Teratogenic Agents   (9-Aug-1999)

V. Beasley

Department of Veterinary Biosciences, College of Veterinary Medicine, University of Illinois at Urbana-Champaign, Urbana, IL, USA.

Chapter Sections
Veratrum
Other Teratogens

Veratrum

Veratrum californicum - False or Western Hellebore
Veratrum viride - Wild Corn, Skunk Cabbage
Veratrum japonicum - Corn Lily

### Veratrum spp.
- Plant - Coarse, erect, herb, 1 - 2 m tall (3.9 feet).
- Stems - Unbranched, leafy throughout.
- Leaves - 15 - 30 cm long (6 - 12 inches), 7.5 - 15 cm wide (3 - 6 inches).
- Flowers - Numerous relatively inconspicuous.
- Rootstock - Thickened, short, perennating.

### Veratrum viride
- Plant - Coarse, perennial, herb, 9.1 - 24.4 dm tall (3 - 8 feet).
- Stem - Unbranched.
- Leaves - Alternate, oval, elliptical, or lanceolate, in ranked groups up the stem, 1.5 - 3.0 dm long (6 - 12 inches), wide (6 inches), sheath stem.
- Flowers - Nnumerous, greenish-yellow, glandless, hairy; in large terminal cluster, 2.0 - 6.1 dm long (8 - 24 inches); lower panicle branches tends to droop.
- Rootstock - Numerous, coarse, fibrous, thick, vertical.

### Description

- Corn Lily, False Hellebore, *Veratrum californicum*. Source: Cornell University, Poisonous Plants Informational Database (www.anisci.cornell.edu/plants/index.html). - To view this image in full size go to the IVIS website at www.ivis.org . -
- False or Western Hellebore, *Veratrum californicum* - Google Image Search. - To view this image in full size go to the IVIS website at www.ivis.org . -
- Wild Corn, Skunk Cabbage, *Veratrum viride* - Google Image Search. - To view this image in full size go to the IVIS website at www.ivis.org . -
- Corn Lily, *Veratrum japonicum* - Google Image Search. - To view this image in full size go to the IVIS website at www.ivis.org . -

### Usual Effects

<table>
<thead>
<tr>
<th>Major Species</th>
<th>Usual Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sheep, cattle</td>
<td>In sheep: causes &quot;monkey face&quot;, cyclops, anophthalmia, cleft palate; shortened maxilla, arthrogryposis, shortened long bones</td>
</tr>
</tbody>
</table>

Full Table for Teratogenic Agents
Toxic Principle

- Primarily glyco-alkaloids. The alkaloids are:
  1. Tertiary amine bases and related esters, or
  2. Secondary amine bases and their glycosides.
- Toxic alkaloids present include: Jervine, veratrosine, pseudojervine, isorubijervine, veratrin, cevadin, veratridin, veradridene, sabadillio.
- Teratogenic alkaloids include: Cyclopamine, veratramine, cycloposine and jervine.
- Note - Cyclopamine is believed to be most important due to its greater concentration in plants.

Susceptible Species

- Sheep.
- Cattle often graze the same areas but rarely eat Veratrum.

Toxicity

- General.
  - All parts are toxic, especially the roots.
  - Roots and rhizomes are 8 - 10 times more toxic than the tops, but contain less teratogenic agents.
  - Teratogen content of leaves and stems decrease rapidly in late summer, and varies among ranges.
  - 1.8 g of dried V. californicum per kg body weight was toxic; 5 g was lethal to sheep; much less is required to cause congenital deformities.
  - Danger of poisoning is greatest in spring when growth is young and succulent.
  - Large amounts are required to produce death, but small amounts will produce clinical signs.
  - Poisoning is seldom acutely fatal due to rapid vomiting and poor intestinal absorption.
- Sabadilla - Veratrum (derivative).
  - Acute oral LD50 in rats is over 4000 mg/kg.

Signs (Sabadilla - Veratrum) in Humans

- General.
  - Salivation, burning of mouth, nausea, vomiting, diarrhea, stomach pain, headache, prostration, hallucinations dyspnea, shallow breathing, weakness, paralysis, spasms, blurred vision, diplopia, confusion, convulsions, slow pulse, or rapid, thready pulse, low blood pressure except with large doses. Low temperature. Transient depression and bronchiolar constriction. Death due to asphyxiation.
  - Chronic exposure can produce irritation to mucous membranes of the nose. Unpleasant taste, salivation.

Signs - Plant Exposure

- Contact with leaves may cause dermatitis.
- Sheep (Toxicosis).
  - Clinical signs first appear in 2 - 3 hours.
  - Excessive salivation purgation, diuresis.
  - General muscular weakness, incoordination.
  - Vomiting.
  - Slow irregular heart rate, slow labored breathing.
  - Cyanosis.
  - Prostration, convulsions, paralysis.
  - If lethal dose is consumed, death will occur in 6 - 18 hours.
- Sheep (Malformations) (Primary problems).
  - More important than acute toxicosis are the cyclopian type "monkey faced" congenital malformations in lambs as well as anophthalmia, cleft palate, hare-lip.
  - Deformities arise in early autumn when flocks of sheep are on mountain meadows containing false hellebore: 10 - 15% of the ewes are barren the next lambing season and 1 - 25% of deformed lambs die. Economic loss is appreciable.
  - These deformities arise from ewes eating the plant during the 12th to 14th day of gestation.
  - Inadequate development of the fetal pituitary glands may result in prolonged gestation. Unusually large fetuses cause dystocia, leading to death of the ewe and fetus.
The types of deformities are directly related to the stage of fetal development at the time of poisoning.

- 0 - 10 days - No obvious effect, although some investigators suspect failure to implant and abortion occurs.
- 12 - 14 days - Cyclopian-type malformations.
- 12 - 34 days - Motor nerve paralysis.
- 24 - 30 days - Cleft palate.
- 25 - 36 days - Hypoplasia of metacarpals and metatarsals.

**Mechanisms of Action**

- **General.**
  - The primary action of alkaloids are to **lower blood pressure** and **decrease heart rate**. Increase activity from thoracic chemoreceptors and pressor receptors to inhibit sympathetic outflow and augment vagal influence. Extracts of *Veratrum* are potent ruminators, emetics, and cause hypotension, decreased heart rate, increased peristalsis, and hyperglycemia. Veratrum alkaloids have been rarely used as hypotensive agents in human medicine.
  - Tertiary amines cause a myotonic response in skeletal muscles and positive inotropic effect on the heart.
  - Ester alkaloids elicit a reflex decrease in heart rate and blood pressure.
  - Secondary amine bases and glycosides antagonize positive chronotropic action of epinephrine in the mammalian heart.

- **Teratogenesis.**
  - The exact mechanism of teratogenesis is not known although a selective inhibition of mitosis at the neural plate stage of embryogenesis is suggested.

**Lesions**

- Lesions of acute toxicosis are not widely reported in naturally exposed animals.
- Malformations of cyclopian-type with hydrocephalus, hair-lip, cleft palate, and displacement of the nose are common.
- Usually the pituitary gland is absent.
- Fetuses exposed at a later stage of development may have shortening of the legs.

**Diagnosis**

Identification of *Veratrum*, evidence of consumption, and appropriate clinical signs and/or especially malformations.

**Treatment**

- Remove animal from access to the plant.
- If animal is left undisturbed, it will usually recover in 3 - 4 hours after onset of clinical signs.
- Unless severe toxicosis has occurred, leave animal undisturbed.
- Administration of oxygen.
- Establish respiration.
- Induce emesis unless contraindicated.
- Endotracheal intubation preceding gastric lavage.
- Activated charcoal and a saline cathartic (magnesium sulfate).

**Prevention**

- *V. californicum* is killed by frost, losses to monkey-faced lambs may be eliminated by delaying breeding until after the first frost, or by preventing access to plants during the critical periods of fetal development.
- Breed ewes 5 weeks before putting them on range containing *Veratrum*.
- Comments.
  - Deformities resulting from *V. californicum* and thalidomide drug are the first 2 documented accounts of mammalian monstrosities in epidemic proportions.
  - Root has been used for medicinal purposes as well as for an insecticide.
American white hellebore

(Veratrum viride)
California False-Hellebore - *Veratrum californicum*. Note the large parallel-veined clasping leaves, the large clusters of flowers, the 3-lobed seed capsule (enlarged, lower right), and seed (enlarged, lower center) of this conspicuous plant.

### Other Teratogens

<table>
<thead>
<tr>
<th>Specific Agents</th>
<th>Major Species</th>
<th>Usual Effects</th>
</tr>
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<tbody>
<tr>
<td><strong>Tobacco</strong> (<strong>Nicotiana</strong>)</td>
<td>Swine, cattle</td>
<td>Arthrogryposis, spinal curvature, torticollis</td>
</tr>
<tr>
<td>(Plant with nicotinic as well as teratogenic alkaloids)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Poison hemlock</strong> (<strong>Conium</strong>)</td>
<td>Swine, cattle</td>
<td>Arthrogryposis, other skeletal malformations, cleft palate</td>
</tr>
<tr>
<td>(Plant with nicotinic as well as teratogenic alkaloids)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Lupine, bluebonnet</strong> (<strong>Lupinus</strong>)</td>
<td>Cattle, sheep</td>
<td>Arthrogryposis, other skeletal malformations, cleft palate</td>
</tr>
<tr>
<td>(Plant with nicotinic as well as teratogenic alkaloids)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Locoweed</strong> (<strong>Astragalus and Oxytropis</strong>)</td>
<td>Herbivores, sheep</td>
<td>Arthrogryposis, or contracted tendons</td>
</tr>
<tr>
<td><strong>Hybrid Sudan or Sudan grass</strong> (<strong>Sorghum</strong>)</td>
<td>Herbivores</td>
<td>Ankylosis, contracted tendons</td>
</tr>
<tr>
<td><strong>Lathyris</strong> (<strong>Lathyrus spp.*)</strong></td>
<td>Herbivores</td>
<td>Various skeletal deformities</td>
</tr>
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<td>------------------------------------</td>
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<tr>
<td><strong>Potato</strong> <em>(Solanum tuberosum)</em></td>
<td>Hamster</td>
<td>Spina bifida, exencephaly</td>
</tr>
<tr>
<td><strong>Fescue</strong> <em>(Festuca</em> with ergot alkaloids produced by the endophytic fungus <em>Acremonium coenophialum)</em></td>
<td>Horses</td>
<td>Dystocia with thick placenta, and oversize, weak foals with overgrown hooves</td>
</tr>
<tr>
<td><strong>Mercury</strong></td>
<td>All species, especially cats</td>
<td>Hypoplasia of the cerebellum and other brain defects</td>
</tr>
<tr>
<td><strong>Organotins</strong></td>
<td>Wildlife in aquatic ecosystems</td>
<td>Skeletal malformations, defective myelogenesis</td>
</tr>
<tr>
<td><strong>Selenium</strong></td>
<td>Poultry, waterfowl</td>
<td>Hypoplasia of upper and/or lower beak, hindlimbs, wings, and eyes</td>
</tr>
<tr>
<td><strong>Halogenated dibenzodioxins and related halogenated aromatics</strong></td>
<td>Laboratory animals, predatory water birds</td>
<td>Cystic kidneys, cleft palate. Crossed beaks in cormorants</td>
</tr>
<tr>
<td><strong>Vitamin A and derivatives such as isotretinoins</strong></td>
<td>Humans, swine, rabbits, other species</td>
<td>Shortened limbs, altered gait, spinal column abnormalities, cleft palate, malformed ears, craniofacial bone and brain anomalies, microphthalmia</td>
</tr>
<tr>
<td><strong>Corticosteroids</strong></td>
<td>Dogs, possibly other species</td>
<td>Cleft palate</td>
</tr>
<tr>
<td><strong>Griseofluvin</strong></td>
<td>Cats</td>
<td>Cyclops</td>
</tr>
<tr>
<td><strong>Thalidomide</strong></td>
<td>Human beings, lab rodents</td>
<td>Hypoplasia of the limbs (phocomelia)</td>
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<tr>
<td><strong>Cocaine</strong></td>
<td>Human beings</td>
<td>Severe neurologic impairment</td>
</tr>
<tr>
<td><strong>Ethanol</strong></td>
<td>Human beings</td>
<td>Shortened palpebral fissures (eye opening is small relative to the globe) and ocular problems, premaxillary abnormalities resulting in a flattened midface and an indistinct philtrum. Low birth weight, learning impairment, mental retardation, and microencephaly. Hearing impairment and ears rotating posteriorly. Gait abnormalities, scoliosis, shortened digits. Atrioventricular septal defects. Renal disorders. Threshold dose is only 1 ounce of alcohol/day (causes reduced birth weight). Overall, 5.9% of human newborn babies are affected by some degree of fetal alcohol syndrome.</td>
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<tr>
<td><strong>Other teratogens</strong></td>
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