

**Hypothesis test results for analysis of estrous cyclicity using the continuous-time Markov model**

Stage <sup>a</sup>	Comparison <sup>b</sup>	p-value <sup>c</sup>	Significance <sup>d</sup>	Stage Length Difference <sup>e</sup> (days)
Diestrus	Low-Control	0.089	None	-1.2
Diestrus	Mid-Control	0.198	None	-1.0
Diestrus	High-Control	0.446	None	-0.8
Estrus	Low-Control	0.011	p < 0.05	0.6
Estrus	Mid-Control	0.719	None	0.2
Estrus	High-Control	1.000	None	0.1
Metestrus	Low-Control	0.284	None	0.2
Metestrus	Mid-Control	0.233	None	0.2
Metestrus	High-Control	0.128	None	0.3

a: Insufficient data to evaluate proestrus stage.

b: Sample sizes for the Control, Low, Mid, and High dose groups respectively were  $n = 10, 10, 10, 10$ .  
Dose levels were 0, 1, 3, 10 mg/mL respectively.

c: The p-values shown were calculated using a permutation null hypothesis testing method and have been adjusted for multiple comparisons using a Hommel correction within each stage.

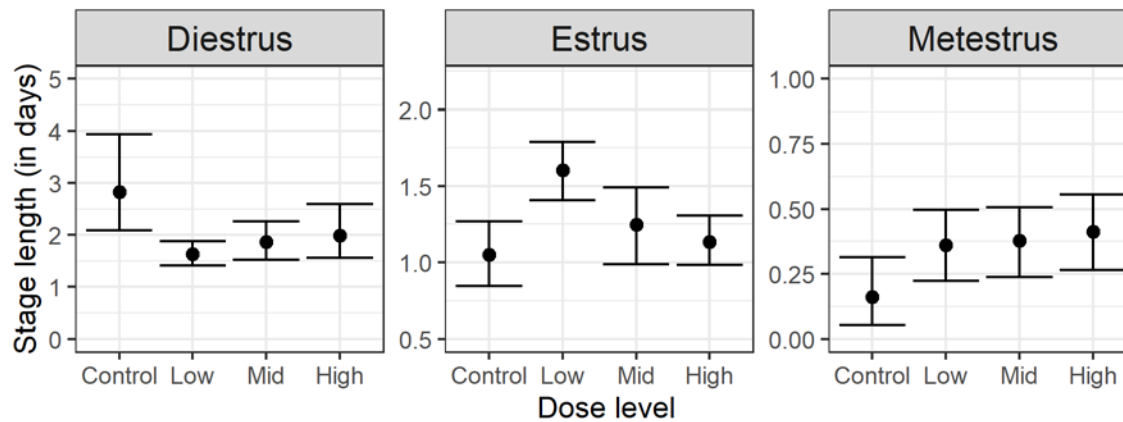
d: Significance is based on the adjusted p-value with a significance level of  $\alpha = 0.05$ .

e: A positive number indicates the estimated stage length in the treated group is longer than in the control group.

**Markov model estimates of stage length and 95% confidence intervals**

	Control (0 mg/mL)		Low dose (1 mg/mL)		Mid dose (3 mg/mL)		High dose (10 mg/mL)	
	Stage Length (days)	95% CI	Stage Length (days)	95% CI	Stage Length (days)	95% CI	Stage Length (days)	95% CI
Diestrus	2.8	(2.1, 3.9)	1.6	(1.4, 1.9)	1.9	(1.5, 2.3)	2.0	(1.6, 2.6)
Proestrus <sup>a</sup>	0.1	--	0.1	--	0.1	--	0.1	--
Estrus	1.0	(0.8, 1.3)	1.6	(1.4, 1.8)	1.2	(1.0, 1.5)	1.1	(1.0, 1.3)
Metestrus	0.2	(0.0, 0.3)	0.4	(0.2, 0.5)	0.4	(0.2, 0.5)	0.4	(0.3, 0.6)

a: Due to a very low number of observations of proestrus, stage lengths were estimated using a profile likelihood approach. As a result, confidence intervals are not available for the proestrus stage length estimate.



Estimates of stage length shown as dots, with bars indicating 95% confidence intervals. Estimates for lengths of proestrus are not shown here due to very low numbers of observations of this stage.