

**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><br>(days) |
|--------------------|-------------------------|----------------------|---------------------------|--|
| Diestrus           | Low-Control             | 0.915                | None                      | 1.0  |
| Diestrus           | Mid-Control             | 1.000                | None                      | -0.1   |
| Diestrus           | High-Control            | 0.399                | None                      | -0.9   |
| Proestrus          | Low-Control             | 0.153                | None                      | -0.2   |
| Proestrus          | Mid-Control             | 0.153                | None                      | -0.2   |
| Proestrus          | High-Control            | 0.018                | p < 0.05                  | -0.3   |
| Estrus             | Low-Control             | 1.000                | None                      | 0.0  |
| Estrus             | Mid-Control             | 1.000                | None                      | 0.1  |
| Estrus             | High-Control            | 1.000                | None                      | 0.1  |

a: Insufficient data to evaluate metestrus stage.

b: Sample sizes for the Control, Low, Mid, and High dose groups respectively were  $n = 10, 10, 10, 10$ . Dose levels were 0, 125, 250, 500 mg/L 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.

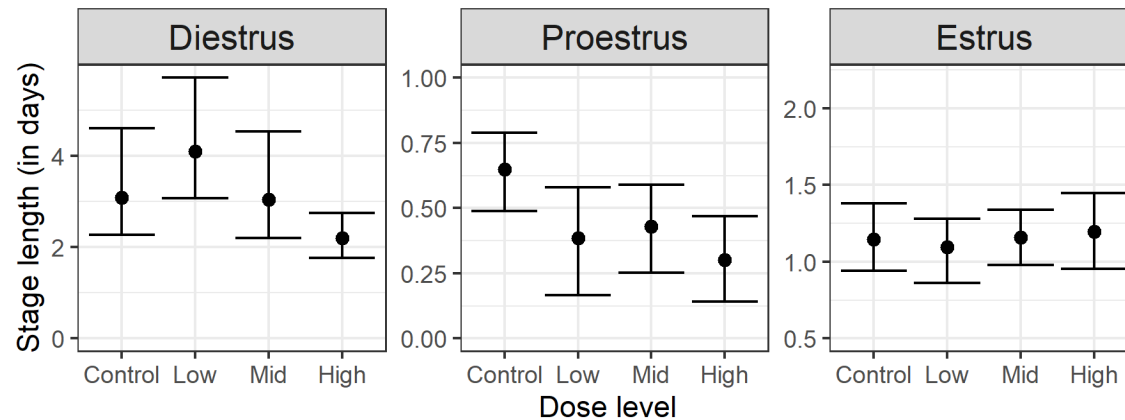
d: Significance is based on the adjusted p-value with a significance level of  $\alpha = 0.05$ .

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<br>(0 mg/L)    |            | Low dose<br>(125 mg/L) |            | Mid dose<br>(250 mg/L) |            | High dose<br>(500 mg/L) |            |
|------------------------|------------------------|------------|------------------------|------------|------------------------|------------|-------------------------|------------|
|                        | Stage Length<br>(days) | 95% CI     | Stage Length<br>(days) | 95% CI     | Stage Length<br>(days) | 95% CI     | Stage Length<br>(days)  | 95% CI     |
| Diestrus               | 3.1                    | (2.3, 4.6) | 4.1                    | (3.1, 5.7) | 3.0                    | (2.2, 4.5) | 2.2                     | (1.8, 2.7) |
| Proestrus              | 0.6                    | (0.5, 0.8) | 0.4                    | (0.2, 0.6) | 0.4                    | (0.2, 0.6) | 0.3                     | (0.1, 0.5) |
| Estrus                 | 1.1                    | (0.9, 1.4) | 1.1                    | (0.9, 1.3) | 1.2                    | (1.0, 1.3) | 1.2                     | (0.9, 1.4) |
| Metestrus <sup>a</sup> | 0.1                    | --         | 0.1                    | --         | 0.1                    | --         | 0.1                     | --         |

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



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