Published December 4, 2014

# Pharmacokinetic differences in exposure to camphor after intraruminal dosing in selectively bred lines of goats[1]

**E. J. Campbell,*[2] R. A. Frost,† T. K. Mosley,‡ J. C. Mosley,† C. J. Lupton,§ C. A. Taylor Jr.,* J. W. Walker,§ D. F. Waldron,§ and J. Musser#**

*Texas AgriLife Research Center, Sonora 76950; †Department of Animal and Range Sciences, Montana State University, Bozeman 59717; ‡Montana State University Extension Service, Livingston 59047; §Texas AgriLife Research & Extension Center, San Angelo 76901; and #Department of Veterinary Pathobiology, Texas A&M University, College Station 77841

**ABSTRACT:** A pharmacokinetic dosing study with camphor was used to determine whether selection lines of high-juniper-consuming goats (HJC, n = 12) and low-juniper-consuming goats (LJC, n = 12) differed in their respective disposition kinetics. Postdosing plasma camphor concentrations were used to examine whether a timed single blood sample collected after intraruminal administration of camphor would be a useful screening test to aid in the identification of HJC. Yearling female Boer × Spanish goats (n = 24) received a single intraruminal dose of monoterpene cocktail (0.270 g/kg of BW) containing 4 different monoterpenes that represented their composition previously reported for Ashe juniper (*Juniperus ashei*). Camphor, the predominant monoterpene in Ashe juniper, was 49.6% of the mix and was the monoterpene analyzed for this study. Blood samples were taken at 15 time points from 0 to 8 h after dosing. Concentrations of camphor were measured in plasma using solid phase extraction and gas chromatography/flame-ionization detection analysis. Maximal plasma concentration of camphor was greater for LJC than HJC ($P = 0.01$), and area under the curve extrapolated to infinity was greater for LJC than HJC ($P < 0.01$). Total systemic exposure (area under the curve) to camphor was 5 times less in HJC goats. We conclude that 1) HJC goats possess internal mechanisms to reduce the bioavailability of camphor, and 2) a blood sample taken at 45 min or at 60 min after intraruminal administration of camphor may be useful for identifying HJC individual animals from within large populations of goats.

**Key words:** camphor, goat, juniper, monoterpene, pharmacokinetics



J. Anim. Sci. 2010. 88:2620–2626
doi:10.2527/jas.2009-2585

## INTRODUCTION

Juniper (*Juniperus* spp.) encroachment on western rangelands decreases livestock production (Taylor and Ralphs, 1992), water yield and quality (Hester et al., 1997), and wildlife habitat (Taylor, 2006). Targeted browsing by goats, often in concert with mechanical removal or prescribed fire, is an effective way to suppress juniper (Taylor, 2008). One limitation is that goats self-regulate their consumption of juniper due to the presence of aversive monoterpenes in its foliage (Riddle et al., 1996). Intake regulation is also inherently variable between individual goats (Riddle et al., 1996; Campbell et al., 2007b). If the variation is due to genetic control of physiological mechanisms, then juniper intake may be improved through selective breeding.

The application of pharmacological techniques has significantly advanced the field of plant-animal interactions (Sorenson et al., 2006). In particular, pharmacokinetic studies with brushtail possum (Boyle and McLean, 2005) and sheep (Dziba et al., 2006) have generated results illustrating relationships between systemic monoterpene concentrations and feeding behavior. A pharmacokinetic study offers a noninvasive technique with which to evaluate absorption, distribution, metabolism, and elimination of monoterpenes, thus gaining a better understanding of the physiological mechanisms driving juniper intake.

[1]This research was supported by the Joe Skeen Institute for Rangeland Restoration (USDA-Cooperative State Research, Education and Extension Service, College Station, TX), and Texas Food and Fibers Commission Project No. b-04-05-02. The authors are grateful to Nick Garza Robert Moen (Texas AgriLife Research, Sonora), Justin Epperson (Texas AgriLife Research, Barnhart), and Mike Pentecost (Texas AgriLife Research, Ozona) for assistance in the pharmacokinetic study, and to Sue Engdahl (Texas AgriLife Research, San Angelo) for assistance in the near-infrared spectroscopy sample analysis.

[2]Corresponding author: erika@sonoratx.net

Received October 16, 2009.
Accepted March 16, 2010.

The objective of the experiment reported here was to determine whether goats selected as high-juniper consumers (**HJC**) or low-juniper consumers (**LJC**) differed in their pharmacokinetic response to intraruminal dosing with camphor, the predominant monoterpene in Ashe juniper. In addition, the pharmacokinetic data were used to determine the ability of a single-point screening test to discriminate between HJC and LJC goats.

## MATERIALS AND METHODS

All procedures involving animals were approved by the Texas A&M University Institutional Agricultural Animal Care and Use Committee.

### *Study Site*

The study site for both experiments was the Texas AgriLife Research Station at Sonora (formerly the Texas A&M University Agricultural Experiment Station at Sonora, 30°15′ N, 100°33′ W) located in the western Edwards Plateau region of Texas. The research station consists of approximately 1,458 ha of rangeland composed of mixtures of grasses, forbs, and woody species. Vegetation on the ranch is characterized by dense, scattered live oak (*Quercus virginiana* Mill.) mottes with grass interspaces. The midgrass component of the grass interspaces is dominated by sideoats grama [*Bouteloua curtipendula* (Michx.) Torr.] and Wright's threeawn (*Aristida wrightii* Nash). Other important midgrasses include fall witchgrass [*Leptoloma cognatum* (Schult.) Chase], Texas wintergrass (*Stipa leucotricha* Trin. & Rupr.), and silver bluestem [*Bothriochloa saccharoides* (Sw.) Rydb.]. Common short grasses are curly-mesquite [*Hilaria belangeri* (Steud.) Nash] and red grama (*Bouteloua trifida* Thurb.). Honey mesquite (*Prosopis glandulosa* Torr.), Ashe, and redberry juniper are prominent woody species that are scattered through the grass interspaces in a savanna-like fashion.

### *Breeding Program*

A selective breeding program was initiated in 2003 to identify sires and dams with the capacity to produce juniper-consuming offspring (Campbell et al., 2007a). These divergent lines were created through 3 yr of annual matings (Waldron et al., 2009). Selection was based on variation among predictions of genetic merit for individual animals from fecal near-infrared spectroscopy estimates of juniper consumption in the pasture environment (Walker et al., 2007).

### *Animals*

Animals were maintained as a group on pasture throughout the year before the dosing experiment. Juniper intake by goats was estimated using near-infrared spectroscopy predictions of fecal samples (Walker et al., 2007) collected when the goats were free grazing on juniper-infested pastures. Genetic merit was calculated using an animal model (Waldron et al., 2009) with intake values from 606 records of 368 goats. The model included fixed effects for age of goat (1, 2, or 3+ yr) and date of sample collection and a random effect for animal.

All animals were sampled on the same day within a year. These values were used to select 12 HJC goats (estimated juniper intake as percentage of diet = 31.2 ± 6.2; estimated genetic merit = +2.6 ± 0.6%) and 12 LJC goats (estimated juniper intake as percentage of diet = 18.6 ± 4.6; estimated genetic merit = −2.1 ± 0.9%). These groups contained the goats with the most extreme breeding values from both sides of the distribution of our source flock of 60 Boer × Spanish yearling nanny goats. All test animals were 12 mo of age and in similar nongestational reproductive status. All goats were housed in metabolism pens (1.5 × 1.0 m) and individually fed a maintenance ration (2.5% BW DM basis) of 100% alfalfa pellets.

### *Rumen Dosing*

The dose was chosen to represent the concentration and composition of monoterpenes present in Ashe juniper leaves (Riddle et al., 1996), the predominant juniper species at the study site. The dose was chosen to be biologically relevant to the monoterpene concentration present in a diet of 30% juniper, which is a quantity of intake identified through previous research as eliciting differences in juniper intake between breeding groups of goats (Campbell et al., 2007b).

Goats were fasted the night before the dosing treatment. An Abbocath-T (18-ga × 5-cm) indwelling intravenous jugular catheter (Abbott Labs, Abbott Park, IL) was inserted for sample collection. At 0900 h, goats (BW = 23.64 kg ± 3.22; n = 24) received a single dose (0.534 mL/kg of BW) of a monoterpene cocktail consisting of camphene (11.5%), limonene (20%), camphor (49.5%), and bornyl acetate (19%) mixed as a 50% solution in vegetable oil to enhance solubility. The dose provided the monoterpenes at 0.270 g/kg and individual oils at 0.031 g/kg (camphene), 0.054 g/kg (limonene), 0.134 g/kg (camphor), and 0.051 g/kg (bornyl acetate). Monoterpenes were purchased from Sigma-Aldrich (Milwaukee, WI). The dose was delivered directly into the rumen with an Abbocath–T 16-ga × 5-cm catheter needle.

Blood samples (10 mL each) were collected from the jugular catheter into lithium heparin-coated Vacutainer blood collection tubes (Becton, Dickinson and Company, Franklin Lakes, NJ) at 0, 1, 3, 6, 12, 18, 30, 45, 60, 90, 120, 180, 240, 360, and 480 min after the administration of the monoterpene cocktail. Heparinized 0.9% NaCl injectable solution (0.5 mL) was used to flush the catheter after each blood sample collection to prevent clotting, and 3 mL of blood was collected and discarded from the catheter before each collection. Samples were

stored on ice for transport to the laboratory, where they were centrifuged 45 min after collection.

### *Sample Analyses*

Concentrations of camphor were measured in plasma using solid phase extraction according to the method developed by Kimball et al. (2004) with a modification in plasma volume. After centrifugation (2,000 × *g* for 10 to 15 min at room temperature), 4 mL of plasma was aliquoted for solid phase extraction using Isolute Solid phase Extraction Columns (C18, 500-mg sorbent, 10-mL reservoir; Biotage, Charlottesville, VA). Blood camphor was identified and quantified using gas chromatography/flame-ionization detection analysis.

The chromatographic system consisted of a Perkin-Elmer Clarus 500 GC equipped with a flame ionization detector and an autosampler. The analytical column was a Restek Rtx-5 column (30 m × 0.25 mm × 0.25 μm) wall coated with 5% diphenyl polysiloxane (Bellefonte, PA). One microliter of sample was administered via splitless injection (split time of 0.5 min) under the following conditions: injection temperature of 200°C and detector temperature of 325°C. The initial oven temperature of 40°C was held for 0.5 min. The first oven ramp was at 5°C/min to 110°C. The final ramp was at 20°C/min to a final temperature of 300°C. The total run time was 24 min. The carrier gas was helium delivered at a constant rate of 39 cm/sec by using electronic pressure control. The detector gasses were hydrogen (45 mL/min) and air (450 mL/min).

To provide an analytical matrix match for the eluted samples, 5 camphor standards in ethyl acetate in the range of interest (1, 5, 10, 30, and 60 μg/mL) were injected into the gas chromatograph in triplicate. Linear regression analyses for the standards were used to verify linearity and consistency and were then used to calculate concentrations from the sample area obtained during the gas chromatography/flame ionization detection analyses.

### *Pharmacokinetic Analysis*

The data were analyzed using a pharmacokinetic data analysis program (PK Solutions 2.0, Summit Research Services, Montrose, CO) that utilized noncompartmental methods of analysis. Pharmacokinetic variables collected directly from the software were half-life of the terminal phase ($\boldsymbol{t_{1/2}\lambda_z}$), maximal concentration ($\mathbf{C_{MAX}}$), time of maximal concentration ($\mathbf{T_{MAX}}$), and area under the curve extrapolated to infinity ($\mathbf{AUC_{0\text{-}\infty}}$).

### *Statistical Analysis*

The pharmacokinetic variables of the individual goats (as the experimental units) in each group were used to determine the median and the first and third quartile values. A computerized statistical package (Statistix 7, Analytical Software, Tallahassee, FL) was used to compare the variables from the treatment groups by the Wilcoxon's rank sum test.

The plasma camphor concentrations of HJC and LJC goats were used to evaluate and determine screening guidelines for future plasma tests to screen for HJC goats. Sensitivity/specificity analysis and the evaluation of the predictive value of a positive test (**PPV**) and the predictive value of a negative test (**NPV**) were used to determine the optimal timed sampling point and the plasma concentration of camphor (i.e., the threshold value) to separate a HJC goat from a LJC goat (Stockham and Scott, 2008). The plasma camphor concentration threshold value was defined as the concentration at or below which the test is called positive for HJC and above which it is called negative. Both sensitivity/specificity and PPV/NPV analyses were evaluated as PPV and NPV are dependent upon trait prevalence in the population. Test sensitivity was defined as the frequency with which the test identified an HJC goat, a true positive, divided by all the HJC goats. Test specificity was defined as the frequency with which the test identified a LJC goat, a true negative, divided by all the LJC goats. The PPV is the probability that a positive test result (i.e., an animal with a plasma concentration at or less than the threshold value) indicates that the animal is truly a HJC goat. The NPV is the probability that a positive test result (i.e., an animal with a plasma concentration greater than the threshold value) indicates a truly LJC goat.

To calculate the sensitivity, specificity, PPV, and NPV at different sampling times, actual measured plasma concentration of camphor from each goat was used. A range of concentrations (0.05, 0.075, 0.1, or 0.15 μg/mL) was evaluated to determine an appropriate threshold value to use in a screening test. Because the true prevalence of HJC goats in the general population is unknown and may vary between herds, PPV and NPV were determined for prevalence levels of 1% HJC and 20% HJC goats in the population.

## RESULTS

The concentrations of camphene, limonene, bornyl acetate detected in the plasma were below reliable limits of detection. Only camphor results are reported because the initial dose of camphor, at 0.132 g/kg, could be reliably detected with a well-developed and validated analytical method for pharmacokinetic analysis of camphor (Kimball et al., 2004; Dziba et al., 2006).

Only 22 goats of the 24 dosed were used in final analyses. Two LJC goats were dropped from the study because none of the monoterpenes could be detected in their plasma.

Median plasma concentration-time curves for the LJC and HJC goats are presented in Figure 1. Pharmacokinetic variables (median, first, and third quartile) for LJC and HJC goats are summarized in Table 1. The $C_{MAX}$ for LJC goats and HJC goats was 0.644 and 0.100 μg/mL ($P = 0.01$), respectively, and the $AUC_{0\text{-}\infty}$ for

**Table 1.** Estimation of pharmacokinetic variables in high-juniper-consuming goats (HJC) and low-juniper-consuming goats (LJC) after the administration of 0.132 g/kg of camphor by intraruminal injection

| | | LJC goats (n = 10) | | | HJC goats (n = 12) | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Quartile | | | Quartile | | |
| Variable[1] | Units | Median | 1st | 3rd | Median | 1st | 3rd | *P*-value |
| $t_{1/2}\lambda_z$ | min | 95 | 85 | 111 | 70 | 50 | 94 | 0.177 |
| $C_{MAX}$ | μg/mL | 0.644 | 0.201 | 1.656 | 0.100 | 0.080 | 0.187 | 0.013 |
| $T_{MAX}$ | min | 48 | 36 | 59 | 48 | 35 | 55 | 0.943 |
| $AUC_{0-\infty}$ | μg·min/mL | 54.5 | 18.9 | 141.3 | 12.6 | 10.4 | 17.4 | 0.004 |

[1] $t_{1/2}\lambda_z$ = half-life of the terminal phase; $C_{MAX}$ = maximal concentration; $T_{MAX}$ = time of maximal concentration; $AUC_{0-\infty}$ = area under the curve extrapolated to infinity.

LJC goats and HJC goats was 54.5 and 12.6 μg·min/mL ($P < 0.01$), respectively. There was no difference for $t_{1/2}\lambda_z$ ($P = 0.18$) or $T_{MAX}$ ($P = 0.94$) between LJC goats and HJC goats.

Predictive statistics for different threshold values (0.05, 0.075, 0.100, 0.150 μg/mL) are summarized in Table 2. Prioritizing a greater sensitivity value will decrease the risk of missing a potential HJC sire in the test population. Conversely, prioritizing a greater specificity value will decrease the risk of incorrectly identifying an LJC sire as an HJC sire. The latter scenario is more acceptable for our breeding program, so the sampling time and threshold values corresponding to the greatest specificity (0.800) and subsequent greatest sensitivity (0.833) were selected. The optimal screening test design based on these data was when a blood sample was collected at 60 min and a concentration threshold value of 0.100 μg/mL was used.

When evaluating the screening test from the perspective of trait prevalence, again preference was given to acceptable risks for our breeding program. In our case, PPV was given priority over NPV. Evaluating these time and threshold points at a 1% prevalence level of HJC goats in the population, the positive and negative predictive values (0.040 and 0.998, respectively) for determining HJC goats were best. If the prevalence level of HJC goats was increased to 20%, which may be the case in a herd that had been selected for HJC, the

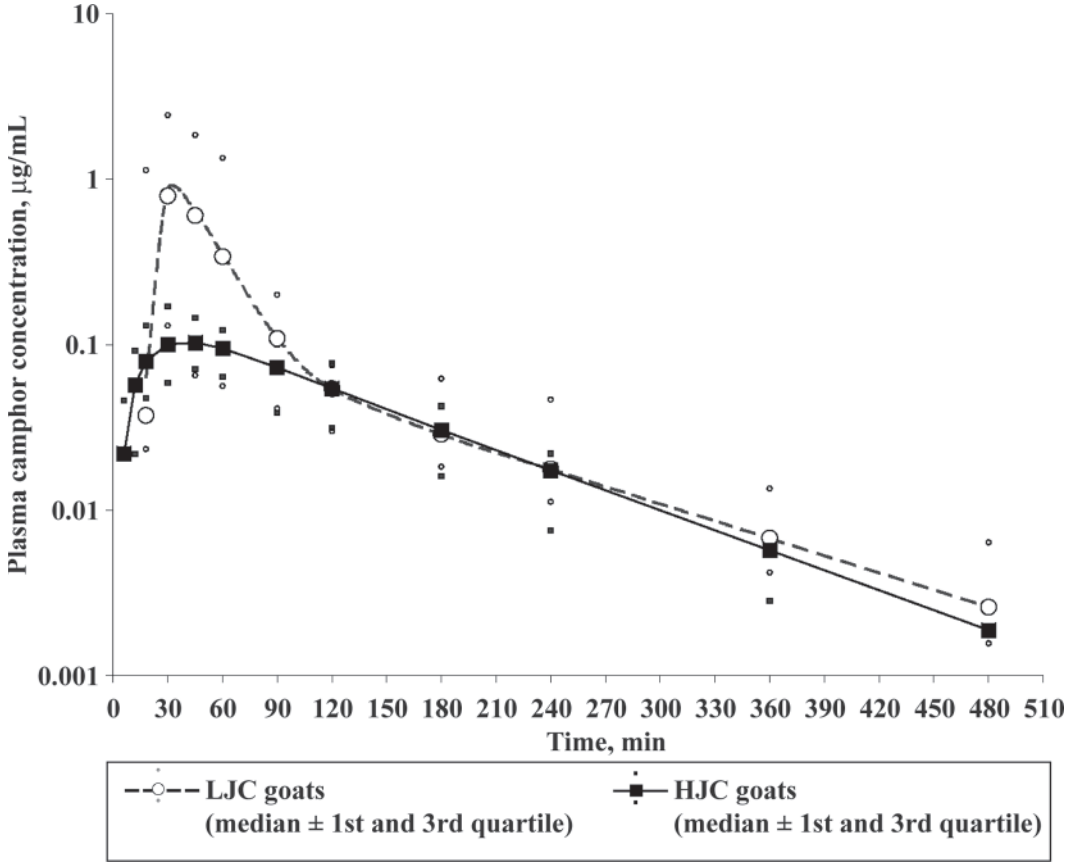


**Figure 1.** Median (±first and third quartile) plasma concentration time curve for low-juniper-consuming (LJC) goats (○) and high-juniper-consuming (HJC) goats (●) after intraruminal administration of camphor at 0.132 g/kg.

**Table 2.** Sensitivity, specificity, and positive and negative predictive values for a timed 1-sample collection using different concentration threshold values below which an animal is to be identified as a high-juniper-consuming goat (HJC)

| Camphor concentration threshold value, μg/mL | Time, min | Sensitivity | Specificity | 1% prevalence of HJC goats in test population | | 20% prevalence of HJC goats in test population | |
|---|---|---|---|---|---|---|---|
| | | | | PPV[1] | NPV[1] | PPV | NPV |
| 0.05 | 30 | 0.667 | 0.500 | 0.013 | 0.993 | 0.250 | 0.857 |
| | 45 | 0.083 | 0.800 | 0.004 | 0.989 | 0.094 | 0.777 |
| | 60 | 0.333 | 0.800 | 0.017 | 0.992 | 0.294 | 0.828 |
| | 90 | 0.455 | 0.800 | 0.022 | 0.993 | 0.363 | 0.854 |
| 0.075 | 30 | 0.833 | 0.400 | 0.014 | 0.996 | 0.258 | 0.905 |
| | 45 | 0.500 | 0.700 | 0.017 | 0.992 | 0.294 | 0.848 |
| | 60 | 0.500 | 0.800 | 0.025 | 0.994 | 0.385 | 0.865 |
| | 90 | 0.833 | 0.700 | 0.027 | 0.9976 | 0.410 | 0.944 |
| 0.100 | 30 | 0.833 | 0.400 | 0.019 | 0.996 | 0.258 | 0.905 |
| | 45 | 0.500 | 0.700 | 0.017 | 0.993 | 0.294 | 0.848 |
| | 60[2] | 0.833[2] | 0.800[2] | 0.040[2] | 0.998[2] | 0.510[2] | 0.950[2] |
| | 90 | 0.750 | 0.700 | 0.025 | 0.996 | 0.385 | 0.918 |
| 0.150 | 30 | 0.833 | 0.400 | 0.014 | 0.996 | 0.258 | 0.905 |
| | 45 | 0.750 | 0.700 | 0.025 | 0.996 | 0.385 | 0.918 |
| | 60 | 0.917 | 0.700 | 0.030 | 0.999 | 0.433 | 0.971 |
| | 90 | 0.917 | 0.500 | 0.018 | 0.998 | 0.314 | 0.960 |

[1]PPV = predictive value of a positive test; NPV = predictive value of a negative test.
[2]Greatest probability of correctly identifying HJC goats.

positive predictive value for identifying a HJC goats at the 60-min sampling point and using a threshold value of 0.100 μg/mL is 0.510 (Table 2).

## DISCUSSION

Results indicated that after a single intraruminal dose, the total systemic exposure to camphor, defined by AUC, was less in HJC than LJC goats, indicating less absorption. The HJC goats apparently possess internal mechanisms that reduce the relative bioavailability of camphor when compared with LJC goats. Rather than greater tolerance for monoterpenes, the HJC goats may have digestive or physiological mechanisms that reduce the systemic exposure resulting from ingestion of monoterpene-containing foliage. In contrast, LJC goats are exposed to a greater circulating dose and greater pharmacologic/toxic activity as more of the monoterpene is available to reach its target site and initiate the negative feedback loop resulting in cessation of feeding behavior.

Use of camphor as a representative monoterpene directly eliciting feeding deterrence is supported by intake studies with snowshoe hares (Sinclair et al., 1988) and sheep (Estell et al., 1998). Camphor is also quantitatively the major compound in Ashe juniper oil (Riddle et al., 1996) and thus likely to have a significant influence on herbivore deterrence.

Antiherbivory properties of monoterpenes in juniper appear to be associated with negative postingestive consequences specifically related to central nervous system triggers for cessation of feeding behavior or satiety. The satiety hypothesis (Provenza, 1995, 1996) and the detoxification-limitation hypothesis (Freeland and Janzen, 1974; Marsh et al., 2006) predict that increased plasma concentrations of phytotoxins induce cessation of feeding. Monoterpenes have been identified as initiating satiety-based feeding cessation in brushtail possums (*Trichosurus vulpecula*; Boyle and McLean, 2004; Marsh et al., 2005) and domestic sheep (Dziba et al., 2006). By selecting goats that exhibit an increased preference for juniper, we were potentially selecting animals with a greater pharmacological tolerance for the terpenoids in juniper, regardless of the specific tolerance mechanism.

Elimination fate of terpenoids in juniper involves hepatic biotransformation through oxidation to highly polar, acidic metabolites for excretion or conjugation with glycine (Wright, 1945), followed by glucuronic acid conjugation (McLean et al., 1993), with substrates varying by monoterpene and herbivore species. Expression of hepatic enzymes involved in oxidation and conjugation is variable in nature, due largely to the influence of genetics. Selective breeding programs for resistance to fescue toxicosis have been reported in sheep (Morris et al., 1989, 1995), cattle (Morris et al., 1998), and mice (Bhathal et al., 1990; Hohenboken and Blodgett, 1997). These selection programs resulted in hepatic microsomal enzyme-based resistance to ergot alkaloids in the fescue. Before this study was conducted, we assumed that the P450 enzyme-based elimination processes were being enhanced through the genetic selection of HJC goats (Campbell et al., 2007a). The similar $t_{1/2}\lambda_z$ between the HJC and LJC goats indicates that the mechanism responsible for differences in camphor bioavailability may not be more efficient hepatic detoxification (Shargel et al., 2005). In retrospect, reducing absorption rather than increasing elimination could be a more adaptive response because monoterpenes in juniper cause mild hepatic injury in the form of lipid

vacuolation at small dosages (0.18 g of oil/kg of BW) and hepatic cellular necrosis at greater dosages (0.36 g of oil/kg of BW; Straka, 2000).

It is interesting to note that the results of our study parallel results from dosing studies with herbivorous woodrats (*Neotoma* spp.; Sorensen and Dearing, 2003). Those authors reported interspecies differences in total exposure to α-pinene, the predominant monoterpene in oneseed juniper [*Juniperus monosperma* (Engelm.) Sarg.]. High-juniper-consuming woodrats (*N. stephensi*) had less total exposure to α-pinene than LJC woodrats (*N. albigula*), but elimination rates did not differ.

Further investigation of preabsorptive and absorptive processes is required to provide an explanation for differences in disposition kinetics between the 2 lines of goats. Review of the literature regarding pharmacokinetic differences in disposition of phytotoxins by herbivores reveals several possibilities for future study, including degradation by rumen microbes before absorption (Allison et al., 1990; Brooker et al., 1994; Duncan et al., 1997), epithelial first pass due to P450 enzyme systems (Watkins, 1997), and the presence of P-glycoprotein efflux transporters that limit absorption of phytotoxins from the gut (Green et al., 2004, 2006; Sorensen and Dearing, 2003, 2006). Future studies will seek to elucidate the exact mechanism involved as proposed in the absorption model (Sorensen and Dearing, 2006), where some herbivores minimize overall exposure to monoterpenes via decreased absorption in the gut rather than through more efficient liver detoxification or greater tissue distribution.

Macronutrient intake and body condition can affect disposition of phytotoxins in livestock such as alkaloids from lupine (*Lupinus* spp.; Lopez-Ortiz et al., 2004; Lee et al., 2008) and monoterpenes in goats (Campbell et al., 2007b; Frost, 2005). In this study, however, body condition and diet nutritive quality were controlled by experimental design, selecting study animals that grazed the same pastures, ate the same basal feed on an individual-animal basis during the preconditioning period, and were in the same nongestational reproductive status.

A broader goal of this research was to provide a physiological and external validation of the fecal near-infrared spectroscopy-based genetic breeding program. The observation of pharmacokinetic differences between the 2 lines supports the genetic selection program and potentially explains interindividual differences in preference for juniper.

As to whether identification of HJC goats can affect population characteristics to the point of effective management of juniper at the landscape level, Ellis et al. (2005) and Waldron et al. (2009) estimated heritability of juniper consumption to be 11 to 13%, indicating that progress from selection has the potential to change the population, but not rapidly. The theoretical expected response to selection is given by the product of the heritability and the selection differential. The response to selection can be increased by improving the accuracy of identifying goats with greater genetic merit for juniper consumption, which would result in a greater selection differential. Development of an accurate, rapid, and relatively noninvasive single-dose, single-sample screening test would allow breeders to screen large populations of goats for extreme outliers to best benefit breeding programs for brush control. The camphor challenge described in this study can provide a useful tool to this effect.

In summary, plants contain phytotoxins, making it necessary for all grazing and browsing animals to have evolved foraging strategies and internal mechanisms to mitigate phytotoxicosis. It is well established that foraging strategies learned from observation of maternal behavior greatly influence consumption of forage containing high concentrations of phytotoxins by goats (Frost et al., 2003; Glasser et al., 2009). Our results are the first to confirm that internal mechanisms in goats also play a role, and individual goats within a population differ in physiological mechanisms responsible for mitigation of phytotoxicosis. We established that 2 lines of goats, selectively bred to be high vs. low consumers of juniper, differ in their pharmacological abilities to tolerate camphor, the predominant monoterpene in Ashe juniper. Bioavailability of camphor, as represented by $AUC_{0\text{-}\infty}$ in the plasma concentration-time curves, was 5 times greater in low consumers despite equal intraruminal doses, thereby creating a greater potential for pharmacological action and negative postingestive feedback resulting in feeding cessation from greater concentrations of plasma camphor. Furthermore, a single blood sample taken at 60 min after intraruminal administration of camphor may be a useful screening test to identify HJC goats in other flocks.

## LITERATURE CITED

Allison, M. J., A. C. Hammond, and R. J. Jones. 1990. Detection of ruminal bacteria that degrade toxic dihydroxypyridine compounds produced from mimosine. Appl. Environ. Microbiol. 56:590–594.

Bhathal, P. S., T. W. Jordan, and I. R. Mackay. 1990. Mouse strain differences in susceptibility to sporidesmin-induced biliary tract injury. Liver 10:193–204.

Boyle, R. R., and S. McLean. 2005. Constraint of feeding by chronic ingestion of 1,8-cineole in the brushtail possum (*Trichosurus vulpecula*). J. Chem. Ecol. 30:757–775.

Brooker, J. D., L. A. Odonovan, I. Skene, K. Clarke, L. Blackall, and P. Musiera. 1999. *Streptococcus-caprinus* sp. nov., a tannin-resistant ruminal bacterium from feral goats. Lett. Appl. Microbiol. 18:313–318.

Campbell, E. S., B. S. Engdahl, C. J. Lupton, C. B. Scott, C. A. Taylor Jr., D. F. Waldron, J. W. Walker, and W. R. Whitworth. 2007a. The use of fecal NIRS to identify levels of consumption of the toxic shrub juniper in a selective breeding program with goats. Pages 386–393 in Poisonous Plants, Global Research Solutions. K. E. Panter, T. L. Wierenga, and J. A. Pfister, ed. CABI Publ., Cambridge, MA.

Campbell, E. S., C. A. Taylor Jr., J. W. Walker, C. J. Lupton, D. F. Waldron, and S. Y. Landau. 2007b. Effects of protein supplementation on juniper intake by goats. Rangeland Ecol. Manag. 60:588–595.

Duncan, A. J., P. Frutos, and S. A. Young. 1997. Rates of oxalic acid degradation in the rumen of sheep and goats in response to different levels of oxalic acid administration. Anim. Sci. 65:451–456.

Dziba, L. E., J. O. Hall, and F. D. Provenza. 2006. Feeding behavior of lambs in relation to kinetics of 1,8-cineole dosed intravenously or into the rumen. J. Chem. Ecol. 32:391–408.

Ellis, C. R., R. E. Jones, C. B. Scott, C. A. Taylor Jr., J. W. Walker, and D. E. Waldron. 2005. Sire influence on juniper consumption by goats. Rangeland Ecol. Manag. 58:324–328.

Estell, R. E., E. L. Fredrickson, M. R. Tellez, K. M. Havstad, W. L. Shupe, D. M. Anderson, and M. D. Remmenga. 1998. Effects of volatile compounds on consumption of alfalfa pellets by sheep. J. Anim. Sci. 76:228–233.

Freeland, W. J., and D. H. Janzen. 1974. Strategies in herbivory by mammals: The role of plant secondary compounds. Am. Nat. 108:269–286.

Frost, R. 2005. Age and body condition of goats influences consumption of redberry juniper (*Juniperus coahuilensis*) and disposition of four monoterpenes. PhD Diss. Univ. Idaho, Moscow.

Frost, R. A., K. L. Launchbaugh, and C. A. Taylor Jr.. 2008. Age and body condition of goats influences consumption of juniper and monoterpene treated feed. Rangeland Ecol. Manag. 61:48–54.

Frost, R. A., C. B. Scott, J. W. Walker, and F. S. Hartmann. 2003. Effects of orgin, genetics, and experiences early in life on bitterweed consumption by sheep. Appl. Anim. Behav. Sci. 84:251–264.

Glasser, T. A., E. D. Ungar, S. Y. Landau, A. Perevolotsky, H. Muklada, and J. W. Walker. 2009. Breed and maternal effects on the intake of tannin-rich browse by juvenile domestic goats (*Capra hircus*). Appl. Anim. Behav. Sci. 119:71–77.

Green, A. K., S. L. Haley, D. B. Barnes, M. D. Dearing, and W. H. Karasov. 2006. Is alpha-pinene a substrate for permeability-glycoprotein in wood rats? J. Chem. Ecol. 32:1197–1211.

Green, A. K., S. L. Haley, M. D. Dearing, D. B. Barnes, and W. H. Karasov. 2004. Intestinal capacity of P-glycoprotein is higher in the juniper specialist, *Neotoma stephensi*, than the sympatric generalist, *Neotoma albigula*. Comp. Biochem. Physiol. Part A 139:325–333.

Hester, J. W., T. L. Thurow, and C. A. Taylor Jr. 1997. Hydrological characteristics of vegetation types as affected by prescribed burning. J. Range Manage. 50:199–204.

Hohenboken, W. D., and D. J. Blodgett. 1997. Growth and physiological responses to toxicosis in lines of mice selected for resistance or susceptibility to endophyte-infected tall fescue in the diet. J. Anim. Sci. 75:2165–2173.

Kimball, B. A., L. E. Dziba, J. J. Johnston, and F. D. Provenza. 2004. Chromatographic analysis of sagebrush monoterpenes in blood plasma. J. Chromatogr. Sci. 42:245–249.

Lee, S. T., K. E. Panter, J. A. Pfister, D. R. Gardner, and K. D. Welch. 2008. The effect of body condition on serum concentrations of two teratogenic alkaloids (anagyrine and ammodendrine) from lupines (*Lupinus* species) that cause crooked calf disease. J. Anim. Sci. 86:2771–2778.

Lopez-Ortiz, S., K. E. Panter, J. A. Pfister, and K. L. Launchbaugh. 2004. The effect of body condition on disposition of alkaloids from silvery lupine (*Lupinus argenteus* Pursh) in sheep. J. Anim. Sci. 82:2798–2805.

Marsh, K. J., W. J. Foley, and I. R. Wallis. 2005. Detoxification rates constrain feeding in common brushtail possums (*Trichosurus vulpecula*). Ecology 86:2946–2954.

Marsh, K. J., I. R. Wallis, R. L. Andrew, and W. J. Foley. 2006. The detoxification limitation hypothesis: Where did it come from and where is it going? J. Chem. Ecol. 32:1247–1266.

McLean, S., W. J. Foley, N. W. Davies, S. Brandon, L. Duo, and A. J. Blackman. 1993. Metabolic fate of dietary terpenes from *Eucalyptus radiate* in common ringtail possum (*Pseudocheirus peregrinus*). J. Chem. Ecol. 19:1625–1643.

Morris, C. A., L. J. Burton, N. R. Towers, N. G. Cullen, J. M. Rendel, and D. L. Johnson. 1998. Genetics of susceptibility to facial eczema in Friesian and Jersey cattle. N. Z. J. Agric. Res. 41:347–357.

Morris, C. A., N. R. Towers, A. G. Campbell, H. H. Meyer, C. Wesselink, and M. Wheeler. 1989. Responses achieved in Romney flocks selected for or against susceptibility to facial eczema, 1975–87. N. Z. J. Agric. Res. 32:379–388.

Morris, C. A., N. R. Towers, M. Wheeler, and C. Wesselink. 1995. Selection for or against facial eczema susceptibility in Romney sheep, as monitored by serum concentrations of a liver enzyme. N. Z. J. Agric. Res. 38:211–219.

Provenza, F. D. 1995. Postingestive feedback as an elementary determinant of food preference and intake in ruminants. J. Range Manage. 48:2–17.

Provenza, F. D. 1996. Acquired aversions as the basis for varied diets of ruminants foraging on rangelands. J. Anim. Sci. 74:2010–2020.

Riddle, R. R., C. A. Taylor Jr., M. M. Kothmann, and J. E. Huston. 1996. Volatile oil contents of ashe and redberry juniper and its relationship to preference by Angora and Spanish goats. J. Range Manage. 49:35–41.

Shargel, L., S. Wu-Pong, and A. B. C. Yu. 2005. Hepatic elimination of drugs. Applied Biopharmaceutics and Pharmacokinetics. 5th ed. http://www.accesspharmacy.com/content.aspx?aID=2480547 Accessed Dec. 14, 2009.

Sinclair, A. R. E., M. K. Jogia, and R. J. Andersen. 1988. Camphor from juvenile white spruce as an antifeedant for snowshoe hares. J. Chem. Ecol. 14:1505–1514.

Sorensen, J. S., and M. D. Dearing. 2003. Elimination of plant toxins by herbivorous woodrats: Revisiting an explanation for dietary specialization in mammalian herbivores. Oecologia 134:88–94.

Sorensen, J. S., and M. D. Dearing. 2006. Efflux transporters as a novel herbivore countermechanism to plant chemical defenses. J. Chem. Ecol. 32:1181–1196.

Sorenson, J. S., M. M. Skopec, and M. D. Dearing. 2006. Application of pharmacological approaches to plant-mammal interactions. J. Chem. Ecol. 32:1229–1246.

Stockham, D. L., and M. A. Scott. 2008. Introductory concepts. Pages 4–51 in Fundamentals of Veterinary Clinical Pathology. 2nd ed. D. L. Stockham and M. A. Scott, ed. Blackwell Publ., Ames, IA.

Straka, E. J. 2000. The physiological effects of monoterpenes on Spanish and Angora goats. PhD Diss. Texas A&M Univ., College Station.

Taylor, C. A., Jr. 2006. Targeted grazing to manage fire risk. Pages 108–115 in Targeted Grazing: A Natural Approach to Vegetation Management and Livestock Enhancement. K. Launchbaugh and J. Walker, ed. Am. Sheep Ind. Assoc., Englewood, CO.

Taylor, C. A., Jr. 2008. Ecological consequences of using prescribed fire and herbivory to manage *Juniperus* encroachment. Pages 239–252 in Western North American *Juniperus* Communities: A Dynamic Vegetation Type. O. W. Van Auken, ed. Springer, New York, NY.

Taylor, C. A. Jr., and M. Ralphs. 1992. Reducing livestock losses from poisonous plants through grazing management. J. Range Manage. 45:9–12.

Waldron, D. F., C. A. Taylor Jr., J. W. Walker, E. S. Campbell, C. J. Lupton, T. D. Willingham, and S. Y. Landau. 2009. Heritability of juniper consumption in goats. J. Anim. Sci. 87:491–495.

Walker, J. W., E. S. Campbell, C. J. Lupton, C. A. Taylor Jr., D. F. Waldron, and S. Y. Landau. 2007. Effects of breed, sex, and age on the variation and ability of fecal near-infrared reflectance spectra to predict the composition of goat diets. J. Anim. Sci. 85:518–526.

Watkins, P. B. 1997. The barrier function of CYP3A4 and P-glycoprotein in the small bowel. Adv. Drug Deliv. Rev. 27:161–170.

Wright, W. E. 1945. Detoxication mechanisms in sheep. Dept. of Chem. Paper No. 25. Univ. Queensland, Brisbane, Australia.