BMD Report for Ki67 labeling index in acetamide treated Wistar rats

A. Input data

Table 1. Ki67 labeling index (%) in livers of Wistar rats gavaged daily with acetamide.

Acetamide dose (mg/kg/day)	Ki67 labeling index (%)		
	Males, day 8	Males, day 29	Females, day 29
0	1.6	3.53	3.47
0	1.03	2.1	2.3
0	2.47	3.67	2.73
0	4.17	2.63	2
0	5.63	2.77	1.7
0	1.97	4.13	1.17
300	5.23	3.2	1.3
300	2.03	3.23	3.77
300	1.73	1.6	1.8
300	1.3	2.67	2.1
300	1.93	1.63	2.93
300	2.27	1.93	4.07
500	1.93	5.03	3.1
500	2.9	3.43	2.77
500	5.67	2.67	3.63
500	3.23	4.37	2.8
500	3.53	3.8	2.5
500	1.7	3.03	1.7
750	1.33	3.17	4.37
750	4.17	4.03	4.03
750	3.57	4.2	3.6
750	3.63	4.77	4.07
750	5.47	4.53	4.33
750	6.73	2.53	4.17
1000	4.1	3.47	3.8
1000	4	5.4	5.97
1000	1.53	3.97	3.9
1000	6.6	3.67	3.5
1000	5.37	4.07	6.07
1000	3.97	4.6	4.23
1500	4.6	5.7	7.37
1500	3.9	4.1	5.97
1500	6.6	37.50[b]	5.57
1500	5.8	6.07	5.63
1500	7.53	4.03	4.7
1500	7.17	4.47	4.9

[a]Determined to be an outlier based on Grubb's test for outliers. Value was omitted for BMD evaluation

B. BMR:
Percent change = 10% (0.1)

BMR for this analysis was determined based on effect size, maximum response, and within-group variation as described by Slob (2017). The following estimates were used (*see figure 1*):

M (maximum fold-change according to fitted model, variable c) = 2.196 to 2.297
s^2 (within-group SD related to the log-transformed observations) = 0.06856 – 0.2092 (mean = 0.1182)

"small" ES $M^{1/8}$ = ~1.1 (see table 2 of Slob (2017)), and therefore CES = 10% is suggested.

C. Software details
PROAST version 66.16 and R version 3.4.1 (2017-06-30)

D. Additional assumptions
None

E. Results

Convergence was achieved for all models and no errors were reported by the PROAST software. The criterion $AIC_{min} > AIC_{full} + 2$ was met for all models.

Table 2. Output from PROAST BMD analysis[a].

Model	# parameters (variance excluded)	AIC		$BMDL_{05}$ (mkd)		$BMDU_{05}$ (mkd)	
		Exponential	Hill	Exponential	Hill	Exponential	Hill
All treatments							
null model-v	4	131.22					
null model-av	6	134.82					
Model 3-v	6	77.92	77.88				
Model 3-av	8	80.94	80.9				
Model 3-bv	8	81.46	81.42				
Model 3-abv	10	79.6	79.56				
Model 5-v	7	75.7[b]	74.86[b]	190	217	492	497
Model 5-av	9	78.74	77.88				
Model 5-bv	9	79.34	78.48				
Model 5-abv	11	78.54	78.34				
Full model	19	101.42					
Full model-v	21	85.1					

AIC: Akaike information criterion; BMDL: lower confidence limit of the benchmark dose; BMDU: upper confidence limit of the benchmark dose.
[a]Outlier value removed for analysis.
[b]Selected model based on lowest AIC.

F. Figures of fitted models

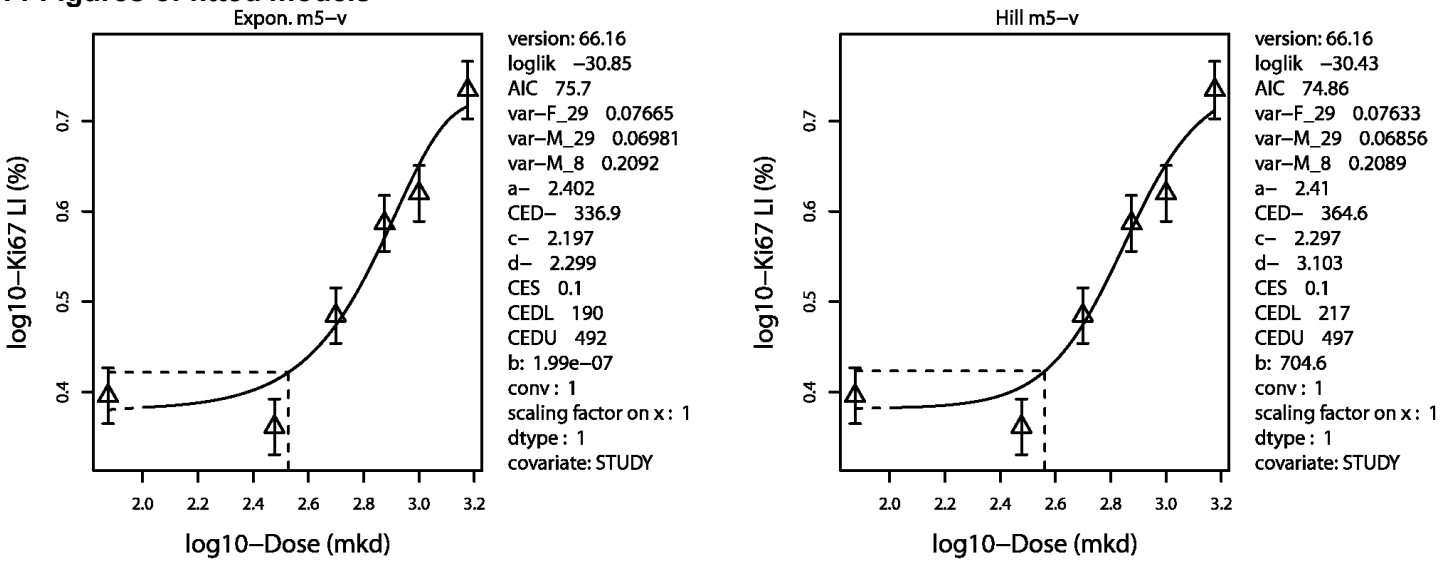

Figure 1. Fitted curves for model 5 - v (lowest AIC) from the exponential model family (left panel) and Hill model family (right panel). Points represent mean hepatic Ki67 labeling index their confidence interval. Dose is plotted on log-scale for better readability; the response in the controls is shown at an arbitrary lower level lower than the lowest non-zero dose.

G. Conclusion

Table 3 summarizes the best fit models (lowest AIC) for each sex and time-point, and their BMD confidence interval. Collectively, these data suggest a $BMDL_{10}$ of 190 mkd for the Ki67 labeling index. This value may serve as the potential RP.

Table 3. Summary of BMD confidence intervals for the hepatic Ki67 labeling index in Wistar rats gavaged daily with acetamide.

Treatment Group	Exponential			Hill		
	$BMDL_{10}$	**$BMDU_{10}$**	**Uncertainty (BMDU/BMDL)**	**$BMDL_{10}$**	**$BMDU_{10}$**	**Uncertainty (BMDU/BMDL)**
All groups	190	492	2.6	217	497	2.3

H. References

Slob, W. (2017). A general theory of effect size, and its consequences for defining the benchmark response (BMR) for continuous endpoints. *Critical reviews in toxicology* **47**(4), 342-351.