuana can be related to THC content to some extent.
- Hashish is a concentrated form of marijuana. Sometimes hashish contains added opium.
- Oral LD_{50} W^{9}-THC rat 661 mg/kg, mice 482 mg/kg.
- Minimal lethal oral dose monkeys and dogs ≥ 3 g/kg.
- Plants can contain 1 - 6% THC, extracts as much as 28% THC.

Signs and Symptoms (Humans)

- THC is a CNS depressant with biphasic clinical signs: euphoria followed by depression.
- Exhilaration, delusions, mental confusion, dilated pupils, blurred vision, poor coordination, weakness, stupor, hallucinations, and coma (with large doses).
- Death may result from its depressing effect on the heartbeat.
- Other symptoms include craving for sweets, increased appetite, dryness of mouth, inflamed eyes, anxiety, aggressiveness, sleep disturbance, tremors, decreased sexual potency, feeling of contentment, increased but faulty perception and imagination, loss of initiative, reduction of will power and concentration, and impairment of lung function.

Signs (Small Animals)

- Ingestion by dogs and rarely cats causes ataxia, vomiting, mydriasis ("glazed eyes"), nystagmus, depression, and sometimes coma. Hypothermia in small animals has been demonstrated and may be dose related.
- Tachycardia or more commonly bradycardia.
- Prolonged depression for 18 - 36 hours is not unusual in marijuana-poisoned dogs.
- Occasionally animals may act hyperexcitable.
- Less frequently reported signs include tremors and salivation.

Comments

- The inner bark contains the tough hemp fibers used in making rope, the fruits are used as bird seed and to produce a useful drying oil, and the dried flowering and fruiting tops are a source of drugs.
- Federal (and state) laws prohibit the possession of living or dried parts of marijuana both in the United States and Canada.

Diagnosis

- Clinical signs.
- History of exposure. The owner(s) may be hesitant to provide the necessary information. Probing questions may be required.

Treatment

- Antiemetic properties may limit the effectiveness of emetic drugs but these may be tried prior to the onset of sedation or ataxia.
- Activated charcoal and a saline cathartic solution.
- Assist respiration if significant respiratory depression occurs.
- Haloperidol has been used to treat human beings with delusions or hallucinations.
- Diazepam has been used to treat people with marijuana associated anxiety and panic.
- Recovery may be slow (up to a few days) but may be hastened by detoxification of the digestive tract.

Marijuana (*Cannabis sativa*) - Note the palmately divided toothed leaves, the male flower (upper left), the female flower (upper right), the female flower with bracts removed (right center), and seed (enlarged, lower right) of this controversial drug plant.

Ivermectin and Milbemycin

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Cause Central Nervous System Depression
Dogs (esp. Collies), cats, foals	Hours to a day	Days to weeks; potentially lethal	

Introduction

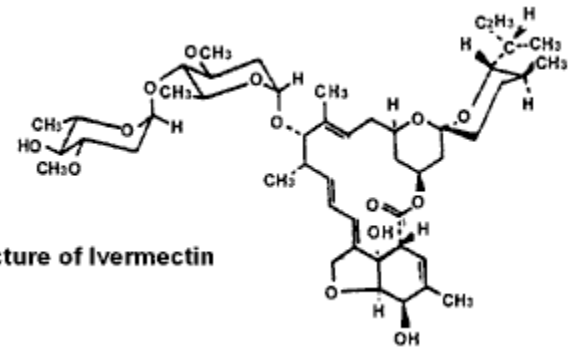
- 22,23-dihydroavermectin B_1.
- One of the class of avermectins, which are polycyclic lactones.
- Fermentation product of *Streptomyces avermitilis*, a soil fungus discovered in Japan.

Available Forms (Sources)

- Heartgard 68 mcg, 136 mcg, 272 mcg sizes (tablets).
- Ivomec - Injectable 10 mg/ml (1%) (suspension) for cattle and swine.
- Eqvalen - Paste 1.87% - Now on the market for horses.
- Zimecterin - Paste (OTC) 1.87%, now on the market for horses.
- Eqvalen Injectable (pulled off the market in 1984 because of *Clostridial myositis* in 1 - 1.5 horses out of 100,000 horses given an injection).
    - Contained polysorbate 80 (Tween 80), a known histamine releaser in dogs (polysorbate 80 is also in other drugs; such as

Konakion, a Vitamin K1 product.

- Interceptor ® tablets, containing milbemycin (another avermectin), are used in dogs for heartworm and hookworm control and occasionally for control of generalized demodecosis (an extra-label use).



Structure of Ivermectin

Toxicity

- Cumulative toxicity possible.
- Varies with species, breed, and age of animals.
- Younger animals appear more susceptible.
- Dogs.

	Single Oral Concentration	Clinical Signs
Beagles	2.0 mg/kg (2,000 µg/kg) 2.5 mg/kg 5.0 mg/kg 40.0 mg/kg	None Mydriasis Tremors Death
Collies	< 50 µg/kg 100 µg/kg - 200 µg/kg	None Tremors, mydriasis, and death

- Cattle and sheep oral ivermectin ≥ 4,000 - 8,000 mg/kg produced ataxia, depression.
- May result in death of migrating *Hypoderma* sp. larva.
- Signs occasionally delayed for 2 - 3 days in any species.

Susceptible Species

- Collies are apparently extremely susceptible to ivermectin.
    - 100 µg/kg is a dose that will have some clinical effects in some collie dogs.
    - 200 µg/kg will cause 30 - 40% to be markedly ataxic and some will go into a coma.
- Poisoning also occurs in shelties, border collies, and other related breeds which also appear to be predisposed.
- Milbemycin has been shown to have a similar therapeutic index to that of ivermectin, and dogs sensitive to ivermectin (especially collie-type breeds) are also sensitive to milbemycin.
- Poisoning occasionally occurs in other breeds of dogs as well.
- Apparently, similar toxic reactions sometimes occur in horses.
- Reactions to dead or dying parasites: (*Onchocerca* microfilaria in horses) die causing subcutaneous reactions, esp. ventral midline edema, colic in horses. In dogs may cause anaphylactic shock from microfilarial die off (controversial).
- Ivermectin ingestions have been associated with paresis and flaccid paralysis in chelonians = red-footed tortoise (*Geochelone carbonaria*) and leopard tortoise (*G. pardalis*). Toxicosis observed at 0.1 mg/kg or less.

Mechanism

- GABA mediation at inhibitory interneurons in mammals occurs only in the CNS; whereas GABA acts peripherally in invertebrates.
- Avermectins increase the activity of GABA receptors in 3 ways:
    1. Avermectins potentiate GABA effect at synapse by stimulating the presynaptic release of GABA.
    2. Avermectins enhance binding of GABA to postsynaptic receptors.
    3. There are also direct GABA agonist effects.

- GABA, the inhibitory neurotransmitter, opens postsynaptic chloride (Cl^-) channels allowing a Cl^- ion influx which causes an inhibitory effect through membrane hyperpolarization.
- Increase in Cl^- ion concentration inside the postsynaptic motor neuron causes retention of a negative charge (low electrical resistance), and subsequent excitatory or inhibitory signals are no longer registered by the recipient cell.
- This contrasts with the excitatory effects of acetylcholine which, instead, allows Na^+ ions to enter.

Absorption, Distribution, Metabolism and Excretion (ADME)

- Active after oral or parenteral exposure.
- Generally the blood brain barrier (BBB) of mammals excludes ivermectin such that the host animal is unaffected by reasonable doses. In collies, the blood-brain barrier is ineffective as an ivermectin barrier. Blood-brain barrier deficiencies have also been postulated in chelonians and some affected horses. In any species, sufficiently high doses can overcome the ability of the BBB to exclude ivermectin from the CNS.
- Parent compound is persistent in the body which may explain, in part, the duration of effects (up to several days) seen in poisoned dogs.
- Excreted in the feces. Low degree of liver metabolism.
- Concentrated in liver and body fat.
- Low GI absorption. Peak plasma concentrations are reached 3 hours after oral administration.
- The half-life in dogs was reportedly 2 - 3 days.

Signs

- Horse.
    - Polysorbate 80 reactions (histamine release) are no longer a significant problem since the equine injectable product is no longer available. Ventral midline pruritis, ventral edema, stiffness, limb edema, fever, eyelid edema, colic, depression, and deaths were also observed in horses given the injectable product. Adverse reactions in a total of 11% of horses in one study. *Clostridial myostitis* occurred much less often.
    - CNS depression can occur in some horses following ivermectin ingestion.
- Dogs.
    - Acute anaphylactic reactions in dogs may result from microfilarial die off.
    - With genuine ivermectin toxicosis (most prevalent syndrome), dogs tend to show depression, ataxia, and sometimes coma, which may be prolonged or proceed to cause death. Some dogs show decreased menace response. Pupils will respond to light. Blindness commonly occurs and with time is reversible. Bradycardia and sinus arrhythmia reported.
- Chelonians.
    - Paresis, flaccid paralysis, may appear "dead".

Lesions

There are no characteristic lesions in ivermectin poisoned animals.

Diagnosis

- Clinical signs.
- Recent exposure to an avermectin. Remember that heartworm or *Onchocerca* die-offs can cause acute reactions, even when an appropriate dose is used.
- Analytical confirmation is **available** at the State Animal Disease Laboratory at Centralia, IL, USA. Desirable specimens include suspected source materials, serum, and liver. Contact the laboratory prior to sample submission. Telephone (618) 532-6701.

Treatment

- Activated charcoal and a saline cathartic are suggested if recently exposed by the oral route. Whether repeated doses of activated charcoal may prevent enterohepatic recycling of ivermectin is not known but it seems appropriate to try this approach until proven ineffective.
- If very recently given by the subcutaneous route and life-threatening toxicosis is anticipated, it may be possible to lessen the fraction absorbed by surgical excision (again no backup data is available).
- Symptomatic, supportive care. **Good nursing care**, most important.
- Atropine may correct bradycardia if present.
- Picrotoxin is a GABA antagonist and could, perhaps, be used to slowly titrate the animal toward normal. Excessive picrotoxin, however, will lead to seizures.

- Physostigmine (cholinesterase inhibitor). May have some benefit in comatose animal. Causes increased concentrations of acetylcholine at neurons. Will have very short beneficial effect. Physostigmine is recommended primarily when owners are inclined to elect euthanasia for ivermectin-poisoned animals. The short-term recovery that often follows physostigmine therapy may reassure the owner that recovery is likely. The drug is given very slowly (over 5 minutes) IV or IM at 1 mg/40 lb (0.06 mg/kg) in the dog.
- Epinephrine is indicated for acute anaphylactic reactions.
- A rapid onset of clinical signs (i.e., within 2 hours) may indicate a high level of exposure and a more guarded to poor prognosis, whereas a slower onset (i.e., after 6 hours) may indicate lower level exposure and a more favorable prognosis.
- Antihistamines are used if the old injectable **Eqvalen** product has caused histamine release and associated reactions.

Amitraz

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Cause Central Nervous System Depression
Dogs, horses, cattle	One hour to 2 days	1 - 3 days; may be lethal to swine, horses, young puppies	

Introduction

- A formamidine pesticide.
- Used as an acaricide and a tick repellant for dogs.

Sources

- Mitaban ® - An acaricidal dip concentrate for use and generalized demodecosis in dogs (19.9% amitraz). The preparation also includes xylene and propylene oxide.
- Tick-repellant collars such as Preventic ® (9% amitraz).
- Agricultural pesticides.

Toxicity

- The LD_{50} in rats is 800 mg/kg.
- In dogs, dermal absorption following dipping is a common route of exposure resulting in toxicosis. Ingestion by dogs of amitraz-containing collars is becoming more common as their use becomes more widespread.
- Amitraz is not approved for use in cats. Toxicosis has been reported in cats following administration of the liquid preparation in the external ear canal.
- Puppies up to 3 - 4 months old seem to be especially sensitive to amitraz.

Mechanism

- Centrally, amitraz exerts toxic effects by acting as an alpha-2 adrenergic agonist.
- These effects are reversible by yohimbine.
- α-2 adrenergic stimulation results in vasodilation, bradycardia, hypotension, coma, and decreased insulin release culminating in hyperglycemia.
- In addition, in the periphery both alpha-1 and alpha-2 receptors are stimulated. The effects at α-1 receptors sometimes result in hypertension.
- Amitraz also inhibits monoamine oxidase.
- Some of the clinical signs of Mitaban ® toxicosis are believed to be caused by xylene and propylene oxide.

Clinical Signs

- Dogs and cats-vomiting, sedation, depression, disorientation, ataxia, gastrointestinal hypomotility, bradycardia, hypotension, hypothermia, hyperglycemia, and seizures. Signs of CNS depression such as depression, ataxia, or coma may be due to coincidental xylene toxicosis. Clinical signs usually begin within hours of exposure. Bradycardia and hypotension appear to be due to the compound's central alpha-2 adrenergic effects and are reversible with yohimbine.
- A report of amitraz toxicosis in a group of horses lists observed signs as: tranquilization, depression, ataxia, and colic due to impaction.

Diagnosis

- History of exposure.
- Clinical signs.

Treatment

- Thoroughly wash with liquid dish detergent if dermal exposure has occurred.
- If a collar has been eaten, induce vomiting and/or remove collar via endoscopy. Administer activated charcoal.
- If solid or liquid preparations without xylene or other solvents have been ingested, give food mixed with activated charcoal then induce vomiting, if not contraindicated by bradycardia, hypotension, ataxia and/or weakness. Note, such problems are common after the onset of Amitraz toxicosis.
- Because hypotension may increase the severity of myocardial ischemia and thus arrhythmias, and because Amitraz may cause marked gut stasis and colic, atropine is contraindicated as a treatment for bradycardia.
- Ingestion of amitraz dip is unusual and is usually coincidental with toxicosis from dermal exposure. The presence of xylene in the formulation may make the wisdom of inducing vomiting or performing gastric lavage questionable. Give activated charcoal and bathe the animal with detergent.
- Yohimbine, 0.1 mg/kg IV antagonizes the alpha-2 adrenergic effects (bradycardia, hypotension, sedation, GI hypomotility), regardless of the route or amount of exposure. Repeat as needed.
- Fluids (IV) should be administered only to hypotensive animals and with care.
- Fluids may be contraindicated with marked bradycardia or hypertension.

Benzyl Alcohol and Benzoic Acid

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Cause Central Nervous System Depression
Cats; neonates of all species	Hours to days with multiple doses	Up to a few days, potentially lethal	

Synonyms (of Benzyl Alcohol) - Benzene methanol, phenylcarbinol, CAS #100-51-6, phenmethylol

Sources

- Benzyl alcohol is sometimes added to "pyrogen-free" (rather than sterile) fluids for parenteral administration, e.g., 1.5% benzyl alcohol added to lactated Ringer's solution.
- Problems in human infants have occurred after quite low-grade exposure including the use of:
    - Sodium chloride USP with preservatives (0.9% benzyl alcohol).
    - Water for injection, bacteriostatic, USP (0.9% benzyl alcohol).
- Benzyl alcohol is clear and almost odorless.
- No longer as widely used as a preservative.
- Benzyl alcohol is available in toothache products as 1 - 2% solutions, mouthwashes, rinses, sprays as 0.05 - 10% solutions.
- Oil of jasmine contains 6% benzyl alcohol.
- Benzoic acid and benzoate salts are used as food preservatives, usually as a 0.1% concentration.
- **Note** - Each ml of Valium ® injectable contains 50 mg of sodium benzoate, 400 mg of propylene glycol, 100 mg of ethyl alcohol, 1.5 mg of benzyl alcohol and 5 mg of diazepam.
- Benzoic acid has been used topically as an antifungal agent and for the control of scabies in dogs.

Benzyl Alcohol
C_7H_8O

Benzoic Acid
$C_7H_6O_2$

Toxicity

- Cats and neonates of all species (such as calves, foals, etc.) are quite susceptible due to deficiency of glucuronyl transferase (poor glucuronide conjugation capacity).
- Toxicosis may occur after oral or parenteral exposure even to volumes of fluids used to correct only mild dehydration.
- Toxicosis reproduced in cats receiving 392 - 686 mg/kg in lactated Ringer's solutions.
- The LD_{50} of benzyl alcohol in dogs is 64 mg/kg.
- Lethal IV dose of benzyl alcohol in a 0.9% solution in dogs was 88 - 113 mg/kg.
- Toxicity from orally administered benzoic acid observed in children at 200 mg/kg/day.
- In humans, rectal administration of benzyl alcohol resulted in toxicosis.

Mechanism

- Benzyl alcohol is rapidly oxidized to benzoic acid. In most species benzoic acid is then conjugated with glycine to form hippuric acid or with glucuronic acid to form benzyl glucuronide. In the cat, more hippuric acid is probably formed. Hippuric acid is also toxic.
- Benzoic acid may accumulate which may contribute to a metabolic acidosis (well documented in neonatal humans) although additional (uncharacterized) mechanisms may also be involved. The acidosis is relatively resistant to bicarbonate administration.

Signs

- Feline:
  - Marked ataxia.
  - Slight to severe hyperesthesia, some animals respond violently to noise.
  - Fasciculations of the muscles of the head and ears.
  - Slight depression progressing to severe depression, inability to stand.
  - Pupils dilated and fixed.
  - Death.
  - Signs may progress to death within hours up to 1 1/2 days or longer depending upon dosage and frequency of administration.
- Foals and calves:
  - Decreased respiratory rate.
  - Gasping.
  - Erratic heart beat.
  - Death.
- Mice (Weanlings):
  - Decreased respiratory rate.
  - Gasping, mental confusion.
  - Ascending paralysis.
  - Subsequent, apparently painless death.
  - Adult mice exhibited no signs after the same doses.
- Classical Signs.
  - CNS depression.
  - Respiratory failure.
  - Vasodilation.
  - Hypotension.
  - Renal failure.

- Convulsions.
- Paralysis.
- High oral exposures may cause gastroenteric irritation.
- Ocular exposures can result in conjunctivitis, concentrated benzyl alcohol can cause corneal necrosis.
- Anemia, thrombocytopenia, and leukopenia reported in benzyl alcohol-poisoned children. Benzyl alcohol administration may induce hemolysis.

Lesions

- Gross postmortem lesions generally absent.
- Intracranial hemorrhages sometimes observed in poisoned children.

Treatment

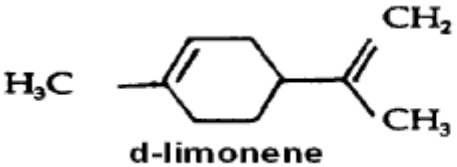
- Correct acidosis with bicarbonate (1 - 3 mEq/kg) in fluids (**not containing benzyl alcohol**).
- Bicarbonate may (perhaps) also promote excretion.
- Fluids to promote excretion.
- Artificial respiration.
- Control seizures with phenobarbital or if necessary pentobarbital.
- Irrigate eyes if ocular exposure has occurred.

Citrus Oil Extracts

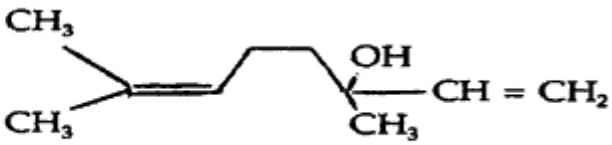
Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Cause Central Nervous System Depression
Cats, dogs	Minutes to hours	Hours to 1 day; unlikely to be lethal	

Sources

- Crude citrus oil extracts have been formulated into preparations labelled for use on pets, "to control itching due to" (in tiny letters), "fleas, ticks, and lice", (in giant letters). This was an attempt to avoid EPA safety testing by avoidance of an insecticidal claim on the label.
- These should not be confused with formulations containing purified d-limonene another citrus derived agent.
- d-limonene has also been used as a wetting and dispersing agent, as a food flavor, and as a fragrance in various detergents.
- A third citrus derivative, linalool, is now on the market alone (in dip solutions) and in a spray product in combination with d-limonene and the mixed function oxidase inhibitor, piperonyl butoxide.



d-limonene



Linalool

Mechanism of Action

- The mechanism of action of these agents is not thoroughly understood.
- There is evidence of both centrally and peripherally acting vasodilation. Prolonged vascular effects of linalool appear to be related to a nervous system mechanism of action.

Absorption, Distribution, Metabolism and Excretion (ADME)

- When applied topically, at least some of the compound(s) is (are) absorbed through the skin which probably accounts for some of the systemic effects. With regard to the absorbed fraction of linalool, a major portion is conjugated in the liver to form a glucuronide or sulfate conjugate with significant excretion in the urine (a total of 55% of administered radiolabel from linalool is excreted in the urine

in one form or another). Some linalool undergoes enterohepatic recycling.
- Orally administered linalool is rapidly absorbed.
- Approximately 25% of orally administered linalool is eliminated by metabolism to CO_2.

Toxicity

- Rat oral LD_{50} = 2790 mg/kg.
- Toxicosis resulting from citrus oil extracts is most likely in cats - Cats died at the recommended concentrations of the preparation containing crude citrus oil.
- Cats are, however, highly tolerant of d-limonene. For example, cats treated with 15 times the recommended concentration in the final dip solution survived with no supportive or detoxification treatment. The cats treated at this level did, however, display marked, although temporary signs of toxicosis. In addition, 2 cats similarly tolerated exposure to 16 times the recommended concentration as did one cat treated at 20 times the recommended rate.
- The tolerance of cats to a spray product containing a combination of d-limonene, linalool, and piperonyl butoxide is less, with 10 times and higher applications producing serious clinical signs. At 20 times the recommended concentration of the 3 active ingredients, the product was potentially lethal. The type of formulation, however, as an already diluted solution for spraying on the animal, would reduce the chance for excessive application to the animal.

Signs

- Cats treated with excessive amounts of citrus-based insecticides tend to display ataxia, central nervous system depression (or generalized paralysis), and at least in the case of d-limonene, profound hypothermia when exposed to high rates of exposure.
- Cats exposed to crude citrus oil products may die after a period of central nervous system depression.
- Cats given excessive exposure to the spray containing linalool, d-limonene and piperonyl butoxide were recumbent for up to 6 days after topical application.
- With topical exposure to d-limonene alone, recovery in healthy cats should be expected within 6 - 12 hours.

Lesions

The only lesion likely to be observed in excessively treated cats is scrotal and associated (self-trauma-induced) perineal dermatitis in male cats.

Treatment

- Bathing in a liquid dish detergent solution is recommended to remove any significant residual insecticide.
- Keep the animal warm but well ventilated.
- Other therapy is symptomatic and supportive.
- Atropine is **not** indicated.

Note

Do not ignore the possibility of other more toxic agents being used on or around the cat and causing the toxic syndrome (i.e., other insecticides or various other toxicants used in the home or on the animal).

Stipa robusta - Sleepy Grass

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Cause Central Nervous System Depression
Horses	Days	Up to 2 days; unlikely to be lethal	

Images

- Sleepy Grass, *Stipa robusta* - Google Image Search. - To view this image in full size go to the IVIS website at www.ivis.org . -

Description

Stout (5/16-inch wide leaves), perennial grass forming erect clumps, 2 - 4 feet tall. Several branches at each node, narrow spikelets about 1/2 inch long tipped by a long, dry, twisted, 1-inch-long awn.

Habitat

Toxicoses reportedly have occurred in the Sacramento and Sierra Blanca Mountains of New Mexico.

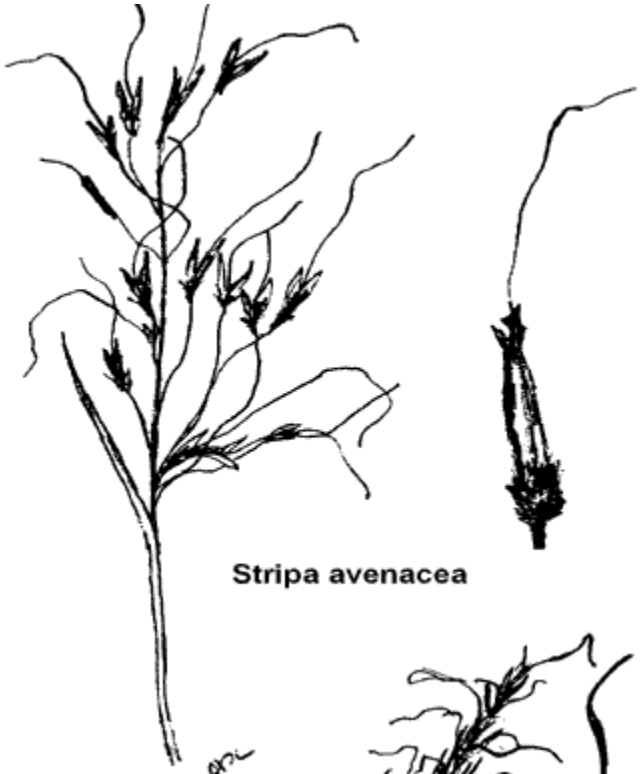
Susceptible Species

Poisoning occurs in horses; cattle are resistant.

Signs

- Varying degrees of CNS depression. May be severe enough to cause somnolence, sternal or lateral recumbancy.
- Once poisoned, horses may avoid thereafter.

Stripa Camata



Stripa avenacea

Stripa viridula

Sleepy Grass

Additional Toxicants

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Cause Central Nervous System Depression
Piperazine	Cats, dogs	Within 24 hours	1 - 3 days; rarely lethal	
Bendodiazepines (e.g. diazepam)	Dogs, cats	1 - 4 hours	Hours to 3 days; rarely lethal in dogs, potentially lethal hepatoxicity in cats (after 1 week of administration)	
Barbiturates Ingestion by carnivores and scavengers [e.g. dogs, foxes, coyotes, raptors, etc.] of pentobarbital or other euthanasia drugs in recently euthanatized animals (generally livestock) can result in severe, potentially lethal (esp. in raptors) toxicosis	All species	Minutes to hours	Hours to a few days; potentially lethal	
Tranquilizers	All species	Minutes	Hours potentially lethal after intra-arterial injection	
Phenothiazine tranquilizers	All animals	Minutes to hours	Hours to 2 days; infrequently lethal	
Isopropanol	Cats, dogs	Minutes	Hours to 1 day; potentially lethal	
Ethanol Ethanol toxicosis occurs occasionally in cage birds, dogs, an cats from alcoholic beverages, dogs that ingest bread dough (causes ethanol toxicosis and/or severe digestivetract distention due to "rising" of the dough *in vivo*), silage-feed or stillage-fed cattle (also brewer's grains), and cedar waxwings that gorge on fruits that have fermented alcohol late in the season.	All species	Minutes	Up to 3 days	
Methylene chloride and other hydrocarbon solvents	All species	Minutes to hours	Hours to 3 days; lethality varies among compounds	

- Piperazine (same mechanism as ivermectin)
- Benzodiazepines
- Phenothiazine in Small Animals (See Toxicants that Affect the Skin)
- Tranquilizers
- Barbiturates (Ingestion by carnivores [e.g., dogs, other mammalians, carnivores, raptors] of pentobarbital in recently euthanatized animals can result in severe, potentially lethal [especially in raptors] toxicosis)
- Ethylene Glycol (See Toxicants that Cause Acidosis)
- Ethanol (Occasionally in cage birds from alcoholic beverages; reported in silage-fed cattle; in small animals that ingest bread dough; and in birds that eat fermented fruits [e.g., cedar waxwings])
- Isopropanol
- Methylene Chloride and Numerous Other Hydrocarbon Solvents (See Toxicants that Affect the Respiratory System)
- Domoic acid (cause of amnesic shellfish poisoning) (Rigid analog of neurotransmitter glutamate. Domoic acid activates Fos, which is correlated with neurologic damage. (See Peng YG, Ramsdell JS. Brain Fos induction is a sensitive biomarker for the lowest observed neuroexcitatory effects of domoic acid. Fundam Appl Toxicol 1996; 31:162-168.)
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