Larkspur Poisoning: As We Now Know It And a Glimpse of the Future

John D. Olsen, *DVM, PhD*
U.S. Department of Agriculture,
Agricultural Research Service,
Poisonous Plant Research Laboratory,
Logan, UT 84321

Synopsis

Larkspur poisoning of grazing cattle occurs often on mountain and high plains areas of the western U.S.A. resulting in significant economic loss.[1] Larkspur poisoning also occurs in other cattle production areas but is recognized less frequently.[2,3] Garden larkspurs are toxic[4] and accidental consumption of them may cause poisoning.[5]

Clinical signs of experimental larkspur poisoning can be described as a progressive continuum, with severity dependent upon dose-rate, physical activity, and individual susceptibility.[6] Acute death accompanied by rapid bloating is often the presenting feature of grazing cattle poisoned by larkspur. Cattle often die in sternal recumbency, sometimes with hind legs extended behind the body. Apparent muscular weakness is a primary clinical sign of larkspur poisoning in cattle, with slight drooling and increased frequency of urination. During poisoning, cattle have episodes of weakness and tremors which may progress to a generalized paresis or paralysis. A sequence of standing, tremors, and lying down occurs repetitively during mild intoxication (Stage 1, Table 1). Standing time becomes shorter as severity of poisoning increases. With further increase in severity and depending upon toxic dose and time after dosage, cattle cannot stand (Stage 2) and eventually are unable to arise, at first from sternal (Stage 3) and finally from lateral (Stage 4) recumbency. Death by asphyxiation (Stage 5) generally occurs due to either bloat, inhalation of ingesta, or loss of effective respiratory muscle function. Gross and light microscopic pathology is neither pathognomonic nor remarkable.

Prognosis can be based upon rate of progression and severity of muscular weakness.[6,7] However, clinical signs are temporarily exacerbated by increased physical activity and may be induced in animals having inconspicuous poisoning. To avoid misjudgement, status should be determined by response to standardized stimulus after the animal has been helped (pushed rather than pulled) to sternal position and rested quietly for 5 to 10 minutes.[6] Moderately affected animals (Stage 2) can stand within several hours, but highly susceptible animals with severe poisoning may require several days to recover. Within 2 hours after an overwhelming lethal dose of plant, cattle may suddenly develop tremors and fall to recumbency within 30 seconds, and be unable to arise before death at 3 to 4 hours after dosage.[7] A toxic dose inducing Stage 3.7 signs for 2 to 3 hours would most likely be fatal in unattended range cattle because repetitive struggling would occur and exacerbate the effect, resulting in inability to regain sternal recumbency and eventually asphyxiation due to bloat.

Table 1. Clinical signs of larkspur poisoning and associated numerical index values used to measure the response after 10 minutes of quiet rest of cattle.[a]

Response Index	Clinical Signs
0	No signs of poisoning during a 40 minute observation period.
	--------- **STAGE 1** --------
1.0	Can stand, but has to periodically lie down after standing > 30 minutes.
1.2	Has to lie down after standing 15, but < 30 minutes.
1.4	Has to lie down after standing 10, but < 15 minutes.
1.6	Has to lie down after standing 5, but < 10 minutes.
1.8	Has to lie down after standing 1, but < 5 minutes.
1.9	Has to lie down after standing < 1 minute.
	--------- **STAGE 2** --------
2.0	Cannot stand when encouraged, but can lift body > 45 cm (fore- or hindlimb).
2.3	Cannot stand but can lift > 30, but < 45 cm.
2.5	Cannot stand but can lift > 15, but < 30 cm.
2.8	Cannot stand but can lift > 2, but < 15 cm.
	--------- **STAGE 3** --------
3.0	Maintains sternal position but cannot lift body > 2 cm when encouraged to stand.
3.2	Cannot lift, rolls to lateral recumbency when trying to stand, regains sternal position in < 1 minute, unassisted.
3.4	Cannot lift, rolls to lateral recumbency when trying to stand, regains sternal position in 1 to 5 minutes, unassisted.
3.5	Cannot lift, falls to lateral recumbency when not trying to stand, regains sternal position in 1 to 5 minutes, unassisted.
3.7	Cannot lift, falls to lateral recumbency when not trying to stand, cannot regain sternal position if unassisted; but can hold sternal position after assistance and when not trying to stand.
3.9	Cannot lift, falls to lateral recumbency when not trying to stand, can maintain sternal position only if head is at side and when not trying to stand.
	--------- **STAGE 4** --------
4.0	Unable to maintain sternal position when resting quietly, even though head is to side and after being helped to sternal position following 10 minute resting period in lateral recumbency without any attempt to stand.
4.6	Can abduct hind leg 15<30 cm. Cannot lift head.
	--------- **STAGE 5** --------
5.0	Death.

[a]See reference[6] for detailed description of clinical signs and methodology (Adapted and reprinted by permission from the *American Journal of Veterinary Research*[6]).

In part, from an invited paper presented at the Twenty-Sixth American Association of Bovine Practitioners Conference, Albuquerque, New Mexico, Sept. 16-19, 1993.

Therapeutic doses of physostigmine (0.08 to 0.23 mg/kg I.V., 0.26 mg/kg S.C.) can temporarily reverse clinical signs of larkspur poisoning.[8-11] But the dosage regimen for anticholinesterase drug to prevent death from a known lethal dose of larkspur is unproven.

To avoid death by bloat or inhalation of ingesta, moderately to severely poisoned cattle should be maintained in sternal recumbency, by physical restraint if necessary, until they regain the ability to stand. The exacerbation of signs due to handling *per se* is self-limiting and has never been the direct sole cause of death in experiments, even for animals at the upper limit of Stage 4 intoxication. At present, medication by injection is considered to be generally "palliative" and not essential for recovery until the animal becomes severely poisoned (Stage 3.7 or greater).

Prevalence of poisoning may be reduced (cost and practicality yet to be determined in particular situations) by: 1. controlled grazing to avoid highly toxic larkspur, 2. herbicide treatment or biological control to reduce availability or preferability of larkspur for grazing, 3. controlled sheep grazing of larkspur ahead of cattle, 4. training of cattle to avoid eating larkspur, 5. grazing of highly susceptible cattle on alternate range, and 6. selection of highly resistant breeding stock.

Diterpenoid Alkaloids in Larkspur

At least 150 diterpenoid alkaloids have been isolated from a wide variety of *Delphinium* and species structurally characterized, mostly within the past 15 years.[4,12,13] Of 15 larkspur species causing poisoning in cattle,[14] 10 have been chemically investigated.

Ultimately, the alkaloid content can be related to toxicity of the plant at a particular phenological stage and/or environmental circumstances. The relative toxicity of *Delphinium* alkaloids and plant extracts can be estimated by their toxicity for mice.[4,15-18] However, direct comparison of toxicity of these alkaloids and extracts for mice and for cattle is largely unreported. Toxicity extracts of plant parts measured by mouse assay generally declines as the plant matures.[16] Rapidly growing parts (or parts having a high metabolic activity) and reproductive parts of the plant often have been reported to be relatively more toxic per g dry wt. (eg., *D. glaucescens*, Table 2). Correspondingly, total alkaloid content also declines with plant maturity. But the decline in toxicity may not be directly proportional to the change in total alkaloid content because relative amounts of particular toxic alkaloids vary[4,12,18] and are major determinants of the plants toxicity.

An early and continual goal of our investigation of larkspur poisoning has been to measure or estimate the toxicity of individual alkaloids for cattle and to quantify toxic alkaloids in poisonous larkspur species.[15,18-20] Collaborative studies begun in 1977,[20,21] related studies by Canadian scientists,[10,17,22] and recent progress in the analysis of diterpenoid alkaloids[23,24] has provided the means to accomplish that goal. At least 35 chromatographic peaks (each representing at least one alkaloid) occurred during analysis of larkspur species administered to cattle in dose-response studies.[25] Many of these alkaloids appeared to be minor constituents and the relative toxicity of most of the alkaloids is undetermined for cattle (for recent mouse comparisons see Manners *et al.*[18]).

Methyllycaconitine (MLA), 14-deacetylnudicauline, and nudicauline, principal highly toxic alkaloids, occur in *D. barbeyi*,[18,20,24] in some other tall larkspurs,[18,21,22,25] and in low larkspurs.[26-29] Other chemically related norditerpenoid alkaloids of intermediate or undetermined toxicity also occur in varied relevant amounts (notably anthranoyllycoctonine, delcosine, and lycoctonine).[4,12,18] Some norditerpenoid alkaloids of relatively low toxicity, such as deltaline[4,12,17,18] have been found to occur in relatively large amounts and thereby

Table 2. Relative toxicity of leaf-petiole extract among *Delphinium, Consolida,* and *Sconitum* at the flowering stage of growth compared by mouse assay.[a]

Species	LD_{50}[b]	Confidence Interval[c]
D. barbeyi	2.0	(1.8 - 2.3)
D. barbeyi (aphid infested)[d]	3.8	(3.2 - 4.5)
D. barbeyi (aphid noninfested)[d]	4.6	(3.9 - 5.5)
D. glaucescens (leaf-petiole)	7.8	(5.0 - 6.7)
(raceme)	4.0	(2.2 - 3.3)
(stem)	11.5	(10.0 - 13.2)
D. occidentale x barbeyi	13.6	(12.1 - 15.4)
D. geyeri	14.6	(12.2 - 17.4)
D. hybridum cv?[e]	22.9	(18.1 - 28.9)
D. tricorne[f]	27.6	(25.2 - 30.0)
Consolida sp. cv?[g]	35.4	(28.8 - 43.5)
D. occidentale (Moist site)[h]	35.7	(33.7 - 37.8)
D. occidentale (Dry site)[h]	38.8	(36.0 - 41.9)
A. columbianum[i]	39.2	(35.8 - 42.9)

[a] Air-dry ground plant extracted with ethanol (95%), evaporated to dryness, extracted with buffered saline, filtered saline extract injected subcutaneously, 1 ml saline extract contained all of the alkaloid present in 1 g of plant except for that lost during extraction.
[b] Microliters of saline extract per g body wt.
[c] Estimation of a confidence interval that will encompass the LD_{50} 95 times in 100 determinations.
[d] Plants for J.D.O. collected in 1986 from rangeland used for cattle grazing, by A.M. (Nancy) Peterson, DVM, Yampa Colorado.
[e] Unclassified horticultural variety, 1.2 to 1.8 m height, most likely "Pacific Giant," collected from private residential floral garden of Anson B. Call, Logan, Utah.
[f] Plant collected for J.D.O. in 1988 from pasture used for cattle grazing, by C.D. Halsey, DVM, Abingdon, Virginia.
[g] Unclassified horticultural variety, about 0.6 m height, collected from private residential floral garden of Anson B. Call, Logan, Utah.
[h] Part of a serial collection of plants during a growing season.
[i] Vegetative stage, 0.5 to 0.6 m height, only sample compared presently.

(Adapted from Collectanea Botanica (Barcelona)[4].)

have the potential for importance in the etiology of larkspur poisoning.

Knowledge of the relative amounts of individual alkaloids occurring in a population of larkspur is important for estimating (or predicting) risk of toxicity for cattle. The unique chemical character and distribution of these alkaloids may also be useful for determining chemical taxonomic relationships within the *Delphinium* genus.[4,12]

Pathophysiologic Effects of Larkspur Poisoning

Failure of the skeletal muscle motor unit appears to be the primary clinical sign of larkspur poisoning in cattle.[6] However, specific alkaloids in larkspur have varied potential for a multitude of effects in the intact animal,[12,17] as well as the probability of a spectrum of interaction with other alkaloids present. Therefore, the integrated effect of the alkaloids consumed may need to be considered as well as the predominant effect of a particular alkaloid.

Although the primary effect in cattle appears as weakness consistent with that of a neuromuscular blockade, central nervous system effects cannot be ignored because potency of binding of MLA to rat neuronal nicotinic acetylcholine receptors was greater than the binding to muscle nicotinic acetycholine receptors.[30] Presently, it is unreported whether the concentration and pathophysiologic effect of MLA (or other larkspur alkaloids) in the brain of cattle is more significant with regard to toxicity than that occurring at the neuromuscular junction. MLA competitively inhibits a neuronal nicotinic receptor sensitive to alpha bungarotoxin (αBTX) but the physiological significance is not fully understood.[31] Also, certain neuronal receptors not blocked by αBTX are blocked by MLA.[31] In this regard, it is noteworthy that difference in species response to poisoning by larkspur extract was evident[32] where hamsters, rats, and mice showed epileptiform seizure effects more often than ruminants. It is also noteworthy that important regions of cattle muscle acetylcholine receptors are identical to rats and mice.[33,34] Recombinant DNA methodology will be useful to further determine how receptor characteristics vary among species (individuals) and if those variations correlate with relative susceptibility and toxic effect. If suitable genetic markers or other blood derived components can be linked to larkspur susceptibility, it may be feasible to identify individuals according to their susceptibility.

The clinical response of cattle to larkspur poisoning has been quantified by numerical rating to provide a basis for reference.[6] Designated stages of poisoning (classified according to clinical signs) have been related to numerical values (Table1).

Early signs of poisoning can be subtle and sometimes brief where only one short episode of tremors and collapse may occur following a single daily dose of larkspur (low toxicity). When the same moderately toxic dose of larkspur was given repetitively as consecutive single daily dosages, poisoning resulted from a short-term cumulative (distribution?) effect with the response being maximal by 3 to 4 days. The signs of poisoning were most severe between 5 and 9 hours after each dosage (Fig. 1).[6]

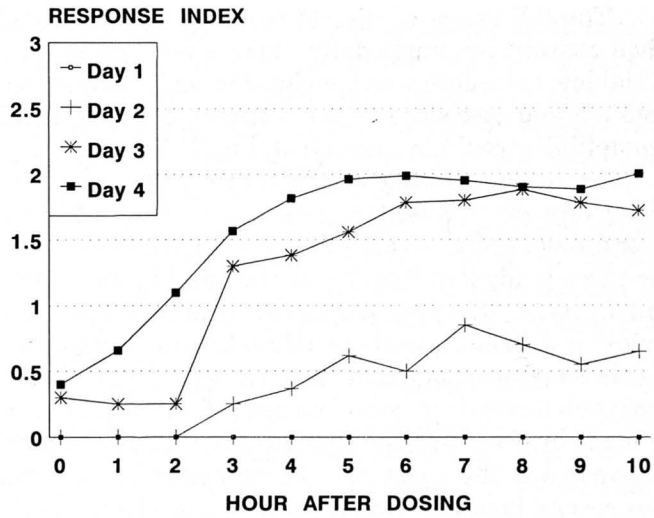

Figure 1. Response of cattle (n=6) to repetition of the same amount of larkspur administered once daily, by gavage, for 4 consecutive days (Reprinted by permission from *American Journal of Veterinary Research*[6]).

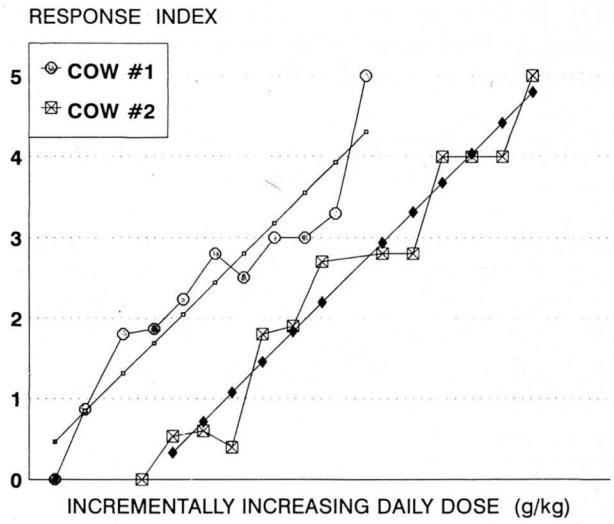

Figure 2. Response of cattle to increasing incremental doses of larkspur administered once daily, by gavage, on consecutive days. Each point represents the average of 3 hourly observations (6 to 8 hours after dosing). The regression line for the data of each cow provides a comparison of response to equipotent doses of plant.

The full range of clinical response was observed when consecutive single daily dosages were given. The initial low toxic dose was increased in daily increments until a lethal dose was reached. Difference in individual susceptibility could be quantified (Fig. 2).[35]

An overwhelming single lethal dose (LD_{100}) of highly toxic plant caused tremors to occur within 2 hours after dosage and all 4 cattle died within 3 to 4 hours.[7] In the same study 2 of 8 cattle (at the two highest doses) had a very rapidly progressing intoxication where they suddenly developed tremors, fell to lateral recumbency within 30 seconds, and could not rise again before death. Prognosis for cattle in lateral recumbency (Stage 4) could be made by observing the change in muscular adductor response and the character of respiratory movements over several hours. During lateral recumbency the cattle retained rumen motility and occasionally eructated. Bloat was readily relieved by helping cattle to sternal position, even at the upper limit of Stage 4 intoxication. Tactile sensory response was maintained at Stage 4 poisoning.

Larkspur extracts have effects equivalent to plant material[7] and can be used to create feed aversions in cattle equal to those induced by lithium chloride, when administered intraruminally.[36,37]

Factors Influencing the Prevalence of Larkspur Poisoning

Both plant and animal factors determine prevalence of larkspur poisoning.[4,12] Plant related factors influence toxicity (alkaloid content) of the plant and determine preferability and/or availability of the plant for grazing. Animal factors influence the susceptibility to poisoning and in part determine the grazing behavior. Environmental factors also influence both the plant and the animal, affecting the amount consumed (eg., Fig. 3) and possibly affecting the relative alkaloid content. Collectively, the alkaloid profile and absolute amount of alkaloids ingested per unit of time, as well as rate of absorption, distribution, receptor binding, metabolism, and elimination of those alkaloids determines whether poisoning occurs.

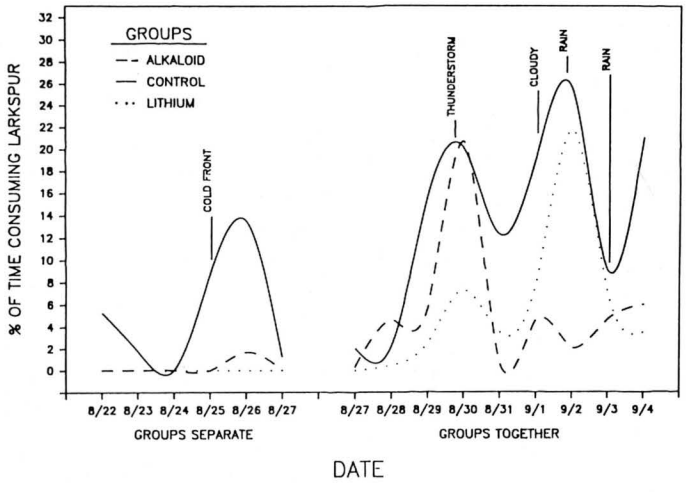

Figure 3. Consumption of larkspur by cattle as influenced by prior aversive conditioning and by environmental climatic factors (Reprinted by permission from Journal of Animal Science[37]).

The particular larkspur population being grazed can vary significantly in toxicity. Plant genetics seem to be a factor because certain species (and some communities within a species) appear to be consistently more toxic, apparently due to the presence of relatively more toxic alkaloids. *Delphinium barbeyi* generally was more toxic than other tall larkspur species while a hybrid population of *D. occidentale* x *barbeyi* was intermediate in toxicity (Table 2).[4,38] But populations of *D. occidentale* with relatively high toxicity also occur.[35]

Larkspur can be a nutritious and palatable forage for cattle. Crude protein was 10.6% or greater in the racemes of *D. occidentale*[39] and 12 to 15% in *D. barbeyi*.[40] When *D. barbeyi* racemes began to elongate, cattle in study pastures always selected flowering racemes and some leaves.[41] Later they selected nearly equivalent amounts of flowers and seed pods and eventually consumption of leaves (and total larkspur consumption) peaked during the pod stage. Cattle preferentially grazed commingled currant (*Ribes* spp.) and larkspur areas and consumed early flowering larkspur as 47% of their total bites during grazing in larkspur areas (18% of their total grazing time); yet no signs of poisoning were observed except for one animal which showed visible signs of distress after one occasion of rapid larkspur ingestion.[41] Very often, virtually all seeded (flowered) *D. barbeyi* plants on cattle allotments (observed during seed collection[42] or toxicity studies[43]) had the raceme and small top leaves grazed and in some larkspur areas only stems remained, while seasonal death loss varied from 13 to 57 head (1.5 to 6.8%).[44] In contrast, during years of drought, larkspur consumption was greatly reduced (peaked at 5 to 7% total consumption) during controlled grazing studies, nevertheless certain individuals consumed larkspur up to 33% of their total bites during a 7 day period while others ate none.[45]

Individual difference in susceptibility and/or grazing preference is a likely factor determining prevalence of poisoning. Deaths due to larkspur poisoning are reported anecdotally to occur from several days to several weeks after cattle are first put on range, associated with storm periods, and during late summer or early fall (pod stage). One might speculate that cattle unaccustomed (unconditioned?) to eating larkspur may overindulge if initially put on range when flowering larkspur is abundant, thereby accounting for early deaths. Similar short

episodes of overindulging consumption may be the cause of death associated with storm periods. Pen studies indicated larkspur poisoning was the result of a short-term cumulative (distribution?) effect with recovery within 5 days after dosing.[6] So if consumption decreased sufficiently at 2 to 4 day intervals, cattle could probably repeatedly consume an otherwise toxic daily dose, without manifesting marked signs of poisoning. The cyclic consumption of larkspur by grazing cattle[41] likewise seemed consistent with such a notion. Aversive feeding behavior occurred in pen studies when cattle consumed a toxic amount of dried ground larkspur mixed with chopped alfalfa hay (1981 data),[36] when infused intraruminally with larkspur extract or lithium chloride,[36,37] and when consuming a 33% larkspur/chopped alfalfa pellet.[46] Aversion to eating flowering larkspur plants, induced during pen studies, resulted in nearly complete abstinence of larkspur consumption during subsequent grazing of larkspur infested rangeland[47] with persistence of the aversion during the following grazing season.[48] Larkspur consumption by averted cattle was significantly less than that of nonaverted cattle during a short grazing study[50] (Fig. 3) even though peer pressure (social facilitation) of nonaverted cohorts grazing larkspur caused averted cattle to start eating larkspur.[49,50] In sum, these observations could be consistent with the occurrence of a negative feed-back mechanism where larkspur (alkaloid?) effects are sensed by the animal and consumption of larkspur altered accordingly, with the result generally being lack of poisoning except where more susceptible individuals gluttonously consume relatively highly toxic plant.

Interventions for Reducing the Prevalence of Larkspur Poisoning

To reduce prevalence of larkspur poisoning, one needs to minimize the rate of intake and maximize the rate of elimination of the toxic alkaloids, particularly for cattle having increased susceptibility. An earlier summation still seems appropriate, "prospects of successful control of larkspur poisoning seem most likely to come from an integrated use of several possible means,"[19] taking into account both plant and animal factors. The cost and practicality for use of selected control methods should be determined according to each grazing situation.

Knowledge of the relative toxicity of different larkspur species throughout their life cycle is important for consideration when formulating management plans for larkspur infested rangeland.[19] Therefore, one needs to measure (and ideally be able to predict) the plant alkaloid content and determine its toxicity, as a guide for controlling grazing to avoid highly toxic plants at a particular locality. Early grazing of larkspur infested range may be an option based upon observations that cattle seldom graze tall larkspur before flowering occurs.[40,41] But consideration should be given to the occurrence of low larkspur as well, because cattle will eat low larkspur in its vegetative stage resulting in fatalities.[51] Also, flowering of low larkspur occurs relatively early in the growing season. Abundance of low larkspur can be great when soil moisture is adequate and cool spring temperatures are predominant.[52] Low and tall larkspur can also be a problem during grazing of managed mountain meadow pastures.[53]

Herbicide control of larkspur can be difficult[54] but it can effectively reduce larkspur availability[55] and efficiently reduce economic loss due to poisoning in particular situations.[44,56] The estimated internal rate of return on the cost of spraying tall larkspur (comparable to expected rates of return from alternative investments) varied from 14 to 133% depending upon the herbicide used, method of application, value of cattle lost, and density (toxicity?) of the larkspur.[56] Timing and application rates for specific herbicides are important for control of tall larkspurs.[55] Picloram was equally effective over all growth stages when applied at 1.1 to 2.2 kg active ingredient (a.i.) per hectare (1 to 2 lb a.i./acre). Metsulfuron was most effective when applied at the vegetative stage; 0.035 kg a.i. per hectare (0.5 oz a.i./acre) killed 95% of *D. occidentale*, but 0.14 kg per hectare (2 oz a.i./acre) was required to kill the same percentage of *D barbeyi*. Glyphosate should be applied as a spot spray to individual plants at the vegetative or bud stage.[55] Low larkspur was controlled with 2-4D at 1.5 to 3 lbs a.i./acre.[57]

Behavior of livestock grazing larkspur needs to be understood and utilized to reduce the prevalence of poisoning.[19,36,37,40,41,45] As mentioned above, cattle did not eat *D. barbeyi* before flowering occurred on particular rangeland and ate relatively little during drought. Early experimental results indicated it may be possible to avoid larkspur poisoning if only cattle with induced aversion to eating larkspur are maintained as grazing cohorts (Fig. 3).[47-50] After 50 cattle deaths in 1981 due to *D. glaucescens* on a Montana grazing allotment, our laboratory was invited to collaborate in evaluation of sheep grazing larkspur 2 to 4 weeks before cattle turn-in, as a means of reducing cattle deaths.[12] Prior study indicated a lethal dose of tall larkspur for sheep was about 4 times greater than the lethal dose for cattle, implying a greater margin of safety for grazing sheep.[7] The sheep seemed to prefer grazing *D. glaucescens* in the early bud stage and at particular times such as early morning when first leaving the bedding area.[58] In 1982, 5 cattle deaths were attributed to larkspur poisoning on the allotment but none occurred in areas where sheep had grazed.[59] In controlled grazing trials, consumption of larkspur by cattle in the sheep-grazed pasture was lower than in

the cattle-only pasture and one cow died from larkspur poisoning in the cattle-only pasture.[60] Further cattle deaths due to larkspur poisoning on the allotment were not observed while early sheep grazing occurred.[61] Early sheep grazing was discontinued after 1990; during 1993, 15 cattle deaths were attributed to larkspur poisoning on the Upper Ruby Allotment when environmental conditions provided for a lush growth of larkspur.[62] Host-specific biological control methods also have potential as means of reducing availability or preferability of larkspur for grazing.[16]

Knowledge of individual susceptibility of cattle could be important to reduce deaths of grazing cattle. Significant difference in susceptibility occurred during laboratory investigations[6] and some cattle required 2 to 6 times more larkspur to induce equivalent toxic signs.[35] If highly susceptible cattle were identified, their management could be modified to grazing on low risk rangeland. Conversely, highly resistant cattle might be selected for grazing high risk areas and for selection of breeding stock.

Acknowledgements

The author thanks L.F. James, G. Manners, B. Stegelmeier, D. Gardner, M. Ralphs, K. Panter, J. Pfister, and other staff of the Poisonous Plant Research Laboratory for their cooperative contribution to the team investigation of larkspur poisoning.

References

1. Nielsen, D.B. and Ralphs, M.H. 1988. Larkspur: Economic considerations. In: James, L.F., Ralph, M.H., and Nielsen, D.B. (Eds.), The Ecology and Economic Impact of Poisonous Plants on Livestock Production, Westview Press, Boulder, CO, pp. 119-129. 2. Halsey, C.D. 1988. *Veterinary Practitioner*, Abingdon, Virginia. Personal communication. 3. Sizelove, W., McIlvaim, E.H., and Burrows, G.E. 1992. Possible larkspur intoxications responsible for acute deaths in cattle. *Vet. Hum. Toxicol.* 34:458-459. 4. Olsen, J.D., Manners, G.D., and Pelletier, S.W. 1990. Poisonous properties of larkspur (*Delphinium* spp.). *Collect. Bot.* (Barcelona) 19:141-151. 5. Elphick, E.E. 1931. Sheep poisoned as the result of eating larkspur (*D. consolidum*). *Vet. Rec.* 11:512-513. 6. Olsen, J.D. and Sisson, D.V. 1991. Description of a scale for rating the clinical response of cattle poisoned by larkspur. *Amer. J. Vet. Res.* 52:488-493. 7. Olsen, J.D. 1978. Tall larkspur poisoning in cattle and sheep. *J. Am. Vet. Med. Assoc.* 173(6):762-765. 8. Marsh, C.D., Clawson, A.B. and Marsh, H. 1913. Larkspur or "Poison Weed." Government Printing Office, Washington D.C. U.S.D.A. *Farmers Bull.* 531. p. 13. 9. Siegmund, O.H. (Ed.) 1967. *The Merck Veterinary Manual.* Merck & Co., Inc., Rahway, N.J. 10. Nation, P.N., Been, M.H., Roth, S.H., and Wilkens, J.L. 1982. Clinical signs and studies of the site of action of purified larkspur alkaloid, methyllycaconitine, administered parenterally to calves. *Canad. Vet. J.* 23:264-266. 11. Pfister, J.A., Panter, K., and Manners, G.D. *In press*; Reversal of tall larkspur (*Delphinium barbeyi*) poisoning in cattle with physostigmine. *Vet and Hum. Toxicol.* 12. Olsen, J.D. and Manners, G.D. 1989. Toxicology of diterpenoid alkaloids in rangeland larkspur (*Delphinium* spp.). In: Cheeke, P. (Ed.) *Toxicants of Plant Origin.* Vol. I. CRC Press, Boca Raton, FL. pp. 291-326. 13. Southon, I.W. and Buckingham, J. 1989. *Dictionary of Alkaloids.* Vol. 2. Chapman and Hall, N.Y., N.Y. 14. Kingsbury, J.M. 1968. Poisonous plants of the United States and Canada. Prentice-Hall, Englewood Cliffs, N.J. p. 131. 15. Olsen, J.D. 1978. Larkspur toxicosis: A review of current research. In: *Effects of Poisonous Plants on Livestock.* Keeler, R.F., Van Kampen, K.R., and James, L.F. (Eds). Academic Press, NY, NY. pp. 535-543. 16. Olsen, J.D. 1983. Relationship of relative total alkaloid concentration and toxicity of Duncecap Larkspur during growth. *J. Range Manage.* 36:550-552. 17. Benn, M.H. and Jacyno, J.M. 1983. The toxicology and pharmacology of diterpenoid alkaloids. In: Pelletier, S.W., (Ed.), *Alkaloids, Chemical and Biological Perspectives*, Vol. 1, John Wiley and Sons, New York, pp. 153-210. 18. Manners, G.D., Panter, K.E., Ralphs, M.H., Pfister, J.A., Olsen, J.D., and James, L. F. 1993. Toxicity and chemical phenology of norditerpenoid alkaloids in the tall larkspurs (*Delphinium species*). *J. Agric. Food Chem.* 41:96-100. 19. Olsen, J.D. 1984. Larkspur poisoning: potential for management. In: Siemer, E.G. and Delaney, R.H. (Eds.) *Proceedings of the Second Intermountain Meadow Symposium.* Colorado St. University Exper. Sta. Special Series #34. pp. 67-72. 20. Pelletier, S.W., Kulanthaivel, P., and Olsen, J.D. 1989. Alkaloids of *Delphinium barbeyi*. Phytochemistry 28:1521-1525. 21 Pelletier, S.W., Daily, O.D. Jr., Mody, N.V., and Olsen, J.D. 1981. Isolation and structure elucidation of the alkaloids of *Delphinium glaucescens* Rybd. *J. Org. Chem.* 46:3284-3293. 22. Nambi-Aiyar, V.N., Benn, M.H., Hanna, T., Jacyno, J., Roth S.H., and Wilkens, J.L. 1979. The principal toxin of *Delphinium brownii* Rydb., and its mode of action. *Experientia* 35:1367-1368. 23. Manners, G.D. and Ralphs, M.H. 1989. Capillary gas chromatography of *Delphinium* alkaloids. *J. Chromatogr.* 466:427-432. 24. Manners, G.D. and Pfister, J.A. 1993. Normal phase liquid chromatographic analysis of toxic norditerpenoid alkaloids. *Phytochemical Analysis* 4:14-18. 25. Olsen, J.D. and Manners, G.D. 1993. Unpublished data. 26. Kulanthaivel, P. and Benn, M. 1985. Diterpenoid alkaloids from *Delphinium nudicaule* Torr. and Gray. *Heterocycles* 23:2515-2519. 27. Kulanthaivel, P. Benn, M., and Majak, W. 1986. The C_{19}-Diterpenoid alkaloids of *Delphinium bicolor. Phytochemistry* 25:1511-1513. 28. Pelletier, S.W., Kulanthaivel, P., and Oosen, J.S. 1989. New Alkaloids from *Delphinium andersonii* Gray. Heterocycles 28:107-110. 29. Majak, W., McDiarmid, R.E., and Benn, M.H. 1987. Isolation and HPLC determination of methyllycaconitine in a species of low larkspur (*Delphinium nattallianum*). *J. Agric. Food Chem.* 35:800-802. 30. Ward, J.M.,Cockcroft, V.B., Lunt, G.G.,. Smillie, F.S., and Wonnacott, S. 1990. Methyllycaconitine: a slective probe for neuronal α-bungarotoxin binding sites. *FEBS* 270:45-48. 31. Alkondon, M. and Albuquerque, E.X. 1993. Diversity of nicotinic acetylcholine receptors in rat hippocampal neurons. I. Pharmacologial and functional evidence for distinct structural subtypes. *J. Pharmacol. Exper. Ther.* 265:1455-1473. 32. Olsen, J.D. and Sisson, D.V. 1991. Toxicity of extracts of tall larkspur *(Delphinium barbeyi)* in mice, hamsters, rats and sheep. *Tox. Letters* 56:33-41. 33. Criado, M., Witzemann, V., Koenen, M., and Sakmann, B. 1988. Nucleotide sequence of the rat muscle acetylcholine receptor e-subunit. *Nucleic Acids Res.* 16:10920. 34. Buonanno, A., Mudd, J., and Merlie, J.P. 1989. Isolation and characterization of the B and ε subunit genes of mouse muscle acetylcholine receptor. *J. Biol. Chem.* 264:7611-7616. 35. Olsen, J.D. 1993. Unpublished data. 36. Olsen, J.D. and Ralphs, M.H. 1986. Feed aversion induced by intraruminal infusion with larkspur extract in cattle. *Am. J. Vet. Res.* 47:1829-1833. 37. Ralphs, M.H. and Olsen, J.D. 1992. Comparison of larkspur alkaloid extract and lithium chloride in maintaining cattle aversion to larkspur in the field. *J. Anim. Sci.* 70:1116-1120. 38. Olsen, J.D. 1977. Toxicity of extract from three larkspur species measured by rat bioassay. *J. Range Manage.* 30:237-238. 39. Logan, J.R. 1973. Evaluation of a Specifically Formulated Supplement for the Prevention of Larkspur Poisoning in Cattle. Masters Thesis. Utah State University. 40. Pfister, J.A., Manners, G.D., Ralphs, M.H., Hong, Z.X. and Lane, M.A. 1988. Effects of phenology, site, and rumen fill on tall larkspur consumption by cattle. *J. Range Manage.* 41:509-514. 41. Pfister, J.A., Ralphs, M.H. Manners, G.D. 1988. Cattle grazing tall larkspur on Utah mountain rangeland. *J.*

Range Manage. 41:118-122. 42. Cronin, E. 1962 to 1976. Plant Physiologist, USDA/ARS Poisonous Plant Tesearch Laboratory. Personal communication. 43. Olsen, J.D. 1973 to 1976. Personal observation. 44. Cronin, E.H. and Nielsen, D.B. 1979. The ecology and control of rangeland larkspur. *Utah Agric. Exp. Sta. Bull.* 499. pp. 1-34. 45. Pfister, J.A. and Manners, G.D. 1991. Mineral salt supplementation of cattle grazing tall larkspur infected rangeland during drought. *J. Range Manage.* 44:105-111. 46. Pfister, J.A., Provenza, F.D., and Manners, G.D. 1990. Ingestion of tall larkspur by cattle. Separating effects of flavor from postingestive consequences. *J. Chem. Ecol.* 16:1697-1705. 47. Olsen, J.D., Ralphs, M.H., and Lane, M.A. 1989. Aversion to eating poisonous larkspur plants induced in cattle by intraruminal infusion with lithium chloride. *J. Anim. Sci.* 67:1980-1985. 48. Lane, M.A., Ralphs, M.H., Olsen, J.D., Provenza, F.D. and Pfister, J.A. 1990. Conditioned taste aversion: potential for reducing cattle loss to larkspur. *J. Range Manage.* 43:127-131. 49. Ralphs, M.H. and Olsen, J.D. 1990. Adverse influence of social facilitation and learning context in training cattle to avoid eating larkspur. *J. Anim. Sci.* 68:1944-1952. 50. Ralphs, M.H. and Olsen, J.D. 1992. Comparison of larkspur alkaloid extract and lithium chloride in maintaining cattle aversion to larkspur in the field. *J. Anim. Sci.* 70:1116-1120. 51. Johnson, A.E. 1972. Research scientist, USDA/ARS Poisonous Plant Research Laboratory. Personal communication. 52. Olsen, J.D. 1993. Personal observation and communication with U.S. Forest Service personnel. 53. Trampe, B. 1984. Meadows in a ranching operation. In: Siemer, E.G. and Delaney, R.H (Eds.) *Proceedings of the Second Intermountain Meadow Symposium.* Colorado St. University Exper. Sta. Special Series #34. pp. 1-6. 54. Ralphs, M.H. and Turner, D.L. 1989. Difficulty in controlling Duncecap Larkspur (*Delphinium occidentale*). *Weed Technol.* 3:335-339. 55. Ralphs, M.H., Evans, J.O., and Dewey, S.A. 1992. Timing of herbicide applications for control of larkspurs (*Delphinium* spp.). *Weed Sci.* 40:264-269. 56. Nielsen, D.B., Ralphs M.H., Evans J.O., and Call, C.A. *In press.* Economic feasibility of controlling tall larkspur on rangelands. *J. Range Manage.* 57. Hyder, D.N., Sneva, F.A., Calvin, L.D. 1956. Chemical control of sagebrush larkspur. *J. Range. Manage.* 9:184-186. 58. Olsen, J.D. 1982. Personal communication with J.T. Helle, sheep owner. Upper Ruby Cattle Allotment, Sheridan Montana Ranger District. 59. Neville, M.A. 1982. Range conservationist, U.S. Forest Service, Sheridan Montana Ranger District. Personal communication. 60. Ralphs, M.H. and Olsen, J.D. 1992. Prior grazing by sheep reduces waxy larksuur consumption by cattle: an observation. *J. Range Manage.* 45:136-139. 61. Alexander, J. III. 1989. Sheep Grazing as a Poisoning Control Method on Tall Larkspur Populated Cattle Range. Masters Thesis. Montana State University. 62. Dallas, D. 1993. Range Conservationist, U.S. Forest Service, Sheridan Montana Ranger District. Personal communication.