2020

Larkspur Poisoning of Cattle: Plant and Animal Factors that Influence Plant Toxicity

Benedict T. Green
The United States Department of Agriculture, Agricultural Research Service, Poisonous Plant Research Laboratory, Logan, Ben.Green@usgs.gov

Dale R. Gardner
The United States Department of Agriculture, Agricultural Research Service, Poisonous Plant Research Laboratory, Logan

Clint A. Stonecipher
The United States Department of Agriculture, Agricultural Research Service, Poisonous Plant Research Laboratory, Logan

Stephen T. Lee
The United States Department of Agriculture, Agricultural Research Service, Poisonous Plant Research Laboratory, Logan

James A. Pfister
The United States Department of Agriculture, Agricultural Research Service, Poisonous Plant Research Laboratory, Logan

See next page for additional authors

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By Benedict T. Green, Dale R. Gardner, Clint A. Stonecipher, Stephen T. Lee, James A. Pfister, Kevin D. Welch, Daniel Cook, T. Zane Davis, and Bryan. L. Stegelmeier

On the Ground

- Toxic larkspurs (*Delphinium* species) cause large economic losses from cattle deaths, increased management costs, and reduced utilization of pastures and rangelands.
- Larkspur toxicity to cattle can vary by geographic location due to toxic alkaloid content.
- Larkspur alkaloid chemistry can be used to predict plant toxicity.
- Cattle breeds differ in their susceptibility to larkspur poisoning.
- As cattle age from yearlings to two-year olds, they become less susceptible to larkspur.
- Heifers are three times more likely to be poisoned at the same dose of larkspur alkaloids than either bulls or steers, suggesting that they must be managed differently on rangelands where larkspur is present.

Keywords: alkaloids; *Delphinium*; larkspur; cattle; beef; rangelands
Rangelands 42(1):1—8
doi 10.1016/j.rala.2020.01.004

Introduction

Toxic larkspurs (*Delphinium* species) poison and kill cattle in western North America, and cattle deaths from larkspur poisoning can be as high as 15%.[1] Millions of dollars are lost from ranching communities due to animal deaths, increased management costs, and the underutilization of nutritious rangelands. Economic costs of larkspur poisoning to ranchers is not only associated with cow deaths, but, for example, other costs include loss of that cow nursing a healthy calf. The rancher must keep the calf alive, and if it survives there is lost income from marketing an early weaned, poor-performing calf. Ranchers must also replace the dead cow to keep herd numbers constant.

Ranchers managing cattle on rangelands with large populations of toxic larkspur are seeking solutions to the larkspur problem. The Poisonous Plant Research Laboratory (PPRL) in Logan, Utah is investigating how to reduce larkspur poisoning of cattle. We provide a brief review of basic information about larkspur and larkspur poisoning of cattle and describe recent research advances and solutions for larkspur poisoning of cattle. Current management recommendations[1] for grazing cattle on ranges containing larkspur are based on the concentration of toxic alkaloids in the larkspur, the quantity of larkspur eaten, and the rate at which larkspur is eaten by cattle. Until recently, we have not considered animal factors, including breed, age, and sex, which research has shown may play a role in cattle poisoning.

The Plants

Larkspurs belong to the buttercup plant family and are identified by their characteristic flower that has a spur, hence the name larkspur (Fig. 1). There are 60 native species of larkspurs in North America that have been divided into three groups: tall, low, and plains.[2] Most cattle deaths are caused by tall larkspur (Fig. 2A and 2B) but low larkspur (Fig. 2C) can poison cattle during cool, wet, springs when growth conditions are optimal for these species (Table 1).[3]

Tall larkspur

Tall larkspurs are 70 to 200 cm in height, have large hollow stems, and wide-bladed leaves (Table 1). These plants grow in mountain rangelands and begin flowering from mid to late July when they have reached 80% of their maximum height. Their flowering ends three weeks later when they enter the pod stage. Tall larkspurs produce large numbers of seedpods and seeds with high concentrations of toxins.[1]

Figure 1. A larkspur flower with the spur indicated by the arrow. Photo courtesy of Jen Green.

Figure 2. A, Tall larkspur. B, An individual tall larkspur raceme. C, Low larkspur. Photos courtesy of Jen Green.

Low larkspur

Low larkspurs are 20 to 60 cm in height and have small, fine, leaves (Table 1). These plants grow in desert shrub, mountain brush, sagebrush, and pinion-juniper communities during the spring and early summer. Low larkspur populations increase when late winters and springs are cool and wet.[4] This is a problem, because, during cool wet weather, the growth of grasses is delayed resulting in fewer alternative forages leading to increased consumption and deaths of grazing cattle.

Plains larkspur

Plains larkspur are about 80 cm tall and have small, fine leaves like low larkspur (Table 1). This larkspur grows on foothills and short grass prairie ranges in Wyoming, Colorado, and northern New Mexico.[5] Plains larkspur starts to grow early in the spring, and then matures later into summer when cattle often consume fatal quantities.[5]

Toxins Present in Larkspurs

Larkspurs contain toxic compounds termed alkaloids (i.e., nitrogen containing hydrocarbons) that are produced by and accumulated in the plant. These toxins are in the stems, leaves, flowers, and seedpods, all of which are eaten by cattle.[1] Two principle classes of alkaloids in larkspur are the toxic *N*-(methylsuccinimido) anthranoyllycoctonine type (MSAL-type) and the less toxic non-MSAL type.[1] The dominant MSAL-type alkaloid is called methyllycaconitine (MLA). In general, MSAL-type alkaloids like MLA, must be present in larkspur plants to poison cattle. Welch et al.[6,7] have shown that the non-MSAL-type alkaloids can increase the toxicity of MSAL-type alkaloids in cattle. Welch et al.[6,7] have also shown that the chemical profiles and alkaloid concentration vary from location to location. Though alkaloid mixtures have different toxicities, the plants with higher MSAL-alkaloid concentrations have a higher potential risk to poison cattle.[4]

Clinical Signs of Larkspur Poisoning in Cattle

The clinical signs of larkspur poisoning in cattle are caused by plant toxins blocking nicotinic acetylcholine receptors (nAChR) to prevent the neurotransmitter acetylcholine from activating nerve and muscle cells.[8] As the larkspur toxins begin to react with muscles and nerves, cattle show clinical signs of poisoning. In single-dose exposures the signs of poisoning occur 7 to 24 hours after eating. A typical visual response to larkspur exposure in cattle starts with trembling, lack of coordination, and rapid heart rate. Next, cattle will lay on their brisket and severe muscle weakness makes them unable to stand. This is followed by lateral recumbency (i.e., unable to maintain an upright posture even when lying down), bloating, and death.[1,8,9]

If cattle are recumbent, it is possible to rescue them by placing them upright on their sternum and administering an injection of the drug neostigmine at a dose of 0.02 mg/kg body weight.[8] Neostigmine has a limited effective duration, therefore affected cattle may require multiple doses.[8] Neostigmine inhibits the enzyme, acetylcholinesterase, which neutralizes the larkspur toxins at the nerves and muscles.[10,11] This treatment maintains muscle function while providing time for the animal to clear the toxic alkaloids from its body, which takes about 4 to 6 hours.[12] The judicious use of "saddlebag drug therapy," although expensive, can save cattle that would otherwise be fatally poisoned. It is important to keep poisoned animals calm and quiet, as a non-fatal dose of larkspur may

Table 1. Major species of larkspur.[27]

Larkspur class	Height at maturity (cm)	Elevation (m)	Plant communities	Risk to cattle
Tall larkspurs				
Sierra larkspur (*D. glaucum*)	90–200	>2,000	Aspen, conifers, alpine meadows	Low
Subalpine larkspur (*D. barbeyi*)	90–180	>2,000	Aspen, conifers, alpine meadows, mountain brush, alpine tundra	Moderate to severe
Smooth larkspur (*D. glaucescens*)	76–90	>2,000	Mountain meadows, sagebrush	Low to moderate
Subalpine larkspur (*D. occidentale*)	90–180	>2,000	Mountain brush sagebrush, conifer, aspen	Low to severe
Low larkspurs				
Two-lobe larkspur (*D. nuttallianum*)	20–60	>1,200	Mountain brush, sagebrush, conifer, aspen	Low to moderate
Little larkspur (*D. bicolor*)	20–40	>800	Mountain brush, sagebrush	Low to moderate
Anderson's larkspur (*D. andersonii*)	10–60	>1,200	Desert shrub, mountain brush, sagebrush, pinion-juniper	Moderate to severe
Plains larkspur				
Geyer's larkspur (*D. geyeri*)	40–80	>1,500	Desert shrub, mountain brush, sagebrush, shortgrass prairie	Moderate to severe

become lethal if affected animals become agitated or are exercised.[8]

Larkspur Alkaloid Composition

Larkspurs contain mixtures of toxic alkaloids (both MSAL- and non-MSAL-type alkaloids as described above), and these mixtures can change by geographic location and larkspur species.[13] We use chemical analysis (i.e., liquid chromatography mass spectrometry and infrared spectrometry) to generate norditerpenoid alkaloid profiles or fingerprints for each geographic location and larkspur species. Each unique alkaloid fingerprint is termed a chemotype. The chemotype and alkaloid concentrations are used to predict larkspur toxicity. This geographical distribution of Chemotype A of *D. occidentale*, which contains toxic MSAL-type alkaloids, overlaps with the distribution of Chemotype B, which does not contain toxic MSAL-type alkaloids (Fig. 3).[14] High concentrations of Chemotype A alkaloids in the plant increase the risk of death in cattle.[14] Conversely, large concentrations of Chemotype B alkaloids in the plant lowers the risk of death in cattle.[14] As more larkspur chemotypes are identified, and their toxicity verified, we will use this information to create chemotype risk estimates (Table 2). Ranchers can use this knowledge to adapt their grazing management of these chemotypes to reduce cattle deaths.

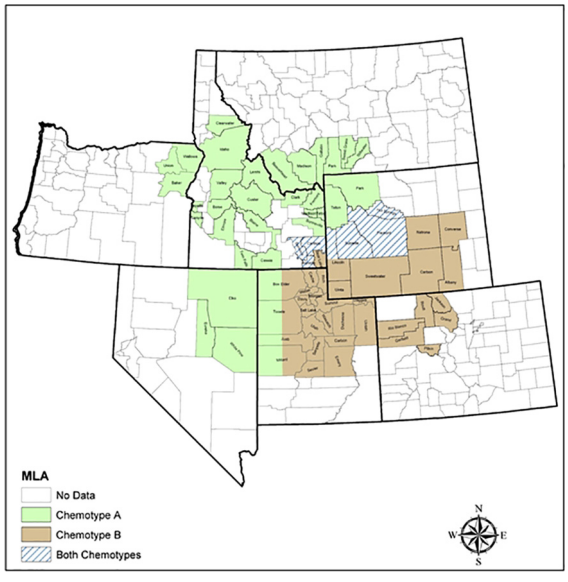

Figure 3. The distribution map of two larkspur chemotypes (Chemotype A shown in green and Chemotype B shown in brown) throughout the geographical distribution of *D. occidentale*.[13] Chemotype A contains the toxin MLA, and Chemotype B does not contain MLA and is much less toxic. Cattle grazing in areas with chemotype B have much less risk of poisoning due to the lack of the toxic alkaloid MLA in the plant.

Table 2. Larkspur alkaloid ratios, which is the ratio of the amount of plant material dosed per kg of body weight to the total alkaloid dose per kg of body weight.[15]

Collection (dosed at 7.5 mg/kg MSAL[a]-type alkaloids	*D. geyeri* Colorado State University, Colorado	*D. barbeyi* Manti, Utah	*D. barbeyi* Crested Butte, Colorado	*D. occidentale* Davis Basin, Idaho	*D. occidentale* Oakley, Idaho	*D. glaucescens* Sheridan, Montana
Alkaloid ratio	6:1	2.5:1	2.3:1	2.9:1	1.6:1	1.4:1
Total alkaloid dose mg/kg body weight	55.8	26.4	25.1	31.5	19.2	17.7
Chemotype risk to cattle	Severe	Severe	Moderate	Moderate	Low	Low

[a] N-(methylsuccinimido)anthranoyllycoctonine type.

In addition to specific alkaloid content, Green et al.[15] has shown that alkaloid concentration, and ratio of non-MSAL- to MSAL-type alkaloids, affects larkspur toxicity in cattle. In an experiment with Angus heifers, we found that the shorter the walking time of the heifers, the greater the toxic potential of a larkspur chemotype (Fig. 4).[15] The results of Green et al.[15] demonstrate that when equivalent alkaloid doses are administered to cattle a chemotype of *D. geyeri* (plains larkspur) had the greatest toxic potential because those heifers walked the least amount of time (Fig. 4). However, for cattle grazing in larkspur containing pastures, larkspur from Manti, Utah would be the most toxic due to a higher concentration of alkaloids in the plant on a per gram basis of plant material in addition to the ratio of alkaloids present in the plant.[15] We continue to investigate larkspur chemotypes and individual larkspur alkaloids to refine the prediction of risk for improved grazing management.

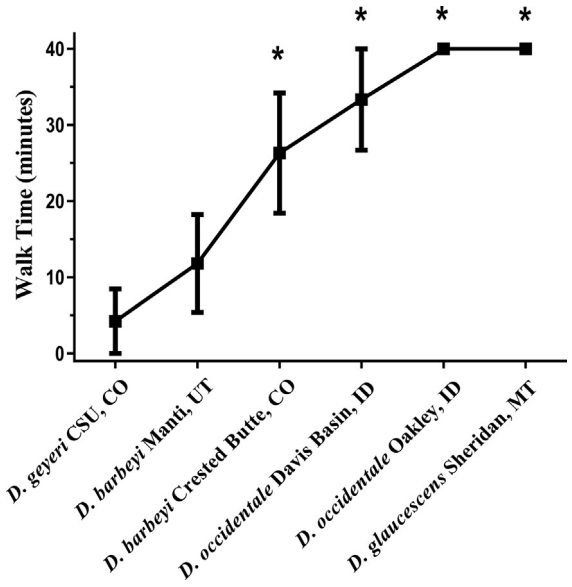

Figure 4. The walk times of six Angus heifers with six different larkspur collections in a Latin-square experimental design.[15] The observed mean ± standard error (SE) of Angus heifer walk times 24 hours after receiving a dose of MSAL-type alkaloids [7.5 mg/kg] in a Latin square study design with a 14-day washout period between dosings. To determine the walk times, the cattle were walked behind a tractor at 5 to 6 kph on a dirt track until they exhibited larkspur-induced exercise fatigue or for 40 minutes. The collections with the shortest walk times have the greatest risk of toxicity to cattle. Cattle dosed with the Oakley and Sheridan collections all walked for 40 minutes, the upper limit of exercise time for the experiment.

Our research has shown that larkspur alkaloid profiles and concentrations can vary by species and population.[15] Several factors may influence the chemical composition and alkaloid concentrations of larkspur. First, the chemotype of a given plant population likely does not change over time as similar profiles have been observed in plants from a given population over the past century.[13] Second, different alkaloid profiles could be due to previously unrecognized larkspur species; however, in one example research performed by the PPRL suggest that this is not the case.[13] Third, when two species of tall larkspur (*D. occidentale* and *D. barbeyi*) that had different concentrations of alkaloids in their native environment were taken and grown in a common garden, there were no differences in the concentrations of toxic alkaloids suggesting that environmental differences may influence the concentration of alkaloids.[16] Lastly, hybridization between larkspur species can result in the gain or loss of toxic compounds in the plant.[17] In summary, genotype and/or environment contribute to the qualitative and quantitative differences observed among larkspur species and populations.

Larkspur Poisonings and Noninvasive Sample Collection

Correctly diagnosing cattle deaths is vital for effective grazing management, and without knowledge of the cause of

cattle deaths, management plans cannot be modified to prevent future losses. Traditionally, blood, tissue samples, and rumen contents have been collected for diagnostic purposes. Stonecipher et al.,[18] using the collection of noninvasive samples from individual animals, has shown that earwax, oral fluid (i.e., saliva), and nasal mucus can identify cattle that have been exposed to larkspur and differentiate between larkspur chemotypes and species. For example, the alkaloids MLA and deltaline have been detected in earwax collected from cattle that received a single oral dose of *D. barbeyi*.[18] Similar results have been observed in other species of larkspur.[18] Using earwax, oral fluids, and nasal mucus for chemical analysis is advantageous because they are noninvasive and simple to collect. They do not require any special handling and can be frozen if chemical analysis will be performed later. Presence of larkspur alkaloids in body tissues or fluids does not prove the animal died from larkspur poisoning. However, the presence of these alkaloids shows that the dead animal consumed larkspur, and may be the cause of death, if all other clinical signs are consistent with larkspur poisoning.

Cattle Breed and Larkspur

Green et al.[19] has identified differences in responses of different cattle breeds to larkspur (Fig. 5). Green et al.[19] used an exercise tolerance test to measure larkspur responses between cattle breeds. Cattle were given a standardized dose of tall larkspur, which causes limited muscle weakness in an average animal. Larkspur-susceptible animals administered the standard dose of tall larkspur can walk no more than 5 minutes before becoming weak and unwilling to walk. Similarly, dosed larkspur-resistant cattle administered the standard dose of tall larkspur can walk for 40 minutes with no apparent clinical signs of intoxication. We evaluated the susceptibility of Angus, Line one Hereford, Jersey, Holstein, and Brahman cattle to larkspur toxicity.[19] Our work found over a two-fold difference between the Angus and Hereford walk times (i.e., exercise tolerance) and even greater differences between the Herefords and the two dairy breeds of cattle, Holstein and Jersey, with the dairy breeds being much more resistant to larkspur poisoning.[20]

One potential explanation for the difference between walk times of Angus and Holstein cattle is the ability of the two breeds to eliminate larkspur toxins from their body. Angus cattle have slower absorption and a lower maximum plasma concentration of the antihelmintic drug moxidectin than do Holstein cattle.[20] However, results from larkspur alkaloid metabolism studies by Green et al.[21,22] with Holstein and Angus steers, and both tall and low larkspur suggest that the two cattle breeds clear larkspur alkaloids in a similar manner. The results of Green et al.[21,22] suggest there is some other biological mechanism behind breed-dependent susceptibility to larkspur. We hypothesize that there are genetic differences between breeds that lead to differences in larkspur susceptibility. In our research, Angus cattle had the greatest variation

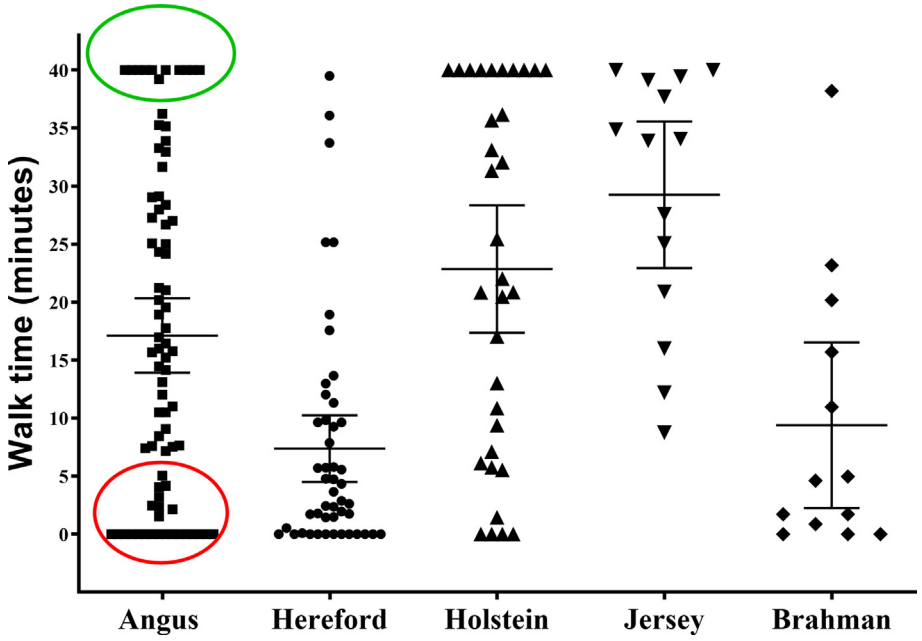

Figure 5. A scatter plot of the walk times (including observed mean ± SE represented by the vertical and horizontal lines within the responses of each breed) for five breeds of cattle depicting the responses to a standardized dose of tall larkspur (8 mg/kg total toxic alkaloid) at 24 hours after oral dosing.[19] To determine the time to signs of poisoning, the cattle were exercised behind a tractor at 5 to 6 kph on a dirt track for 40 minutes or until they exhibited larkspur-induced muscle weakness. Examples of resistant (green circle) and susceptible (red circle) animals are depicted for Angus cattle.

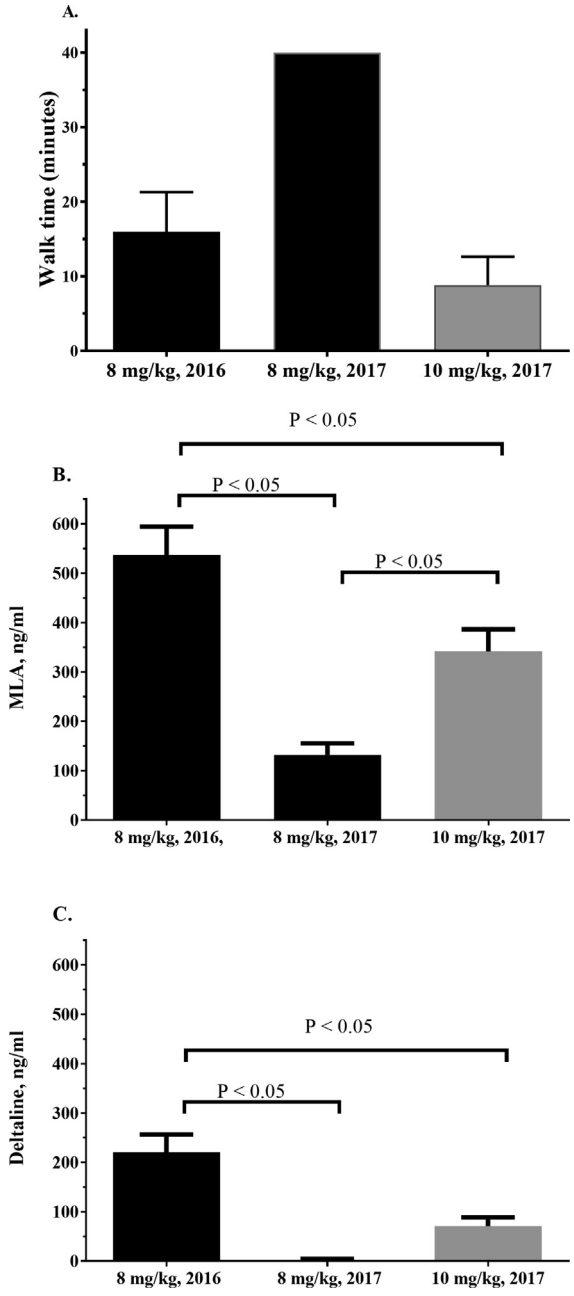

Figure 6. The walk times of Angus steers (A), serum concentrations of MLA (B), and of deltaline (C) at 24 hours after oral dosing with *D. barbeyi*.[23] A, Walk times (observed mean ± SEM) of 10 Angus steers that received an oral dose of MSAL-type alkaloids in the form of dried ground *D. barbeyi*. The walking times represent the steers being dosed with 8 mg/kg MSAL-type alkaloids as yearlings in 2016, and 2-year olds in 2017. The same 10 steers also received a dose of 10 mg/kg MSAL-type alkaloids in 2017 to evaluate if they still responded to larkspur alkaloids. The concentration of deltaline for the 8 mg/kg, 2017 dose in panel C was 3 ± 2 ng/mL.

of responses to larkspur and the distribution of responses from our experiments with Angus cattle suggests it may be possible to identify resistant animals and manage larkspur poisoning in cattle by selecting for resistance. Genetically resistant cattle could be selected for grazing on rangelands where larkspur occurs.

Cattle Age and Larkspur

Age is a factor in larkspur poisoning because ranchers report that replacement yearlings are most susceptible to larkspur intoxication.[23] Studies conducted by Pfister et al.[24] have shown that yearling heifers consume more larkspur than mature cows and that heifers tend to exhibit more severe clinical signs of larkspur intoxication. Similarly, the studies of Green et al.[23] with Angus steers have shown that as they age, they become more resistant to larkspur (Fig. 6A). Ten Angus steers were dosed with 8 mg/kg of MSAL-type alkaloids in the form of dried ground larkspur as yearlings and walked an average of 16.0 ± 5.3 minutes.[23] At two years of age, the same steers were dosed with the same concentration of MSAL-type alkaloids and they all walked for 40 minutes, which was a 24-minute increase.[23] This experiment suggests that over one year, the steers became more resistant to an 8-mg/kg MSAL-type alkaloids dose of larkspur.[23]

To determine if the steers still responded to larkspur, they were re-dosed with a 25% greater amount of larkspur alkaloids (i.e., 10 mg/kg dose of MSAL-type alkaloids). After which the steers walked an average of 8.8 ± 3.8 minutes. This suggests they were still susceptible to larkspur alkaloid toxicity, but at a higher dose.[23] Green et al.[23] also measured the concentrations of two larkspur alkaloids, deltaline and methyllycaconitine, in the blood (Fig. 6B and 6C). Differences were observed for both deltaline and methyllycaconitine concentrations between samples taken when the steers were yearlings and two-year olds. This indicates that as cattle age they can tolerate more larkspur in their diet. We do not know if resistance continues as animals get older, but we suspect that age-related differences in resistance will plateau at maturity. Further research is needed to better understand the biological mechanism underlying the observed age-dependent changes in animal susceptibility to larkspur alkaloids because age-related changes in susceptibility will result in more management options for livestock producers to reduce risk and cattle losses.

Cattle Sex and Larkspur

We learned from ranchers that the greatest losses from larkspur often occur in replacement heifers. Green et al.[25] has shown that young female cattle respond differently to larkspur than young males of the same breed. When 123 yearling Angus bulls, steers, and heifers were administered larkspur 8 mg/kg of MSAL-type alkaloids, the severity of the poisoning depended on the sex of the cattle (Fig. 7).[25] The yearling heifers walked significantly less time than either the bulls or the steers ($P < 0.05$).[25] We used these results to calculate the susceptibility of a heifer to larkspur intoxication and we found that heifers relative to bulls are 3.3 times more susceptible to larkspur ($P = 0.0008$, 95% CI 1.6–6.6).[25]

The differences between heifers and bulls could be explained by the estrogen-dependent differential expression of nAChRs, which are the target of larkspur toxins. For

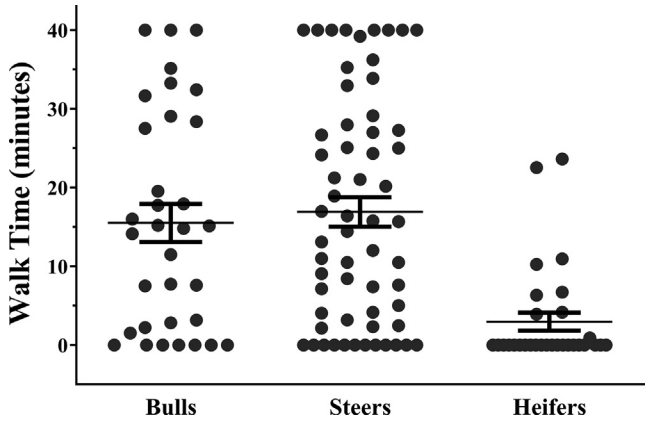

Figure 7. The observed mean ± SE represented by the vertical and horizontal lines of walk times for yearling Angus bulls ($n = 33$), Angus steers ($n = 60$), and Angus heifers ($n = 33$) dosed with 8 mg/kg of MSAL-type alkaloids of dried ground *D. barbeyi*.[25] A longer walk time corresponds to greater resistance to the toxic effects of larkspur. Fixed model analysis with censoring (censReg in R; R Core Team, 2013) was used to compare heifer to bull and steer walk times. Heifers walked 23.44 ± 4.47 minutes less than the average for bulls and steers ($P = 5.94 \times 10^{-7}$), while walking times for bulls and steers did not differ ($P = 0.55$).[19]

example, El-Mas et al.[26] have documented sex-dependent differences in the vasodilatory effects of nicotine in the kidneys of female rats, which was abolished by the estrogen-blocker tamoxifen. The greater susceptibility of yearling Angus heifers to larkspur indicates they must be more carefully managed than either bulls or steers on larkspur containing rangelands. However, a tolerable larkspur exposure limit is unknown for these cattle; it is also unknown when cattle should be removed from larkspur-containing pastures to prevent losses.

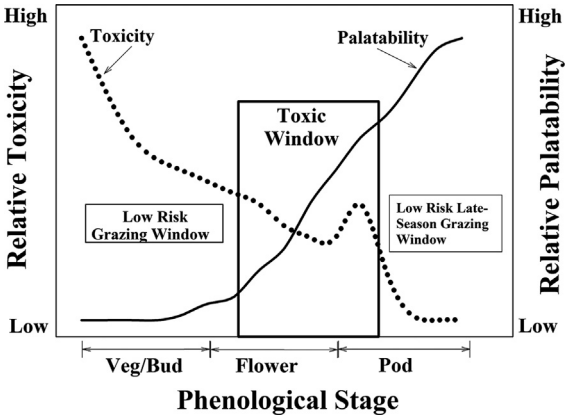

Figure 8. The *Delphinium* toxicity and palatability relationship in cattle from Pfister et al.,[1] which is used as a management guide for toxic tall larkspur-infested pastures. The toxic window is the plant growth stage when the concentration of toxic alkaloids is enough to intoxicate cattle, and larkspur consumption by cattle increases due to increased palatability. There are low-risk grazing windows early before flowering, during the veg/bud stage and late after the seedpods shatter during the pod stage.

Cattle Grazing of Larkspur

Cattle grazing on pastures with larkspur can be managed by chemical analysis of the larkspur alkaloid chemotype and alkaloid concentrations. For example, chemotypes with lower concentrations of MSAL-type alkaloids are managed differently than chemotypes with higher concentrations. Based on this knowledge plus the plant growth stage a window of toxicity can be determined using relative toxicity and relative palatability (Fig. 8). Pfister et al.[1] has shown, in general, that cattle begin to consume tall larkspur (*D. barbeyi* and *D. occidentale*, but not *D. glaucescens*) as it starts to flower and then matures to the pod stage. During the flower through pod stages, the alkaloid concentrations are high, which increases the risk of larkspur poisoning within the "toxic window" (Fig. 8).[1] The toxic window is about a five-week period of elevated plant toxicity that starts at the flower stage and ends after the pods have shattered.[1] To reduce the risk of larkspur poisoning, we recommend that cattle graze early in the summer until the larkspur flowers, which is typically four to six weeks depending on elevation, weather, and available forage.[1] After this time, which falls into the toxic window, we suggest producers remove cattle from larkspur-containing pastures. Cattle can return to graze these same pastures late in the season when the pods begin to shatter, and larkspur plants begin to dry out. This grazing scheme has been used to successfully reduce cattle exposure to toxic tall larkspur alkaloids when the risk of poisoning is greatest.

The concept of a toxic window is limited because it was developed based on grazing studies with steers with the assumption that all cattle respond to larkspur similarly (Fig. 8).[1] As described above, Green et al.[25] suggests that yearling heifers should be more carefully managed than either bulls or steers. However, currently the length of time (i.e., number of weeks) the toxic window exists is unknown for heifers. Also unknown is how older cattle or cow/calf pairs respond during the toxic window, although we speculate, they would be more resistant than a first-calf heifer and her calf.[25]

Low larkspurs are short-lived compared with tall larkspurs, and thus grazing management is simpler. Much of the potential for low larkspurs to kill cattle is related to their density (i.e., plants/square meter).[3] Cattle consume low larkspurs in proportion to their density, and if the density of low larkspurs is high (i.e., >5 plants/square meter), then the risk to cattle is much higher. In years with high densities of low larkspur, cattle producers can reduce risk by avoiding these larkspur-infested pastures for about 4 weeks until the plants have dried up.[3]

Conclusions

Our aim was to provide a brief review of basic information about larkspur and larkspur poisoning in cattle, and to describe recent research advances and solutions for larkspur poisoning in cattle. We emphasized the importance of plant chemotype, cattle age, and sex as contributing to cattle losses

and how these might be used to predict risk and develop management plans to avoid poisoning.

Declarations of Interest

None.

Acknowledgments

The authors thank Kermit Price, Scott Larsen, Anita McCollum, Ed Knoppel, Joseph Jacobsen, and Jessie Roper for their help with the larkspur experiments. This research was support by USDA/ARS.

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Authors are at the United States Department of Agriculture, Agricultural Research Service, Poisonous Plant Research Laboratory, Logan, UT, USA (Ben.Green@usgs.gov).