Alkaloids as Anti-Quality Factors in Plants on Western U.S. Rangelands

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Alkaloids as anti-quality factors in plants on western U.S. rangelands

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Abstract

Alkaloids constitute the largest class of plant secondary compounds, occurring in 20 to 30% of perennial herbaceous species in North America. Alkaloid-containing plants are of interest, first because alkaloids often have pronounced physiological reactions when ingested by livestock, and second because alkaloids have distinctive taste characteristics. Thus, alkaloids may kill, injure, or reduce productivity of livestock, and have the potential to directly or indirectly alter diet selection. We review 7 major categories of toxic alkaloids, including pyrrolizidine (e.g., *Senecio*), quinolizidine (e.g., *Lupinus*), indolizidine (e.g., *Astragalus*), diterpenoid (e.g., *Delphinium*), piperidine (e.g., *Conium*), pyridine (e.g., *Nicotiana*), and steroidal (*Veratrum*-type) alkaloids. Clinically, effects on animal production vary from minimal feed refusal to abortion, birth defects, wasting diseases, agalactia, and death. There are marked species differences in reactions to alkaloids. This has been attributed to rumen metabolism, alkaloid absorption, metabolism, excretion or directly related to their affinity to target tissues such as binding at receptor sites. In spite of alkaloids reputed bitter taste to livestock, some alkaloid-containing plant genera (e.g., *Delphinium*, *Veratrum*, *Astragalus*, *Oxytropis*, and *Lupinus*) are often readily ingested by livestock. Management schemes to prevent losses are usually based on recognizing the particular toxic plant, knowing the mechanism of toxicity, and understanding the temporal dynamics of plant alkaloid concentration and consumption by livestock. Once these aforementioned aspects are understood, losses may be reduced by maintaining optimal forage conditions, adjusting grazing pressure and timing of grazing, aversive conditioning, strategic supplementation, changing livestock species, and herbicidal control.

Key Words: poisonous plants, plant toxins, forage quality, diet selection, grazing management

Resumen

Los alcaloides constituyen la clase mas grande de compuestos secundarios de las plantas y ocurren en un 20 a 30% de las especies herbáceas perennes de Norte América. Las plantas que contienen alcaloides son de interés, primero porque cuando el ganado consume alcaloides a menudo producen pronunciadas reacciones fisiológicas y segundo porque tienen caracteristicas distintivas de sabor. Así, los alcaloides pueden matar, dañar o reducir la productividad del ganado y tienen el potencial para alterar directa o indirectamente la selección de la dieta. Revisamos 7 categorías principales de alcaloides tóxicos, incluyendo pirrolizidinae (por ejemplo, *Senecio*), quinolizidina (por ejemplo, *Lupinus*), indolizidina (por ejemplo, *Astragalus*), diterpenoide (por ejemplo, *Delphinium*), piperidina (por ejemplo, *Conium)*, pyridina (por ejemplo, Nicotiana), and esteroidal (tipo *Veratrum*). Clínicamente, los efectos de los alcaloides sobre la producción animal varían desde el rechazo mínimo del alimento al aborto, defectos de nacimiento, enfermedades mermantes, agalacia y la muerte. Hay marcadas diferencias entre especies en cuanto a las reacciones a los alcaloides. Esto has sido atribuido al metabolismo del rumen, la absorción del alcaloide, el metabolismo, la excreción o directamente relacionado a su afinidad con los tejidos blanco, tal como fijarse en sitios receptores. A pesar de que los alcaloides tiene reputación de ser de sabor amargo para el ganado, algunos géneros de plantas que contienen alcaloides (por ejemplo, *Delphinium*, *Veratrum*, *Astragalus*, *Oxytropis* y *Lupinus*) a menudo son ingeridas por el ganado. Los esquemas de manejo para prevenir perdidas usualmente son basados en reconocer una planta tóxica en particular, conociendo el mecanismo de toxicidad y entendiendo las dinámicas temporales de la concentración de alcaloides en la planta y su consumo por el ganado. Una vez los aspectos antes mencionados son entendidos, las perdidas se pueden reducir manteniendo condiciones forrajeras óptimas, ajustando la presión y tiempo de apacentamiento, induciendo un condicionamiento aversivo, utilizando suplementación estratégica, cambiando las especies de ganado y controlando las especies toxicas con herbicidas

Alkaloids are a chemically-diverse group of plant compounds with widely varying biological activities when consumed. Although most effects are thought to be detrimental, many alkaloids have been developed into beneficial drugs and pharmaceuticals. Range plants that contain alkaloids, poison more livestock worldwide than any other class of toxic compounds. The economic loss to the livestock industry specifically from alkaloid-containing plants is not known, but livestock losses in cattle and sheep in the western states to all toxic plants are estimated to exceed $340 million (Nielsen et al. 1988), not including horses

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Table 1. Direct and indirect economic losses from poisonous plants related to production and off take from domestic livestock and wildlife. Alkaloid-containing plants are responsible for the majority of livestock losses to poisonous plants worldwide.

Direct losses	*Indirect losses*
Death	Added fencing to restrict access
Wasting/reduced weight gains	Herding costs
Neurological incapacitation (horses)	Supplemental feeding
Abortions	Changes in grazing management
Weak/small offspring	Increased veterinary costs for treatment
Reduced fertility	Lack of immune response to vaccines
Birth defects	Lost opportunity to graze forage
Inability to sell/harvest animals	Lost nutrients in ungrazed forages
	Reduced land values
	Reduced value of grazing permits
	Herbicide costs for suppression
	Increased risk in overall enterprise

and goats. This estimate includes only death and reproductive losses (e.g., abortions), but other indirect costs also impact the livestock industry (Table 1). Our objective is to scrutinize the effects of alkaloid-containing plants on livestock production on western rangelands and outline management solutions. We sequentially review 7 major categories of toxic alkaloids, including pyrrolizidine, quinolizidine, indolizidine, diterpenoid, piperidine, pyridine, and steroidal alkaloids.

Alkaloids—Definition and Distribution

Alkaloids are difficult to define because of their diversity, but the alkaloid chemist S.W. Pelletier (1983) defined alkaloids as "a cyclic organic compound containing nitrogen..." The presence of a nitrogen atom usually makes alkaloids basic, as suggested by their name. Alkaloids are classified by their heterocylic ring structure and the location of the nitrogen atom in the ring. Ring structure is important because specific structural features are responsible for the biological activity of the individual compounds. Some alkaloids possess a close structural similarity with neurotransmitters such as acetylcholine (Ach), dopamine and serotonin. This structural similarity partially explains the toxicity of some alkaloids in the central nervous system (CNS).

Alkaloids occur in about 20% of all vascular plants, with most found in dicotyledons (Hegnauer 1963, 1988, Hazlett and Sawyer 1998). More than 33% of annual herbs in North America contain alkaloids (Levin 1976). Fortunately for livestock producers, the only monocotyledon family with significant (> 0.05% of dry weight) alkaloid concentration is Liliaceae (Robinson 1979). Obviously, this statement ignores alkaloids in monocots produced by fungal endophytes (see Thompson et al. this volume). The major alkaloid-containing plants on western ranges are classified by the type of alkaloid they contain (Table 2).

Do Alkaloids Alter Diet Selection?

Alkaloids are reported to taste bitter (Bate-Smith 1972). Garcia and Hankins (1975) argued that animals acquire natural aversions to most alkaloids because bitter taste is often linked with toxicity. Some forage plants such as reed canarygrass (*Phalaris arundinaceae* L.) and certain lupines (*Lupinus* spp.) are unpalatable because of high alkaloid concentrations (Ralphs and Olsen 1987). Nonetheless, Robinson (1979) and Glendinning (1994) concluded that alkaloids are not universally repellent to herbivores. Additionally, Molyneux and Ralphs (1992) suggest that some toxic alkaloids are not bitter tasting to livestock. Sheep (Arnold and Hill 1972), cattle (Pfister et al. 1996a, Panter et al. 1997), and pigs (Panter et al. 1985) do not necessarily avoid bitter tastes, nor do sheep form stronger aversions to bitter than to sweet flavors (Launchbaugh et al. 1993). As a rule, grazing animals are not deterred by the supposed bitterness of alkaloid-containing plants. Intake of alkaloid-containing plants is primarily regulated by positive or negative postingestive consequences (see Launchbaugh et al. this volume).

Indolizidine alkaloids

Major Plant Species

The indolizidine alkaloid, swainsonine, is the toxin in locoweeds (Molyneux and James 1982), found within the *Astragalus* and *Oxytropis* genera of the Fabaceae. There are more than 350 species of *Astragalus* and about 30 species of *Oxytropis* in North America. Of these species, only about 10 *Astragalus* and 2

Table 2. Major classes of plant alkaloids, livestock species primarily affected, body system(s) affected, and major plant genera containing the alkaloids.

Type of Alkaloid	Animal Species Primarily Affected	Body System(s) Affected	Plants Containing Toxin	
			Common name	Scientific name
Diterpene	Cattle	Muscle paralysis	larkspur	*Delphinium* species
Pyrrolizidine	Cattle, horses	Liver toxin; photosensitization	groundsel houndstongue	*Senecio* species *Cynoglossum officinale*
Steroidal (solanum type)	Cattle, sheep, horses	CNS[1] toxin; digestive tract	nightshades	*Solanum* species
Steroidal (veratrum type)	Sheep	Birth defects; lung congestion	skunk cabbage death camas	*Veratrum* species *Zigadenus* species
Piperidine	Cattle, sheep, horses, pigs	CNS toxin; birth defects	poison hemlock lupine tobacco	*Conium maculatum* *Lupinus* species *Nicotiana* species
Quinolizidine	Cattle, sheep, horses	Respiratory paralysis;birth defects	lupine	*Lupinus* species
Indolizidine	Horses, cattle, sheep	Digestive, reproductive & CNS	locoweed	*Astragalus* and *Oxytropis* spp.
Pyridine	Cattle, horses, pigs, sheep	CNS toxin; birth defects	tobacco	*Nicotiana* species

[1]CNS = central nervous system

Table 3. Major locoweed species containing indolizidine alkaloids, primary distribution in the western U.S., and range of swainsonine concentration (mg/g dry weight).

Scientific name[1]	Common name	Distribution	Range in Concentration
Astragalus			----(mg/g)----
allochrous	rattleweed	southern California east to Texas	0.7 to 11.5[2,3]
bisulcatus	two-grooved milkvetch	southern Canada south to New Mexico	0.0 to 0.4[2,3]
drummondii	Drummond milkvetch	southern Canada south to northern N.M.	0.60[3]
emoryanus	red-stemmed peavine	Utah and southwestern states into Texas	0.5 to 1[4]
lentiginosus	freckled milkvetch	western Canada to California; Rocky Mountains south into Arizona to Texas	0.05 to 0.4[3,6,7]
lonchocarpus	great rushy milkvetch	Nevada, Utah, Colorado, and southwestern states	0.0 to 4.4[2,3,5]
missouriensis	Missouri milkvetch	southern Canada south to New Mexico and Texas	0.12 to 0.18[2,3]
mollissimus	woolly locoweed	Utah and Wyoming south to Mexico	0.02 to 10.3[2,4,5,6]
praelongus	stinking milkvetch	Utah, Nevada, Colorado and southwestern states east into Texas	0.03 to 0.2[2,3,5]
tephrodes	ashen milkvetch	Nevada, southwestern Utah and New Mexico, Arizona, and California	0.0 to 0.9[2,3]
Oxytropis			
lambertii	Lambert's locoweed	southern Canada south to Arizona and New Mexico	0.2 to 1.0[2,5]
sericea	whitepoint locoweed	northwest Canada south to Nevada, New Mexico and Oklahoma	0.05 to 1.2[3,5,7]

[1]Many species have one or several varieties, but that level of detail is beyond the scope of this paper
[2]Smith et al. 1992
[3]Fox et al. 1998
[4]Davis et al. 1984
[5]R.J. Molyneux, personal communication
[6]D.R. Gardner, personal communication
[7]Molyneux et al. 1989

Oxytropis species have been found to contain swainsonine (Table 3). Many of these toxic species are located around the Colorado Plateau, the Great Basin, and portions of the Great Plains. Some *Astragalus* species contain nitro-toxins (e.g., *Astragalus miser* Dougl. ex Hook; see Majak and Benn, this volume) or selenium (e.g., *Astragalus bisulcatus* (Hook.) Gray). Other genera worldwide contain swainsonine, including *Swainsona* spp. (Colegate and Dorling 1997) and *Ipomoea* (Molyneux et al. 1995). Within the U.S., *Ipomoea* spp. (morning glory) have not been examined for swainsonine, but *Ipomoea batatas* (L.) Lam. (sweet potato) can be toxic to livestock through an unrelated mechanism.

Mechanism of Intoxication

Swainsonine has a chemical structure similar to mannose and glucose, and this similarity may be the basis of its toxicity (Colegate et al. 1989). Swainsonine inhibits several intracellular mannosidase enzymes responsible for cleaving sugar molecules from oligosaccharides (Broquist 1986). Inhibition of ∝-mannosidase and subsequent failure to trim mannose from oligosaccharides, results in accumulation of mannose-rich oligosaccharides in lysosomes and causes cellular disruption, and eventual cell death (Dorling et al. 1989, Elbein 1989). These accumulated oligosaccharides damage cells in thyroid, brain, pancreas, and kidney tissue, characterized as foamy cytoplasmic vacuolation (Van Kampen and James 1970, Stegelmeier et al. 1995a). Inhibition of Golgi mannosidase II results in abnormal glycosylation of proteins, affecting hormones, membrane receptors, and enzymes throughout the body. Once a sufficient number of cells are damaged, signs of poisoning are seen, which may occur within 3 weeks (Van Kampen and James 1970). Microscopically, damage in the CNS results from vacuolar degeneration of both neurons and glia (Stegelmeier et al. 1994). Pathological lesions appear within 1 week after locoweed feeding begins (Van Kampen and James 1970), and when locoweed feeding ceases, the cytoplasmic vacuoles disappear quickly (James and Van Kampen 1971). Residual CNS lesions may resolve quickly depending on the extent of intoxication (Pfister et al. 1996b), but once a particular threshold is exceeded, CNS damage becomes permanent (James and Van Kampen 1971), and the animal likely will display long-term abnormal behavior (Pfister et al. 1996b).

There appears to be a dose-response threshold for swainsonine, such that incomplete enzyme inhibition occurs at lower doses. Doses at or above the threshold result in similar etiology and further increases in dosage do not increase the severity of intoxication (Stegelmeier et al. 1995a); however, this threshold is low and relatively small doses have been shown to produce both clinical and histologic lesions. For example, sheep were intoxicated with average daily swainsonine doses of 0.21 mg/kg body weight/day (as ingested plant material, Pfister et al. 1996b).

Swainsonine is water-soluble, and is rapidly excreted (Stegelmeier et al. 1995b). Clearance time ($T_{1/2}$) for swainsonine from most tissues is about 20 hours; however, for the liver and kidneys it is much longer and requires about 60 hours. Swainsonine is distributed throughout all tissues and is present in many animal products. Thus, current recommendations are that animal products not be used, and intoxicated animals withheld from slaughter for about 8 days after animals discontinue locoweed ingestion ($T_{1/2}$ x 10; Stegelmeier et al. 1998a). Lactating animals that eat locoweed will excrete swainsonine into the milk within 30 min (Broquist 1986); therefore nursing young may become intoxicated (James and Hartley 1977).

Clinical Signs

The symptoms of locoweed poisoning are lethargy, muscular incoordination,

intention tremors, nervousness, and excitability, progressing to emaciation, possible maniacal behavior when stressed, and death. Horses may be particularly susceptible to intoxication (James and Van Kampen 1971) and may be dangerous when handled. Abortions and water belly (i.e., hydrops amnii) often occur when pregnant animals eat locoweed (Ralphs et al. 1994b). If the fetus survives *in utero* intoxication, the newborn offspring often exhibits abnormal suckling behavior, and may not survive (Pfister et al. 1993). Grazing animals that consume locoweeds at higher elevations (e.g., > 2200 m) are increasingly susceptible to congestive right heart failure (James et al. 1983).

Locoweed poisoning may be diagnosed by determining if animals have been exposed to locoweed, and by evaluating clinical and pathological signs; affected animals show typical overt signs of poisoning while living, and have pathological lesions upon post-mortem examination. With living animals, definitive diagnostic tests using serum can verify consumption of locoweed (Stegelmeier et al. 1995b). Serum tests are not very reliable, however, if suspected animals have not recently (i.e., within 2–3 days) been eating locoweed, as serum swainsonine quickly disappears, and enzyme concentrations quickly return to normal ranges. Future work will determine if other diagnostic assays, such as determining glycosylation of specific proteins, may be better indicators of intoxication.

Effects on Livestock Nutrition and Grazing Behavior

A dominant feature of locoweed poisoning in livestock is gradual emaciation (i.e., wasting, Marsh 1909), which may not cease when animals are removed from locoweed (James et al. 1969). In studies at our laboratory, rats, sheep, cattle, and horses have all shown declines in food intake and body condition while eating locoweed, and the wasting continued after locoweed feeding ceased. Steers lost weight while grazing locoweed, and gains did not resume for 45–60 days after locoweed feeding ceased (Ralphs et al. 2000). Overtly intoxicated horses, when removed from locoweed-infested pastures, continued to decline in body condition over 4 weeks even though their appetites did not diminish (Pfister unpublished data). The loss of productive function may result directly from neurological damage because of impaired ability to prehend and masticate food (Ralphs et al. 1991b). Ralphs et al. (1991b) reported that sheep had seizures that severely disrupted prehension and mastication. The loss of body condition may also be a direct result of swainsonine on hormonal and digestive functions (Stegelmeier et al. 1995a). Both aspects probably operate simultaneously to cause weight loss, because weight loss is not fully attributable to lower food intake (Velastegui et al. 1992).

Mildly or moderately intoxicated animals can be salvaged and returned to near normalcy by removing them from locoweed, and offering supplements (Marsh 1909). This does not ensure that such animals will be fully productive and normal, but they may regain sufficient body weight to allow resale (Torell et al. 1999b). Notwithstanding, severely intoxicated animals may not regain lost body weight even with supplemental feeding, and will never be productive no matter how intensive the rehabilitation.

There are pervasive anecdotal accounts of addiction or of animals "seeking out" locoweed in preference to other desirable forage. Marsh (1909) reported that locoweed was addictive to various animals, including mules, pigs and pronghorn antelope. Lewin (1931) described livestock addiction to locoweed and to the Australian plant *Swainsona*, long before it was known that *Swainsona* and locoweed contained the same toxin. Recent reports of toxicity in South America (Peru and Brazil) from morning glory vines (*Ipomoea* spp.) indicate that livestock become addicted or dependent on these plants (Molyneux, personal communication; Tokarnia et al. 1992). Ralphs et al. (1990) reported that dried, ground whitepoint locoweed (*Oxytropis sericea* Nutt. in T. & G.) was not addictive, but some animals habituated or become accustomed to eating the plant material. The obsessive consumption that producers observe may result from locoweed being relatively more palatable than associated forage (Ralphs et al. 1993), or alternatively, locoweed may have pharmacological properties that are reinforcing (Pfister 1999).

Management and Control

Swainsonine usually occurs at very low concentrations (0.01 to 0.3% of dry weight) in locoweeds (Table 3), with much of the toxin found in the seeds. Fluctuations in swainsonine concentration as the plants mature have little effect on how much locoweed is eaten (Ralphs and Molyneux 1989). The growth habits of locoweed in relation to other available forages generally determine if and how much of the plant is eaten. Livestock producers should not over-stock or over-utilize locoweed-infested ranges, and should manage for sufficient desirable forage so that grazing pressure does not impel livestock to begin eating locoweed. When animals become overtly intoxicated, the most economical solution may be to remove them from pasture, and allow time for recovery before selling (Torell et al. 1999b).

Whitepoint locoweed (*Oxytropis sericea*)

Whitepoint locoweed begins growth in late winter and early spring on shortgrass prairie rangelands, and the green leaves are often more palatable than are dormant grasses. Livestock readily consume green locoweed leaves during the spring when cool-season grasses are just beginning growth, and warm-season grasses are dormant (Ralphs et al. 1993). Grazing of whitepoint locoweed may cease when warm season grasses begin active growth in early summer (Ralphs et al. 1993), or livestock may switch diet selection to other green locoweeds (*Oxytropis lambertii* Pursh, Ralphs unpublished data), if available. On mountain rangelands, cattle prefer immature seed pods of whitepoint locoweed, but may also eat mature pods and green leaves later in the summer, particularly if grazing pressure is excessive. (Ralphs 1987). In contrast to shortgrass prairie rangelands, whitepoint locoweed on high elevation rangelands is grazed during summer even though other forage is also green and actively growing (Ralphs et al. 1986, Ralphs et al. 1987, Ralphs 1987). Simple changes in grazing management can have profound positive impacts on losses to whitepoint locoweed. For example, Ralphs et al. (1984) reported reductions in cattle losses from over 20% to less than 3% annually from a simple change in grazing management.

Specklepod locoweed (*Astragalus lentiginosus* Dougl. ex Hook.)

Limited studies with cattle and horses (Pfister unpublished data) suggest that, during spring, likelihood of animals eating locoweed increases greatly when animals begin to search avidly for newly growing cool-season grasses (i.e., "chasing green"). Cattle prefer dormant grasses to specklepod locoweed (var. *diphysus)* during much of the spring, but once cattle begin eagerly selecting green grass, they also begin eating still-green, but drying, locoweed. During winter, cattle will even eat toxic black stems from previous growing seasons (Ralphs et al. 1988). During spring, horses intensely search for green grass,

Table 4. Characteristics, relative toxicity, and general concentration range of toxic alkaloids of the dominant larkspur species in the western U.S.

Class/Species	Typical height at maturity	Elevation	Associated plant communities	Typical risk of losses[1]	Alkaloid concentration[2]
	--(cm)--	--(m)--			--(mg/g)--
Tall Larkspurs					
D. glaucum	90–200	>2000	aspen, conifers, alpine meadows	low	1–20
D. barbeyi	90-180	>2200	aspen, conifers, alpine meadow, mountain brush, alpine tundra	moderate to severe	1–29
D. glaucescens	76–90	>2000	mountain meadows, sagebrush	low to moderate	1–12
D. occidentale	90–180	>2000	mountain brush, sagebrush, conifer, aspen	low to severe	0–18
Low Larkspurs					
D. nuttallianum	20–60	>1200	mountain brush, sagebrush, aspen, conifer, mountain and foothill meadows	low to severe	2–4
D. bicolor	20–40	>800	mountain brush, sagebrush,	low to severe	—
D. andersonii	10–60	>1200	desert shrub, mountain brush, sagebrush, pinion-juniper	low to moderate	1–4
Plains Larkspur					
D. geyeri	40-80	>1500	desert shrub, mountain brush, sagebrush shortgrass prairie	low to severe	1-4

[1]The risk of losing cattle to these species is a subjective evaluation based on plant toxicity, numbers of grazing cattle threatened during the growing season, and the geographical distribution of the larkspur species. *D. glaucescens* is relatively more toxic late in the growing season compared to mature plants of the other species.
[2]These concentrations are general values, and were determined by examining numerous samples collected over the past 6 years at the Poisonous Plant Research Laboratory. The values for low and plains larkspurs should be considered preliminary because they are based on small sample sizes. Multi-site and year analysis for low and plains larkspurs is ongoing (Gardner, unpublished data). For further references see review by Pfister et al. (1999). For concentrations in Canadian low larkspur, see Majak (1993).

and simultaneously select green locoweed. Once horses begin to eat locoweed, consumption may continue until they become very intoxicated.

Woolly locoweed (*Astragalus mollissimus* Torr.)

Woolly locoweed is not very palatable to grazing cattle, and probably is not selected by livestock unless grazing pressure is excessive (Ralphs et al. 1993). Consumption of woolly locoweed appears to cease with the growth of warm-season grasses (Ralphs et al. 1993).

Social facilitation

When some animals begin to eat locoweed, these 'locoeaters' can influence other grazing animals, including nursing calves, to begin eating locoweed through social modeling (Ralphs et al. 1994a). In most situations, ranchers should remove animals that eat locoweed to eliminate social influences, and to prevent progressive intoxication. Some producers in New Mexico with locoweed-infested pastures have reduced their locoweed losses by systematically, over several years, removing any cow from their herds seen eating locoweed, before the animal either becomes intoxicated or influences her calf or companions to eat locoweed (D. Graham, personal communication).

Aversive Conditioning

Grazing animals may be conditioned so that they will avoid toxic plants, including locoweed, in future encounters (Ralphs et al. 1997a). In this procedure, animals are given a taste of the plant in a corral, then dosed via stomach pump with a solution of lithium chloride (LiCl) at 200 mg/kg body weight. The LiCl-induced illness is associated with the taste of the toxic plant, and animals avoid eating the target species (Ralphs 1992). Averted animals must not be allowed to graze with non-averted companions, as social facilitation can quickly extinguish the aversion (Ralphs 1997).

Cyclic or "on-off" grazing

Livestock can be poisoned by low level locoweed doses given for as little as 4 weeks (Pfister et al. 1996b). Nonetheless, considering both swainsonine's rapid clearance and dose-response threshold, it may be possible to expose animals briefly to locoweed with a low-risk of intoxication, if they are then allowed to recover on locoweed-free ranges. Recent work with sheep (Stegelmeier unpublished data) shows that animals repeatedly given locoweed for 10 days with a 14-day recovery period had no detectable permanent damage. On-off grazing schemes may work, but must be approached with caution as they have not been tested under field situations.

Herbicidal control

Producers should, if possible, provide a locoweed-free pasture for spring or fall grazing when animals are most likely to eat locoweed. Herbicidal control of locoweed (Ralphs and Ueckert 1988, McDaniel 1999) in some pastures can provide a relatively "loco-free" pasture for critical times. Herbicidal treatment for this specific purpose is often economical, even though general spraying to eliminate locoweed on a ranch-wide basis is usually not economical (Torell et al. 1999a).

Diterpenoid alkaloids

Major Plant Species

Toxic C_{19} and C_{20} norditerpenoid alkaloids occur primarily in 2 genera from Ranunculaceae: larkspurs (*Delphinium* spp.) and monkshood (*Aconitum* spp.). There are over 50 species each of *Delphinium* and *Aconitum*, but only a few are known to cause livestock poisoning. Monkshoods are highly toxic plants, but we believe that most reports of livestock losses to monkshood are attributable to larkspur (Knight and Pfister 1997). The 2 plants grow together in wet mountain habitats and are easily confused; furthermore, monkshood is not usually grazed by cattle. Larkspurs are divided into 3 general categories based primarily on mature plant height and distribution: low, tall, and plains (Table 4). Most research has focused on tall larkspurs (Pfister et al. 1999). Livestock losses in the western United States to all types of larkspurs probably exceed $10 million dollars annually.

Toxic Alkaloids and Occurrence

Larkspurs contain many (> 18) norditerpenoid alkaloids of which the most toxic are methyllycaconitine (MLA), 14-deacetylnudicauline (DAN), and nudicauline (NUD; Manners et al. 1993, 1995). Both MLA and DAN occur to some extent in all classes of larkspurs, whereas NUD has not been found in tall larkspurs. A fourth alkaloid, deltaline, is relatively low in toxicity, but is the dominant alkaloid in most tall larkspurs, comprising ≥ 40% of the alkaloid composition, while MLA and DAN together comprise another 20 to 50% of the alkaloid mix in tall larkspurs. The MLA is the dominant alkaloid in low larkspurs (Majak et al. 1987, Majak and Engelsjord 1988, Bai et al. 1994).

The concentration of MLA and DAN is highest in immature larkspurs (Pfister et al. 1994a, Ralphs et al. 1997b). In tall larkspurs, MLA concentrations may exceed 20 mg/g. In a Canadian study, Majak (1993) reported high concentrations of MLA (up to 8.7 mg/g) in vegetative low larkspurs, and 2 mg/g in flowering plants. Before shattering, tall larkspur pods are relatively high in toxicity (MLA + DAN = 7 to 12 mg/g). Toxicity declines rapidly in tall larkspurs once pods begin to shatter (Gardner and Pfister 2000), whereas concentrations are relatively stable in low larkspurs after the vegetative stage (Majak 1993, Gardner, unpublished data).

Mechanism of intoxication

The primary result of larkspur toxicosis in livestock is neuromuscular paralysis, as nicotinic acetylcholine (nAch) receptors in the muscle and brain are blocked by MLA and related alkaloids (Aiyar et al. 1979, Dobelis et al. 1999). Animals usually die from respiratory failure (i.e., asphyxiation) when the muscles of the diaphragm are paralyzed or the CNS respiratory center is depressed. Larkspur alkaloid binding to nAch receptors appears to be correlated to toxicity in various tissues (Kukel and Jennings 1994), and may explain sheep tolerance to larkspur if larkspur toxins bind less avidly to nAch receptors in sheep (Stegelmeier et al. 1998b).

Toxicity, but not lethality of MLA + DAN has been established for cattle by oral doses of dried tall larkspur (Pfister et al. 1994b, 1997a). Cattle typically show clinical signs when given an MLA + DAN dose of about 20 mg/kg body weight (Pfister and Cheney 1998). A 450 kg cow may show clinical signs after rapidly eating 1.8 kg of tall larkspur (≈ 7.2 kg wet weight). Assuming the plant material used in Olsen's (1978) LD_{50} study (vegetative and early flowering tall larkspur) contained 12 mg/g of toxic alkaloid, the LD_{50} of MLA + DAN in cattle would be about 30 mg/kg. Early studies by Marsh et al. (1916) suggest that the lethal dose is lower when tall larkspur is given repeatedly over 3 to 4 days.

Clinical Signs

Clinical signs of intoxication include muscular weakness and trembling, straddled stance, periodic collapse into sternal recumbency, respiratory difficulty, and finally death while in lateral recumbency. Moderately-intoxicated animals will periodically collapse while moving, and be in sternal recumbency for 10 to 30 min; when the temporary paralysis subsides, affected animals may show muscular trembling, but will be able to walk and graze. Severely-intoxicated animals will be laterally-recumbent, and will be unable to do more than thrash about. Marsh et al. (1916) reported that bloat seldom occurs in intoxicated animals, but our observations suggest that bloat can be a significant component of larkspur fatalities. Bloating may occur as a result of paralysis of the rumen eructation (belching) mechanism. Cattle may die from bloat alone or asphyxiation from aspirated rumen contents while recumbent from larkspur paralysis. Some success of early remedies for larkspur poisoning (e.g., bacon fat and turpentine given orally, Glover 1906) may have been due to bloat reduction.

Diagnosis and Treatment

Diagnosis of larkspur poisoning is usually by association, as dead or sick animals are found near larkspur plants. Because larkspur poisoning causes no tissue lesions, pathological examination can only rule out other possible causes of death. Currently, no field test exists to determine if animals have been poisoned by larkspur. Blood or rumen fluid may contain larkspur alkaloids (Holstege et al. 1996); even so, cattle can eat substantial quantities of larkspur without ill effect, and the presence of alkaloids in body fluids only suggests larkspur intoxication.

A variety of remedies have been applied by ranchers (e.g., bleeding by cutting the tail), but most are without scientific rationale. Treated animals probably survive because they did not eat a lethal dose of larkspur and did not bloat. Drugs that increase acetylcholine concentration at the neuromuscular junction have potential for

Table 5. Relative pyrrolizidine alkaloid (PA) concentration and toxicity of various PA-containing plant species on western U.S. rangelands.

Scientific name	Common name	Distribution	Concentration[1]	Lethal Dose[2]
			---mg/g---	---mg/g---.
Cynoglossum officinale	houndstongue	widespread weed in North America	0.5 to 21[3]	5 to 60[4]
Senecio longilobus	threadleaf groundsel	midwest south into Texas and west into New Mexico and Arizona	1 to 87[5]	10 to 13[6]
riddellii	Riddell's groundsel	midwest south into west Texas and New Mexico	2 to 180[5]	15 to 45[7]
jacobaea	tansy ragwort	weed in northwestern U.S.	0.2 to 9[5]	2 to 3[8]
vulgaris	common groundsel	weed in western U.S.	2 to 3[5]	Not available

[1]The concentration of total pyrrolizidine alkaloids (N-oxide and free base) in dry plant material. Concentrations vary greatly depending on growing conditions and plant part. The high value for *S. riddellii* (180 mg/g) is the highest recorded concentration of any type of alkaloid in any plant yet recorded (Molyneux and Johnson 1984).
[2]Lethal dose may be acute (short-term) or chronic (long-term) depending on dose, because toxicity from pyrrolizidine alkaloids may be delayed by weeks or months from the time animals ingest the plant.
[3]Pfister et al. 1992; Van Damm et al. 1994
[4]Baker et al. 1991; Stegelmeier et al. 1996
[5]Johnson et al. 1985a; Molyneux and Johnson 1984
[6]Johnson and Molyneux 1984
[7]Johnson et al. 1985b; Molyneux et al. 1991
[8]Johnson and Smart 1983

reversing larkspur toxicity. The cholinergic drug, physostigmine (0.08 mg/kg i.v.), has been successfully used under field and pen conditions to reverse clinical larkspur intoxication (Nation et al. 1982, Pfister et al. 1994c). Our current recommendation is that ranchers not attempt to move partially-paralyzed or recumbent animals, as stress is detrimental. If intoxicated animals bloat, passing a stomach tube or puncturing the rumen with a knife or trocar will relieve gas pressure.

Impacts on Animal Nutrition and Behavior

Larkspur poisoning is acute, rather than chronic, thus, animals that survive show essentially no long-term detrimental effects. Ingestion of larkspur at sub-acute doses has no negative impact on ruminal fermentation or digestive function (Pfister et al. 1989). Larkspur poisoning probably has no long-term effect on diet selection or grazing behavior, although previously-poisoned animals eat less larkspur and other forage for a few days after a toxic episode (Pfister et al. 1997a, Pfister and Cheney 1998). Eventually, larkspur consumption returns to previous levels, and animals may be intoxicated again.

Grazing Management

Tall larkspur (*D. barbeyi* Huth and *D. occidentale* (Wats.) Wats.)

Cattle eat little or no tall larkspur before the plant has elongated flowering racemes (Pfister et al. 1988a, 1997b). Cattle generally begin consuming tall larkspur after flowering racemes are elongated, and consumption increases as larkspur matures. Consumption usually peaks during the pod stage of growth in late summer, when cattle may eat large quantities (25 to 60% of diet, Pfister et al. 1988b).

The period of greatest risk on tall larkspur ranges extends from the flower stage into the pod stage. Many ranchers typically defer grazing on tall larkspur-infested ranges until the flower stage to avoid death losses. This approach wastes much valuable forage, and often places cattle into larkspur-infested pastures when risk of losses is high. An additional 4 to 6 weeks of grazing may be obtained by grazing these ranges early, before larkspur elongates flowering racemes (Pfister et al. 1997b). The risk of losing cattle is low when grazing before flowering even though larkspur is very toxic, because larkspur consumption is very low. Once pods are mature and begin to shatter, larkspur ranges can usually be grazed with impunity because pod toxicity declines rapidly, and leaf toxicity is low (Gardner and Pfister 2000).

Low larkspur (*D. nuttallianum* Pritz.) and Plains larkspur (*D. geyeri* Greene)

Consumption of low larkspur by cattle appears to increase once low larkspur has flowered, and higher grazing pressure will increase amounts of low larkspur eaten (Pfister and Gardner 1999). Spring grazing of low larkspur-infested ranges can be problematic, as there may not be sufficient forage growth to graze these ranges before larkspur flowers, but risk appears to increase once flowering occurs. Fortunately, in most years low larkspurs are short-lived, so producers must avoid heavily infested areas for about 4 weeks during peak toxicity. Four years of grazing studies on plains larkspur-infested ranges have shown few distinct patterns of consumption by lactating cows (Pfister, unpublished data).

Other Management Options

Aversive Conditioning

Cattle can be trained to avoid eating tall larkspur through aversive conditioning (Ralphs 1997), as previously noted with locoweed. Social facilitation, whereby one animal influences another to eat a particular plant, will quickly extinguish the aversion, thus, averted cattle must be grazed separately from non-averted cattle (Lane et al. 1990, Ralphs 1997). Animals experienced in eating larkspur may also be successfully averted, although the aversion is initially more difficult to induce and may be more fragile and less persistent than for naive animals (Ralphs 1997).

Grazing Sheep Before Cattle

Marsh et al. (1916) recommended that ranchers graze sheep before cattle to take advantage of the low toxicity to sheep, and Aldous (1917) noted that sheep grazing on immature *D. occidentale* in Nevada had reduced the poisoning risk to cattle. On tall larkspur-infested ranges where larkspur grows as discrete patches, sheep can be herded into or bedded on the patches to reduce larkspur availability or acceptability to cattle (Ralphs et al. 1991a, Ralphs and Olsen 1992). In those areas where larkspur is uniformly spaced over a pasture, sheep must eat immature larkspur and leave sufficient feed for cattle. This can be problematic, because early growth tall larkspur may not be palatable to sheep (Ralphs et al. 1991a). Sheep grazing has successfully reduced cattle losses on ranges with *D. glaucescens* in southwestern Montana (J. Helle, personal communication).

Herbicidal Control

Larkspur losses can be economically reduced if dense larkspur populations are controlled by herbicides. Picloram, metsulfuron, and glyphosate have proven to be effective in killing tall larkspurs when applied at specific growth stages (Mickelsen et al. 1990, Ralphs et al. 1991c, 1992). These herbicides do not reduce toxic alkaloid concentrations in treated larkspur plants, and metsulfuron may increase toxicity (Ralphs et al. 1998). Therefore, sprayed areas should not be grazed until larkspur has withered and decomposed.

Pyrrolizidine Alkaloids

Major Plant Species

Pyrrolizidine alkaloids (PAs) occur on western U.S. rangelands primarily in *Senecio* spp. (Asteraceae), and in *Cynoglossum officinale* L., (houndstongue, Boraginaceae). In the southeastern U.S., *Crotalaria* spp. (Fabaceae) also contain pyrrolizidine alkaloids. Worldwide, PAs are probably the most economically-important plant toxins impacting human health, as PAs contaminate grain for poultry, ruminant, and nonruminant livestock, and human consumption, as well as herbal teas (Huxtable 1989). About 3% of the flowering plants in the world (> 6000 species) contain PAs (Smith and Culvenor 1981), and there are currently nearly 300 individual known PAs (Roitman and Panter 1995). The alkaloid concentrations in range plants and subsequent toxicity vary widely (Table 5).

Mechanism of intoxication

The PAs occur in either the free-base or N-oxide form in plants, but neither of these forms is toxic to animals *per se* (Winter and Segall 1989). The toxicity of PAs is due to the formation of toxic metabolites in the liver termed pyrroles. Pyrroles are formed as a detoxification intermediate through the action of liver enzyme systems, primarily mixed function oxidases (MFOs), but the exact mechanism is not clear (Winter and Segall 1989). Pyrroles form adducts within the liver with hepatic proteins and nucleic acids, and damage liver cells, causing enlarged hepatocytes, abnormal bile secretion, and fibrosis (Stegelmeier et al. 1996). A dysfunctional liver leads to other syndromes such as chronic wasting disease and photosensitization. The PAs can also cause lesions in the lungs and brain.

Clinical Signs and Diagnosis

Poisoning from PAs may be either acute (high-dose and short-term) or chronic (lower-dose and long-term). Acute intoxication is less common, as most animals poisoned by PAs develop clinical signs slowly over many weeks or months (Cheeke 1989). Acute intoxication can kill animals within 1 day if sufficient plant material is ingested (Baker et al. 1991). Chronic intoxication usually results from ingestion of the PA-containing plant for several weeks (Baker et al. 1991, Stegelmeier et al. 1996). Typical clinical signs include depression and lethargy, anorexia, and ascites (fluid accumulation in abdomen). None of these signs are specific for PA–induced toxicity, thus, the diagnosis is usually made from a liver biopsy and associated histopathology. Enlarged liver cells were the dominant lesion seen in horses 6 months after they were dosed with a low dose of alkaloids. Serum chemistry changes may be dramatic, as many liver enzymes are altered, but these changes are also not specific for PA-poisoning. Wasting disease (i.e., severe emaciation) as a result of liver damage is commonly noted, as is "hard, yellow liver" disease; all these conditions may be related to PA-induced damage to the liver, but can be caused by other toxic plants and diseases (Stegelmeier et al. 1996).

Younger animals are more susceptible to PA-induced toxicosis because the higher metabolic activity of growing liver tissue encourages pyrrole formation and results in more extensive liver damage (Cheeke 1989). The PAs are transferred in milk to nursing young, and there is a danger of human consumption via milk (Molyneux and James 1990). There are marked species differences in tolerance for PAs, as goats and sheep are relatively more resistant to PA-poisoning than cattle and horses (Cheeke and Huan 1995). Detoxification of PAs occurs to a limited extent in the rumen (Wachenheim et al. 1992), but the liver appears to be the major site of detoxification (Cheeke 1994).

Impacts on Animal Nutrition and Behavior

Poisoning by PAs clearly has a great impact on the nutrition of grazing and penfed animals. Animals with compromised liver function will generally show slow weight loss over a long period of time (perhaps years). Further, PA-intoxication may interfere with mineral and vitamin nutrition to further degrade animal performance (Cheeke 1989).

Intoxication by PAs can affect animal behavior directly. For example, horses may show typical "head pressing" behavior as a result of ammonia toxicity from liver damage (Cheeke 1989). Intoxicated animals may become intractable and difficult to handle as the disease progresses; in the final stages of poisoning animals may stagger greatly. Liver damage can lead to secondary photosensitization, and as affected animals are sensitive to sunlight, they become solitary and spend excessive amounts of time seeking shade instead of grazing. Severe sunburn may occur especially on exposed areas such as the nose, vulva, udder, etc. Photosensitized, lactating cows will often develop very inflamed and sensitive udders, especially light-pigmented animals, and will prematurely wean their nursing young.

Management and Control

Senecio species

Managing rangelands so that plant communities are in good condition and adequate forage is available is crucial to reducing losses to *Senecio* spp. (Merrill and Schuster 1978). Generally, senecios are not very palatable, and are avoided by grazing livestock if other forage is available. Drought stress and overgrazing can increase populations of threadlleaf groundsel, as the plant is an aggressive invader (Sharrow et al. 1988). Drought is an especially dangerous time because other forage may be lacking and the toxic alkaloid concentration in senecio plants increases during drought (Molyneux and Johnson 1984), so grazing animals may ingest higher quantities of more toxic forage. *Senecio* species are also most toxic when plants are reproducing, thus avoiding pastures when these plants are in bud, flower, or seed is prudent. Proper grazing management must consider stocking rates, as improper stocking may increase the amount of toxic plant consumed when alternative forages become limited. Excessive stocking may lead to degradation of the desirable plant community allowing *Senecio* species to increase. Herbicidal control may alleviate some problems if incorporated into an overall management program (Sharrow et al. 1988).

Houndstongue (*Cynoglossum officinale*)

Houndstongue is not only a toxic plant, but also a noxious weed that is increasing in North America. The plant spreads from bur-like seeds that cling to animals and humans alike, and invades disturbed areas. Houndstongue is generally unpalatable when growing on rangelands, but we have observed lactating cows eat green houndstongue when other forage was adequate (Pfister unpublished observations). When houndstongue contaminates hay, it is readily eaten by cattle and horses, and is quite toxic (Baker et al. 1989).

Quinolizidine Alkaloids

Major Plant Species

The most problematic plant genera with quinolizidine alkaloids is *Lupinus* (Fabaceae). Although lupine is cultivated in some parts of the world as forage or grain (so-called sweet lupine), in the western U.S. many wild lupine species are toxic to livestock because of high alkaloid concentrations (Keeler 1989). Wink et al. (1995) recently reported on the alkaloid concentration of 36 lupine species from North America; most contain quinolizidine alkaloids, but a few also contain piperidine alkaloids or both types of alkaloids.

Mechanisms of Intoxication

Quinolizidine alkaloids are both toxic and teratogenic (i.e., causing birth defects) to livestock (Panter and James 1995). Lupines cause respiratory failure in sheep (Kingsbury 1964), but the mechanism is unknown. Lupine alkaloids bind differentially to both nicotinic and muscarinic Ach receptors (Schmeller et al. 1994), and affect Na^+ and K^+ ion channels (Wink et al. 1995), but a specific relationship to toxicity has not been developed. Birth defects are apparently caused by the effects of 2 different, but related, alkaloids, anagyrine (a quinolizidine alkaloid, Table 6) and ammodendrine (a piperidine alkaloid; Panter et al. 1992). For unknown reasons, cattle are uniquely sensitive to the effects of anagyrine, and ingestion of alkaloid-rich lupine causes the condition "crooked calf disease" in bovine offspring (Table 6, Keeler 1989, Panter et al. 1994). Crooked calf disease has been associated with *Lupinus laxiflorus* Douglas ex Lindl., *L. caudatus* Kellogg, and *L. sericea* Pursh (Panter et al. 1992). Crooked calf disease is caused by reductions in fetal movement during a susceptible period in gestation (Panter et al. 1988a). This reduction in fetal movement at the critical time is likely to interfer with bone, muscle and ligament development, resulting in mild to lethal skeletal malformations and cleft palate in calves (Panter et al. 1990, 1988a). Even though many calves are born alive, most of these deformities make them virtually worthless, and most deformed calves are destroyed shortly after birth.

Table 6. Potentially teratogenic Lupinus species on western U.S. rangelands[1]. Ingestion by pregnant cattle of *Lupinus* species with teratogenic alkaloids (quinolizidine or piperidine) from gestation day 40–100 may cause severe deformities in calves (i.e., crooked calf disease).

Scientific name	Common name
Lupinus	
albicaulis	pine lupine
albifrons	white face lupine
alpestris	mountain silvery lupine
andersonii	Anderson's lupine
argentous	silvery lupine
arbustus[2]	spur lupine
bakeri[2]	
burkei	Burke's lupine
caudatus	tailcup lupine
densiflorus	
elatus	
elagans	
excubitus	
erectus	tall silvery lupine
evermannii	Everman's lupine
formosus[2]	Lunara lupine
holosericeus	
humicola	lowland lupine
latifolius	broadleaf lupine
laxiflorus	looseflower lupine
leucophyllus	velvet lupine
longifolius	
montigenus	Mt. Rose lupine
nootkatensis	Nootka lupine (Alaska)
polyphyllus	Washington lupine
rivularis	stream lupine
ruber	red lupine
sericeus	silky lupine
sulphureus	yellow lupine

[1]Adapted from Davis (1982), Davis and Stout (1986) and Wink et al. (1995). Species were listed if they contain any of the quinolizidine alkaloid, anagyrine.
[2]These species contain piperidine alkaloids (e.g., ammondendrine) that are also teratogenic when eaten by cattle (Panter et al. 1998b).

Clinical signs

Lupine toxicity is seen clinically as a neurologic disease that progresses from depression and lethargy to muscular weakness, collapse, respiratory failure and death (Panter et al. 1999). Animals that survive for 1 or 2 days may recover completely (Panter et al. 1999), or they may succumb several days later (Kingsbury 1964). Pregnant cows that eat small amounts of lupine may not show clinical signs of intoxication, but give birth to deformed offspring (e.g., cleft palate, Panter et al. 1994). While sheep, goats, and cattle may show signs of acute lupine toxicity such as depression and death, the anygyrine-containing lupines cause birth defects in cattle only (Panter et al. 1998b).

Impacts on Animal Nutrition

Many lupines are not toxic to livestock, and plant breeders have conducted extensive breeding programs to enhance lupines nutritional properties and to reduce their alkaloid content for both livestock and human consumption (Aniszewski 1993). Lupines, being legumes, may contain > 20% crude protein (Panter et al. 1999). So-called "sweet" lupines are relatively low in alkaloid concentrations, and are an excellent source of protein for livestock (Stanford et al. 1996). Range-grown lupines, particularly the seed pods, are a good source of nutrition if they are low enough in alkaloids that toxicity problems do not develop (Panter et al. 1999).

Management and Control

Losses of livestock from lupine poisoning can largely be prevented by understanding 2 interrelated aspects. First, the highest concentrations of toxic alkaloids tend to occur in immature lupine plants and seed pods. Anagyrine concentrations are highest (> 5 mg/g) in early growth, and decline to less than 0.5 mg/g after seed shatter, except that concentrations increase when lupine seeds ripen (Keeler 1976). Second, pregnant cattle are susceptible to the teratogenic effects of alkaloids during a window from days 40 to 70 of gestation, occasionally extending to 100 days (Panter et al. 1997). Birth defects in cattle can be prevented by using breeding or grazing programs that avoid placing pregnant cattle in lupine-dominated pastures in the first trimester of gestation (Keeler et al. 1977, Panter et al. 1992, 1999). Alternatively, risk can be reduced by allowing only short-term access to lupines by pregnant cattle in some form of rotational grazing scheme (Panter et al. 1999). Herbicidal control of lupines is feasible (Ralphs et al. 1991d), but chemical control is usually more expensive than altering a grazing management program.

Acute toxicity problems are less common now, but large sheep losses occurred frequently 100 years ago (Chesnut and Wilcox 1901). Deaths losses usually occur when livestock, usually sheep, ingest a large amount of seed pods in a short period of time (James et al. 1968). This can occur from contaminated hay or from hungry animals gaining access to lupine-dominated forage, and can be prevented by using lupine-free hay and avoiding lupine-dominated ranges when other forage is scarce. During some years, lupine populations will temporarily expand on rangelands not normally problematic. Livestock producers need to be aware of lupine populations and be sufficiently alert to alter grazing or breeding programs when these eruptions occur. Lupine populations increased dramatically during 1997 in Washington, Oregon, Idaho, and Montana, causing severe losses. For example, producers in Adams County, Washington lost over 30% of their calves (> 4000 calves) from lupine-caused birth defects (Panter et al. 1999).

Piperidine Alkaloids

Major Plant Species

Piperidine alkaloids are broadly distributed in nature, but only a few range plants have sufficient amounts to cause toxicity problems for domestic livestock. Several *Lupinus* species (Fabaceae) contain piperidine alkaloids (Table 6), in addition to quinolizidine alkaloids (Roitman and Panter 1995). The suspected toxic piperidine alkaloids in *Lupinus* are ammondendrine and N-methyl hystrine (Panter and James 1995). Recently, 8 yearling steers died after eating *Lupinus argenteus* Pursh containing high levels of ammondendrine and N-methyl ammodendrine (Panter, personal communication). These cattle began grazing *L. argenteus* after grasses were depleted.

The most prominent species containing piperidine alkaloids is poison hemlock (*Conium maculatum* L., Apiaceae). Only 1 species of *Conium* grows in North America, and should not be confused with water hemlock (*Cicuta maculata* L.). Poison hemlock grows in disturbed areas, waste land, and along waterways, invading perennial hayfields and pastures. The first alkaloid ever characterized (coniine) was isolated from poison hemlock in 1827 (Panter and Keeler 1989). In addition to coniine, poison hemlock contains 4 other alkaloids, of which the most toxic alkaloid is ϒ-coniceine, the biogenic precursor for the other *Conium* alkaloids (Panter and Keeler 1989). The ϒ-coniceine is about 8 times more toxic than coniine (Bowman and Sanghvi 1963, Panter et al. 1998a), and this difference has important management implications.

Alkaloid Occurrence

The alkaloid concentration and distribution of alkaloids in poison hemlock are affected by many factors, including environmental changes and plant maturity (Cromwell 1956, Leete and Olson 1972). Drought stress increases total alkaloid concentrations (Fairbairn and Challen 1959). Immature poison hemlock often has a high concentration of ϒ-coniceine, which may then be converted predominately into coniine during active growth. During flowering, concentrations of ϒ-coniceine also shift to coniine. Thus, coniine is

the major alkaloid in mature plants and seed, whereas Υ-coniceine dominates the alkaloid mix in early growth and fall regrowth. Leaves from young or regrowing plants contain 3 to 6 mg/g of toxic alkaloids, whereas immature and mature fruit may contain > 10 mg/g (Cromwell 1956).

Mechanism of Intoxication

Poison hemlock alkaloids act on both smooth and striated muscle; the effect on skeletal muscle is a curare-like neuromuscular blockage, similar to larkspurs. Unlike larkspur alkaloids, blockage occurs only after initial muscular stimulation (Bowman and Sanghvi 1963). When the dose is sufficient, the blockage causes muscular paralysis, resulting in depressed respiration. The specific site of blockage at the neuromuscular junction is not known, nor is the exact mechanism (Panter and Keeler 1989). Poison hemlock alkaloids are also potent teratogens, and ingestion during pregnancy induces skeletal malformations that are virtually indistinguishable from those caused by lupines (Panter et al. 1988b). The mechanism of fetotoxicity is thought to be the same, namely reductions in fetal movement during critical phases of gestation (Panter et al. 1988a).

Clinical Signs and Diagnosis

Poison hemlock causes initial CNS stimulation with frequent urination and defecation, dilated pupils, increased heart rate, muscular weakness and trembling and ataxia. This initial stage is followed by depression with further muscular weakness, collapse, and death due to respiratory paralysis (Panter et al. 1988b). Although animals exhibit tremors, muscular weakness and collapse, they do not have true seizures and may recover quickly if a sublethal dose was eaten. Although poison hemlock is fetotoxic to pregnant animals as are lupines, *Conium* is more universally teratogenic, affecting cattle, sheep, goats, and pigs (Panter and Keeler 1989). Most pregnant animals that later develop terata after ingesting poison hemlock also show initial signs of acute toxicity, and many are fatally intoxicated, unlike the teratogenesis from lupine alkaloids. The severity of birth defects varies according to the dose and the animal species. Sheep are less sensitive than are cattle, goats, and pigs (Panter et al. 1988b). Similar birth defects can be caused by genetic, traumatic, or other environmental toxins and the clinical signs and lesions are nonspecific. Because there are no definitive pathological lesions, the diagnosis of poison hemlock toxicity is made from a knowledge of exposure to the plant, and from clinical signs. Additionally, many reports suggest that affected animals have a "mousy" odor on their breath or urine. Alkaloid screening can detect the presence of poison hemlock alkaloids in body fluids, providing confirmation that animals were ingesting the plant (Galey et al. 1992).

Management and Control

The most critical time of the year to avoid poison hemlock is spring because the plant often appears before other forage has emerged. Green seed pods may be eaten in mid-to-late summer (Panter and Keeler 1989). Furthermore, poison hemlock may regrow in fall after seed shatter. Ingestion during fall may coincide with fetotoxicity in pregnant cattle, if they are in the first trimester (days 30–75, Panter et al. 1988b). If poison hemlock has invaded hay fields, the contaminated hay can poison livestock. Even though toxicity decreases upon drying, sufficient toxin may be retained to poison livestock (Galey et al. 1992). Cattle appear to be particularly susceptible because of their acceptance of the plant and their sensitivity to the teratogenic alkaloids. Poison hemlock can be easily controlled with phenoxy herbicides (Panter et al. 1988b).

Impacts on Grazing Behavior

Poison hemlock is reported to be habituating or even addictive (Kingsbury 1964, Panter and Keeler 1989). Goats (Copithorne 1937), cows (Penny 1953), and pigs (Panter et al. 1985) readily eat fresh hemlock, even when intoxicated. Panter (1983) reported that intoxicated pigs "relished" the plant, and seemingly developed a craving for poison hemlock.

Related Pyridine Alkaloids

Tree and wild tobacco (*Nicotiana* spp., Solanaceae) are the primary toxic plants in the U.S. that contain pyridine alkaloids, closely related to piperidine alkaloids (Roitman and Panter 1995). Several species of *Nicotiana* poison livestock in the western U.S. (Kingsbury 1964), including *N. tabacum* (Burley tobacco), *N. glauca* (tree tobacco), *N. trigonophylla* (wild tobacco) and *N. attenuata* (wild tobacco). Tree and wild tobacco plants are generally not palatable to livestock grazing on rangelands (Panter et al. 1992). These plants contain nicotine, a well-known toxin, and more importantly, the teratogenic piperidine alkaloid, anabasine (Keeler 1979). Anabasine causes fetal malformations virtually indistinguishable from those caused by *Lupinus* and *Conium* (Panter and James 1995).

Steroidal (*Veratrum*-type) Alkaloids

Major Plant Species

The steroidal veratrum-type alkaloids are found primarily in *Veratrum* species (false hellebore) and *Zigadenus* species (death camas, Liliaceae). Western false-hellebore (*Veratrum californicum* Durand) is the dominant species in the western U.S., and occurs in moist mountain meadows, and along slopes and stream banks. Death camas grows on plains, prairies, and foothill ranges throughout the western U.S. There are several species of death camas, and all should be considered toxic even though toxicity can vary within and among species (Panter and James 1989).

Alkaloids and Mechanism of Intoxication

Veratrum species

False hellebore has long been recognized as a toxic plant for livestock (Hall and Yates 1915), although false-hellebore-induced fetotoxicity in sheep was not reported until 1962 (Binns et al. 1962). The primary teratogen is cyclopamine; the closely-related alkaloid veratramine is very toxic but does not produce abnormalities (Keeler 1983). Ingestion of false hellebore by pregnant sheep on gestation day 14 results in "monkey-faced" or cyclopian lambs with potentially severe craniofacial defects (Binns et al. 1962). The facial defects result from the toxic insult to the neural tube such that the embryonic forebrain fails to divide normally. *Veratrum* alkaloids have a structural resemblance to cholesterol. Recent work suggests that a disruption in cholesterol transport within cells prevents brain cells from recognizing signals to divide properly (Incardona et al. 1998). Other work suggests that cyclopamine may act by competitive binding at Ach receptors (Keeler 1988). Other defects and fetal death are possible at later stages of gestation up to 33 days (Keeler et al. 1986). Sheep are primarily affected because of their propensity to eat false hellebore but cattle and goats are also susceptible. A single dose of 1.5 g of purified alkaloid will cause deformities in sheep (Keeler 1983).

Death camas

Zygadenine was the first steroidal alkaloid found in death camas, but the toxicity has been attributed to zygacine, an acetyl ester of zygadenine (Majak et al. 1992, Makeiff et al. 1997). Zygacine concentrations range from 2 to 4 mg/g, and are highest in vegetative tissue and pods (Majak et al. 1992). Majak et al. (1992) also reported that 2 related forms of zygadenine were not detected in vegetative plants, but concentrations of these alkaloids increased dramatically in pods. The mechanism of action is not known. Zygadenine and numerous related alkaloids were found in death camas (Lang and Smith 1998) collected at the site where 23 cows died in Nebraska (Collett et al. 1996).

Clinical Signs and Diagnosis

Veratrum species

Clinical signs of acute false hellebore poisoning, relatively rare in livestock, include salivation, recumbency, reduced heart rate, and dyspnea (Kingsbury 1964). The fetotoxic effects of false hellebore are not generally overt for the dam. If fetal deformities are severe, the hormonal signals inducing parturition are disrupted and the dead and deformed fetus will be carried well beyond term. These ewes will eventually show clinical signs from the extended gestation and usually die (James 1999).

Death camas

Death camas toxicity is characterized by excessive salivation, frothing around the mouth, nausea and sometimes vomition (Kingsbury 1964, Panter et al. 1987). If the dose is sufficient, muscular weakness is followed by ataxia, recumbency, and death. Affected animals have a rapid, weak heartbeat, and respiratory distress. Death is from heart failure (Panter et al. 1987). Diagnosis is made by recognizing the clinical signs of poisoning, association of affected animals with populations of grazed plants, and pathological examination of tissues from dead animals (Panter and James 1989).

Management and Control

Veratrum species

Livestock management to avoid losses to false hellebore are relatively simple. First, since the window of fetotoxicity is relatively narrow (i.e., 14 to 33 days gestation), pregnant animals (particularly sheep) should not be allowed access to veratrum-infested pastures during this period. Cattle rarely eat the plant, therefore no special management is needed. For sheep, false hellebore is quite palatable, and herders must keep bred sheep from ingesting false hellebore for about 1 month after the rams are removed (Panter et al. 1992). This is not difficult to accomplish because false hellebore is limited in distribution to moist mountain habitats and grows in easy to identify dense patches. Although effective herbicidal control is available (Williams and Cronin 1981), it may not be practical given the location of the major populations in National Forests and the ease with which the problem can be solved by grazing management.

Death camas

Death camas is one of the first plants to grow during spring, and animals may graze the plant if other forage is lacking. Generally, recognizing the presence of death camas and understanding the acutely toxic nature of the plant will aid in avoiding problems. Panter et al. (1987) identified 3 contributing circumstances that resulted in loss of over 250 sheep in one band. First, hungry ewes with lambs were driven through the death camas-infested pasture. Second, sheep were bedded near the death camas, so the plant was readily available for grazing. Third, the herder stressed the sheep by rapidly driving them from the area, thus increasing the death loss (Panter et al. 1987). Death camas can be controlled by phenoxy herbicides (Ralphs et al. 1991d).

Conclusions

Alkaloid-containing plants exact a heavy economic toll on livestock production in rangelands of western North America. Losses to these plants can be reduced or eliminated by recognizing the toxic plant responsible for specific losses, understanding when livestock graze the plant and how the toxin affects animals, altering management schemes or animal species to reduce the risk of losses, or using herbicidal control. Management of each toxic plant species is based on knowledge of the temporal and spatial dynamics of alkaloid concentration and consumption by livestock. Losses may be reduced by ensuring that livestock are not exposed or have reduced exposure either during periods of greatest risk (e.g., highest toxin concentrations), or when they are most likely to eat the plant in amounts sufficient to cause toxicity.

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