Does Plant Taxonomy Represent Toxic Risk?

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The Dose Makes the Poison

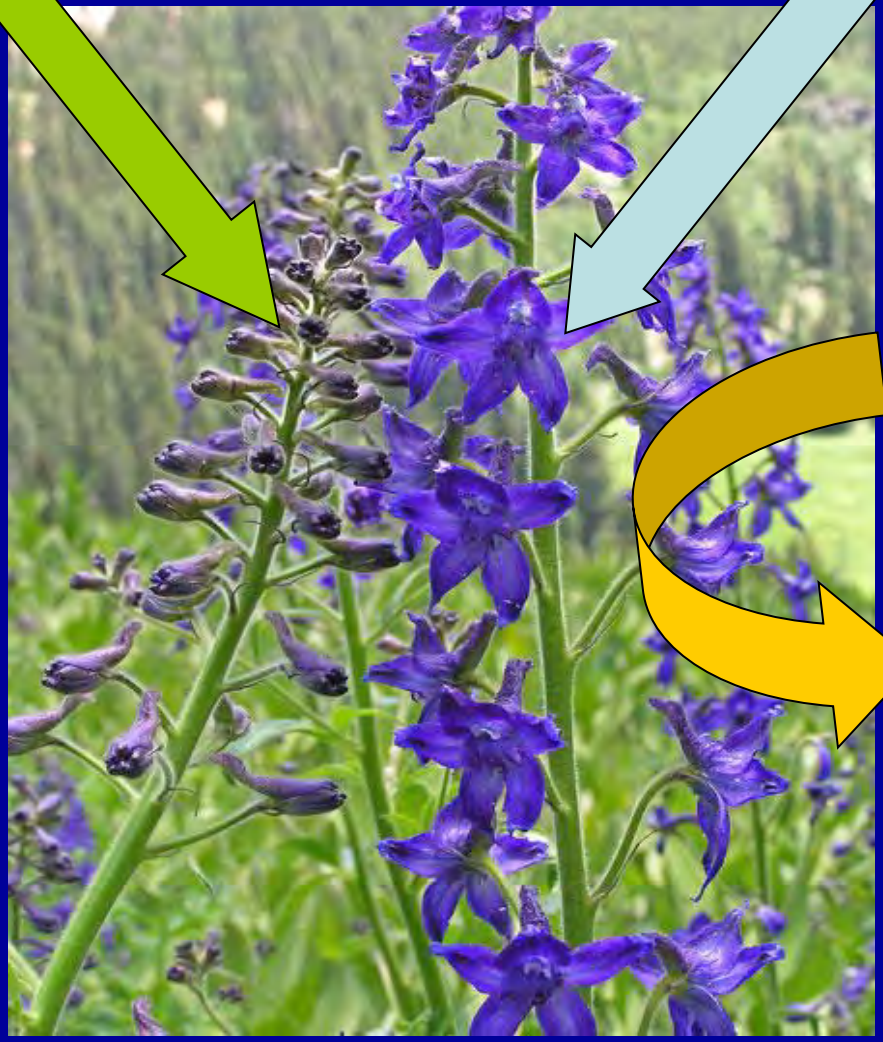
"All substances are poisons;
there is none which is not a poison.
The right dose differentiates a poison from a remedy."

Paracelsus (1493-1541)

Genotype

Genotype x Environment

Environment

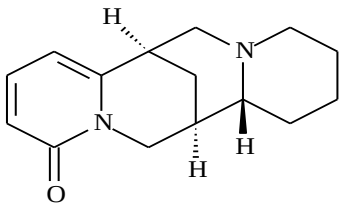


Chemical Phenotype

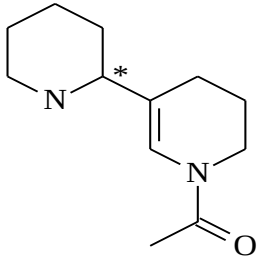
Quantitative and Qualitative

Lupine Induced Crooked-Calf Disease

Teratogenic Alkaloids



Anagyrine



Ammodendrine

-Not all Lupine species contain the teratogenic alkaloids

-Species are not uniform in their alkaloid composition

Malformations occur during days 40-100 of gestation

Lupine Induced Crooked-Calf Disease

Teratogenic Effects

Torticollis

Cleft Palate

Kyphosis

Objective

To characterize the alkaloids profiles of *L. sulphureus* throughout its geographical distribution

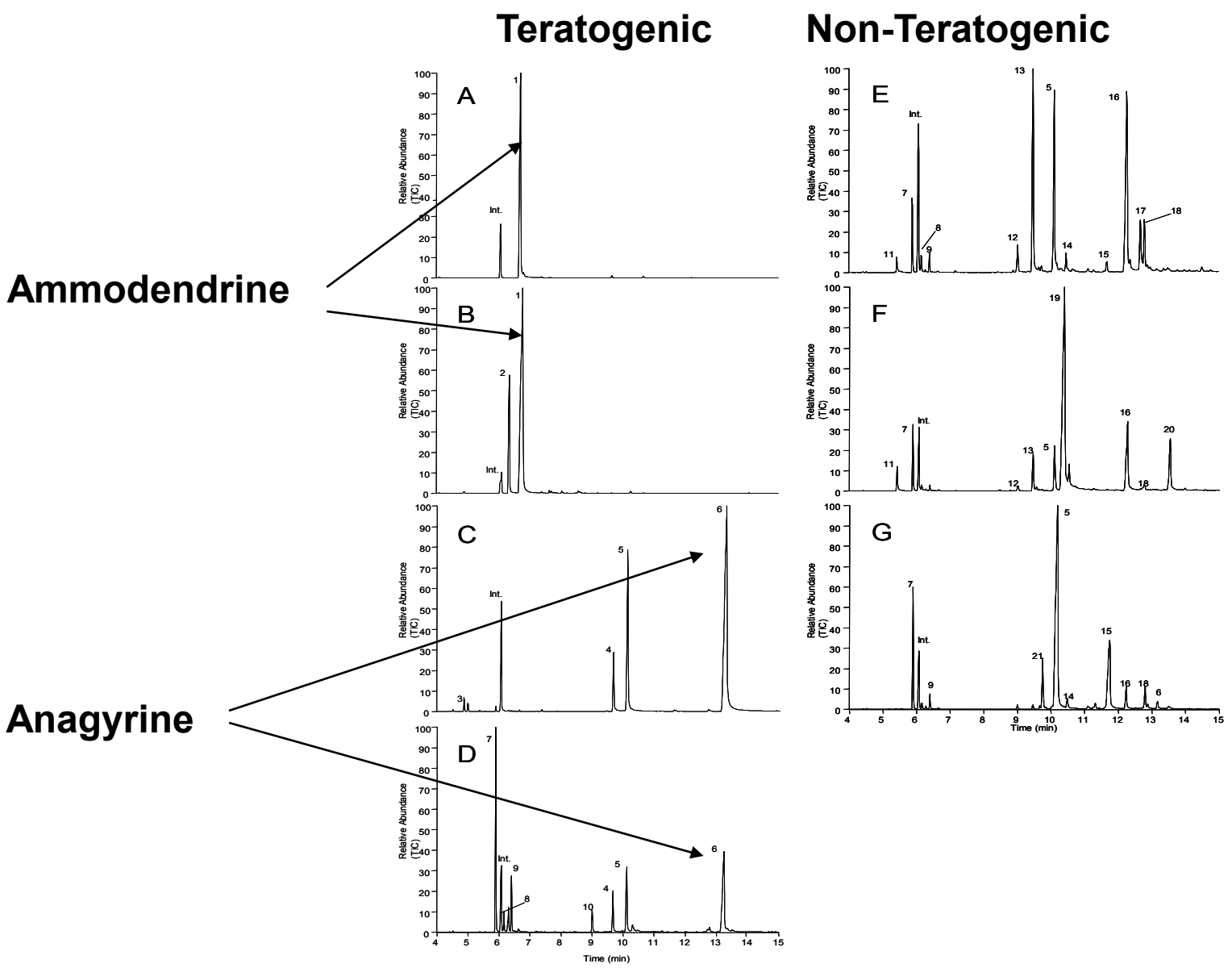
Experimental Design

-Plant Material
  - -Field Collections – 4 to 6 plants per population
  - -Herbarium Specimens from cooperating herbaria

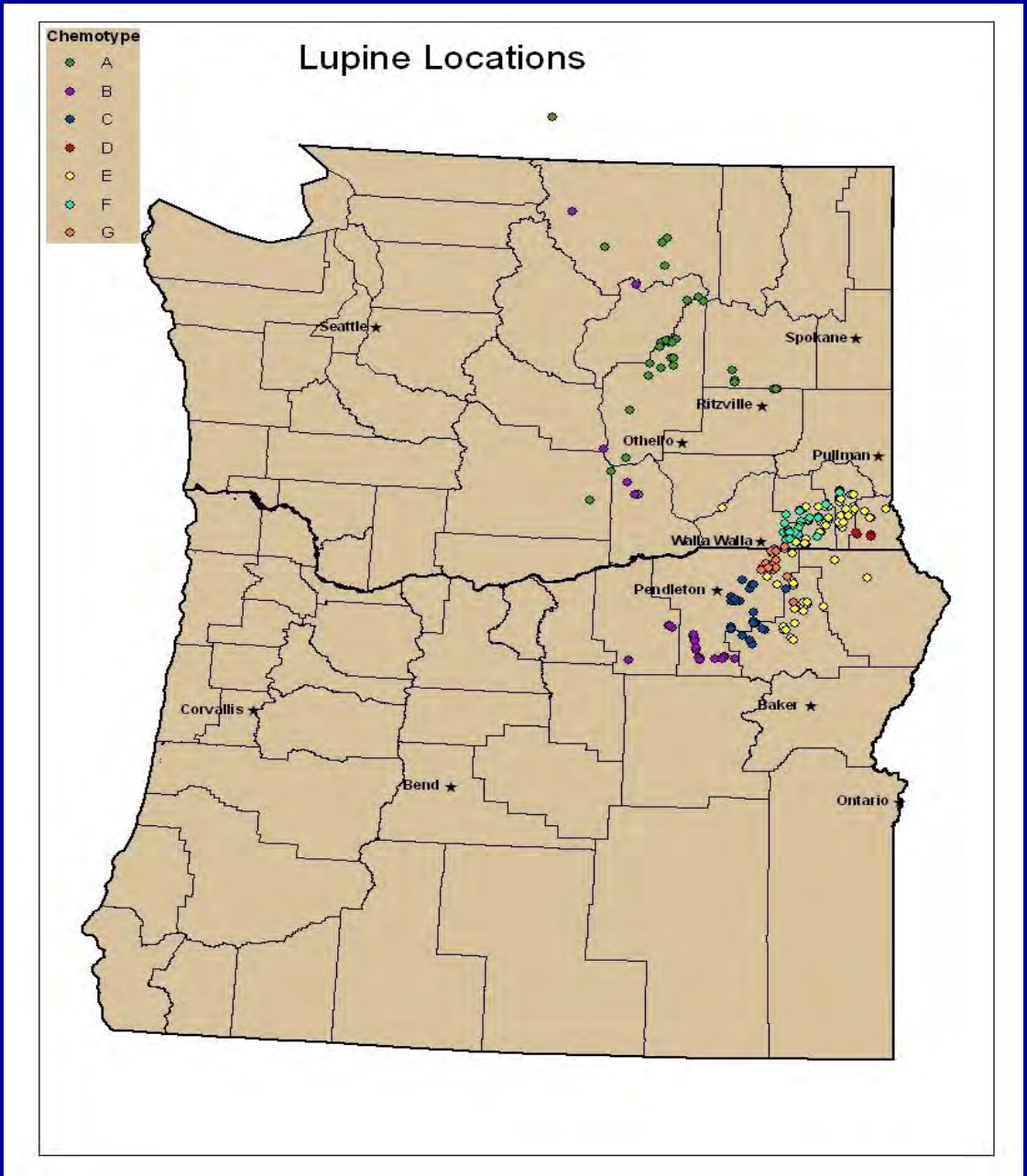
-Alkaloids Extracted and analyzed
  - -GC/FID for fingerprint determination
  - -GC/MS for alkaloid identification

-Fingerprints were defined by presence or absence of major alkaloids

Chemotypes of *Lupinus sulphureus*



Distribution of *Lupinus sulphureus* chemotypes



Tall larkspurs

-Tall larkspurs: found in mountain habitat in the western U.S. - generally moist sites - 6,000 to 10,000 feet elevation

-Tall larkspur sites typically snow-covered during winter

-Tall larkspurs grow in forb-dominated sites; very nutritious forage and high carrying capacity

Clinical signs of larkspur poisoning

-Staggering gait

-Muscular trembles

-Periodic sternal then lateral recumbency (this can lead to death for various reasons)

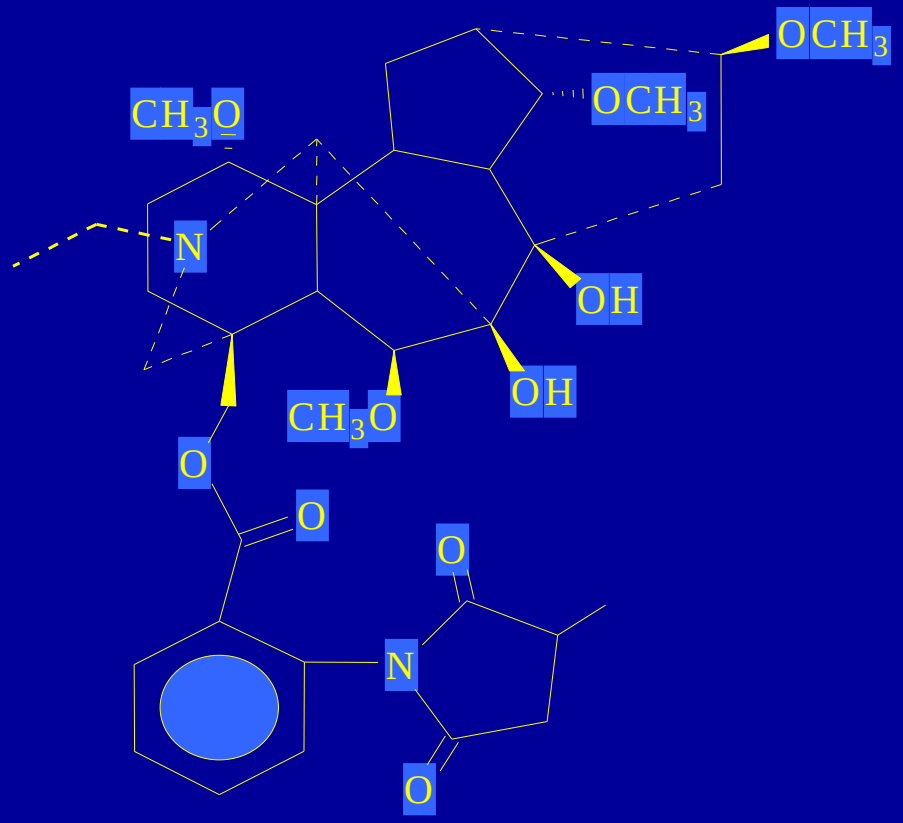
-Difficulty breathing (rapid and shallow)

-Death occurs from respiratory paralysis and/or bloat

How Does Larkspur Kill cows?

Answer: Neuromuscular paralysis

Dominant toxic alkaloid in larkspurs



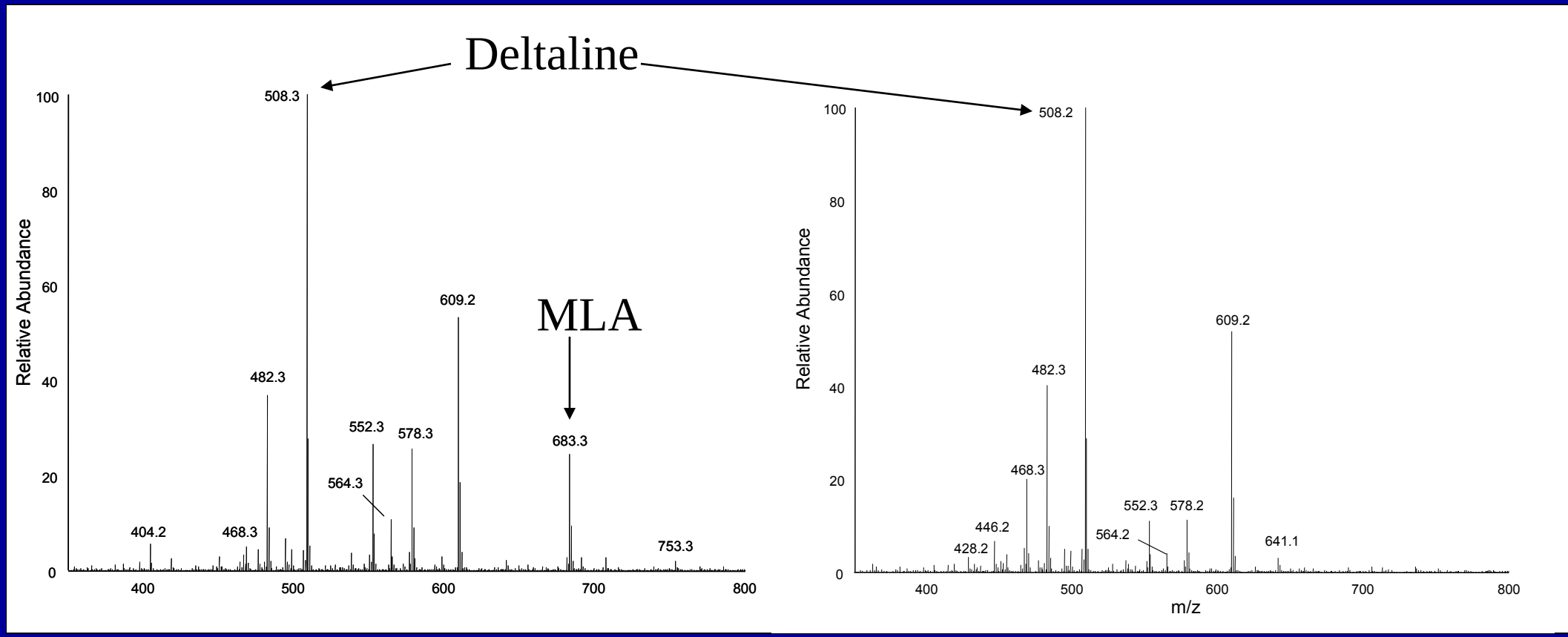
Methyllycaconitine

- There are numerous diterpenoid alkaloids in larkspurs (> 20)
- Ester function at C18 is very important for toxicity
- Deltaline most common alkaloid in tall larkspurs but not very toxic
  LD_{50}=110 mg/kg
- Methyllycaconitine = MLA
  LD_{50}=4 mg/kg

Objective:

To characterize the alkaloid profiles of *D. occidentale* throughout its geographical distribution.

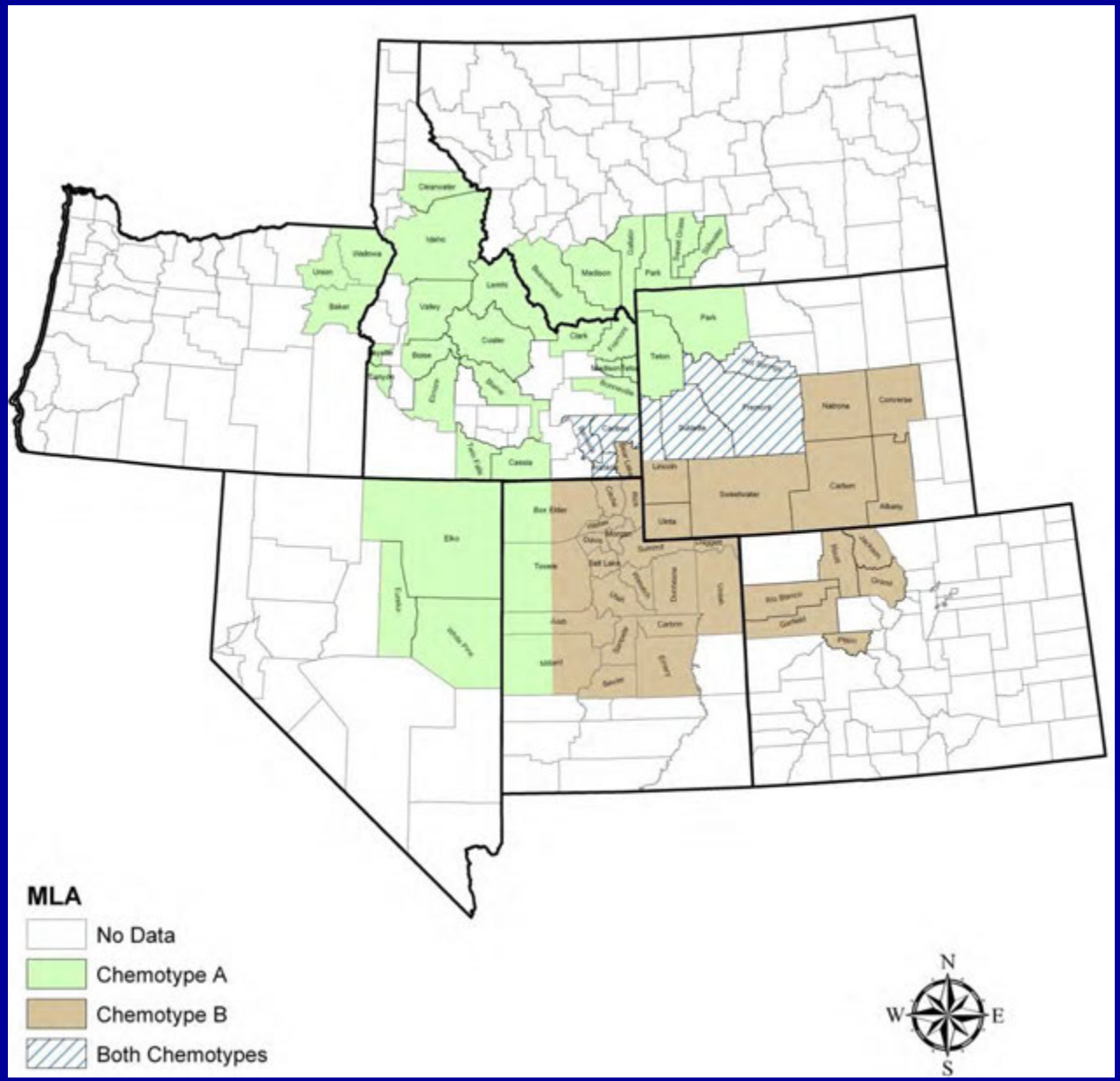
Electrospray mass spectra from samples representing each chemotype of *D. occidentale*



Chemotype A

Chemotype B

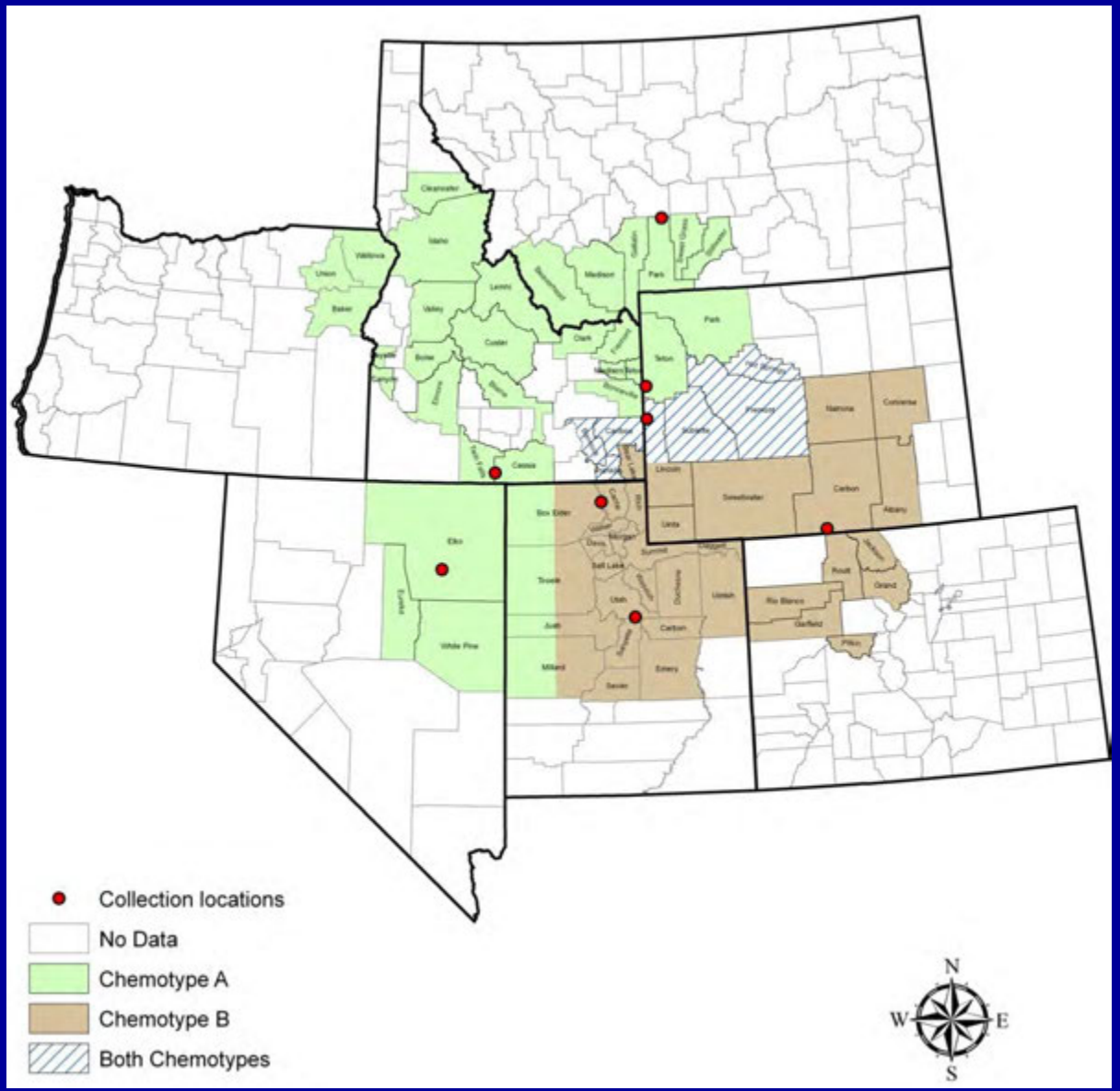
Distribution of chemotypes A and B of *D. occidentale*



Objective:

Do the chemotypes A (+MSAL) and B (-MSAL) of *D. occidentale* differ in their toxicity?

Collection Locations of chemotypes A and B of *D. occidentale*



Alkaloid composition of collections representing chemotypes A and B of *D. occidentale*

D. occidentale (City, State)	MSAL, mg/g	MDL, mg/g	Total Alkaloid, mg/g	MDL : MSAL
Wilsal, MT	2.7	8.0	10.7	3.0
Twin Falls, ID	2.9	5.3	8.2	1.8
Victor, ID	4.5	13.8	18.3	3.1
Elko, NV	6.3	11.1	17.4	1.8
Baggs, WY	0	14.7	14.7	
Fairview, UT	0	21.3	21.3	
Logan, UT	0	20.2	20.2	
Afton, WY	0	15.1	15.1	

Differential toxicity of chemotypes A and B of *D. occidentale* in mice

D. occidentale	LD_{50}		
(City, State)	mg Total Alkaloid / kg BW	mg MSAL / kg BW	plant material (g) / kg B.W.[2]
Wilsal, MT	9.6±0.8[c]	2.4 ±0.2[a]	0.9
Twin Falls, ID	6.2±0.6[d]	2.2 ±0.2[a]	0.8
Victor, ID	9.8±0.4[c]	2.4 ±0.1[a]	0.5
Elko, NV	6.2±1.4[d]	2.2 ±0.5[a]	0.4
Baggs, WY	60.8 ±2.8[a]	N.A.	4.1
Fairview, UT	58.1 ±2.4[a]	N.A.	2.7
Logan, UT	55.3 ±7.1[a]	N.A.	2.7
Afton, WY	42.7 ±6.0[b]	N.A.	2.8

Differential toxicity of chemotypes A and B of *D. occidentale* in cattle

D. occidentale		Dose (mg/kg BW)	Heart Rate (bpm)[2]		Exercise to Collapse[3]	
(City, State)	Animals (#)	Total Alkaloid (MSAL)	Time (0)	Time (24)	Y/N (#)	Time (min)
Victor, ID	8	37.6 (8.8 MSAL)	74.5 ±7.7	99.8 ±13.5[a]	Y (12)	17 ±9.9
Logan, UT	8	37.6 (0 MSAL)	77.4 ±11.2	84.2 ±8.7	N (12)	N.A.

Locoweeds

Astragalus and *Oxytropis* species that contain the toxin swainsonine

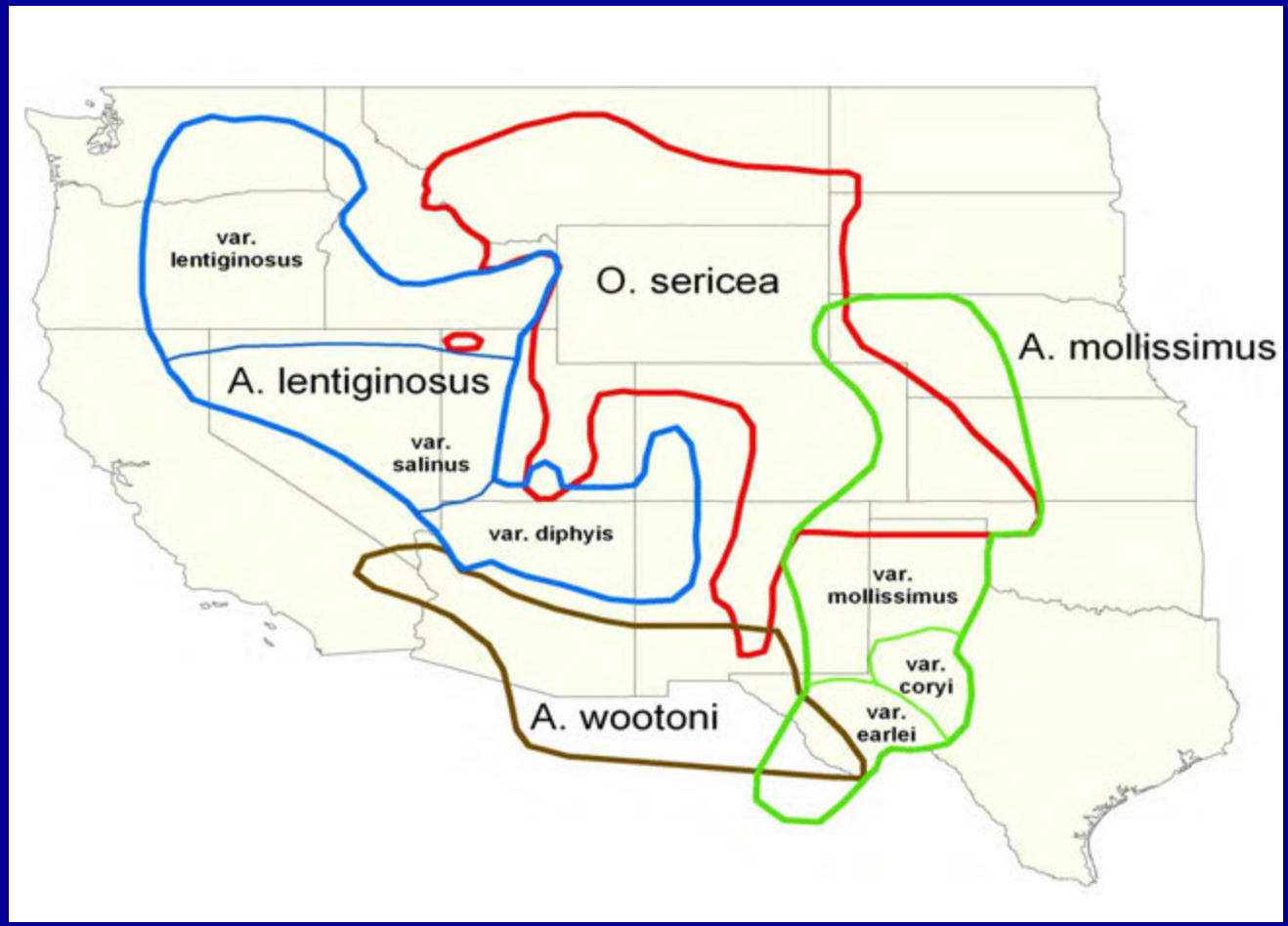
Oxytropis sericea
"White Point Loco"

Astragalus mollissimus
"Wooly Loco"

Astragalus lentiginosus
"Spotted Loco"

Two other toxic syndromes associated with Astragalus species: Selenium poisoning and nitrotoxins

Distribution of the Major Locoweed Species



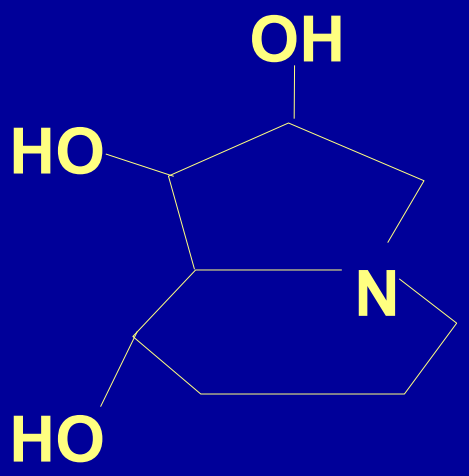
Rank Order of toxicity:

A. wootoni > A.mollissimus = A. lentiginosus > O. sericea

(garbancillo) (wooly loco) (spotted loco) (white point loco)

Locoweed Toxicology

Swainsonine



Inhibits

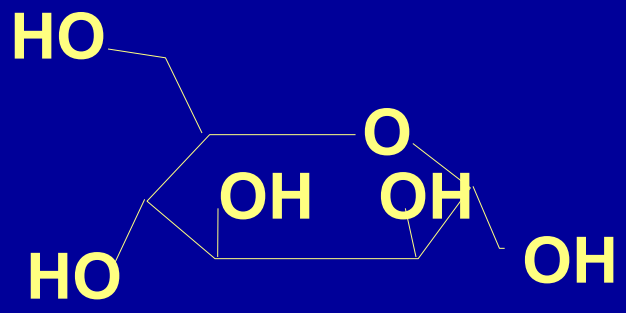
α **-Mannosidase**

Mannosidase II

Lysosomal Storage Disease

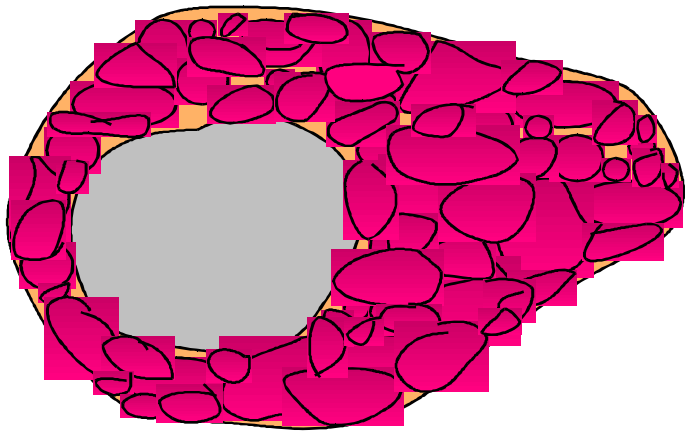
Altered Glycoprotein Synthesis

D-Mannose

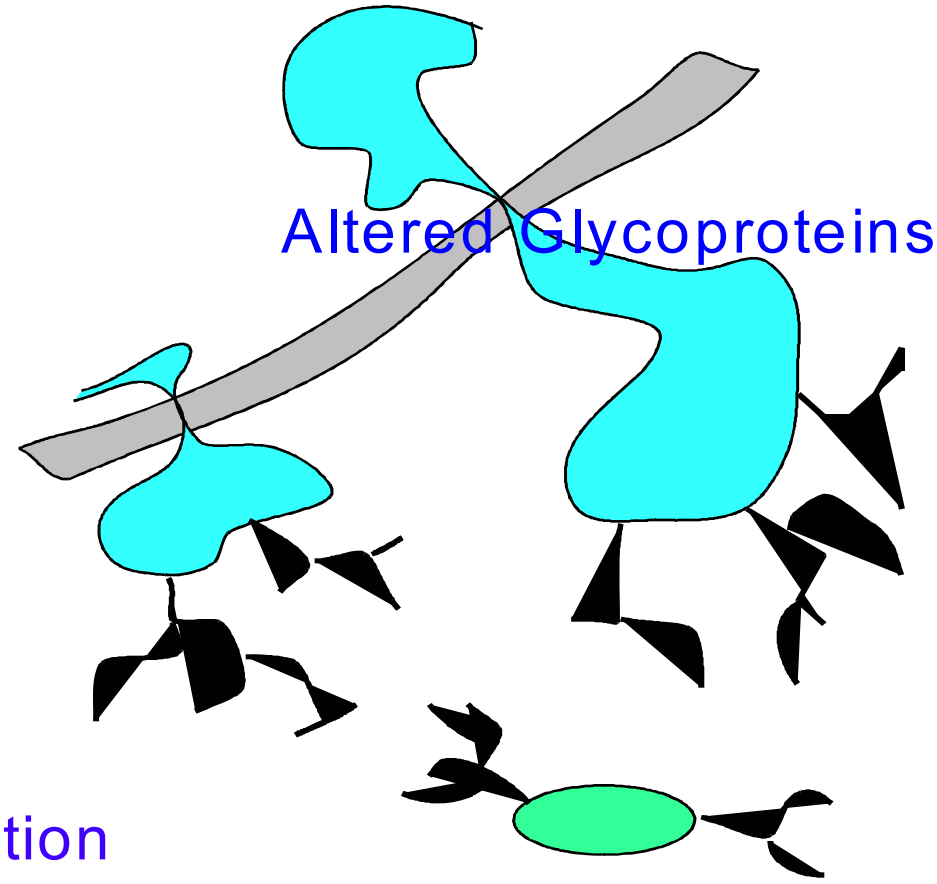


Locoweed Toxicology

α-Mannosidase Inhibition



Altered Glycoproteins



Cellular Constipation

Mannosidase II Inhibition

Clinical Signs of Locoism

-Weight Loss

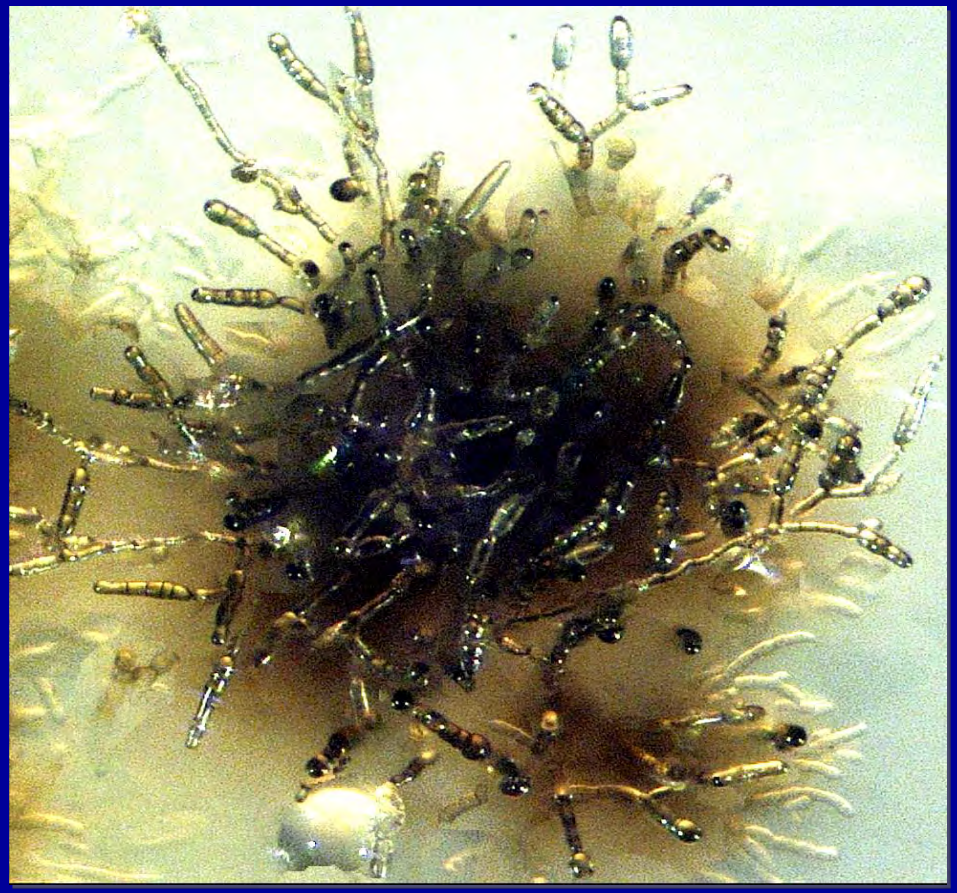
-Abnormal Behavior

-Reproductive Problems

-Wasting Type Condition

Locoweed Endophyte (*Undifilum oxytropis*)

- Fungal endophyte isolated from toxic locoweeds
- Produces swainsonine in culture
- Cultured from stems, leaves, seeds, and flowers of toxic field plants
- Localized to seed coat
- Embryo culture produces plants without swainsonine



Oxytropis lambertii and swainsonine

Table 3. *O. lambertii* Populations and Mean Swainsonine Concentration

location	*O. lambertii* var.	stage[a]	GPS coordinates	voucher no.[b]	mean[c] (% dry wt ± SD)	range
Meade, KS	*articulata*	pod	37° 10′ 09 N; 100° 23′ 03 W	27698	<0.0001	
Knowles, OK	*articulata*	early pod	36° 55′ 15 N; 100° 18′ 23 W	27689	<0.0001	
Buffalo, OK	*articulata*	pod	30° 48′ 44 N; 99° 46′ 22 W	27697	<0.0001	
Flagstaff, AZ	*bigelovii*	vegetative	35° 23′ 41 N; 111° 34′ 46 W	27665	0.054 ± 0.027	0.022−0.106
Springerville, AZ	*bigelovii*	vegetative	34° 00′ 49 N; 109° 10′ 48 W	27667	0.026 ± 0.021	0.0−0.065
Kingston, NM	*bigelovii*	vegetative	32° 52′ 51 N; 107° 51′ 55 W	27668	0.016 ± 0.013	0.0−0.043
Winston, NM	*bigelovii*	flower	33° 21′ 43 N; 107° 34′ 41 W	27669	0.038 ± 0.035	0.0−0.068
Kanab, UT	*bigelovii*	vegetative	37° 06′ 19 N; 111° 51′ 28 W	27661	0.008 ± 0.016	0.0−0.047
Ferron, UT	*bigelovii*	flower	39° 06′ 57 N; 111° 17′ 36 W	440983	<0.0001	
Fort Collins, CO	*bigelovii*	flower	40° 56′ 39 N; 105° 15′ 33 W	440980	0.0002	
Ocate, NM	*bigelovii*	pod	36° 15′ 11 N; 105° 02′ 32 W	27672	0.0006	
Capulin, NM	*bigelovii*	flower	36° 41′ 25 N; 104° 08′ 35 W	440981	0.0001	
Sophia, NM	*bigelovii*	flower	36° 28′ 06 N; 103° 59′ 54 W	440982	<0.0001	
Sidney, NE	*lambertii*	flower	41° 09′ 18 N; 103° 05′ 27 W	27704	0.0007	
Hot Springs, SD	*lambertii*	flower	43° 24′ 35 N; 103° 26′ 23 W	27717	0.0001	
Lusk, WY	*lambertii*	flower	43° 05′ 12 N; 104° 19′ 36 W	27721	<0.0001	

[a] Phenological growth stages. [b] Voucher specimens deposited in Monte L. Bean Herbarium, Brigham Young University, Provo, UT. [c] For those samples with initial swainsoine levels at <0.001%, a separate bulk sample was analyzed with quantitation down to 0.0001% (1 ppm) and the presence of swainsonine confirmed by GC-MS.

Oxytropis lambertii and swainsonine

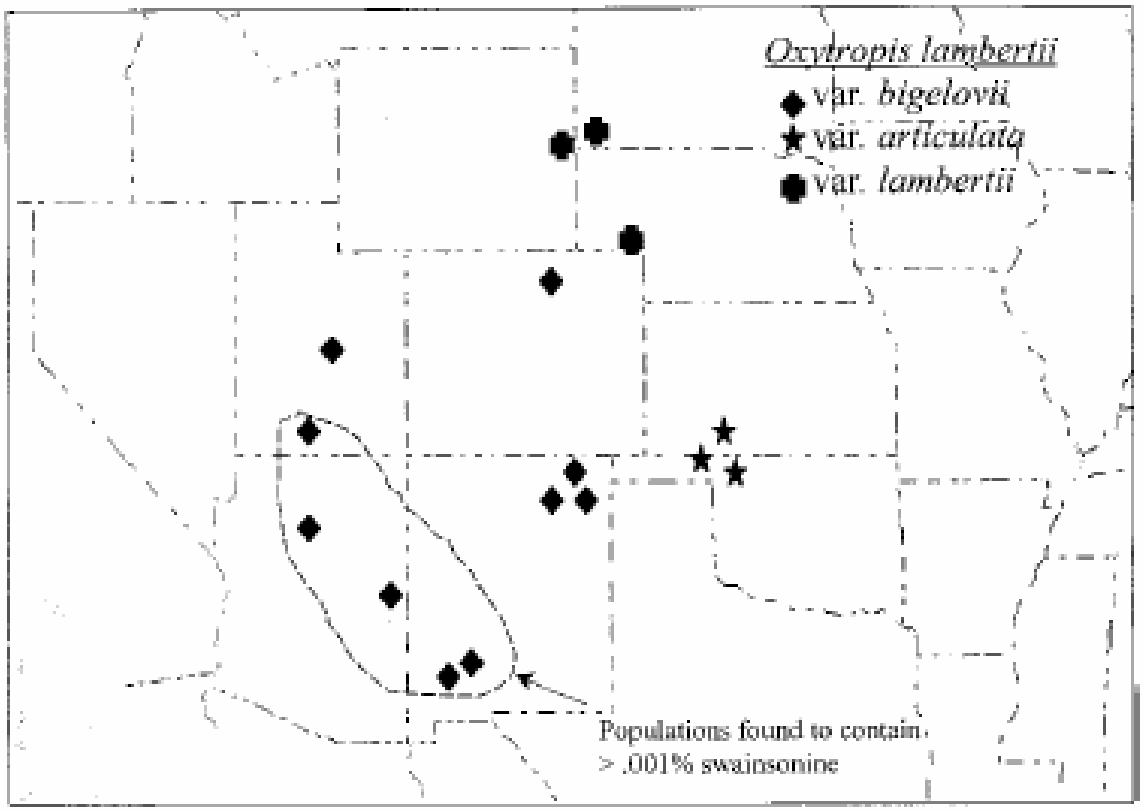


Figure 3. Map showing the 16 locations for collection of *O. lambertii* var. *lambertii*, *articulata*, and *bigelovii* from western United States.

Acknowledgements

-USDA ARS

-The PPRL staff