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Impact of plant toxins on fetal and neonatal development: A review

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Abstract

Many poisonous plants grazed by livestock on ranges and pastures in the western USA are fetotoxic causing fetal malformations, embryonic or fetal death, abortion, or early parturition. Decreased incidence of plant-induced livestock malformations may be accomplished through grazing management strategies. To develop these strategies one must understand some basic principles of toxicology and teratology such as susceptible livestock species, type of compound and concentration in the plant and its disposition in the animal, dose response, and the susceptible gestational period. Much of this information is known for certain plants; however, additional information will enhance our ability to control livestock losses from these plants.

Certain criteria may be established to maximize grazing management methods to minimize teratogenic effects of poisonous plants. When the suspect plant grows in a restricted habitat, poses a hazard only at certain growth stages or when the susceptible period of pregnancy is relatively short, minor adjustments in management methods can be considerably successful in reducing incidence of malformations and subsequent financial loss.

Key Words: poisonous plants, birth defects, fetal toxicity, embryonic death, abortion, range management

The impacts of toxins from poisonous range plants on the embryo, fetus, and neonate are dramatic and the consequences are economically important to the livestock industry. The key to the significance of the toxicoses from poisonous plants lies in the ubiquitous nature of the plants and exposure of livestock on rangelands and pastures. Thousands of species of plants in the world are known to be hazardous (Kingsbury 1964, Everist 1974).

Research in the past 40 years has implicated many plants in the cause of embryonic death, abortion, or teratogenesis in livestock. Historically, these malformations often went undiagnosed and/or unreported because of the negative impact on the sale of breeding stock or because the death of offspring was not associated with any malformation such as cleft palate or heart anomalies. However, examinations of experimental evidence have demonstrated that many livestock losses due to embryonic death, abortion, and teratogenesis are induced by poisonous plants. Grazing management strategies using results of research over the last 40 years and applying some basic concepts of toxicology and teratology have reduced losses to livestock producers. These basic concepts were originally presented by Wilson (1977) and further reviewed by Keeler (1978). (1) Livestock species and breed differences affect the toxicity and teratogenicity of plants; (2) the malformations induced depend on the amount of plant maternally ingested and the subsequent dose of putative compound presented to the fetus; (3) stages of plant growth affect the concentration of teratogenic compounds; (4) the embryo or fetus must be exposed to the teratogen at a susceptible period of gestation. Each of these factors and others play a role in grazing management strategies to reduce losses from poisonous plant-induced birth defects.

In this review, plants affecting embryonic, fetal, and neonatal development, susceptible livestock species, plant growth stages of highest risk, and gestational periods of susceptibility will be discussed. Included are species of *Veratrum, Lupinus, Conium, Nicotiana, Astragalus,* and *Oxytropis* genera. Table 1 summarizes the fetotoxic effects of these plants.

Veratrum

Veratrum californicum Durand (false hellebore) is a common mountain range plant that grows in moist areas and is responsible for the induction of several congenital birth defects in sheep (Keeler 1984a). The teratogenic compound is a steroidal alkaloid, cyclopamine. The most widely known malformations include congenital cyclopia and related craniofacial deformities commonly referred to as "monkey faced lamb disease". The facial defects result from neural tube defects induced when pregnant ewes ingest the plant on day 14 of gestation (Binns et al. 1965). A high incidence of embryonic death is induced at this early period of gestation (14th day) and also the 19th to 21st day of gestation (Keeler 1990). Sheep are the primary species affected by this plant; however, the cyclopic defect has also been experimentally induced in calves and goats when their dams were exposed on the 14th day of gestation (Binns et al. 1972).

Further research has demonstrated that other birth defects may be induced when the plant is ingested by pregnant sheep during later periods of gestation (Keeler and Stuart 1987). Various limb defects have been induced when *Veratrum* was experimentally fed during days 27 to 32 of gestation. Although the metacarpal, metatarsal, and tibial bones were markedly shortened, no changes in femur length, fetal weights, crown-rump length or thoracic girth diameter occurred. Metacarpal, tibial, and radial bone shortening was most pronounced during the treatment periods of gestation days 27 to 29 and 28 to 30 and metatarsal shortening most marked on days 30 to 32 (Keeler and Stuart 1987). There was always bilateral symmetry in limb bone shortening in any given lamb.

Tracheal stenosis has been induced in new-born lambs by feeding *Veratrum* to pregnant ewes on days 31, 32, and 33 of gestation. Tracheal defects resulted in neonatal death from tracheal collapse and suffocation (Keeler et al. 1985). The defect was characterized by lateral flattening of the trachea throughout its entire length. Cartilaginous tracheal rings were reduced in number, nonuniform in size and shape, irregularly spaced, and abnormally oriented. The tracheal rings were thinner than those of controls and had zones of chondrogenesis on outer and inner surfaces which were of equal width rather than of unequal width as in controls. This type of

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Table 1. Poisonous plants; the livestock species affected; the stage of gestation when fetus is most susceptible; and the type of birth defects associated with their ingestion.

Plant	Animal species	Stage of gestation	Birth defect
Veratrum californicum Durand (False hellebore)	sheep	14th day	Embryonic death, craniofacial defects [i.e., congenital cyclopic (monkey-faced) lamb].
		19–21 days	Embryonic death
		27–32 days	Limb defects [i.e., shortening of metacarpus, metatarsus and tibia].
		31–33 days	Tracheal defects; tracheal collapse, suffocation and death.
Conium maculatum L. (Poison-hemlock)	cow	55–75 days	Limb, spine and neck malformations [i.e., arthrogryposis, scoliosis and torticollis].
	sow	30–45 days	Cleft palate.
		43–62 days	Skeletal defects similar to the cow.
	sheep	30–60 days	Skeletal defects similar to the cow.
	goat	30–60 days	Skeletal defects similar to the cow and cleft palate.
Lupinus caudatus Kell. and *sericeus* Pursh. (Tail cup lupine and silky lupine)	cow	55–75 days	Skeletal malformations [i.e., arthrogryposis, scoliosis, torticollis, multiple contractures].
L. formosus Greene (Lunara lupine)	cow	40–70 days	Cleft palate and skeletal defects similar to *L. caudatus*-induced.
Nicotiana glauca Graham (tree tobacco)	cow	45–75 days	Skeletal defects similar to *Conium*- and *Lupinus*-induced.
	sow	18–68 days	Cleft palate and skeletal defects similar to those induced in the cow by *Conium* and *Lupinus*.
	sheep	30–60 days	Cleft palate and skeletal defects similar to the sow.
	goat	30–60 days	Cleft palate and skeletal defects similar to the sow.
Astragalus and *Oxytropis* spp.	cow	all stages	Fetal death, abortion.
	sheep	all stages	Fetal death, abortion and contraction limb defects.

defect would normally pass unrecognized among other causes of neonatal death.

From a grazing management perspective, 2 factors played significantly in reducing losses from epidemic proportion to insignificant levels: (1) the greatest losses resulted from a lethal cyclopic facial defect, the susceptible gestational period being very narrow (14th day only); (2) the plant habitat was limited to stands growing in wet locations. Therefore, preventing ewes from grazing in areas where this plant grows until after the rams had been removed for 15 days significantly reduced losses. Further research implicated other susceptible periods, as previously described, and subsequent management strategies have been further refined to prevent losses due to embryonic and neonatal death.

Lupinus, Conium, and *Nicotiana*

Plant species of the genera *Lupinus, Conium,* and *Nicotiana* induce similar acute neurotoxic and fetotoxic effects including teratogenesis. *Conium, Nicotiana* and some *Lupinus* contain piperidine alkaloids whereas most *Lupinus* contain quinolizidine alkaloids.

Lupinus formosus Greene (lunara lupine) (Keeler and Panter 1989), *L. caudatus* Kelb (tail cup lupine) (Shupe et al. 1967), *L. sericeus* Pursh. (silky lupine) (Shupe et al. 1967), *Conium maculatum* L. (poison-hemlock) (Keeler 1974), *Nicotiana tabacum L.* (burley tobacco) (Crowe 1969) and *Nicotiana glauca* Graham (wild tree tobacco) (Keeler 1979) have all induced congenital defects of variable severity in livestock species. The types of birth defects include multiple congenital contractures (MCC) such as over-or under-extension or flexure of the joints, joint rigidity, and immobility. Front limbs may be laterally rotated, bowed or severely flexed (arthrogryposis). Often curvature of the spine (scoliosis), twisting of the neck (torticollis), rib cage anomalies, spinal depression (kyphosis), dissymmetry of the skull and cleft palate are observed.

Lupinus

About 100 species of *Lupinus* occur in the U.S. and Canada and most are native (Kingsbury 1964). The quinolizidine alkaloids predominate; however, in a few, piperidines and other types of alkaloids have also been found (Keeler 1989).

Lupinus laxiflorus Dougl. (Wagnon 1960), *L. caudatus* (Shupe et al. 1967, Keeler 1976, and *L. sericeus* (Shupe et al. 1967, Keeler 1976) have been implicated in "crooked calf disease" by feeding trials and/or epizootiologic data. Anagyrine, a quinolizidine alkaloid, is believed to be responsible for the malformations based on epidemiologic data and experimental trials (Keeler 1976). Anagyrine-containing lupines are suspected of causing birth defects in cattle only. Recently, Keeler and Panter (1989) fed *Lupinus formosus* (a piperidine alkaloid-containing lupine) to cattle and induced severe arthrogryposis, scoliosis, kyphosis, torticollis, rib cage anomalies, and cleft palate. The plant is virtually devoid of anagyrine but contains large amounts of the piperidine alkaloid, ammodendrine, which is believed to be the teratogen (Keeler and Panter 1989).

Several species of *Lupinus,* containing the quinolizidine alkaloid teratogen anagyrine, induce acute neurotoxic effects in cows and subsequent birth defects in their calves. Neither sheep nor hamster offspring, however, were congenitally deformed following maternal ingestion of *L. caudatus, L. sericeus* or anagyrine-rich preparations therefrom (Keeler 1984b). Panter et al. (1990) fed *Lupinus caudatus* to pregnant goats to measure toxicity and teratogenicity (Panter et al. 1990). High anagyrine concentrations comparable to other teratogenic lupines were detected (Keeler, unpublished data) and other collections of *L. caudatus* from this site had been teratogenic in cows. However, clinical signs of toxicosis in goats were minor, fetal movement was not affected, and no fetal malformations were observed (Panter et al. 1990).

There are similarities in the teratogenic expression in cattle among deformities induced by *Conium* (coniine), *Nicotiana glauca* (anabasine), *Lupinus caudatus* (anagyrine) and *Lupinus formosus*

(presumably ammodendrine) Keeler and Panter 1989). All of the above plants have induced MCC in cattle. In addition, *Lupinus caudatus* and *L. formosus* have induced cleft palate in cattle. Keeler and Panter (1989) suggested that ammodendrine possessed similar teratogenicity to that of coniine and anabasine because all 3 are α-substituted piperidine alkaloids meeting the chemical structural requirements to be teratogenic as suggested by Keeler and Balls (1978). The lack of teratogenic responses in experiments with goats (Panter et al. 1990), sheep (Keeler 1984b), and hamsters exposed to *Lupinus caudatus, Lupinus sericeus* or anagyrine extracts therefrom seems to suggest that cattle are uniquely sensitive to the teratogenic effects of anagyrine. Keeler and Panter (1989) have hypothesized that this might be explained either by a difference in metabolic capabilities of cattle or of bovine rumen microflora such that activation of anagyrine to a piperidine meeting the structural requirements for teratogenicity occurs only in this species.

Management changes based on information learned about susceptible gestational period in cows, alkaloid content, and relative toxicity in relation to plant growth stage have been implemented on many ranches once experiencing large losses due to "crooked calf disease". Slight changes in breeding programs and grazing schedules coupled with fencing and herbicide treatment have allowed ranchers to successfully continue grazing these lupine-infested ranges, yet reduce their losses significantly. Some ranches converted to a fall calving schedule, others delayed breeding or turned bulls in early; thus, cows exposed to lupine at its most teratogenic stage (early growth or seed pod stage) were not exposed to these plants during the critical gestational period (40 to 70 days of gestation).

Conium

Conium maculatum (poison-hemlock) was introduced into the U.S. as an ornamental and has since become widespread. The plant grows in waste places, along road sides, ditch banks, fence rows, and in uncultivated areas where adequate moisture is available (Kingsbury 1964). Poison-hemlock is a prolific seed producer, and, if not controlled, may dominate small areas and may encroach on alfalfa fields, grass pastures, and meadows. Its seed is poisonous and may contaminate grain.

Studies at the USDA/ARS Poisonous Plant Research Laboratory have demonstrated the neurotoxic and teratogenic effects of *Conium* in cattle, horses, pigs, sheep, and goats (Keeler and Balls 1978, Panter 1983, Panter et al. 1988, Panter et al. 1990). Poison-hemlock appears to be least acutely toxic to pigs, followed by sheep and goats, and most acutely toxic to cows. However, the teratogenic effects are most severe in cows and pigs, of intermediate severity in goats, and least severe in sheep.

Poison-hemlock contains 8 piperidine alkaloids (Panter and Keeler 1989). Coniine and γ-coniceine are the predominant alkaloids. Coniine usually predominates in the seed and mature plant, whereas γ-coniceine predominates in the early vegetative stage of plant growth (Panter 1983, Fairbairn and Suwal 1961). Coniine is known to be teratogenic, γ-coniceine is believed to be teratogenic, but to the author's knowledge the teratogenicity of the other conium alkaloids is untested.

Keeler and Balls (1978) fed many commercially available analogs of piperidine alkaloids to test their teratogenicity. They concluded from the experimental trials that simple piperidine alkaloids must meet certain structural criteria to be teratogenic. The length of the side chain alpha to the nitrogen and the degree of unsaturation in the piperidine ring affected teratogenicity. They speculated that piperidine alkaloids with a saturated ring and with a side chain alpha to the N at least 3 carbons in length were considered potential teratogens. There are many plants that livestock graze containing alkaloids that meet these structural criteria (Keeler and Balls 1978).

The clinical signs expressed in livestock from poison-hemlock are similar in all animal species thus far tested and are similar to those of *Lupinus* in cattle. Clinical signs of poisoning include muscular weakness, incoordination, trembling, knuckling at the fetlock joints, excessive salivation, and central nervous system (CNS) stimulation and/or peripheral or local effects (characterized by frequent urination, defecation, and dilated pupils). The initial stimulation is soon followed by depression resulting in relaxation, sternal recumbency, and death in extreme cases. Cows and pigs are temporarily "blinded" by the nictitating membrane covering the eyes. Cattle, pigs, goats, and elk have shown a preference or desire to ingest more plants after initial exposure (Panter and Keeler 1989).

Congenital skeletal malformations in calves (Keeler and Balls 1978), pigs (Panter 1983), sheep and goats (Panter et al. 1990) from ingestion of poison-hemlock have been reported. In calves, arthrogryposis, scoliosis, torticollis, excessive flexure of the carpal joints resulted when fresh *Conium* or coniine was administered by gavage to the dams during gestation days 55 through 75 (Keeler and Balls 1978). In pigs, similar malformations resulted when fresh plant and seed were fed *ad libitum* to pregnant sows during gestation days 43 to 52 (Panter et al. 1983). In sheep, carpal flexure was observed in lambs when pregnant ewes were administered pure coniine by gavage during days 25 to 35 of gestation. Similar effects occurred when fresh *Conium* was administered by gavage to sheep and goats during days 30 to 60 of gestation (Panter et al. 1988, Panter et al. 1990). The excessive flexure resolved spontaneously in lambs and kids as they grew and matured. In goats, *Conium* seed administered by gavage during days 30 to 60 of gestation resulted in skeletal deformities and cleft palate in their offspring similar to those described in cattle ingesting *Lupinus caudatus* (Panter et al. 1990).

Panter (1983) speculated that *Conium* induced cleft palate and MCC type skeletal malformations by reducing fetal movement i.e., perhaps the alkaloids were sedating or immobilizing the fetus. This mechanism was supported by experimental results when Panter et al. (1988) observed a relationship between reduced fetal movement and transient MCC type limb defects in sheep using radio-ultrasound. Further research established that sustained reductions in fetal movement over a period of 30 days (days 30 to 60 of gestation) was invariably associated with cleft palate and MCC in goats (Panter et al. 1990).

Management strategies minimizing loss from poison-hemlock induced malformations are similar to those described for lupine, i.e., avoid grazing early growth stages of the plant during susceptible gestational periods. Poison-hemlock is a toxicity problem early in spring because it is often the first green forage to emerge. Even though poison-hemlock is a considerable toxicity problem to cattle, sheep, goats, and horses at this time of year, it is usually not a teratogenic problem except to horses whose breeding programs and susceptible gestational stage coincides with high risk spring plants. Poison-hemlock is believed to contribute to "contracted foal syndrome"; however, research has not proven this. Regrowth and sprouting of seedlings of poison-hemlock occur in late summer and fall. The plant is equally toxic and teratogenic in the fall at early growth stages and poses a high risk to cattle, sheep, and goats because of breeding schedules. Poison-hemlock remains green long after other forage has frozen and dried. Animals may develop a taste for poison-hemlock once ingestion has been initiated.

Nicotiana

Crowe (1969) reported outbreaks of fetal aberrations in newborn pigs from farms in Kentucky and Missouri from 1967 to 1969. All sows had been exposed to and many had been observed eating waste burley tobacco *(Nicotiana tabacum)* stalks. The skeletal

abnormalities were similar to those induced by *Conium* and *Lupinus* in cattle. The forelegs were extended or flexed in a fixed position at the elbow and carpus, with joints ankylosed and limbs intertwined or clasping the thorax (Crowe 1969). In some cases, ankylosis of pelvic limbs occurred with flexed joints. Occasionally, the stifles were extended, whereas, the hocks were acutely flexed.

Crowe and Swerczek (1974) experimentally induced the skeletal malformation in pigs by feeding tobacco stalks to pregnant sows. The tobacco stalks contained 0.25% nicotine with other tobacco alkaloids. These alkaloids were suspected as the possible teratogens. An alkaloid-containing fraction from burley tobacco induced the defects (Crowe and Swerczek 1974); however, pure nicotine, the principal alkaloid, did not.

Keeler et al. (1981) reported the effects of experimental feeding of *Nicotiana glauca* to pregnant cows. Keeler had speculated that if an alkaloid were responsible, then a more likely candidate than nicotine as the teratogen would be anabasine, one of the minor alkaloids from burley tobacco but the major alkaloid in *Nicotiana glauca. Nicotiana glauca* proved to be teratogenic (Keeler 1979). Anabasine is an α-substituted pyridino-piperidine and is unlike nicotine, which is devoid of a piperidine ring. In cattle and other species, the α-substituted piperidine alkaloid coniine from *Conium* produced the skeletal abnormalities (Keeler 1974). Thus, the α-substituted piperidines like anabasine were suspected teratogens because of structural similarity to coniine. Further, anabasine was known to be teratogenic in chicks and was suspected as a teratogen in other species. The suspicion that anabasine was the teratogen in *Nicotiana glauca* and burley tobacco stalks was confirmed by Keeler in subsequent experiments using pure anabasine isolated from *Nicotiana glauca* (Keeler 1979).

The research described above for species of *Lupinus, Conium,* and *Nicotiana* is significant not only for the livestock industry, but also for human health. The research by Panter et al. (1988, 1990) suggests that alkaloids from these plants are crossing the placenta and may directly affect fetal health and physiology in part by reducing fetal movement.

The duration of time during which fetal movement is inhibited has proven to be very important. Thus, in the ewe and goat, *Conium* plant inhibited fetal movement for 5 to 9 hours after gavage, but by 12 hours fetal movement was not significantly different from controls. The lambs and kids from these ewes and goats had moderate carpal flexure, but no neck, spinal column or rib cage abnormalities. Carpal flexure resolved spontaneously in a few weeks after birth. In goats fed *Conium* seed or *Nicotiana* on the other hand, inhibited fetal movement was sustained from dose to dose over a period of 30 days and resulted in severe skeletal malformations and cleft palate (Panter et al. 1990). Furthermore, the timing of fetal movement inhibition is no doubt important. Panter (1983) determined that cleft palate is induced in swine by *Conium* between the 30th and 45th days of gestation. The insult time for cleft palate induction is surely much narrower than this. The palate is fused in the pig by day 34 (Evans and Sack 1973), suggesting that one could induce cleft palate in swine by feeding *Conium* from 30 to 35 days. In the sheep and presumably the goat, the palate is fused by 38 days (Evans and Sack 1973), and by 56 to 58 days in the human (Shepard 1976), suggesting sensitive periods only slightly later in gestation time in these 2 species.

Nicotiana species are not considered major range plant problems but rather limited problems where tobacco by-products have been fed to pregnant livestock. *Nicotiana glauca* and other species grow on ranges, but because of the low palatability are generally low risk. By understanding the potential for toxicity and teratogenicity of this genera of plants one can easily protect livestock by avoiding feeding by-products.

Locoweeds

Locoweeds adversely affect reproduction in livestock. Locoweed causes fetal malformations, delayed placentation, reduced placental and uterine vascular development, hydrops amnii, abnormal cotyledonary development, interruption of fetal fluid balance, and abortion (James et al. 1981). Locoweed poisoning occurs in all classes of grazing livestock, and multiple effects have been observed (James et al. 1981). Clinical signs of locoweed poisoning include aberrant behavior, ataxia, weakness, emaciation, rough hair coat, and death (James et al. 1981). The severity of clinical signs varies with the length of time locoweed has been ingested.

Panter et al. (1987) used radio-ultrasound to monitor the effects of locoweed on fetal and placental development in ewes. Their observations were similar to the results of others at necropsy (Van Kampen and James 1971), i.e., fluid accumulation in the placenta (hydrops allantois, hydrops amnii) altered cotyledonary development, and fetal death followed by abortion. Fetal heart rate was reduced and fetal heart contractions were irregular and weak. Fetal cardiac insufficiency and right heart failure, similar to that occurring in calves and cows that ingest locoweed at high elevation, may contribute to the fluid accumulation in the fetus and placenta and thereby cause fetal death and abortion (Panter et al. 1987).

A condition known as high mountain disease or congestive right heart failure has been reported in cattle grazing locoweed at high elevations (James et al. 1983). These studies suggest that consumption of locoweeds at high elevation exacerbates the hypoxic effects, thus increasing incidence and severity of high mountain disease. Based on gross observations and necropsies, the appearance of these animals is similar to that of fetuses from ewes that have ingested locoweed during pregnancy. Cattle have severe edema along the underline, brisket, jaws, and the thoracic and abdominal cavities. The hearts of calves grazing locoweed at high elevation and in fetal lambs from ewes fed locoweed have right ventricular hypertrophy, dilatation and rounding of the apex (Panter et al. 1987). High mountain disease may result when the effects of locoweed exacerbate the hypoxia of high elevation, thus increasing the vascular resistance and/or vasoconstriction, causing the right ventricle to work excessively. Such effects are believed to result in hypertrophy, cardiac insufficiency, edema, hydrothorax, and ascites.

The mammalian fetus is normally hypoxic and hypertensive relative to the dam because the airways are filled with fluid and the fetus must take up oxygen from the placenta. Locoweed may cause a vasoconstriction or increased vascular resistance in the fetus similar to that which it causes in cattle at high elevation. The workload on the fetal heart may increase, causing hypertrophy, dilatation, cardiac insufficiency, fluid accumulation, fetal death, and abortion.

Serum progesterone and cotyledonary prostaglandin concentrations were altered in pregnant ewes fed *Astragalus lentiginosus* (locoweed) (Ellis et al. 1985). Serum progesterone values were significantly reduced in a dose-dependent manner. Cotyledonary prostaglandins (6-keto-PGF_1, PGF_2, and PGE_2) were elevated and were significantly higher than controls. Prostaglandin levels also tended to be higher, however, not significantly so. Ultrasound studies by Panter et al. (1987) suggested that at least one fetus in each ewe fed locoweed died 2 to 3 days before abortion occurred. Ellis et al. (1985) reported that myometrial concentrations of PGF_1, PFD_2, and PGE were significantly higher in ewes bearing dead fetuses than in those bearing live fetuses. Thus, the ultrasound study by Panter et al. (1987) and the study reported by Ellis et al. (1985) are consistent with the hypothesis that fetal death or necrotic changes in the fetus may induce the cotyledonary prosta-

glandin synthesis that results in abortion. In the case of locoweed-induced abortion, tissue necrosis after fetal death may stimulate prostaglandin production and subsequent abortion.

Management to avoid locoweed related toxic, teratogenic, and abortifacient potential is difficult because of the ubiquitous nature of the plant, its ability to thrive during adverse climatic conditions, and its generalized and consistent toxicity regardless of plant growth stage, animal species ingesting it, and its relative palatability, particularly when other forage is scarce (early spring, fall, and winter). Management strategies reducing losses include intermittent grazing alternating between loco-free pastures and loco-infested pastures; increasing stocking rate and shortening grazing time, thus decreasing amount of toxin ingested per animal; grazing management practices maximizing grass production; herbicide control; and frequent observation of cattle, subsequently removing those individuals who tend to be habitual grazers of locoweed.

Conclusion

Poisonous plants in pastures and ranges have a marked impact on fetal and neonatal survival and development. Some of those plants and their toxins have been discussed in this review. However, there are many more plants on the range, known and unknown, that may also affect the *in utero* environment, causing adverse effects on the embryo or fetus. The knowledge of how these plants affect the unborn and their consequences on the neonate and ultimately the adult will help us to better manage livestock to avoid losses on range bearing these plants.

Condition of range, available moisture, climatic changes, and grazing management practices affect the propensity for livestock to graze poisonous plants. Drought and overgrazing are often 2 factors that deplete good quality forage, reduce grass competition and allow the relatively deep rooted poisonous forbs to proliferate. Early spring and late fall are times when poisoning conditions occur because poisonous plants emerge before adequate amounts of quality forage are available and remain green in the fall after good quality forage has been depleted or decimated. Utilization of poisonous plants is important and economically feasible; however, a balance allowing utilization of just the right amount of this type of forage without the toxic results is the optimum goal.

We may speculate that with advancement in technology we may manipulate embryos, fetuses, dams, or gastrointestinal microorganisms to change their susceptibility to poisonous plants. Perhaps *in utero* aversive conditioning, in which a conditioned response before birth to avoid these plants, may be induced by maternal exposure to certain plants coupled with an induced fetal gastro intestinal disturbance by an emetic such as lithium chloride. Alternatively, introduction of genetic material into the embryo or fetus may become feasible, so that although the animal may later ingest these plants, it would detoxify their harmful constituents more efficiently such that no harm would come to themselves or their offspring. Perhaps selecting resistant animals and through superovulation and embryo splitting techniques, entire herds with genetic resistance to certain plant toxins may be produced. Certainly, this is not economically feasible at this time; however, technologically this is not so unreasonable.

How we manage our livestock on western ranges is changing. Enhancing the ability of livestock to graze western ranges containing poisonous plants often leads to a more economical and productive use of these areas. What seems most important here is that, despite the presence of toxic plants, these lands serve as a source of high quality animal protein for a growing human population; however, further research is needed to identify methods by which poisonous plant-induced harmful effects on grazing animals and the associated economic losses can be reduced.

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