Introduction: The development of the mammalian embryo/fetus is a very complex biological process requiring synchronization of numerous biochemical and physiological events. Interference of any of these processes via genetic aberrations, environmental insult, nutritional imbalances, physical restrictions or combinations thereof can result in congenital anomalies. The term congenital anomaly is an all-encompassing term and may be used to describe all forms of developmental defects present at birth including functional, structural, metabolic or behavioral abnormalities.

The term teratology (teras=monster; ology=science of) is literally defined as “the study of monsters or monstrosities”, or the study of congenital malformations. The word teratology was introduced by Etienne Geoffroy de St. Hilaire (1772-1844), who developed a theory of “amniotic adhesions” as the cause of all malformations. While this is true for some malformations we now know this phenomenon is only responsible for a limited number of defects.

Historically, teratology had its origin centuries ago with its roots established in ancient mythology. Descriptions of congenital malformations and their omens are recorded on clay tablets of the Babylonians over 4000 years ago (Persaud, Chudley, Skalko, 1985). These historical depictions are fun reading and the associated proposed causes ranged from astronomical, to witchcraft, to sinful and unnatural behavior to simply unexplainable happenings.

The science of teratology and the current emphasis on screening of pharmaceuticals received tremendous support after the thalidomide issue of the early 1960’s. Severe birth defects resulted after mothers ingested the mild sedative thalidomide. Even though laboratory tests with rats and mice and other species had shown the drug to be safe, it turned out that the human was super sensitive and unfortunately this was not understood until it was too late for many.

Principles of Teratology: While the exact molecular mechanism(s) is (are) often undetermined for many developmental anomalies, the induction of malformations or birth defects may be the result of single or multiple events. These abnormal and often unusual circumstances result in very specific and time related events causing tissues to either fail to differentiate and/or develop normally or in incorrect tissue-tissue interaction. Subsequently, these failures result in abnormal development. Abnormal development occurs when a threshold of genetic and environmental insults is reached and the fetal compensatory mechanisms are overwhelmed.

Six basic principles of teratology were originally defined by J.G.Wilson (1959) and further described by him in 1977. These principles have withstood the test of time and are applicable for not only developmental toxicology specifically but can be easily adapted to study reproductive dysfunction in general. Those principles are outlined below with a brief summary of Wilson’s discussion of each.

1) Susceptibility to teratogenesis depends on the genotype of the conceptus and the manner in which this interacts with environmental factors.

The interaction between genetic and environmental influences to produce a defect varies widely. For example, cattle are very sensitive to the teratogenic effects of the lupine alkaloid anagyrine whereas sheep and goats are resistant. Cattle will abort in
the last trimester of pregnancy if ponderosa pine needles are ingested yet sheep, goats and elk can eat the needles without harm. In humans, the best historical example comes from thalidomide. Man and other higher primates are extremely sensitive whereas most mammalian laboratory species were quite resistant.

2) **Susceptibility to teratogenic agents varies with the developmental stage at the time of exposure.**

Developmental stage of the embryo/fetus at time of exposure or insult often determines the type of defect. The embryo is much more sensitive than the fetus, especially during organogenesis. This is effectively illustrated by induction of severe cranial facial birth defects in sheep after maternal ingestion of *Veratrum*. For example, on the 14th day of gestation the grotesque birth defect, cyclopia is induced and if ingestion of *Veratrum* occurs during the 19th through the 33rd days of gestation other defects such as cleft palate, tracheal stenosis or carpal hypoplasia may occur. However, with other teratogens, the insult time is clearly in the fetal period, as in the case of *Lupinus*/*Conium*/*Nicotiana*-induced contracture malformations, where by these skeletal malformations may be induced from days 40-100 in cattle, 30-60 in pigs, sheep and goats. Interestingly, cleft palate is induced by *Lupinus*/*Conium*/*Nicotiana* species at the transition period between the defined embryo/fetal period i.e. 35-41 days in sheep and goats, 40-50 days in cattle and 30-40 days in pigs.

3) **Teratogenic agents act in specific ways (mechanisms) on developing cells and tissues to initiate abnormal embryogenesis (pathogenesis).**

Teratogenic agents act on cells or tissues through specific biochemical pathways to induce the abnormal development. For example, *Veratrum*-induced cranial facial defects have now been associated with the expression of proteins controlled by the sonic hedgehog gene. This specific mechanism and the use of the *Veratrum* alkaloid, cyclopaamine, has provided tremendous information about cell function and is a significant biomedical tool to study many different disease conditions for human medicine.

4) **The final manifestations of abnormal development are death, malformation, growth retardation, and functional disorder.**

Of these four different manifestations of abnormal development, malformation may be the best understood, in terms of types of causation, time of induction, and perhaps also of developmental history or pathogenesis. While malformations have traditionally been used as the main criterion in estimating adverse effects, probably because structural defects were more conspicuous, this does not justify ignoring changes in mortality, growth rate, or functional capacity in evaluating the cause of teratogenesis in a herd or flock.

5) **The access of adverse environmental influences to developing tissues depends on the nature of the influences (agent).**

The access and adverse influence to embryonic or fetal tissues or organs depend upon the biological, chemical, or physical nature of the teratogen. For example, cyclopaamine is the primary teratogen in *Veratrum* and has been extensively used in biomedical research and is a specific inhibitor of sonic hedgehog expression. The optimized derivative, cyclopaamine 4-one-3-ene, is more potent and has been shown to be more toxic in embryo culture systems. Similarly, very minor but specific structural differences among teratogenic piperidine alkaloids found in *Conium*,
Nicotiana and certain Lupinus species can change mammalian toxicity 2-10 fold. It is presumed this same relationship occurs with teratogenic potency.

6) **Manifestations of deviant development increase in degree as dosage increases from the no-effect to the totally lethal level.**

The presence or absence of maternal toxicity is not a reliable indicator of embroyotoxicity. Certainly the dose of the teratogen, the size of dam and stage of development influence the degree of insult from the no effect level to lethality. For example the degree of maternal toxicity can be a gauge as to the level of fetotoxicity with the teratogenic piperidine alkaloids. However, maternal toxicity is the same with many of the quinolizidine alkaloids yet they are not fetotoxic because it is presumed these alkaloids are unable to cross the placenta to gain access to the fetus. The thalidomide disaster of the 60’s illustrates the other extreme where it is virtually devoid of maternal toxic effects in humans at any prescribed dose.

Many genetic, bacterial, and viral factors are responsible for certain malformations and some of these are similar to defects induced by plant or chemical teratogens. Causes of human congenital malformations remain obscure with 20-25% of developmental defects due to genetic anomalies, 5% from identifiable toxicants and the vast majority (40-60%) from unknown causes, probably associated with gene-toxicant interactions. While Wilson’s principles defining abnormal development have been validated consistently over time, the mechanisms responsible for xenobiotic-induced congenital defects remain elusive and few studies have identified the pathways of the abnormalities. However, this area of research is rapidly progressing using molecular tools superimposed upon toxins with known effects. Table 1 outlines teratogenic plants and Table 2 outlines other xenobiotics responsible for malformations.

**Diagnosis of Teratogenesis:** Diagnosis of the cause of plant or chemical teratogenesis may require a significant investment in time and money to investigate the many potential causes. The type of defect may immediately suggest the cause and can provide information about time of insult. A complete clinical history may be required to provide critical information about the background such as nutritional status, any disease outbreaks, unusual circumstances or aberrant behaviors, approximate location of the animals at the time of insult or other factors.

Teratogenesis, although a significant economic factor for livestock producers, is only one facet of a larger issue concerning reproductive function in livestock in general. Minor problems with reproductive parameters such as reduced conception rates, animals recycling, infertility, abortions, etc. (on a smaller scale) may be early warning signs of larger problems to come. Delineation of the causes of teratogenesis specifically, and reproductive dysfunction in general, require a thorough investigation into management practices and potential infectious or nutritional causes while looking for potential toxicants. This investigation often requires a systematic approach into individual and herd/flock history, close examination of involved animals, samples of blood, urine, feces and tissue, postmortem examination, and samples of feed and/or tissue for toxicologic screening. The extent of testing becomes an economic question between the practitioner and client and may require consultation or direct inovlement of pathologists, toxicologists, geneticists, epidemiologists and others for positive diagnosis.

When birth defects occur in a herd or flock, there is an elevated level of anxiety because of the visual impact on a producer that relies on these animals for economic survival. The veterinarian is often the first line of defense for the producer to look for answers. The survival of
many animals and the economic survival of a producer may depend upon the decisions of a practitioner or consultant. Therefore, the practitioner, researcher, ranch manager, extension agent etc. may follow a few guidelines to investigate the causes of the dysfunction.

1) Defining the individual incident is the first step. Because of research information already available, characterization of the defect and its etiology may be immediate, as some defects are pathognomic. For example, because of extensive research in the 60’s and 70’s, if congenital cyclopia in lambs occur, one immediately suspects a probable maternal ingestion of *Veratrum californicum* during early gestation. Similarly, skeletal contracture malformations in calves on western ranges immediately suggest lupine-induced “crooked calf disease”. Understanding The timing of embryonic development and estimating time of cessation of normal development may provide important clues as to whether the anomaly may be genetic or environmental. Retrospective analysis from time of birth can provide information as to where the animal was at the time of insult.

2) The incidence or prevalence of the defect or dysfunction is important in discerning the etiology. Malformations clustered within a rather confined time frame or within a specific group of animals can provide significant information as to the cause, genetic vs environmental.

3) A thorough history and examination of the maternal exposures or environment is important. Herd/flock records or individual animal history may be key. Has she had a deformed offspring before? Has she experience reproductive dysfunction in the past? Is there a pattern developing among a group of females?

4) A review of related animals or genetic analysis of a herd or flock maybe required. This maybe relatively simple i.e. has a new bull been introduced? Or it may be complex requiring a complex genetic analysis consulting the expertise of a geneticist and or statistician. Analysis should proceed from the simplest form of evaluating inheritance to the more complex methods requiring extensive analysis and or laboratory methods.

5) If there appears to be no obvious cause or environmental link, then a more detailed examination or an epidemiological approach maybe required. Epidemiologic evaluations usually have 3 elements: retrospective comparisons, detailed descriptive epidemiology and field trials.

**Plant Teratogens:** Teratogens synthesized by certain poisonous plants ingested by livestock are responsible for some of the naturally occurring congenital defects reported. Table 1 lists some of these plants, the teratogenic compounds (where known), the type of birth defect, the sensitive livestock species and the susceptible stages of gestation. Extensive research has been done on a few of these plants including *Veratrum, Lupinus, Conium* and *Nicotiana*. These plants and their teratogenic effects are described in more detail.

**Lupinus spp., Conium maculatum, and Nicotiana glauca:** *Lupinus* spp. (lupines) contain quinolizidine and piperidine alkaloids, whereas *Conium maculatum* (poison-hemlock) and *Nicotiana glauca* (wild tree tobacco) contain piperidine alkaloids (Figure 1). Piperidine and quinolizidine alkaloids are widely distributed in nature and most possess a certain level of toxicity. Some are teratogenic, depending on structural characteristics which are only partially understood.

Lupines have caused large losses to the sheep and cattle industries in the past and they continue to cause significant losses to the cattle industry in the western U.S. Large calf losses
from congenital birth defects have been recorded in Oregon, Idaho, Montana, and Washington from 1992-1997. While huge death losses were reported in sheep in the early 1900's, the teratogenic effects (crooked calf disease) are responsible for most recent losses associated with lupine. In 1992, 56% of the calves from a single herd of cows either died or were destroyed. In the spring of 1997 over 4000 calves (>35% of the calf crop) in Adams County, Washington were destroyed due to lupine-induced crooked calf disease. Similar but less severe losses were reported in Montana, Oregon, and British Columbia.

Poison-hemlock (Conium maculatum) has historic significance as the “tea” used for execution in ancient Greece and the decoction used to execute Socrates. Toxicoses in livestock frequently occur and field incidences of teratogenic effects in cattle and pigs have been reported. The teratogenic effects are the same as those induced in cattle by lupines, i.e., cleft palate and multiple congenital skeletal contractures (MCC).

While Nicotiana glauca has not been associated with field cases of teratogenesis in livestock, there have been reported cases of overt poisoning. However, the domesticated relative, N. tabacum, caused epidemic proportion outbreaks of malformations in newborn pigs in the late 1960's in Kentucky after tobacco stalks were fed to pregnant sows. Experimentally, N. glauca is teratogenic in cattle, pigs, sheep, and goats and was used to establish that anabasine was the teratogenic alkaloid in N. tabacum. These malformations are of the same type as those in lupine induced crooked calf disease.

Lupine Toxicity: Stockmen have long recognized the toxicity of lupines, especially in late summer and fall when the pods and seeds are present. The clinical signs of poisoning begin with nervousness, depression, grinding of the teeth, frothing around the mouth, relaxation of the nictitating membrane of the eye, frequent urination and defecation and lethargy. These progress to muscular weakness and fasciculations, ataxia, collapse, sternal recumbency leading to lateral recumbency, respiratory failure, and death. Signs may appear as early as one hour after ingestion and progressively get worse over the course of 24 to 48 hours even if further ingestion does not occur. Generally, if death does not occur within this time frame, the animal recovers completely.

More than 150 quinolizidine alkaloids have been structurally identified from genera of the Leguminosae family, including Lupinus, Laburnum, Cytisus, Thermopsis and Sophora. Quinolizidine alkaloids occur naturally as N-oxides as well as free bases, but very little research has been done on the toxicity or teratogenicity of the N-oxides. However, the structurally similar pyrrolizidine N-oxides have been shown to be reduced to the corresponding free bases in the
rumen, and it seems likely that quinolizidine alkaloids could undergo a similar conversion.

Eighteen western American lupine species have been shown to contain the teratogen anagyrine (Figure 1) with 14 of these containing teratogenic levels. Lupine alkaloids are produced by leaf chloroplasts and are translocated via the phloem and stored in epidermal cells and in seeds. Little is known about individual alkaloid toxicity, however, 14 alkaloids isolated from *Lupinus albus*, *L. mutabilis*, and *Anagyris foetida* were analyzed for their affinity to nicotinic and/or muscarinic acetylcholine receptors. Of the 14 compounds tested, the \( \alpha \)-pyridones (N-methyl cytisine and cytisine) showed the highest affinities at the nicotinic receptor while several quinolizidine alkaloid types including the teratogen anagyrine were more active at the muscarinic receptor.

Piperidine and quinolizidine alkaloid content and profile vary between lupine species and in individual plants depending on environmental conditions, season of the year and stage of plant growth. Typically, alkaloid content is highest during early growth stages, decreases through the flower stage, and increases in the seeds and pods. This knowledge has been used in management strategies to reduce losses. For many lupines, the time and degree of seeding varies from year to year. Some species of lupines are readily grazed by livestock and are acceptable forage under certain range conditions. Most deaths have occurred under conditions in which animals consume large amounts of pods or toxic plants in a brief period. This may happen when livestock are driven through an area of heavy lupine growth, unloaded into such an area, trailed through an area where the grass is covered by snow but the lupine is not, or when animals are forced to eat the plants due to over-grazing. A recent report described the death of 10 yearling stocker calves after grazing *Lupinus argenteus* containing predominantly the piperidine alkaloids ammodendrine and N-methyl ammodendrine (Figure 1). Most poisonings occur in the late summer and fall because seed pods are present and lupine remains green after other forage has matured or dried. Most calf losses occur because of teratogenic effects resulting from their mothers grazing lupine plants or pods during susceptible stages of pregnancy.

Conium maculatum and Nicotiana spp. Toxicity: The clinical signs of poisoning from ingestion of *Conium maculatum* and *N. glauca* are similar in all animal species thus far tested and appear to be the same as those caused by lupine in cattle. They include early signs of nervousness, occlusion of the eyes by the nictitating membrane (most pronounced in pigs and occasionally seen in cows, sheep and goats) and progressing quickly through a pattern of nervous system stimulation with peripheral and local effects which include frequent urination and defecation, dilated pupils, trembling, incoordination, and excessive salivation. The stimulation soon progresses to depression resulting in relaxation, recumbency, and eventually death from respiratory paralysis if the dosage is high enough. Cattle, pigs, goats, and elk have demonstrated a preference for *Conium maculatum* plant once they have acquired a taste for it.

Conine, (-coniceine, and N-methyl coniine (Figure 1) are the principal alkaloids in *Conium maculatum* with relative concentration depending on the stage of plant growth. Gamma-coniceine, a metabolic precursor of coniine and N-methyl coniine; is at highest concentration in early plant growth producing coniine and N-methyl coniine as the plant matures. Coniine, (-coniceine and N-methyl coniine have been shown to be toxic and teratogenic. Structural differences impart significant differences in toxicity ((-coniceine>coniine>N-methyl coniine; Table 1), but teratogenic potency is unknown although we believe it is related to toxicity.
Field cases of the toxic effects of poison-hemlock have been reported in cattle, swine, horses, sheep, goats, elk, turkeys, quail and chickens, wild geese and humans. The teratogenic effects have been experimentally induced in cattle, swine, goats and sheep.

**Susceptible Periods of Gestation:** The teratogenic effects of *Lupinus* spp., *Conium maculatum*, and *Nicotiana* spp. are similar, and the mechanism of action is believed to be similar in susceptible livestock species. The periods of gestation when the fetus is susceptible to these plant teratogens have been partially defined in cattle, sheep, goats, and swine. The severity and type of the malformations also depend on the alkaloid dosage ingested, the stage of pregnancy when the plants are eaten, and the length of time ingestion takes place. In swine, only cleft palate occurred when *Conium maculatum* was fed during days 30-41 of gestation. Skeletal defects, predominantly the forelimbs, spine, and neck, without cleft palate were induced when pregnant sows were fed *Conium maculatum* during gestation days 40-53. When feeding included days 50-63, rear limbs were affected also. When the feeding period included days 30-60, all combinations of the defects described occurred. In sheep and goats, the teratogenic insult period is similar to pigs and includes days 30-60. In goats, a narrow period for cleft palate induction only was defined to include days 35-41. The critical gestational period for exposure in cattle is 40-70 days with susceptible periods extending to 100 days. The cleft palate induction period in cattle was recently defined as gestation days 40-50.

**Structure-Activity Relationship:** Keeler and Balls fed commercially available structural analogs of coniine to pregnant cows to compare structural relationships to teratogenic effects. Results suggested that the piperidine alkaloids must meet certain structural criteria to be teratogenic. Based on these data, Keeler and Balls speculated that the piperidine or 1,2-dehydropiperidine alkaloids with a side chain of at least three carbon atoms in length adjacent to the nitrogen atom might be considered potential teratogens. Note that the piperidine alkaloids in Figure 1 meet these criteria. Additionally, the 1, 2-dehydropiperidine alkaloids (–coniine, anabaseine, N-acetyl hystrine) are more toxic than either the piperidine or N-methyl piperidine analogues (Figure 1).

While all the alkaloids in Figure 1 are believed to have teratogenic activity, only coniine and anabasine have been experimentally tested in their purified form. Coniine, a simple piperidine from poison-hemlock, and anabasine, a simple piperidine from tree tobacco (*N. glauca*), induced the same defects in cattle, sheep, pigs and goats. In other experiments, plant material with predominantly (–coniine or ammodendrine were teratogenic in cattle and goats.

**Mechanism of Action:** The proposed mechanism of action for *Lupinus*, *Conium maculatum*, and *N. glauca*-induced contracture defects and cleft palate involves a chemically induced reduction in fetal movement much as one would expect with a sedative, neuromuscular blocking agent, or anesthetic. This mechanism of action was supported by experiments using radio ultrasound where a direct relationship between reduced fetal activity and severity of contracture-type skeletal defects and cleft palate in sheep and goats was recorded. Further research suggests that this inhibition of fetal movement must be over a protracted period of time during specific stages of gestation. Further ultrasonographic studies showed that strong fetal movement becomes evident in the untreated goat at about day 35 gestation and that these first movements are extension-type of the fetal head and neck. The heads of fetuses under the influence of anabasine through days 35-41 of gestation remained tightly flexed against the sternum and no
movement was seen. Subsequently, the newborn goats had cleft palate but no other defects. We suggested that these cleft palates were caused by mechanical interference by the tongue between palate shelves during programmed palate closure time (day 38 in goats; days 40 to 50 in cows).

Even though research at the Poisonous Plant Research Lab has been limited to the three genera mentioned above, there are others that contain piperidine and quinolizidine alkaloids structurally similar to what would be expected to be toxic and teratogenic. These include species of the genera *Genista, Prosopis, Lobelia, Cytisus, Sophora, Pinus, Punica, Duboisia, Sedum, Withania, Carica, Hydrangea, Dichroa, Cassia, Ammondendron, Liparia, Colidium* and others. Many plant species or varieties from these genera may be included in animal and human diets, however, toxicity and teratogenicity are a matter of dose, rate of ingestion, and alkaloid level and composition in the plant.

*Veratrum californicum*: *Veratrum californicum* grows throughout the Western United States in mountainous areas that are grazed by livestock and wildlife. During the 1950's up to 25% of pregnant ewes grazing in the mountains of Central Idaho gave birth to lambs suffering from serious craniofacial defects. These malformations varied from the extreme, cyclopia, to mildly deformed upper jaws. Research demonstrated that ingestion of *Veratrum* by sheep on day 14 of gestation induced grotesque craniofacial birth defects in offspring, dramatically highlighted by cyclopia. The primary *Veratrum* alkaloid responsible for the terata induction was 11-deoxojervine, which R.F. Keeler named cyclopamine Figure 2. Keeler further discovered that cyclopamine induced not only craniofacial malformations on day 14, but also induced limb defects on days 28-31 and tracheal stenosis on days 31-33. Structural optimization (cyclopamine 4-ene-3-one ) has demonstrated important features of the compound that impart teratogenic potency.

![Cyclopamine](image1.png)  ![Cyclopamine-3-one-4-ene](image2.png)

**Figure 2. Veratrum alkaloids**

Recent advances in molecular biology and genetics have provided insight into the mechanisms underlying the induction of cyclopamine’s teratogenic expressions. Investigation of a variety of sonic hedgehog-dependent cell types, derived from the neural tube and somites of chick embryo explants with cyclopamine-induced malformations has shown clearly that virtually all aspects of Sonic hedgehog signaling are interrupted in these tissues upon exposure to cyclopamine.

**Other Chemical Teratogens**: The extensive use of chemicals, drugs and hormones in livestock has raised concern about their possible effects on embryonic and fetal development in animals and their residues in animal products for human consumption is of concern for human health. K.T. Szabo, 1989 compiled a 20 year record involving over 50,000 fetuses examined at the Reproductive Toxicology Department of Smith Kline and French Laboratories, Philadelphia, Pennsylvania. The fetuses examined were primarily from the mouse, rat and rabbit and this brief report describes the type and frequency of congenital malformations. There is not enough space
in these notes to adequately review all the information available. Table 2 represents a portion of
this and the reader is referred to K.R. Szabo, 1989 (Congenital Malformations in Laboratory and

**Table 1.** Teratogenic Plants

<table>
<thead>
<tr>
<th>Plant Stage</th>
<th>Toxicant</th>
<th>Effects</th>
<th>Species and Stage of Development</th>
</tr>
</thead>
</table>
| **Veratrum californicum**  
  (skunk cabbage, false hellebore) | Steroidal alkaloids, cyclopamine, jervine cycloposine | Cyclopia, cleft palate, limb defects, tracheal stenosis and embryonic death | Cattle, goats, sheep; day 14 cyclopia, days 28-31 limb reductions; days 31-33 tracheal stenosis (sheep) |
| **Veratrum eschscholtzii** | Unknown, possibly same as above | Cyclopia | Horses |
| **Veratrum album** | Same as above | Cyclopia | Llamas and alpacas |
| **Oxytropis/Astragalus** | Swainsosnine, swainsosnine N-oxide | Bowed limbs, embryo or fetal death | Sheep, cattle, horses; most stages of pregnancy |
| **Lupinus spp**  
  L. caudatus  
  L. sericeus  
  L. nootkatensis  
  L. laxiflorus  
  L. sulphureus  
  L. formosus  
  L. arbustus  
  L. argenteus | Quinolizidine Alkaloid Anagyrine  
  Piperidine Alkaloid Ammodendrine | Cleft palate, contracture-type skeletal defects  
  Cleft palate, contracture-type skeletal defects | Cattle, 40-100 days gestation (cleft palate only 40-50 days gestation)  
  Cattle, 40-100; cleft palate only 40-50; sheep and goats, 30-60; cleft palate only 35-41 |
| **Nicotiana tabacum**  
  N. glauca | Anabasine | Cleft palate, contracture-type skeletal defects | Pigs, 30-60 (cleft palate only 30-40); cattle, 40-100 (cleft palate only 40-50) sheep and goats, 30-60 ; (cleft palate only 35-41) |
| **Conium maculatum**  
  (Poison-hemlock) | Coniine and γ-coniceine | Cleft palate, contracture-type skeletal defects | Same as above |
| **Prunus serotina**  
  (wild black cherry) | Cyanogenic compounds suspected | Cleft palate, contracture-type skeletal defects | Pigs |
| **Datura stramonium**  
  (jimsonweed) | Unknown, possibly alkaloids | Cleft palate, contracture-type skeletal defects | Pigs |
| **Sorghum vulgare**  
  S. sudanese | Cyanogenic compounds suspected | Contracture-type skeletal defects | Horses |
| **Lathyrus spp**  
  L. cicera  
  L. odoratus | Lathyrogens | Skeletal defects | Cattle and sheep |
<table>
<thead>
<tr>
<th>Toxicant</th>
<th>Source</th>
<th>Effect</th>
<th>Animal Species</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parabendazole</td>
<td>Anthelmintic</td>
<td>Vertebral column and other skeletal defects</td>
<td>Sheep, goats, cattle and pigs</td>
</tr>
<tr>
<td>Methallibure</td>
<td>Pituitary Inhibitor (used for synchronization in pigs)</td>
<td>Contracture-type defects</td>
<td>Pigs, 30-50 days gestation</td>
</tr>
<tr>
<td>Riboflavin Deficiency</td>
<td>Vitamin</td>
<td>Cleft palate, limb reductions</td>
<td>Mammals, birds</td>
</tr>
<tr>
<td>Sulphonamides</td>
<td>Sulphur Bacteriostatic Agents</td>
<td>Beak and feet defects</td>
<td>Chickens</td>
</tr>
<tr>
<td>Tetrahydrothalamide</td>
<td>Captan fungicides</td>
<td>Skull, limb, and visceral defects</td>
<td>Chickens</td>
</tr>
<tr>
<td>Tryptophane</td>
<td>Amino Acid</td>
<td>Limb and visceral defects</td>
<td>Chickens</td>
</tr>
<tr>
<td>Trichlorfon</td>
<td>Organophosphoric Insecticide</td>
<td>Cerebral hypoplasia</td>
<td>Pigs</td>
</tr>
<tr>
<td>Aminoacetonitrile</td>
<td>Synthetic osteolathyrogen</td>
<td>Skeletal defects</td>
<td>Cattle and Sheep</td>
</tr>
<tr>
<td>Vitamine A deficiency</td>
<td>Vitamin</td>
<td>Ocular, facial, and CNS defects</td>
<td>Pigs, cattle, rabbits</td>
</tr>
<tr>
<td>Copper Deficiency</td>
<td>Trace Element</td>
<td>Skeletal and brain defects</td>
<td>Sheep, pigs, horses</td>
</tr>
<tr>
<td>Manganese Deficiency</td>
<td>Trace Element</td>
<td>Limbs and vertebrae defects</td>
<td>Rabbits and calves</td>
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<tr>
<td>Molybdenum Excess</td>
<td>Trace Element</td>
<td>Demyelination resulting in CNS defects</td>
<td>Sheep</td>
</tr>
<tr>
<td>Selenium Toxicity</td>
<td>Trace Element</td>
<td>Fetal hoof defects</td>
<td>Cattle and horses</td>
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<td>Miconazole</td>
<td>Antifungals</td>
<td>Embryotoxic</td>
<td>Rat, Rabbit</td>
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<td>Theophylline</td>
<td>Bronchodilators</td>
<td>Teratogenic</td>
<td>Mouse</td>
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<tr>
<td>Nifedipine, Verapamil</td>
<td>Cardiovascular Agents</td>
<td>Embryotoxic, Teratogenic</td>
<td>Mouse, Rabbit, Rat</td>
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<td>Furosemide</td>
<td>Diuretics</td>
<td>Embryotoxic, Teratogenic and Abortifacient</td>
<td>Rat, Rabbit</td>
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<tr>
<td>Pentobarbital</td>
<td>Hypnotics</td>
<td>Teratogenic, Embryotoxic</td>
<td>Mouse, Rabbit, Guinea Pig</td>
</tr>
</tbody>
</table>

Many other teratogens with reference to rodent models are listed in Shepard, 1998 and Szabo, 1989.

**Conclusion:** Limitation of space has prevented more extensive coverage of the huge number of teratogenic agents, species differences, the types of malformation induced, etc. Extensive reviews may be found in T.H. Shepard’s Catalog of Teratogenic Agents, The Johns Hopkins University Press, Baltimore and K.T. Szabo referred to above. Other references used in this brief review will be provided upon request.