BMD Report for plasma ALT in acetamide treated Wistar rats

A. Input data

Table 1. Plasma ALT (U/L) of Wistar rats gavaged daily with acetamide.

Acetamide dose (mg/kg/day)	ALT (U/L)			
	Males, day 8	Males, day 29	Females, day 8	Females, day 29
0	44	54	45	49
0	36	46	40	32
0	51	43	41	36
0	42	36	43	56
0	38	43	40	39
0	46	42	35	38
300	36	39	45	38
300	29	47	47	35
300	45	46	36	39
300	35	46	44	29
300	67	38	42	36
300	46	44	30	44
500	42	42	34	37
500	39	40	48	49
500	54	51	37	38
500	46	54	50	36
500	56	47	42	30
500	48	51	39	38
750	51	43	42	46
750	50	51	52	43
750	62	40	39	42
750	50	41	41	55
750	62	34	50	38
750	41	39	39	40
1000	60	57	54	42
1000	55	28	42	41
1000	39	71	47	48
1000	85	58	60	66
1000	43	68	54	45
1000	48	49	50	45
1500	60	57	47	35
1500	48	47	52	236
1500	53	105	74	57
1500	65	58	52	51
1500	34	48	46	34
1500	74	65	61	107

B. BMR:
A conservative percent change of 10% was used for ALT (Slob, 2017).

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

D. Additional assumptions
Outlier values were not excluded as they corresponded with other measurements of liver damage, including ALT.

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.

Model	# parameters (variance excluded)	AIC		$BMDL_{05}$ (mkd)		$BMDU_{05}$ (mkd)	
		Exponential	Hill	Exponential	Hill	Exponential	Hill
All treatments							
null model-v	5	14.22					
null model-av	8	17					
Model 3-v	7	-25.08	-25.08[b]		393		933
Model 3-av	10	-23.48	-23.5				
Model 3-bv	10	-20.92	-20.92				
Model 3-abv	13	-20.1	-20.1				
Model 5-v	8	-25.22[b]	-24.94	509		897	
Model 5-av	11	-23.72	-23.42				
Model 5-bv	11	-23.62	-22.58				
Model 5-abv	14	-18.1	-18.1				
Full model	25	20.1					
Full model-v	28	-0.8					

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

F. Figure of fitted models

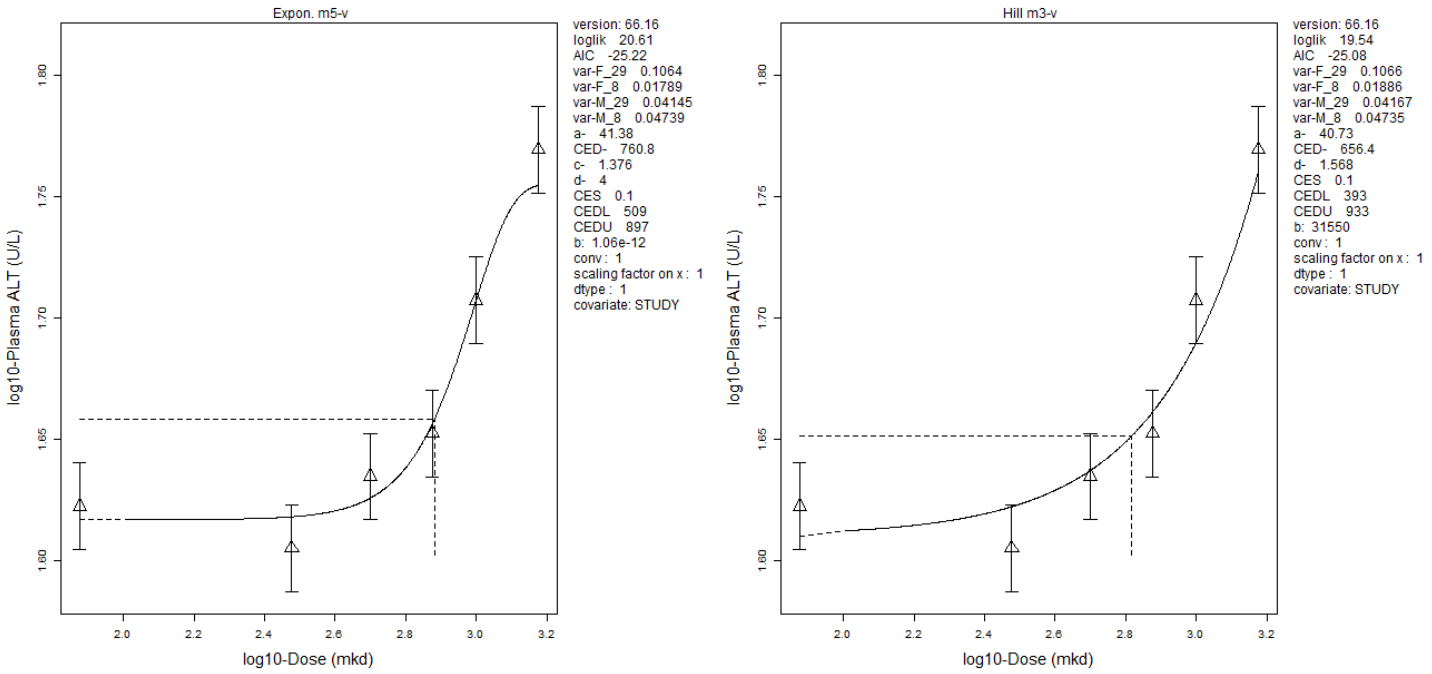

Figure 1. Fitted curves for model 5 - v (lowest AIC) from the exponential model family (left panel) and model 5 - v from the Hill model family (right panel). Points represent mean plasma ALT and their confidence interval. Dose is plotted on log-scale for better readability; the response in the controls 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 393 mkd for plasma ALT levels. This value may serve as the potential RP.

Table 3. Summary of BMD confidence intervals for plasma ALT measurements 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	509	897	1.8	393	933	2.4

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. PMID: 27805866