BENCHMARK DOSE MODELING REPORT FOR GENX

SUPPLEMENTAL DOCUMENTATION

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Prepared for:
North Carolina Secretaries' Science Advisory Board

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Foreword

The purpose of the supplemental documentation for the Benchmark Dose Modeling Report for GenX is to provide the North Carolina Secretaries' Science Advisory Board (SAB) with more information from the Benchmark Dose Software (BMDS) Wizard. Appendix B in the previously provided Benchmark Dose Modeling Report only included model outputs for models that met all model fit criteria. The N.C. Department of Health and Human Services (DHHS) updated the BMDS Wizard output reports to include all models that were run for each endpoint, regardless of if the model met all model fit criteria. For continuous data types, only models with appropriate variance (either constant variance or modeled variance) are included. This supplemental documentation does not alter the content or conclusions of the previously provided report, but does provide more information from the modeling software.

This supplemental documentation includes BMDS Wizard output reports for endpoints where no model outputs were included in the previous report. This is because no models met all model fit criteria and no BMDL was chosen. These endpoints include:

- Alkaline phosphatase in males (28-day mice and 2-year rat)
- Alanine aminotransferase in females (90-day mice) and males at 12 months (2-year rat)
- Sorbitol dehydrogenase in females (90-day mice)

Some endpoints were modeled with the BMDS Wizard, but no output reports for these endpoints are available because the neither constant variance nor modeled variance models fit the data, so all model output was unusable. These endpoints include:

- Hematocrit in males (90-day rat)
- Albumin to globulin ratio in males at 12 months (2-year rat)
- Alanine aminotransferase in males (28-day mice and 90-day mice)
- Sorbitol dehydrogenase in males (28-day mice and 90-day mice)
- Liver weight to brain weight in males (90-day rat) and females (reproductive mice)
- Combined fetal weights (Prenatal and developmental rat)

All data used for benchmark dose modeling can be found in Appendix A of the Benchmark Dose Modeling Report for GenX that was previously provided to the SAB.

CONTENTS

BMDS WIZARD OUTPUT REPORT

BMDS Summary of 28-Day Oral (Gavage) Toxicity Study of H-28397 in Mice with a 28-day Recovery – Hemoglobin (g/dL) in Males

1.1. BMDS Summary of Hemoglobin g/dL Males (28 Day Mice GenX)

Table 1. Summary of BMD Modeling Results for Hemoglobin in Males (28-Day Mice); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD$_{1SD}$ (mg/kg/day)	BMDL$_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2) Exponential (M3)[b]	0.0321	-4.9996	20.5	13.5	1.52	BMDLs from models that met model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values > 2.0; appropriate variance (continuous data only)) were compared. Selected BMDL is from model with lowest AIC and lowest BMDL.
Exponential (M4) Exponential (M5)[c]	0.241	-8.5015	2.08	0.0607	34.2	
Hill	**0.287**	**-8.7441**	**0.343**	**0.0492**	**6.97**	
Power[d] Polynomial 3°[e] Polynomial 2°[f] Linear	0.0315	-4.9610	20.8	13.9	1.50	

[a] Constant variance case presented (BMDS Test 2 *p*-value = 0.933), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 3, and 30 mg/kg/day were 0.16, -0.31, 0.79, -0.61, respectively.

[b] For the Exponential (M3) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M2) model.

[c] For the Exponential (M5) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M4) model.

[d] For the Power model, the power parameter estimate was 1. The models in this row reduced to the Linear model.

[e] For the Polynomial 3° model, the b3 coefficient estimates was 0 (boundary of parameters space). The models in this row reduced to the Polynomial 2° model. For the Polynomial 3° model, the b3 and b2 coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Linear model.

[f] For the Polynomial 2° model, the b2 coefficient estimate was 0 (boundary of parameters space). The models in this row reduced to the Linear model.

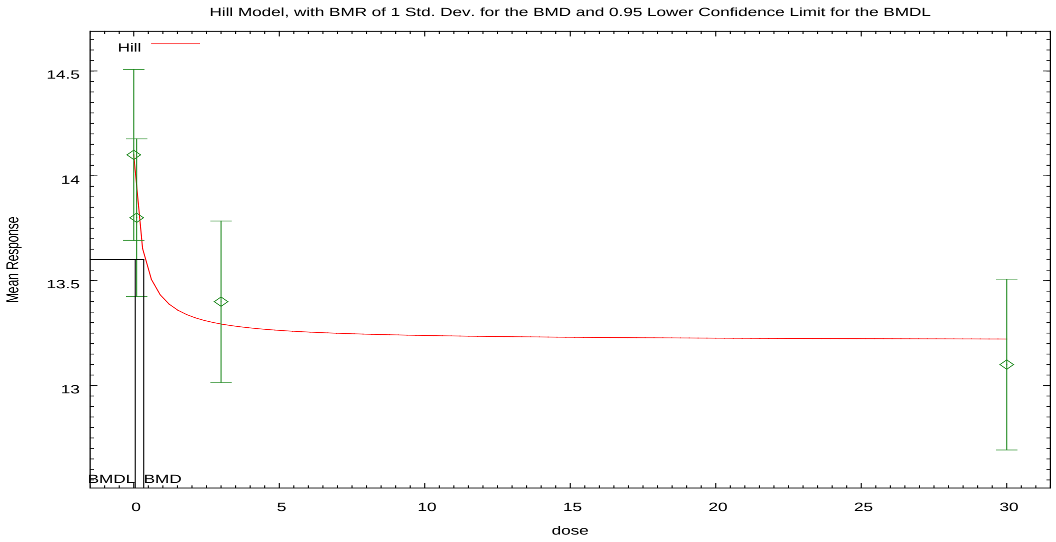

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Figure 1. Plot of mean response by dose with fitted curve for Hill model with constant variance for Hemoglobin in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 0.342989

BMDL at the 95% confidence level = 0.0491937

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.224816	0.246437
rho	n/a	0
intercept	14.0748	14.1
v	-0.887431	-1
n	1	0.796114
k	0.298961	1.55

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	9	14.1	14.1	0.53	0.47	0.159
0.1	8	13.8	13.9	0.45	0.47	-0.312
3	8	13.4	13.3	0.46	0.47	0.789
30	9	13.1	13.2	0.53	0.47	-0.608

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	8.938828	5	-7.877655

A2	9.156399	8	-2.312799
A3	8.938828	5	-7.877655
fitted	8.372034	4	-8.744068
R	-0.034215	2	4.068429

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	18.3812	6	0.005347
Test 2	0.435143	3	0.9329
Test 3	0.435143	3	0.9329
Test 4	1.13359	1	0.287

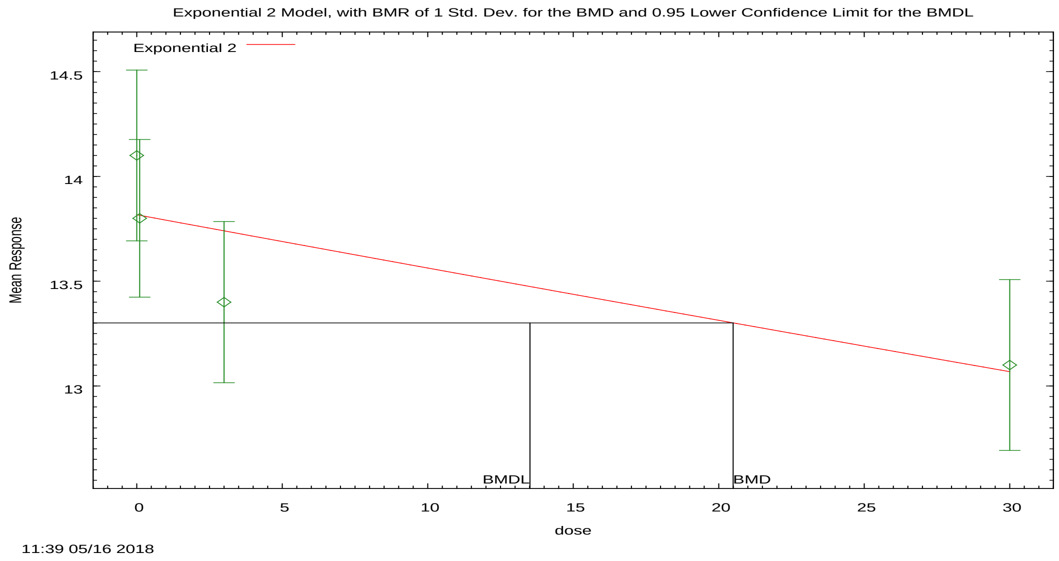

Figure 2. Plot of mean response by dose with fitted curve for Exponential (M2) model with constant variance for Hemoglobin in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 20.4946

BMDL at the 95% confidence level = 13.5131

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-1.32352	-1.52581
rho	n/a	0
a	13.8168	13.3792
b	0.00185691	0.00184061
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	9	14.1	13.82	0.53	0.52	1.647
0.1	8	13.8	13.81	0.45	0.52	-0.07817
3	8	13.4	13.74	0.46	0.52	-1.864
30	9	13.1	13.07	0.53	0.52	0.1851

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	8.938828	5	-7.877655
A2	9.156399	8	-2.312799
A3	8.938828	5	-7.877655
R	-0.03421454	2	4.068429
2	5.49979	3	-4.99958

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	18.38	6	0.005347
Test 2	0.4351	3	0.9329

Test 3	0.4351	3	0.9329
Test 4	6.878	2	0.0321

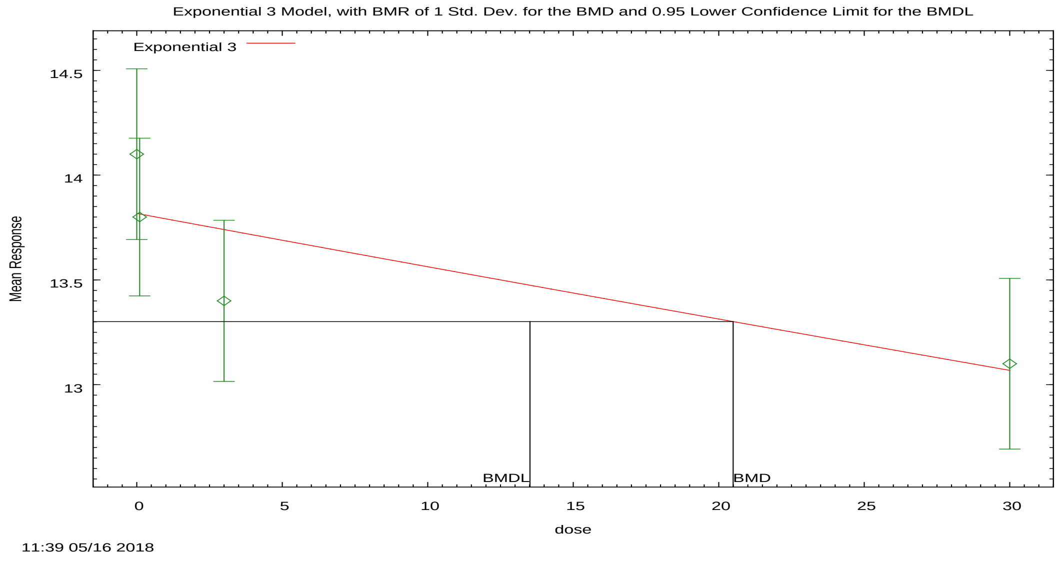

Figure 3. Plot of mean response by dose with fitted curve for Exponential (M3) model with constant variance for Hemoglobin in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 20.4946

BMDL at the 95% confidence level = 13.5131

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-1.32352	-1.52581
rho	n/a	0

a	13.8168	13.3792
b	0.00185691	0.00184061
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	9	14.1	13.82	0.53	0.52	1.647
0.1	8	13.8	13.81	0.45	0.52	-0.07817
3	8	13.4	13.74	0.46	0.52	-1.864
30	9	13.1	13.07	0.53	0.52	0.1851

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	8.938828	5	-7.877655
A2	9.156399	8	-2.312799
A3	8.938828	5	-7.877655
R	-0.03421454	2	4.068429
3	5.49979	3	-4.99958

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	18.38	6	0.005347
Test 2	0.4351	3	0.9329
Test 3	0.4351	3	0.9329
Test 5a	6.878	2	0.0321

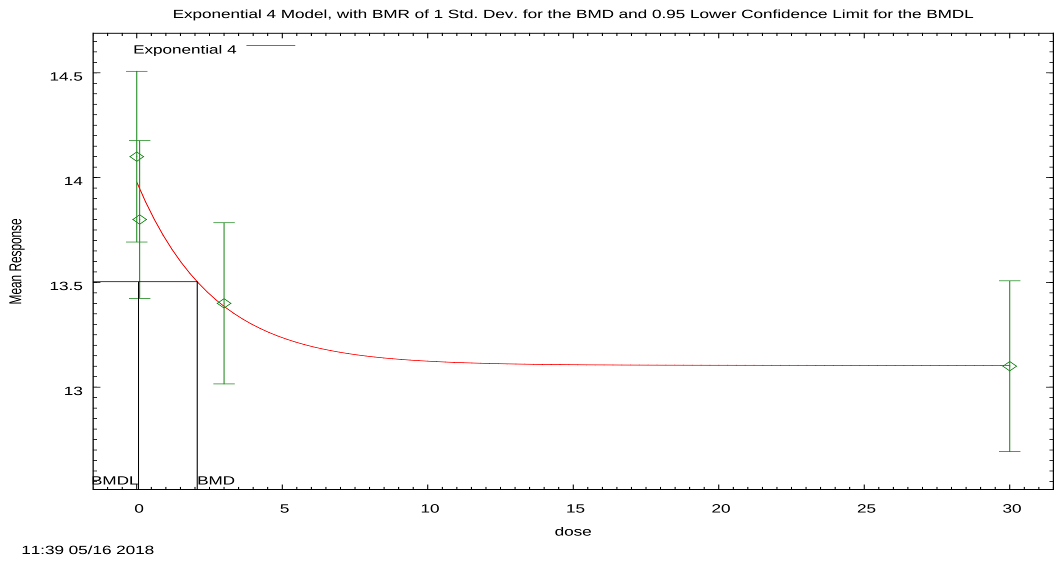

Figure 4. Plot of mean response by dose with fitted curve for Exponential (M4) model with constant variance for Hemoglobin in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 2.07626

BMDL at the 95% confidence level = 0.0606788

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-1.48534	-1.52581
rho	n/a	0
a	13.9789	14.805
b	0.378088	0.0465873
c	0.937413	0.842701

d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	9	14.1	13.98	0.53	0.48	0.7637
0.1	8	13.8	13.95	0.45	0.48	-0.8702
3	8	13.4	13.39	0.46	0.48	0.08685
30	9	13.1	13.1	0.53	0.48	-0.0251

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	8.938828	5	-7.877655
A2	9.156399	8	-2.312799
A3	8.938828	5	-7.877655
R	-0.03421454	2	4.068429
4	8.250725	4	-8.50145

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	18.38	6	0.005347
Test 2	0.4351	3	0.9329
Test 3	0.4351	3	0.9329
Test 6a	1.376	1	0.2407

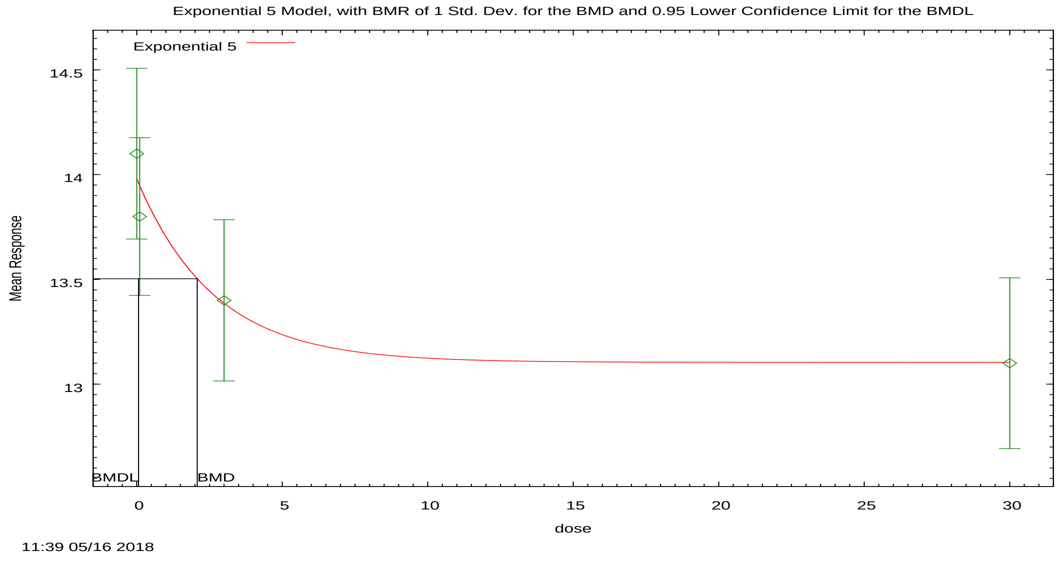

Figure 5. Plot of mean response by dose with fitted curve for Exponential (M5) model with constant variance for Hemoglobin in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 2.07626

BMDL at the 95% confidence level = 0.0606788

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-1.48534	-1.52581
rho	n/a	0
a	13.9789	14.805
b	0.378087	0.0465873
c	0.937413	0.842701

d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	9	14.1	13.98	0.53	0.48	0.7637
0.1	8	13.8	13.95	0.45	0.48	-0.8702
3	8	13.4	13.39	0.46	0.48	0.08685
30	9	13.1	13.1	0.53	0.48	-0.0251

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	8.938828	5	-7.877655
A2	9.156399	8	-2.312799
A3	8.938828	5	-7.877655
R	-0.03421454	2	4.068429
5	8.250725	4	-8.50145

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	18.38	6	0.005347
Test 2	0.4351	3	0.9329
Test 3	0.4351	3	0.9329
Test 7a	1.376	1	0.2407

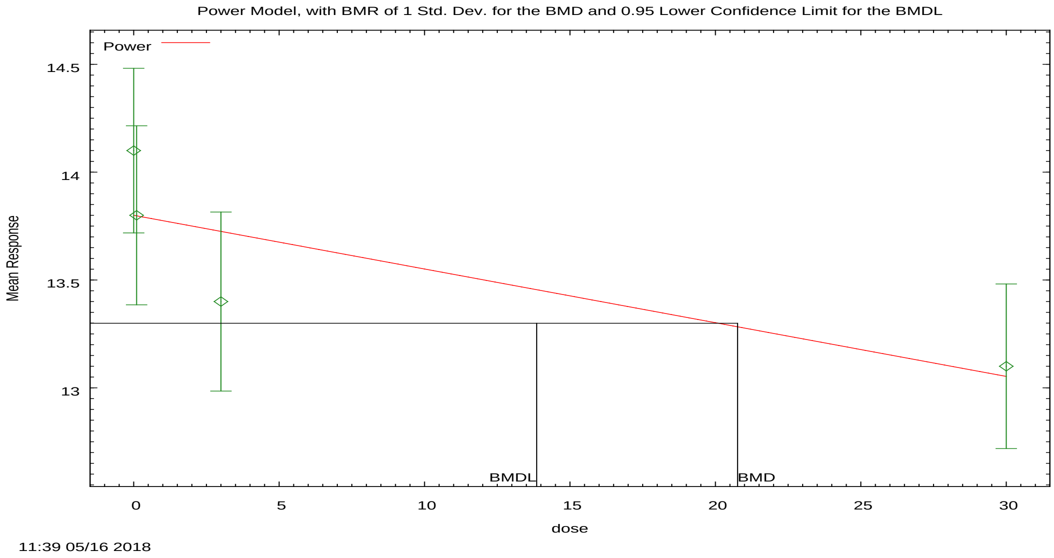

Figure 6. Plot of mean response by dose with fitted curve for Power model with constant variance for Hemoglobin in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 20.7618

BMDL at the 95% confidence level = 13.855

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.2665	0.246437
rho	n/a	0
control	13.8156	14.1
slope	-0.0248647	-2.33333
power	1	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	9	14.1	13.8	0.53	0.52	1.65
0.1	8	13.8	13.8	0.45	0.52	-0.0718
3	8	13.4	13.7	0.46	0.52	-1.87
30	9	13.1	13.1	0.53	0.52	0.176

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	8.938828	5	-7.877655
A2	9.156399	8	-2.312799
A3	8.938828	5	-7.877655
fitted	5.480494	3	-4.960988
R	-0.034215	2	4.068429

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	18.3812	6	0.005347
Test 2	0.435143	3	0.9329
Test 3	0.435143	3	0.9329
Test 4	6.91667	2	0.03148

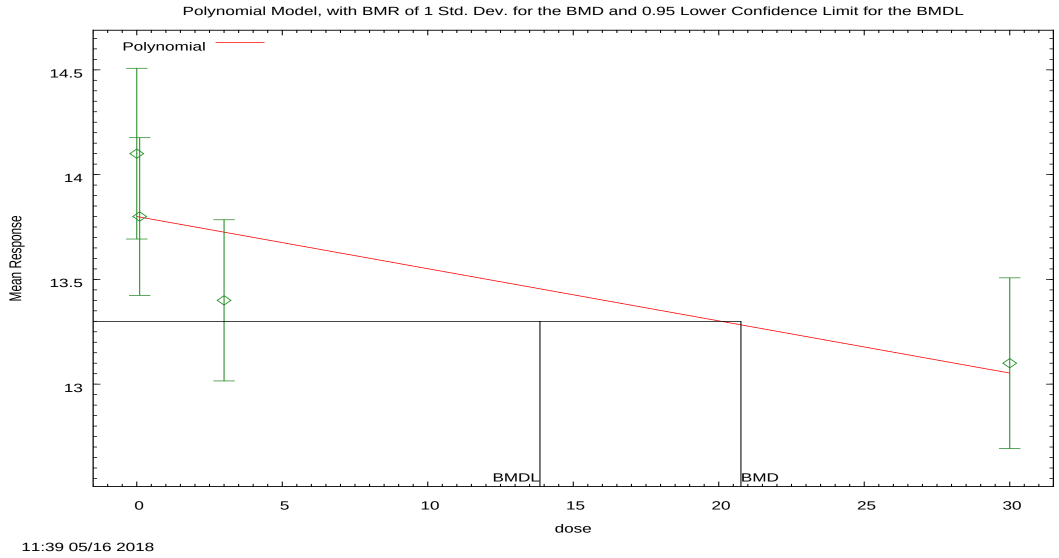

Figure 7. Plot of mean response by dose with fitted curve for Polynomial 3° model with constant variance for Hemoglobin in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 20.7618

BMDL at the 95% confidence level = 13.855

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.2665	0.246437
rho	n/a	0
beta_0	13.8156	14.1
beta_1	-0.0248647	-3.1049
beta_2	0	0

beta_3	0	-0.0316594

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	9	14.1	13.8	0.53	0.52	1.65
0.1	8	13.8	13.8	0.45	0.52	-0.0718
3	8	13.4	13.7	0.46	0.52	-1.87
30	9	13.1	13.1	0.53	0.52	0.176

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	8.938828	5	-7.877655
A2	9.156399	8	-2.312799
A3	8.938828	5	-7.877655
fitted	5.480494	3	-4.960988
R	-0.034215	2	4.068429

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	18.3812	6	0.005347
Test 2	0.435143	3	0.9329
Test 3	0.435143	3	0.9329
Test 4	6.91667	2	0.03148

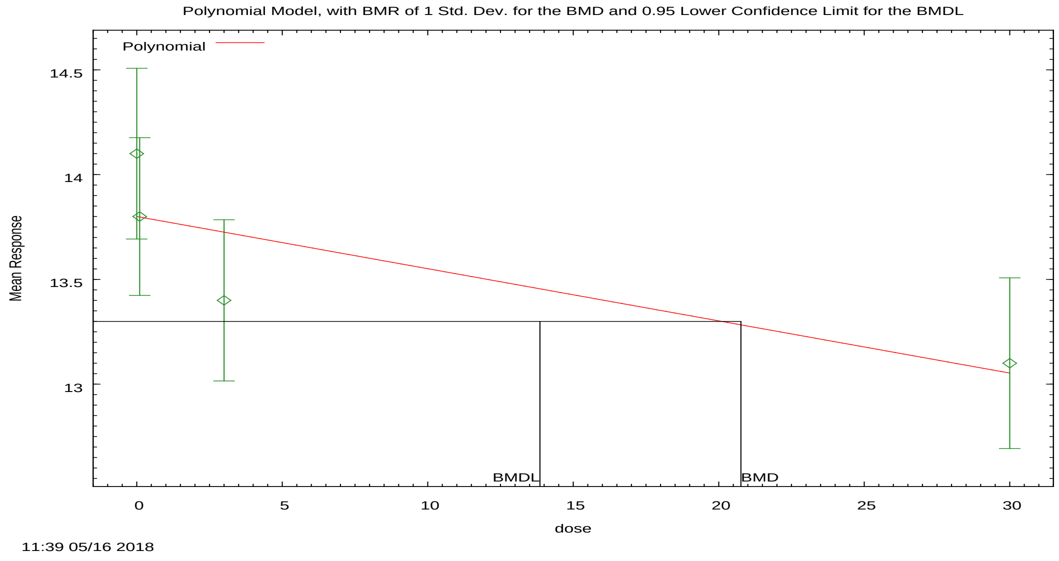

Figure 8. Plot of mean response by dose with fitted curve for Polynomial 2° model with constant variance for Hemoglobin in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 20.7618

BMDL at the 95% confidence level = 13.855

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.2665	0.246437
rho	n/a	0
beta_0	13.8156	13.9629
beta_1	-0.0248647	-0.207243
beta_2	0	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	9	14.1	13.8	0.53	0.52	1.65
0.1	8	13.8	13.8	0.45	0.52	-0.0718
3	8	13.4	13.7	0.46	0.52	-1.87
30	9	13.1	13.1	0.53	0.52	0.176

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	8.938828	5	-7.877655
A2	9.156399	8	-2.312799
A3	8.938828	5	-7.877655
fitted	5.480494	3	-4.960988
R	-0.034215	2	4.068429

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	18.3812	6	0.005347
Test 2	0.435143	3	0.9329
Test 3	0.435143	3	0.9329
Test 4	6.91667	2	0.03148

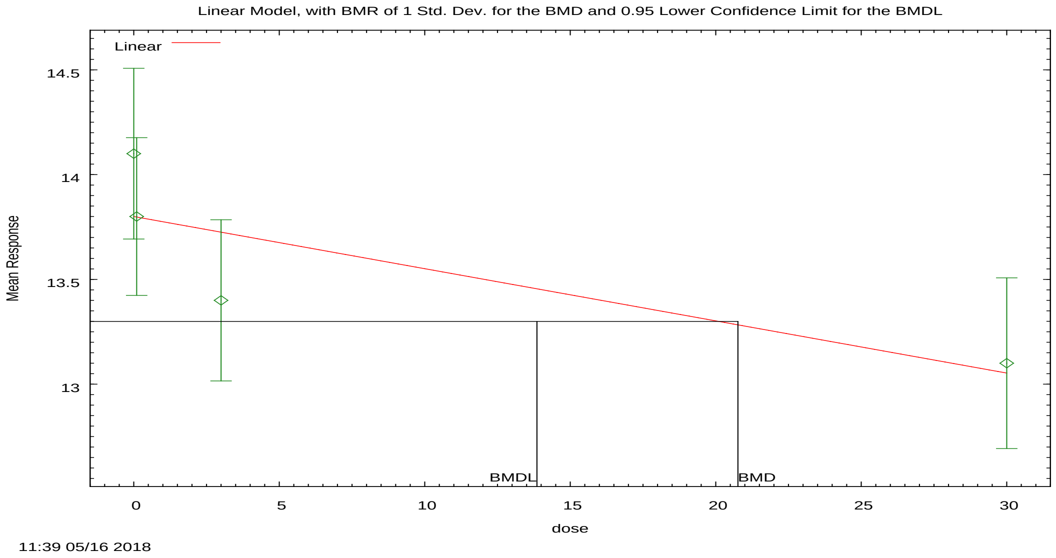

Figure 9. Plot of mean response by dose with fitted curve for Linear model with constant variance for Hemoglobin in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 20.7618

BMDL at the 95% confidence level = 13.855

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.2665	0.246437
rho	n/a	0
beta_0	13.8156	13.803
beta_1	-0.0248647	-0.0245313

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	9	14.1	13.8	0.53	0.52	1.65
0.1	8	13.8	13.8	0.45	0.52	-0.0718
3	8	13.4	13.7	0.46	0.52	-1.87
30	9	13.1	13.1	0.53	0.52	0.176

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	8.938828	5	-7.877655
A2	9.156399	8	-2.312799
A3	8.938828	5	-7.877655
fitted	5.480494	3	-4.960988
R	-0.034215	2	4.068429

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	18.3812	6	0.005347
Test 2	0.435143	3	0.9329
Test 3	0.435143	3	0.9329
Test 4	6.91667	2	0.03148

BMDS WIZARD OUTPUT REPORT

BMDS Summary of 28-Day Oral (Gavage) Toxicity Study of H-28397 in Rats with a 28-day Recovery – Hemoglobin (g/dL) in Males

1.2. BMDS Summary of Hemoglobin (g/dL) Males (28 Day Rats GenX)

Table 2. Summary of BMD Modeling Results for Hemoglobin in Males (28-Day Rats); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD$_{1SD}$ (mg/kg/day)	BMDL$_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2) Exponential (M3)[b]	0.0807	-12.891	14.0	10.3	1.36	Only one model met model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). Selected BMDL is from this model.
Exponential (M4)	**0.731**	**-15.807**	**2.44**	**1.19**	**2.06**	
Exponential (M5)	N/A[c]	-13.925	2.91	1.21	2.41	
Hill	N/A[c]	-13.925	2.89	0.906	3.19	
Power[d] Polynomial 3°[e] Polynomial 2°[f] Linear	0.0780	-12.824	14.3	10.6	1.35	

[a] Constant variance case presented (BMDS Test 2 *p*-value = 0.383), selected model in bold; scaled residuals for selected model for doses 0, 0.3, 3, and 30 mg/kg/day were -0.22, 0.26, -0.05, 0.01, respectively.
[b] For the Exponential (M3) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M2) model.
[c] No available degrees of freedom to calculate a goodness of fit value.
[d] For the Power model, the power parameter estimate was 1. The models in this row reduced to the Linear model.
[e] For the Polynomial 3° model, the b3 coefficient estimates was 0 (boundary of parameters space). The models in this row reduced to the Polynomial 2° model. For the Polynomial 3° model, the b3 and b2 coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Linear model.
[f] For the Polynomial 2° model, the b2 coefficient estimate was 0 (boundary of parameters space). The models in this row reduced to the Linear model.

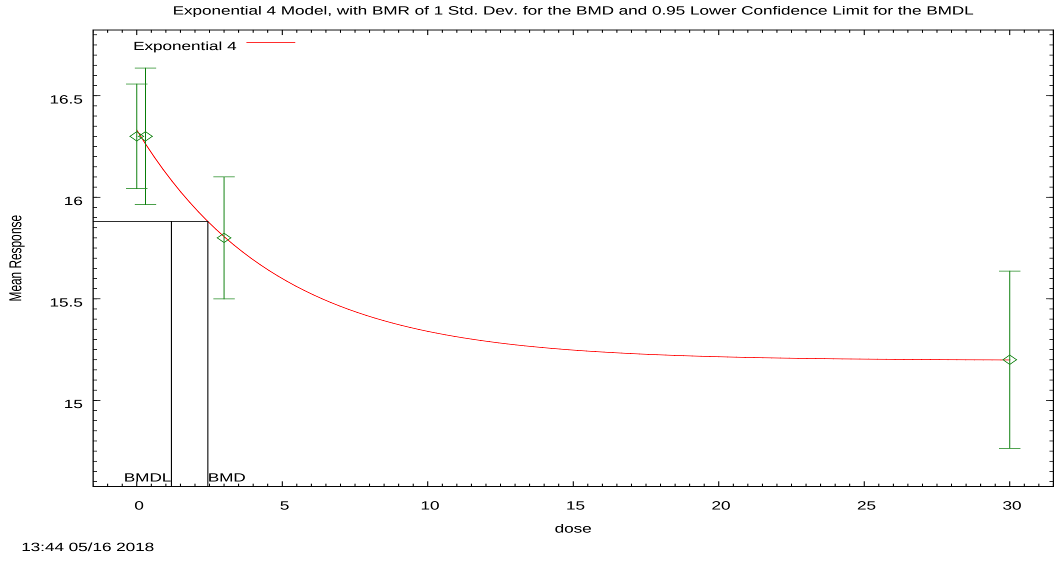

Figure 10. Plot of mean response by dose with fitted curve for Exponential (M4) model with constant variance for Hemoglobin in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 2.4439

BMDL at the 95% confidence level = 1.18907

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-1.59517	-1.59813
rho	n/a	0
a	16.3313	17.115
b	0.207026	0.0450856
c	0.930541	0.845819
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	16.3	16.33	0.36	0.45	-0.2197
0.3	10	16.3	16.26	0.47	0.45	0.2599
3	10	15.8	15.81	0.42	0.45	-0.04565
30	10	15.2	15.2	0.61	0.45	0.005483

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC

A1	11.96254	5	-13.92508
A2	13.49192	8	-10.98384
A3	11.96254	5	-13.92508
R	-2.034667	2	8.069334
4	11.90349	4	-15.80699

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.05	6	<0.0001
Test 2	3.059	3	0.3827
Test 3	3.059	3	0.3827
Test 6a	0.1181	1	0.7311

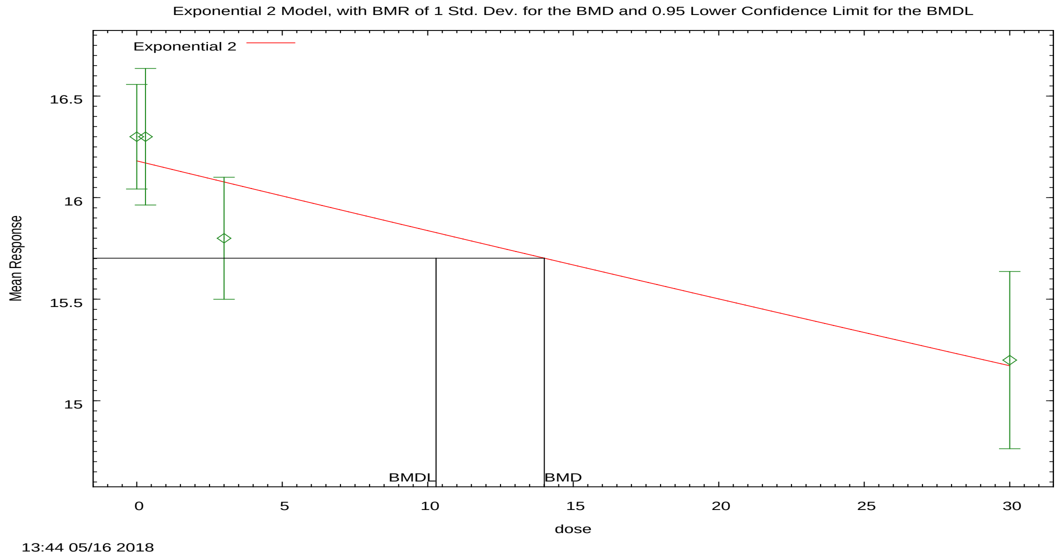

Figure 11. Plot of mean response by dose with fitted curve for Exponential (M2) model with constant variance for Hemoglobin in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 14.0048

BMDL at the 95% confidence level = 10.2849

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-1.47228	-1.59813
rho	n/a	0
a	16.1807	15.6136
b	0.00214552	0.00213419
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	16.3	16.18	0.36	0.48	0.7876
0.3	10	16.3	16.17	0.47	0.48	0.8563
3	10	15.8	16.08	0.42	0.48	-1.828
30	10	15.2	15.17	0.61	0.48	0.1846

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	11.96254	5	-13.92508
A2	13.49192	8	-10.98384
A3	11.96254	5	-13.92508
R	-2.034667	2	8.069334
2	9.445631	3	-12.89126

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value

Test 1	31.05	6	<0.0001
Test 2	3.059	3	0.3827
Test 3	3.059	3	0.3827
Test 4	5.034	2	0.08071

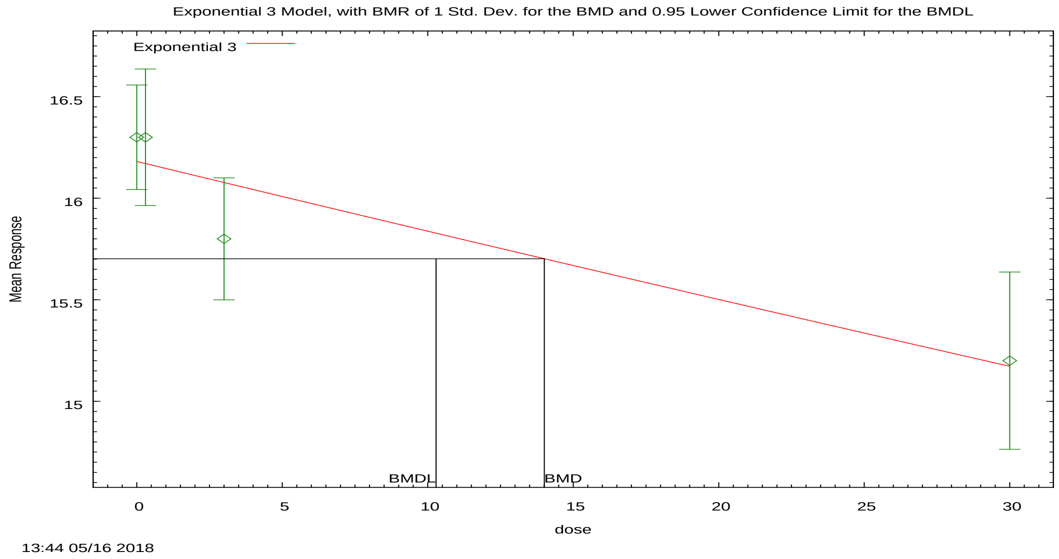

Figure 12. Plot of mean response by dose with fitted curve for Exponential (M3) model with constant variance for Hemoglobin in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 14.0048

BMDL at the 95% confidence level = 10.2849

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values

lnalpha	-1.47228	-1.59813
rho	n/a	0
a	16.1807	15.6136
b	0.00214552	0.00213419
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	16.3	16.18	0.36	0.48	0.7876
0.3	10	16.3	16.17	0.47	0.48	0.8563
3	10	15.8	16.08	0.42	0.48	-1.828
30	10	15.2	15.17	0.61	0.48	0.1846

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	11.96254	5	-13.92508
A2	13.49192	8	-10.98384
A3	11.96254	5	-13.92508
R	-2.034667	2	8.069334
3	9.445631	3	-12.89126

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.05	6	<0.0001
Test 2	3.059	3	0.3827
Test 3	3.059	3	0.3827
Test 5a	5.034	2	0.08071

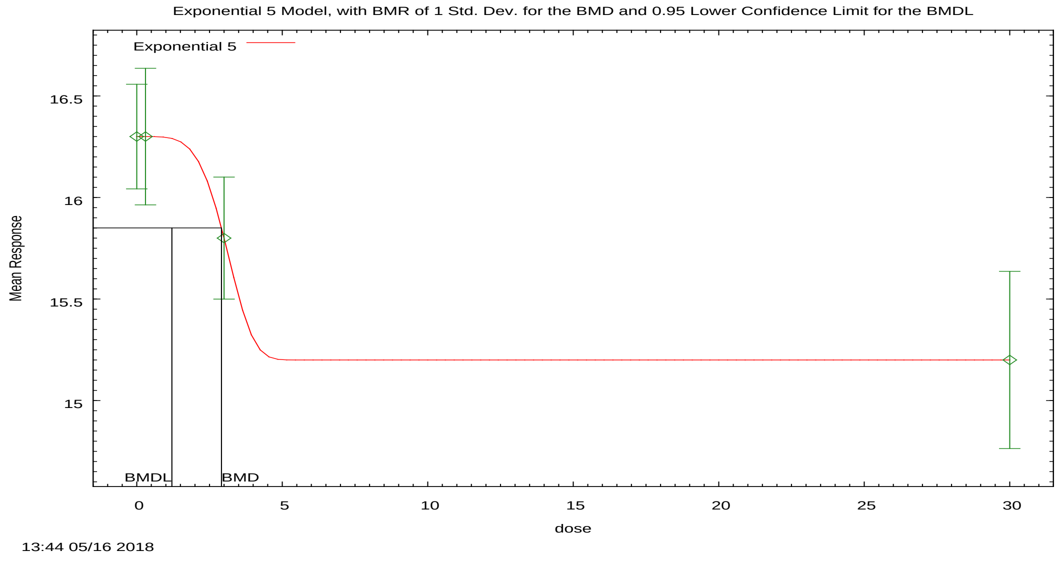

Figure 13. Plot of mean response by dose with fitted curve for Exponential (M5) model with constant variance for Hemoglobin in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 2.91069

BMDL at the 95% confidence level = 1.20656

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-1.59813	-1.59813
rho	n/a	0
a	16.3	17.115
b	0.299728	0.0450856
c	0.932515	0.845819

d	4.7112	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	16.3	16.3	0.36	0.45	-0.00004575
0.3	10	16.3	16.3	0.47	0.45	0.00004541
3	10	15.8	15.8	0.42	0.45	-0.0000002073
30	10	15.2	15.2	0.61	0.45	-0.0000002999

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	11.96254	5	-13.92508
A2	13.49192	8	-10.98384
A3	11.96254	5	-13.92508
R	-2.034667	2	8.069334
5	11.96254	5	-13.92508

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.05	6	<0.0001
Test 2	3.059	3	0.3827
Test 3	3.059	3	0.3827
Test 7a	0.000000004155	0	N/A

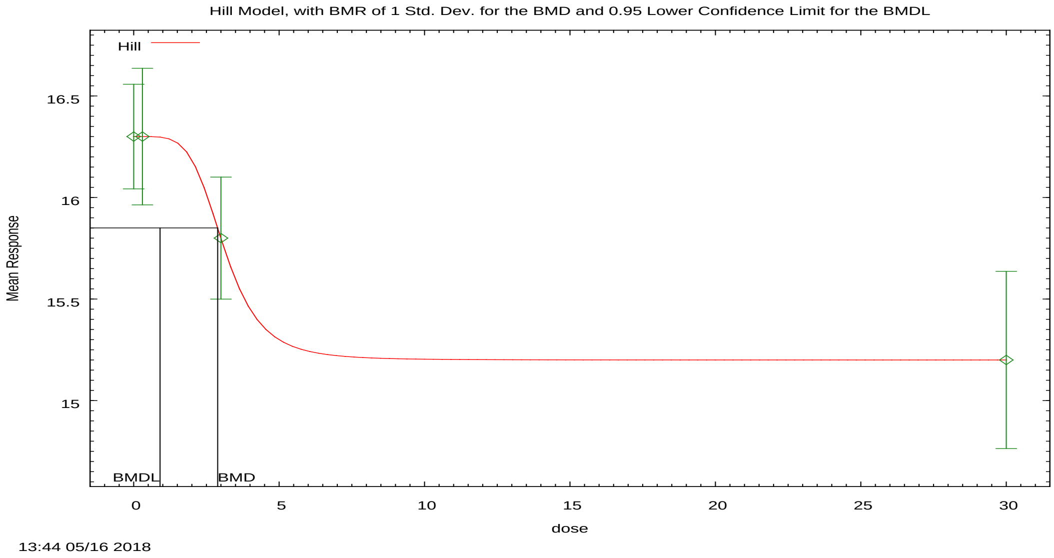

Figure 14. Plot of mean response by dose with fitted curve for Hill model with constant variance for Hemoglobin in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 2.88712

BMDL at the 95% confidence level = 0.906305

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.202275	0.22475
rho	n/a	0
intercept	16.3	16.3
v	-1.10002	-1.1
n	4.85942	0.325798

k	3.11471	5.25

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	16.3	16.3	0.36	0.45	-0.0000442
0.3	10	16.3	16.3	0.47	0.45	0.0000449
3	10	15.8	15.8	0.42	0.45	0.00000338
30	10	15.2	15.2	0.61	0.45	0.000000875

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	11.962542	5	-13.925085
A2	13.491918	8	-10.983835
A3	11.962542	5	-13.925085
fitted	11.962542	5	-13.925085
R	-2.034667	2	8.069334

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.0532	6	<0.0001
Test 2	3.05875	3	0.3827
Test 3	3.05875	3	0.3827
Test 4	0.00000000398149	0	N/A

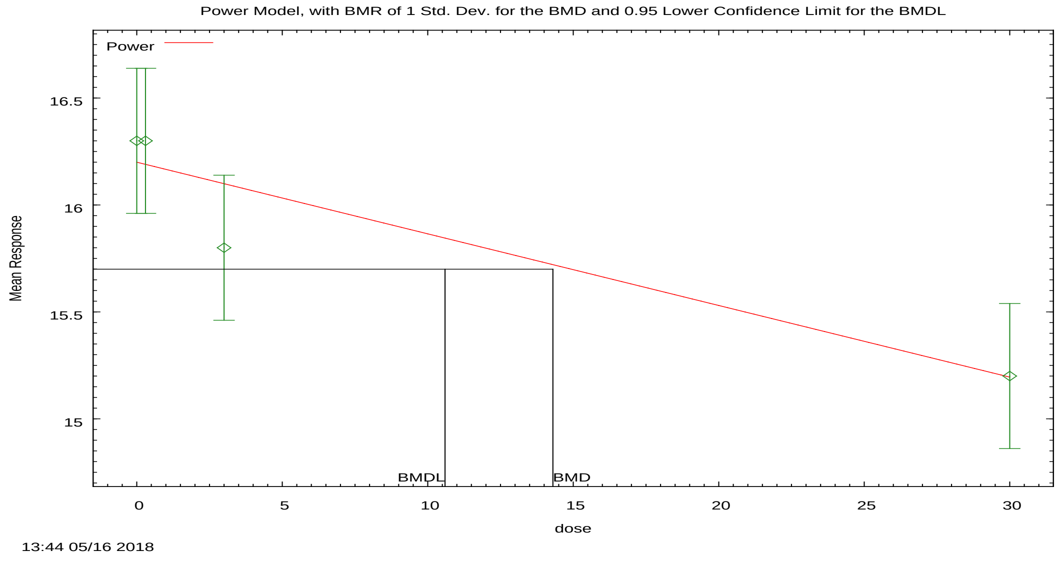

Figure 15. Plot of mean response by dose with fitted curve for Power model with constant variance for Hemoglobin in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 14.3009

BMDL at the 95% confidence level = 10.5936

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.229788	0.22475
rho	n/a	0
control	16.1791	16.3
slope	-0.0335197	-2.69297
power	1	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	16.3	16.2	0.36	0.48	0.798
0.3	10	16.3	16.2	0.47	0.48	0.864
3	10	15.8	16.1	0.42	0.48	-1.84
30	10	15.2	15.2	0.61	0.48	0.175

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	11.962542	5	-13.925085
A2	13.491918	8	-10.983835
A3	11.962542	5	-13.925085
fitted	9.41194	3	-12.823879
R	-2.034667	2	8.069334

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.0532	6	<0.0001
Test 2	3.05875	3	0.3827
Test 3	3.05875	3	0.3827
Test 4	5.10121	2	0.07803

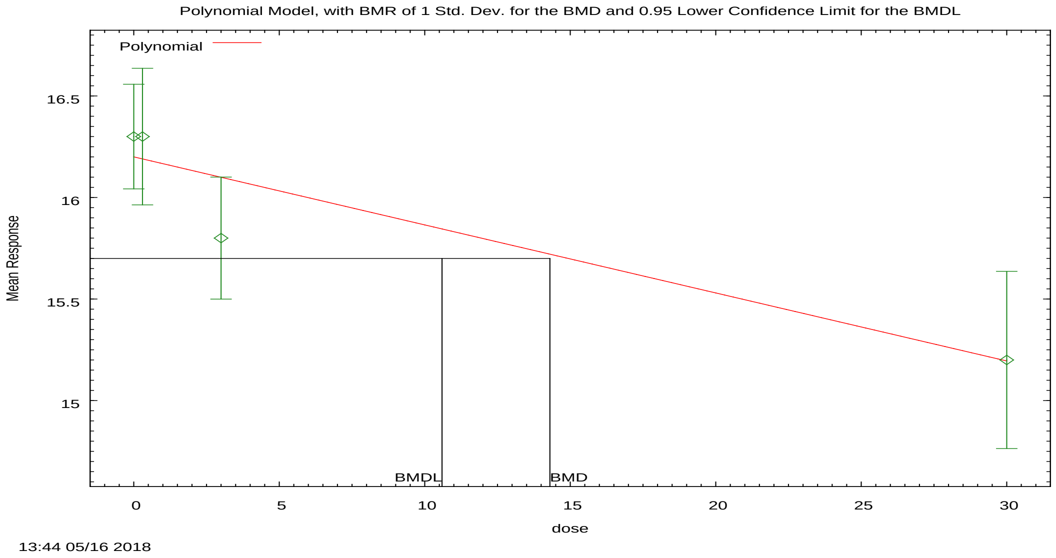

Figure 16. Plot of mean response by dose with fitted curve for Polynomial 3° model with constant variance for Hemoglobin in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + …

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 14.3009

BMDL at the 95% confidence level = 10.5936

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.229788	0.22475
rho	n/a	0
beta_0	16.1791	16.3
beta_1	-0.0335197	0
beta_2	0	-0.0691221

beta_3	0	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	16.3	16.2	0.36	0.48	0.798
0.3	10	16.3	16.2	0.47	0.48	0.864
3	10	15.8	16.1	0.42	0.48	-1.84
30	10	15.2	15.2	0.61	0.48	0.175

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	11.962542	5	-13.925085
A2	13.491918	8	-10.983835
A3	11.962542	5	-13.925085
fitted	9.41194	3	-12.823879
R	-2.034667	2	8.069334

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.0532	6	<0.0001
Test 2	3.05875	3	0.3827
Test 3	3.05875	3	0.3827
Test 4	5.10121	2	0.07803

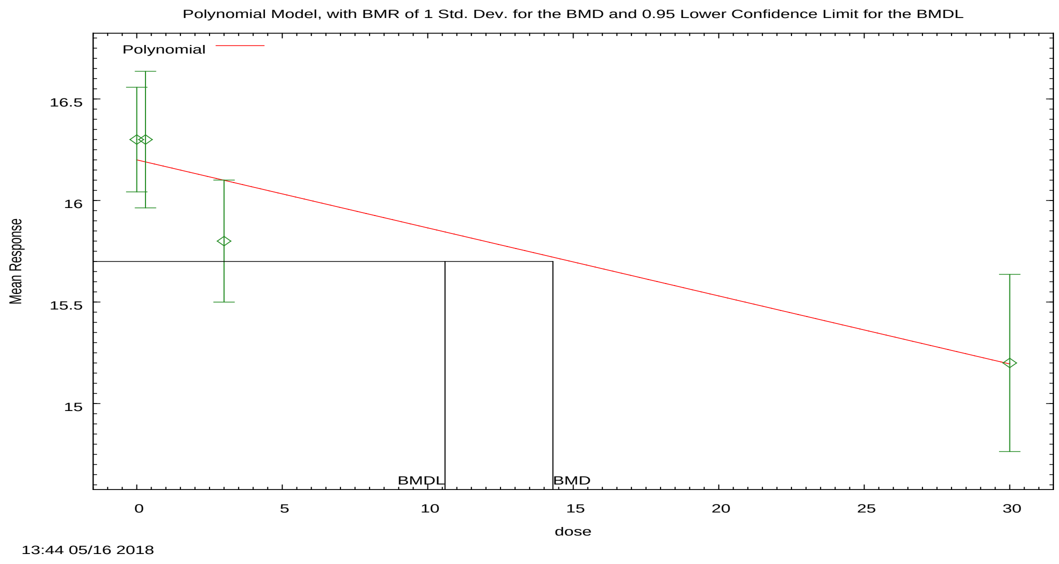

Figure 17. Plot of mean response by dose with fitted curve for Polynomial 2° model with constant variance for Hemoglobin in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + …

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 14.3009

BMDL at the 95% confidence level = 10.5936

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.229788	0.22475
rho	n/a	0
beta_0	16.1791	16.3266
beta_1	-0.0335197	-0.189646
beta_2	0	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	16.3	16.2	0.36	0.48	0.798
0.3	10	16.3	16.2	0.47	0.48	0.864
3	10	15.8	16.1	0.42	0.48	-1.84
30	10	15.2	15.2	0.61	0.48	0.175

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	11.962542	5	-13.925085
A2	13.491918	8	-10.983835
A3	11.962542	5	-13.925085
fitted	9.41194	3	-12.823879
R	-2.034667	2	8.069334

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.0532	6	<0.0001
Test 2	3.05875	3	0.3827
Test 3	3.05875	3	0.3827
Test 4	5.10121	2	0.07803

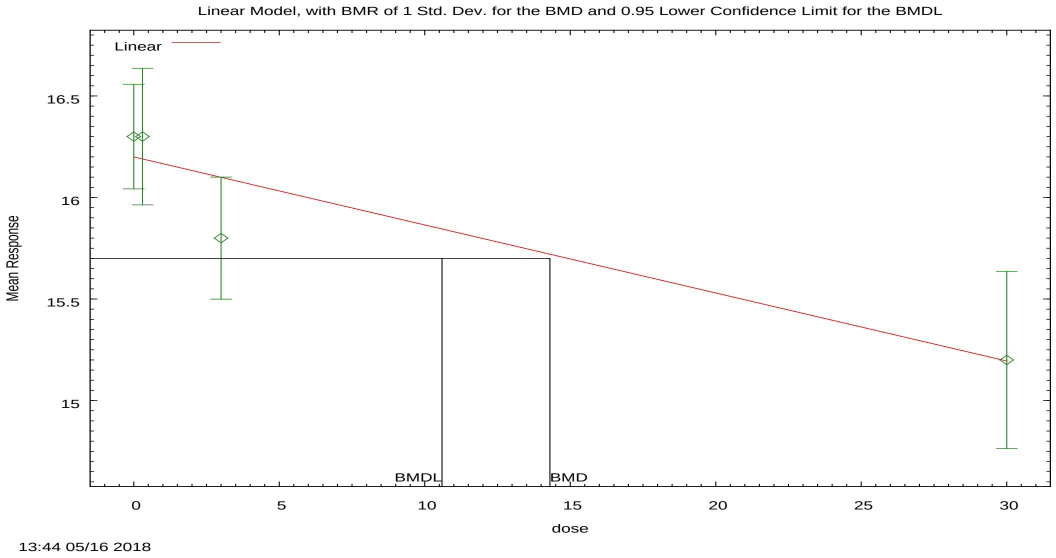

Figure 18. Plot of mean response by dose with fitted curve for Linear model with constant variance for Hemoglobin in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 14.3009

BMDL at the 95% confidence level = 10.5936

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.229788	0.22475
rho	n/a	0
beta_0	16.1791	16.1791
beta_1	-0.0335197	-0.0335197

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	16.3	16.2	0.36	0.48	0.798
0.3	10	16.3	16.2	0.47	0.48	0.864
3	10	15.8	16.1	0.42	0.48	-1.84
30	10	15.2	15.2	0.61	0.48	0.175

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	11.962542	5	-13.925085
A2	13.491918	8	-10.983835
A3	11.962542	5	-13.925085
fitted	9.41194	3	-12.823879
R	-2.034667	2	8.069334

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.0532	6	<0.0001
Test 2	3.05875	3	0.3827
Test 3	3.05875	3	0.3827
Test 4	5.10121	2	0.07803

BMDS WIZARD OUTPUT REPORT

BMDS Summary of 90-Day Oral (Gavage) Toxicity Study of H-28548 in Rats with a 28-Day Recovery – Hemoglobin (g/dL) in Males

1.3. BMDS Summary of Hemoglobin (g/dL) Males (90 Day Rats GenX)

Table 3. Summary of BMD Modeling Results for Hemoglobin in Males (90-Day Rats); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD_{1SD} (mg/kg/day)	BMDL_{1SD} (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2) Exponential (M3)[b]	0.0113	26.870	41.0	30.5	1.34	BMDLs from models that met model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values > 2.0; appropriate variance (continuous data only)) were compared. Selected BMDL is from model with lowest AIC and lowest BMDL.
Exponential (M4) Exponential (M5)[c]	0.787	19.971	5.80	3.23	1.80	
Hill	**0.798**	**19.963**	**5.15**	**2.12**	**2.42**	
Power[d] Polynomial 3°[e] Polynomial 2°[f] Linear	0.0102	27.066	42.9	32.4	1.32	

[a] Constant variance case presented (BMDS Test 2 *p*-value = 0.294), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 10, and 100 mg/kg/day were 0.18, -0.18, 0.01, 0, respectively.

[b] For the Exponential (M3) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M2) model.

[c] For the Exponential (M5) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M4) model.

[d] For the Power model, the power parameter estimate was 1. The models in this row reduced to the Linear model.

[e] For the Polynomial 3° model, the b3 coefficient estimates was 0 (boundary of parameters space). The models in this row reduced to the Polynomial 2° model. For the Polynomial 3° model, the b3 and b2 coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Linear model.

[f] For the Polynomial 2° model, the b2 coefficient estimate was 0 (boundary of parameters space). The models in this row reduced to the Linear model.

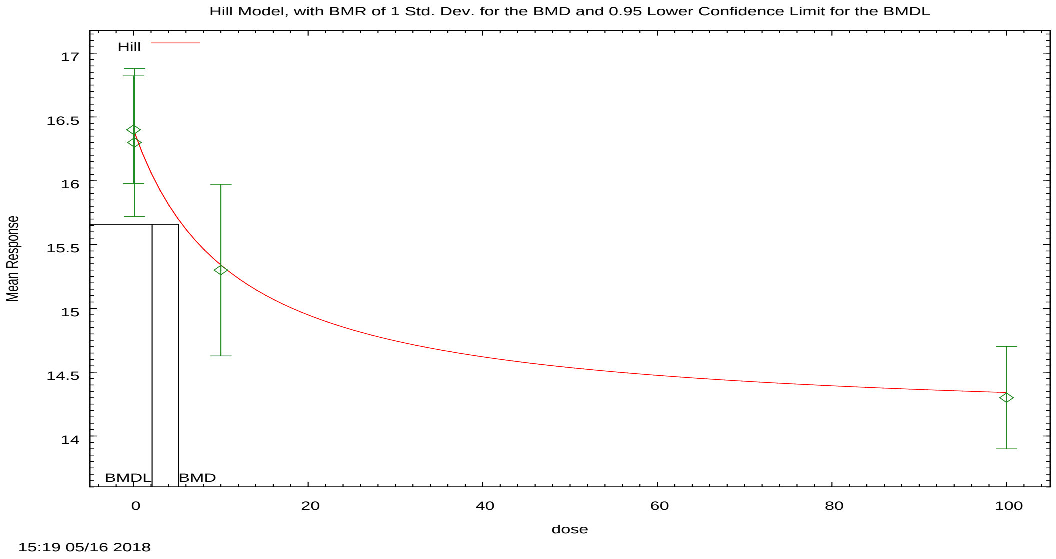

Figure 19. Plot of mean response by dose with fitted curve for Hill model with constant variance for Hemoglobin in Males (90-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 5.14707

BMDL at the 95% confidence level = 2.12258

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.496125	0.55035
rho	n/a	0
intercept	16.3603	16.4
v	-2.30015	-2.1
n	1	1.26758
k	11.6611	9.505

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	16.4	16.4	0.59	0.7	0.178
0.1	10	16.3	16.3	0.81	0.7	-0.183
10	10	15.3	15.3	0.94	0.7	0.00689
100	10	14.3	14.3	0.56	0.7	-0.00182

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC

A1	-5.948773	5	21.897546
A2	-4.092313	8	24.184626
A3	-5.948773	5	21.897546
fitted	-5.981439	4	19.962879
R	-24.012887	2	52.025773

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	39.8411	6	<0.0001
Test 2	3.71292	3	0.2942
Test 3	3.71292	3	0.2942
Test 4	0.0653329	1	0.7983

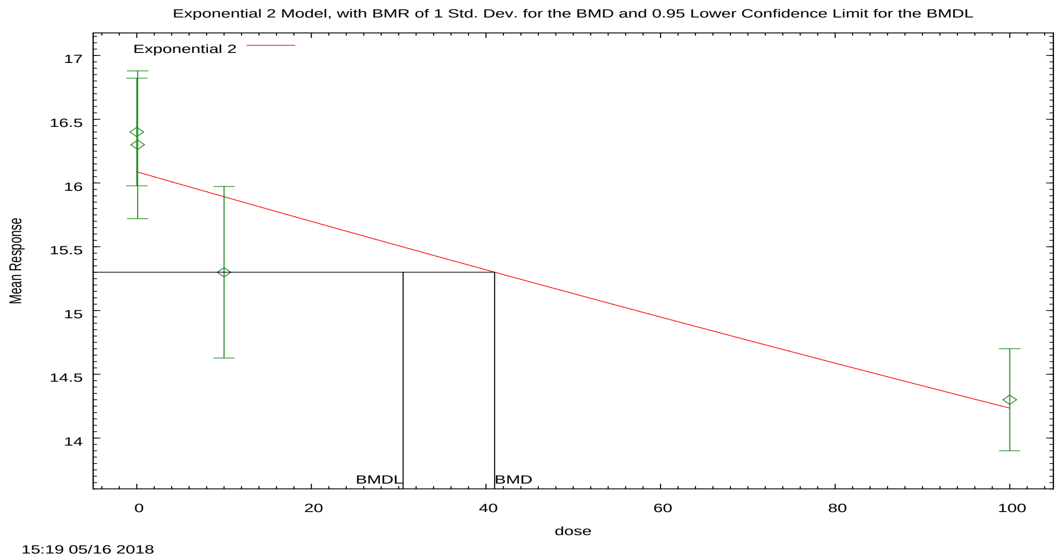

Figure 20. Plot of mean response by dose with fitted curve for Exponential (M2) model with constant variance for Hemoglobin in Males (90-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 40.9903

BMDL at the 95% confidence level = 30.5103

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-0.478251	-0.702561
rho	n/a	0
a	16.0877	15.0423
b	0.00122412	0.00120888
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	16.4	16.09	0.59	0.79	1.254
0.1	10	16.3	16.09	0.81	0.79	0.8606
10	10	15.3	15.89	0.94	0.79	-2.378
100	10	14.3	14.23	0.56	0.79	0.2645

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-5.948773	5	21.89755
A2	-4.092313	8	24.18463
A3	-5.948773	5	21.89755
R	-24.01289	2	52.02577
2	-10.43498	3	26.86996

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value

Test 1	39.84	6	<0.0001
Test 2	3.713	3	0.2942
Test 3	3.713	3	0.2942
Test 4	8.972	2	0.01126

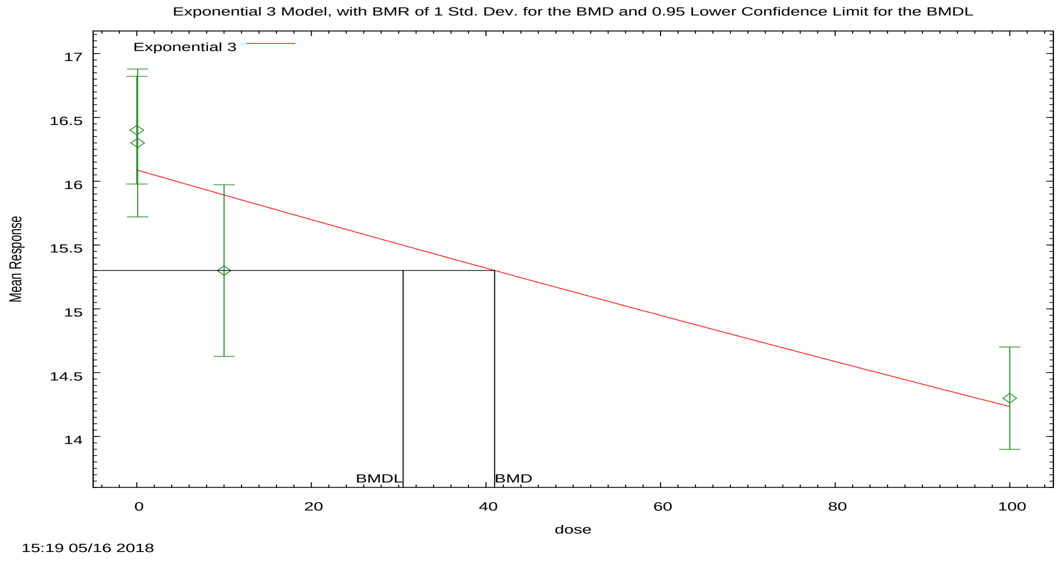

Figure 21. Plot of mean response by dose with fitted curve for Exponential (M3) model with constant variance for Hemoglobin in Males (90-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 40.9903

BMDL at the 95% confidence level = 30.5103

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values

lnalpha	-0.478251	-0.702561
rho	n/a	0
a	16.0877	15.0423
b	0.00122412	0.00120888
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	16.4	16.09	0.59	0.79	1.254
0.1	10	16.3	16.09	0.81	0.79	0.8606
10	10	15.3	15.89	0.94	0.79	-2.378
100	10	14.3	14.23	0.56	0.79	0.2645

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-5.948773	5	21.89755
A2	-4.092313	8	24.18463
A3	-5.948773	5	21.89755
R	-24.01289	2	52.02577
3	-10.43498	3	26.86996

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	39.84	6	<0.0001
Test 2	3.713	3	0.2942
Test 3	3.713	3	0.2942
Test 5a	8.972	2	0.01126

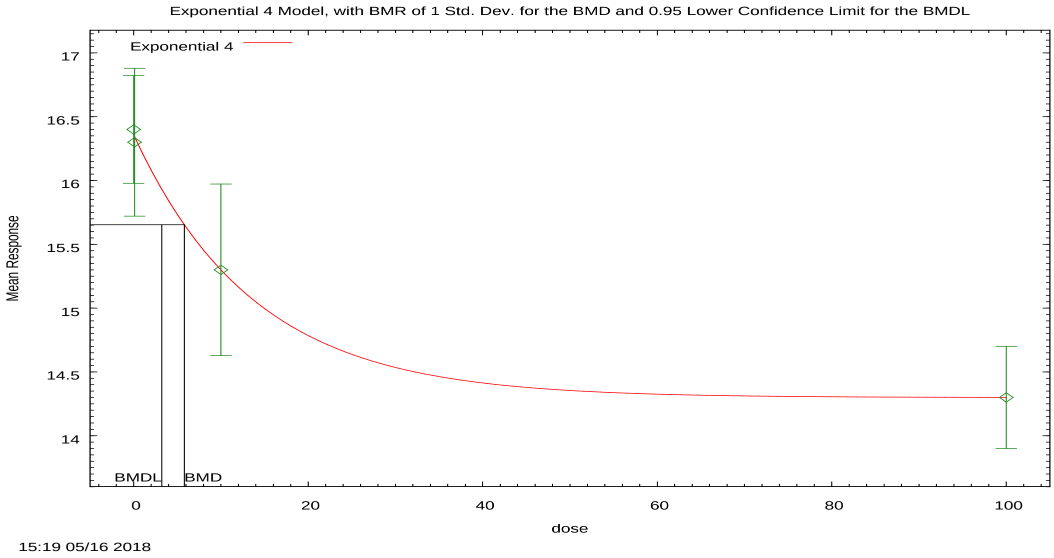

Figure 22. Plot of mean response by dose with fitted curve for Exponential (M4) model with constant variance for Hemoglobin in Males (90-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 5.80078

BMDL at the 95% confidence level = 3.22524

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-0.700731	-0.702561
rho	n/a	0
a	16.3578	17.22
b	0.0721802	0.0172469
c	0.874119	0.790885

d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	16.4	16.36	0.59	0.7	0.1896
0.1	10	16.3	16.34	0.81	0.7	-0.1929
10	10	15.3	15.3	0.94	0.7	0.003951
100	10	14.3	14.3	0.56	0.7	-0.0006445

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-5.948773	5	21.89755
A2	-4.092313	8	24.18463
A3	-5.948773	5	21.89755
R	-24.01289	2	52.02577
4	-5.985381	4	19.97076

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	39.84	6	<0.0001
Test 2	3.713	3	0.2942
Test 3	3.713	3	0.2942
Test 6a	0.07322	1	0.7867

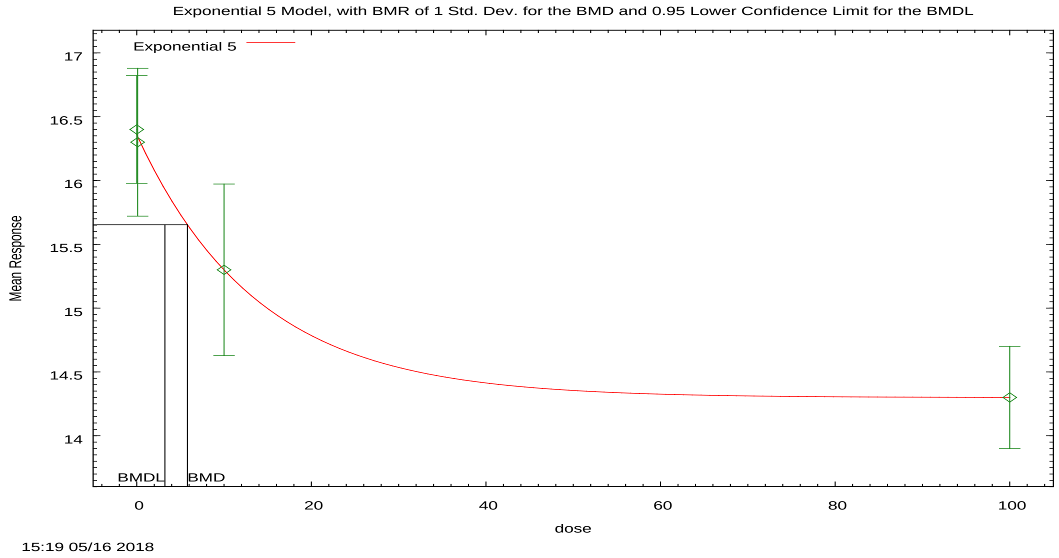

Figure 23. Plot of mean response by dose with fitted curve for Exponential (M5) model with constant variance for Hemoglobin in Males (90-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 5.80078

BMDL at the 95% confidence level = 3.22524

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-0.700731	-0.702561
rho	n/a	0
a	16.3578	17.22
b	0.0721802	0.0172469
c	0.874119	0.790885

d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	16.4	16.36	0.59	0.7	0.1896
0.1	10	16.3	16.34	0.81	0.7	-0.1929
10	10	15.3	15.3	0.94	0.7	0.003951
100	10	14.3	14.3	0.56	0.7	-0.0006443

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-5.948773	5	21.89755
A2	-4.092313	8	24.18463
A3	-5.948773	5	21.89755
R	-24.01289	2	52.02577
5	-5.985381	4	19.97076

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	39.84	6	<0.0001
Test 2	3.713	3	0.2942
Test 3	3.713	3	0.2942
Test 7a	0.07322	1	0.7867

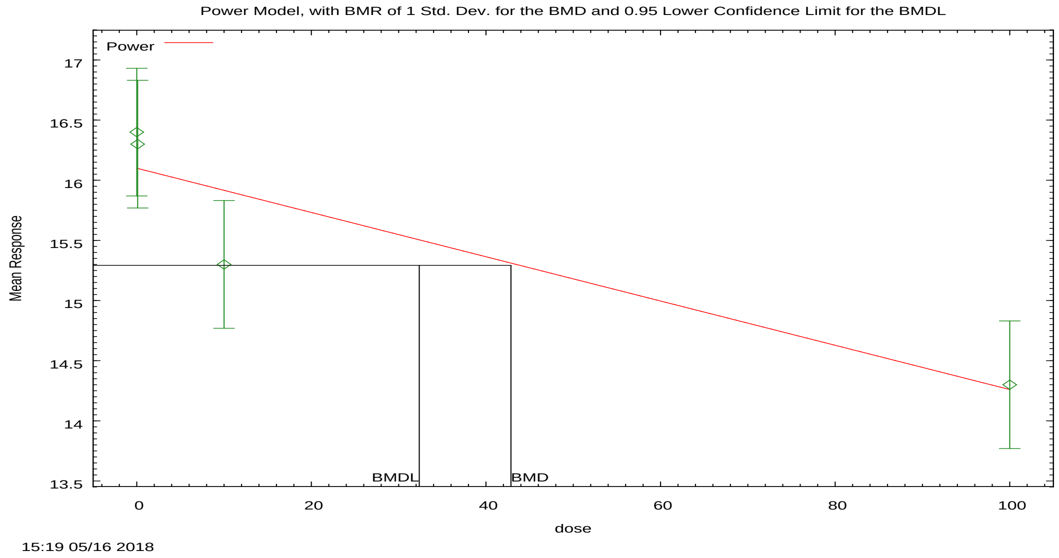

Figure 24. Plot of mean response by dose with fitted curve for Power model with constant variance for Hemoglobin in Males (90-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 42.8617

BMDL at the 95% confidence level = 32.3608

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.62292	0.55035
rho	n/a	0
control	16.0818	16.4
slope	-0.0184139	-4.2
power	1	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	16.4	16.1	0.59	0.79	1.27
0.1	10	16.3	16.1	0.81	0.79	0.881
10	10	15.3	15.9	0.94	0.79	-2.39
100	10	14.3	14.2	0.56	0.79	0.239

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-5.948773	5	21.897546
A2	-4.092313	8	24.184626
A3	-5.948773	5	21.897546
fitted	-10.533249	3	27.066498
R	-24.012887	2	52.025773

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	39.8411	6	<0.0001
Test 2	3.71292	3	0.2942
Test 3	3.71292	3	0.2942
Test 4	9.16895	2	0.01021

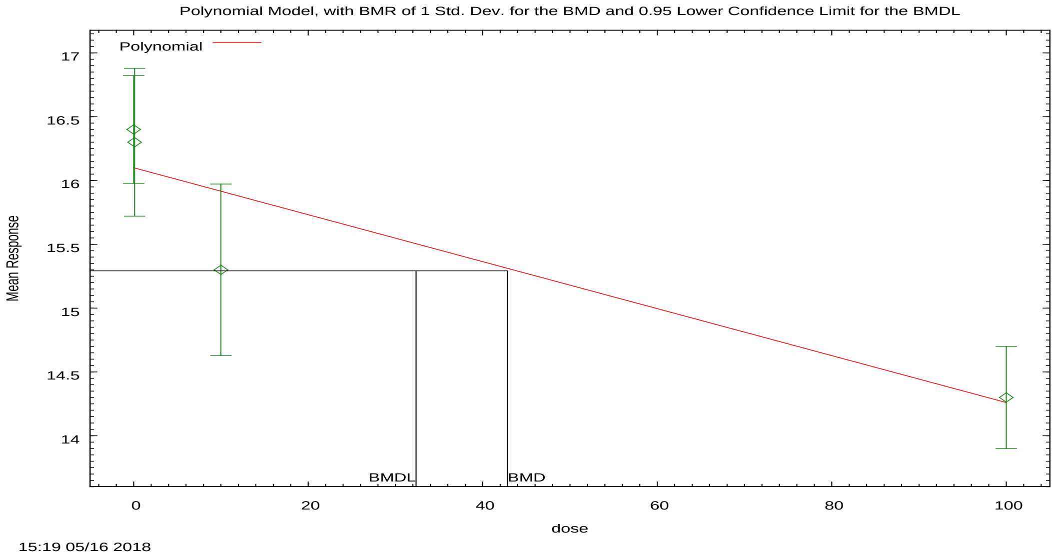

Figure 25. Plot of mean response by dose with fitted curve for Polynomial 3° model with constant variance for Hemoglobin in Males (90-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 42.8617

BMDL at the 95% confidence level = 32.3608

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.62292	0.55035
rho	n/a	0
beta_0	16.0818	16.4
beta_1	-0.0184139	-1.00988
beta_2	0	0

beta_3	0	-0.000889991

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	16.4	16.1	0.59	0.79	1.27
0.1	10	16.3	16.1	0.81	0.79	0.881
10	10	15.3	15.9	0.94	0.79	-2.39
100	10	14.3	14.2	0.56	0.79	0.239

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-5.948773	5	21.897546
A2	-4.092313	8	24.184626
A3	-5.948773	5	21.897546
fitted	-10.533249	3	27.066498
R	-24.012887	2	52.025773

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	39.8411	6	<0.0001
Test 2	3.71292	3	0.2942
Test 3	3.71292	3	0.2942
Test 4	9.16895	2	0.01021

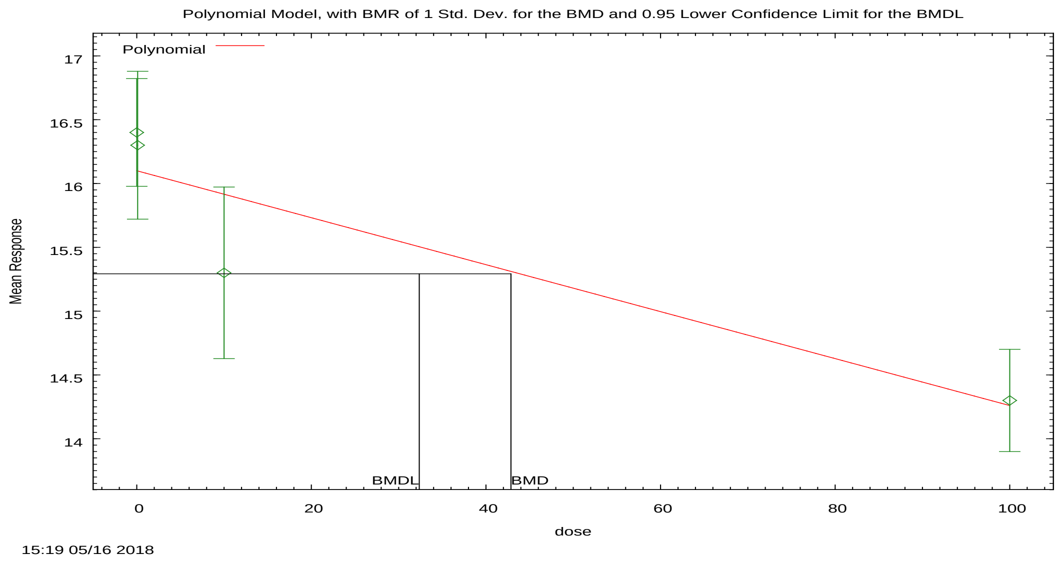

Figure 26. Plot of mean response by dose with fitted curve for Polynomial 2° model with constant variance for Hemoglobin in Males (90-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 42.8617

BMDL at the 95% confidence level = 32.3608

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.62292	0.55035
rho	n/a	0
beta_0	16.0818	16.356
beta_1	-0.0184139	-0.115103
beta_2	0	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	16.4	16.1	0.59	0.79	1.27
0.1	10	16.3	16.1	0.81	0.79	0.881
10	10	15.3	15.9	0.94	0.79	-2.39
100	10	14.3	14.2	0.56	0.79	0.239

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-5.948773	5	21.897546
A2	-4.092313	8	24.184626
A3	-5.948773	5	21.897546
fitted	-10.533249	3	27.066498
R	-24.012887	2	52.025773

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	39.8411	6	<0.0001
Test 2	3.71292	3	0.2942
Test 3	3.71292	3	0.2942
Test 4	9.16895	2	0.01021

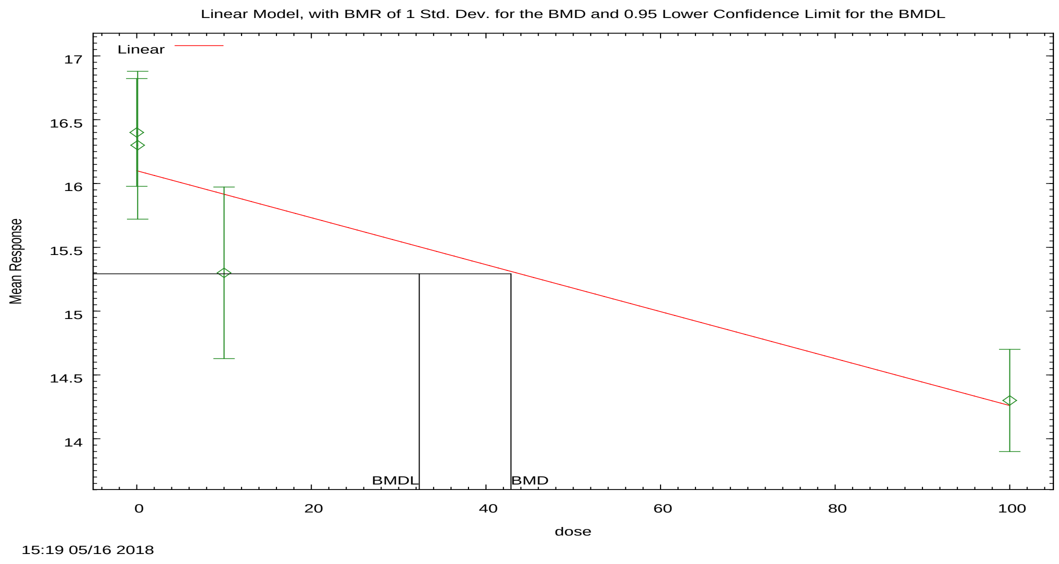

Figure 27. Plot of mean response by dose with fitted curve for Linear model with constant variance for Hemoglobin in Males (90-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 42.8617

BMDL at the 95% confidence level = 32.3608

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.62292	0.55035
rho	n/a	0
beta_0	16.0818	16.0818
beta_1	-0.0184139	-0.0184139

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	16.4	16.1	0.59	0.79	1.27
0.1	10	16.3	16.1	0.81	0.79	0.881
10	10	15.3	15.9	0.94	0.79	-2.39
100	10	14.3	14.2	0.56	0.79	0.239

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-5.948773	5	21.897546
A2	-4.092313	8	24.184626
A3	-5.948773	5	21.897546
fitted	-10.533249	3	27.066498
R	-24.012887	2	52.025773

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	39.8411	6	<0.0001
Test 2	3.71292	3	0.2942
Test 3	3.71292	3	0.2942
Test 4	9.16895	2	0.01021

BMDS WIZARD OUTPUT REPORT

BMDS Summary of H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats – Hemoglobin (g/dL) at 6-month timepoint in Males

1.4. BMDS Summary of Hemoglobin (g/dL) Males 6 months (2 Year Rats GenX)

Table 4. Summary of BMD Modeling Results for Hemoglobin in Males at 6 months (2-Year Rats); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD_{1SD} (mg/kg/day)	$BMDL_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2)	0.439	32.762	37.1	24.5	1.51	BMDLs from models that met model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values > 2.0; appropriate variance (continuous data only)) were compared. BMDLs from included models were not sufficiently close (> 3-fold difference), so the lowest BMDL was selected.
Exponential (M3)	0.220	34.621	46.9	24.7	1.90	
Exponential (M4)	**0.439**	**32.762**	**37.1**	**3.55**	**10.4**	
Exponential (M5)	N/A[b]	36.621	29.2	1.08	26.9	
Hill	N/A[b]	36.621	43.5	error[c]	error	
Power	0.220	34.621	46.7	25.3	1.84	
Polynomial 3°	0.471	32.621	45.4	39.8	1.14	
Polynomial 2°	0.470	32.624	43.3	25.3	1.71	
Linear	0.440	32.757	37.4	25.1	1.49	

[a] Constant variance case presented (BMDS Test 2 *p*-value = 0.115), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 1, and 50 mg/kg/day were -0.03, -0.88, 0.92, -0.02, respectively.

[b] No available degrees of freedom to calculate a goodness of fit value.

[c] BMD or BMDL computation failed for this model.

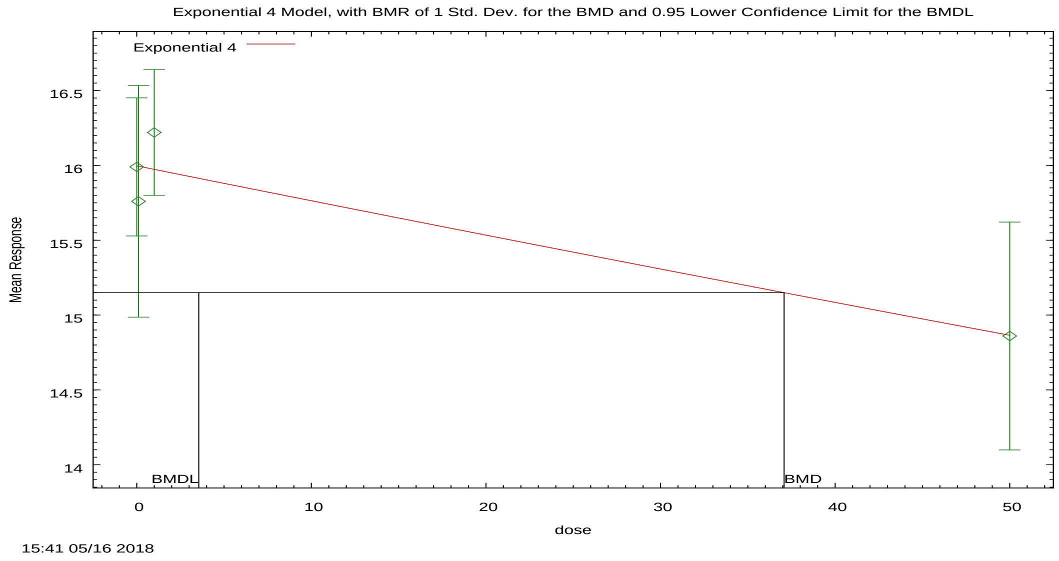

Figure 28. Plot of mean response by dose with fitted curve for Exponential (M4) model with constant variance for Hemoglobin in Males at 6 months (2-

Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 37.0764

BMDL at the 95% confidence level = 3.55258

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-0.330954	-0.372125
rho	n/a	0
a	15.997	17.031
b	0.00146813	0.0282075
c	0	0.830978
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	15.99	16	0.64	0.85	-0.02616
0.1	10	15.76	15.99	1.08	0.85	-0.8756
1	10	16.22	15.97	0.59	0.85	0.9196
50	10	14.86	14.86	1.06	0.85	-0.01788

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-12.5575	5	35.115
A2	-9.588901	8	35.1778

A3	-12.5575	5	35.115
R	-19.08199	2	42.16398
4	-13.38092	3	32.76184

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	18.99	6	0.004187
Test 2	5.937	3	0.1147
Test 3	5.937	3	0.1147
Test 6a	1.647	2	0.4389

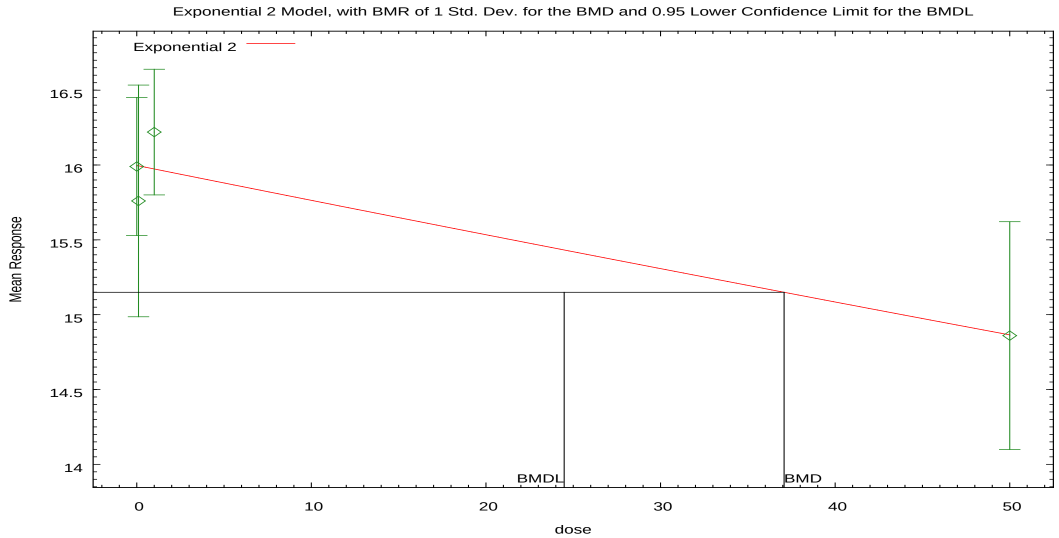

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Figure 29. Plot of mean response by dose with fitted curve for Exponential (M2) model with constant variance for Hemoglobin in Males at 6 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 37.0764

BMDL at the 95% confidence level = 24.4798

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-0.330954	-0.372125
rho	n/a	0
a	15.997	15.4073
b	0.00146813	0.00146778
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	15.99	16	0.64	0.85	-0.02617
0.1	10	15.76	15.99	1.08	0.85	-0.8756
1	10	16.22	15.97	0.59	0.85	0.9196
50	10	14.86	14.86	1.06	0.85	-0.01788

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-12.5575	5	35.115
A2	-9.588901	8	35.1778
A3	-12.5575	5	35.115
R	-19.08199	2	42.16398
2	-13.38092	3	32.76184

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	18.99	6	0.004187
Test 2	5.937	3	0.1147

Test 3	5.937	3	0.1147
Test 4	1.647	2	0.4389

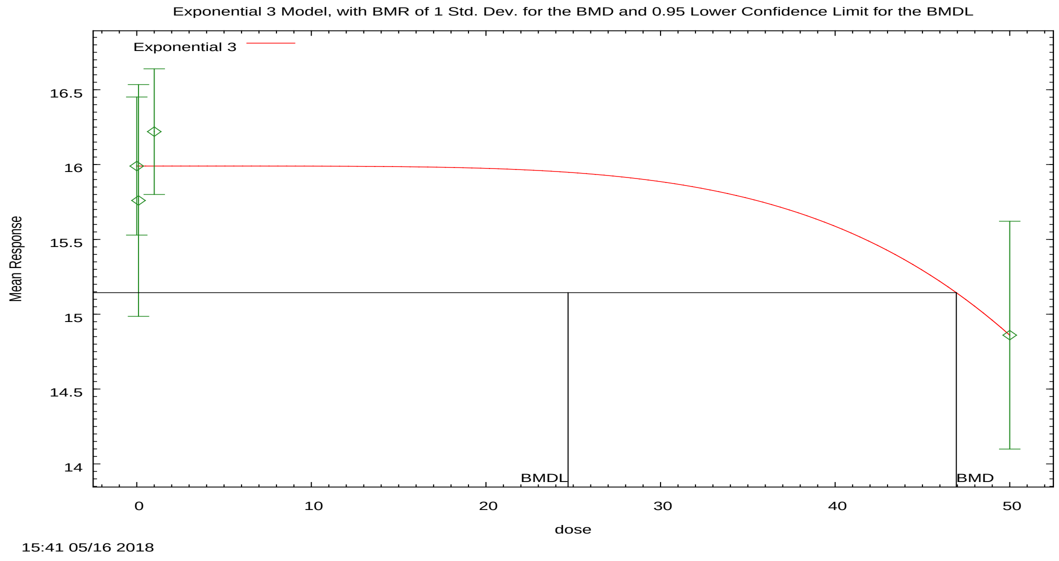

Figure 30. Plot of mean response by dose with fitted curve for Exponential (M3) model with constant variance for Hemoglobin in Males at 6 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 46.9404

BMDL at the 95% confidence level = 24.704

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-0.334469	-0.372125

rho	n/a	0
a	15.99	15.4073
b	0.0115132	0.00146778
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	15.99	15.99	0.64	0.85	-0.000000004659
0.1	10	15.76	15.99	1.08	0.85	-0.8597
1	10	16.22	15.99	0.59	0.85	0.8597
50	10	14.86	14.86	1.06	0.85	0.00000003753

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-12.5575	5	35.115
A2	-9.588901	8	35.1778
A3	-12.5575	5	35.115
R	-19.08199	2	42.16398
3	-13.31062	4	34.62125

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	18.99	6	0.004187
Test 2	5.937	3	0.1147
Test 3	5.937	3	0.1147
Test 5a	1.506	1	0.2197

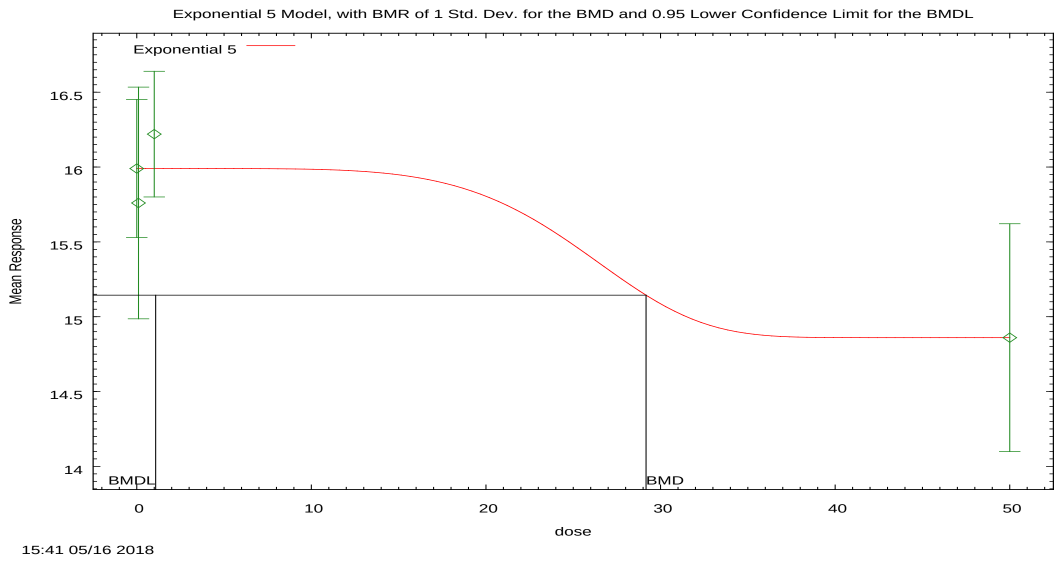

Figure 31. Plot of mean response by dose with fitted curve for Exponential (M5) model with constant variance for Hemoglobin in Males at 6 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 29.1698

BMDL at the 95% confidence level = 1.08248

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-0.334469	-0.372125
rho	n/a	0
a	15.99	17.031
b	0.0363876	0.0282075

c	0.929331	0.830978
d	5.41582	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	15.99	15.99	0.64	0.85	-0.00000009368
0.1	10	15.76	15.99	1.08	0.85	-0.8597
1	10	16.22	15.99	0.59	0.85	0.8597
50	10	14.86	14.86	1.06	0.85	-0.0000002029

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-12.5575	5	35.115
A2	-9.588901	8	35.1778
A3	-12.5575	5	35.115
R	-19.08199	2	42.16398
5	-13.31062	5	36.62125

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	18.99	6	0.004187
Test 2	5.937	3	0.1147
Test 3	5.937	3	0.1147
Test 7a	1.506	0	N/A

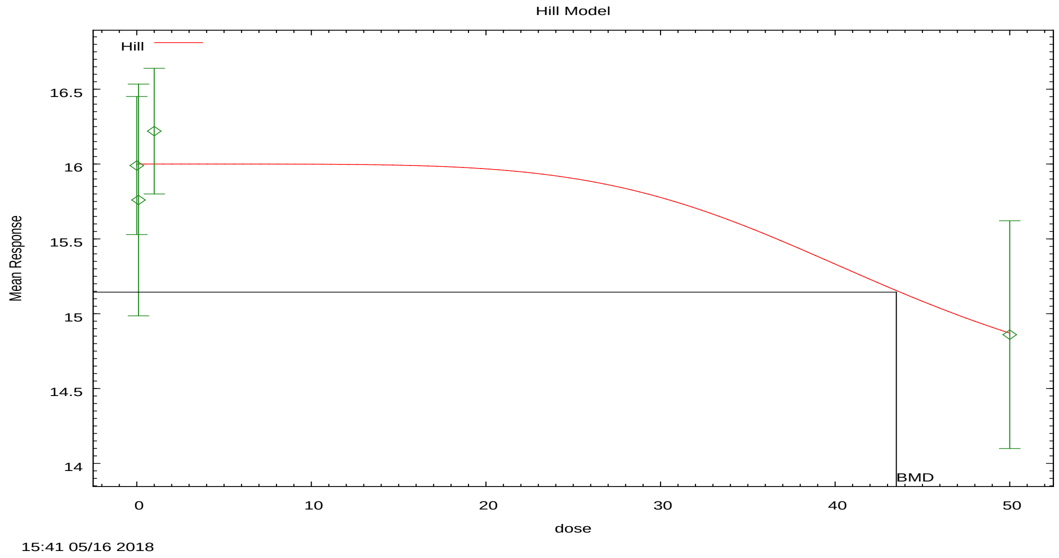

Figure 32. Plot of mean response by dose with fitted curve for Hill model with constant variance for Hemoglobin in Males at 6 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A constant variance model is fit

THE MODEL HAS PROBABLY NOT CONVERGED!!!

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 43.5036

BMDL at the 95% confidence level = error

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.715718	0.765854
rho	n/a	0
intercept	15.99	15.99
v	-1.67847	-1.13

n	5.07771	0.239697
k	43.3656	29.6434

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	16	16	0.64	0.85	-0.0000000173
0.1	10	15.8	16	1.08	0.85	-0.86
1	10	16.2	16	0.59	0.85	0.86
50	10	14.9	14.9	1.06	0.85	0.000000308

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-12.557502	5	35.115004
A2	-9.588901	8	35.177802
A3	-12.557502	5	35.115004
fitted	-13.310623	5	36.621247
R	-19.081988	2	42.163976

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	18.9862	6	0.004187
Test 2	5.9372	3	0.1147
Test 3	5.9372	3	0.1147
Test 4	1.50624	0	N/A

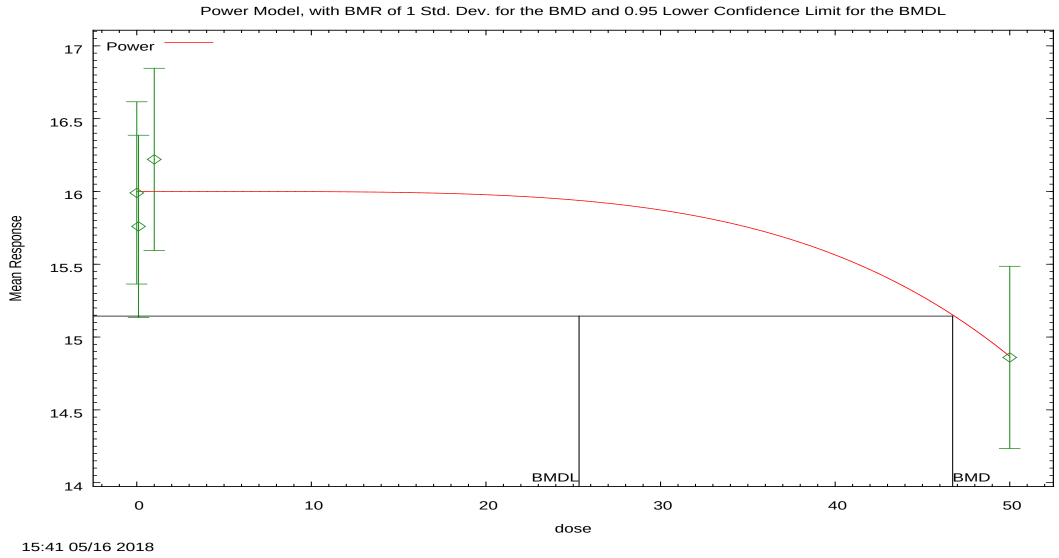

Figure 33. Plot of mean response by dose with fitted curve for Power model with constant variance for Hemoglobin in Males at 6 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 46.7298

BMDL at the 95% confidence level = 25.3338

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.715718	0.765854
rho	n/a	0
control	15.99	14.86
slope	-0.0000000606318	1.36
power	4.27929	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	16	16	0.64	0.85	-0.0000000602
0.1	10	15.8	16	1.08	0.85	-0.86
1	10	16.2	16	0.59	0.85	0.86
50	10	14.9	14.9	1.06	0.85	-0.0000000458

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-12.557502	5	35.115004
A2	-9.588901	8	35.177802
A3	-12.557502	5	35.115004
fitted	-13.310623	4	34.621247
R	-19.081988	2	42.163976

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	18.9862	6	0.004187
Test 2	5.9372	3	0.1147
Test 3	5.9372	3	0.1147
Test 4	1.50624	1	0.2197

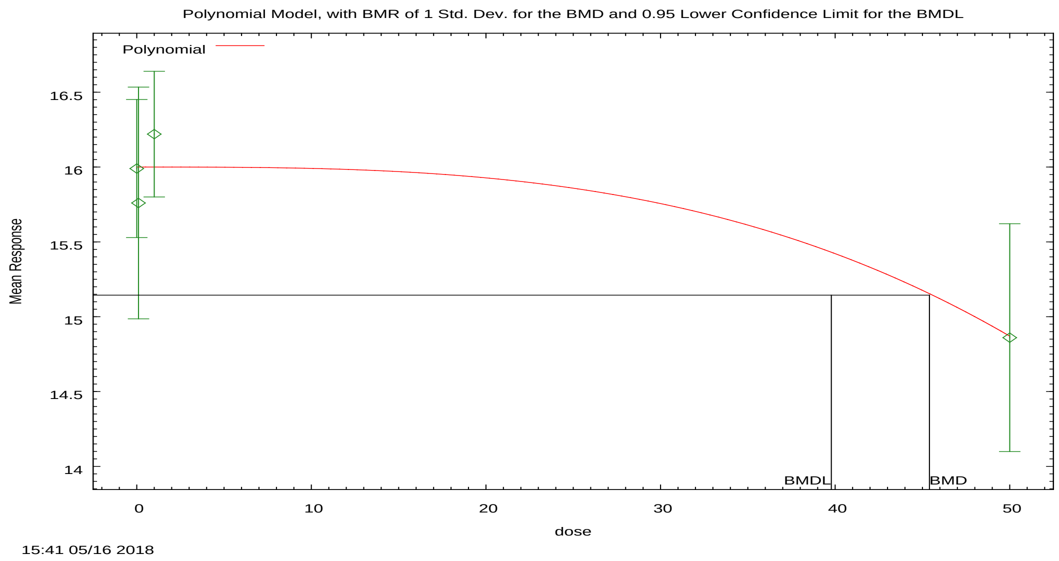

Figure 34. Plot of mean response by dose with fitted curve for Polynomial 3° model with constant variance for Hemoglobin in Males at 6 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 45.4012

BMDL at the 95% confidence level = 39.7802

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.715719	0.765854
rho	n/a	0
beta_0	15.99	15.99
beta_1	-8.20886E-24	-2.58676
beta_2	-9.65457E-27	0

beta_3	-0.00000904001	-0.0564382

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	16	16	0.64	0.85	-0.00000858
0.1	10	15.8	16	1.08	0.85	-0.86
1	10	16.2	16	0.59	0.85	0.86
50	10	14.9	14.9	1.06	0.85	-0.00000577

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-12.557502	5	35.115004
A2	-9.588901	8	35.177802
A3	-12.557502	5	35.115004
fitted	-13.310652	3	32.621305
R	-19.081988	2	42.163976

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	18.9862	6	0.004187
Test 2	5.9372	3	0.1147
Test 3	5.9372	3	0.1147
Test 4	1.5063	2	0.4709

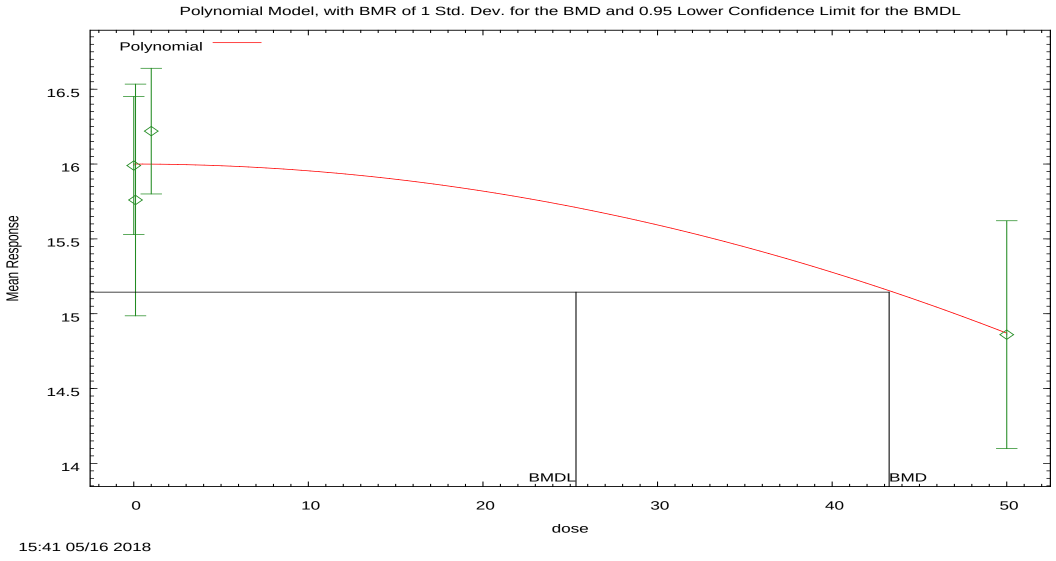

Figure 35. Plot of mean response by dose with fitted curve for Polynomial 2° model with constant variance for Hemoglobin in Males at 6 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 43.2632

BMDL at the 95% confidence level = 25.3293

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.71577	0.765854
rho	n/a	0
beta_0	15.9901	15.8647
beta_1	0	0
beta_2	-0.000452012	-0.00737093

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	16	16	0.64	0.85	-0.000454
0.1	10	15.8	16	1.08	0.85	-0.86
1	10	16.2	16	0.59	0.85	0.861
50	10	14.9	14.9	1.06	0.85	-0.00034

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-12.557502	5	35.115004
A2	-9.588901	8	35.177802
A3	-12.557502	5	35.115004
fitted	-13.312062	3	32.624125
R	-19.081988	2	42.163976

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	18.9862	6	0.004187
Test 2	5.9372	3	0.1147
Test 3	5.9372	3	0.1147
Test 4	1.50912	2	0.4702

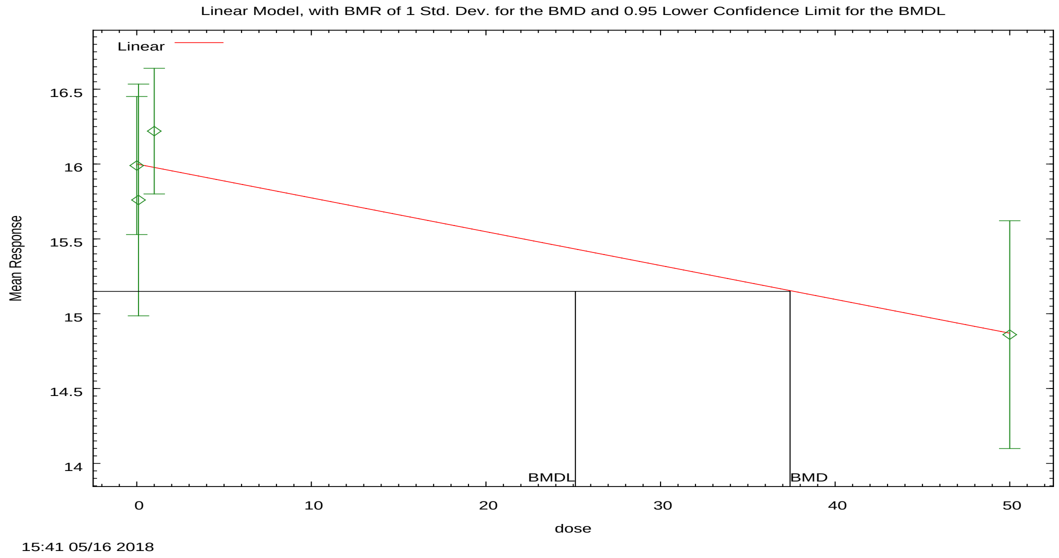

Figure 36. Plot of mean response by dose with fitted curve for Linear model with constant variance for Hemoglobin in Males at 6 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 37.4185

BMDL at the 95% confidence level = 25.1224

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.718147	0.765854
rho	n/a	0
beta_0	15.9968	15.9968
beta_1	-0.0226475	-0.0226475

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	16	16	0.64	0.85	-0.0255
0.1	10	15.8	16	1.08	0.85	-0.875
1	10	16.2	16	0.59	0.85	0.917
50	10	14.9	14.9	1.06	0.85	-0.0166

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-12.557502	5	35.115004
A2	-9.588901	8	35.177802
A3	-12.557502	5	35.115004
fitted	-13.378368	3	32.756735
R	-19.081988	2	42.163976

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	18.9862	6	0.004187
Test 2	5.9372	3	0.1147
Test 3	5.9372	3	0.1147
Test 4	1.64173	2	0.4401

BMDS WIZARD OUTPUT REPORT

BMDS Summary of 28-Day Oral (Gavage) Toxicity Study of H-28397 in Mice with a 28-day Recovery – Hematocrit (%) in Males

1.5. BMDS Summary of Hematocrit (%) Males (28 Day Mice GenX)

Table 5. Summary of BMD Modeling Results for Hematocrit in Males (28-Day Mice); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD$_{1SD}$ (mg/kg/day)	BMDL$_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2) Exponential (M3)[b]	0.0259	68.525	26.6	16.2	1.64	Only one model met model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). Selected BMDL is from this model.
Exponential (M4)	0.0743	66.399	2.55	0.00599	426	
Exponential (M5)	0.0743	66.399	2.55	0.00658	388	
Hill	**0.416**	**63.876**	**0.122**	**0.00589**	**20.7**	
Power[c] Polynomial 3°[d] Polynomial 2°[e] Linear	0.0256	68.545	26.8	16.5	1.62	

[a] Constant variance case presented (BMDS Test 2 *p*-value = 0.555), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 3, and 30 mg/kg/day were 0.01, -0.06, 0.61, -0.53, respectively.

[b] For the Exponential (M3) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M2) model.

[c] For the Power model, the power parameter estimate was 1. The models in this row reduced to the Linear model.

[d] For the Polynomial 3° model, the b3 coefficient estimates was 0 (boundary of parameters space). The models in this row reduced to the Polynomial 2° model. For the Polynomial 3° model, the b3 and b2 coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Linear model.

[e] For the Polynomial 2° model, the b2 coefficient estimate was 0 (boundary of parameters space). The models in this row reduced to the Linear model.

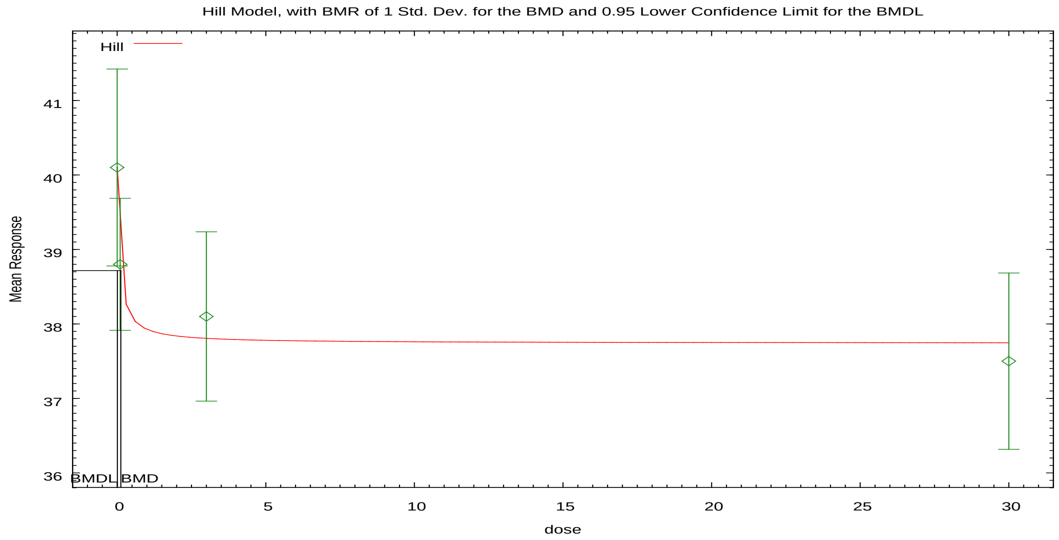

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Figure 37. Plot of mean response by dose with fitted curve for Hill model with constant variance for Hematocrit in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 0.121759

BMDL at the 95% confidence level = 0.00588873

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	1.90295	2.11508
rho	n/a	0
intercept	40.0946	40.1
v	-2.35783	-2.6
n	1	0.176992
k	0.0863544	0.1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	9	40.1	40.1	1.72	1.38	0.0117
0.1	8	38.8	38.8	1.06	1.38	-0.0602
3	8	38.1	37.8	1.36	1.38	0.609
30	9	37.5	37.7	1.54	1.38	-0.53

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC

A1	-27.606801	5	65.213603
A2	-26.564691	8	69.129382
A3	-27.606801	5	65.213603
fitted	-27.937879	4	63.875758
R	-34.799167	2	73.598334

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	16.469	6	0.01145
Test 2	2.08422	3	0.5551
Test 3	2.08422	3	0.5551
Test 4	0.662155	1	0.4158

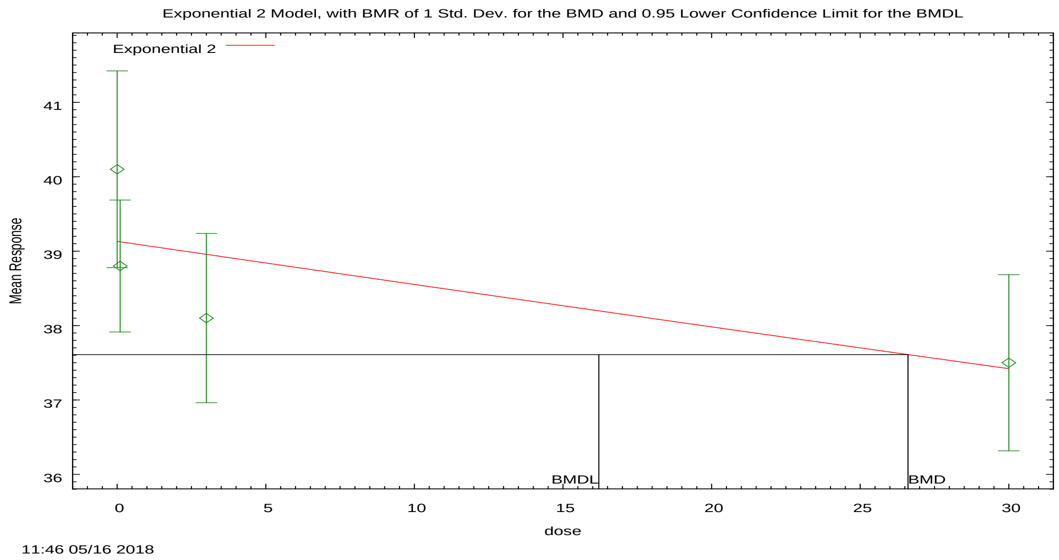


Figure 38. Plot of mean response by dose with fitted curve for Exponential (M2) model with constant variance for Hematocrit in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 26.6079

BMDL at the 95% confidence level = 16.2043

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	0.838957	0.623929
rho	n/a	0
a	39.1306	38.1316
b	0.00149016	0.00147576
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	9	40.1	39.13	1.72	1.52	1.912
0.1	8	38.8	39.12	1.06	1.52	-0.6038
3	8	38.1	38.96	1.36	1.52	-1.592
30	9	37.5	37.42	1.54	1.52	0.1582

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-27.6068	5	65.2136
A2	-26.56469	8	69.12938
A3	-27.6068	5	65.2136
R	-34.79917	2	73.59833
2	-31.26227	3	68.52455

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value

Test 1	16.47	6	0.01145
Test 2	2.084	3	0.5551
Test 3	2.084	3	0.5551
Test 4	7.311	2	0.02585

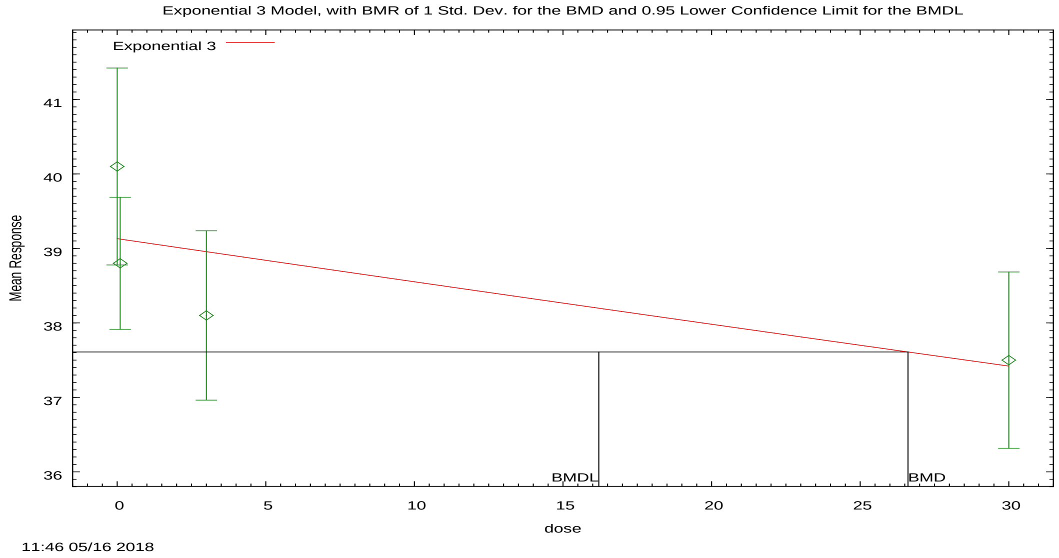


Figure 39. Plot of mean response by dose with fitted curve for Exponential (M3) model with constant variance for Hematocrit in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 26.6079

BMDL at the 95% confidence level = 16.2043

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values

lnalpha	0.838957	0.623929
rho	n/a	0
a	39.1306	38.1316
b	0.00149016	0.00147576
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	9	40.1	39.13	1.72	1.52	1.912
0.1	8	38.8	39.12	1.06	1.52	-0.6038
3	8	38.1	38.96	1.36	1.52	-1.592
30	9	37.5	37.42	1.54	1.52	0.1582

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-27.6068	5	65.2136
A2	-26.56469	8	69.12938
A3	-27.6068	5	65.2136
R	-34.79917	2	73.59833
3	-31.26227	3	68.52455

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	16.47	6	0.01145
Test 2	2.084	3	0.5551
Test 3	2.084	3	0.5551
Test 5a	7.311	2	0.02585

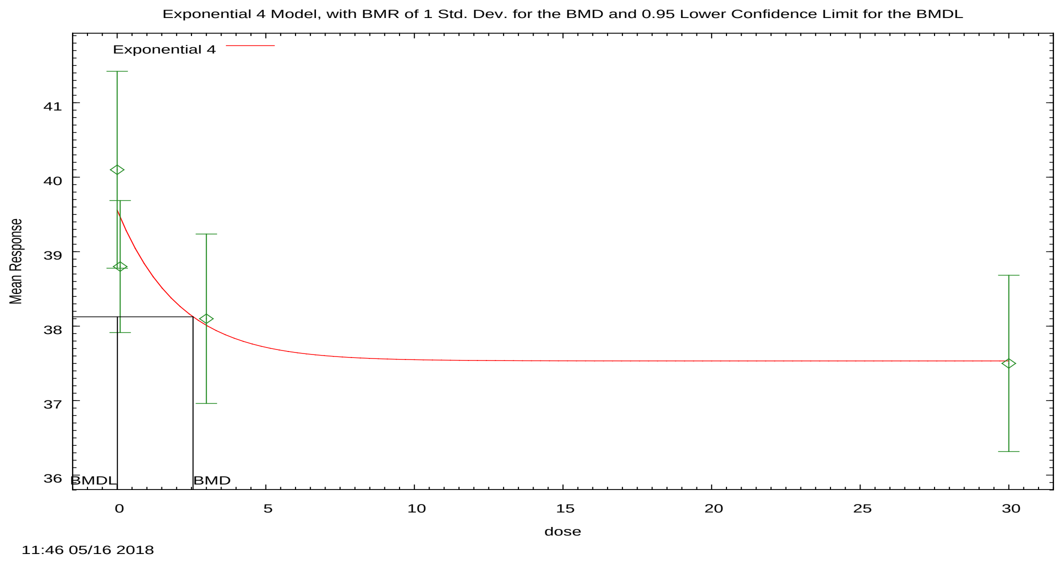


Figure 40. Plot of mean response by dose with fitted curve for Exponential (M4) model with constant variance for Hematocrit in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 2.55178

BMDL at the 95% confidence level = 0.00599229

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	0.717617	0.623929
rho	n/a	0
a	39.5575	42.105
b	0.481184	0.0454117
c	0.948817	0.84822

d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	9	40.1	39.56	1.72	1.43	1.137
0.1	8	38.8	39.46	1.06	1.43	-1.309
3	8	38.1	38.01	1.36	1.43	0.1761
30	9	37.5	37.53	1.54	1.43	-0.06887

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-27.6068	5	65.2136
A2	-26.56469	8	69.12938
A3	-27.6068	5	65.2136
R	-34.79917	2	73.59833
4	-29.19949	4	66.39898

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	16.47	6	0.01145
Test 2	2.084	3	0.5551
Test 3	2.084	3	0.5551
Test 6a	3.185	1	0.0743

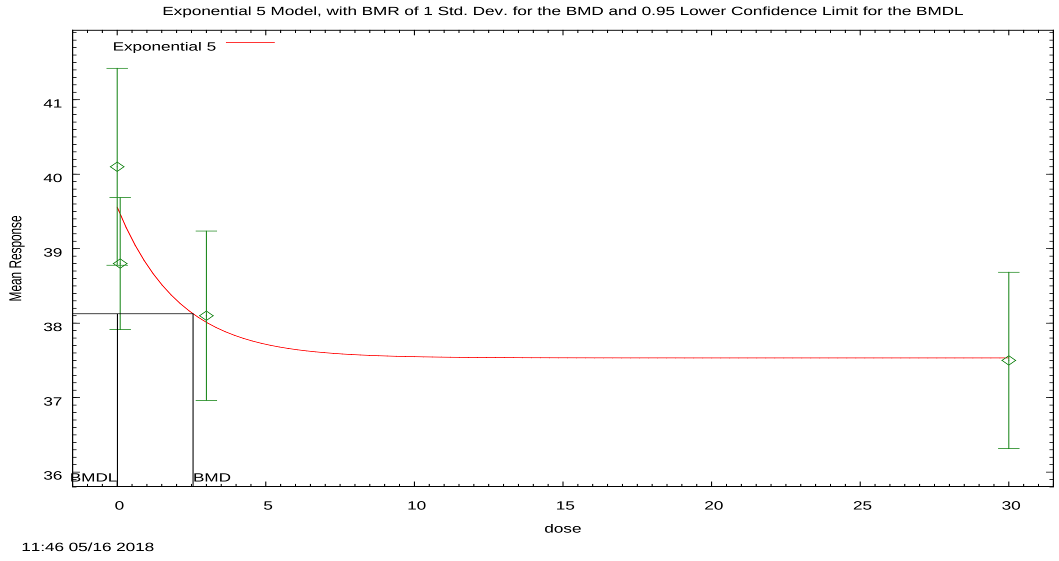


Figure 41. Plot of mean response by dose with fitted curve for Exponential (M5) model with constant variance for Hematocrit in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 2.55177

BMDL at the 95% confidence level = 0.00657763

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	0.717617	0.623929
rho	n/a	0
a	39.5575	42.105
b	0.481185	0.0454117
c	0.948817	0.84822

d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	9	40.1	39.56	1.72	1.43	1.137
0.1	8	38.8	39.46	1.06	1.43	-1.309
3	8	38.1	38.01	1.36	1.43	0.1761
30	9	37.5	37.53	1.54	1.43	-0.06887

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-27.6068	5	65.2136
A2	-26.56469	8	69.12938
A3	-27.6068	5	65.2136
R	-34.79917	2	73.59833
5	-29.19949	4	66.39898

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	16.47	6	0.01145
Test 2	2.084	3	0.5551
Test 3	2.084	3	0.5551
Test 7a	3.185	1	0.0743

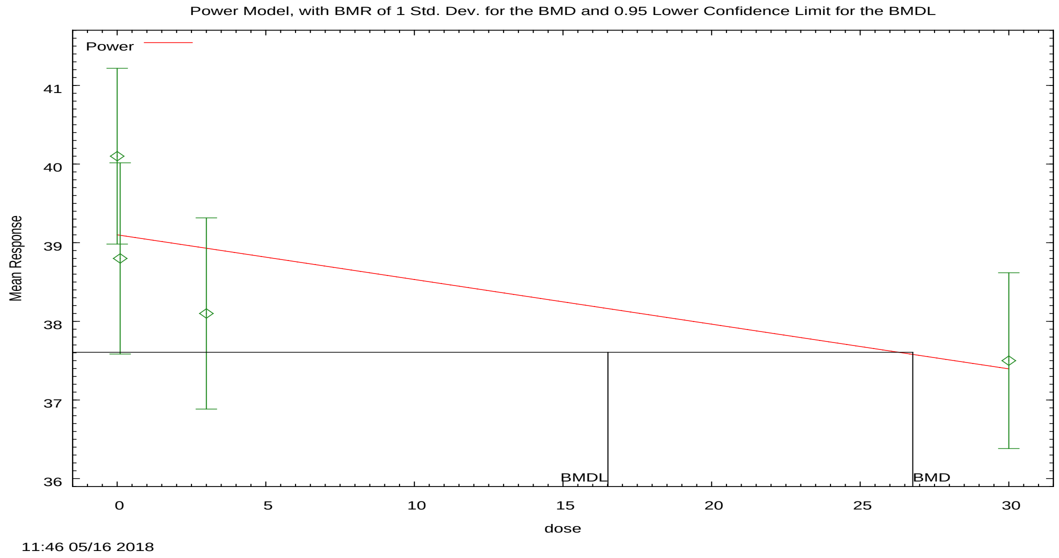


Figure 42. Plot of mean response by dose with fitted curve for Power model with constant variance for Hematocrit in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 26.7678

BMDL at the 95% confidence level = 16.5116

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	2.31536	2.11508
rho	n/a	0
control	39.1282	40.1
slope	-0.0568457	-5.63333
power	1	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	9	40.1	39.1	1.72	1.52	1.92
0.1	8	38.8	39.1	1.06	1.52	-0.599
3	8	38.1	39	1.36	1.52	-1.59
30	9	37.5	37.4	1.54	1.52	0.152

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-27.606801	5	65.213603
A2	-26.564691	8	69.129382
A3	-27.606801	5	65.213603
fitted	-31.272636	3	68.545272
R	-34.799167	2	73.598334

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	16.469	6	0.01145
Test 2	2.08422	3	0.5551
Test 3	2.08422	3	0.5551
Test 4	7.33167	2	0.02558

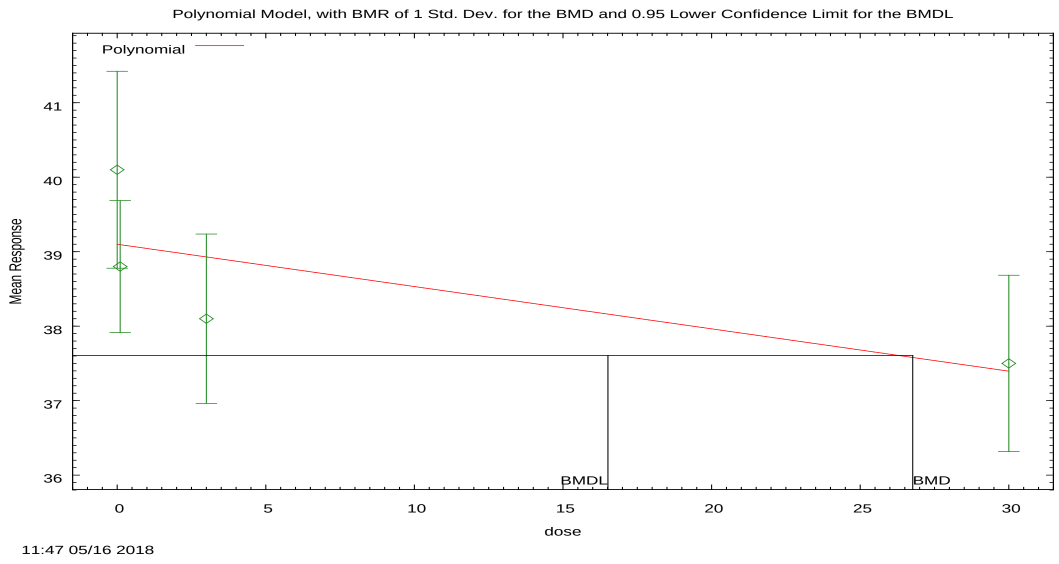


Figure 43. Plot of mean response by dose with fitted curve for Polynomial 3° model with constant variance for Hematocrit in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 26.7678

BMDL at the 95% confidence level = 16.5116

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	2.31536	2.11508
rho	n/a	0
beta_0	39.1282	40.1
beta_1	-0.0568457	-13.4677
beta_2	0	0

beta_3	0	-0.141518

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	9	40.1	39.1	1.72	1.52	1.92
0.1	8	38.8	39.1	1.06	1.52	-0.599
3	8	38.1	39	1.36	1.52	-1.59
30	9	37.5	37.4	1.54	1.52	0.152

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-27.606801	5	65.213603
A2	-26.564691	8	69.129382
A3	-27.606801	5	65.213603
fitted	-31.272636	3	68.545272
R	-34.799167	2	73.598334

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	16.469	6	0.01145
Test 2	2.08422	3	0.5551
Test 3	2.08422	3	0.5551
Test 4	7.33167	2	0.02558

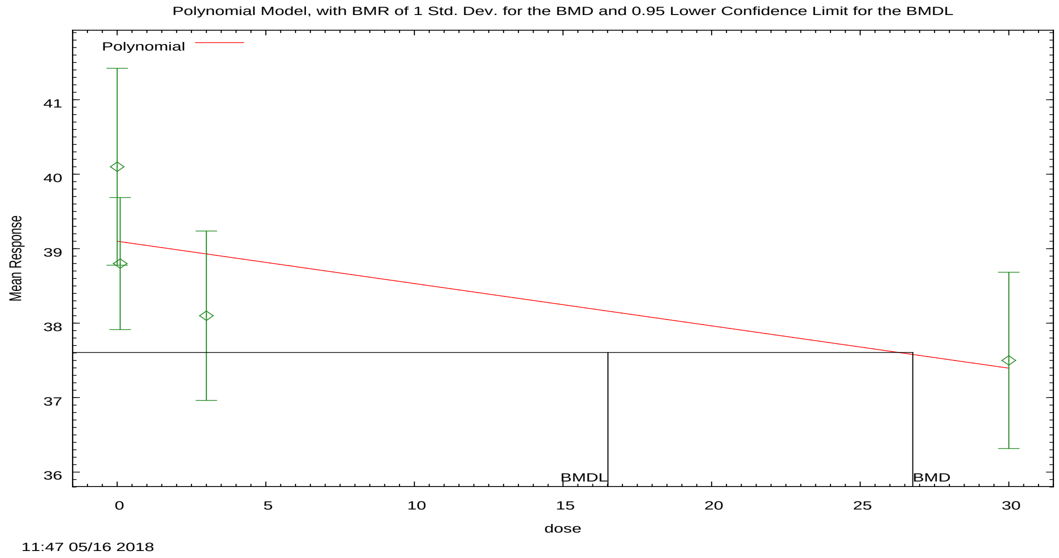


Figure 44. Plot of mean response by dose with fitted curve for Polynomial 2° model with constant variance for Hematocrit in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 26.7678

BMDL at the 95% confidence level = 16.5116

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	2.31536	2.11508
rho	n/a	0
beta_0	39.1282	39.4873
beta_1	-0.0568457	-0.515152
beta_2	0	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	9	40.1	39.1	1.72	1.52	1.92
0.1	8	38.8	39.1	1.06	1.52	-0.599
3	8	38.1	39	1.36	1.52	-1.59
30	9	37.5	37.4	1.54	1.52	0.152

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-27.606801	5	65.213603
A2	-26.564691	8	69.129382
A3	-27.606801	5	65.213603
fitted	-31.272636	3	68.545272
R	-34.799167	2	73.598334

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	16.469	6	0.01145
Test 2	2.08422	3	0.5551
Test 3	2.08422	3	0.5551
Test 4	7.33167	2	0.02558

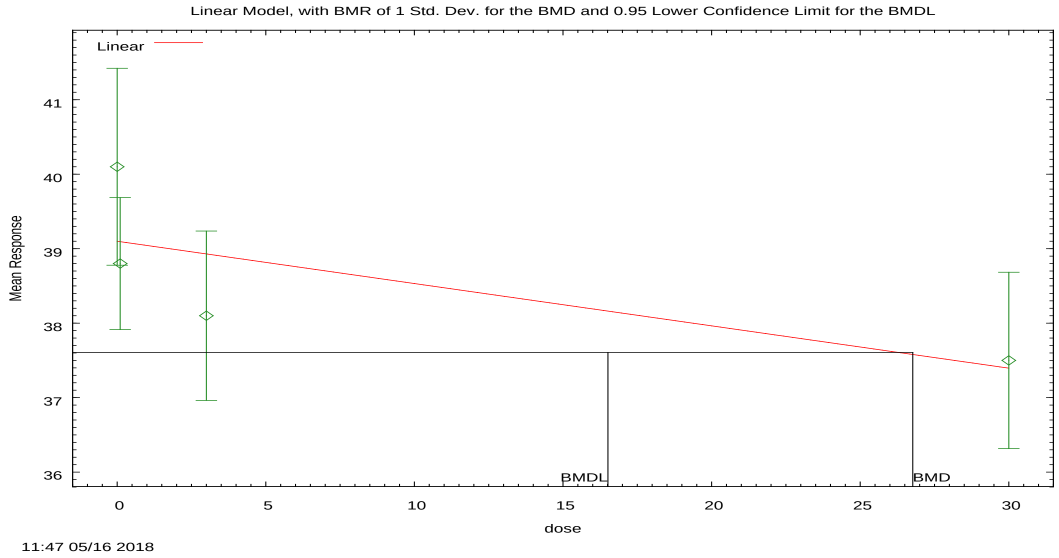


Figure 45. Plot of mean response by dose with fitted curve for Linear model with constant variance for Hematocrit in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 26.7678

BMDL at the 95% confidence level = 16.5116

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	2.31536	2.11508
rho	n/a	0
beta_0	39.1282	39.085
beta_1	-0.0568457	-0.055593

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	9	40.1	39.1	1.72	1.52	1.92
0.1	8	38.8	39.1	1.06	1.52	-0.599
3	8	38.1	39	1.36	1.52	-1.59
30	9	37.5	37.4	1.54	1.52	0.152

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-27.606801	5	65.213603
A2	-26.564691	8	69.129382
A3	-27.606801	5	65.213603
fitted	-31.272636	3	68.545272
R	-34.799167	2	73.598334

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	16.469	6	0.01145
Test 2	2.08422	3	0.5551
Test 3	2.08422	3	0.5551
Test 4	7.33167	2	0.02558

BMDS WIZARD OUTPUT REPORT

BMDS Summary of 28-Day Oral (Gavage) Toxicity Study of H-28397 in Rats with a 28-day Recovery – Hematocrit (%) in Males

1.6. BMDS Summary of Hematocrit (%) Males (28 Day Rats GenX)

Table 6. Summary of BMD Modeling Results for Hematocrit in Males (28-Day Rats); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD_{1SD} (mg/kg/day)	$BMDL_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2) Exponential (M3)[b]	0.0164	83.111	16.2	11.6	1.41	BMDLs from models that met model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values > 2.0; appropriate variance (continuous data only)) were compared. Selected BMDL is from model with lowest AIC and lowest BMDL.
Exponential (M4) Exponential (M5)[c]	0.53	77.289	1.76	0.738	2.39	
Hill	**0.676**	**77.070**	**1.35**	**0.357**	**3.78**	
Power[d] Polynomial 3°[e] Polynomial 2°[f] Linear	0.0159	83.185	16.6	11.9	1.39	

[a] Constant variance case presented (BMDS Test 2 *p*-value = 0.908), selected model in bold; scaled residuals for selected model for doses 0, 0.3, 3, and 30 mg/kg/day were 0.22, -0.32, 0.15, -0.05, respectively.

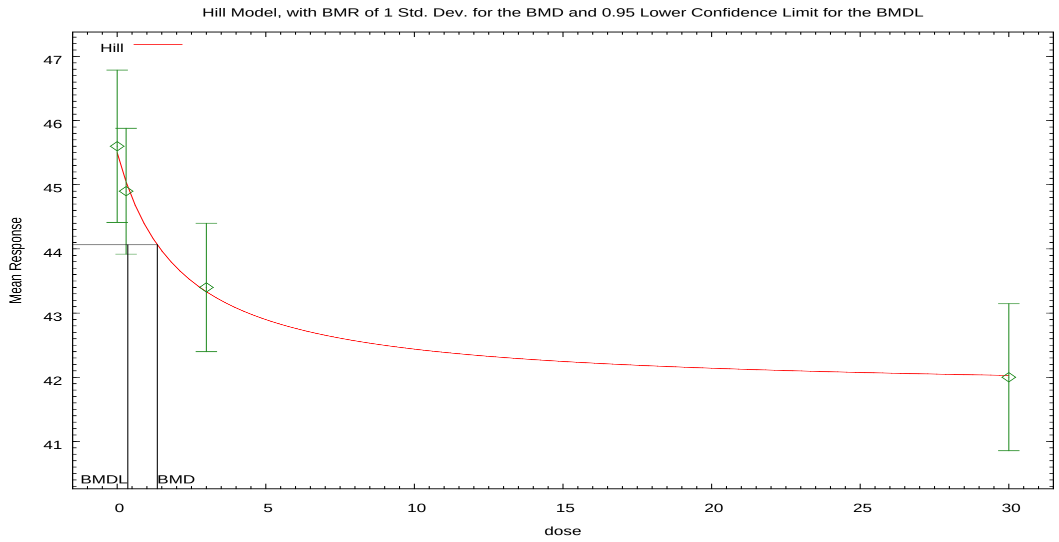
[b] For the Exponential (M3) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M2) model.

[c] For the Exponential (M5) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M4) model.

[d] For the Power model, the power parameter estimate was 1. The models in this row reduced to the Linear model.

[e] For the Polynomial 3° model, the b3 coefficient estimates was 0 (boundary of parameters space). The models in this row reduced to the Polynomial 2° model. For the Polynomial 3° model, the b3 and b2 coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Linear model.

[f] For the Polynomial 2° model, the b2 coefficient estimate was 0 (boundary of parameters space). The models in this row reduced to the Linear model.



Hill Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

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Figure 46. Plot of mean response by dose with fitted curve for Hill model with constant variance for Hematocrit in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 1.35004

BMDL at the 95% confidence level = 0.357169

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	2.06835	2.28813
rho	n/a	0
intercept	45.501	45.6
v	-3.72485	-3.6
n	1	1.17389
k	2.14654	2.28

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	45.6	45.5	1.66	1.44	0.218
0.3	10	44.9	45	1.37	1.44	-0.317
3	10	43.4	43.3	1.4	1.44	0.154
30	10	42	42	1.6	1.44	-0.0548

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-34.447444	5	78.894888
A2	-34.173832	8	84.347664
A3	-34.447444	5	78.894888
fitted	-34.535063	4	77.070127
R	-47.681776	2	99.363552

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	27.0159	6	0.0001438
Test 2	0.547224	3	0.9084
Test 3	0.547224	3	0.9084
Test 4	0.175239	1	0.6755

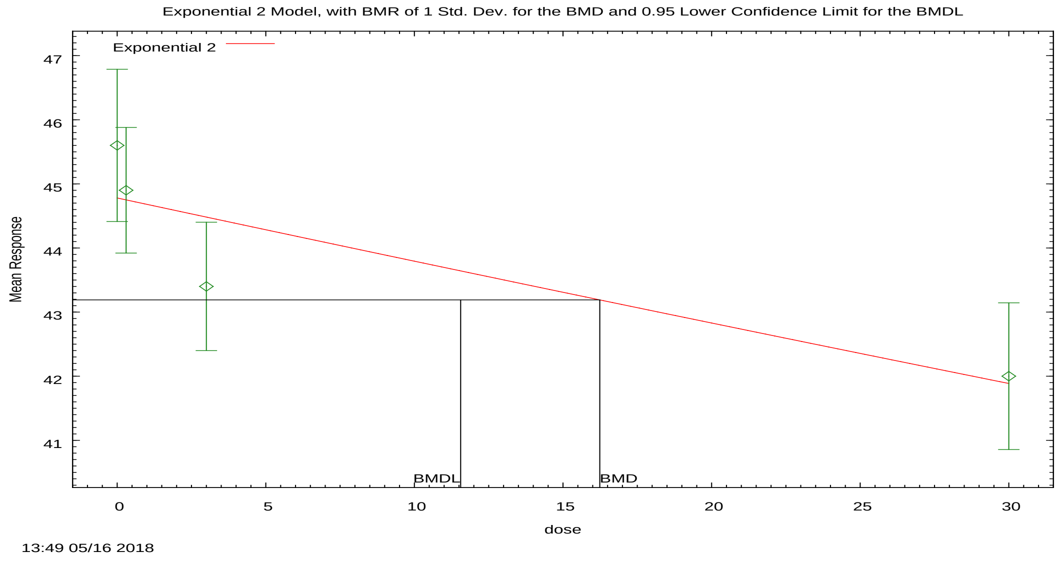

Figure 47. Plot of mean response by dose with fitted curve for Exponential (M2) model with constant variance for Hematocrit in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 16.2379

BMDL at the 95% confidence level = 11.5562

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	0.92777	0.722372
rho	n/a	0
a	44.7804	43.1524
b	0.00222676	0.00220782
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	45.6	44.78	1.66	1.59	1.63
0.3	10	44.9	44.75	1.37	1.59	0.2973
3	10	43.4	44.48	1.4	1.59	-2.152
30	10	42	41.89	1.6	1.59	0.2254

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-34.44744	5	78.89489
A2	-34.17383	8	84.34766
A3	-34.44744	5	78.89489
R	-47.68178	2	99.36355
2	-38.5554	3	83.11081

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	27.02	6	0.0001438
Test 2	0.5472	3	0.9084
Test 3	0.5472	3	0.9084
Test 4	8.216	2	0.01644

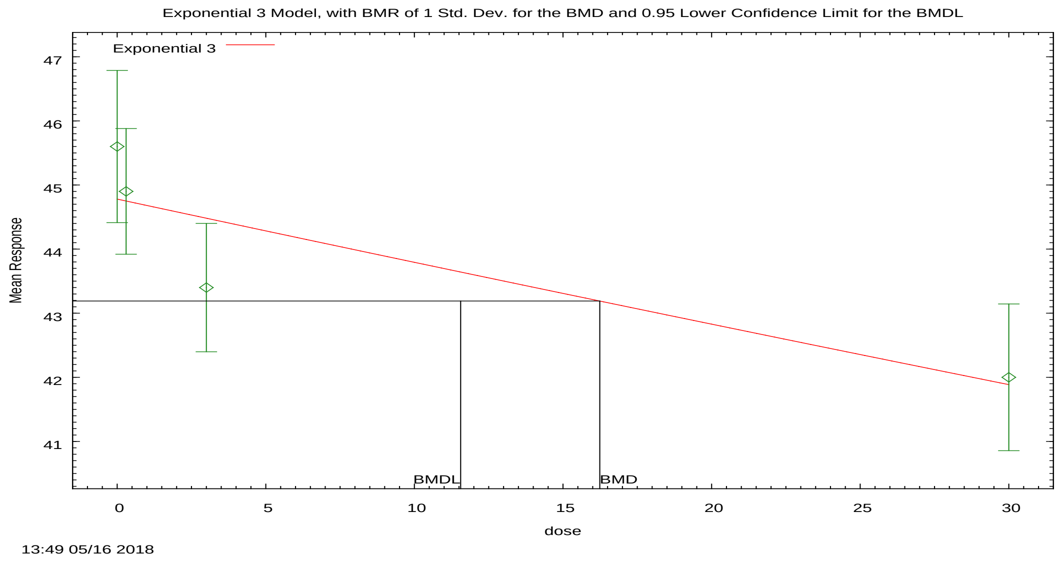

Figure 48. Plot of mean response by dose with fitted curve for Exponential (M3) model with constant variance for Hematocrit in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 16.2379

BMDL at the 95% confidence level = 11.5562

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	0.92777	0.722372
rho	n/a	0
a	44.7804	43.1524
b	0.00222676	0.00220782
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	45.6	44.78	1.66	1.59	1.63
0.3	10	44.9	44.75	1.37	1.59	0.2973
3	10	43.4	44.48	1.4	1.59	-2.152
30	10	42	41.89	1.6	1.59	0.2254

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-34.44744	5	78.89489
A2	-34.17383	8	84.34766
A3	-34.44744	5	78.89489
R	-47.68178	2	99.36355
3	-38.5554	3	83.11081

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	27.02	6	0.0001438
Test 2	0.5472	3	0.9084
Test 3	0.5472	3	0.9084
Test 5a	8.216	2	0.01644

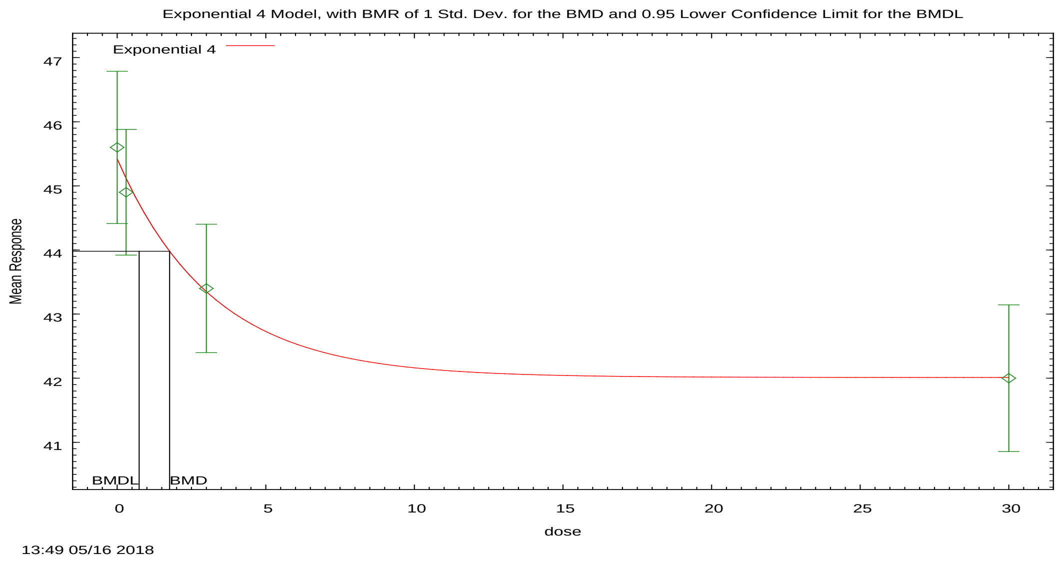

Figure 49. Plot of mean response by dose with fitted curve for Exponential (M4) model with constant variance for Hematocrit in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 1.76258

BMDL at the 95% confidence level = 0.738122

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	0.732232	0.722372
rho	n/a	0
a	45.4219	47.88
b	0.31179	0.0481796
c	0.924905	0.835422

d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	45.6	45.42	1.66	1.44	0.3906
0.3	10	44.9	45.12	1.37	1.44	-0.4765
3	10	43.4	43.35	1.4	1.44	0.1106
30	10	42	42.01	1.6	1.44	-0.02467

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-34.44744	5	78.89489
A2	-34.17383	8	84.34766
A3	-34.44744	5	78.89489
R	-47.68178	2	99.36355
4	-34.64464	4	77.28927

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	27.02	6	0.0001438
Test 2	0.5472	3	0.9084
Test 3	0.5472	3	0.9084
Test 6a	0.3944	1	0.53

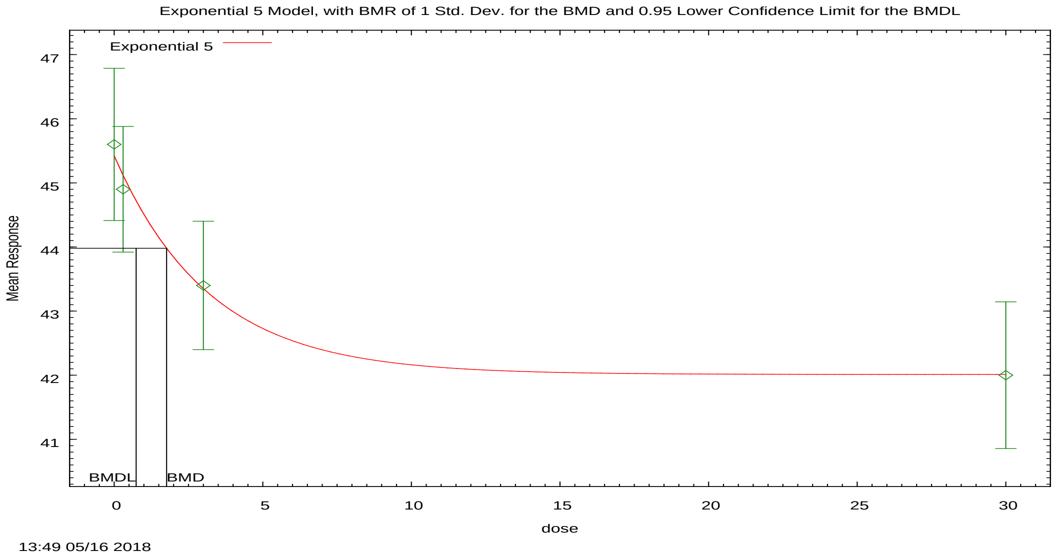

Figure 50. Plot of mean response by dose with fitted curve for Exponential (M5) model with constant variance for Hematocrit in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 1.76258

BMDL at the 95% confidence level = 0.738122

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	0.732232	0.722372
rho	n/a	0
a	45.4219	47.88
b	0.31179	0.0481796
c	0.924905	0.835422

d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	45.6	45.42	1.66	1.44	0.3906
0.3	10	44.9	45.12	1.37	1.44	-0.4765
3	10	43.4	43.35	1.4	1.44	0.1106
30	10	42	42.01	1.6	1.44	-0.02467

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-34.44744	5	78.89489
A2	-34.17383	8	84.34766
A3	-34.44744	5	78.89489
R	-47.68178	2	99.36355
5	-34.64464	4	77.28927

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	27.02	6	0.0001438
Test 2	0.5472	3	0.9084
Test 3	0.5472	3	0.9084
Test 7a	0.3944	1	0.53

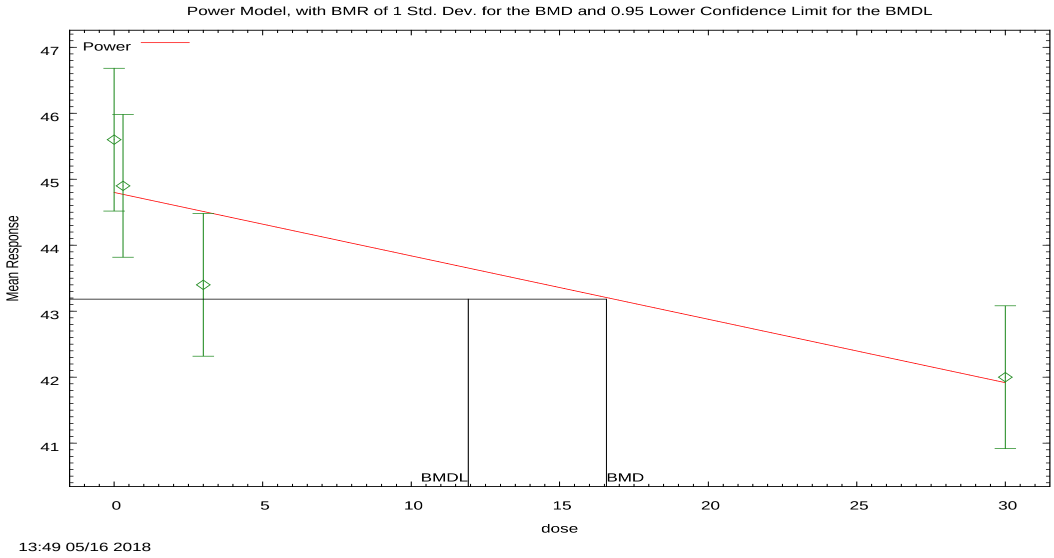

Figure 51. Plot of mean response by dose with fitted curve for Power model with constant variance for Hematocrit in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 16.5698

BMDL at the 95% confidence level = 11.9179

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	2.53353	2.28813
rho	n/a	0
control	44.7747	45.6
slope	-0.0960605	-10.5553
power	1	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	45.6	44.8	1.66	1.59	1.64
0.3	10	44.9	44.7	1.37	1.59	0.306
3	10	43.4	44.5	1.4	1.59	-2.16
30	10	42	41.9	1.6	1.59	0.213

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-34.447444	5	78.894888
A2	-34.173832	8	84.347664
A3	-34.447444	5	78.894888
fitted	-38.592269	3	83.184538
R	-47.681776	2	99.363552

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	27.0159	6	0.0001438
Test 2	0.547224	3	0.9084
Test 3	0.547224	3	0.9084
Test 4	8.28965	2	0.01585

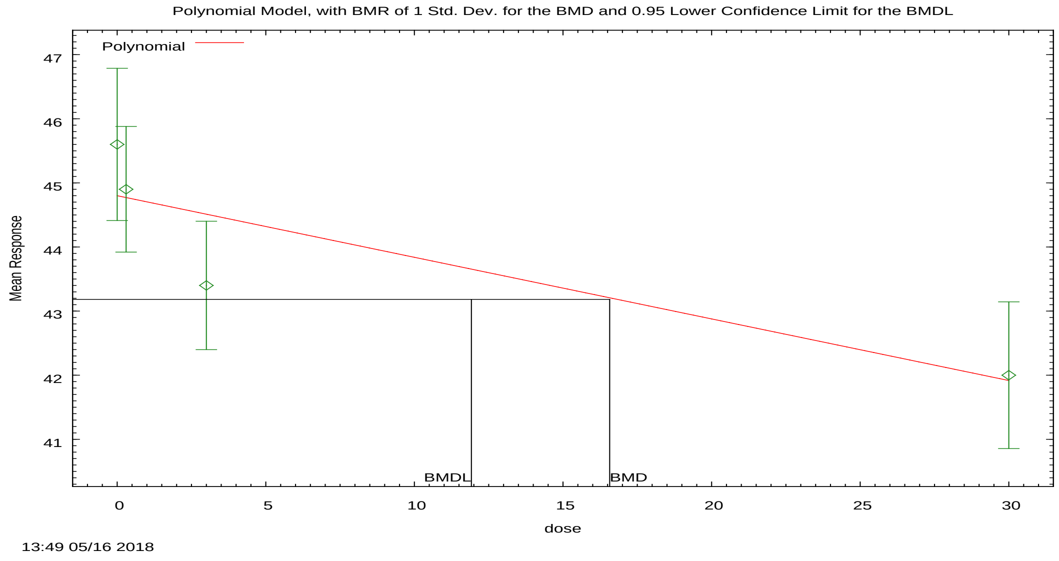

Figure 52. Plot of mean response by dose with fitted curve for Polynomial 3° model with constant variance for Hematocrit in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 16.5698

BMDL at the 95% confidence level = 11.9179

Parameter Estimates

Variable	**Estimate**	**Default Initial Parameter Values**
alpha	2.53353	2.28813
rho	n/a	0
beta_0	44.7747	45.6
beta_1	-0.0960604	-2.52838
beta_2	0	0

beta_3	0	-0.0191878

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	45.6	44.8	1.66	1.59	1.64
0.3	10	44.9	44.7	1.37	1.59	0.306
3	10	43.4	44.5	1.4	1.59	-2.16
30	10	42	41.9	1.6	1.59	0.213

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-34.447444	5	78.894888
A2	-34.173832	8	84.347664
A3	-34.447444	5	78.894888
fitted	-38.592269	3	83.184538
R	-47.681776	2	99.363552

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	27.0159	6	0.0001438
Test 2	0.547224	3	0.9084
Test 3	0.547224	3	0.9084
Test 4	8.28965	2	0.01585

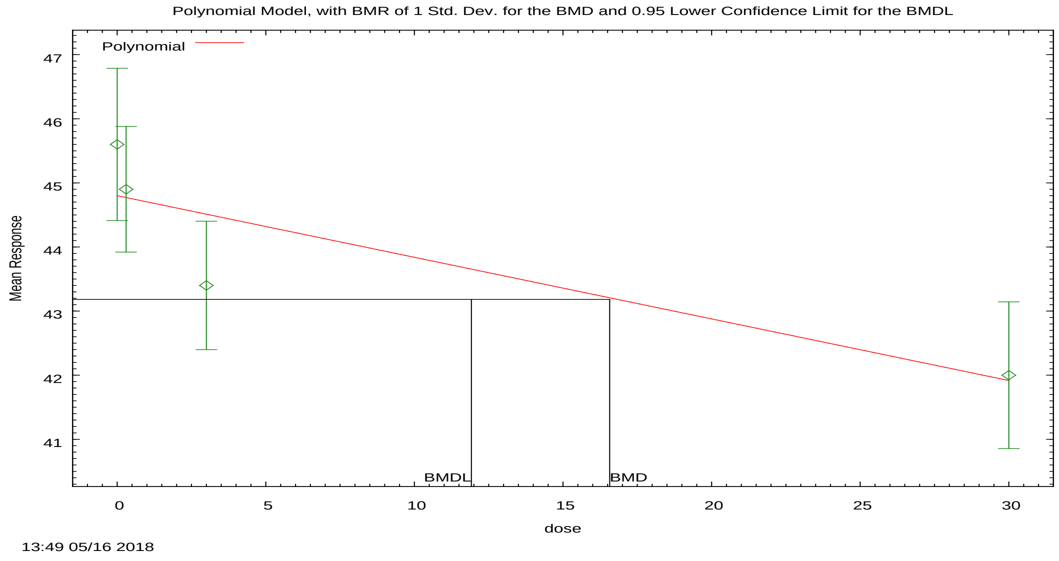

Figure 53. Plot of mean response by dose with fitted curve for Polynomial 2° model with constant variance for Hematocrit in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 16.5698

BMDL at the 95% confidence level = 11.9179

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	2.53353	2.28813
rho	n/a	0
beta_0	44.7747	45.3723
beta_1	-0.0960605	-0.728393
beta_2	0	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	45.6	44.8	1.66	1.59	1.64
0.3	10	44.9	44.7	1.37	1.59	0.306
3	10	43.4	44.5	1.4	1.59	-2.16
30	10	42	41.9	1.6	1.59	0.213

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-34.447444	5	78.894888
A2	-34.173832	8	84.347664
A3	-34.447444	5	78.894888
fitted	-38.592269	3	83.184538
R	-47.681776	2	99.363552

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	27.0159	6	0.0001438
Test 2	0.547224	3	0.9084
Test 3	0.547224	3	0.9084
Test 4	8.28965	2	0.01585

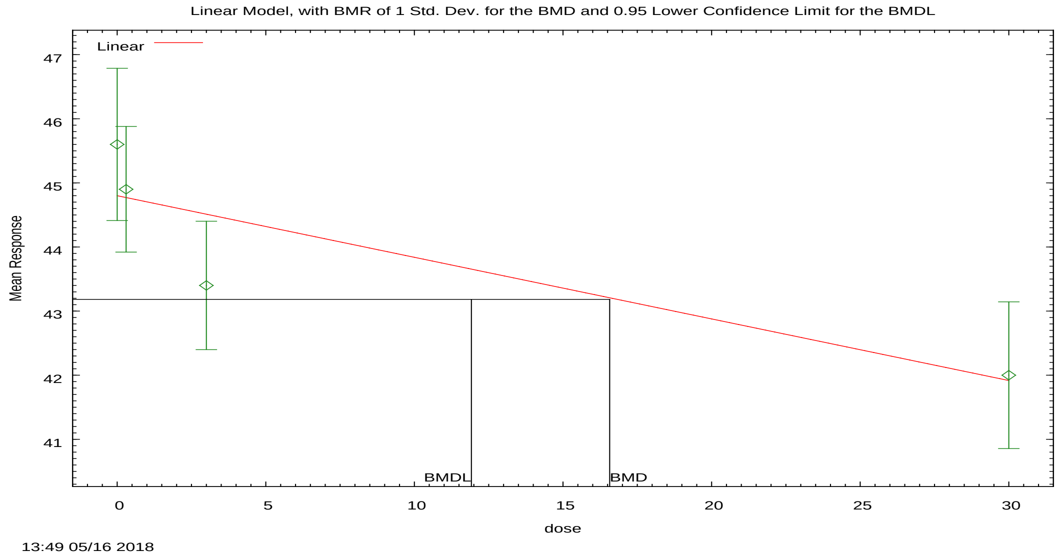

Figure 54. Plot of mean response by dose with fitted curve for Linear model with constant variance for Hematocrit in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 16.5698

BMDL at the 95% confidence level = 11.9179

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	2.53353	2.28813
rho	n/a	0
beta_0	44.7747	44.7747
beta_1	-0.0960605	-0.0960605

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	45.6	44.8	1.66	1.59	1.64
0.3	10	44.9	44.7	1.37	1.59	0.306
3	10	43.4	44.5	1.4	1.59	-2.16
30	10	42	41.9	1.6	1.59	0.213

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-34.447444	5	78.894888
A2	-34.173832	8	84.347664
A3	-34.447444	5	78.894888
fitted	-38.592269	3	83.184538
R	-47.681776	2	99.363552

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	27.0159	6	0.0001438
Test 2	0.547224	3	0.9084
Test 3	0.547224	3	0.9084
Test 4	8.28965	2	0.01585

BMDS WIZARD OUTPUT REPORT

BMDS Summary of H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats – Hematocrit (%) at 6-month timepoint in Males

1.7. BMDS Summary of Hematocrit (%) Males 6 months (2 Year Rats GenX)

Table 7. Summary of BMD Modeling Results for Hematocrit in Males at 6 months (2-Year Rats); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD_{1SD} (mg/kg/day)	$BMDL_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2)	0.435	120.46	36.9	24.4	1.51	BMDLs from models that met model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values > 2.0; appropriate variance (continuous data only)) were compared. BMDLs from included models were sufficiently close (< 3-fold difference), so the BMDL from the model with the lowest AIC was selected.
Exponential (M3)	0.219	122.31	46.8	24.7	1.90	
Exponential (M4)	0.197	122.46	36.9	24.4	1.51	
Exponential (M5)	N/A[b]	124.31	36.2	1.08	33.3	
Hill	N/A[b]	124.31	42.1	error[c]	error	
Power	0.219	122.31	46.4	25.3	1.84	
Polynomial 3°	**0.469**	**120.31**	**45.3**	**25.3**	**1.79**	
Polynomial 2°	0.468	120.31	43.2	35.4	1.22	
Linear	0.436	120.46	37.3	25.1	1.49	

[a] Constant variance case presented (BMDS Test 2 *p*-value = 0.339), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 1, and 50 mg/kg/day were -0.12, -0.8, 0.92, 0, respectively.

[b] No available degrees of freedom to calculate a goodness of fit value.

[c] BMD or BMDL computation failed for this model.

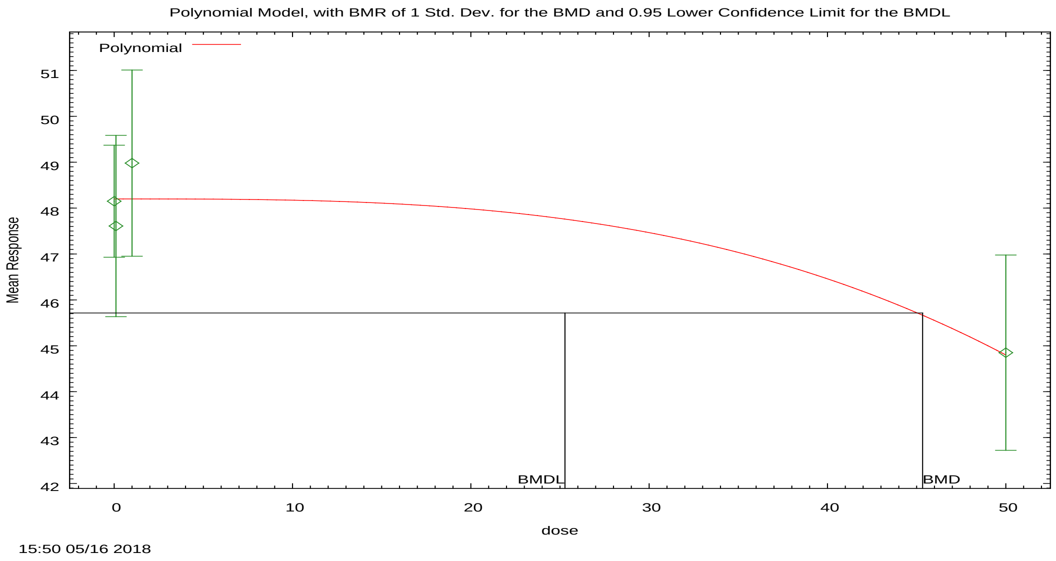

Figure 55. Plot of mean response by dose with fitted curve for Polynomial 3° model with constant variance for Hematocrit in Males at 6 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + …

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 45.3334

BMDL at the 95% confidence level = 25.279

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	6.40912	6.85666
rho	n/a	0
beta_0	48.2467	48.15
beta_1	0	-6.10613
beta_2	-5.6392E-25	0
beta_3	-0.0000271733	-0.139088

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	48.1	48.2	1.71	2.53	-0.121
0.1	10	47.6	48.2	2.76	2.53	-0.795
1	10	49	48.2	2.84	2.53	0.916
50	10	44.9	44.9	2.97	2.53	-0.00000696

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-56.397207	5	122.794415
A2	-54.716879	8	125.433759
A3	-56.397207	5	122.794415

fitted	-57.15445	3	120.3089
R	-62.970874	2	129.941748

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	16.508	6	0.01127
Test 2	3.36066	3	0.3393
Test 3	3.36066	3	0.3393
Test 4	1.51449	2	0.469

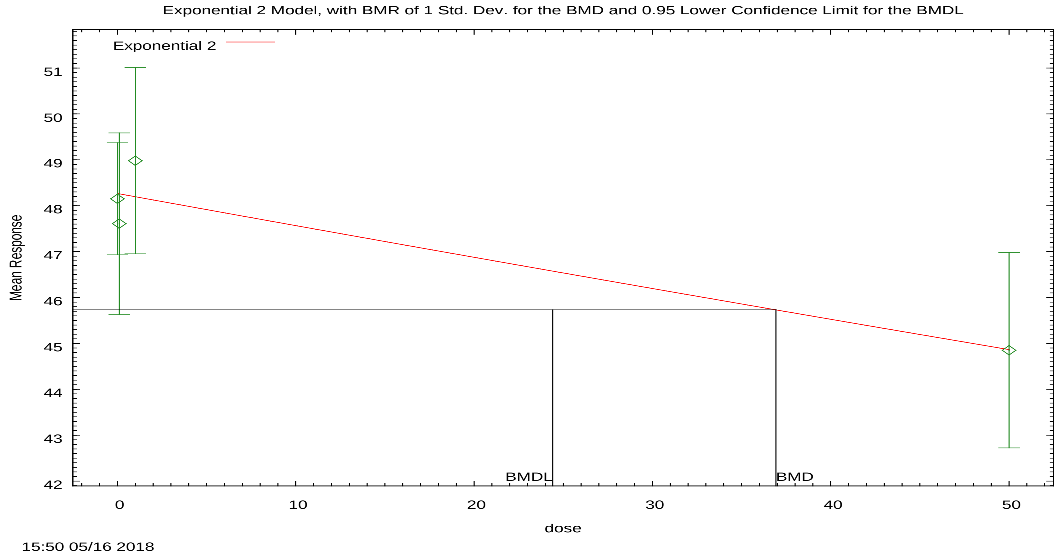

Figure 56. Plot of mean response by dose with fitted curve for Exponential (M2) model with constant variance for Hematocrit in Males at 6 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 36.9284

BMDL at the 95% confidence level = 24.4126

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	1.86153	1.81986
rho	n/a	0
a	48.2674	46.4954
b	0.00146177	0.00146151
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	48.15	48.27	1.71	2.54	-0.1464
0.1	10	47.61	48.26	2.76	2.54	-0.8108
1	10	48.98	48.2	2.84	2.54	0.9763
50	10	44.85	44.87	2.97	2.54	-0.01923

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-56.39721	5	122.7944
A2	-54.71688	8	125.4338
A3	-56.39721	5	122.7944
R	-62.97087	2	129.9417
2	-57.23054	3	120.4611

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	16.51	6	0.01127
Test 2	3.361	3	0.3393
Test 3	3.361	3	0.3393

Test 4	1.667	2	0.4346

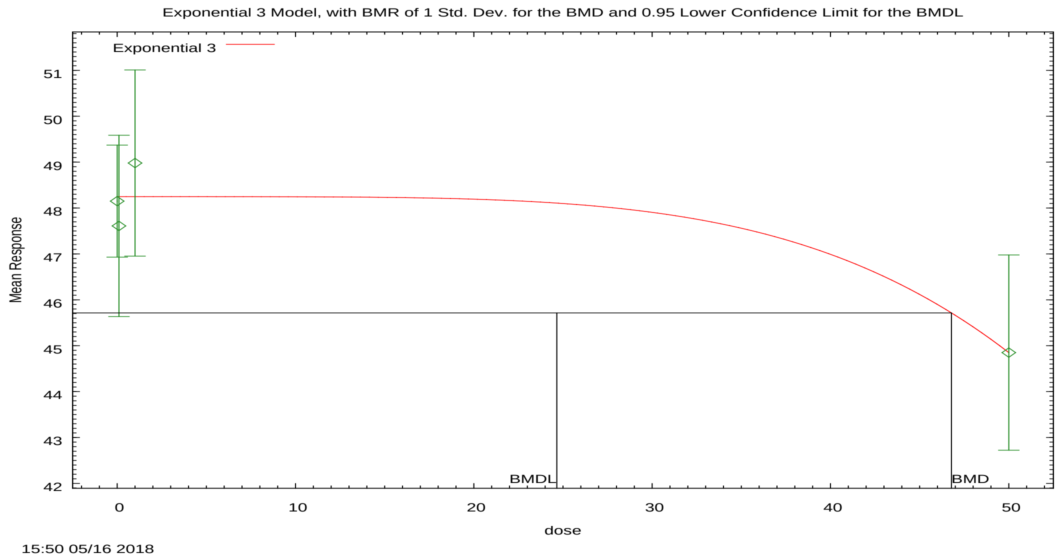

Figure 57. Plot of mean response by dose with fitted curve for Exponential (M3) model with constant variance for Hematocrit in Males at 6 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 46.7835

BMDL at the 95% confidence level = 24.6546

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	1.85772	1.81986
rho	n/a	0

a	48.2467	46.4954
b	0.0112697	0.00146151
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	48.15	48.25	1.71	2.53	-0.1207
0.1	10	47.61	48.25	2.76	2.53	-0.7953
1	10	48.98	48.25	2.84	2.53	0.916
50	10	44.85	44.85	2.97	2.53	-0.0000000655

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-56.39721	5	122.7944
A2	-54.71688	8	125.4338
A3	-56.39721	5	122.7944
R	-62.97087	2	129.9417
3	-57.15442	4	122.3088

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	16.51	6	0.01127
Test 2	3.361	3	0.3393
Test 3	3.361	3	0.3393
Test 5a	1.514	1	0.2185

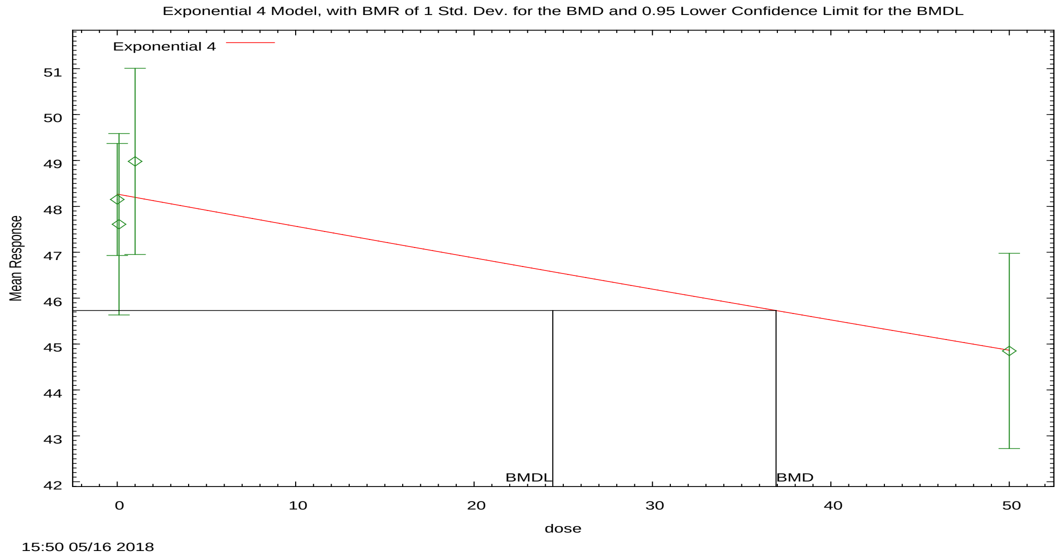

Figure 58. Plot of mean response by dose with fitted curve for Exponential (M4) model with constant variance for Hematocrit in Males at 6 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 36.9284

BMDL at the 95% confidence level = 24.4126

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	1.86153	1.81986
rho	n/a	0
a	48.2674	51.429
b	0.00146177	0.0282678

c	0.000000000174759	0.830549
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	48.15	48.27	1.71	2.54	-0.1464
0.1	10	47.61	48.26	2.76	2.54	-0.8108
1	10	48.98	48.2	2.84	2.54	0.9763
50	10	44.85	44.87	2.97	2.54	-0.01923

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-56.39721	5	122.7944
A2	-54.71688	8	125.4338
A3	-56.39721	5	122.7944
R	-62.97087	2	129.9417
4	-57.23054	4	122.4611

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	16.51	6	0.01127
Test 2	3.361	3	0.3393
Test 3	3.361	3	0.3393
Test 6a	1.667	1	0.1967

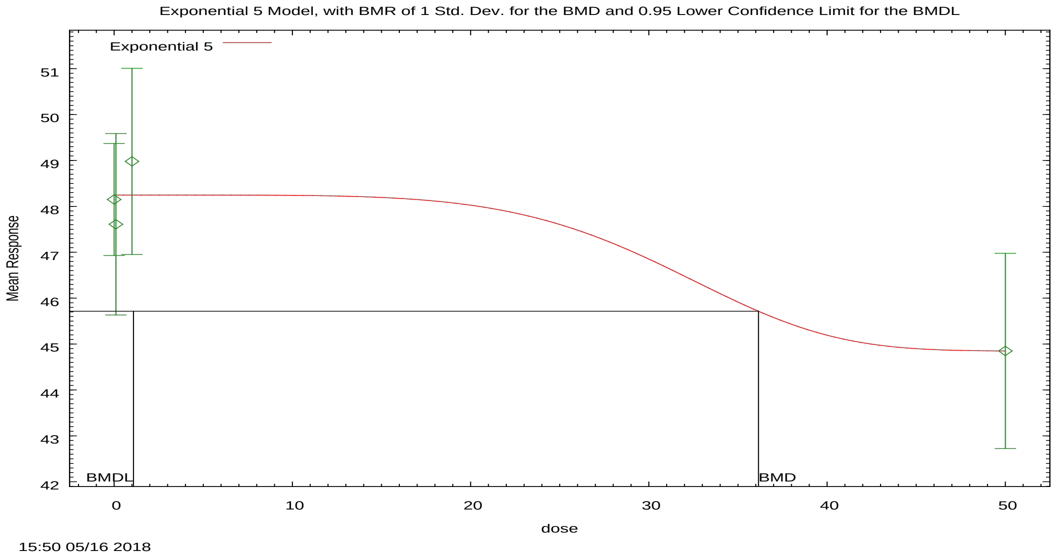

Figure 59. Plot of mean response by dose with fitted curve for Exponential (M5) model with constant variance for Hematocrit in Males at 6 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 36.151

BMDL at the 95% confidence level = 1.08483

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	1.85772	1.81986
rho	n/a	0
a	48.2467	51.429
b	0.0294062	0.0282678

c	0.929541	0.830549
d	5.09304	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	48.15	48.25	1.71	2.53	-0.1207
0.1	10	47.61	48.25	2.76	2.53	-0.7953
1	10	48.98	48.25	2.84	2.53	0.916
50	10	44.85	44.85	2.97	2.53	-0.00000001585

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-56.39721	5	122.7944
A2	-54.71688	8	125.4338
A3	-56.39721	5	122.7944
R	-62.97087	2	129.9417
5	-57.15442	5	124.3088

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	16.51	6	0.01127
Test 2	3.361	3	0.3393
Test 3	3.361	3	0.3393
Test 7a	1.514	0	N/A

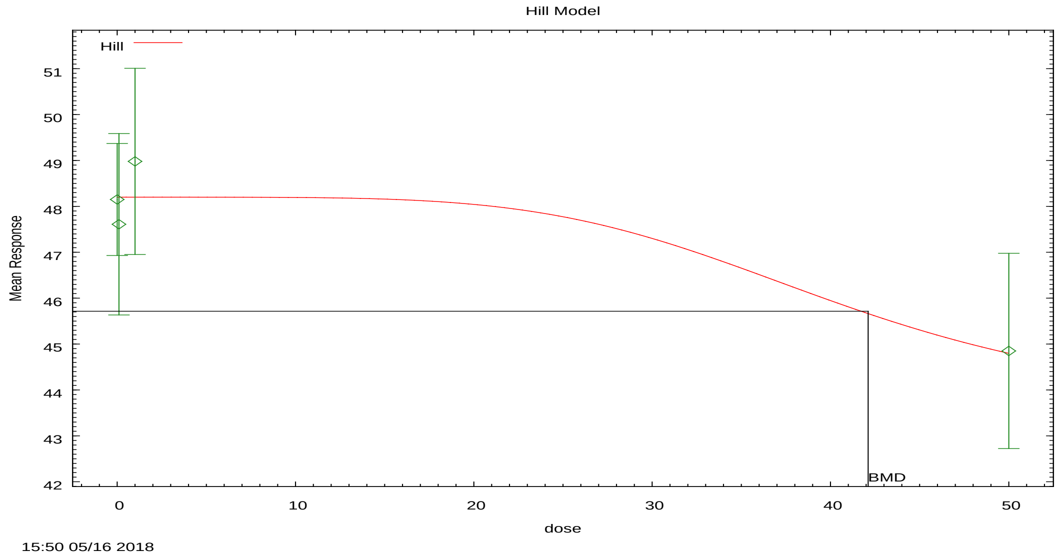

Figure 60. Plot of mean response by dose with fitted curve for Hill model with constant variance for Hematocrit in Males at 6 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A constant variance model is fit

THE MODEL HAS PROBABLY NOT CONVERGED!!!

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 42.1125

BMDL at the 95% confidence level = error

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	6.40911	6.85666
rho	n/a	0
intercept	48.2467	48.15
v	-4.66716	-3.3

n	4.73703	0.285322
k	40.6267	30.4237

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	48.1	48.2	1.71	2.53	-0.121
0.1	10	47.6	48.2	2.76	2.53	-0.795
1	10	49	48.2	2.84	2.53	0.916
50	10	44.9	44.8	2.97	2.53	0.000000279

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-56.397207	5	122.794415
A2	-54.716879	8	125.433759
A3	-56.397207	5	122.794415
fitted	-57.154419	5	124.308838
R	-62.970874	2	129.941748

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	16.508	6	0.01127
Test 2	3.36066	3	0.3393
Test 3	3.36066	3	0.3393
Test 4	1.51442	0	N/A

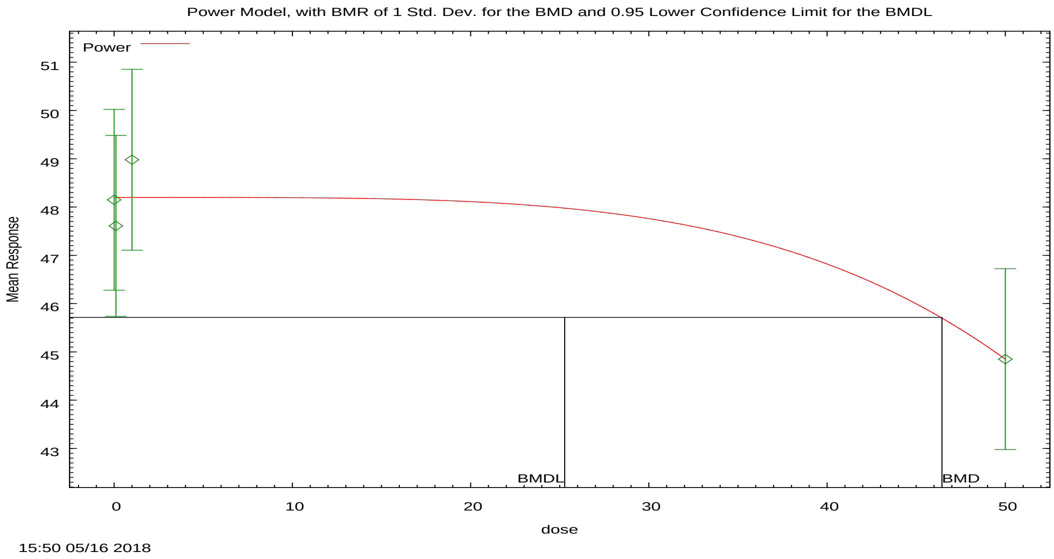

Figure 61. Plot of mean response by dose with fitted curve for Power model with constant variance for Hematocrit in Males at 6 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 46.4432

BMDL at the 95% confidence level = 25.2791

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	6.40911	6.85666
rho	n/a	0
control	48.2467	44.85
slope	-0.000000580442	4.13
power	3.98317	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	48.1	48.2	1.71	2.53	-0.121
0.1	10	47.6	48.2	2.76	2.53	-0.795
1	10	49	48.2	2.84	2.53	0.916
50	10	44.9	44.9	2.97	2.53	-0.000000144

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-56.397207	5	122.794415
A2	-54.716879	8	125.433759
A3	-56.397207	5	122.794415
fitted	-57.154419	4	122.308839
R	-62.970874	2	129.941748

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	16.508	6	0.01127
Test 2	3.36066	3	0.3393
Test 3	3.36066	3	0.3393
Test 4	1.51442	1	0.2185

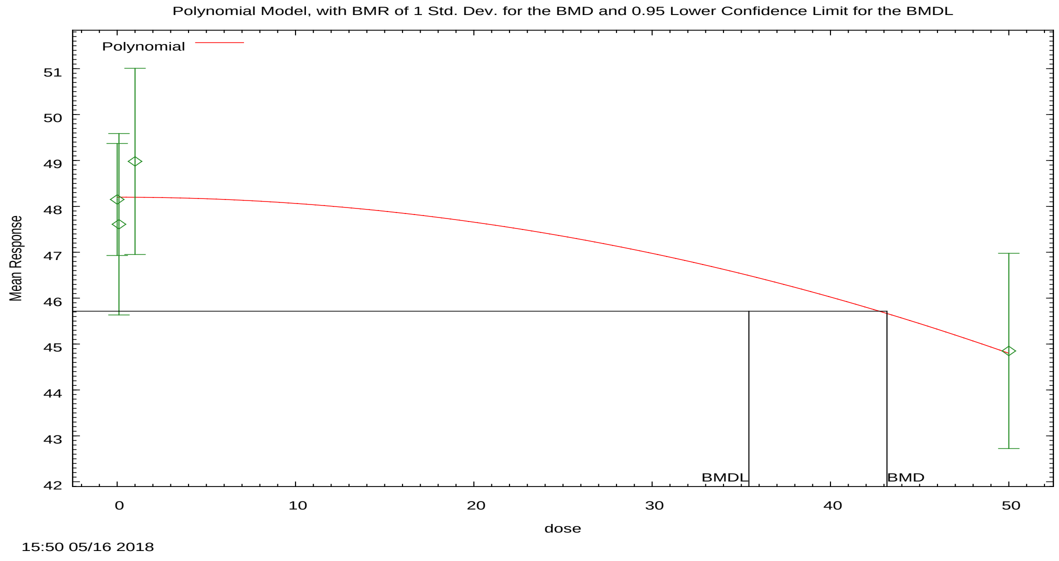

Figure 62. Plot of mean response by dose with fitted curve for Polynomial 2° model with constant variance for Hematocrit in Males at 6 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 43.1665

BMDL at the 95% confidence level = 35.4249

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	6.40961	6.85666
rho	n/a	0
beta_0	48.247	47.8412
beta_1	-9.04729E-26	0
beta_2	-0.00135869	-0.0237465

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	48.1	48.2	1.71	2.53	-0.121
0.1	10	47.6	48.2	2.76	2.53	-0.796
1	10	49	48.2	2.84	2.53	0.917
50	10	44.9	44.9	2.97	2.53	-0.000364

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-56.397207	5	122.794415
A2	-54.716879	8	125.433759
A3	-56.397207	5	122.794415
fitted	-57.155961	3	120.311922
R	-62.970874	2	129.941748

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	16.508	6	0.01127
Test 2	3.36066	3	0.3393
Test 3	3.36066	3	0.3393
Test 4	1.51751	2	0.4682

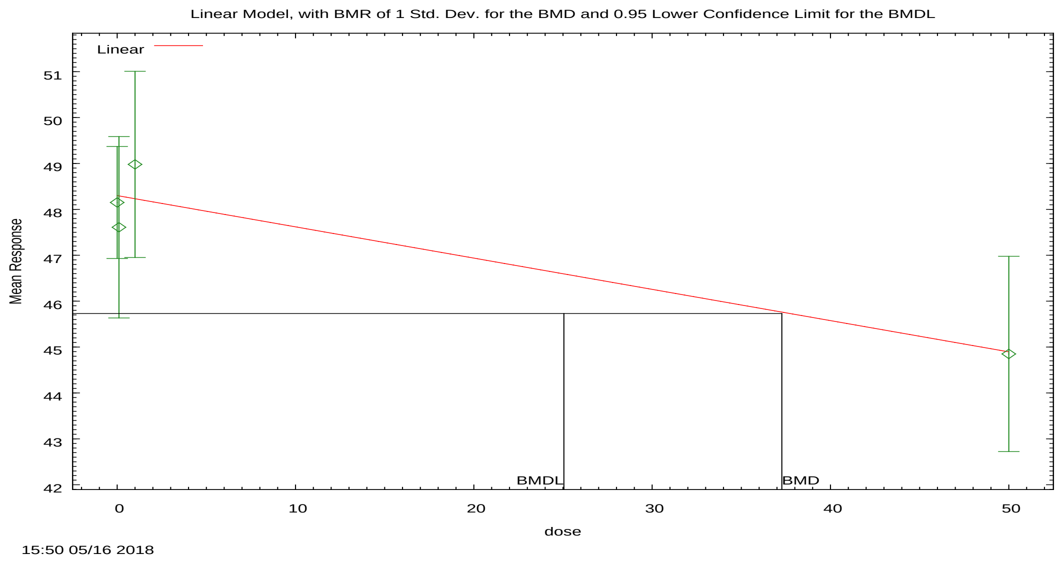

Figure 63. Plot of mean response by dose with fitted curve for Linear model with constant variance for Hematocrit in Males at 6 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 37.2705

BMDL at the 95% confidence level = 25.0508

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	6.43267	6.85666
rho	n/a	0
beta_0	48.2668	48.2668
beta_1	-0.0680504	-0.0680504

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	48.1	48.3	1.71	2.54	-0.146
0.1	10	47.6	48.3	2.76	2.54	-0.81
1	10	49	48.2	2.84	2.54	0.974
50	10	44.9	44.9	2.97	2.54	-0.0179

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-56.397207	5	122.794415
A2	-54.716879	8	125.433759
A3	-56.397207	5	122.794415
fitted	-57.227793	3	120.455586
R	-62.970874	2	129.941748

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	16.508	6	0.01127
Test 2	3.36066	3	0.3393
Test 3	3.36066	3	0.3393
Test 4	1.66117	2	0.4358

BMDS WIZARD OUTPUT REPORT

BMDS Summary of 28-Day Oral (Gavage) Toxicity Study of H-28397 in Mice with a 28-day Recovery – Albumin to Globulin Ratio in Males

1.8. BMDS Summary of Albumin to Globulin Ratio Males (28 Day Mice GenX)

Table 8. Summary of BMD Modeling Results for Albumin to Globulin Ratio in Males (28-Day Mice); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD_{1SD} (mg/kg/day)	BMDL_{1SD} (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2) Exponential (M3)[b]	<0.0001	-73.454	10.3	7.79	1.32	Only one model met model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). Selected BMDL is from this model.
Exponential (M4) Exponential (M5)[c]	**0.999**	**-93.451**	**0.775**	**0.464**	**1.67**	
Hill	N/A[d]	-91.451	0.705	0.313	2.25	
Power[e] Polynomial 2°[f] Linear[g]	<0.0001	-74.496	8.72	6.25	1.40	
Polynomial 3°[h]	<0.0001	-74.496	8.72	6.25	1.40	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = 0.0996), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 3, and 30 mg/kg/day were 0, 0.06, -0.15, 0.09, respectively.

[b] For the Exponential (M3) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M2) model.

[c] For the Exponential (M5) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M4) model.

[d] No available degrees of freedom to calculate a goodness of fit value.

[e] For the Power model, the power parameter estimate was 1. The models in this row reduced to the Linear model.

[f] For the Polynomial 2° model, the b2 coefficient estimate was 0 (boundary of parameters space). The models in this row reduced to the Linear model.

[g] The Linear model may appear equivalent to the Polynomial 3° model, however differences exist in digits not displayed in the table.

[h] The Polynomial 3° model may appear equivalent to the Power model, however differences exist in digits not displayed in the table. This also applies to the Polynomial 2° model. This also applies to the Linear model.

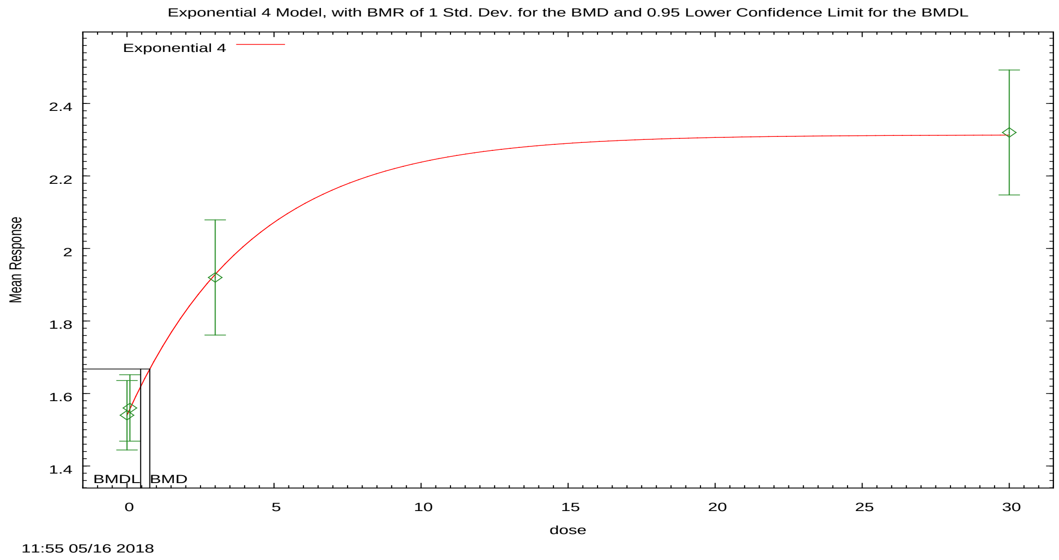

Figure 64. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Albumin to Globulin Ratio in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 0.774566

BMDL at the 95% confidence level = 0.464264

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-5.54159	-5.41198
rho	3.29978	3.23182
a	1.53988	1.463
b	0.232774	0.0722953
c	1.50243	1.66507
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.54	1.54	0.13	0.13	0.003022
0.1	10	1.56	1.56	0.13	0.13	0.05642
3	10	1.92	1.93	0.22	0.19	-0.1489
30	10	2.32	2.31	0.24	0.25	0.09068

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	48.91325	5	-87.82651
A2	52.04398	8	-88.08796
A3	51.72568	6	-91.45137
R	20.32428	2	-36.64857
4	51.72568	5	-93.45137

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	63.44	6	<0.0001
Test 2	6.261	3	0.09956
Test 3	0.6366	2	0.7274
Test 6a	0.0000004765	1	0.9994

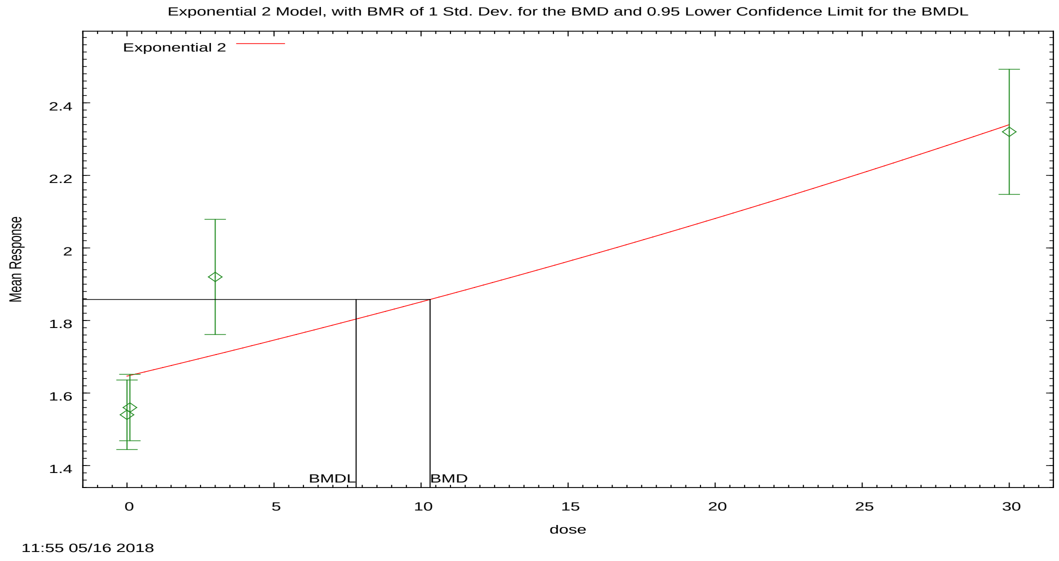

Figure 65. Plot of mean response by dose with fitted curve for Exponential (M2) model with modeled variance for Albumin to Globulin Ratio in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 10.3062

BMDL at the 95% confidence level = 7.79109

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-3.48813	-5.41198
rho	0.758549	3.23182
a	1.64655	1.63743
b	0.01171	0.0120196
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.54	1.65	0.13	0.21	-1.595
0.1	10	1.56	1.65	0.13	0.21	-1.324
3	10	1.92	1.7	0.22	0.21	3.17
30	10	2.32	2.34	0.24	0.24	-0.257

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	48.91325	5	-87.82651
A2	52.04398	8	-88.08796
A3	51.72568	6	-91.45137
R	20.32428	2	-36.64857
2	40.72708	4	-73.45417

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	63.44	6	<0.0001
Test 2	6.261	3	0.09956
Test 3	0.6366	2	0.7274
Test 4	22	2	<0.0001

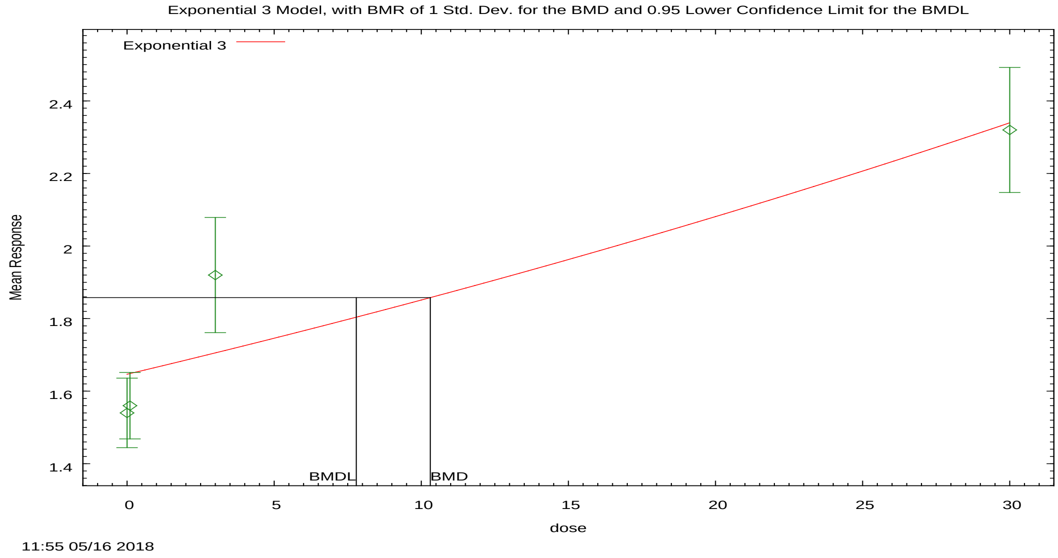

Figure 66. Plot of mean response by dose with fitted curve for Exponential (M3) model with modeled variance for Albumin to Globulin Ratio in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 10.3062

BMDL at the 95% confidence level = 7.79109

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-3.48813	-5.41198
rho	0.758548	3.23182
a	1.64655	1.63743
b	0.01171	0.0120196
c	n/a	0
d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.54	1.65	0.13	0.21	-1.595
0.1	10	1.56	1.65	0.13	0.21	-1.324
3	10	1.92	1.7	0.22	0.21	3.17
30	10	2.32	2.34	0.24	0.24	-0.257

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	48.91325	5	-87.82651
A2	52.04398	8	-88.08796
A3	51.72568	6	-91.45137
R	20.32428	2	-36.64857
3	40.72708	4	-73.45417

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	63.44	6	<0.0001
Test 2	6.261	3	0.09956
Test 3	0.6366	2	0.7274
Test 5a	22	2	<0.0001

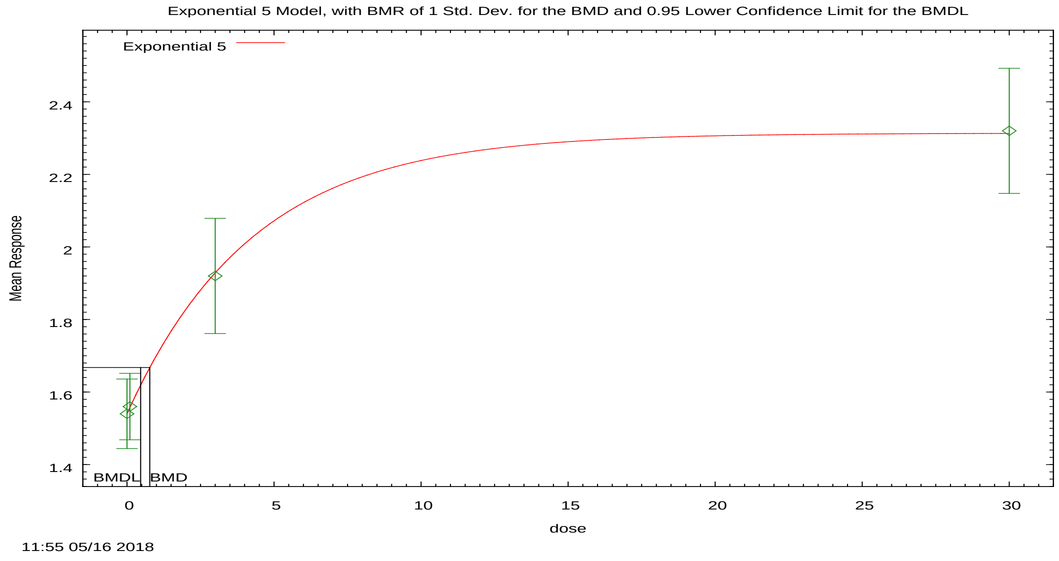

Figure 67. Plot of mean response by dose with fitted curve for Exponential (M5) model with modeled variance for Albumin to Globulin Ratio in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 0.774566

BMDL at the 95% confidence level = 0.464264

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-5.54159	-5.41198
rho	3.29978	3.23182
a	1.53988	1.463
b	0.232774	0.0722953

c	1.50243	1.66507
d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.54	1.54	0.13	0.13	0.003022
0.1	10	1.56	1.56	0.13	0.13	0.05642
3	10	1.92	1.93	0.22	0.19	-0.1489
30	10	2.32	2.31	0.24	0.25	0.09068

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	48.91325	5	-87.82651
A2	52.04398	8	-88.08796
A3	51.72568	6	-91.45137
R	20.32428	2	-36.64857
5	51.72568	5	-93.45137

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	63.44	6	<0.0001
Test 2	6.261	3	0.09956
Test 3	0.6366	2	0.7274
Test 7a	0.0000004765	1	0.9994

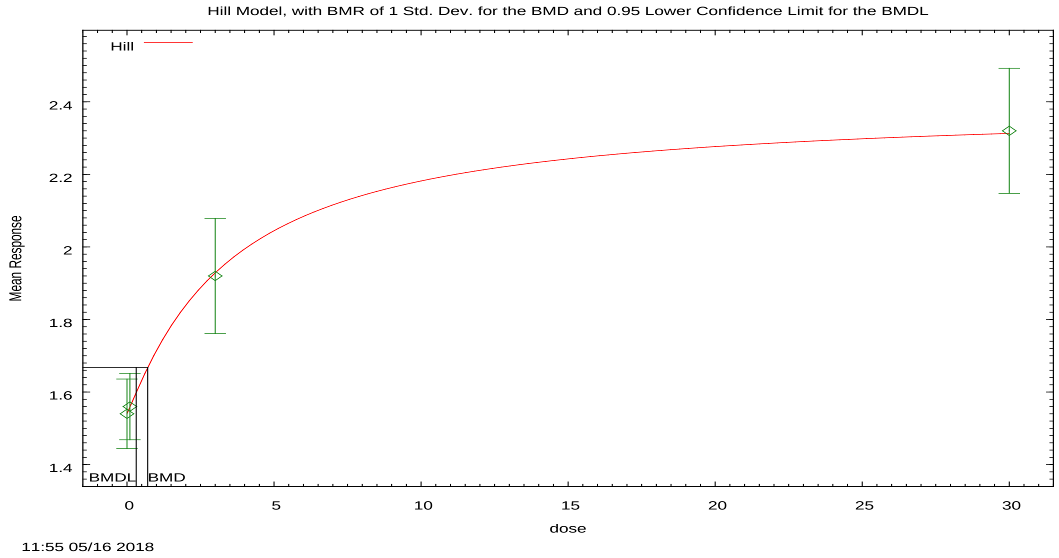

Figure 68. Plot of mean response by dose with fitted curve for Hill model with modeled variance for Albumin to Globulin Ratio in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A modeled variance is fit

Warning: Likelihood for fitted model larger than the Likelihood for model A3.

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 0.705233

BMDL at the 95% confidence level = 0.313181

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-5.54158	-3.3403
rho	3.29976	0
intercept	1.53986	1.54
v	0.849098	0.78

n	1.07989	0.295906
k	3.5068	56.325

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.54	1.54	0.13	0.13	0.00348
0.1	10	1.56	1.56	0.13	0.13	0.0559
3	10	1.92	1.93	0.22	0.18	-0.149
30	10	2.32	2.31	0.24	0.25	0.0907

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	48.913254	5	-87.826509
A2	52.043978	8	-88.087955
A3	51.725684	6	-91.451368
fitted	51.725684	6	-91.451368
R	20.324284	2	-36.648568

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	63.4394	6	<0.0001
Test 2	6.26145	3	0.09956
Test 3	0.636587	2	0.7274
Test 4	-1.7053E-13	0	N/A

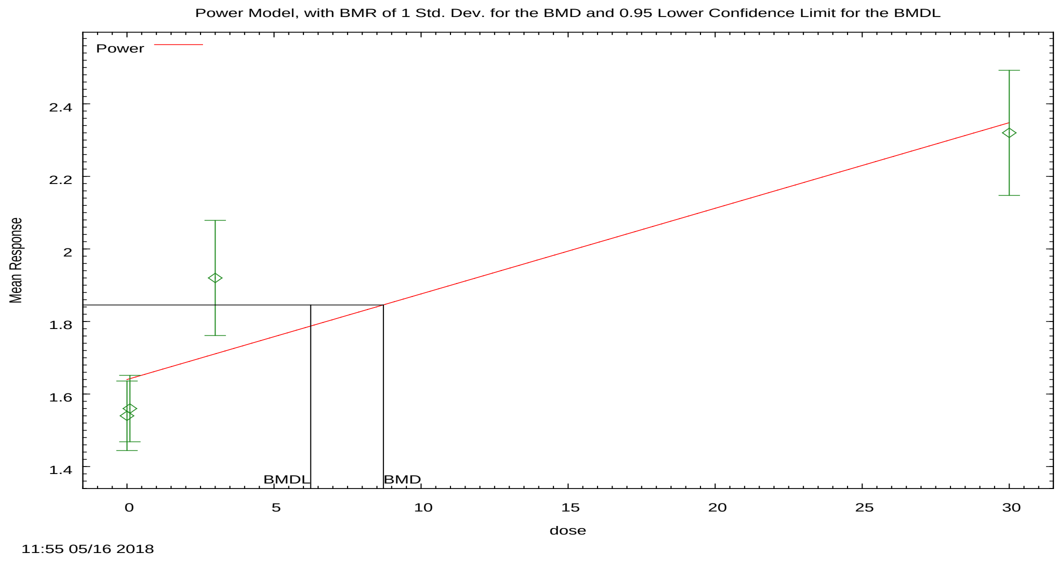

Figure 69. Plot of mean response by dose with fitted curve for Power model with modeled variance for Albumin to Globulin Ratio in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 8.71976

BMDL at the 95% confidence level = 6.24707

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-3.63569	-3.3403
rho	0.96328	0
control	1.63947	1.54
slope	0.0236278	0.0828657
power	1	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.54	1.64	0.13	0.21	-1.53
0.1	10	1.56	1.64	0.13	0.21	-1.26
3	10	1.92	1.71	0.22	0.21	3.15
30	10	2.32	2.35	0.24	0.24	-0.365

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	48.913254	5	-87.826509
A2	52.043978	8	-88.087955
A3	51.725684	6	-91.451368
fitted	41.248063	4	-74.496127
R	20.324284	2	-36.648568

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	63.4394	6	<0.0001
Test 2	6.26145	3	0.09956
Test 3	0.636587	2	0.7274
Test 4	20.9552	2	<0.0001

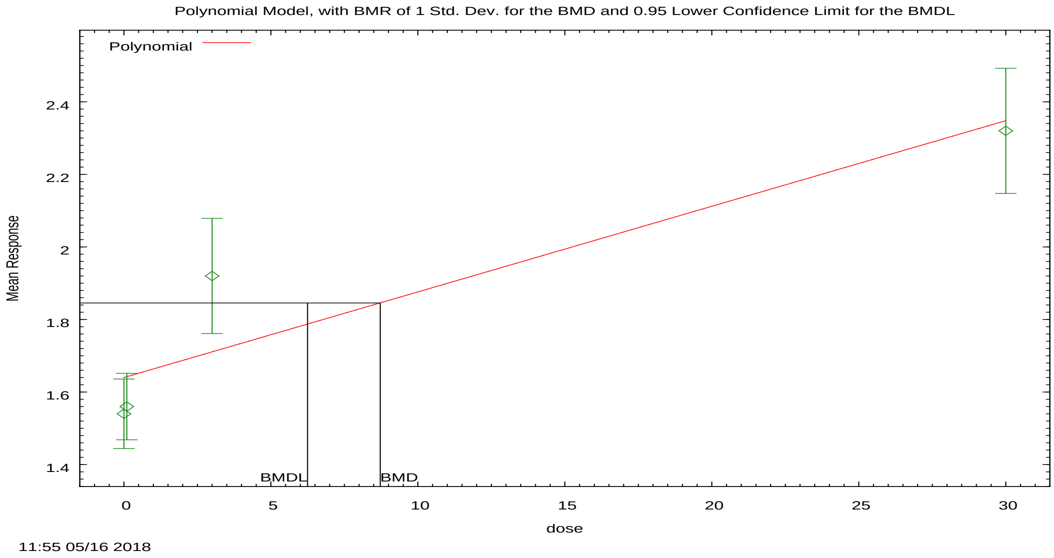

Figure 70. Plot of mean response by dose with fitted curve for Polynomial 3° model with modeled variance for Albumin to Globulin Ratio in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 8.71975

BMDL at the 95% confidence level = 6.24707

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-3.6357	-3.3403
rho	0.963286	0
beta_0	1.63947	1.54
beta_1	0.0236279	0.202745
beta_2	0	0

beta_3	0	0.000721035

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.54	1.64	0.13	0.21	-1.53
0.1	10	1.56	1.64	0.13	0.21	-1.26
3	10	1.92	1.71	0.22	0.21	3.15
30	10	2.32	2.35	0.24	0.24	-0.365

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	48.913254	5	-87.826509
A2	52.043978	8	-88.087955
A3	51.725684	6	-91.451368
fitted	41.248063	4	-74.496127
R	20.324284	2	-36.648568

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	63.4394	6	<0.0001
Test 2	6.26145	3	0.09956
Test 3	0.636587	2	0.7274
Test 4	20.9552	2	<0.0001

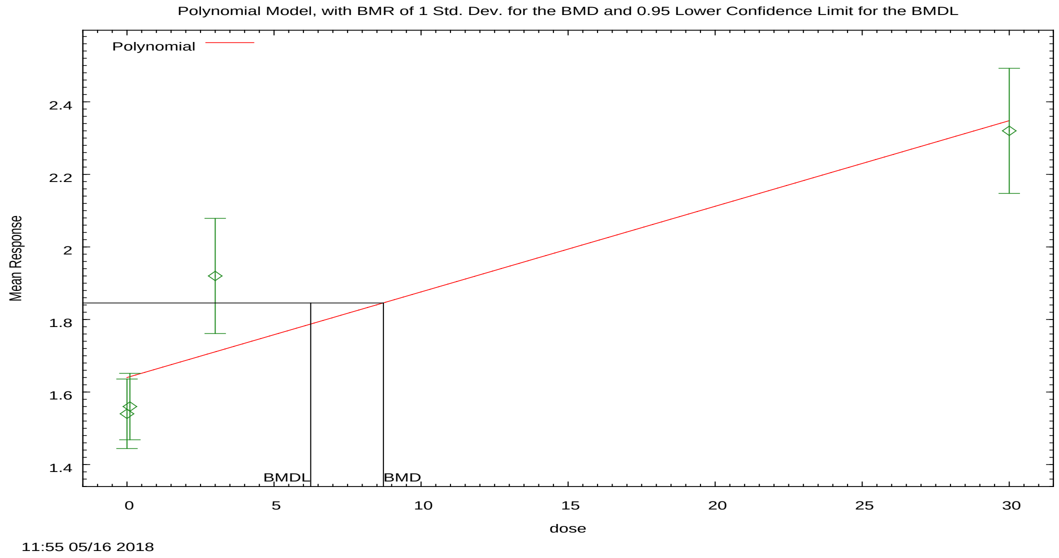

Figure 71. Plot of mean response by dose with fitted curve for Polynomial 2° model with modeled variance for Albumin to Globulin Ratio in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 8.71976

BMDL at the 95% confidence level = 6.24707

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-3.63569	-3.3403
rho	0.96328	0
beta_0	1.63947	1.54312
beta_1	0.0236278	0.136752
beta_2	0	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.54	1.64	0.13	0.21	-1.53
0.1	10	1.56	1.64	0.13	0.21	-1.26
3	10	1.92	1.71	0.22	0.21	3.15
30	10	2.32	2.35	0.24	0.24	-0.365

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	48.913254	5	-87.826509
A2	52.043978	8	-88.087955
A3	51.725684	6	-91.451368
fitted	41.248063	4	-74.496127
R	20.324284	2	-36.648568

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	63.4394	6	<0.0001
Test 2	6.26145	3	0.09956
Test 3	0.636587	2	0.7274
Test 4	20.9552	2	<0.0001

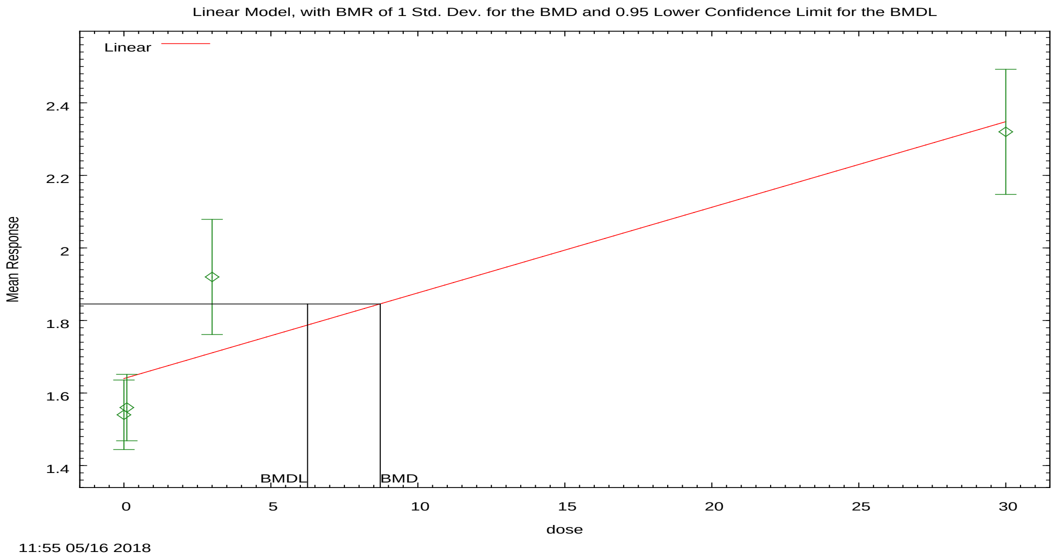

Figure 72. Plot of mean response by dose with fitted curve for Linear model with modeled variance for Albumin to Globulin Ratio in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 8.71976

BMDL at the 95% confidence level = 6.24707

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-3.63569	-3.3403
rho	0.963279	0
beta_0	1.63947	1.64246
beta_1	0.0236278	0.0232677

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.54	1.64	0.13	0.21	-1.53
0.1	10	1.56	1.64	0.13	0.21	-1.26
3	10	1.92	1.71	0.22	0.21	3.15
30	10	2.32	2.35	0.24	0.24	-0.365

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	48.913254	5	-87.826509
A2	52.043978	8	-88.087955
A3	51.725684	6	-91.451368
fitted	41.248063	4	-74.496127
R	20.324284	2	-36.648568

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	63.4394	6	<0.0001
Test 2	6.26145	3	0.09956
Test 3	0.636587	2	0.7274
Test 4	20.9552	2	<0.0001

BMDS WIZARD OUTPUT REPORT

BMDS Summary of 28-Day Oral (Gavage) Toxicity Study of H-28397 in Mice with a 28-day Recovery – Albumin to Globulin Ratio in Females

1.9. BMDS Summary of Albumin to Globulin Ratio Females (28 Day Mice GenX)

Table 9. Summary of BMD Modeling Results for Albumin to Globulin Ratio in Females (28-Day Mice); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD_{1SD} (mg/kg/day)	$BMDL_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2) Exponential (M3)[b]	0.00175	-98.689	11.6	9.13	1.27	BMDLs from models that met model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values > 2.0; appropriate variance (continuous data only)) were compared. Selected BMDL is from model with lowest AIC and lowest BMDL.
Exponential (M4) Exponential (M5)[c]	0.538	-109.00	1.42	0.863	1.64	
Hill	**0.573**	**-109.07**	**1.22**	**0.595**	**2.04**	
Power[d] Polynomial 3°[e] Polynomial 2°[f] Linear	0.00216	-99.106	10.7	8.29	1.29	

[a] Constant variance case presented (BMDS Test 2 *p*-value = 0.119), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 3, and 30 mg/kg/day were -0.38, 0.41, -0.05, 0.01, respectively.

[b] For the Exponential (M3) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M2) model.

[c] For the Exponential (M5) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M4) model.

[d] For the Power model, the power parameter estimate was 1. The models in this row reduced to the Linear model.

[e] For the Polynomial 3° model, the b3 coefficient estimates was 0 (boundary of parameters space). The models in this row reduced to the Polynomial 2° model. For the Polynomial 3° model, the b3 and b2 coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Linear model.

[f] For the Polynomial 2° model, the b2 coefficient estimate was 0 (boundary of parameters space). The models in this row reduced to the Linear model.

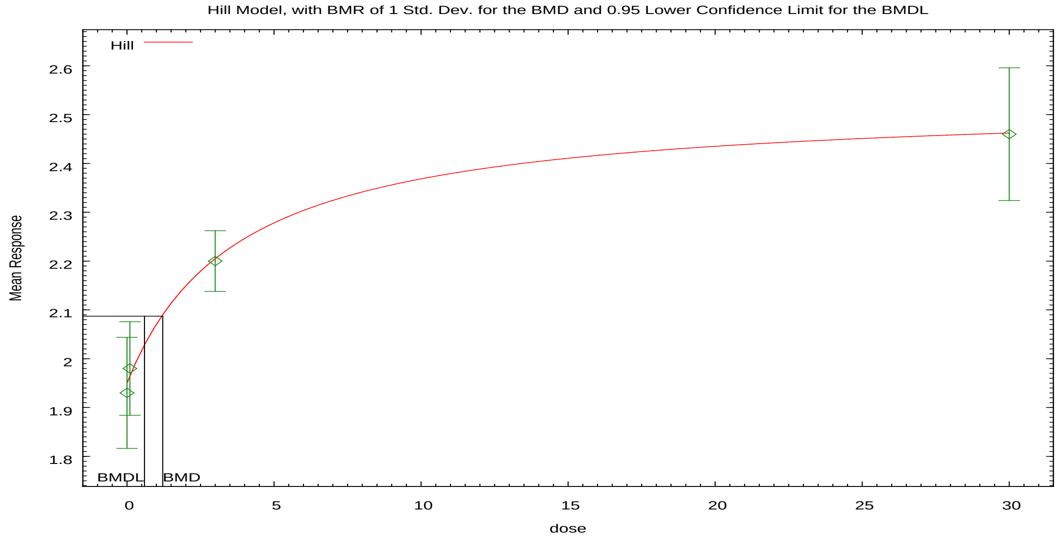

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Figure 73. Plot of mean response by dose with fitted curve for Hill model with constant variance for Albumin to Globulin Ratio in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 1.21611

BMDL at the 95% confidence level = 0.595276

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.0197096	0.0217265
rho	n/a	0
intercept	1.94679	1.93
v	0.577417	0.53
n	1	0.330384
k	3.78567	3.06591

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.93	1.95	0.16	0.14	-0.378
0.1	10	1.98	1.96	0.13	0.14	0.413
3	10	2.2	2.2	0.09	0.14	-0.0465
30	10	2.46	2.46	0.19	0.14	0.0112

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC

A1	58.691662	5	-107.383323
A2	61.62066	8	-107.241319
A3	58.691662	5	-107.383323
fitted	58.532951	4	-109.065902
R	35.142939	2	-66.285878

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	52.9554	6	<0.0001
Test 2	5.858	3	0.1187
Test 3	5.858	3	0.1187
Test 4	0.317422	1	0.5732

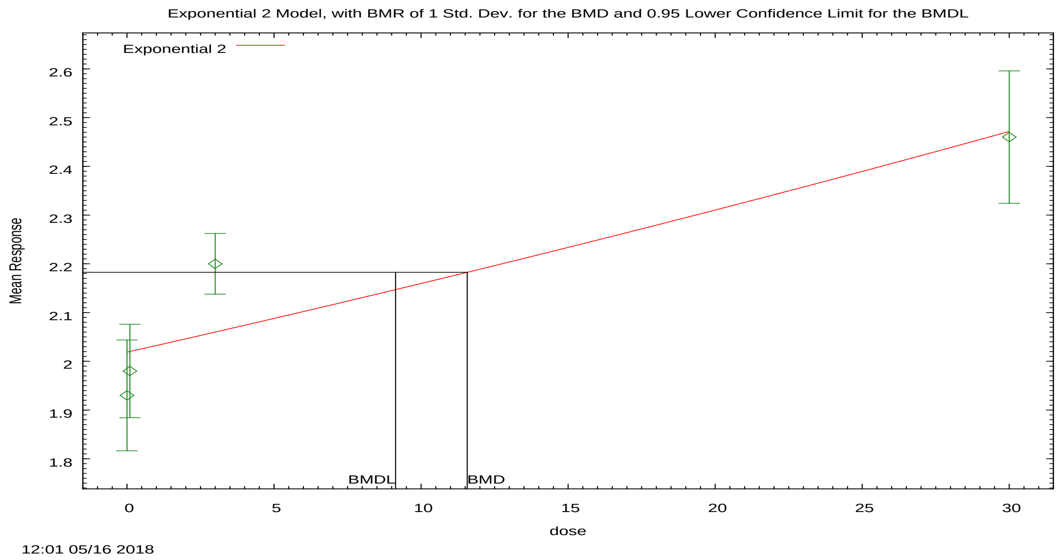

Figure 74. Plot of mean response by dose with fitted curve for Exponential (M2) model with constant variance for Albumin to Globulin Ratio in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 11.5691

BMDL at the 95% confidence level = 9.13206

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-3.61722	-3.93458
rho	n/a	0
a	2.01868	2.01446
b	0.00674689	0.00688324
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.93	2.02	0.16	0.16	-1.711
0.1	10	1.98	2.02	0.13	0.16	-0.7727
3	10	2.2	2.06	0.09	0.16	2.702
30	10	2.46	2.47	0.19	0.16	-0.2231

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	58.69166	5	-107.3833
A2	61.62066	8	-107.2413
A3	58.69166	5	-107.3833
R	35.14294	2	-66.28588
2	52.34439	3	-98.68877

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	52.96	6	<0.0001
Test 2	5.858	3	0.1187
Test 3	5.858	3	0.1187
Test 4	12.69	2	0.001752

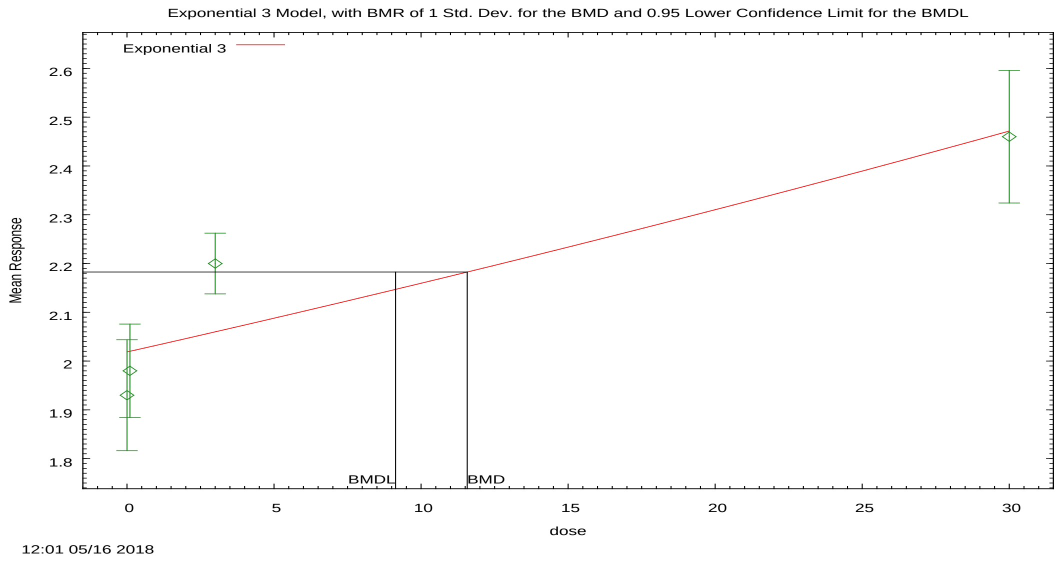

Figure 75. Plot of mean response by dose with fitted curve for Exponential (M3) model with constant variance for Albumin to Globulin Ratio in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 11.5691

BMDL at the 95% confidence level = 9.13206

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-3.61722	-3.93458
rho	n/a	0
a	2.01868	2.01446
b	0.00674689	0.00688324
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.93	2.02	0.16	0.16	-1.711
0.1	10	1.98	2.02	0.13	0.16	-0.7727
3	10	2.2	2.06	0.09	0.16	2.702
30	10	2.46	2.47	0.19	0.16	-0.2231

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	58.69166	5	-107.3833
A2	61.62066	8	-107.2413
A3	58.69166	5	-107.3833
R	35.14294	2	-66.28588
3	52.34439	3	-98.68877

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	52.96	6	<0.0001
Test 2	5.858	3	0.1187
Test 3	5.858	3	0.1187
Test 5a	12.69	2	0.001752

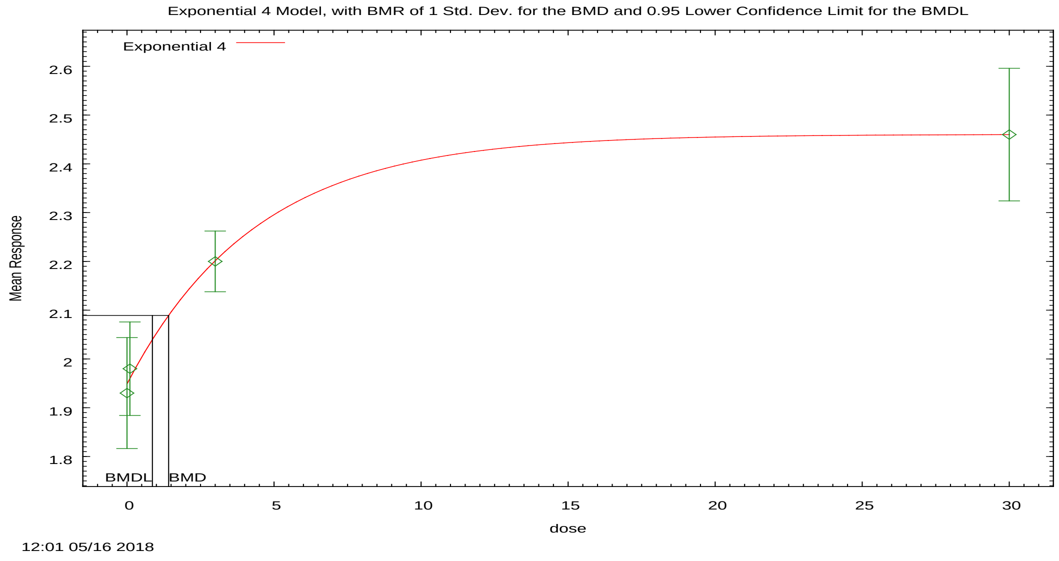

Figure 76. Plot of mean response by dose with fitted curve for Exponential (M4) model with constant variance for Albumin to Globulin Ratio in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 1.41534

BMDL at the 95% confidence level = 0.863474

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-3.92511	-3.93458
rho	n/a	0
a	1.94872	1.8335
b	0.226816	0.0618833

c	1.26256	1.40878
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.93	1.95	0.16	0.14	-0.4213
0.1	10	1.98	1.96	0.13	0.14	0.4458
3	10	2.2	2.2	0.09	0.14	-0.02878
30	10	2.46	2.46	0.19	0.14	0.004218

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	58.69166	5	-107.3833
A2	61.62066	8	-107.2413
A3	58.69166	5	-107.3833
R	35.14294	2	-66.28588
4	58.50222	4	-109.0044

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	52.96	6	<0.0001
Test 2	5.858	3	0.1187
Test 3	5.858	3	0.1187
Test 6a	0.3789	1	0.5382

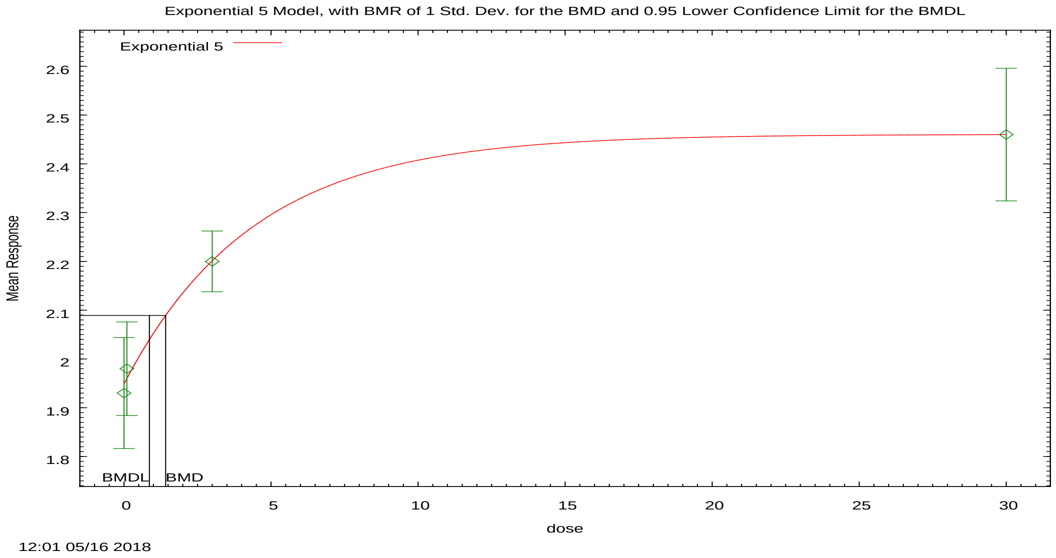

Figure 77. Plot of mean response by dose with fitted curve for Exponential (M5) model with constant variance for Albumin to Globulin Ratio in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 1.41534

BMDL at the 95% confidence level = 0.863474

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-3.92511	-3.93458
rho	n/a	0
a	1.94872	1.8335
b	0.226816	0.0618833

c	1.26256	1.40878
d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.93	1.95	0.16	0.14	-0.4213
0.1	10	1.98	1.96	0.13	0.14	0.4458
3	10	2.2	2.2	0.09	0.14	-0.02878
30	10	2.46	2.46	0.19	0.14	0.004213

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	58.69166	5	-107.3833
A2	61.62066	8	-107.2413
A3	58.69166	5	-107.3833
R	35.14294	2	-66.28588
5	58.50222	4	-109.0044

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	52.96	6	<0.0001
Test 2	5.858	3	0.1187
Test 3	5.858	3	0.1187
Test 7a	0.3789	1	0.5382

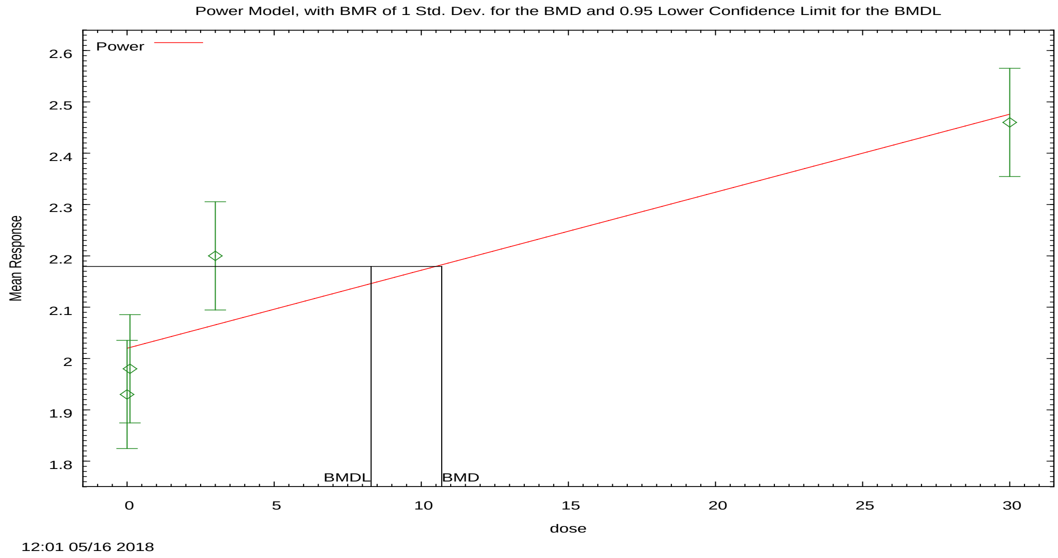

Figure 78. Plot of mean response by dose with fitted curve for Power model with constant variance for Albumin to Globulin Ratio in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 10.695

BMDL at the 95% confidence level = 8.29343

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.0265786	0.0217265
rho	n/a	0
control	2.01636	1.93
slope	0.0152435	0.126978
power	1	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.93	2.02	0.16	0.16	-1.68
0.1	10	1.98	2.02	0.13	0.16	-0.735
3	10	2.2	2.06	0.09	0.16	2.68
30	10	2.46	2.47	0.19	0.16	-0.265

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	58.691662	5	-107.383323
A2	61.62066	8	-107.241319
A3	58.691662	5	-107.383323
fitted	52.552971	3	-99.105942
R	35.142939	2	-66.285878

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	52.9554	6	<0.0001
Test 2	5.858	3	0.1187
Test 3	5.858	3	0.1187
Test 4	12.2774	2	0.002158

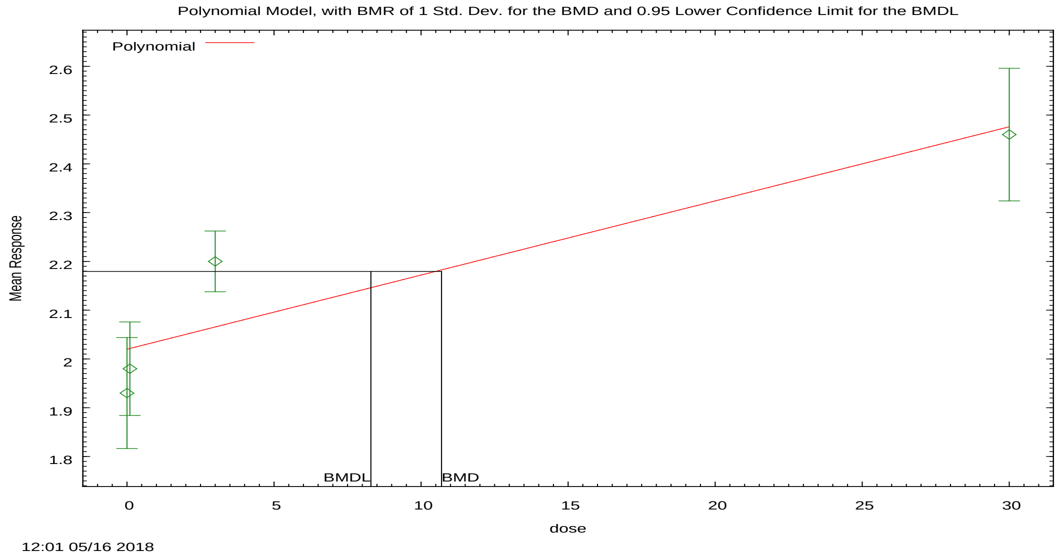

Figure 79. Plot of mean response by dose with fitted curve for Polynomial 3° model with constant variance for Albumin to Globulin Ratio in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 10.695

BMDL at the 95% confidence level = 8.29343

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.0265786	0.0217265
rho	n/a	0
beta_0	2.01636	1.93
beta_1	0.0152435	0.51553

beta_2	5.74431E-29	0
beta_3	0	0.00463881

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.93	2.02	0.16	0.16	-1.68
0.1	10	1.98	2.02	0.13	0.16	-0.735
3	10	2.2	2.06	0.09	0.16	2.68
30	10	2.46	2.47	0.19	0.16	-0.265

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	58.691662	5	-107.383323
A2	61.62066	8	-107.241319
A3	58.691662	5	-107.383323
fitted	52.552971	3	-99.105942
R	35.142939	2	-66.285878

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	52.9554	6	<0.0001
Test 2	5.858	3	0.1187
Test 3	5.858	3	0.1187
Test 4	12.2774	2	0.002158

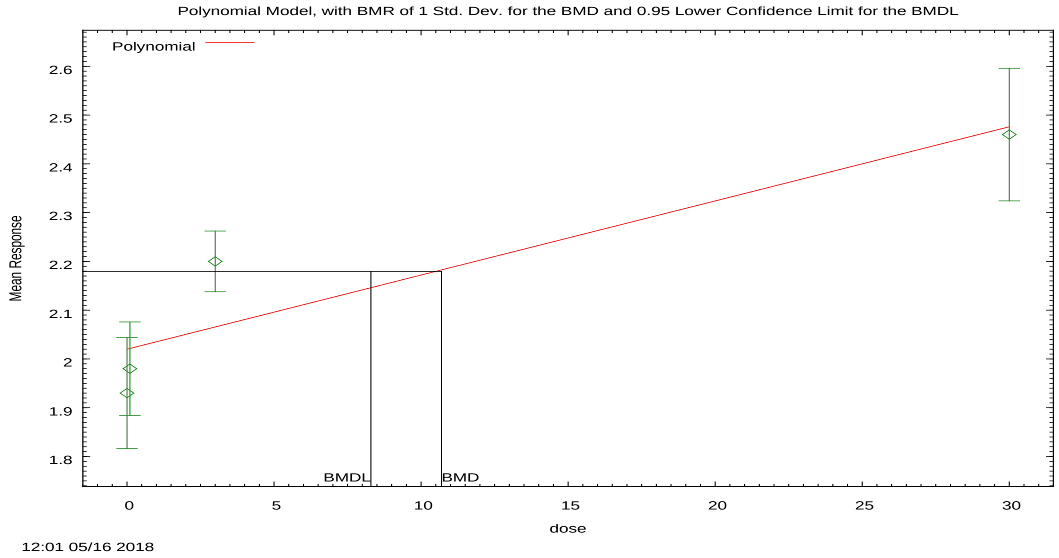

Figure 80. Plot of mean response by dose with fitted curve for Polynomial 2° model with constant variance for Albumin to Globulin Ratio in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 10.695

BMDL at the 95% confidence level = 8.29343

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.0265786	0.0217265
rho	n/a	0
beta_0	2.01636	1.95008
beta_1	0.0152435	0.0909581

beta_2	0	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.93	2.02	0.16	0.16	-1.68
0.1	10	1.98	2.02	0.13	0.16	-0.735
3	10	2.2	2.06	0.09	0.16	2.68
30	10	2.46	2.47	0.19	0.16	-0.265

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	58.691662	5	-107.383323
A2	61.62066	8	-107.241319
A3	58.691662	5	-107.383323
fitted	52.552971	3	-99.105942
R	35.142939	2	-66.285878

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	52.9554	6	<0.0001
Test 2	5.858	3	0.1187
Test 3	5.858	3	0.1187
Test 4	12.2774	2	0.002158

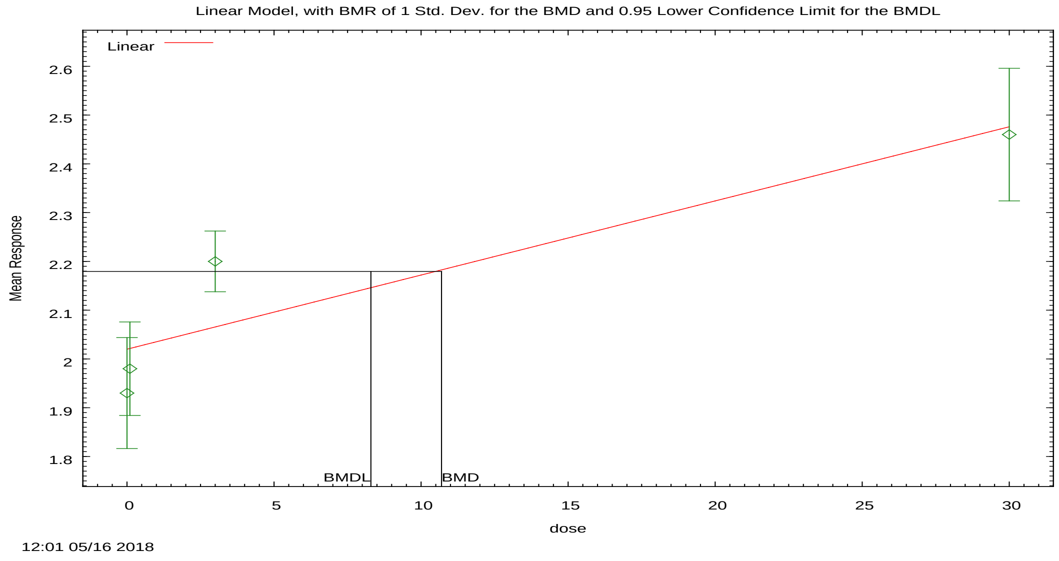

Figure 81. Plot of mean response by dose with fitted curve for Linear model with constant variance for Albumin to Globulin Ratio in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 10.695

BMDL at the 95% confidence level = 8.29343

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.0265786	0.0217265
rho	n/a	0
beta_0	2.01636	2.01636
beta_1	0.0152435	0.0152435

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.93	2.02	0.16	0.16	-1.68
0.1	10	1.98	2.02	0.13	0.16	-0.735
3	10	2.2	2.06	0.09	0.16	2.68
30	10	2.46	2.47	0.19	0.16	-0.265

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	58.691662	5	-107.383323
A2	61.62066	8	-107.241319
A3	58.691662	5	-107.383323
fitted	52.552971	3	-99.105942
R	35.142939	2	-66.285878

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	52.9554	6	<0.0001
Test 2	5.858	3	0.1187
Test 3	5.858	3	0.1187
Test 4	12.2774	2	0.002158

BMDS WIZARD OUTPUT REPORT

BMDS Summary of 28-Day Oral (Gavage) Toxicity Study of H-28397 in Rats with a 28-day Recovery – Albumin to Globulin Ratio in Males

1.10. BMDS Summary of Albumin to Globulin ratio Males (28 Day Rats GenX)

Table 10. Summary of BMD Modeling Results for Albumin to Globulin Ratio in Males (28-Day Rats); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD_{1SD} (mg/kg/day)	$BMDL_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2) Exponential (M3)[b]	0.0361	-77.595	10.7	8.62	1.24	BMDLs from models that met model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values > 2.0; appropriate variance (continuous data only)) were compared. Selected BMDL is from model with lowest AIC and lowest BMDL.
Exponential (M4) Exponential (M5)[c]	0.511	-81.804	2.07	1.17	1.76	
Hill	**0.544**	**-81.868**	**1.94**	**0.945**	**2.05**	
Power[d] Polynomial 3°[e] Polynomial 2°[f] Linear	0.0456	-78.061	9.58	7.53	1.27	

[a] Constant variance case presented (BMDS Test 2 *p*-value = 0.764), selected model in bold; scaled residuals for selected model for doses 0, 0.3, 3, and 30 mg/kg/day were -0.38, 0.46, -0.1, 0.01, respectively.
[b] For the Exponential (M3) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M2) model.
[c] For the Exponential (M5) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M4) model.
[d] For the Power model, the power parameter estimate was 1. The models in this row reduced to the Linear model.
[e] For the Polynomial 3° model, the b3 coefficient estimates was 0 (boundary of parameters space). The models in this row reduced to the Polynomial 2° model. For the Polynomial 3° model, the b3 and b2 coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Linear model.
[f] For the Polynomial 2° model, the b2 coefficient estimate was 0 (boundary of parameters space). The models in this row reduced to the Linear model.

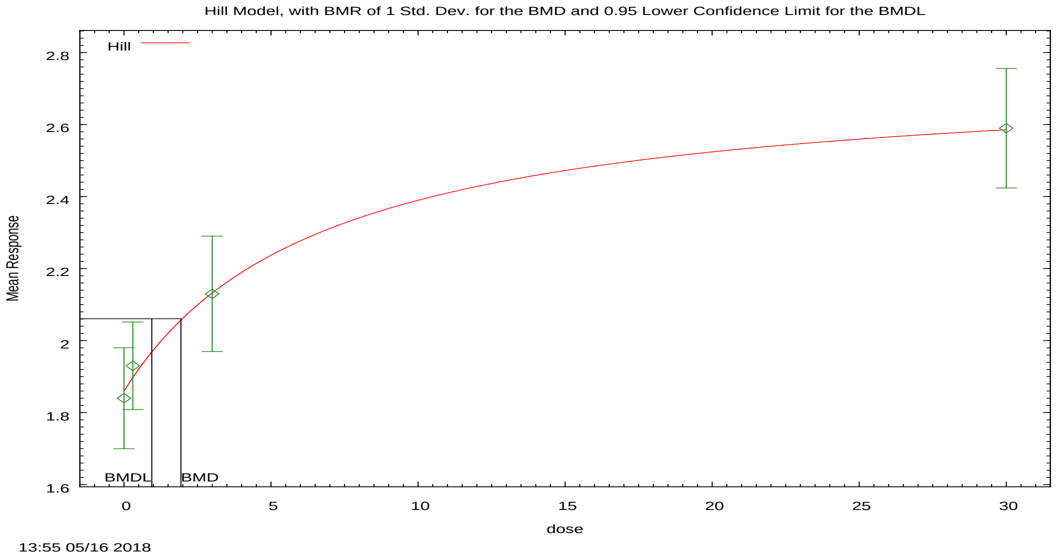

Figure 82. Plot of mean response by dose with fitted curve for Hill model with constant variance for Albumin to Globulin Ratio in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 1.93577

BMDL at the 95% confidence level = 0.944663

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.0389019	0.042829
rho	n/a	0
intercept	1.86356	1.84
v	0.890165	0.75
n	1	0.274093
k	6.80075	52.0109

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.84	1.86	0.2	0.2	-0.378
0.3	10	1.93	1.9	0.17	0.2	0.462
3	10	2.13	2.14	0.22	0.2	-0.0969
30	10	2.59	2.59	0.23	0.2	0.0124

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	45.118007	5	-80.236014

A2	45.694456	8	-75.388913
A3	45.118007	5	-80.236014
fitted	44.934219	4	-81.868439
R	22.006792	2	-40.013584

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	47.3753	6	<0.0001
Test 2	1.1529	3	0.7643
Test 3	1.1529	3	0.7643
Test 4	0.367575	1	0.5443

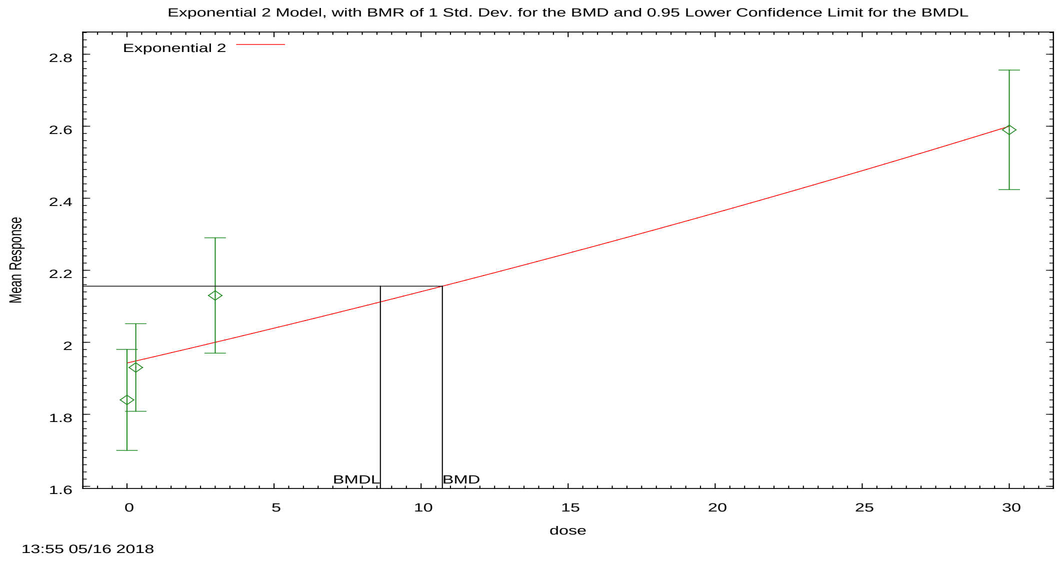

Figure 83. Plot of mean response by dose with fitted curve for Exponential (M2) model with constant variance for Albumin to Globulin Ratio in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 10.724

BMDL at the 95% confidence level = 8.61641

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-3.08988	-3.2559
rho	n/a	0
a	1.94249	1.9376
b	0.0097164	0.00988805
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.84	1.94	0.2	0.21	-1.519
0.3	10	1.93	1.95	0.17	0.21	-0.2692
3	10	2.13	2	0.22	0.21	1.928
30	10	2.59	2.6	0.23	0.21	-0.1463

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	45.11801	5	-80.23601
A2	45.69446	8	-75.38891
A3	45.11801	5	-80.23601
R	22.00679	2	-40.01358
2	41.79755	3	-77.5951

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value

Test 1	47.38	6	<0.0001
Test 2	1.153	3	0.7643
Test 3	1.153	3	0.7643
Test 4	6.641	2	0.03614

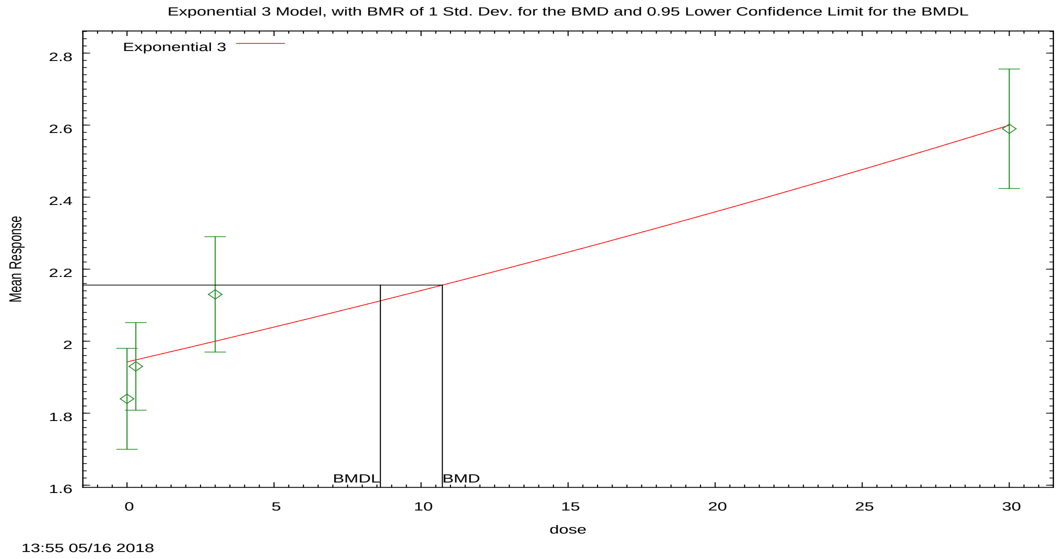

Figure 84. Plot of mean response by dose with fitted curve for Exponential (M3) model with constant variance for Albumin to Globulin Ratio in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 10.724

BMDL at the 95% confidence level = 8.61641

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-3.08988	-3.2559
rho	n/a	0
a	1.94249	1.9376
b	0.0097164	0.00988805
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.84	1.94	0.2	0.21	-1.519
0.3	10	1.93	1.95	0.17	0.21	-0.2692
3	10	2.13	2	0.22	0.21	1.928
30	10	2.59	2.6	0.23	0.21	-0.1463

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	45.11801	5	-80.23601
A2	45.69446	8	-75.38891
A3	45.11801	5	-80.23601
R	22.00679	2	-40.01358
3	41.79755	3	-77.5951

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	47.38	6	<0.0001
Test 2	1.153	3	0.7643
Test 3	1.153	3	0.7643
Test 5a	6.641	2	0.03614

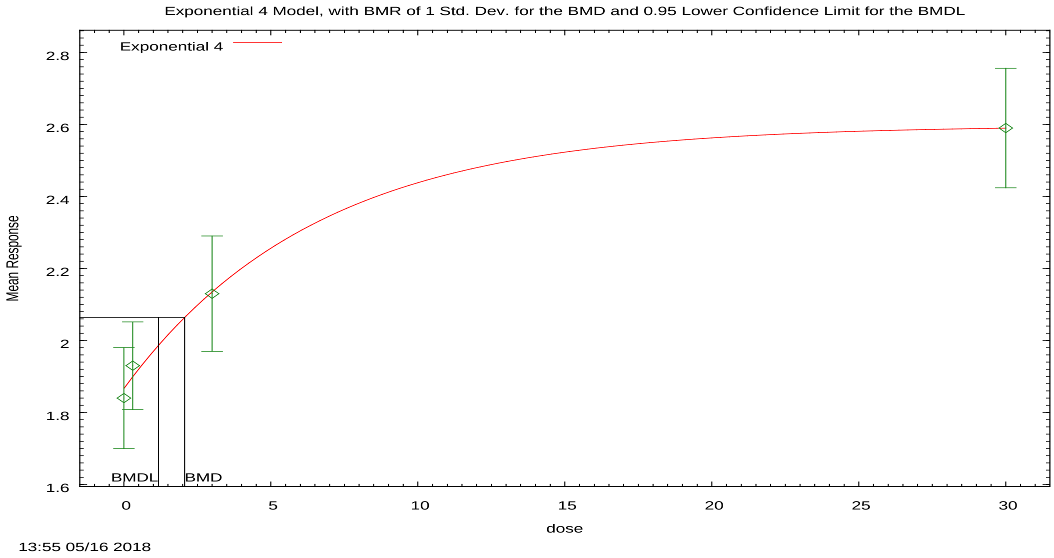

Figure 85. Plot of mean response by dose with fitted curve for Exponential (M4) model with constant variance for Albumin to Globulin Ratio in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 2.06536

BMDL at the 95% confidence level = 1.1729

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-3.24509	-3.2559
rho	n/a	0
a	1.86649	1.748
b	0.152473	0.0682174

c	1.39148	1.55578
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.84	1.87	0.2	0.2	-0.4243
0.3	10	1.93	1.9	0.17	0.2	0.4941
3	10	2.13	2.13	0.22	0.2	-0.07551
30	10	2.59	2.59	0.23	0.2	0.005683

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	45.11801	5	-80.23601
A2	45.69446	8	-75.38891
A3	45.11801	5	-80.23601
R	22.00679	2	-40.01358
4	44.90188	4	-81.80377

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	47.38	6	<0.0001
Test 2	1.153	3	0.7643
Test 3	1.153	3	0.7643
Test 6a	0.4322	1	0.5109

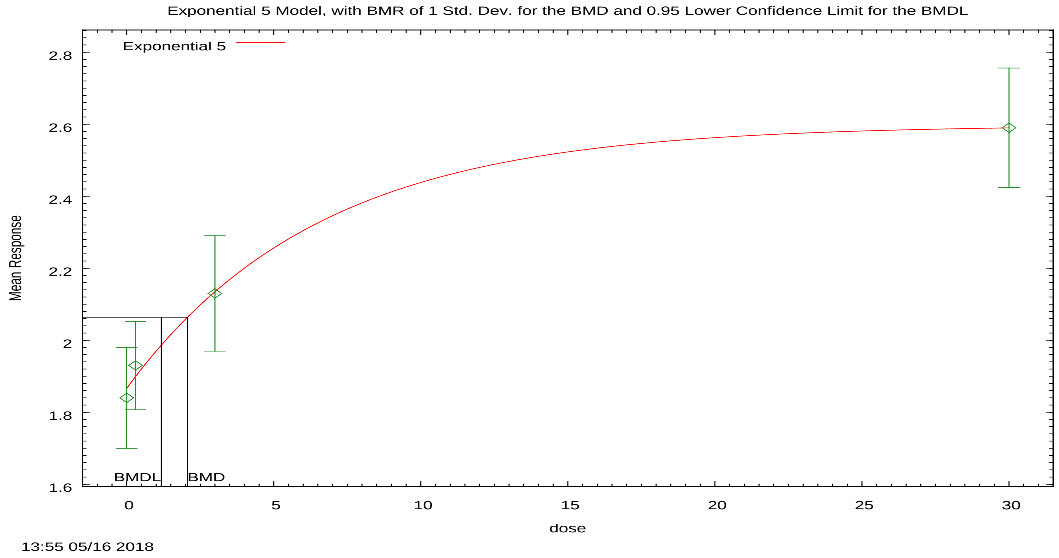

Figure 86. Plot of mean response by dose with fitted curve for Exponential (M5) model with constant variance for Albumin to Globulin Ratio in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 2.06536

BMDL at the 95% confidence level = 1.1729

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-3.24509	-3.2559
rho	n/a	0
a	1.86649	1.748
b	0.152473	0.0682174

c	1.39148	1.55578
d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.84	1.87	0.2	0.2	-0.4243
0.3	10	1.93	1.9	0.17	0.2	0.4941
3	10	2.13	2.13	0.22	0.2	-0.07551
30	10	2.59	2.59	0.23	0.2	0.005683

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	45.11801	5	-80.23601
A2	45.69446	8	-75.38891
A3	45.11801	5	-80.23601
R	22.00679	2	-40.01358
5	44.90188	4	-81.80377

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	47.38	6	<0.0001
Test 2	1.153	3	0.7643
Test 3	1.153	3	0.7643
Test 7a	0.4322	1	0.5109

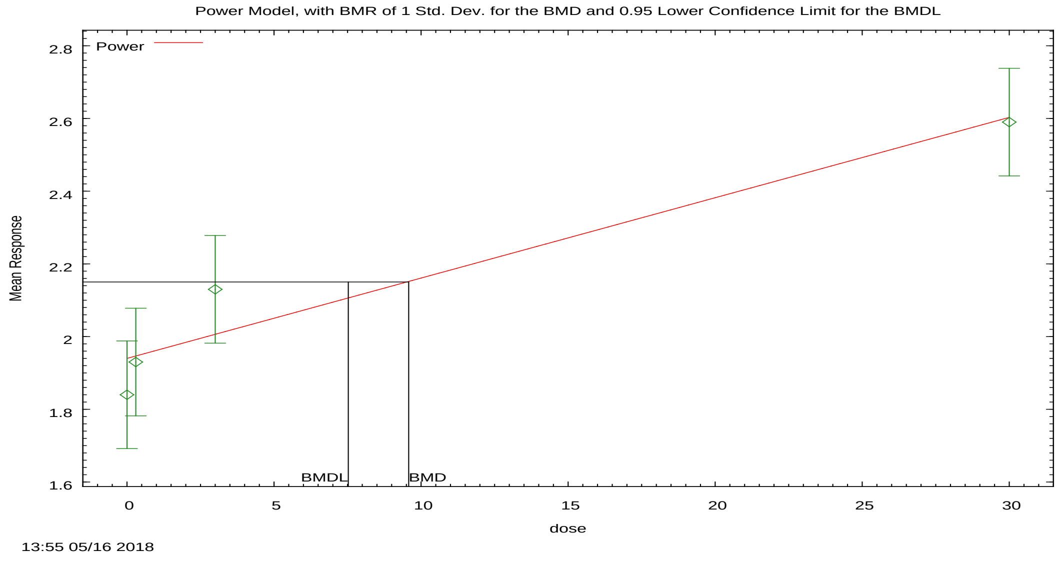

Figure 87. Plot of mean response by dose with fitted curve for Power model with constant variance for Albumin to Globulin Ratio in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 9.57917

BMDL at the 95% confidence level = 7.52523

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.0449805	0.042829
rho	n/a	0
control	1.93818	1.84
slope	0.0221403	0.156668
power	1	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.84	1.94	0.2	0.21	-1.46
0.3	10	1.93	1.94	0.17	0.21	-0.221
3	10	2.13	2	0.22	0.21	1.87
30	10	2.59	2.6	0.23	0.21	-0.185

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	45.118007	5	-80.236014
A2	45.694456	8	-75.388913
A3	45.118007	5	-80.236014
fitted	42.030543	3	-78.061087
R	22.006792	2	-40.013584

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	47.3753	6	<0.0001
Test 2	1.1529	3	0.7643
Test 3	1.1529	3	0.7643
Test 4	6.17493	2	0.04562

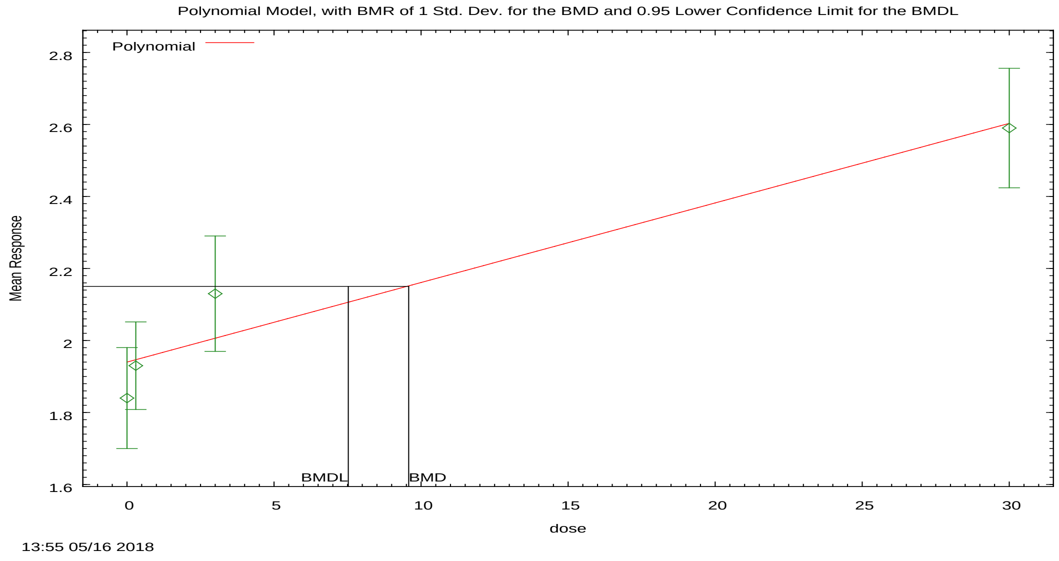

Figure 88. Plot of mean response by dose with fitted curve for Polynomial 3° model with constant variance for Albumin to Globulin Ratio in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 9.57917

BMDL at the 95% confidence level = 7.52523

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.0449805	0.042829
rho	n/a	0
beta_0	1.93818	1.84
beta_1	0.0221403	0.324794
beta_2	0	0

beta_3	0	0.00244627

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.84	1.94	0.2	0.21	-1.46
0.3	10	1.93	1.94	0.17	0.21	-0.221
3	10	2.13	2	0.22	0.21	1.87
30	10	2.59	2.6	0.23	0.21	-0.185

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	45.118007	5	-80.236014
A2	45.694456	8	-75.388913
A3	45.118007	5	-80.236014
fitted	42.030543	3	-78.061087
R	22.006792	2	-40.013584

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	47.3753	6	<0.0001
Test 2	1.1529	3	0.7643
Test 3	1.1529	3	0.7643
Test 4	6.17493	2	0.04562

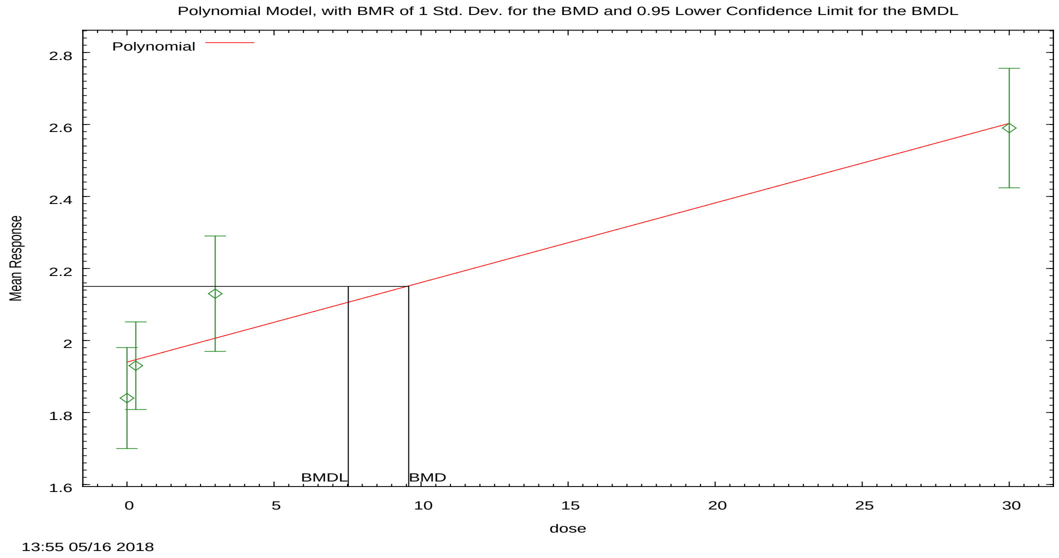

Figure 89. Plot of mean response by dose with fitted curve for Polynomial 2° model with constant variance for Albumin to Globulin Ratio in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 9.57917

BMDL at the 95% confidence level = 7.52523

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.0449805	0.042829
rho	n/a	0
beta_0	1.93818	1.86903
beta_1	0.0221403	0.0953114
beta_2	0	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.84	1.94	0.2	0.21	-1.46
0.3	10	1.93	1.94	0.17	0.21	-0.221
3	10	2.13	2	0.22	0.21	1.87
30	10	2.59	2.6	0.23	0.21	-0.185

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	45.118007	5	-80.236014
A2	45.694456	8	-75.388913
A3	45.118007	5	-80.236014
fitted	42.030543	3	-78.061087
R	22.006792	2	-40.013584

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	47.3753	6	<0.0001
Test 2	1.1529	3	0.7643
Test 3	1.1529	3	0.7643
Test 4	6.17493	2	0.04562

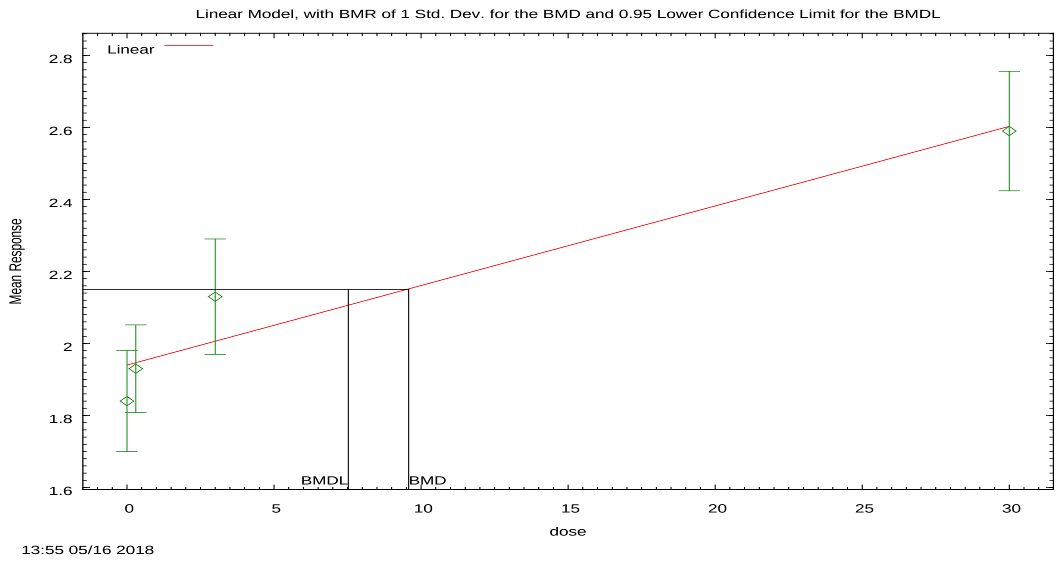
Linear Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

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Figure 90. Plot of mean response by dose with fitted curve for Linear model with constant variance for Albumin to Globulin Ratio in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 9.57917

BMDL at the 95% confidence level = 7.52523

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.0449805	0.042829
rho	n/a	0
beta_0	1.93818	1.93818
beta_1	0.0221403	0.0221403

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.84	1.94	0.2	0.21	-1.46
0.3	10	1.93	1.94	0.17	0.21	-0.221
3	10	2.13	2	0.22	0.21	1.87
30	10	2.59	2.6	0.23	0.21	-0.185

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	45.118007	5	-80.236014
A2	45.694456	8	-75.388913
A3	45.118007	5	-80.236014
fitted	42.030543	3	-78.061087
R	22.006792	2	-40.013584

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	47.3753	6	<0.0001
Test 2	1.1529	3	0.7643
Test 3	1.1529	3	0.7643
Test 4	6.17493	2	0.04562

BMDS WIZARD OUTPUT REPORT

BMDS Summary of 90-Day Oral (Gavage) Toxicity Study of H-28548 in Rats with a 28-Day Recovery – Albumin to Globulin Ratio in Males

1.11. BMDS Summary of Albumin to globulin ration Males (90 Day Rats GenX)

Table 11. Summary of BMD Modeling Results for Albumin to Globulin Ratio in Males (90-Day Rats); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD_{1SD} (mg/kg/day)	BMDL_{1SD} (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2) Exponential (M3)[b]	3.57E-04	-52.840	58.6	38.3	1.53	Only one model met model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). Selected BMDL is from this model.
Exponential (M4) Exponential (M5)[c]	**0.287**	**-65.584**	**3.39**	**0.0741**	**45.8**	
Hill	0.317	-65.718	2.10	error[d]	error	
Power[e] Polynomial 3°[f] Polynomial 2°[g] Linear	4.29E-04	-53.210	53.6	32.6	1.64	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = 0.0976), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 10, and 100 mg/kg/day were -0.72, 0.73, 0.01, -0.02, respectively.
[b] For the Exponential (M3) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M2) model.
[c] For the Exponential (M5) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M4) model.
[d] BMD or BMDL computation failed for this model.
[e] For the Power model, the power parameter estimate was 1. The models in this row reduced to the Linear model.
[f] For the Polynomial 3° model, the b3 coefficient estimates was 0 (boundary of parameters space). The models in this row reduced to the Polynomial 2° model. For the Polynomial 3° model, the b3 and b2 coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Linear model.
[g] For the Polynomial 2° model, the b2 coefficient estimate was 0 (boundary of parameters space). The models in this row reduced to the Linear model.

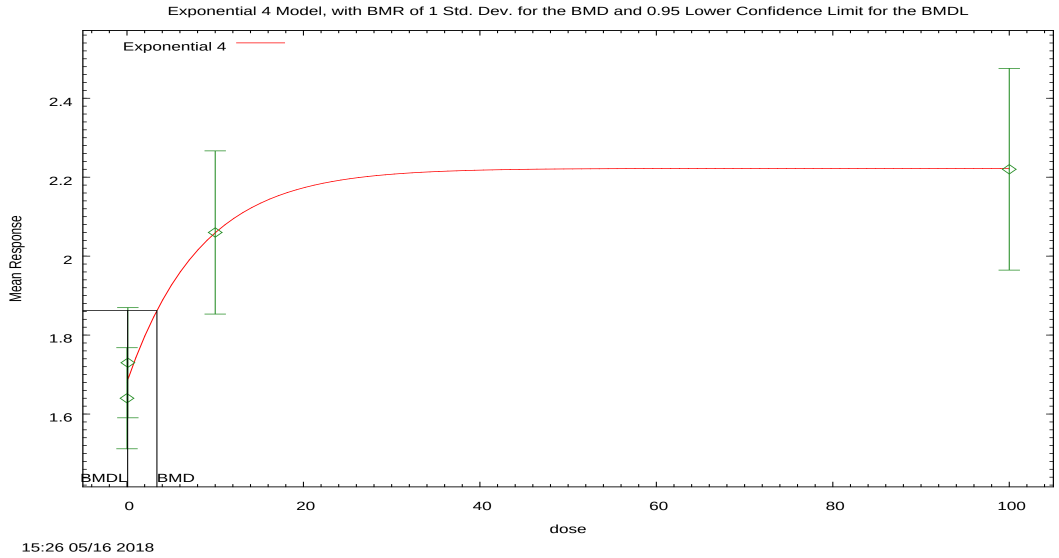

Figure 91. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Albumin to Globulin Ratio in Males (90-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 3.39438

BMDL at the 95% confidence level = 0.0740762

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-5.68779	-5.73506
rho	4.36573	4.55995
a	1.68125	1.558
b	0.119894	0.0202556
c	1.32183	1.49615
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.64	1.68	0.18	0.18	-0.7212
0.1	10	1.73	1.69	0.2	0.18	0.7332
10	10	2.06	2.06	0.29	0.28	0.0091
100	10	2.22	2.22	0.36	0.33	-0.02215

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	35.21855	5	-60.4371
A2	38.37194	8	-60.74389
A3	38.35916	6	-64.71831
R	22.53874	2	-41.07748
4	37.79209	5	-65.58419

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.67	6	<0.0001
Test 2	6.307	3	0.0976
Test 3	0.02558	2	0.9873
Test 6a	1.134	1	0.2869

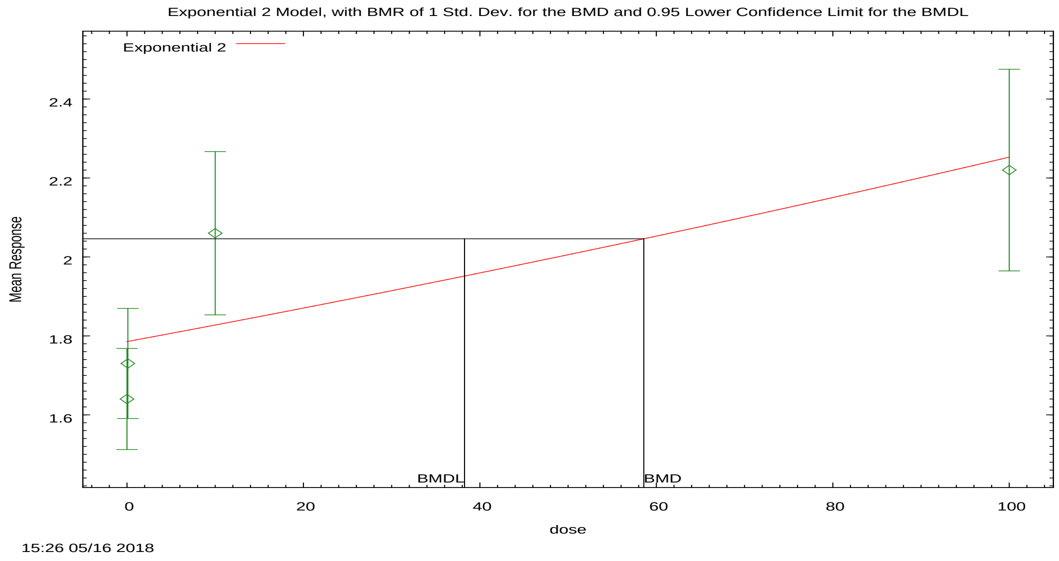

Figure 92. Plot of mean response by dose with fitted curve for Exponential (M2) model with modeled variance for Albumin to Globulin Ratio in Males (90-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 58.5756

BMDL at the 95% confidence level = 38.2584

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-4.22829	-5.73506
rho	2.65236	4.55995
a	1.78551	1.77993
b	0.00232455	0.00233187
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.64	1.79	0.18	0.26	-1.767
0.1	10	1.73	1.79	0.2	0.26	-0.6788
10	10	2.06	1.83	0.29	0.27	2.737
100	10	2.22	2.25	0.36	0.35	-0.2923

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	35.21855	5	-60.4371
A2	38.37194	8	-60.74389
A3	38.35916	6	-64.71831
R	22.53874	2	-41.07748
2	30.42	4	-52.84

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.67	6	<0.0001
Test 2	6.307	3	0.0976
Test 3	0.02558	2	0.9873
Test 4	15.88	2	0.0003565

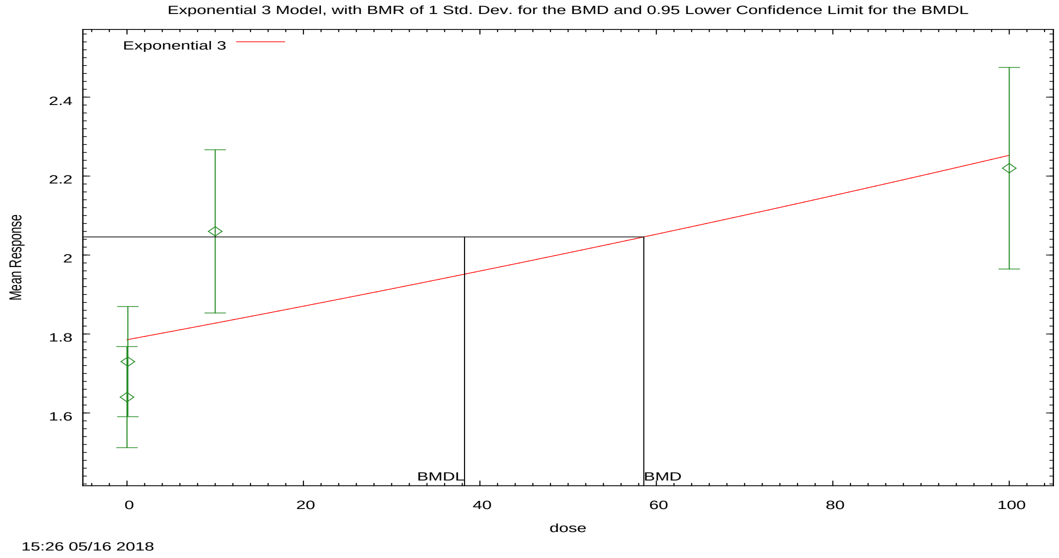

Figure 93. Plot of mean response by dose with fitted curve for Exponential (M3) model with modeled variance for Albumin to Globulin Ratio in Males (90-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 58.5756

BMDL at the 95% confidence level = 38.2584

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-4.22829	-5.73506
rho	2.65236	4.55995
a	1.78551	1.77993
b	0.00232455	0.00233187
c	n/a	0
d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.64	1.79	0.18	0.26	-1.767
0.1	10	1.73	1.79	0.2	0.26	-0.6788
10	10	2.06	1.83	0.29	0.27	2.737
100	10	2.22	2.25	0.36	0.35	-0.2923

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	35.21855	5	-60.4371
A2	38.37194	8	-60.74389
A3	38.35916	6	-64.71831
R	22.53874	2	-41.07748
3	30.42	4	-52.84

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.67	6	<0.0001
Test 2	6.307	3	0.0976
Test 3	0.02558	2	0.9873
Test 5a	15.88	2	0.0003565

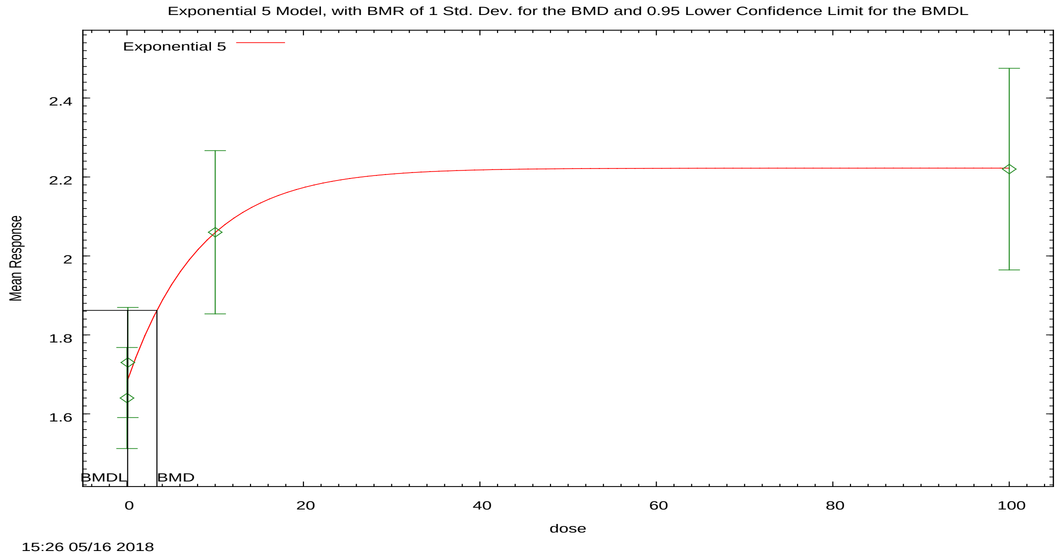

Figure 94. Plot of mean response by dose with fitted curve for Exponential (M5) model with modeled variance for Albumin to Globulin Ratio in Males (90-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 3.39438

BMDL at the 95% confidence level = 0.0740762

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-5.68779	-5.73506
rho	4.36573	4.55995
a	1.68125	1.558
b	0.119894	0.0202556

c	1.32183	1.49615
d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.64	1.68	0.18	0.18	-0.7212
0.1	10	1.73	1.69	0.2	0.18	0.7332
10	10	2.06	2.06	0.29	0.28	0.0091
100	10	2.22	2.22	0.36	0.33	-0.02215

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	35.21855	5	-60.4371
A2	38.37194	8	-60.74389
A3	38.35916	6	-64.71831
R	22.53874	2	-41.07748
5	37.79209	5	-65.58419

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.67	6	<0.0001
Test 2	6.307	3	0.0976
Test 3	0.02558	2	0.9873
Test 7a	1.134	1	0.2869

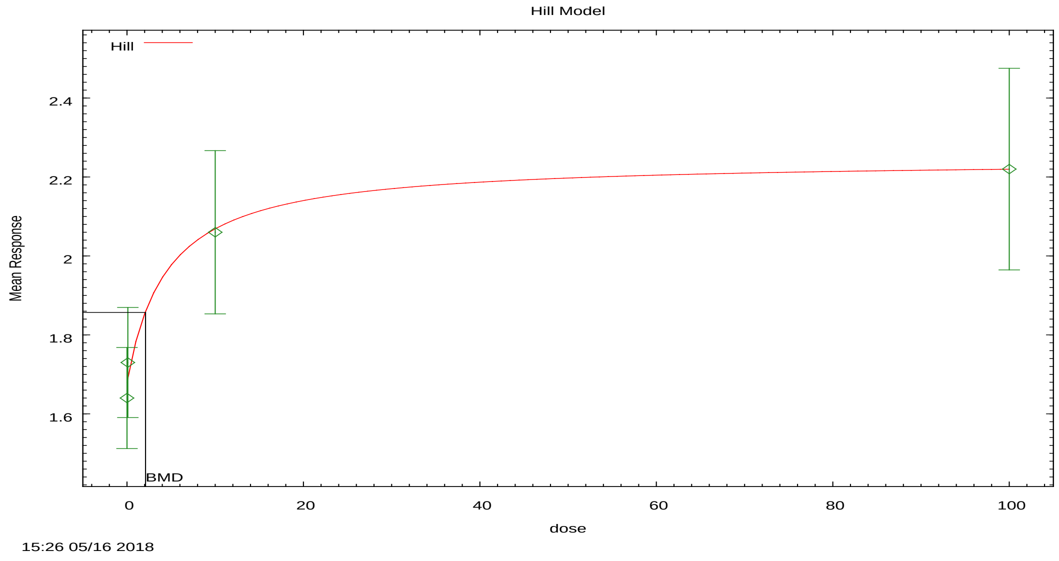

Figure 95. Plot of mean response by dose with fitted curve for Hill model with modeled variance for Albumin to Globulin Ratio in Males (90-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 2.10363

BMDL at the 95% confidence level = error

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-5.71034	-2.65557
rho	4.39592	0
intercept	1.67749	1.64
v	0.563704	0.58
n	1	0.17171

k	4.50647	13.9

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.64	1.68	0.18	0.18	-0.661
0.1	10	1.73	1.69	0.2	0.18	0.699
10	10	2.06	2.07	0.29	0.28	-0.0678
100	10	2.22	2.22	0.36	0.33	0.0297

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	35.218548	5	-60.437095
A2	38.371943	8	-60.743886
A3	38.359155	6	-64.718311
fitted	37.859149	5	-65.718297
R	22.53874	2	-41.07748

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.6664	6	<0.0001
Test 2	6.30679	3	0.0976
Test 3	0.0255757	2	0.9873
Test 4	1.00001	1	0.3173

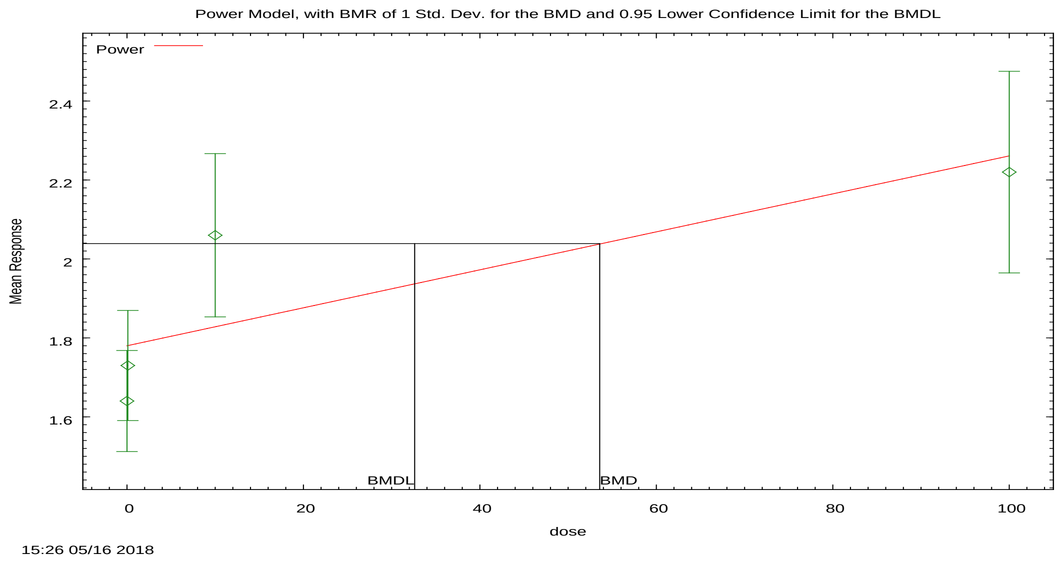

Figure 96. Plot of mean response by dose with fitted curve for Power model with modeled variance for Albumin to Globulin Ratio in Males (90-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 53.5795

BMDL at the 95% confidence level = 32.6083

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-4.29434	-2.65557
rho	2.7405	0
control	1.78111	1.64
slope	0.00480846	0.160496
power	1	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.64	1.78	0.18	0.26	-1.73
0.1	10	1.73	1.78	0.2	0.26	-0.633
10	10	2.06	1.83	0.29	0.27	2.73
100	10	2.22	2.26	0.36	0.36	-0.371

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	35.218548	5	-60.437095
A2	38.371943	8	-60.743886
A3	38.359155	6	-64.718311
fitted	30.605013	4	-53.210026
R	22.53874	2	-41.07748

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.6664	6	<0.0001
Test 2	6.30679	3	0.0976
Test 3	0.0255757	2	0.9873
Test 4	15.5083	2	0.000429

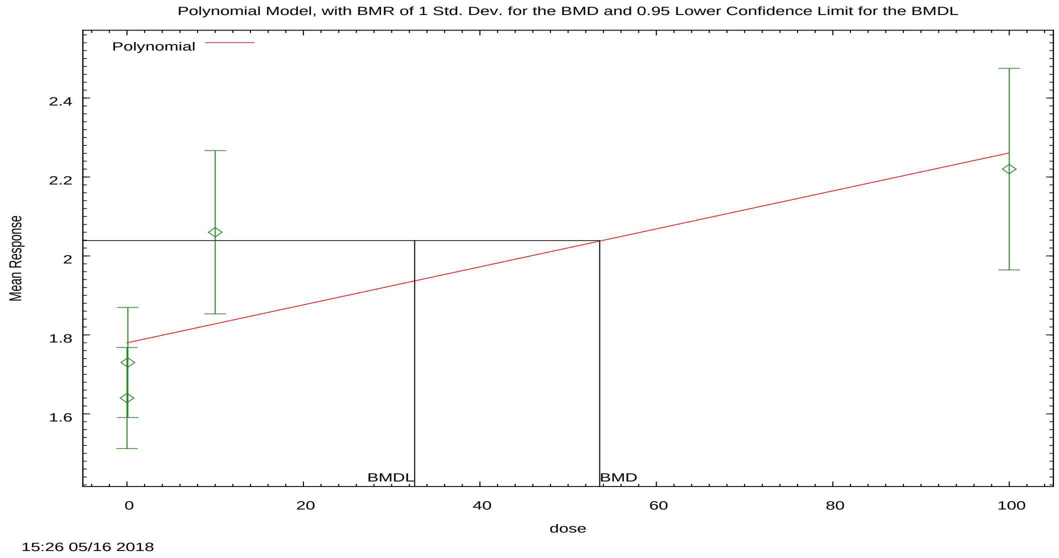

Figure 97. Plot of mean response by dose with fitted curve for Polynomial 3° model with modeled variance for Albumin to Globulin Ratio in Males (90-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 53.5795

BMDL at the 95% confidence level = 32.6083

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-4.29434	-2.65557
rho	2.7405	0
beta_0	1.78111	1.64
beta_1	0.00480846	0.90953
beta_2	0	0

beta_3	0	0.000863508

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.64	1.78	0.18	0.26	-1.73
0.1	10	1.73	1.78	0.2	0.26	-0.633
10	10	2.06	1.83	0.29	0.27	2.73
100	10	2.22	2.26	0.36	0.36	-0.371

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	35.218548	5	-60.437095
A2	38.371943	8	-60.743886
A3	38.359155	6	-64.718311
fitted	30.605013	4	-53.210026
R	22.53874	2	-41.07748

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.6664	6	<0.0001
Test 2	6.30679	3	0.0976
Test 3	0.0255757	2	0.9873
Test 4	15.5083	2	0.000429

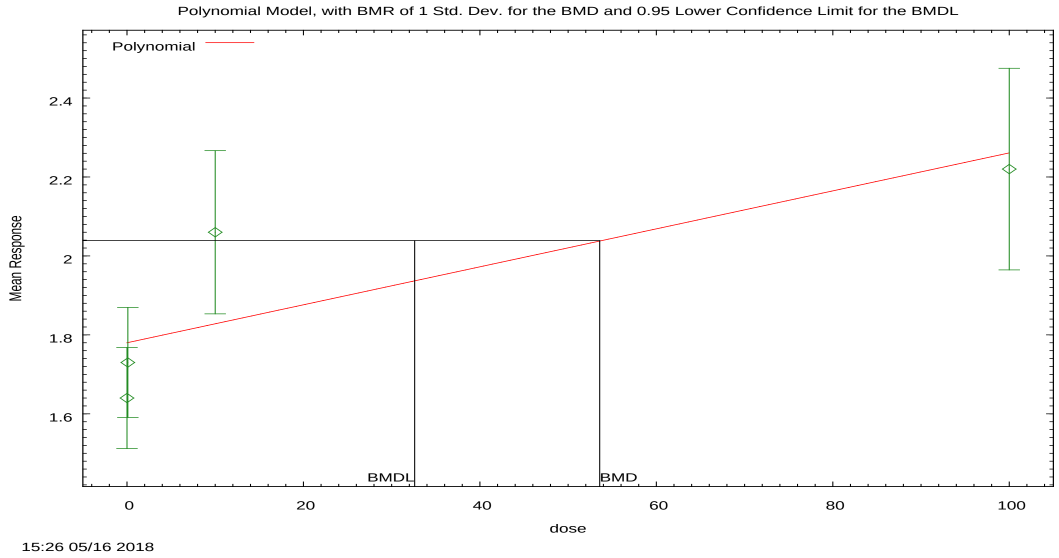

Figure 98. Plot of mean response by dose with fitted curve for Polynomial 2° model with modeled variance for Albumin to Globulin Ratio in Males (90-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 53.5795

BMDL at the 95% confidence level = 32.6083

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-4.29434	-2.65557
rho	2.74049	0
beta_0	1.78111	1.6827
beta_1	0.00480845	0.041379
beta_2	0	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.64	1.78	0.18	0.26	-1.73
0.1	10	1.73	1.78	0.2	0.26	-0.633
10	10	2.06	1.83	0.29	0.27	2.73
100	10	2.22	2.26	0.36	0.36	-0.371

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	35.218548	5	-60.437095
A2	38.371943	8	-60.743886
A3	38.359155	6	-64.718311
fitted	30.605013	4	-53.210026
R	22.53874	2	-41.07748

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.6664	6	<0.0001
Test 2	6.30679	3	0.0976
Test 3	0.0255757	2	0.9873
Test 4	15.5083	2	0.000429

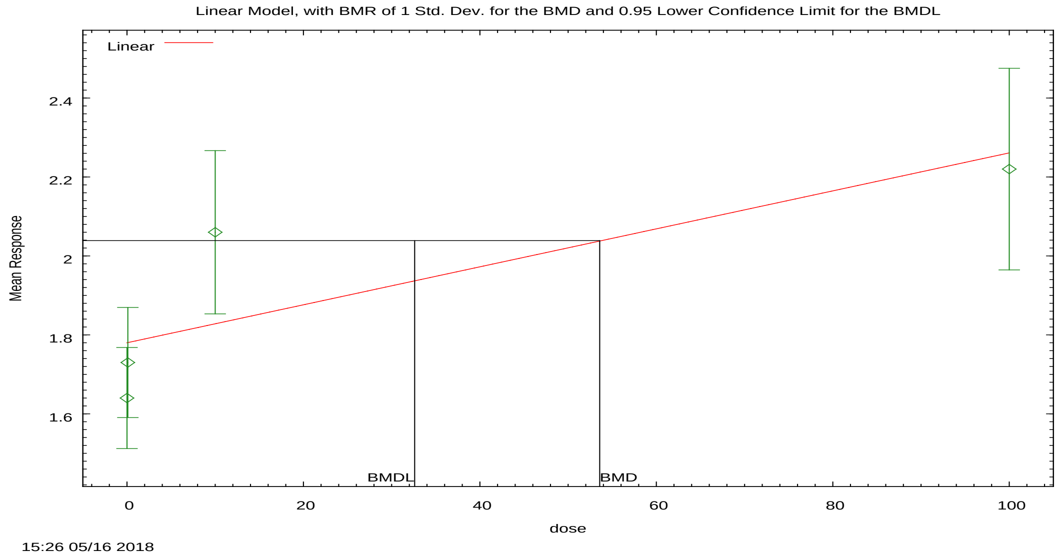

Figure 99. Plot of mean response by dose with fitted curve for Linear model with modeled variance for Albumin to Globulin Ratio in Males (90-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 53.5795

BMDL at the 95% confidence level = 32.6083

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-4.29434	-2.65557
rho	2.7405	0
beta_0	1.78111	1.7871
beta_1	0.00480846	0.00455573

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.64	1.78	0.18	0.26	-1.73
0.1	10	1.73	1.78	0.2	0.26	-0.633
10	10	2.06	1.83	0.29	0.27	2.73
100	10	2.22	2.26	0.36	0.36	-0.371

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	35.218548	5	-60.437095
A2	38.371943	8	-60.743886
A3	38.359155	6	-64.718311
fitted	30.605013	4	-53.210026
R	22.53874	2	-41.07748

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.6664	6	<0.0001
Test 2	6.30679	3	0.0976
Test 3	0.0255757	2	0.9873
Test 4	15.5083	2	0.000429

BMDS WIZARD OUTPUT REPORT

BMDS Summary of 28-Day Oral (Gavage) Toxicity Study of H-28397 in Mice with a 28-day Recovery – Alkaline Phosphatase (U/L) in Males

1.12. BMDS Summary of Alkaline Phosphatase (U/L) Males (28 Day Mice GenX)

Table 12. Summary of BMD Modeling Results for Alkaline Phosphatase in Males (28-day mice); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD$_{1SD}$ (mg/kg/day)	BMDL$_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2) Exponential (M3)[b]	0.00187	391.80	3.47	2.78	1.25	No models met all model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). No BMDL was selected.
Exponential (M4)	0.00390	389.57	0.862	0.606	1.42	
Exponential (M5)	N/A[c]	387.31	1.43	0.862	1.66	
Hill	N/A[c]	386.96	2.48	error[d]	error	
Power	0.0435	385.31	1.43	0.862	1.66	
Polynomial 3°[e]	0.0344	385.71	1.25	0.774	1.62	
Polynomial 2°[f]	0.0344	385.71	1.25	0.774	1.62	
Linear	0.0155	387.57	0.862	0.606	1.42	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = <0.0001, BMDS Test 3 *p*-value = 0.776), no model was selected as a best-fitting model.

[b] For the Exponential (M3) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M2) model.

[c] No available degrees of freedom to calculate a goodness of fit value.

[d] BMD or BMDL computation failed for this model.

[e] The Polynomial 3° model may appear equivalent to the Polynomial 2° model, however differences exist in digits not displayed in the table.

[f] The Polynomial 2° model may appear equivalent to the Polynomial 3° model, however differences exist in digits not displayed in the table.

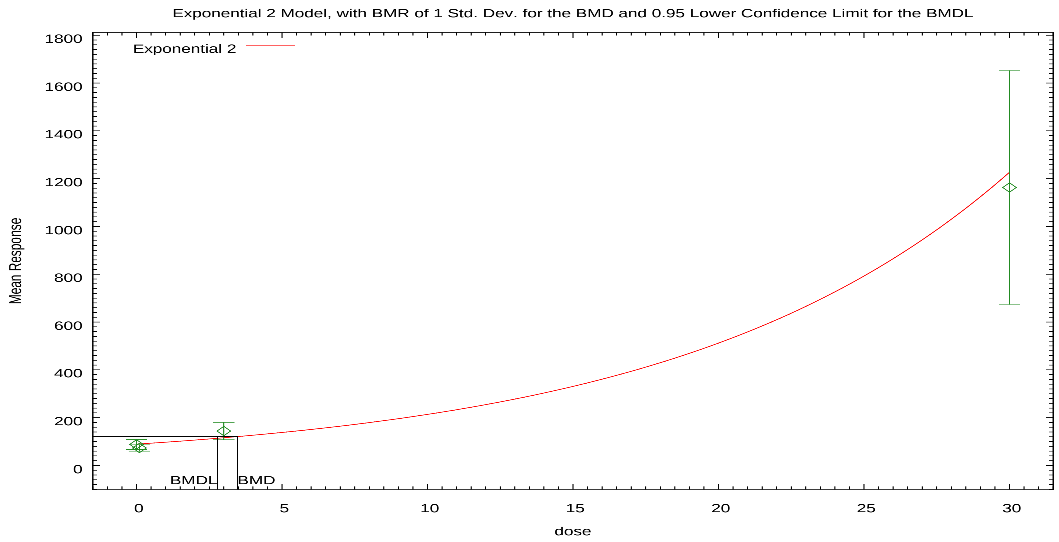

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Figure 100. Plot of mean response by dose with fitted curve for Exponential (M2) model with modeled variance for Alkaline Phosphatase in Males (28-day mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 3.47188

BMDL at the 95% confidence level = 2.78094

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-3.5774	-4.80015
rho	2.33475	2.53385
a	89.1533	88.4408
b	0.0873921	0.0866173
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	88	89.15	29.5	31.6	-0.1154
0.1	10	73	89.94	18.2	31.93	-1.677
3	10	144	115.9	51.2	42.92	2.072
30	10	1163	1227	682.4	674.4	-0.2989

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC

A1	-251.3551	5	512.7101
A2	-185.3645	8	386.7289
A3	-185.6179	6	383.2357
R	-273.3673	2	550.7345
2	-191.8982	4	391.7964

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	176	6	<0.0001
Test 2	132	3	<0.0001
Test 3	0.5068	2	0.7761
Test 4	12.56	2	0.001873

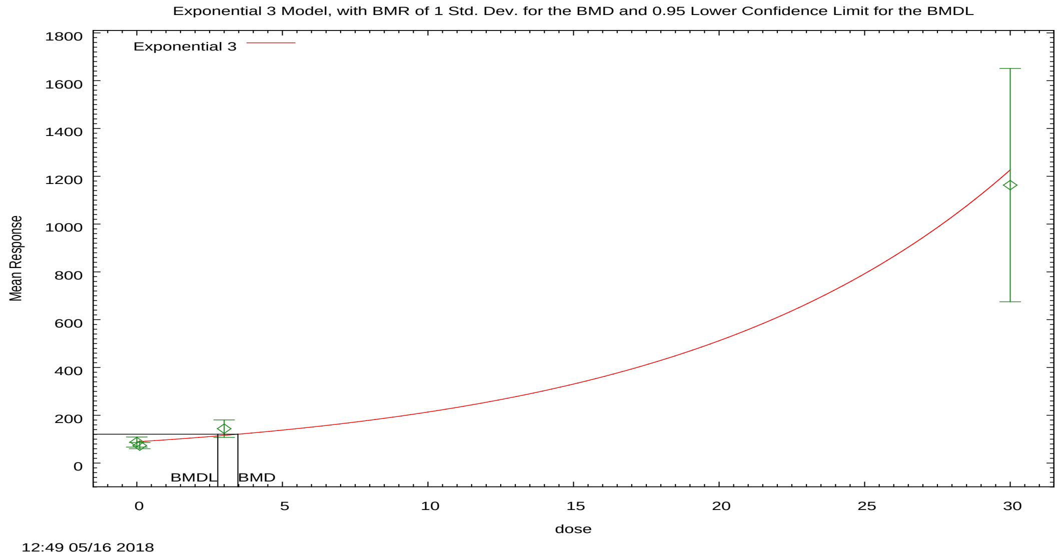

Figure 101. Plot of mean response by dose with fitted curve for Exponential (M3) model with modeled variance for Alkaline Phosphatase in Males (28-day mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 3.47188

BMDL at the 95% confidence level = 2.78094

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-3.57739	-4.80015
rho	2.33475	2.53385
a	89.1533	88.4408
b	0.0873921	0.0866173
c	n/a	0
d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	88	89.15	29.5	31.6	-0.1154
0.1	10	73	89.94	18.2	31.93	-1.677
3	10	144	115.9	51.2	42.92	2.072
30	10	1163	1227	682.4	674.4	-0.2989

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-251.3551	5	512.7101
A2	-185.3645	8	386.7289
A3	-185.6179	6	383.2357
R	-273.3673	2	550.7345
3	-191.8982	4	391.7964

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value

Test 1	176	6	<0.0001
Test 2	132	3	<0.0001
Test 3	0.5068	2	0.7761
Test 5a	12.56	2	0.001873

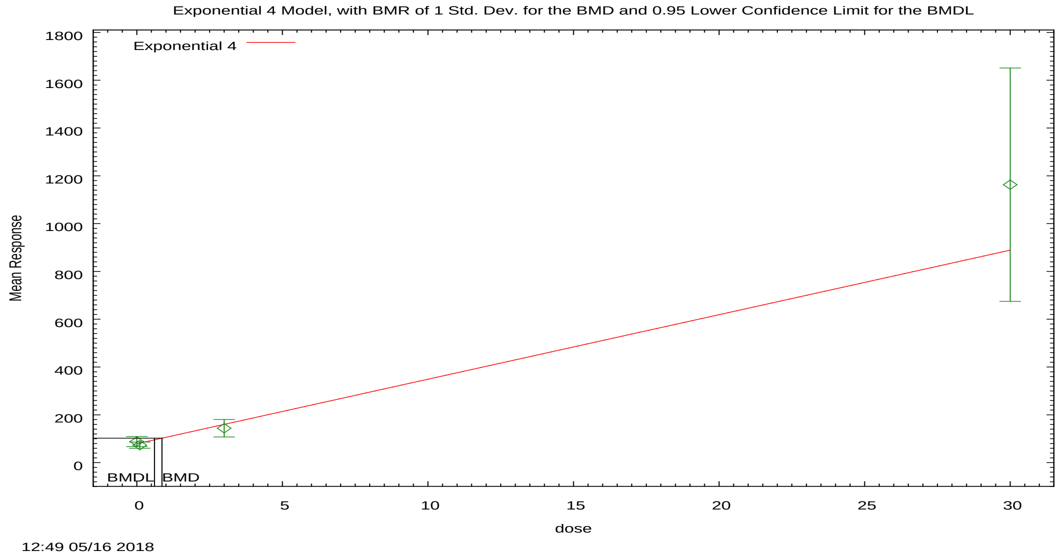

Figure 102. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Alkaline Phosphatase in Males (28-day mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 0.862411

BMDL at the 95% confidence level = 0.606488

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values

lnalpha	-5.83404	-4.80015
rho	2.7762	2.53385
a	78.9796	69.35
b	0.000000651607	0.0000312636
c	524659	16770
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	88	78.98	29.5	23.29	1.225
0.1	10	73	81.68	18.2	24.4	-1.125
3	10	144	160	51.2	62.03	-0.8147
30	10	1163	889	682.4	670.7	1.292

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-251.3551	5	512.7101
A2	-185.3645	8	386.7289
A3	-185.6179	6	383.2357
R	-273.3673	2	550.7345
4	-189.7831	5	389.5662

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	176	6	<0.0001
Test 2	132	3	<0.0001
Test 3	0.5068	2	0.7761
Test 6a	8.33	1	0.003899

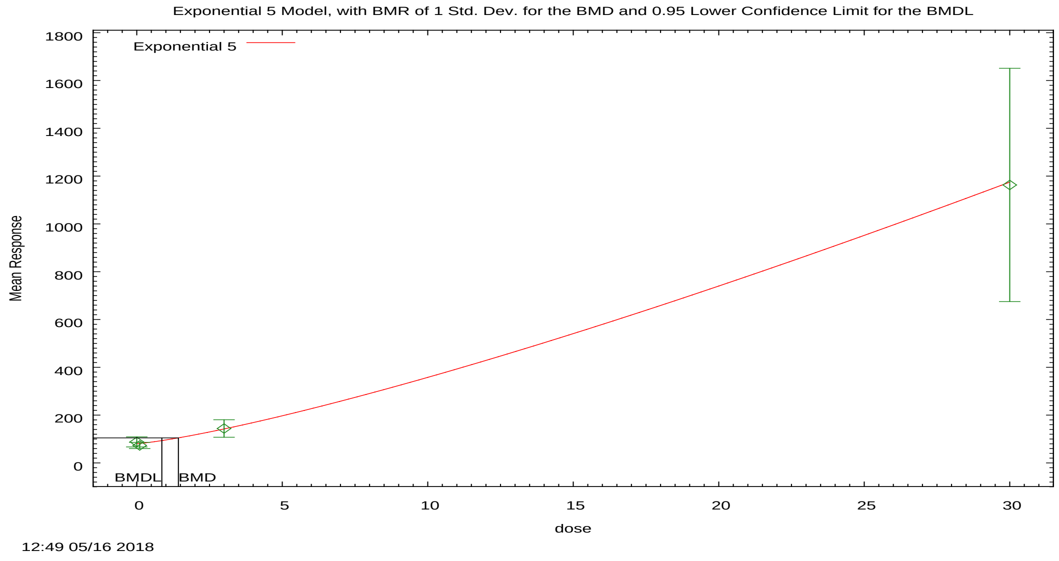

Figure 103. Plot of mean response by dose with fitted curve for Exponential (M5) model with modeled variance for Alkaline Phosphatase in Males (28-day mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 1.42988

BMDL at the 95% confidence level = 0.861795

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-4.32796	-4.80015
rho	2.44313	2.53385
a	80.4279	69.35
b	0.000198274	0.0000312636
c	8224.2	16770

d	1.24954	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	88	80.43	29.5	24.42	0.9805
0.1	10	73	81.31	18.2	24.75	-1.061
3	10	144	142.1	51.2	48.94	0.1246
30	10	1163	1175	682.4	646.1	-0.05686

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-251.3551	5	512.7101
A2	-185.3645	8	386.7289
A3	-185.6179	6	383.2357
R	-273.3673	2	550.7345
5	-187.656	6	387.312

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	176	6	<0.0001
Test 2	132	3	<0.0001
Test 3	0.5068	2	0.7761
Test 7a	4.076	0	N/A

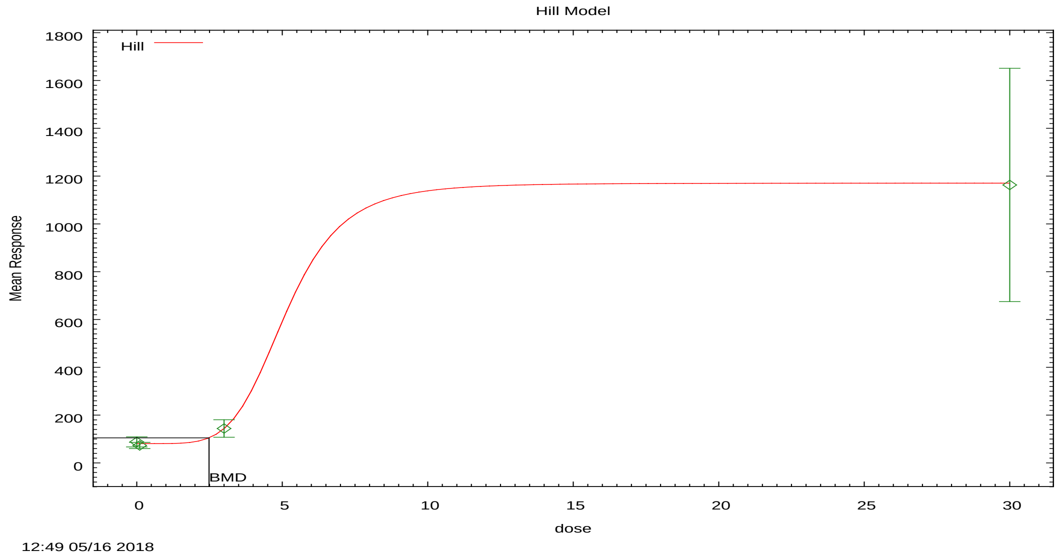

Figure 104. Plot of mean response by dose with fitted curve for Hill model with modeled variance for Alkaline Phosphatase in Males (28-day mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 2.48314

BMDL at the 95% confidence level = error

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-4.3962	11.6731
rho	2.45514	0
intercept	80.6007	88
v	1085.21	1075
n	5.21813	1.0781

k	5.12055	44.2419

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	88	80.6	29.5	24.3	0.963
0.1	10	73	80.6	18.2	24.3	-0.989
3	10	144	143	51.2	49.3	0.0381
30	10	1160	1170	682	645	-0.0132

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-251.355063	5	512.710125
A2	-185.364464	8	386.728927
A3	-185.617874	6	383.235747
fitted	-187.481591	6	386.963182
R	-273.367267	2	550.734534

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	176.006	6	<0.0001
Test 2	131.981	3	<0.0001
Test 3	0.50682	2	0.7761
Test 4	3.72743	0	N/A

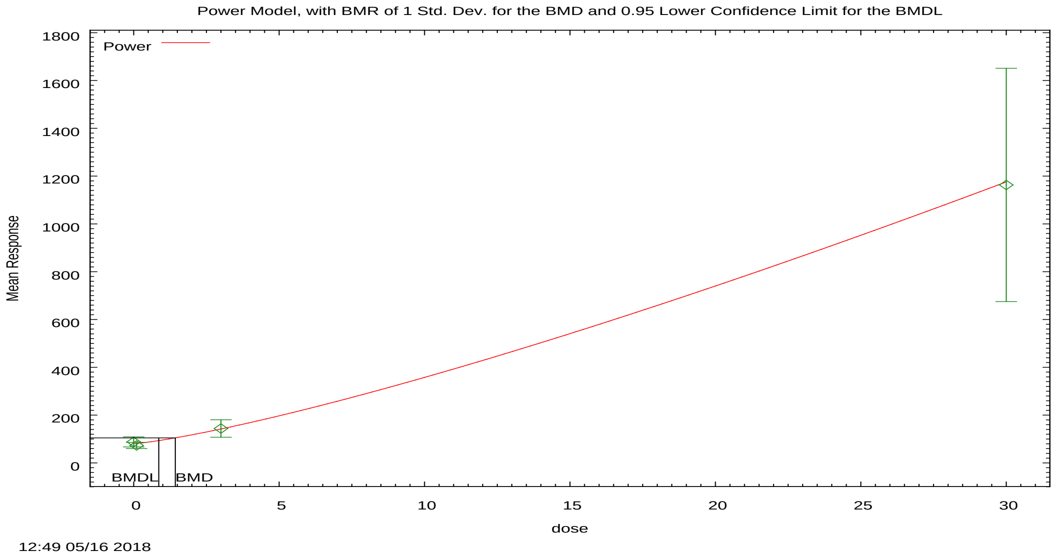

Figure 105. Plot of mean response by dose with fitted curve for Power model with modeled variance for Alkaline Phosphatase in Males (28-day mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 1.42969

BMDL at the 95% confidence level = 0.861719

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-4.32785	11.6731
rho	2.44311	0
control	80.4278	73
slope	15.6259	19.2891
power	1.24922	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	88	80.4	29.5	24.4	0.98
0.1	10	73	81.3	18.2	24.7	-1.06
3	10	144	142	51.2	48.9	0.125
30	10	1160	1170	682	646	-0.0569

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-251.355063	5	512.710125
A2	-185.364464	8	386.728927
A3	-185.617874	6	383.235747
fitted	-187.656196	5	385.312392
R	-273.367267	2	550.734534

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	176.006	6	<0.0001
Test 2	131.981	3	<0.0001
Test 3	0.50682	2	0.7761
Test 4	4.07664	1	0.04348

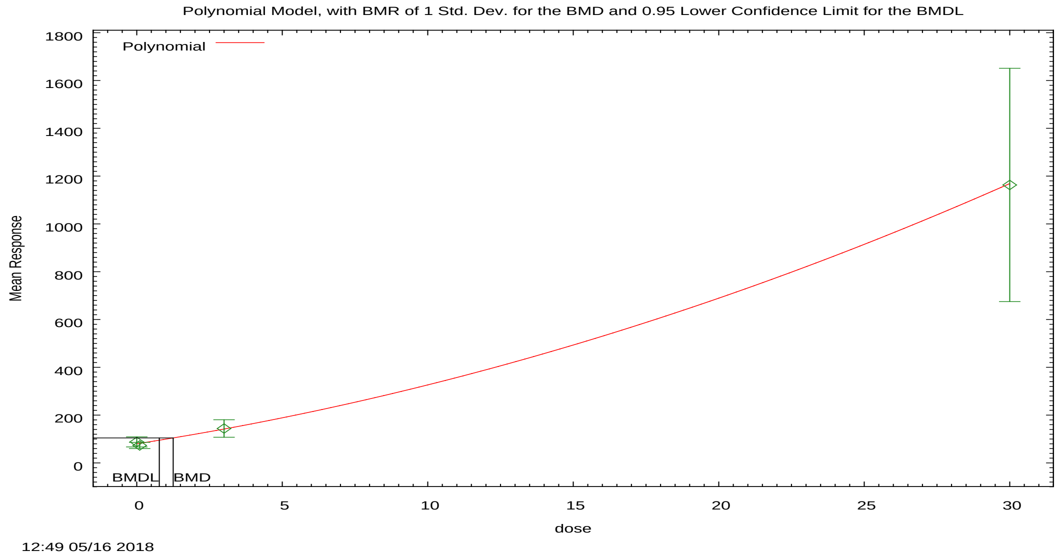

Figure 106. Plot of mean response by dose with fitted curve for Polynomial 3° model with modeled variance for Alkaline Phosphatase in Males (28-day mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 1.2518

BMDL at the 95% confidence level = 0.773778

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-4.3077	11.6731
rho	2.44135	0
beta_0	80.122	88
beta_1	18.8097	0
beta_2	0.583222	0

beta_3	0	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	88	80.1	29.5	24.5	1.02
0.1	10	73	82	18.2	25.2	-1.13
3	10	144	142	51.2	49.1	0.142
30	10	1160	1170	682	645	-0.031

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-251.355063	5	512.710125
A2	-185.364464	8	386.728927
A3	-185.617874	6	383.235747
fitted	-187.855409	5	385.710818
R	-273.367267	2	550.734534

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	176.006	6	<0.0001
Test 2	131.981	3	<0.0001
Test 3	0.50682	2	0.7761
Test 4	4.47507	1	0.03439

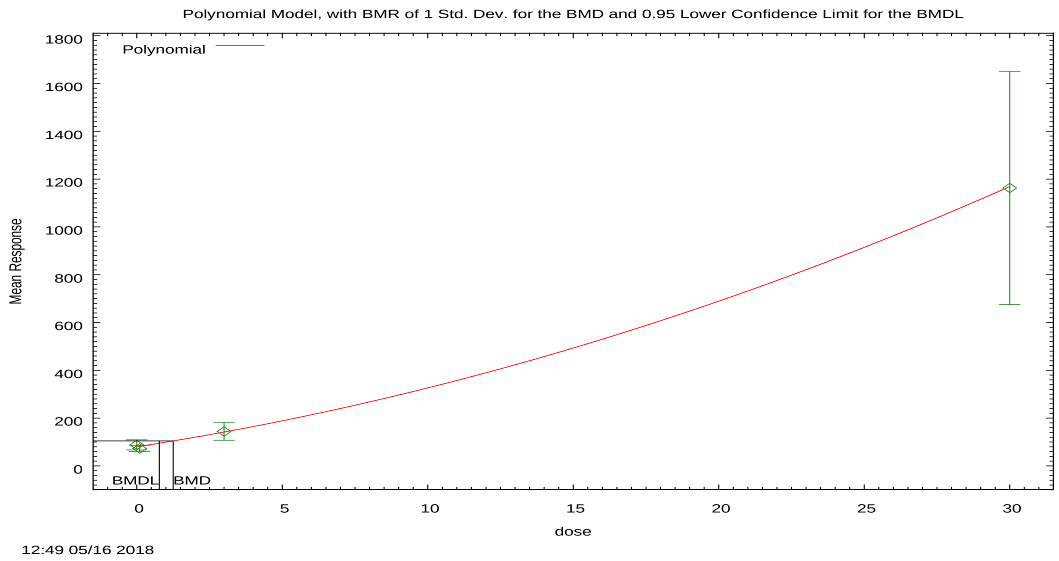

Figure 107. Plot of mean response by dose with fitted curve for Polynomial 2° model with modeled variance for Alkaline Phosphatase in Males (28-day mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 1.25179

BMDL at the 95% confidence level = 0.773789

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-4.3077	11.6731
rho	2.44134	0
beta_0	80.122	79.6705
beta_1	18.8097	0
beta_2	0.583221	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	88	80.1	29.5	24.5	1.02
0.1	10	73	82	18.2	25.2	-1.13
3	10	144	142	51.2	49.1	0.142
30	10	1160	1170	682	645	-0.031

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-251.355063	5	512.710125
A2	-185.364464	8	386.728927
A3	-185.617874	6	383.235747
fitted	-187.855409	5	385.710818
R	-273.367267	2	550.734534

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	176.006	6	<0.0001
Test 2	131.981	3	<0.0001
Test 3	0.50682	2	0.7761
Test 4	4.47507	1	0.03439

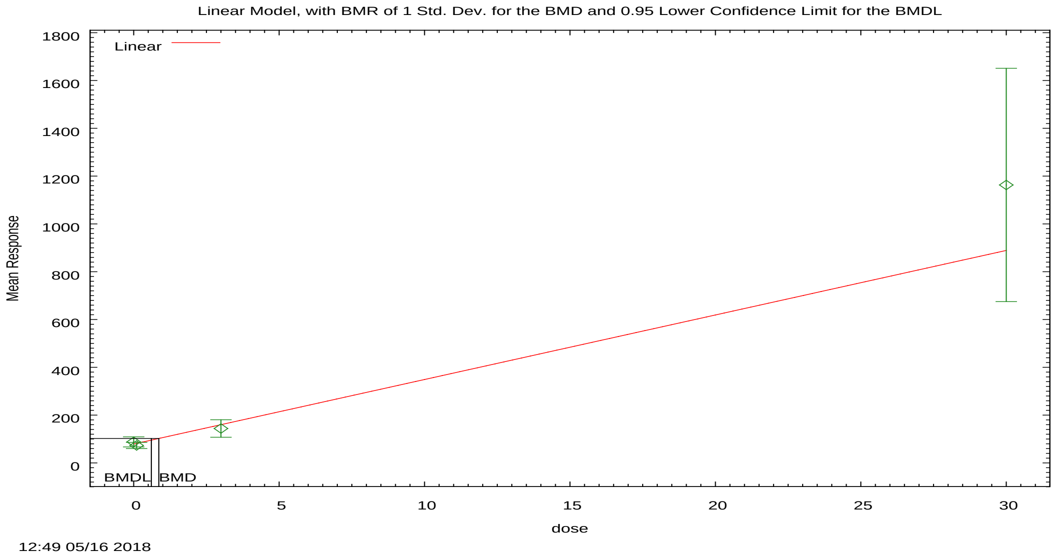

Figure 108. Plot of mean response by dose with fitted curve for Linear model with modeled variance for Alkaline Phosphatase in Males (28-day mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 0.862413

BMDL at the 95% confidence level = 0.606491

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-5.83399	11.6731
rho	2.77619	0
beta_0	78.9795	64.9602
beta_1	27.0008	36.5003

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	88	79	29.5	23.3	1.23
0.1	10	73	81.7	18.2	24.4	-1.12
3	10	144	160	51.2	62	-0.815
30	10	1160	889	682	671	1.29

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-251.355063	5	512.710125
A2	-185.364464	8	386.728927
A3	-185.617874	6	383.235747
fitted	-189.783063	4	387.566127
R	-273.367267	2	550.734534

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	176.006	6	<0.0001
Test 2	131.981	3	<0.0001
Test 3	0.50682	2	0.7761
Test 4	8.33038	2	0.01553

BMDS WIZARD OUTPUT REPORT

BMDS Summary of 28-Day Oral (Gavage) Toxicity Study of H-28397 in Mice with a 28-day Recovery – Alkaline Phosphatase (U/L) in Females

1.13. BMDS Summary of Alkaline Phosphatase (U/L) (28 Day Mice GenX)

Table 13. Summary of BMD Modeling Results for Alkaline Phosphatase in Females (28-Day Mice); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD_{1SD} (mg/kg/day)	$BMDL_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2)	**0.535**	**307.32**	**6.97**	**5.55**	1.26	BMDLs from models that met model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values > 2.0; appropriate variance (continuous data only)) were compared. BMDLs from included models were sufficiently close (< 3-fold difference), so the BMDL from the model with the lowest AIC was selected.
Exponential (M3)	0.458	308.62	13.3	5.72	2.32	
Exponential (M4)	0.128	310.38	4.97	3.73	1.33	
Exponential (M5)	N/A[b]	310.62	12.1	error[c]	error	
Hill	N/A[b]	310.62	9.70	error[c]	error	
Power	0.458	308.62	12.1	4.18	2.89	
Polynomial 3°	0.461	308.61	15.0	4.18	3.58	
Polynomial 2°	0.458	308.62	12.0	4.18	2.88	
Linear	0.315	308.38	4.97	3.73	1.33	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = 0.00267), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 3, and 30 mg/kg/day were -0.27, 0.78, -0.56, 0.05, respectively.

[b] No available degrees of freedom to calculate a goodness of fit value.

[c] BMD or BMDL computation failed for this model.

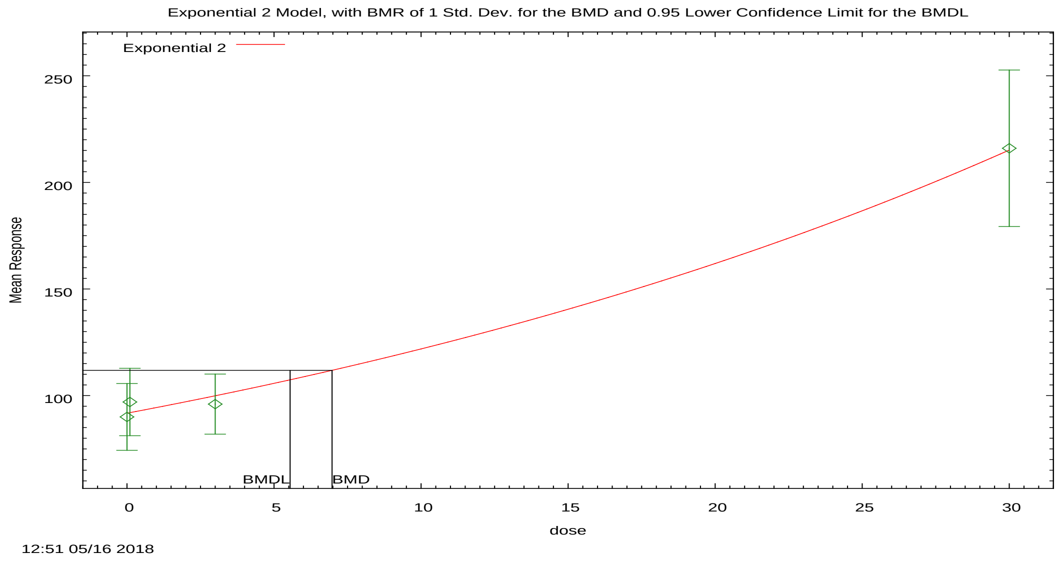

Figure 109. Plot of mean response by dose with fitted curve for Exponential (M2) model with modeled variance for Alkaline Phosphatase in Females (28-

Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 6.97274

BMDL at the 95% confidence level = 5.54681

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-3.25046	-3.48696
rho	2.04737	2.11151
a	91.7451	91.6649
b	0.0284134	0.0284468
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	90	91.75	21.9	20.1	-0.2745
0.1	10	97	92.01	22.1	20.16	0.7833
3	10	96	99.91	19.7	21.94	-0.5635
30	10	216	215.2	51.3	48.11	0.05472

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-155.9868	5	321.9736

A2	-148.8965	8	313.7931
A3	-149.0341	6	310.0682
R	-184.213	2	372.4261
2	-149.6606	4	307.3212

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	70.63	6	<0.0001
Test 2	14.18	3	0.002669
Test 3	0.2752	2	0.8715
Test 4	1.253	2	0.5345

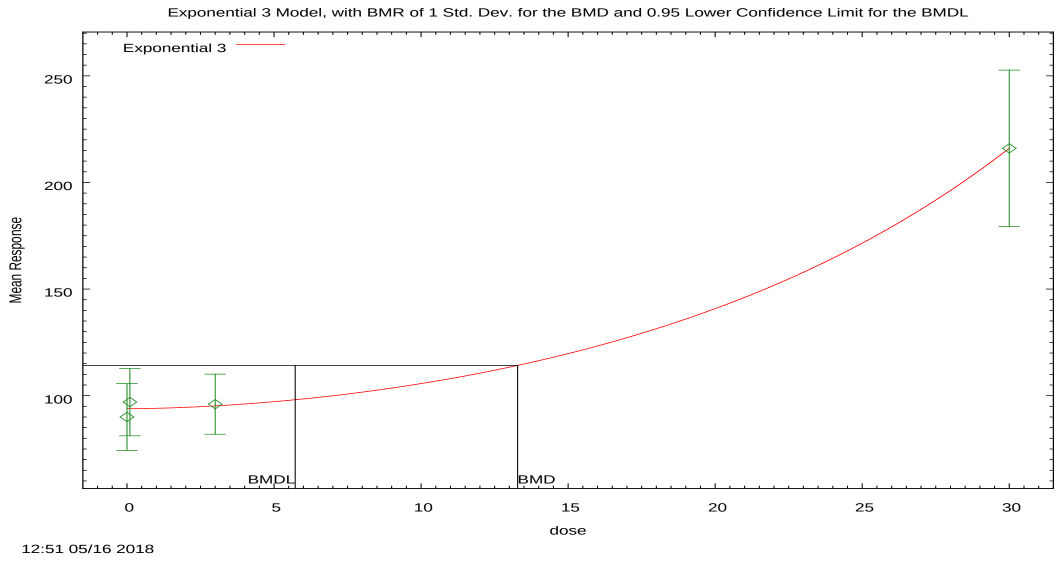

Figure 110. Plot of mean response by dose with fitted curve for Exponential (M3) model with modeled variance for Alkaline Phosphatase in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 13.2823

BMDL at the 95% confidence level = 5.72002

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-3.49022	-3.48696
rho	2.09422	2.11151
a	93.8856	91.6649
b	0.0300844	0.0284468
c	n/a	0
d	1.77762	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	90	93.89	21.9	20.31	-0.6051
0.1	10	97	93.89	22.1	20.31	0.4845
3	10	96	95.2	19.7	20.6	0.1227
30	10	216	216	51.3	48.6	-0.002149

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-155.9868	5	321.9736
A2	-148.8965	8	313.7931
A3	-149.0341	6	310.0682
R	-184.213	2	372.4261
3	-149.3095	5	308.6191

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value

Test 1	70.63	6	<0.0001
Test 2	14.18	3	0.002669
Test 3	0.2752	2	0.8715
Test 5a	0.5508	1	0.458

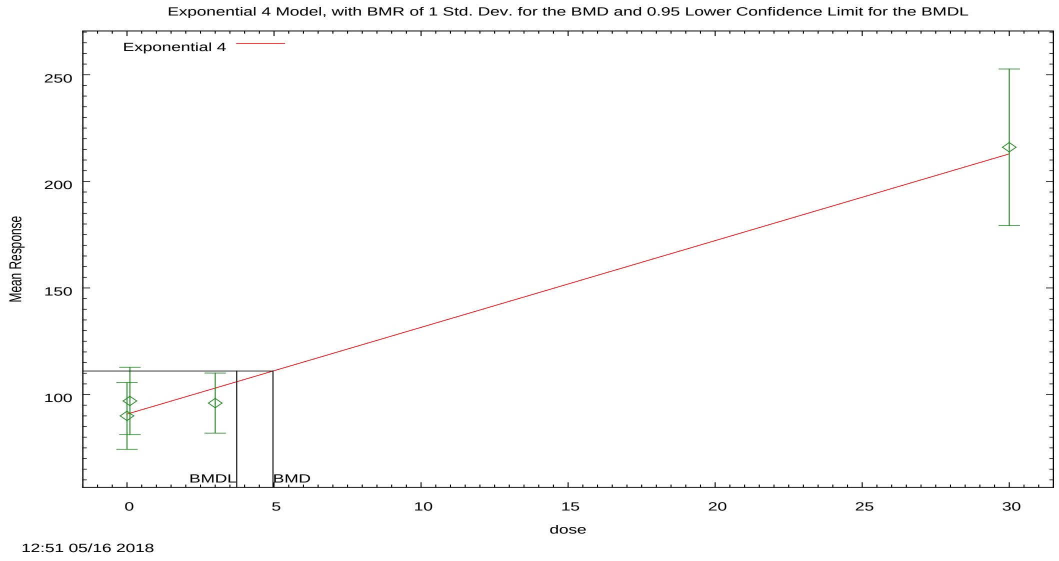

Figure 111. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Alkaline Phosphatase in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 4.96504

BMDL at the 95% confidence level = 3.73159

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-3.13899	-3.48696
rho	2.02929	2.11151
a	90.8386	85.5
b	0.000000267161	0.0000201196
c	167634	2526.32
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	90	90.84	21.9	20.2	-0.1313
0.1	10	97	91.25	22.1	20.29	0.8968
3	10	96	103	19.7	22.95	-0.9703
30	10	216	212.9	51.3	47.93	0.2055

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-155.9868	5	321.9736
A2	-148.8965	8	313.7931
A3	-149.0341	6	310.0682
R	-184.213	2	372.4261
4	-150.1908	5	310.3816

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	70.63	6	<0.0001
Test 2	14.18	3	0.002669
Test 3	0.2752	2	0.8715
Test 6a	2.313	1	0.1283

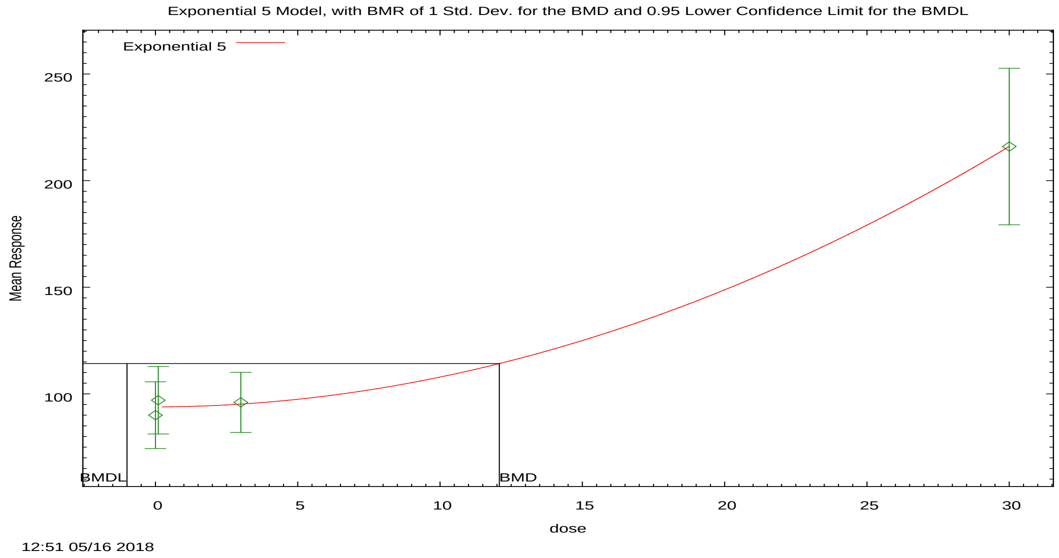

Figure 112. Plot of mean response by dose with fitted curve for Exponential (M5) model with modeled variance for Alkaline Phosphatase in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 12.0822

BMDL at the 95% confidence level = error

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-3.49045	-3.48696
rho	2.09427	2.11151
a	93.8909	85.5
b	0.000236033	0.0000201196

c	22680.7	2526.32
d	1.97282	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	90	93.89	21.9	20.31	-0.6059
0.1	10	97	93.89	22.1	20.31	0.4839
3	10	96	95.19	19.7	20.6	0.1241
30	10	216	216	51.3	48.6	-0.002132

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-155.9868	5	321.9736
A2	-148.8965	8	313.7931
A3	-149.0341	6	310.0682
R	-184.213	2	372.4261
5	-149.3096	6	310.6193

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	70.63	6	<0.0001
Test 2	14.18	3	0.002669
Test 3	0.2752	2	0.8715
Test 7a	0.5511	0	N/A

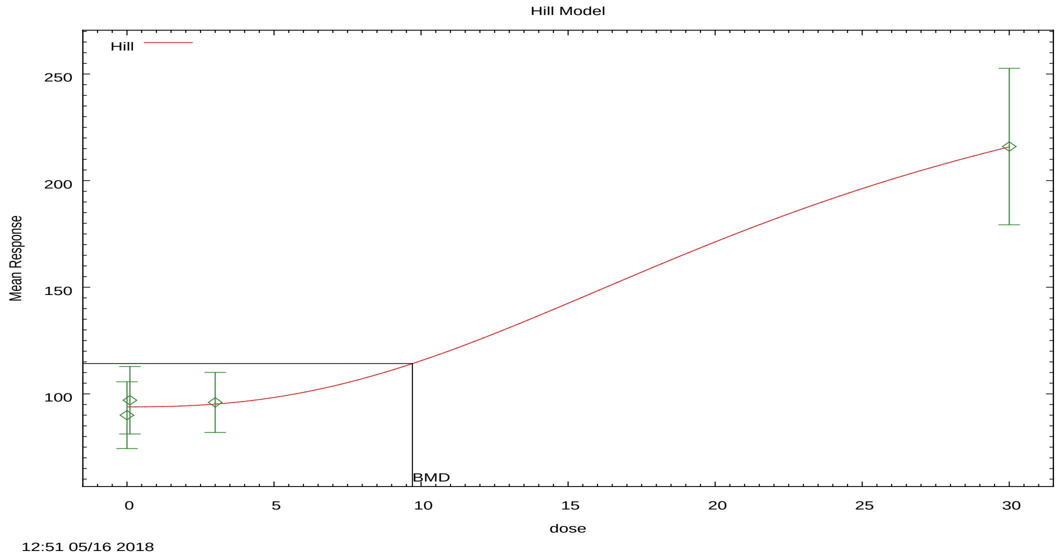

Figure 113. Plot of mean response by dose with fitted curve for Hill model with modeled variance for Alkaline Phosphatase in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 9.70479

BMDL at the 95% confidence level = error

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-3.49065	6.9047
rho	2.09431	0
intercept	93.8955	90
v	185.095	126
n	2.44226	0.789505

k	22.8708	44.175

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	90	93.9	21.9	20.3	-0.607
0.1	10	97	93.9	22.1	20.3	0.483
3	10	96	95.2	19.7	20.6	0.125
30	10	216	216	51.3	48.6	-0.00212

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-155.986802	5	321.973604
A2	-148.896526	8	313.793052
A3	-149.034119	6	310.068237
fitted	-149.309756	6	310.619511
R	-184.213048	2	372.426096

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	70.633	6	<0.0001
Test 2	14.1806	3	0.002669
Test 3	0.275185	2	0.8715
Test 4	0.551274	0	N/A

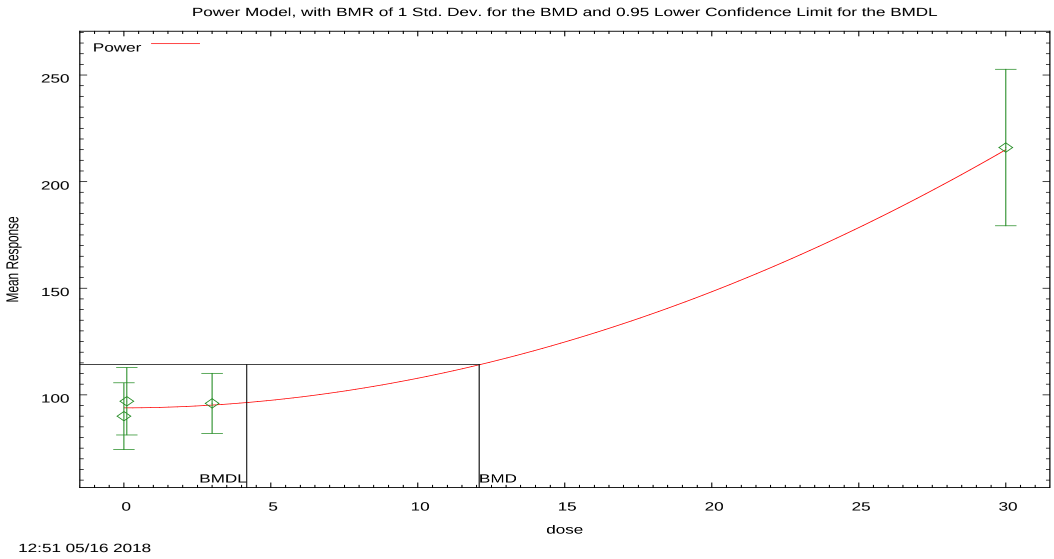

Figure 114. Plot of mean response by dose with fitted curve for Power model with modeled variance for Alkaline Phosphatase in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 12.0822

BMDL at the 95% confidence level = 4.181

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-3.49043	6.9047
rho	2.09426	0
control	93.8909	90
slope	0.148867	12.3966
power	1.9728	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	90	93.9	21.9	20.3	-0.606
0.1	10	97	93.9	22.1	20.3	0.484
3	10	96	95.2	19.7	20.6	0.124
30	10	216	216	51.3	48.6	-0.00214

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-155.986802	5	321.973604
A2	-148.896526	8	313.793052
A3	-149.034119	6	310.068237
fitted	-149.30965	5	308.619299
R	-184.213048	2	372.426096

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	70.633	6	<0.0001
Test 2	14.1806	3	0.002669
Test 3	0.275185	2	0.8715
Test 4	0.551062	1	0.4579

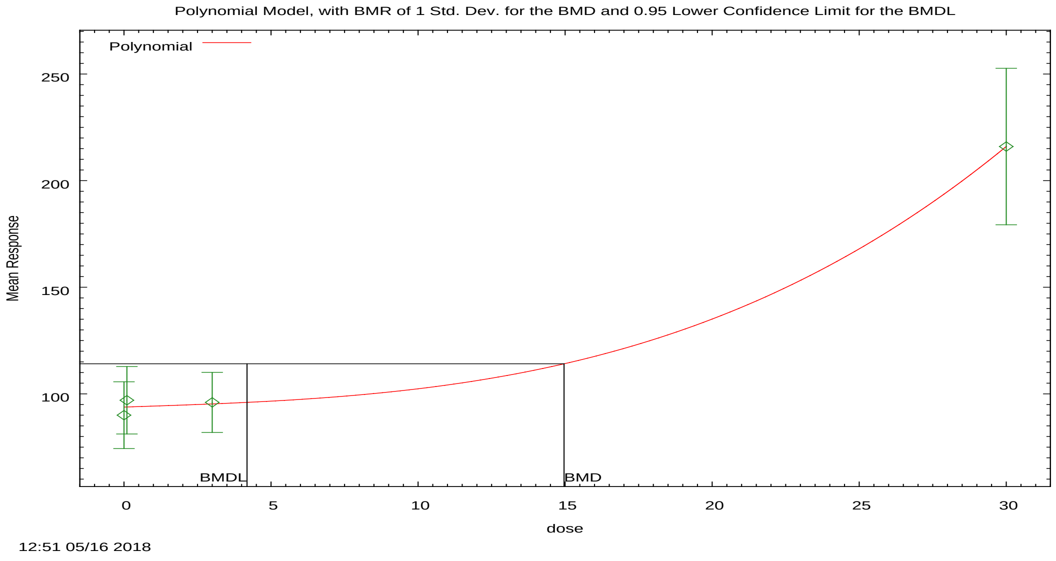

Figure 115. Plot of mean response by dose with fitted curve for Polynomial 3° model with modeled variance for Alkaline Phosphatase in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 14.9627

BMDL at the 95% confidence level = 4.18359

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-3.48864	6.9047
rho	2.09385	0
beta_0	93.8164	90
beta_1	0.456035	0
beta_2	2.21944E-13	0

beta_3	0.00401997	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	90	93.8	21.9	20.3	-0.595
0.1	10	97	93.9	22.1	20.3	0.489
3	10	96	95.3	19.7	20.6	0.108
30	10	216	216	51.3	48.6	-0.00239

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-155.986802	5	321.973604
A2	-148.896526	8	313.793052
A3	-149.034119	6	310.068237
fitted	-149.306152	5	308.612304
R	-184.213048	2	372.426096

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	70.633	6	<0.0001
Test 2	14.1806	3	0.002669
Test 3	0.275185	2	0.8715
Test 4	0.544067	1	0.4608

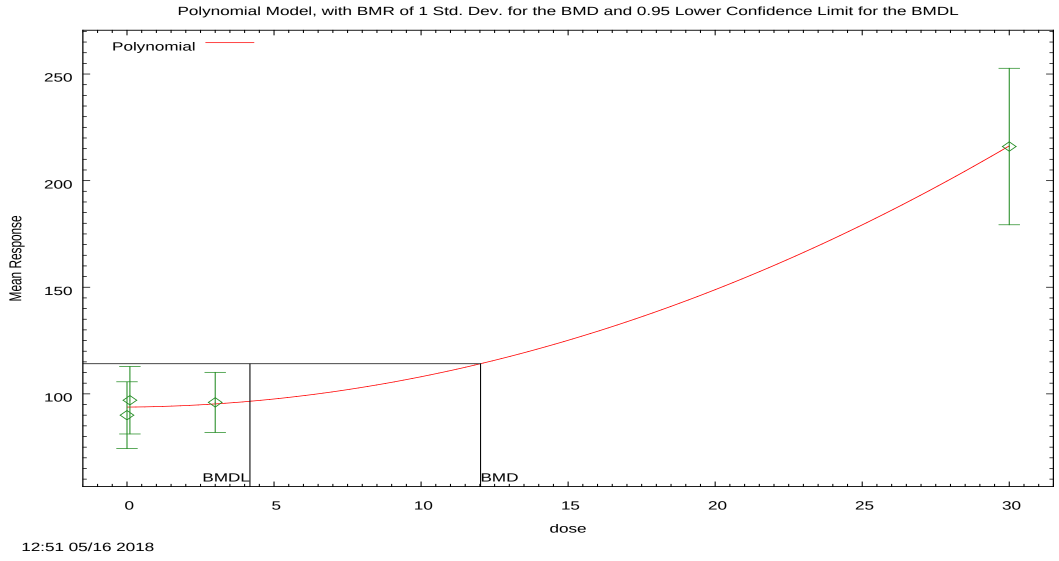

Figure 116. Plot of mean response by dose with fitted curve for Polynomial 2° model with modeled variance for Alkaline Phosphatase in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 12.022

BMDL at the 95% confidence level = 4.18135

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-3.48753	6.9047
rho	2.09365	0
beta_0	93.8305	93.407
beta_1	0.0931736	0
beta_2	0.132672	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	90	93.8	21.9	20.3	-0.597
0.1	10	97	93.8	22.1	20.3	0.492
3	10	96	95.3	19.7	20.6	0.107
30	10	216	216	51.3	48.6	-0.00199

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-155.986802	5	321.973604
A2	-148.896526	8	313.793052
A3	-149.034119	6	310.068237
fitted	-149.309169	5	308.618338
R	-184.213048	2	372.426096

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	70.633	6	<0.0001
Test 2	14.1806	3	0.002669
Test 3	0.275185	2	0.8715
Test 4	0.550101	1	0.4583

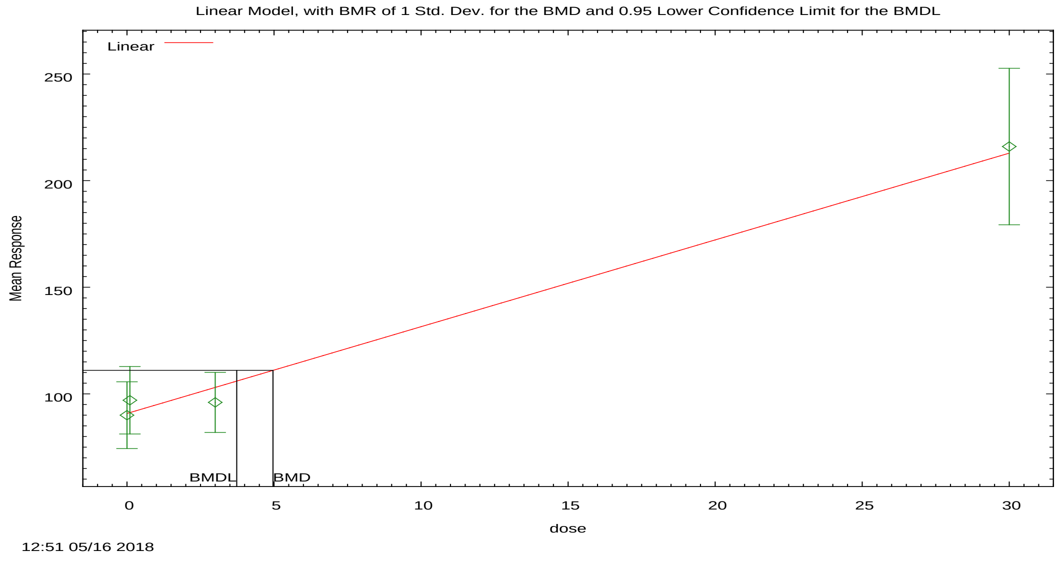

Figure 117. Plot of mean response by dose with fitted curve for Linear model with modeled variance for Alkaline Phosphatase in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 4.96506

BMDL at the 95% confidence level = 3.7316

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-3.13897	6.9047
rho	2.02929	0
beta_0	90.8386	90.2423
beta_1	4.0682	4.17012

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	90	90.8	21.9	20.2	-0.131
0.1	10	97	91.2	22.1	20.3	0.897
3	10	96	103	19.7	23	-0.97
30	10	216	213	51.3	47.9	0.206

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-155.986802	5	321.973604
A2	-148.896526	8	313.793052
A3	-149.034119	6	310.068237
fitted	-150.190806	4	308.381612
R	-184.213048	2	372.426096

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	70.633	6	<0.0001
Test 2	14.1806	3	0.002669
Test 3	0.275185	2	0.8715
Test 4	2.31338	2	0.3145

BMDS WIZARD OUTPUT REPORT

Summary of H-28548: Subchronic Toxicity 90-Day Gavage Study in Mice – Alkaline Phosphatase (U/L) in Males

1.14. BMDS Summary of Alkaline Phosphatase (U/L) Males (90 Day Mice GenX)

Table 14. Summary of BMD Modeling Results for Alkaline Phosphatase in Males (90-Day Mice); BMR = 1 std. dev. change from control mean

Model[a]	**Goodness of fit**		**BMD_{1SD} (mg/kg/day)**	**BMDL_{1SD} (mg/kg/day)**	**BMD/BMDL**	**Basis for model selection**
	***p*-value**	**AIC**				
Exponential (M2) **Exponential (M3)**[b]	**0.384**	**344.14**	**0.596**	**0.480**	1.24	BMDLs from models that met model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values > 2.0; appropriate variance (continuous data only)) were compared. BMDLs from included models were sufficiently close (< 3-fold difference), so the BMDL from the model with the lowest AIC was selected.
Exponential (M4)	0.0253	349.23	0.183	0.122	1.50	
Exponential (M5)	N/A[c]	347.24	0.383	0.190	2.02	
Hill	N/A[c]	347.24	0.383	error[d]	error	
Power	0.314	345.24	0.383	0.190	2.02	
Polynomial 3°	0.502	344.68	0.329	0.173	1.90	
Polynomial 2°	0.452	344.79	0.343	0.176	1.95	
Linear	0.0820	347.23	0.183	0.122	1.50	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = <0.0001), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 0.5, and 5 mg/kg/day were -0.38, 0.03, 0.41, -0.06, respectively.

[b] For the Exponential (M3) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M2) model.

[c] No available degrees of freedom to calculate a goodness of fit value.

[d] BMD or BMDL computation failed for this model.

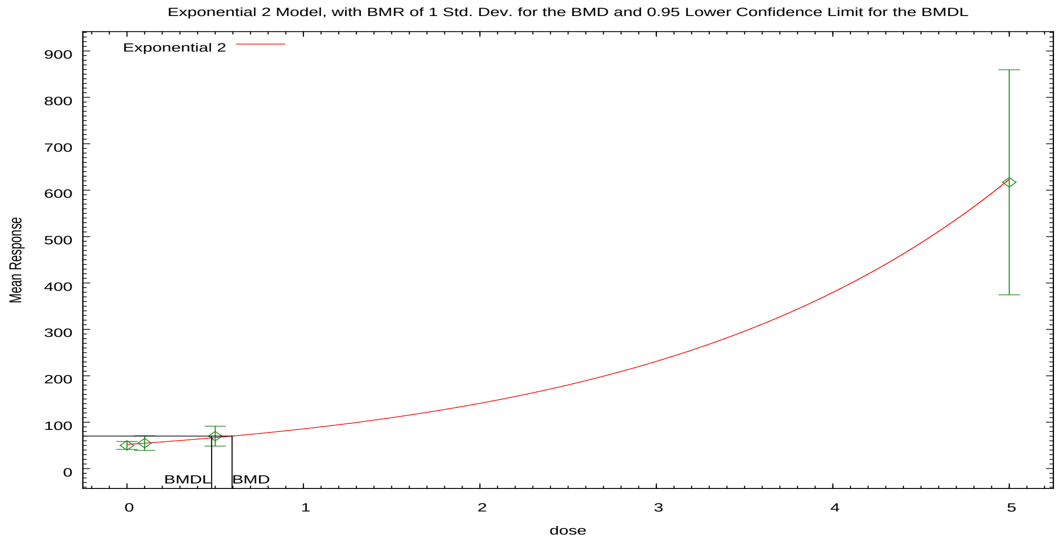
Exponential 2 Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

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Figure 118. Plot of mean response by dose with fitted curve for Exponential (M2) model with modeled variance for Alkaline Phosphatase in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 0.595588

BMDL at the 95% confidence level = 0.479579

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-3.50607	-3.88175
rho	2.34657	2.42747
a	52.176	52.2193
b	0.496121	0.494806
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	50	52.18	12	17.94	-0.3836
0.1	10	55	54.83	22	19.01	0.02831
0.5	10	70	66.87	30	24	0.4131
5	10	617	623.4	339	329.4	-0.06168

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC

A1	-223.4711	5	456.9422
A2	-165.9243	8	347.8485
A3	-167.1141	6	346.2282
R	-246.9552	2	497.9105
2	-168.0715	4	344.143

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	162.1	6	<0.0001
Test 2	115.1	3	<0.0001
Test 3	2.38	2	0.3043
Test 4	1.915	2	0.3839

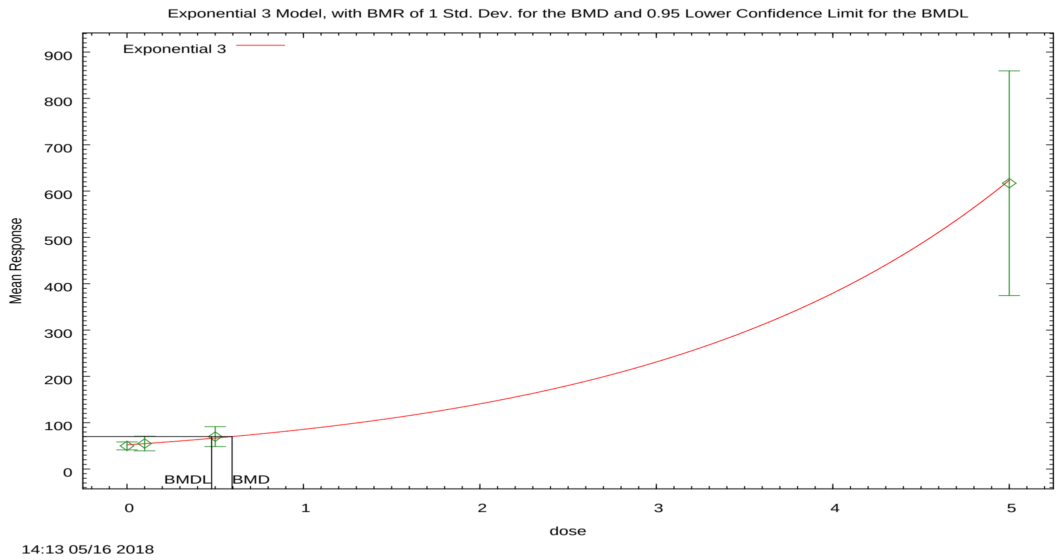
Exponential 3 Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

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Figure 119. Plot of mean response by dose with fitted curve for Exponential (M3) model with modeled variance for Alkaline Phosphatase in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 0.595588

BMDL at the 95% confidence level = 0.479579

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-3.50607	-3.88175
rho	2.34657	2.42747
a	52.176	52.2193
b	0.496121	0.494806
c	n/a	0
d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	50	52.18	12	17.94	-0.3836
0.1	10	55	54.83	22	19.01	0.02831
0.5	10	70	66.87	30	24	0.4131
5	10	617	623.4	339	329.4	-0.06168

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-223.4711	5	456.9422
A2	-165.9243	8	347.8485
A3	-167.1141	6	346.2282
R	-246.9552	2	497.9105
3	-168.0715	4	344.143

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value

Test 1	162.1	6	<0.0001
Test 2	115.1	3	<0.0001
Test 3	2.38	2	0.3043
Test 5a	1.915	2	0.3839

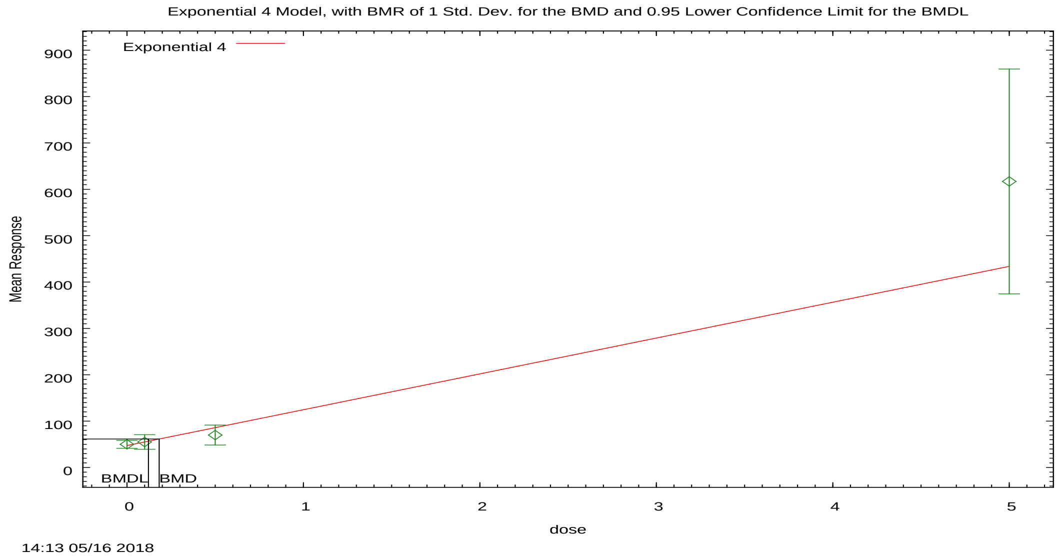

Figure 120. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Alkaline Phosphatase in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 0.182554

BMDL at the 95% confidence level = 0.121505

Parameter Estimates

Variable	**Estimate**	**Default Initial Parameter Values**

lnalpha	-6.0962	-3.88175
rho	2.95247	2.42747
a	47.3623	47.5
b	0.00000281194	0.000183571
c	580402	12989.5
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	50	47.36	12	14.11	0.5911
0.1	10	55	55.09	22	17.64	-0.0165
0.5	10	70	86.01	30	34.05	-1.487
5	10	617	433.8	339	371.2	1.56

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-223.4711	5	456.9422
A2	-165.9243	8	347.8485
A3	-167.1141	6	346.2282
R	-246.9552	2	497.9105
4	-169.6147	5	349.2294

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	162.1	6	<0.0001
Test 2	115.1	3	<0.0001
Test 3	2.38	2	0.3043
Test 6a	5.001	1	0.02533

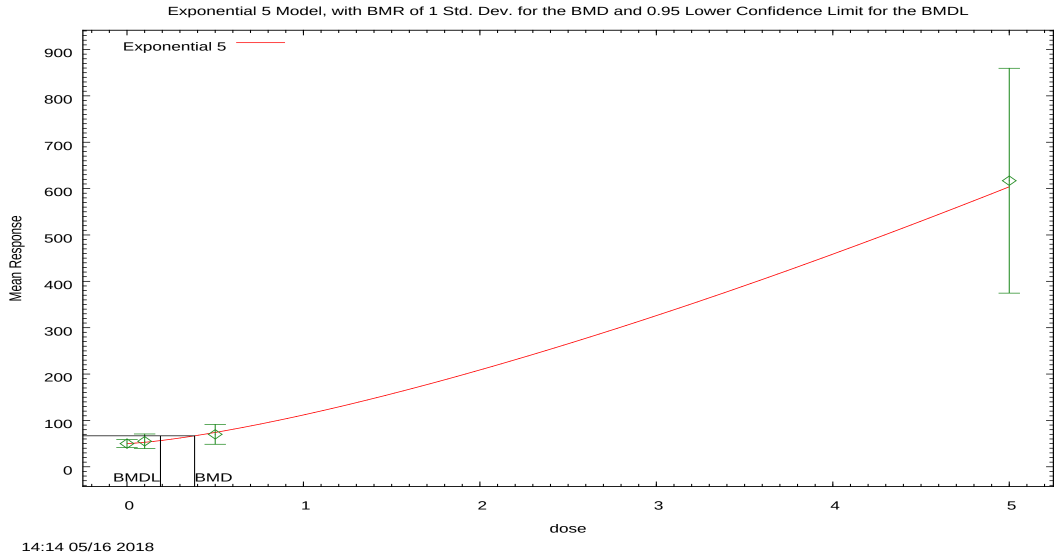

Figure 121. Plot of mean response by dose with fitted curve for Exponential (M5) model with modeled variance for Alkaline Phosphatase in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 0.383064

BMDL at the 95% confidence level = 0.189841

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-3.74074	-3.88175
rho	2.39323	2.42747
a	50.1106	47.5
b	0.0000952421	0.000183571
c	374606	12989.5

d	1.36363	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	50	50.11	12	16.67	-0.02099
0.1	10	55	52.78	22	17.74	0.3957
0.5	10	70	74.08	30	26.61	-0.4848
5	10	617	603.8	339	327.6	0.1275

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-223.4711	5	456.9422
A2	-165.9243	8	347.8485
A3	-167.1141	6	346.2282
R	-246.9552	2	497.9105
5	-167.6203	6	347.2407

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	162.1	6	<0.0001
Test 2	115.1	3	<0.0001
Test 3	2.38	2	0.3043
Test 7a	1.012	0	N/A

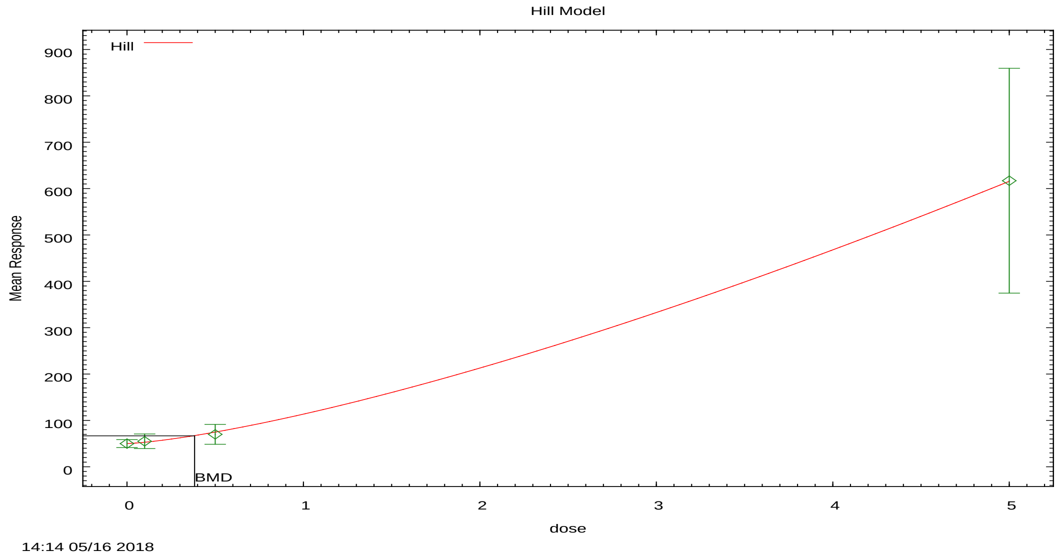

Figure 122. Plot of mean response by dose with fitted curve for Hill model with modeled variance for Alkaline Phosphatase in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 0.383177

BMDL at the 95% confidence level = error

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-3.74061	10.2789
rho	2.3932	0
intercept	50.1127	50
v	335963	567
n	1.36437	1.16578

k	547.321	7.33227

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	50	50.1	12	16.7	-0.0214
0.1	10	55	52.8	22	17.7	0.396
0.5	10	70	74.1	30	26.6	-0.485
5	10	617	604	339	328	0.128

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-223.471076	5	456.942152
A2	-165.924256	8	347.848511
A3	-167.114116	6	346.228232
fitted	-167.620788	6	347.241575
R	-246.955243	2	497.910486

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	162.062	6	<0.0001
Test 2	115.094	3	<0.0001
Test 3	2.37972	2	0.3043
Test 4	1.01334	0	N/A

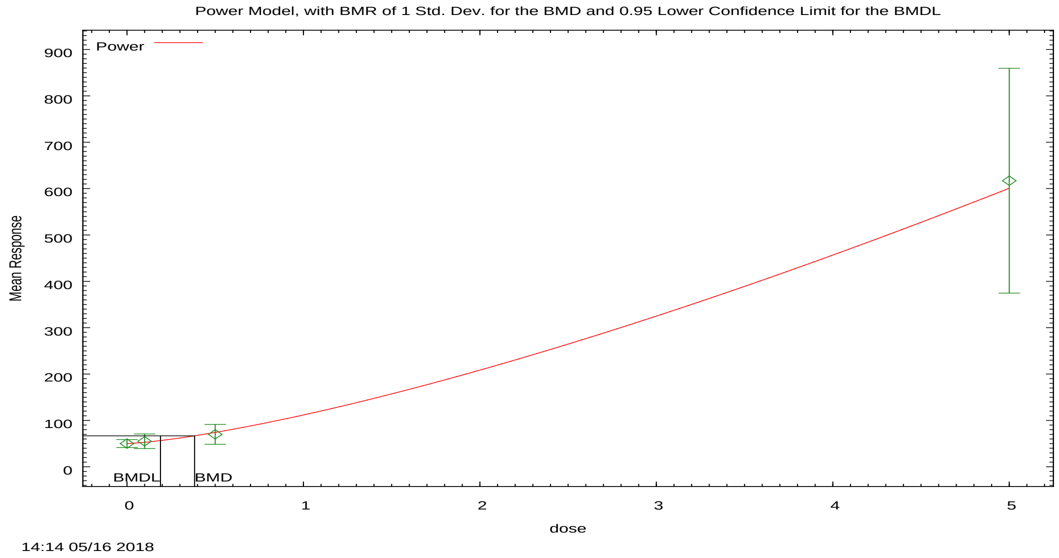

Figure 123. Plot of mean response by dose with fitted curve for Power model with modeled variance for Alkaline Phosphatase in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 0.383064

BMDL at the 95% confidence level = 0.189838

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-3.74074	10.2789
rho	2.39323	0
control	50.1106	50
slope	61.6774	78.8136
power	1.36362	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	50	50.1	12	16.7	-0.021
0.1	10	55	52.8	22	17.7	0.396
0.5	10	70	74.1	30	26.6	-0.485
5	10	617	604	339	328	0.128

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-223.471076	5	456.942152
A2	-165.924256	8	347.848511
A3	-167.114116	6	346.228232
fitted	-167.62034	5	345.24068
R	-246.955243	2	497.910486

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	162.062	6	<0.0001
Test 2	115.094	3	<0.0001
Test 3	2.37972	2	0.3043
Test 4	1.01245	1	0.3143

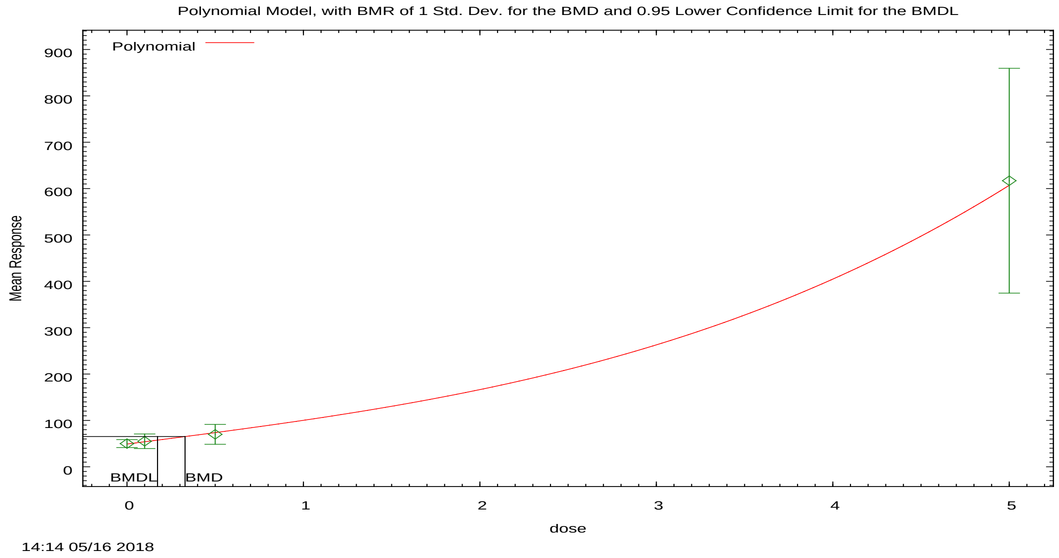

Figure 124. Plot of mean response by dose with fitted curve for Polynomial 3° model with modeled variance for Alkaline Phosphatase in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 0.329181

BMDL at the 95% confidence level = 0.172959

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-3.78821	10.2789
rho	2.40012	0
beta_0	49.095	50
beta_1	48.6274	52.9215
beta_2	0	0

beta_3	2.51926	8.43084

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	50	49.1	12	16.1	0.178
0.1	10	55	54	22	18	0.182
0.5	10	70	73.7	30	26.2	-0.449
5	10	617	607	339	329	0.0947

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-223.471076	5	456.942152
A2	-165.924256	8	347.848511
A3	-167.114116	6	346.228232
fitted	-167.340021	5	344.680042
R	-246.955243	2	497.910486

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	162.062	6	<0.0001
Test 2	115.094	3	<0.0001
Test 3	2.37972	2	0.3043
Test 4	0.45181	1	0.5015

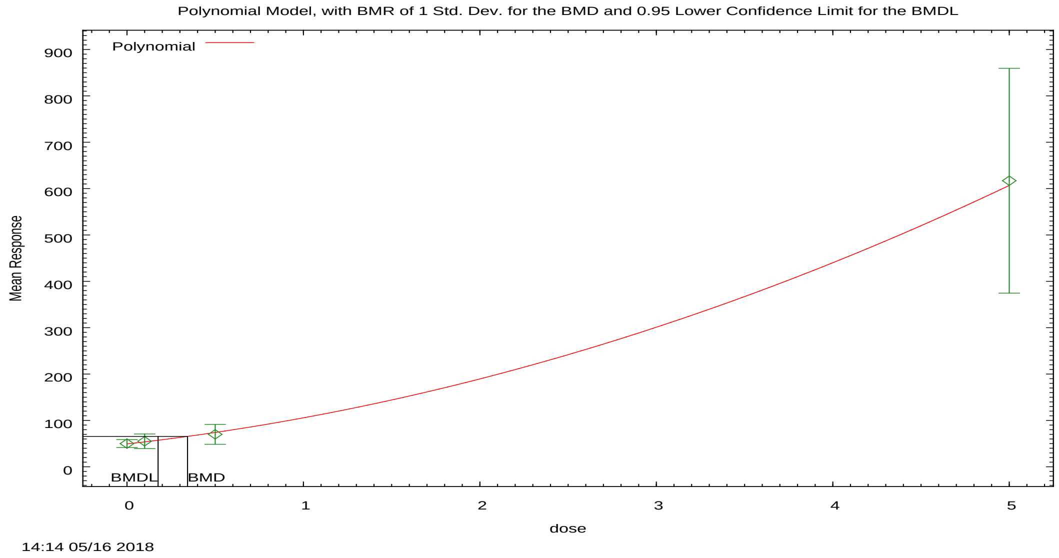

Figure 125. Plot of mean response by dose with fitted curve for Polynomial 2° model with modeled variance for Alkaline Phosphatase in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 0.343149

BMDL at the 95% confidence level = 0.176227

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-3.78664	10.2789
rho	2.40053	0
beta_0	49.2818	50.7795
beta_1	42.4794	30.6108
beta_2	13.7541	16.5266

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	50	49.3	12	16.2	0.14
0.1	10	55	53.7	22	17.9	0.235
0.5	10	70	74	30	26.4	-0.475
5	10	617	606	339	329	0.11

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-223.471076	5	456.942152
A2	-165.924256	8	347.848511
A3	-167.114116	6	346.228232
fitted	-167.396602	5	344.793204
R	-246.955243	2	497.910486

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	162.062	6	<0.0001
Test 2	115.094	3	<0.0001
Test 3	2.37972	2	0.3043
Test 4	0.564972	1	0.4523

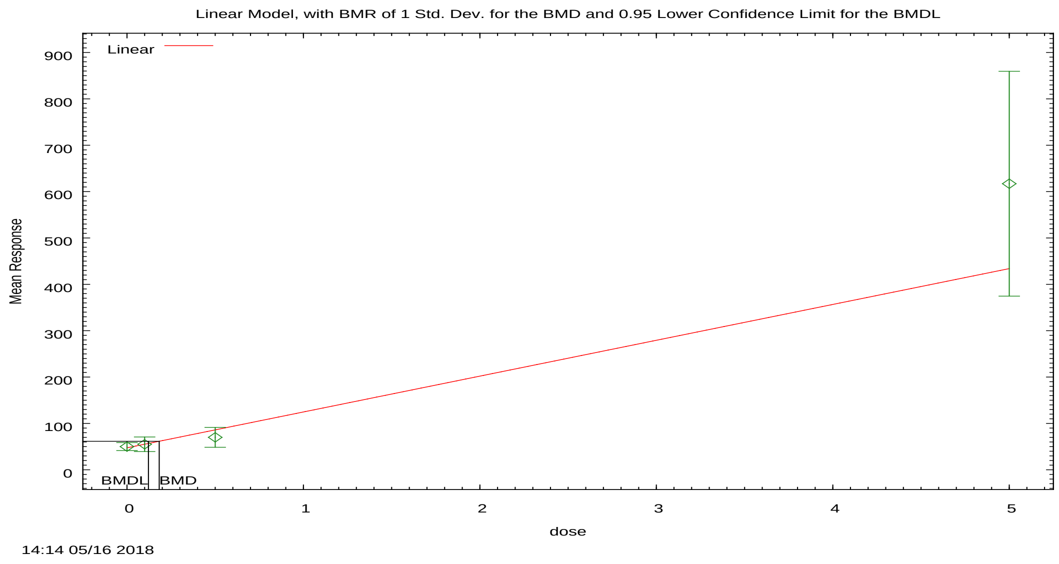

Figure 126. Plot of mean response by dose with fitted curve for Linear model with modeled variance for Alkaline Phosphatase in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 0.182565

BMDL at the 95% confidence level = 0.121506

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-6.09677	10.2789
rho	2.95261	0
beta_0	47.3627	35.9231
beta_1	77.2924	115.769

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	50	47.4	12	14.1	0.591
0.1	10	55	55.1	22	17.6	-0.0165
0.5	10	70	86	30	34	-1.49
5	10	617	434	339	371	1.56

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-223.471076	5	456.942152
A2	-165.924256	8	347.848511
A3	-167.114116	6	346.228232
fitted	-169.614675	4	347.22935
R	-246.955243	2	497.910486

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	162.062	6	<0.0001
Test 2	115.094	3	<0.0001
Test 3	2.37972	2	0.3043
Test 4	5.00112	2	0.08204

BMDS WIZARD OUTPUT REPORT

BMDS Summary of H-28548: Subchronic Toxicity 90-Day Gavage Study in Mice – Alkaline Phosphatase (U/L) in Females

1.15. BMDS Summary of Alkaline Phosphatase (U/L) Females (90 Day Mice GenX)

Table 15. Summary of BMD Modeling Results for Alkaline Phosphatase in Females (90-Day Mice); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD$_{1SD}$ (mg/kg/day)	BMDL$_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2)	0.279	285.79	1.55	1.23	1.27	BMDLs from models that met model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values > 2.0; appropriate variance (continuous data only)) were compared. BMDLs from included models were sufficiently close (< 3-fold difference), so the BMDL from the model with the lowest AIC was selected.
Exponential (M3)	0.123	287.61	4.29	1.24	3.48	
Exponential (M4)	0.0877	288.15	1.13	0.833	1.36	
Exponential (M5)	N/A[b]	289.61	4.12	0.538	7.67	
Hill	N/A[b]	289.61	4.09	error[c]	error	
Power	**0.305**	**285.61**	**4.62**	**0.859**	**5.37**	
Polynomial 3°	0.126	287.58	2.69	0.861	3.13	
Polynomial 2°	0.123	287.62	2.22	0.859	2.59	
Linear	0.233	286.15	1.13	0.833	1.36	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = 0.0751), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 0.5, and 5 mg/kg/day were -0.97, 0.88, 0.1, 0, respectively.

[b] No available degrees of freedom to calculate a goodness of fit value.

[c] BMD or BMDL computation failed for this model.

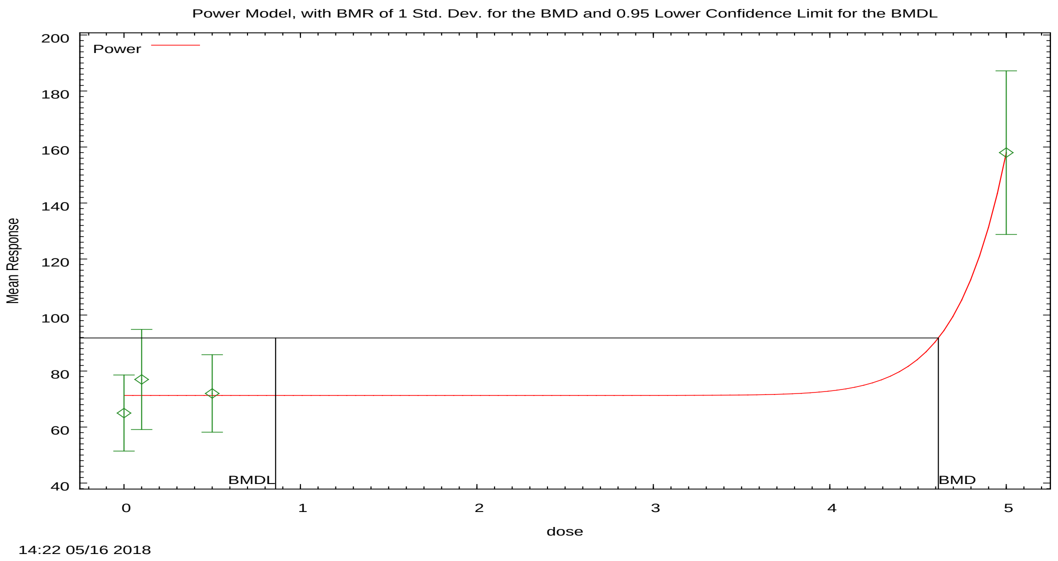

Figure 127. Plot of mean response by dose with fitted curve for Power model with modeled variance for Alkaline Phosphatase in Females (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 4.61514

BMDL at the 95% confidence level = 0.85933

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	0.0547528	6.51767
rho	1.40296	0
control	71.3103	65
slope	2.27252E-11	25.7584
power	18	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	65	71.3	19	20.5	-0.973
0.1	10	77	71.3	25	20.5	0.877
0.5	9	72	71.3	18	20.5	0.101
5	9	158	158	38	35.8	-0.0000000501

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-140.722467	5	291.444934
A2	-137.271117	8	290.542234
A3	-137.618003	6	287.236006
fitted	-138.80647	4	285.61294

R	-163.256735	2	330.513469

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	51.9712	6	<0.0001
Test 2	6.9027	3	0.07506
Test 3	0.693772	2	0.7069
Test 4	2.37693	2	0.3047

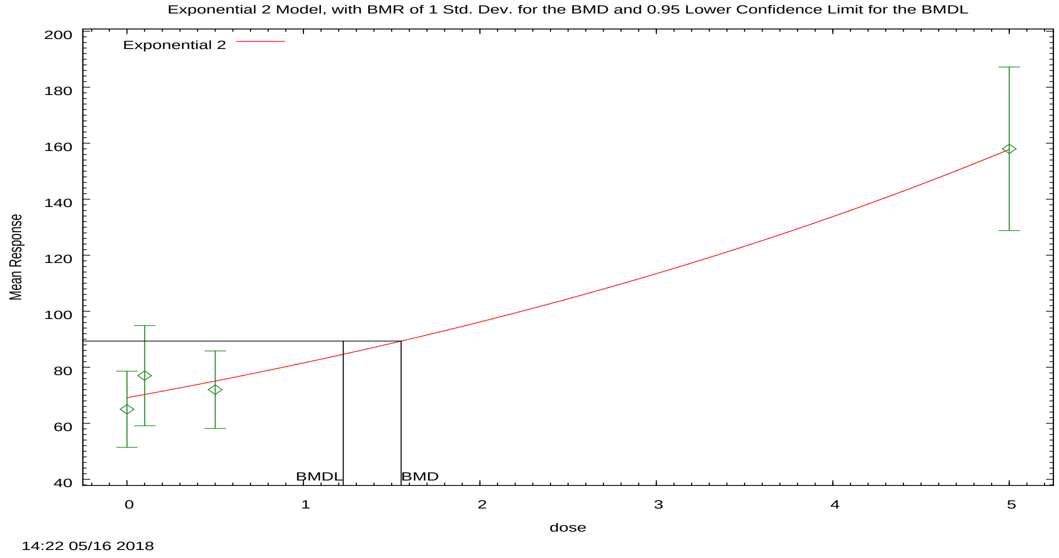

Figure 128. Plot of mean response by dose with fitted curve for Exponential (M2) model with modeled variance for Alkaline Phosphatase in Females (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 1.55374

BMDL at the 95% confidence level = 1.22565

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	0.261796	-0.767201
rho	1.35758	1.59325
a	69.1285	68.977
b	0.16507	0.165384
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	65	69.13	19	20.21	-0.646
0.1	10	77	70.28	25	20.44	1.04
0.5	9	72	75.08	18	21.38	-0.4317
5	9	158	157.8	38	35.39	0.0171

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-140.7225	5	291.4449
A2	-137.2711	8	290.5422
A3	-137.618	6	287.236
R	-163.2567	2	330.5135
2	-138.895	4	285.79

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	51.97	6	<0.0001
Test 2	6.903	3	0.07506
Test 3	0.6938	2	0.7069
Test 4	2.554	2	0.2789

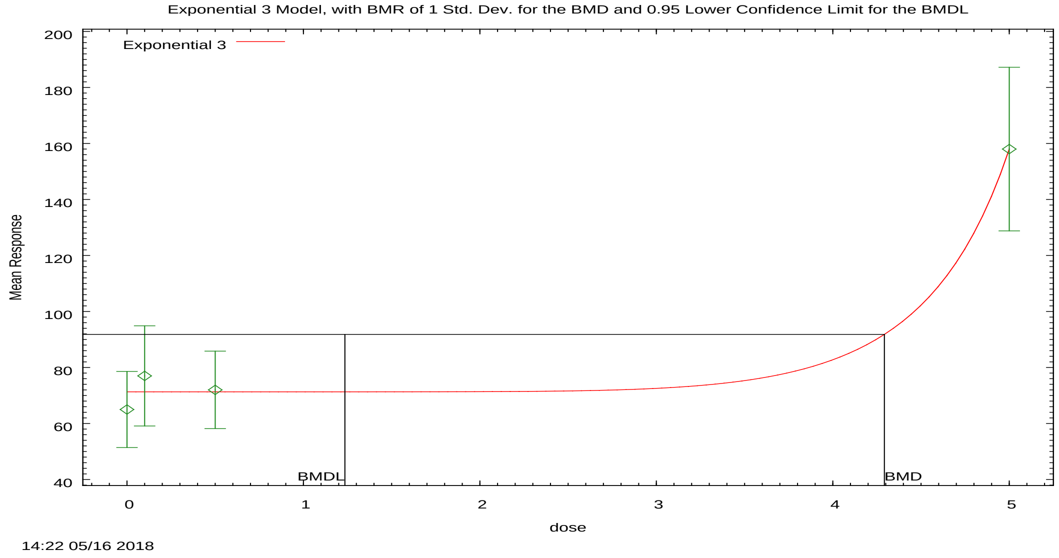

Figure 129. Plot of mean response by dose with fitted curve for Exponential (M3) model with modeled variance for Alkaline Phosphatase in Females (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 4.29214

BMDL at the 95% confidence level = 1.23501

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	0.0547497	-0.767201
rho	1.40296	1.59325
a	71.3103	68.977

b	0.194002	0.165384
c	n/a	0
d	7.51202	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	65	71.31	19	20.5	-0.9732
0.1	10	77	71.31	25	20.5	0.8775
0.5	9	72	71.31	18	20.5	0.1009
5	9	158	158	38	35.83	0.00000007256

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-140.7225	5	291.4449
A2	-137.2711	8	290.5422
A3	-137.618	6	287.236
R	-163.2567	2	330.5135
3	-138.8065	5	287.6129

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	51.97	6	<0.0001
Test 2	6.903	3	0.07506
Test 3	0.6938	2	0.7069
Test 5a	2.377	1	0.1231

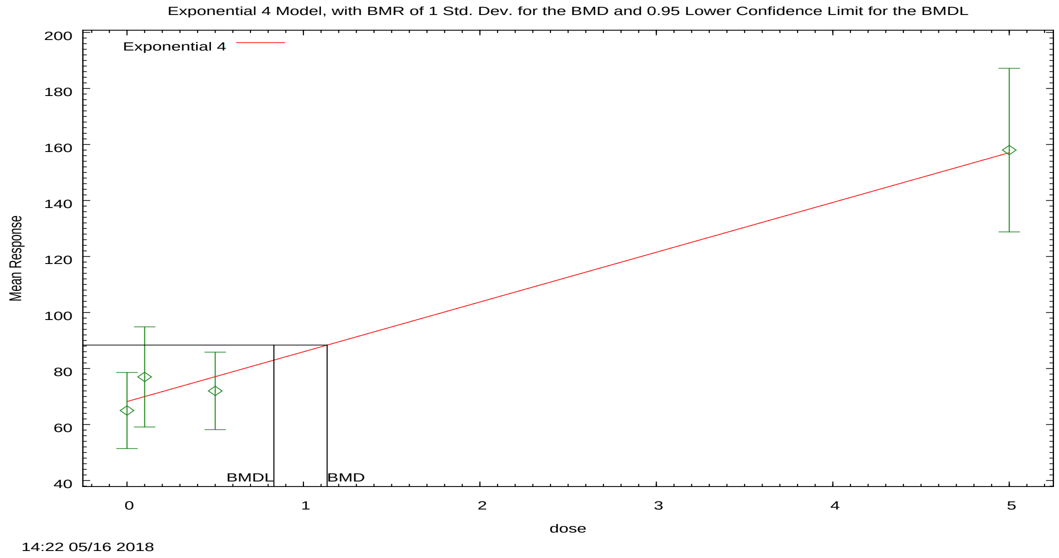

Figure 130. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Alkaline Phosphatase in Females (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 1.13417

BMDL at the 95% confidence level = 0.832528

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	0.359445	-0.767201
rho	1.33766	1.59325
a	68.1982	61.75
b	0.0000374361	0.0952247

c	6964.05	5.11741
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	65	68.2	19	20.16	-0.5016
0.1	10	77	69.98	25	20.51	1.083
0.5	9	72	77.09	18	21.88	-0.6973
5	9	158	157.1	38	35.23	0.0787

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-140.7225	5	291.4449
A2	-137.2711	8	290.5422
A3	-137.618	6	287.236
R	-163.2567	2	330.5135
4	-139.0761	5	288.1521

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	51.97	6	<0.0001
Test 2	6.903	3	0.07506
Test 3	0.6938	2	0.7069
Test 6a	2.916	1	0.0877

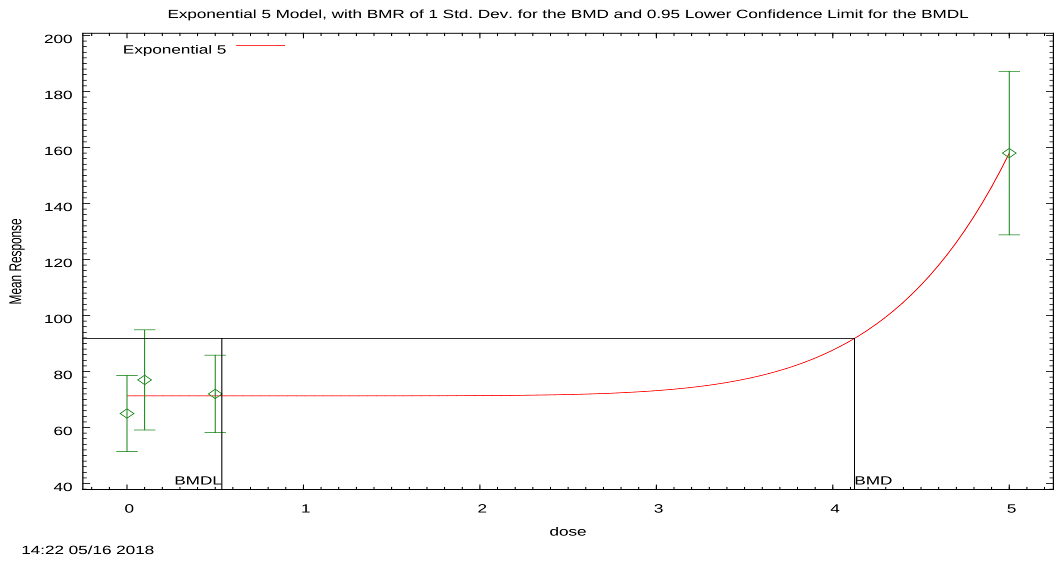

Figure 131. Plot of mean response by dose with fitted curve for Exponential (M5) model with modeled variance for Alkaline Phosphatase in Females (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 4.12265

BMDL at the 95% confidence level = 0.537501

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	0.0547522	-0.767201
rho	1.40296	1.59325
a	71.3103	61.75
b	0.136575	0.0952247

c	23.5345	5.11741
d	7.58207	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	65	71.31	19	20.5	-0.9732
0.1	10	77	71.31	25	20.5	0.8775
0.5	9	72	71.31	18	20.5	0.1009
5	9	158	158	38	35.83	0.00000005944

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-140.7225	5	291.4449
A2	-137.2711	8	290.5422
A3	-137.618	6	287.236
R	-163.2567	2	330.5135
5	-138.8065	6	289.6129

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	51.97	6	<0.0001
Test 2	6.903	3	0.07506
Test 3	0.6938	2	0.7069
Test 7a	2.377	0	N/A

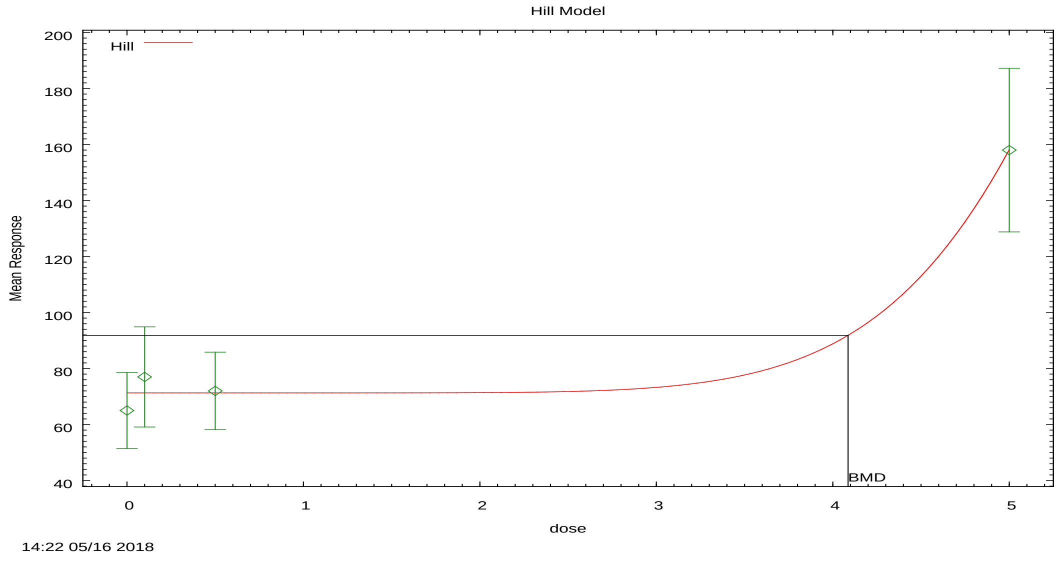

Figure 132. Plot of mean response by dose with fitted curve for Hill model with modeled variance for Alkaline Phosphatase in Females (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 4.08647

BMDL at the 95% confidence level = error

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	0.0547498	6.51767
rho	1.40296	0
intercept	71.3104	65
v	677.844	93
n	7.67176	0.686281

k	6.42163	7.43314

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	65	71.3	19	20.5	-0.973
0.1	10	77	71.3	25	20.5	0.877
0.5	9	72	71.3	18	20.5	0.101
5	9	158	158	38	35.8	-0.00000112

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-140.722467	5	291.444934
A2	-137.271117	8	290.542234
A3	-137.618003	6	287.236006
fitted	-138.80647	6	289.61294
R	-163.256735	2	330.513469

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	51.9712	6	<0.0001
Test 2	6.9027	3	0.07506
Test 3	0.693772	2	0.7069
Test 4	2.37693	0	N/A

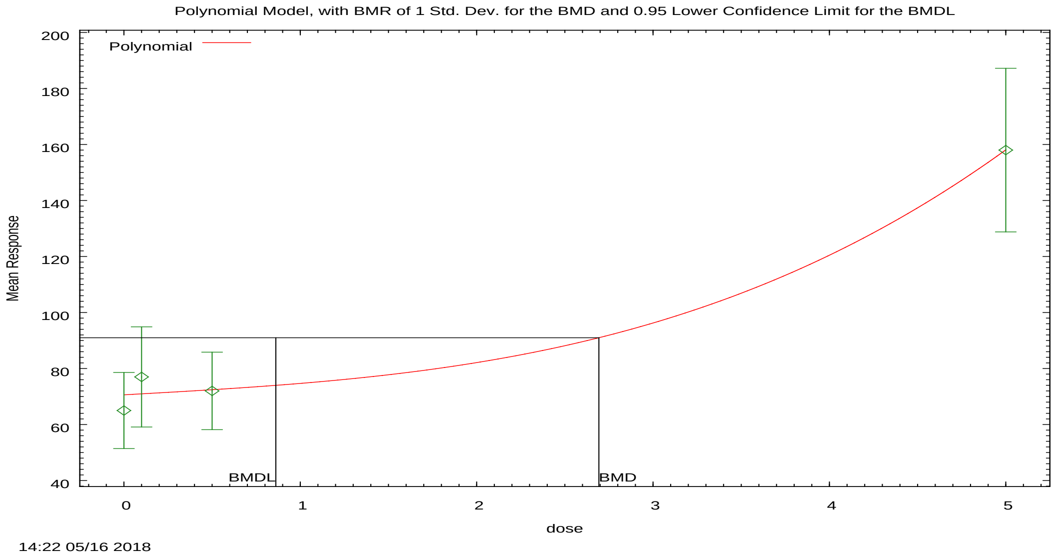

Figure 133. Plot of mean response by dose with fitted curve for Polynomial 3° model with modeled variance for Alkaline Phosphatase in Females (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 2.69286

BMDL at the 95% confidence level = 0.861199

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	0.10566	6.51767
rho	1.39137	0
beta_0	70.6107	65
beta_1	3.51553	0
beta_2	1.95415E-22	0

beta_3	0.55879	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	65	70.6	19	20.4	-0.871
0.1	10	77	71	25	20.4	0.934
0.5	9	72	72.4	18	20.7	-0.0634
5	9	158	158	38	35.7	-0.00311

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-140.722467	5	291.444934
A2	-137.271117	8	290.542234
A3	-137.618003	6	287.236006
fitted	-138.789061	5	287.578122
R	-163.256735	2	330.513469

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	51.9712	6	<0.0001
Test 2	6.9027	3	0.07506
Test 3	0.693772	2	0.7069
Test 4	2.34212	1	0.1259

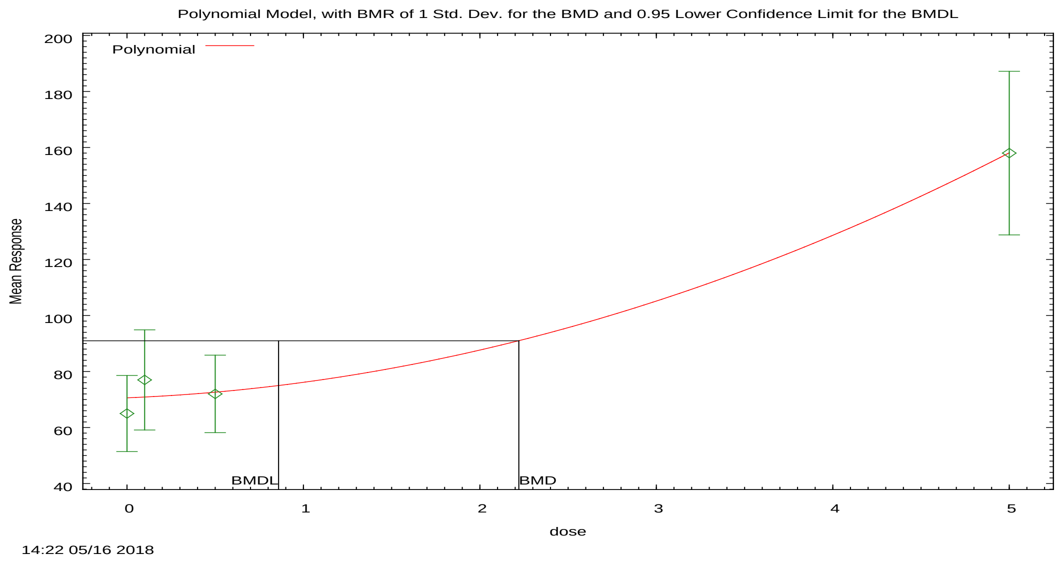

Figure 134. Plot of mean response by dose with fitted curve for Polynomial 2° model with modeled variance for Alkaline Phosphatase in Females (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 2.22069

BMDL at the 95% confidence level = 0.859021

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	0.124773	6.51767
rho	1.38731	0
beta_0	70.5826	70.0193
beta_1	2.54926	0
beta_2	2.98701	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	65	70.6	19	20.4	-0.866
0.1	10	77	70.9	25	20.4	0.948
0.5	9	72	72.6	18	20.8	-0.0871
5	9	158	158	38	35.7	-0.000349

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-140.722467	5	291.444934
A2	-137.271117	8	290.542234
A3	-137.618003	6	287.236006
fitted	-138.809366	5	287.618731
R	-163.256735	2	330.513469

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	51.9712	6	<0.0001
Test 2	6.9027	3	0.07506
Test 3	0.693772	2	0.7069
Test 4	2.38273	1	0.1227

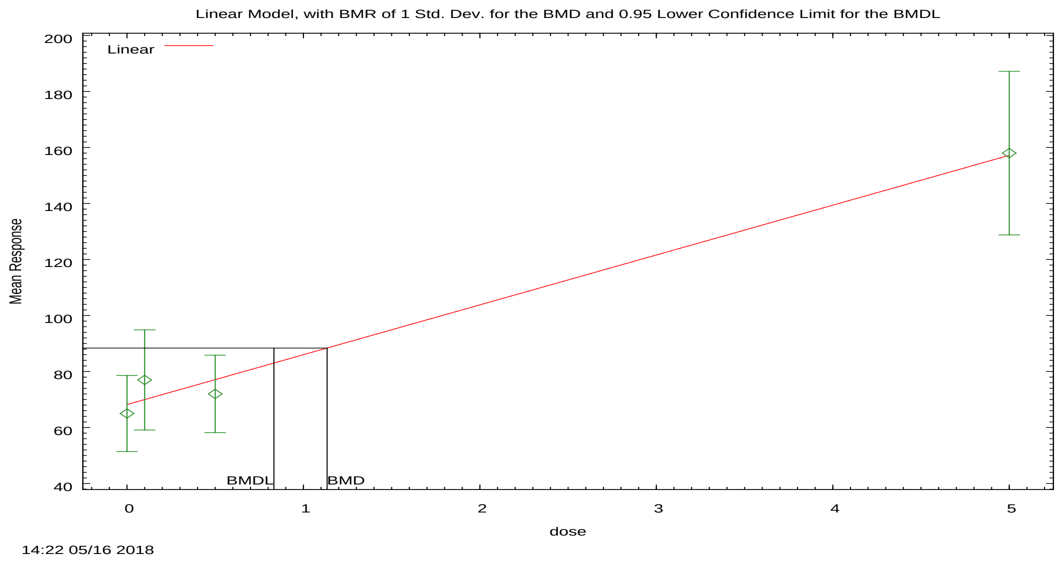

Figure 135. Plot of mean response by dose with fitted curve for Linear model with modeled variance for Alkaline Phosphatase in Females (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 1.13426

BMDL at the 95% confidence level = 0.8326

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	0.359446	6.51767
rho	1.33766	0
beta_0	68.1984	67.853
beta_1	17.7756	17.9621

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	65	68.2	19	20.2	-0.502
0.1	10	77	70	25	20.5	1.08
0.5	9	72	77.1	18	21.9	-0.697
5	9	158	157	38	35.2	0.0787

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-140.722467	5	291.444934
A2	-137.271117	8	290.542234
A3	-137.618003	6	287.236006
fitted	-139.076002	4	286.152004
R	-163.256735	2	330.513469

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	51.9712	6	<0.0001
Test 2	6.9027	3	0.07506
Test 3	0.693772	2	0.7069
Test 4	2.916	2	0.2327

BMDS WIZARD OUTPUT REPORT

BMDS Summary of 90-Day Oral (Gavage) Toxicity Study of H-28548 in Rats with a 28-Day Recovery – Alkaline Phosphatase (U/L) in Males

1.16. BMDS Summary of Alkaline Phosphatase (U/L) Males (90 Day Rats GenX)

Table 16. Summary of BMD Modeling Results for Alkaline Phosphatase in Males (90-Day Rats); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD$_{1SD}$ (mg/kg/day)	BMDL$_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	***p*-value**	**AIC**				
Exponential (M2) Exponential (M3)[b]	<0.0001	314.53	37.5	27.8	1.35	Only one model met model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). Selected BMDL is from this model.
Exponential (M4)	**0.952**	**295.55**	**2.66**	**1.43**	**1.86**	
Exponential (M5)	N/A[c]	297.54	3.37	1.43	2.35	
Hill	N/A[c]	297.54	3.00	error[d]	error	
Power[e] Polynomial 3°[f] Polynomial 2°[g] Linear	<0.0001	312.47	26.6	17.0	1.56	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = 7.40E-04), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 10, and 100 mg/kg/day were 0.22, -0.14, -0.25, 0.18, respectively.

[b] For the Exponential (M3) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M2) model.

[c] No available degrees of freedom to calculate a goodness of fit value.

[d] BMD or BMDL computation failed for this model.

[e] For the Power model, the power parameter estimate was 1. The models in this row reduced to the Linear model.

[f] For the Polynomial 3° model, the b3 coefficient estimates was 0 (boundary of parameters space). The models in this row reduced to the Polynomial 2° model. For the Polynomial 3° model, the b3 and b2 coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Linear model.

[g] For the Polynomial 2° model, the b2 coefficient estimate was 0 (boundary of parameters space). The models in this row reduced to the Linear model.

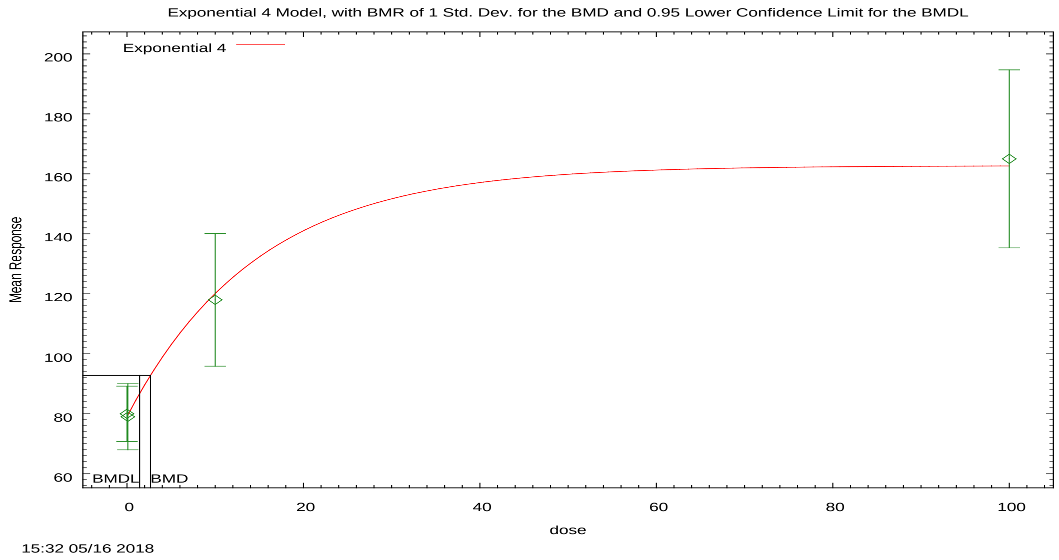

Figure 136. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Alkaline Phosphatase in Males (90-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 2.65934

BMDL at the 95% confidence level = 1.43235

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-8.41546	-8.09011
rho	3.12538	3.07366
a	79.043	75.05
b	0.0675108	0.0250925
c	2.05869	2.30846
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	80	79.04	12.9	13.75	0.2201
0.1	10	79	79.61	15.4	13.91	-0.1378
10	10	118	120.1	30.9	26.45	-0.2538
100	10	165	162.6	41.5	42.46	0.1767

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC

A1	-150.8247	5	311.6494
A2	-142.3732	8	300.7465
A3	-142.7721	6	297.5442
R	-171.3096	2	346.6191
4	-142.7739	5	295.5478

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	57.87	6	<0.0001
Test 2	16.9	3	0.00074
Test 3	0.7977	2	0.6711
Test 6a	0.003674	1	0.9517

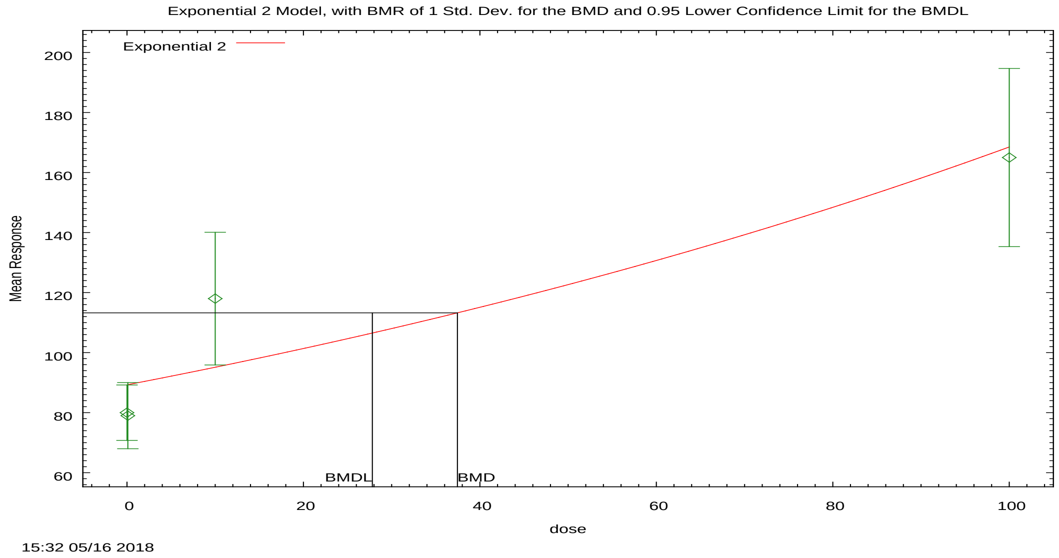

Figure 137. Plot of mean response by dose with fitted curve for Exponential (M2) model with modeled variance for Alkaline Phosphatase in Males (90-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 37.4536

BMDL at the 95% confidence level = 27.8113

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-1.56933	-8.09011
rho	1.76412	3.07366
a	89.2804	88.0519
b	0.00635285	0.00650678
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	80	89.28	12.9	23.98	-1.224
0.1	10	79	89.34	15.4	24	-1.362
10	10	118	95.14	30.9	25.37	2.85
100	10	165	168.5	41.5	42	-0.2652

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-150.8247	5	311.6494
A2	-142.3732	8	300.7465
A3	-142.7721	6	297.5442
R	-171.3096	2	346.6191
2	-153.264	4	314.528

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value

Test 1	57.87	6	<0.0001
Test 2	16.9	3	0.00074
Test 3	0.7977	2	0.6711
Test 4	20.98	2	<0.0001

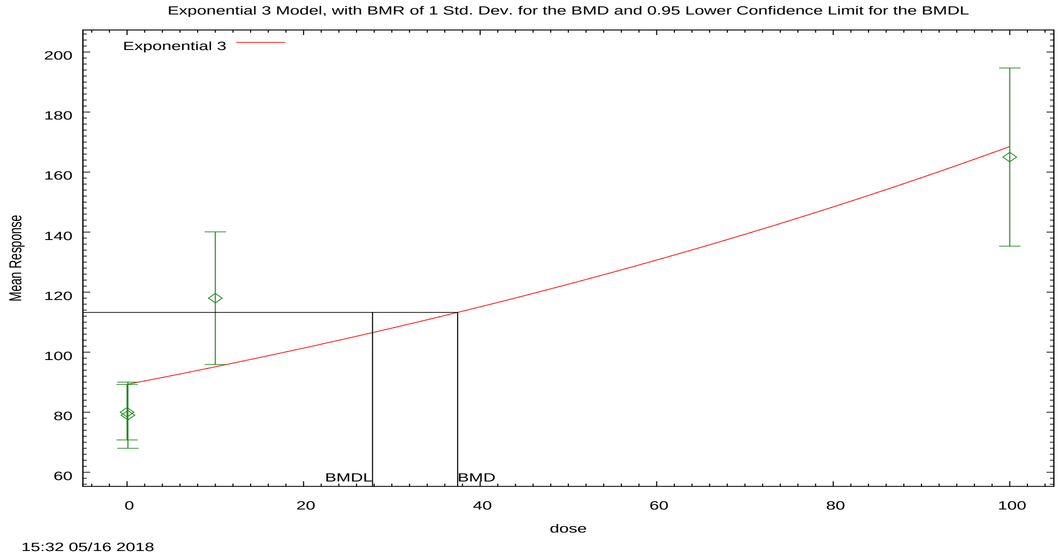

Figure 138. Plot of mean response by dose with fitted curve for Exponential (M3) model with modeled variance for Alkaline Phosphatase in Males (90-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 37.4536

BMDL at the 95% confidence level = 27.8113

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values

lnalpha	-1.56932	-8.09011
rho	1.76412	3.07366
a	89.2804	88.0519
b	0.00635285	0.00650678
c	n/a	0
d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	80	89.28	12.9	23.98	-1.224
0.1	10	79	89.34	15.4	24	-1.362
10	10	118	95.14	30.9	25.37	2.85
100	10	165	168.5	41.5	42	-0.2652

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-150.8247	5	311.6494
A2	-142.3732	8	300.7465
A3	-142.7721	6	297.5442
R	-171.3096	2	346.6191
3	-153.264	4	314.528

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	57.87	6	<0.0001
Test 2	16.9	3	0.00074
Test 3	0.7977	2	0.6711
Test 5a	20.98	2	<0.0001

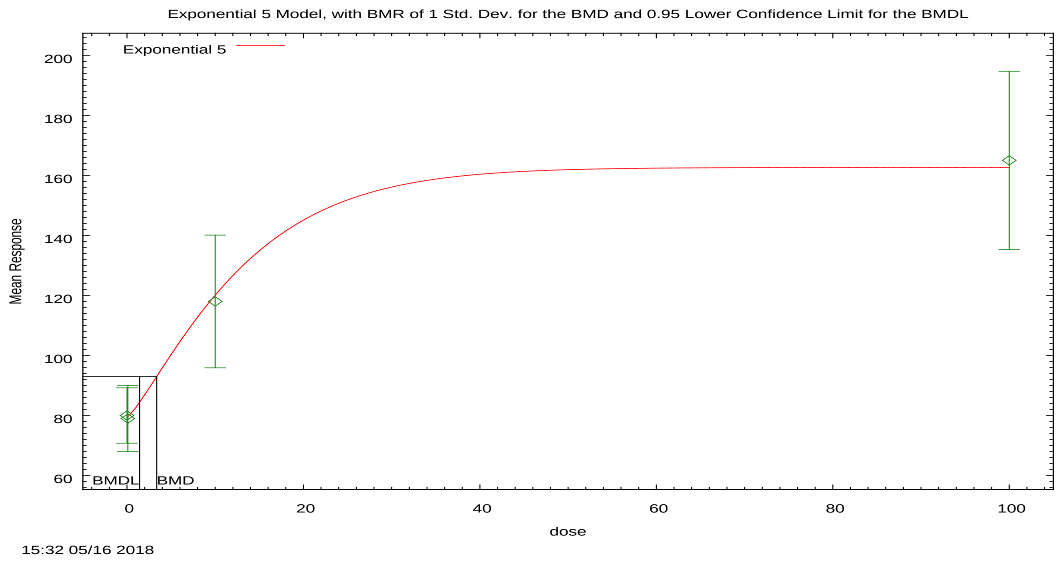

Figure 139. Plot of mean response by dose with fitted curve for Exponential (M5) model with modeled variance for Alkaline Phosphatase in Males (90-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 3.36987

BMDL at the 95% confidence level = 1.43304

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-8.40364	-8.09011
rho	3.12282	3.07366
a	79.2095	75.05
b	0.0722146	0.0250925
c	2.05331	2.30846

d	1.2101	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	80	79.21	12.9	13.8	0.1811
0.1	10	79	79.42	15.4	13.86	-0.09651
10	10	118	120.1	30.9	26.45	-0.2554
100	10	165	162.6	41.5	42.44	0.1758

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-150.8247	5	311.6494
A2	-142.3732	8	300.7465
A3	-142.7721	6	297.5442
R	-171.3096	2	346.6191
5	-142.7721	6	297.5442

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	57.87	6	<0.0001
Test 2	16.9	3	0.00074
Test 3	0.7977	2	0.6711
Test 7a	-0.000000000005002	0	N/A

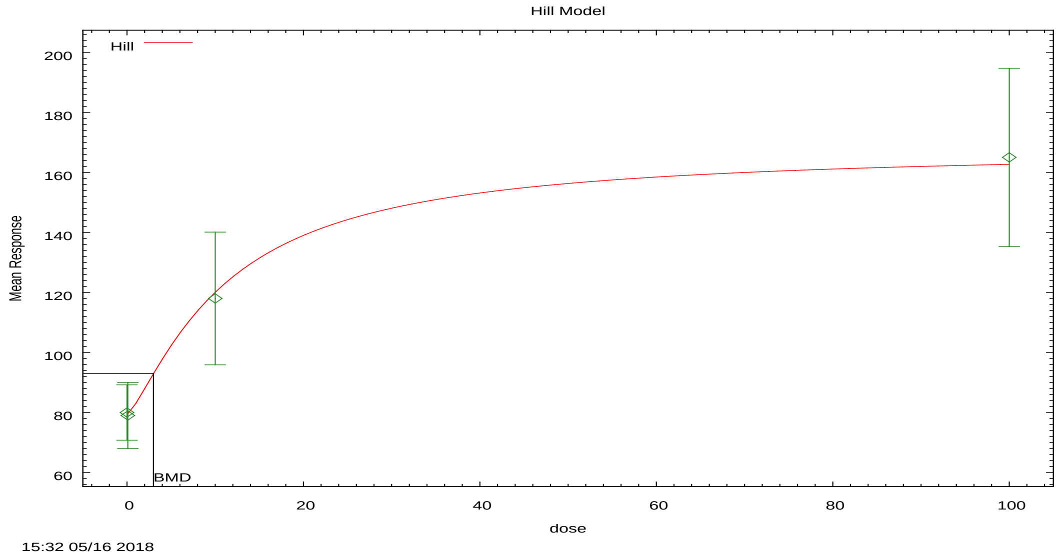

Figure 140. Plot of mean response by dose with fitted curve for Hill model with modeled variance for Alkaline Phosphatase in Males (90-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 2.99517

BMDL at the 95% confidence level = error

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-8.40365	6.6466
rho	3.12283	0
intercept	79.2094	80
v	88.5842	85
n	1.27533	0.073347

k	11.268	181.383

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	80	79.2	12.9	13.8	0.181
0.1	10	79	79.4	15.4	13.9	-0.0965
10	10	118	120	30.9	26.4	-0.255
100	10	165	163	41.5	42.4	0.176

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-150.82469	5	311.649381
A2	-142.373234	8	300.746468
A3	-142.772075	6	297.544151
fitted	-142.772075	6	297.544151
R	-171.309565	2	346.61913

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	57.8727	6	<0.0001
Test 2	16.9029	3	0.00074
Test 3	0.797683	2	0.6711
Test 4	2.58638E-11	0	N/A

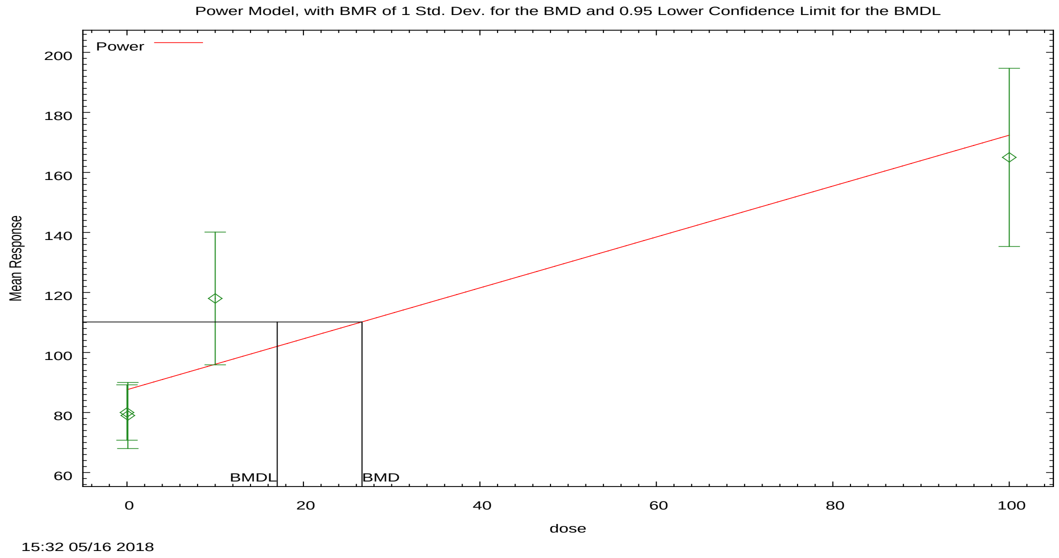

Figure 141. Plot of mean response by dose with fitted curve for Power model with modeled variance for Alkaline Phosphatase in Males (90-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 26.6376

BMDL at the 95% confidence level = 17.0313

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-2.49476	6.6466
rho	1.95201	0
control	87.5703	79
slope	0.848249	17.686
power	1	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	80	87.6	12.9	22.6	-1.06
0.1	10	79	87.7	15.4	22.6	-1.21
10	10	118	96.1	30.9	24.7	2.81
100	10	165	172	41.5	43.8	-0.534

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-150.82469	5	311.649381
A2	-142.373234	8	300.746468
A3	-142.772075	6	297.544151
fitted	-152.232546	4	312.465092
R	-171.309565	2	346.61913

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	57.8727	6	<0.0001
Test 2	16.9029	3	0.00074
Test 3	0.797683	2	0.6711
Test 4	18.9209	2	<0.0001

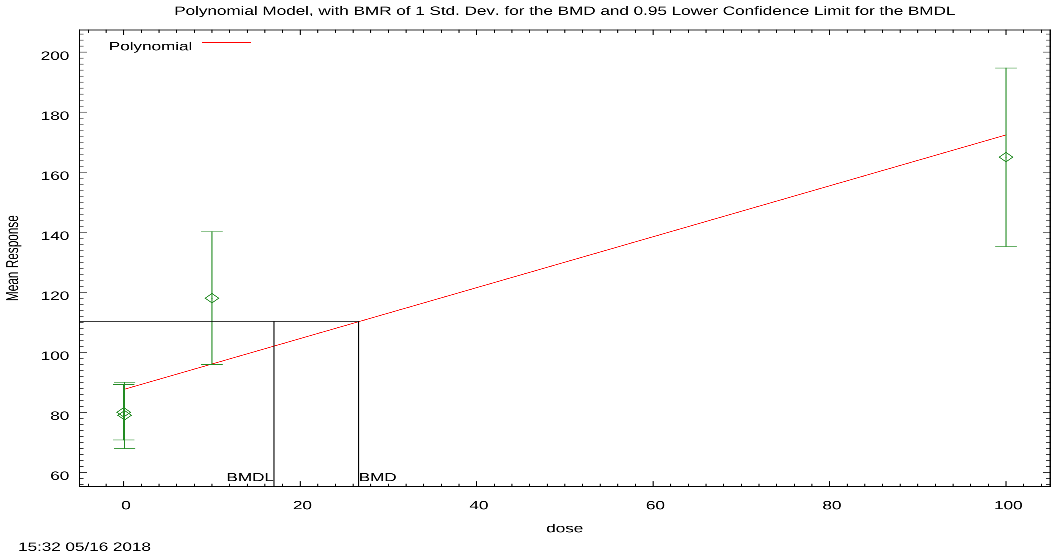

Figure 142. Plot of mean response by dose with fitted curve for Polynomial 3° model with modeled variance for Alkaline Phosphatase in Males (90-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 26.6376

BMDL at the 95% confidence level = 17.0313

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-2.49476	6.6466
rho	1.95201	0
beta_0	87.5703	80
beta_1	0.848249	0
beta_2	0	0

beta_3	0	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	80	87.6	12.9	22.6	-1.06
0.1	10	79	87.7	15.4	22.6	-1.21
10	10	118	96.1	30.9	24.7	2.81
100	10	165	172	41.5	43.8	-0.534

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-150.82469	5	311.649381
A2	-142.373234	8	300.746468
A3	-142.772075	6	297.544151
fitted	-152.232546	4	312.465092
R	-171.309565	2	346.61913

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	57.8727	6	<0.0001
Test 2	16.9029	3	0.00074
Test 3	0.797683	2	0.6711
Test 4	18.9209	2	<0.0001

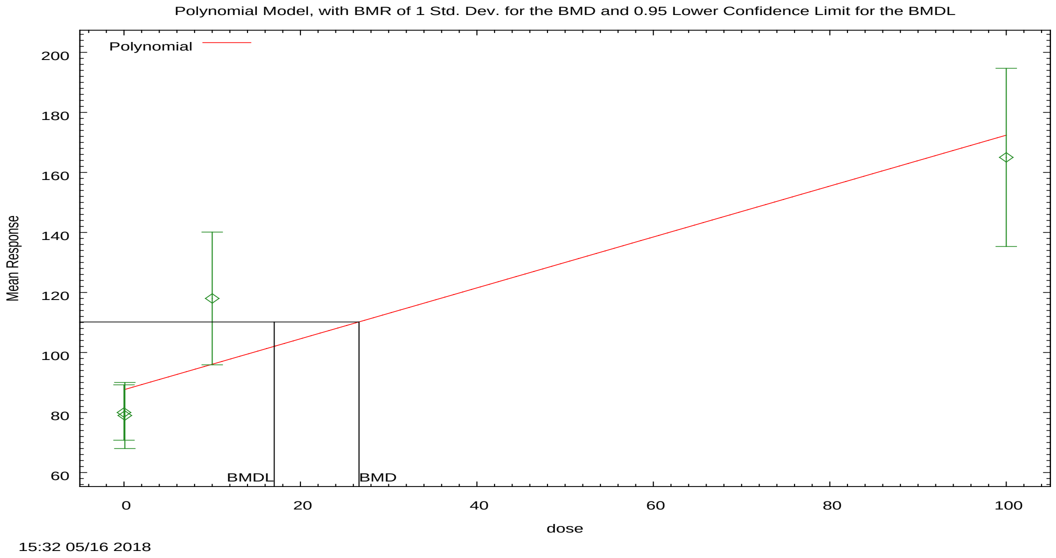

Figure 143. Plot of mean response by dose with fitted curve for Polynomial 2° model with modeled variance for Alkaline Phosphatase in Males (90-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 26.6376

BMDL at the 95% confidence level = 17.0313

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-2.49473	6.6466
rho	1.952	0
beta_0	87.5703	79.2939
beta_1	0.84825	0
beta_2	0	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	80	87.6	12.9	22.6	-1.06
0.1	10	79	87.7	15.4	22.6	-1.21
10	10	118	96.1	30.9	24.7	2.81
100	10	165	172	41.5	43.8	-0.534

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-150.82469	5	311.649381
A2	-142.373234	8	300.746468
A3	-142.772075	6	297.544151
fitted	-152.232546	4	312.465092
R	-171.309565	2	346.61913

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	57.8727	6	<0.0001
Test 2	16.9029	3	0.00074
Test 3	0.797683	2	0.6711
Test 4	18.9209	2	<0.0001

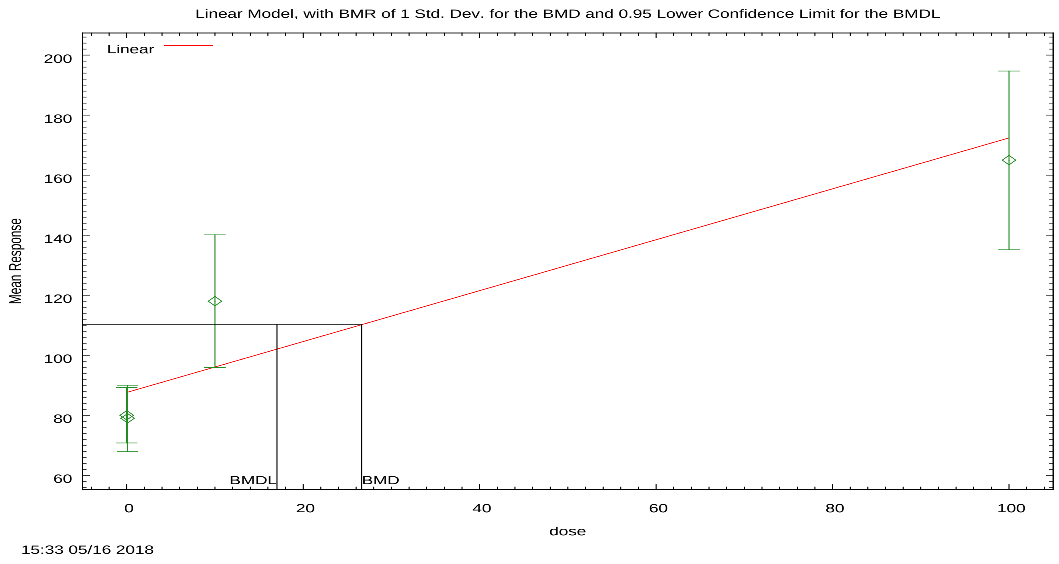

Figure 144. Plot of mean response by dose with fitted curve for Linear model with modeled variance for Alkaline Phosphatase in Males (90-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 26.6376

BMDL at the 95% confidence level = 17.0313

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-2.49476	6.6466
rho	1.95201	0
beta_0	87.5703	89.0008
beta_1	0.848249	0.78108

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	80	87.6	12.9	22.6	-1.06
0.1	10	79	87.7	15.4	22.6	-1.21
10	10	118	96.1	30.9	24.7	2.81
100	10	165	172	41.5	43.8	-0.534

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-150.82469	5	311.649381
A2	-142.373234	8	300.746468
A3	-142.772075	6	297.544151
fitted	-152.232546	4	312.465092
R	-171.309565	2	346.61913

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	57.8727	6	<0.0001
Test 2	16.9029	3	0.00074
Test 3	0.797683	2	0.6711
Test 4	18.9209	2	<0.0001

BMDS WIZARD OUTPUT REPORT

H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats – Alkaline Phosphatase (U/L) in Males at 12-month timepoint

1.17. BMDS Summary of Alkaline Phosphatase (U/L) Males 12 months (2 Year Rats GenX)

Table 17. Summary of BMD Modeling Results for Alkaline Phosphatase in Males at 12 months (2-year rats); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD_{1SD} (mg/kg/day)	$BMDL_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2) Exponential (M3)[b]	0.00186	329.74	16.0	12.4	1.30	No models met all model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). No BMDL was selected.
Exponential (M4) Exponential (M5)[c]	0.0202	324.56	0.690	0.312	2.21	
Hill	0.0226	324.36	0.615	0.589	1.05	
Power[d] Polynomial 2°[e] Linear	0.00228	329.33	11.5	8.10	1.42	
Polynomial 3°	<0.0001	502.76	0.808	0.0319	25.3	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = <0.0001, BMDS Test 3 *p*-value = 0.759), no model was selected as a best-fitting model.

[b] For the Exponential (M3) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M2) model.

[c] For the Exponential (M5) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M4) model.

[d] For the Power model, the power parameter estimate was 1. The models in this row reduced to the Linear model.

[e] For the Polynomial 2° model, the b2 coefficient estimate was 0 (boundary of parameters space). The models in this row reduced to the Linear model.

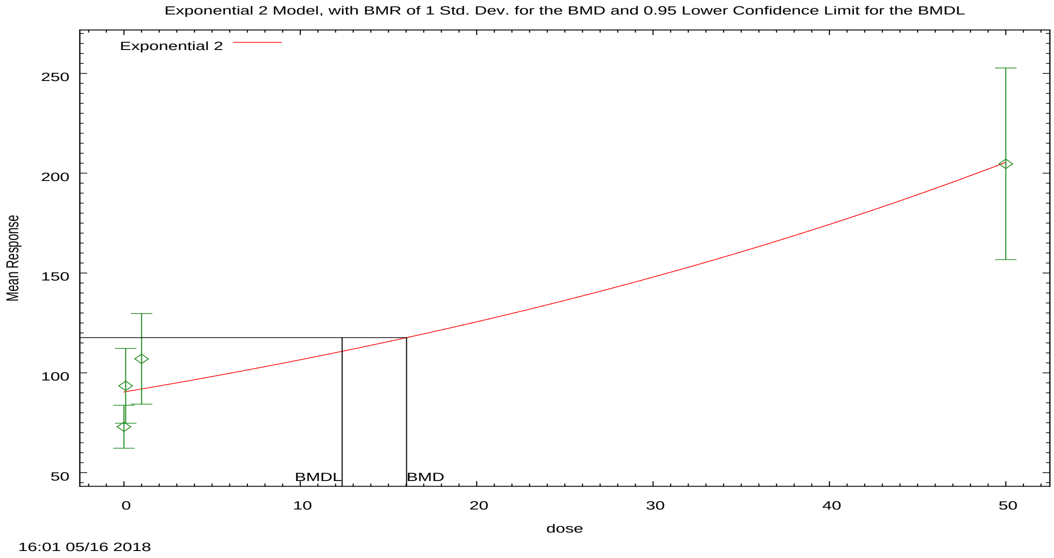

Figure 145. Plot of mean response by dose with fitted curve for Exponential (M2) model with modeled variance for Alkaline Phosphatase in Males at 12 months (2-year rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 16.0244

BMDL at the 95% confidence level = 12.3721

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-2.78302	-6.18686
rho	2.08447	2.76421
a	90.4273	89.4073
b	0.0164117	0.0166338
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	73	90.43	15.06	27.2	-2.026
0.1	10	93.5	90.58	26.22	27.25	0.3394
1	10	107	91.92	31.7	27.67	1.723
50	10	204.7	205.4	67.12	63.98	-0.03635

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-165.5237	5	341.0474

A2	-154.3064	8	324.6128
A3	-154.5829	6	321.1657
R	-185.9252	2	375.8503
2	-160.8715	4	329.7431

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	63.24	6	<0.0001
Test 2	22.43	3	<0.0001
Test 3	0.5529	2	0.7585
Test 4	12.58	2	0.001857

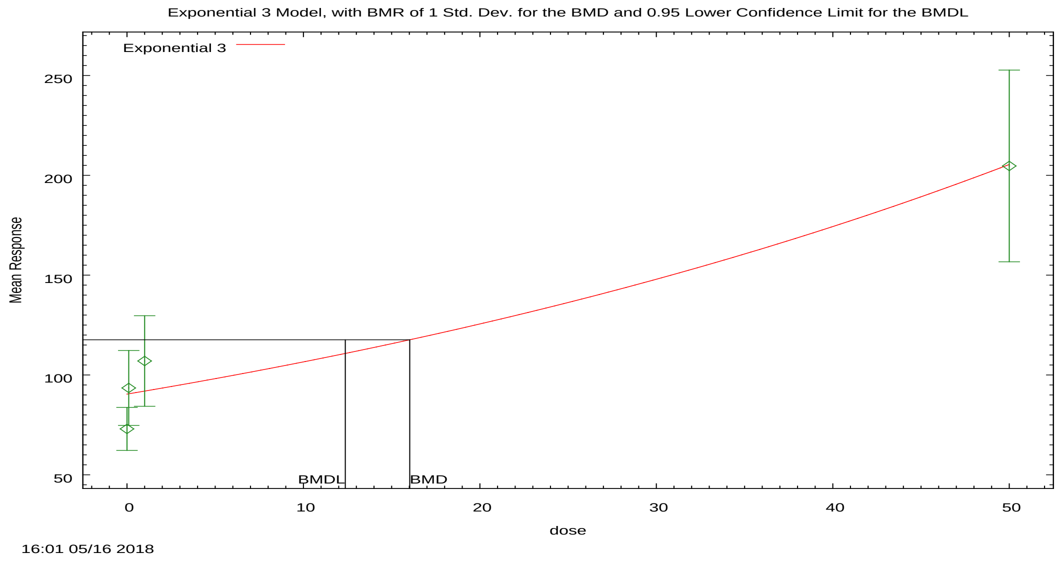

Figure 146. Plot of mean response by dose with fitted curve for Exponential (M3) model with modeled variance for Alkaline Phosphatase in Males at 12 months (2-year rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 16.0244

BMDL at the 95% confidence level = 12.3721

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-2.78302	-6.18686
rho	2.08446	2.76421
a	90.4273	89.4073
b	0.0164117	0.0166338
c	n/a	0
d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	73	90.43	15.06	27.2	-2.026
0.1	10	93.5	90.58	26.22	27.25	0.3394
1	10	107	91.92	31.7	27.67	1.723
50	10	204.7	205.4	67.12	63.98	-0.03635

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-165.5237	5	341.0474
A2	-154.3064	8	324.6128
A3	-154.5829	6	321.1657
R	-185.9252	2	375.8503
3	-160.8715	4	329.7431

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value

Test 1	63.24	6	<0.0001
Test 2	22.43	3	<0.0001
Test 3	0.5529	2	0.7585
Test 5a	12.58	2	0.001857

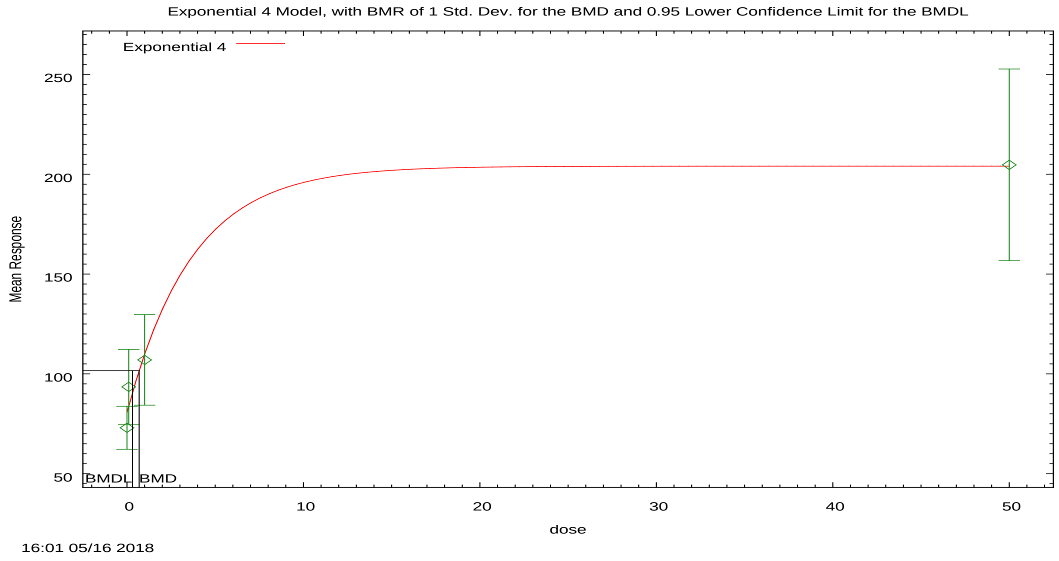

Figure 147. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Alkaline Phosphatase in Males at 12 months (2-year rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 0.689781

BMDL at the 95% confidence level = 0.311869

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-4.36848	-6.18686
rho	2.38557	2.76421
a	80.4861	69.35
b	0.271622	0.0532044
c	2.53522	3.09928
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	73	80.49	15.06	21.11	-1.121
0.1	10	93.5	83.8	26.22	22.15	1.385
1	10	107	109.9	31.7	30.6	-0.2972
50	10	204.7	204	67.12	64.04	0.03213

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-165.5237	5	341.0474
A2	-154.3064	8	324.6128
A3	-154.5829	6	321.1657
R	-185.9252	2	375.8503
4	-157.2824	5	324.5648

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	63.24	6	<0.0001
Test 2	22.43	3	<0.0001
Test 3	0.5529	2	0.7585
Test 6a	5.399	1	0.02015

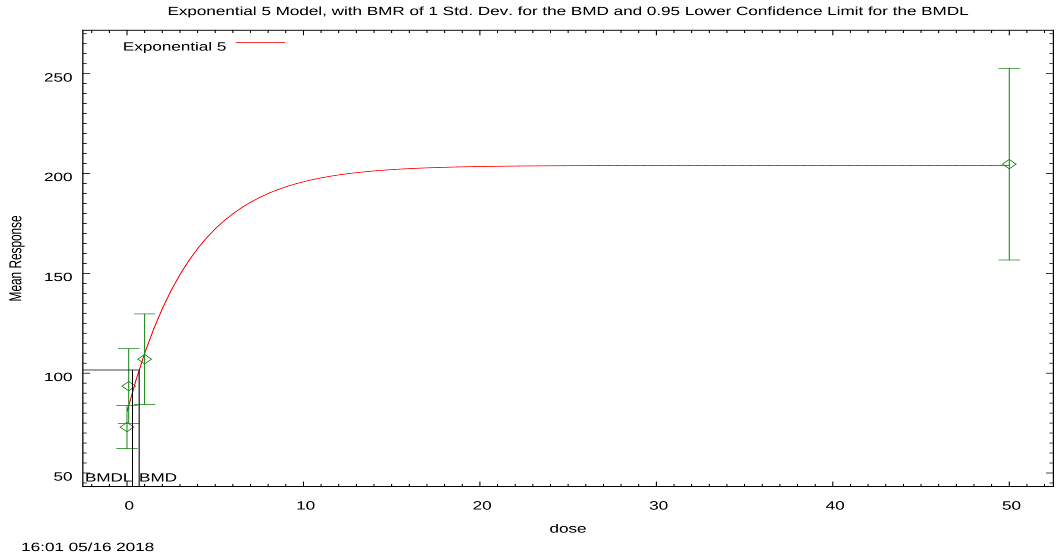

Figure 148. Plot of mean response by dose with fitted curve for Exponential (M5) model with modeled variance for Alkaline Phosphatase in Males at 12 months (2-year rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 0.689781

BMDL at the 95% confidence level = 0.311869

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-4.36848	-6.18686
rho	2.38557	2.76421
a	80.4861	69.35
b	0.271622	0.0532044

c	2.53522	3.09928
d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	73	80.49	15.06	21.11	-1.121
0.1	10	93.5	83.8	26.22	22.15	1.385
1	10	107	109.9	31.7	30.6	-0.2972
50	10	204.7	204	67.12	64.04	0.03213

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-165.5237	5	341.0474
A2	-154.3064	8	324.6128
A3	-154.5829	6	321.1657
R	-185.9252	2	375.8503
5	-157.2824	5	324.5648

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	63.24	6	<0.0001
Test 2	22.43	3	<0.0001
Test 3	0.5529	2	0.7585
Test 7a	5.399	1	0.02015

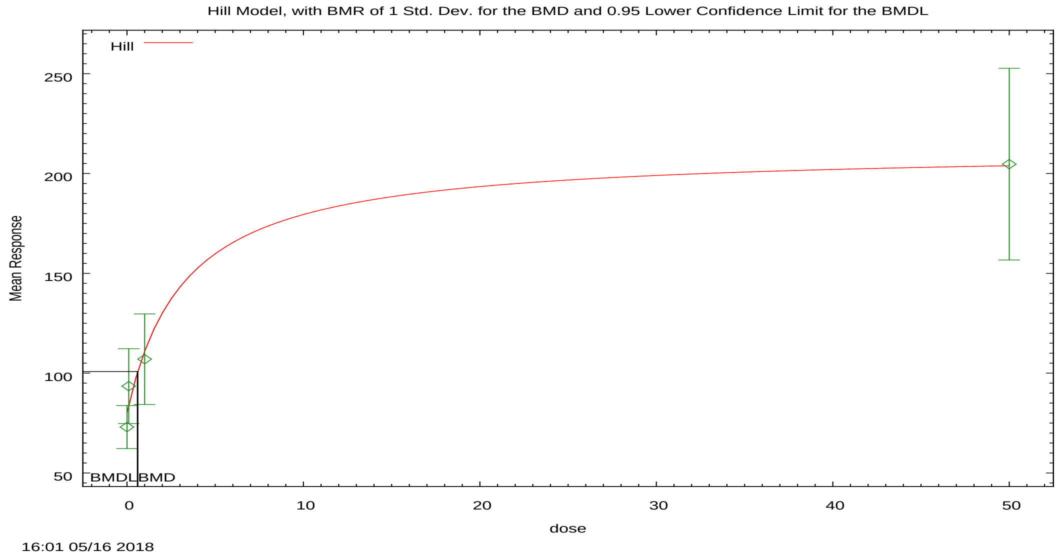

Figure 149. Plot of mean response by dose with fitted curve for Hill model with modeled variance for Alkaline Phosphatase in Males at 12 months (2-year rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 0.615474

BMDL at the 95% confidence level = 0.588643

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-4.47685	7.38154
rho	2.40759	0
intercept	79.9709	73
v	131.519	131.7

n	1	0.245207
k	3.2713	83.0261

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	73	80	15.1	20.8	-1.06
0.1	10	93.5	83.9	26.2	22.1	1.38
1	10	107	111	31.7	30.8	-0.386
50	10	205	203	67.1	64.1	0.0635

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-165.523688	5	341.047376
A2	-154.306424	8	324.612848
A3	-154.582873	6	321.165747
fitted	-157.180973	5	324.361945
R	-185.925167	2	375.850335

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	63.2375	6	<0.0001
Test 2	22.4345	3	<0.0001
Test 3	0.552899	2	0.7585
Test 4	5.1962	1	0.02264

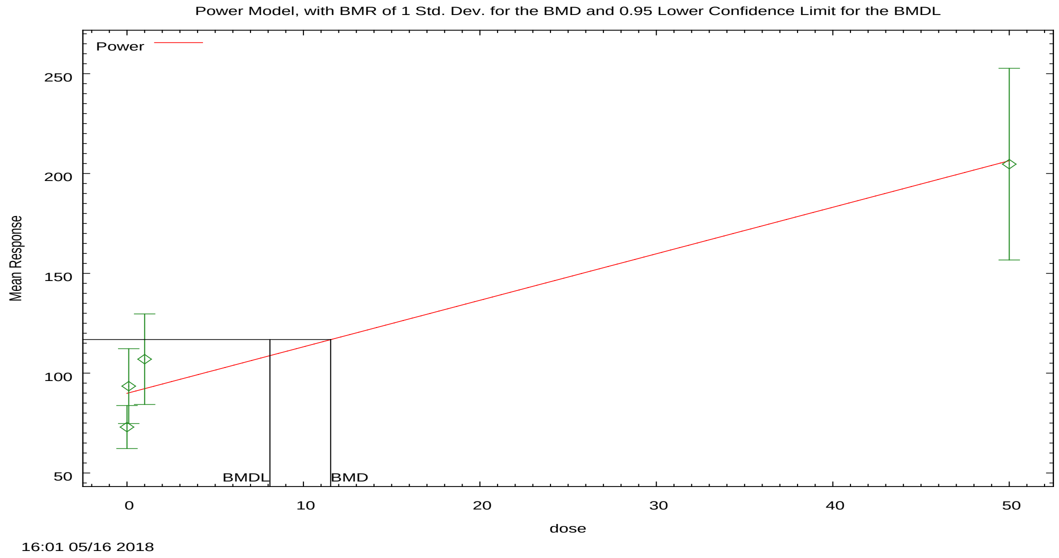

Figure 150. Plot of mean response by dose with fitted curve for Power model with modeled variance for Alkaline Phosphatase in Males at 12 months (2-year rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 11.5414

BMDL at the 95% confidence level = 8.10154

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-2.82854	7.38154
rho	2.09209	0
control	89.9371	73
slope	2.33044	40.0502

power	1	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	73	89.9	15.1	26.9	-1.99
0.1	10	93.5	90.2	26.2	27	0.39
1	10	107	92.3	31.7	27.6	1.69
50	10	205	206	67.1	64.2	-0.0867

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-165.523688	5	341.047376
A2	-154.306424	8	324.612848
A3	-154.582873	6	321.165747
fitted	-160.667071	4	329.334142
R	-185.925167	2	375.850335

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	63.2375	6	<0.0001
Test 2	22.4345	3	<0.0001
Test 3	0.552899	2	0.7585
Test 4	12.1684	2	0.002279

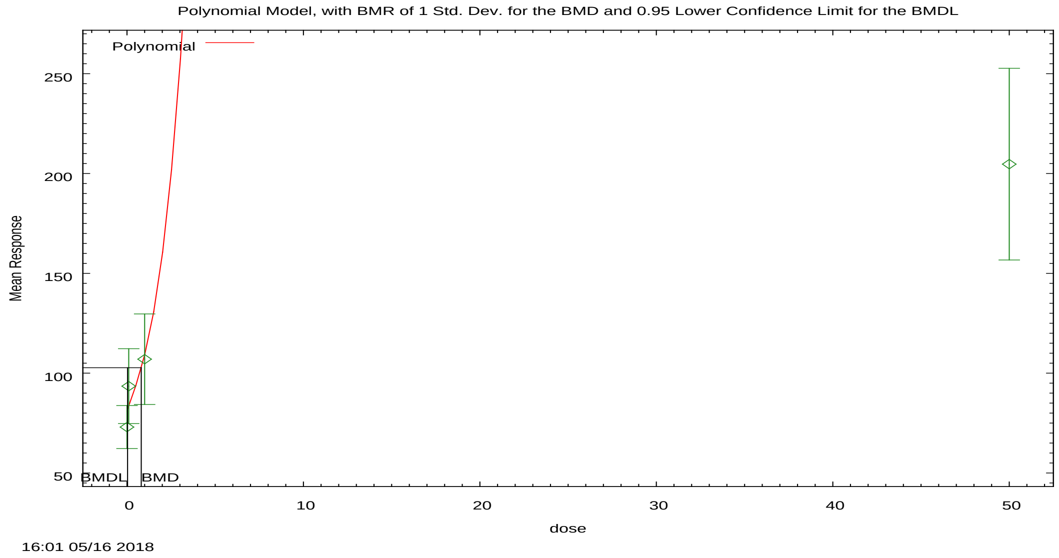

Figure 151. Plot of mean response by dose with fitted curve for Polynomial 3° model with modeled variance for Alkaline Phosphatase in Males at 12 months (2-year rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

THE MODEL HAS PROBABLY NOT CONVERGED!!!

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 0.808167

BMDL at the 95% confidence level = 0.0319281

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-3.99342	7.38154
rho	2.30613	0
beta_0	81.1399	73

beta_1	24.3069	224.379
beta_2	0	0
beta_3	3.69216	3.79479

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	73	81.1	15.1	21.6	-1.19
0.1	10	93.5	83.6	26.2	22.3	1.4
1	10	107	109	31.7	30.4	-0.223
50	10	205	463000	67.1	463000	-3.16

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-165.523688	5	341.047376
A2	-154.306424	8	324.612848
A3	-154.582873	6	321.165747
fitted	-246.381182	5	502.762365
R	-185.925167	2	375.850335

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	63.2375	6	<0.0001
Test 2	22.4345	3	<0.0001
Test 3	0.552899	2	0.7585
Test 4	183.597	1	<0.0001

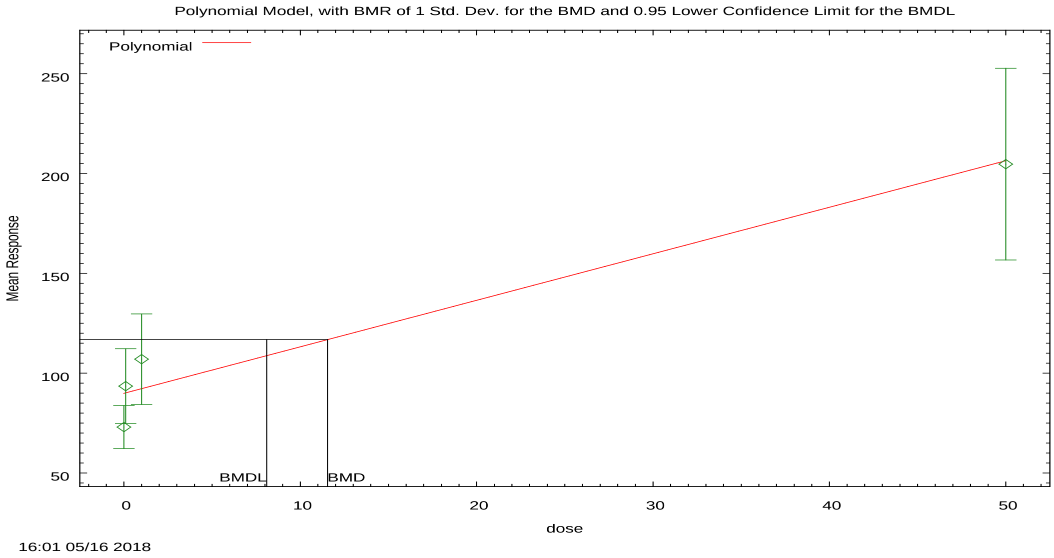

Figure 152. Plot of mean response by dose with fitted curve for Polynomial 2° model with modeled variance for Alkaline Phosphatase in Males at 12 months (2-year rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 11.5414

BMDL at the 95% confidence level = 8.10154

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-2.82853	7.38154
rho	2.09208	0
beta_0	89.9371	81.424
beta_1	2.33044	27.0223

beta_2	0	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	73	89.9	15.1	26.9	-1.99
0.1	10	93.5	90.2	26.2	27	0.39
1	10	107	92.3	31.7	27.6	1.69
50	10	205	206	67.1	64.2	-0.0867

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-165.523688	5	341.047376
A2	-154.306424	8	324.612848
A3	-154.582873	6	321.165747
fitted	-160.667071	4	329.334142
R	-185.925167	2	375.850335

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	63.2375	6	<0.0001
Test 2	22.4345	3	<0.0001
Test 3	0.552899	2	0.7585
Test 4	12.1684	2	0.002279

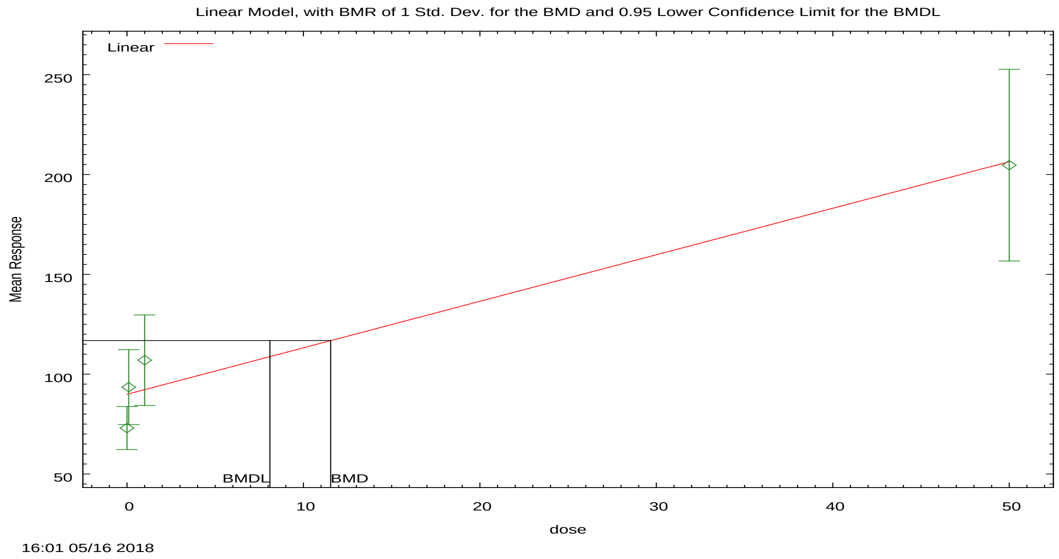

Figure 153. Plot of mean response by dose with fitted curve for Linear model with modeled variance for Alkaline Phosphatase in Males at 12 months (2-year rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 11.5414

BMDL at the 95% confidence level = 8.10154

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-2.82853	7.38154
rho	2.09208	0
beta_0	89.9371	90.2265
beta_1	2.33044	2.29538

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	73	89.9	15.1	26.9	-1.99
0.1	10	93.5	90.2	26.2	27	0.39
1	10	107	92.3	31.7	27.6	1.69
50	10	205	206	67.1	64.2	-0.0867

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-165.523688	5	341.047376
A2	-154.306424	8	324.612848
A3	-154.582873	6	321.165747
fitted	-160.667071	4	329.334142
R	-185.925167	2	375.850335

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	63.2375	6	<0.0001
Test 2	22.4345	3	<0.0001
Test 3	0.552899	2	0.7585
Test 4	12.1684	2	0.002279

BMDS WIZARD OUTPUT REPORT

BMDS Summary of H-28548: Subchronic Toxicity 90-Day Gavage Study in Mice – Alanine Aminotransferase (U/L) in Females

1.18. BMDS Summary of Alanine Aminotransferase (U/L) Females (90 Day Mice GenX)

Table 18. Summary of BMD Modeling Results for Alanine Aminotransferase in Females (90-day mice); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD_{1SD} (mg/kg/day)	$BMDL_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2)	0.0421	226.75	3.07	1.92	1.60	No models met all model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). No BMDL was selected.
Exponential (M3)	0.0292	227.17	4.68	2.22	2.11	
Exponential (M4)	0.00999	229.05	2.96	1.65	1.79	
Exponential (M5)	N/A[b]	229.17	4.65	0.547	8.50	
Hill	0.0292	227.17	3.96	error[c]	error	
Power	0.0928	225.17	4.83	2.08	2.32	
Polynomial 3°	0.0919	225.19	4.08	3.37	1.21	
Polynomial 2°	0.0845	225.36	3.70	2.77	1.33	
Linear	0.0362	227.05	2.96	1.65	1.79	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = 0.00197, BMDS Test 3 *p*-value = 0.554), no model was selected as a best-fitting model.

[b] No available degrees of freedom to calculate a goodness of fit value.

[c] BMD or BMDL computation failed for this model.

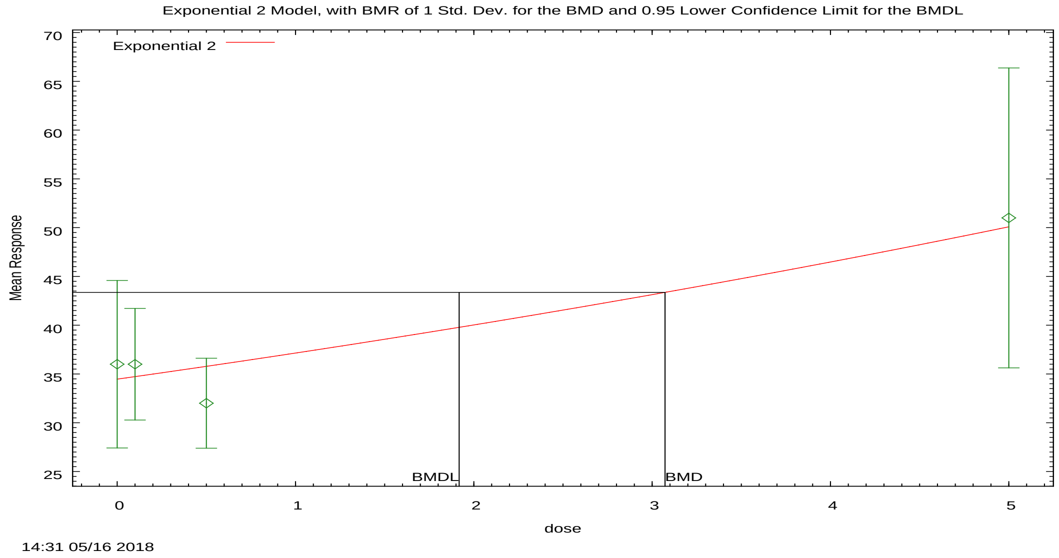

Figure 154. Plot of mean response by dose with fitted curve for Exponential (M2) model with modeled variance for Alanine Aminotransferase in Females (90-day mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 3.07219

BMDL at the 95% confidence level = 1.91774

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-9.37773	-12.8534
rho	3.88374	4.81423
a	34.4695	34.3083
b	0.0747248	0.0773011
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	36	34.47	12	8.9	0.5441
0.1	10	36	34.73	8	9.02	0.4457
0.5	9	32	35.78	6	9.56	-1.186
5	9	51	50.08	20	18.38	0.1496

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-113.0335	5	236.0671

A2	-105.6173	8	227.2345
A3	-106.2087	6	224.4174
R	-118.8274	2	241.6548
2	-109.377	4	226.7541

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	26.42	6	0.0001859
Test 2	14.83	3	0.001965
Test 3	1.183	2	0.5535
Test 4	6.337	2	0.04207

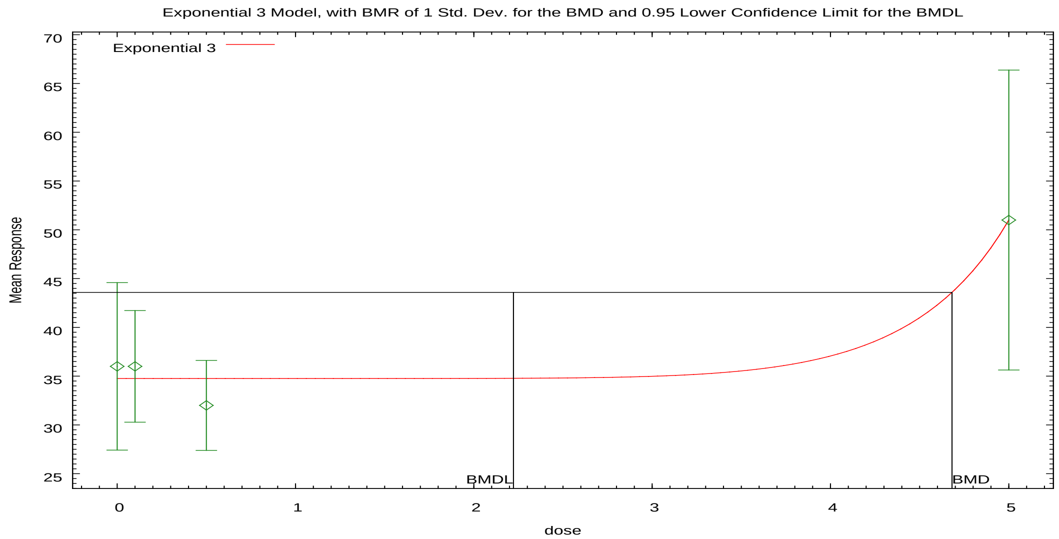

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Figure 155. Plot of mean response by dose with fitted curve for Exponential (M3) model with modeled variance for Alanine Aminotransferase in Females (90-day mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 4.68144

BMDL at the 95% confidence level = 2.22228

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-9.69539	-12.8534
rho	3.95976	4.81423
a	34.7586	34.3083
b	0.177438	0.0773011
c	n/a	0
d	8.00925	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	36	34.76	12	8.83	0.4447
0.1	10	36	34.76	8	8.83	0.4447
0.5	9	32	34.76	6	8.83	-0.9376
5	9	51	51	20	18.86	0.0000000912

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-113.0335	5	236.0671
A2	-105.6173	8	227.2345
A3	-106.2087	6	224.4174
R	-118.8274	2	241.6548
3	-108.5866	5	227.1732

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value

Test 1	26.42	6	0.0001859
Test 2	14.83	3	0.001965
Test 3	1.183	2	0.5535
Test 5a	4.756	1	0.0292

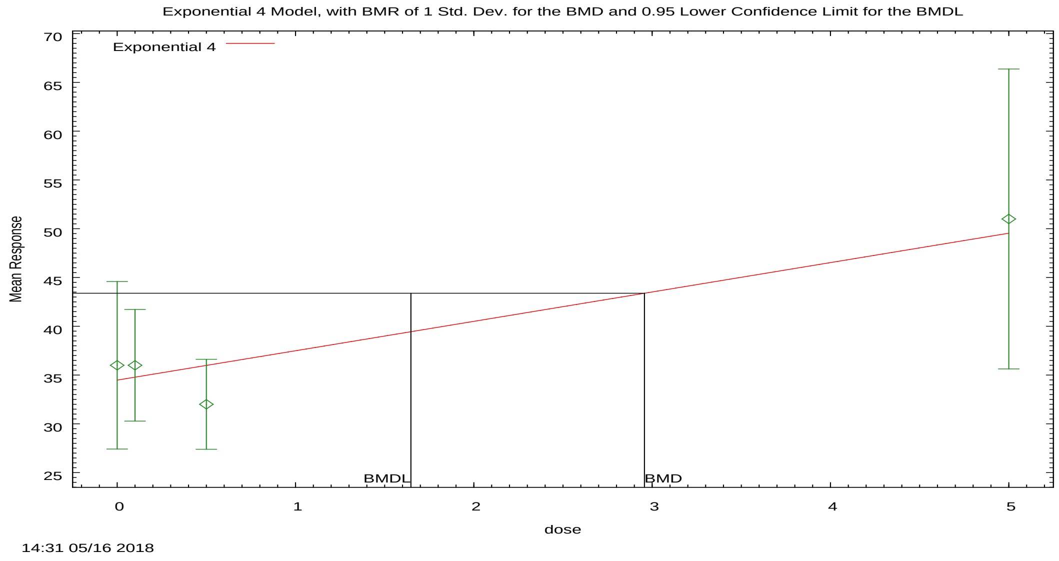

Figure 156. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Alanine Aminotransferase in Females (90-day mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 2.95667

BMDL at the 95% confidence level = 1.64717

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-9.72233	-12.8534
rho	3.98146	4.81423
a	34.4785	30.4
b	0.0000118979	0.0679252
c	7343.68	3.35526
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	36	34.48	12	8.91	0.5403
0.1	10	36	34.78	8	9.06	0.4259
0.5	9	32	35.98	6	9.7	-1.233
5	9	51	49.54	20	18.32	0.2393

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-113.0335	5	236.0671
A2	-105.6173	8	227.2345
A3	-106.2087	6	224.4174
R	-118.8274	2	241.6548
4	-109.5268	5	229.0536

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	26.42	6	0.0001859
Test 2	14.83	3	0.001965
Test 3	1.183	2	0.5535
Test 6a	6.636	1	0.009993

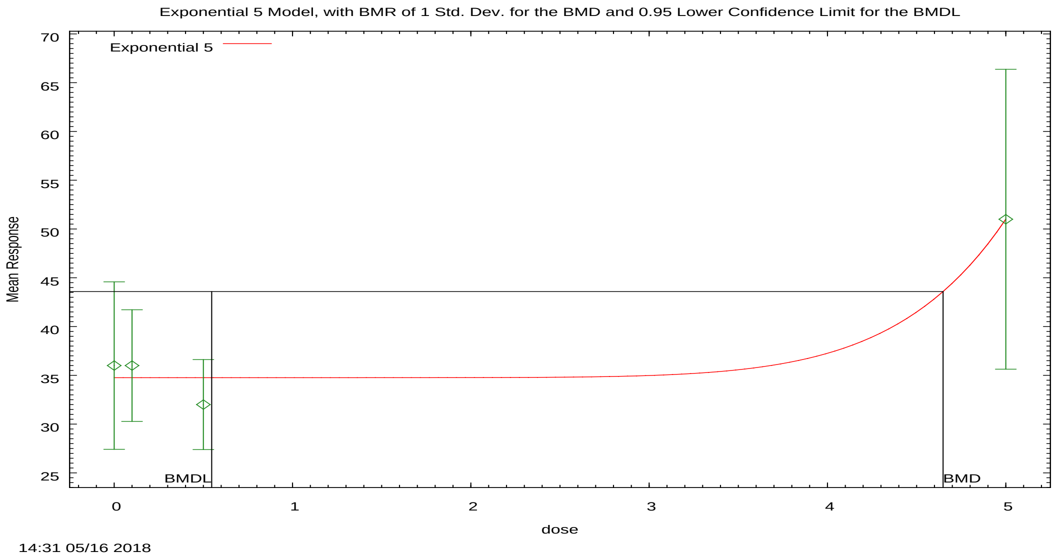

Figure 157. Plot of mean response by dose with fitted curve for Exponential (M5) model with modeled variance for Alanine Aminotransferase in Females (90-day mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 4.64816

BMDL at the 95% confidence level = 0.546826

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-9.69539	-12.8534
rho	3.95976	4.81423
a	34.7586	30.4
b	0.128205	0.0679252

c	21.0879	3.35526
d	8.43124	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	36	34.76	12	8.83	0.4447
0.1	10	36	34.76	8	8.83	0.4447
0.5	9	32	34.76	6	8.83	-0.9376
5	9	51	51	20	18.86	0.000000007321

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-113.0335	5	236.0671
A2	-105.6173	8	227.2345
A3	-106.2087	6	224.4174
R	-118.8274	2	241.6548
5	-108.5866	6	229.1732

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	26.42	6	0.0001859
Test 2	14.83	3	0.001965
Test 3	1.183	2	0.5535
Test 7a	4.756	0	N/A

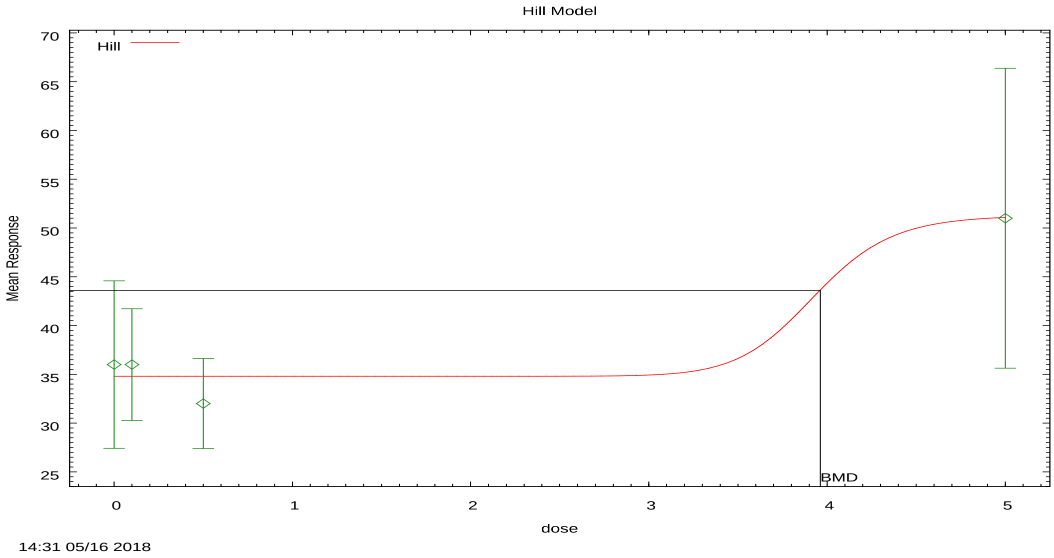

Figure 158. Plot of mean response by dose with fitted curve for Hill model with modeled variance for Alanine Aminotransferase in Females (90-day mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 3.96196

BMDL at the 95% confidence level = error

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-9.69546	5.06036
rho	3.95977	0
intercept	34.7586	36
v	16.4542	15
n	18	18

k	3.92996	6.77632

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	36	34.8	12	8.83	0.445
0.1	10	36	34.8	8	8.83	0.445
0.5	9	32	34.8	6	8.83	-0.938
5	9	51	51	20	18.9	0.00000763

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-113.033529	5	236.067058
A2	-105.617255	8	227.23451
A3	-106.208714	6	224.417429
fitted	-108.586593	5	227.173186
R	-118.827402	2	241.654805

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	26.4203	6	0.0001859
Test 2	14.8325	3	0.001965
Test 3	1.18292	2	0.5535
Test 4	4.75576	1	0.0292

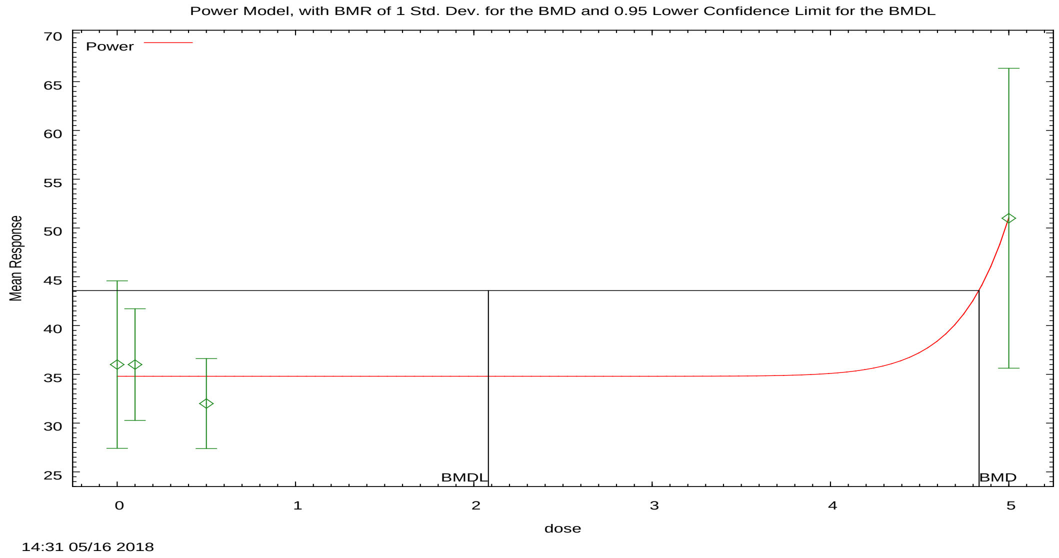

Figure 159. Plot of mean response by dose with fitted curve for Power model with modeled variance for Alanine Aminotransferase in Females (90-day mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 4.83345

BMDL at the 95% confidence level = 2.08154

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-9.69538	5.06036
rho	3.95975	0
control	34.7586	32
slope	4.25758E-12	10.0082
power	18	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	36	34.8	12	8.83	0.445
0.1	10	36	34.8	8	8.83	0.445
0.5	9	32	34.8	6	8.83	-0.938
5	9	51	51	20	18.9	-0.000000706

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-113.033529	5	236.067058
A2	-105.617255	8	227.23451
A3	-106.208714	6	224.417429
fitted	-108.586593	4	225.173186
R	-118.827402	2	241.654805

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	26.4203	6	0.0001859
Test 2	14.8325	3	0.001965
Test 3	1.18292	2	0.5535
Test 4	4.75576	2	0.09275

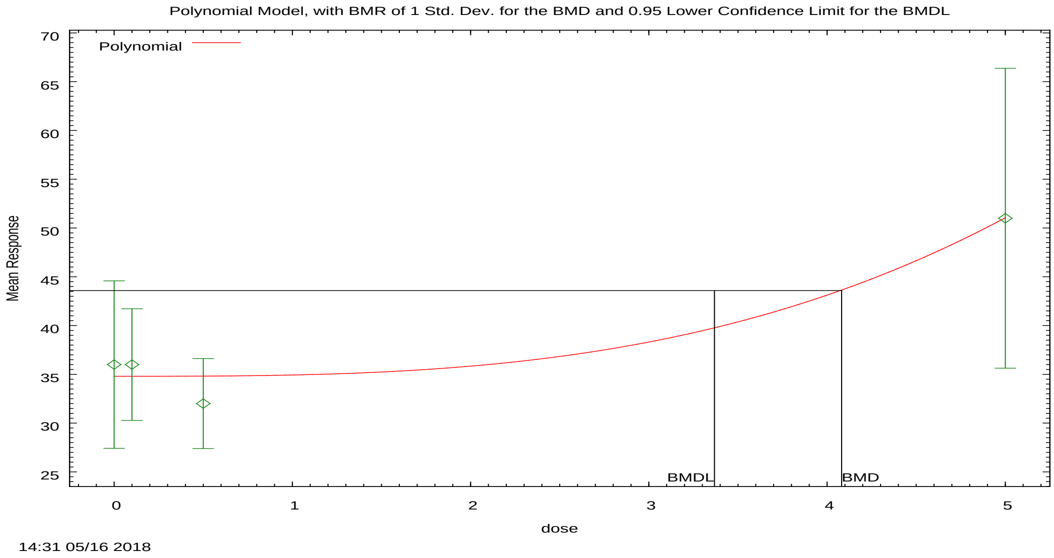

Figure 160. Plot of mean response by dose with fitted curve for Polynomial 3° model with modeled variance for Alanine Aminotransferase in Females (90-day mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 4.08145

BMDL at the 95% confidence level = 3.36805

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-9.69464	5.06036
rho	3.9597	0
beta_0	34.7561	36
beta_1	6.94793E-21	0

beta_2	8.42501E-21	0
beta_3	0.129837	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	36	34.8	12	8.83	0.446
0.1	10	36	34.8	8	8.83	0.446
0.5	9	32	34.8	6	8.84	-0.941
5	9	51	51	20	18.9	0.00227

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-113.033529	5	236.067058
A2	-105.617255	8	227.23451
A3	-106.208714	6	224.417429
fitted	-108.595863	4	225.191725
R	-118.827402	2	241.654805

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	26.4203	6	0.0001859
Test 2	14.8325	3	0.001965
Test 3	1.18292	2	0.5535
Test 4	4.7743	2	0.09189

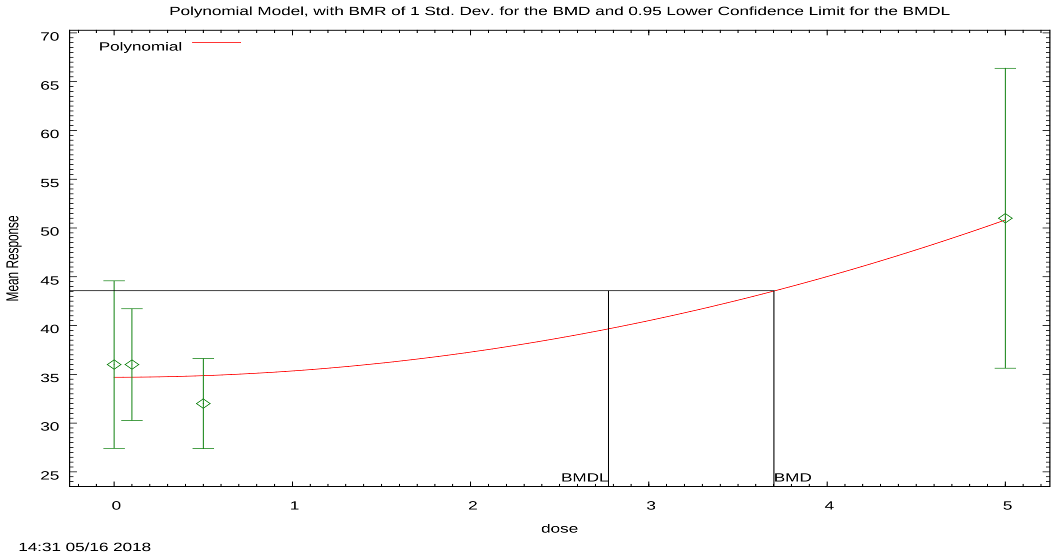

Figure 161. Plot of mean response by dose with fitted curve for Polynomial 2° model with modeled variance for Alanine Aminotransferase in Females (90-day mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 3.70148

BMDL at the 95% confidence level = 2.77406

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-9.68809	5.06036
rho	3.95919	0
beta_0	34.7327	36.4235
beta_1	1.03398E-26	0

beta_2	0.644978	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	36	34.7	12	8.84	0.454
0.1	10	36	34.7	8	8.84	0.451
0.5	9	32	34.9	6	8.92	-0.973
5	9	51	50.9	20	18.8	0.0228

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-113.033529	5	236.067058
A2	-105.617255	8	227.23451
A3	-106.208714	6	224.417429
fitted	-108.679471	4	225.358943
R	-118.827402	2	241.654805

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	26.4203	6	0.0001859
Test 2	14.8325	3	0.001965
Test 3	1.18292	2	0.5535
Test 4	4.94151	2	0.08452

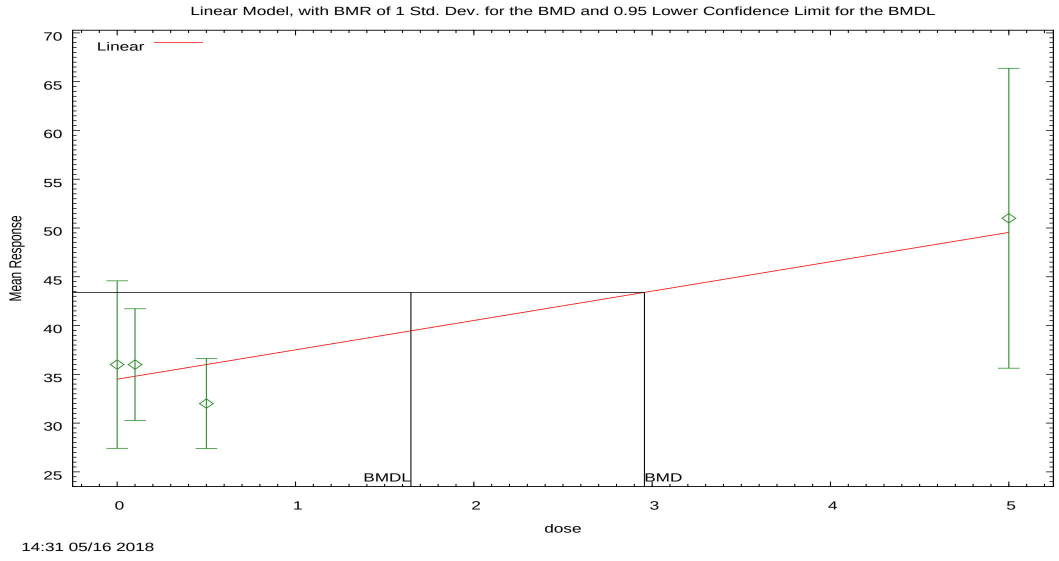

Figure 162. Plot of mean response by dose with fitted curve for Linear model with modeled variance for Alanine Aminotransferase in Females (90-day mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 2.95668

BMDL at the 95% confidence level = 1.64721

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-9.72219	5.06036
rho	3.98142	0
beta_0	34.4785	34.1208
beta_1	3.01207	3.30654

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	36	34.5	12	8.91	0.54
0.1	10	36	34.8	8	9.06	0.426
0.5	9	32	36	6	9.7	-1.23
5	9	51	49.5	20	18.3	0.239

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-113.033529	5	236.067058
A2	-105.617255	8	227.23451
A3	-106.208714	6	224.417429
fitted	-109.526767	4	227.053534
R	-118.827402	2	241.654805

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	26.4203	6	0.0001859
Test 2	14.8325	3	0.001965
Test 3	1.18292	2	0.5535
Test 4	6.63611	2	0.03622

BMDS WIZARD OUTPUT REPORT

Summary of H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats – Alanine Aminotransferase (U/L) at 12-month timepoint in Males

1.19. BMDS Summary of Alanine Aminotransferase (U/L) Males 12 months (2 Year Rats GenX)

Table 19. Summary of BMD Modeling Results for Alanine Aminotransferase in males at 12 months (2-year rats); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD_{1SD} (mg/kg/day)	$BMDL_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2)	0.0403	269.38	8.75	6.57	1.33	No models met all model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). No BMDL was selected.
Exponential (M3)	0.0139	271.01	34.5	6.70	5.15	
Exponential (M4)	0.00847	271.89	4.99	3.18	1.57	
Exponential (M5)	N/A[b]	273.01	23.0	1.04	22.2	
Hill	N/A[b]	273.01	30.3	error[c]	error	
Power	0.0486	269.01	44.0	3.43	12.8	
Polynomial 3°	0.0486	269.01	23.1	3.43	6.74	
Polynomial 2°	0.0484	269.01	15.7	12.5	1.25	
Linear	0.0313	269.89	4.99	3.18	1.57	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = <0.0001, BMDS Test 3 *p*-value = 0.213), no model was selected as a best-fitting model.

[b] No available degrees of freedom to calculate a goodness of fit value.

[c] BMD or BMDL computation failed for this model.

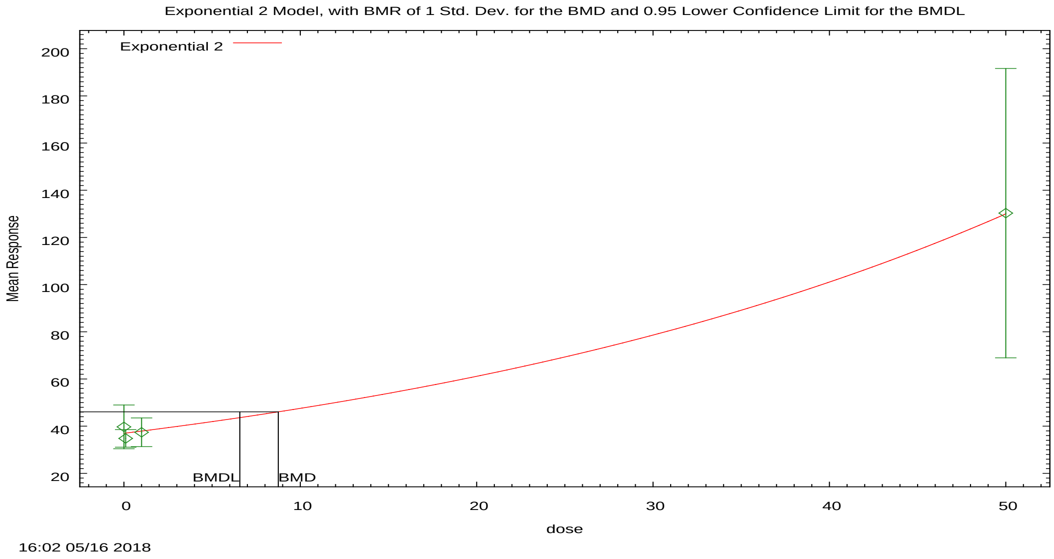

Figure 163. Plot of mean response by dose with fitted curve for Exponential (M2) model with modeled variance for Alanine Aminotransferase in males at 12 months (2-year rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 8.75352

BMDL at the 95% confidence level = 6.57192

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-8.1416	-9.5406
rho	3.47864	3.80156
a	36.975	36.9077
b	0.0251427	0.0252212
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	39.7	36.97	12.97	9.1	0.9467
0.1	10	34.8	37.07	5.2	9.14	-0.7845
1	10	37.4	37.92	8.51	9.51	-0.1717
50	10	130.3	130	85.73	81.06	0.01251

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-168.9305	5	347.861

A2	-125.9302	8	267.8604
A3	-127.4788	6	266.9576
R	-182.2661	2	368.5321
2	-130.6895	4	269.3789

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	112.7	6	<0.0001
Test 2	86	3	<0.0001
Test 3	3.097	2	0.2125
Test 4	6.421	2	0.04033

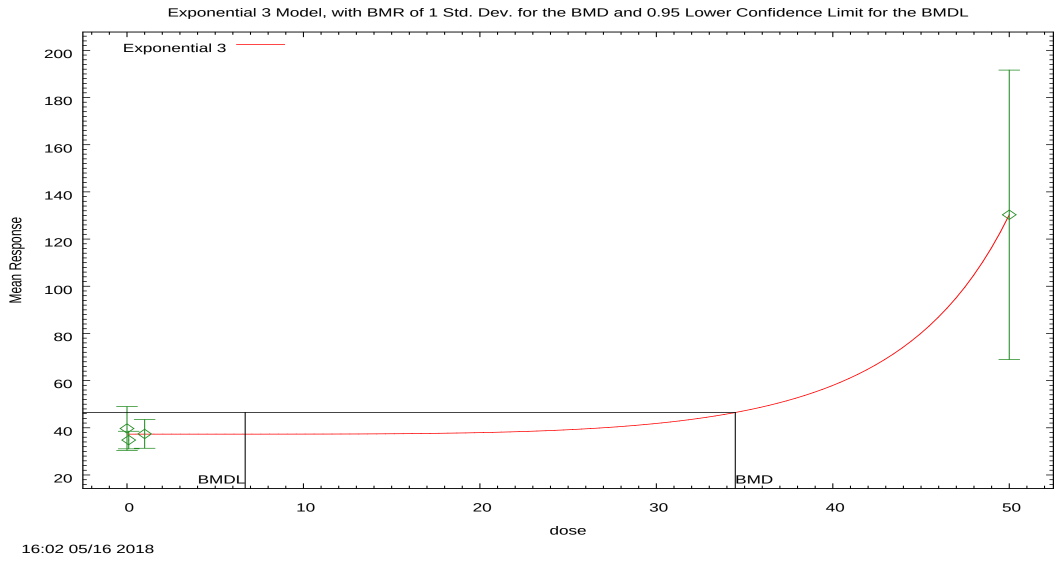

Figure 164. Plot of mean response by dose with fitted curve for Exponential (M3) model with modeled variance for Alanine Aminotransferase in males at 12 months (2-year rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 34.4731

BMDL at the 95% confidence level = 6.69773

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-8.18733	-9.5406
rho	3.48767	3.80156
a	37.3	36.9077
b	0.0209812	0.0252212
c	n/a	0
d	4.67298	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	39.7	37.3	12.97	9.18	0.8266
0.1	10	34.8	37.3	5.2	9.18	-0.861
1	10	37.4	37.3	8.51	9.18	0.03444
50	10	130.3	130.3	85.73	81.33	-0.0000002128

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-168.9305	5	347.861
A2	-125.9302	8	267.8604
A3	-127.4788	6	266.9576
R	-182.2661	2	368.5321
3	-130.5029	5	271.0058

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value

Test 1	112.7	6	<0.0001
Test 2	86	3	<0.0001
Test 3	3.097	2	0.2125
Test 5a	6.048	1	0.01392

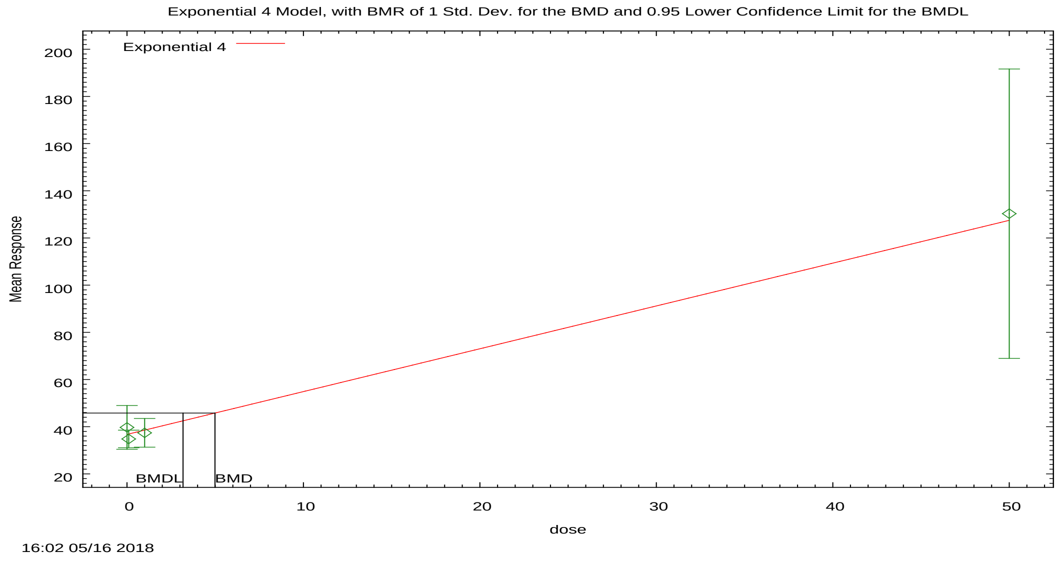

Figure 165. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Alanine Aminotransferase in males at 12 months (2-year rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 4.98667

BMDL at the 95% confidence level = 3.1776

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-8.26968	-9.5406
rho	3.5176	3.80156
a	36.7276	33.06
b	0.0000066833	0.0553539
c	7396.78	4.13838
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	39.7	36.73	12.97	9.05	1.038
0.1	10	34.8	36.91	5.2	9.13	-0.7304
1	10	37.4	38.54	8.51	9.85	-0.3668
50	10	130.3	127.5	85.73	80.78	0.1103

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-168.9305	5	347.861
A2	-125.9302	8	267.8604
A3	-127.4788	6	266.9576
R	-182.2661	2	368.5321
4	-130.9443	5	271.8885

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	112.7	6	<0.0001
Test 2	86	3	<0.0001
Test 3	3.097	2	0.2125
Test 6a	6.931	1	0.008472

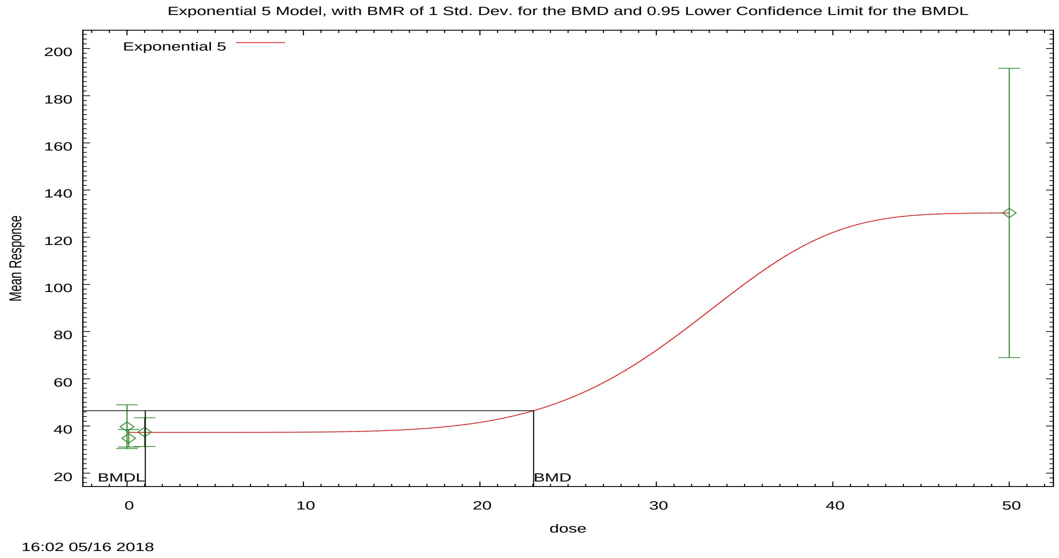

Figure 166. Plot of mean response by dose with fitted curve for Exponential (M5) model with modeled variance for Alanine Aminotransferase in males at 12 months (2-year rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 23.0428

BMDL at the 95% confidence level = 1.0372

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-8.18733	-9.5406
rho	3.48767	3.80156
a	37.3	33.06
b	0.0291834	0.0553539

c	3.49374	4.13838
d	5.70564	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	39.7	37.3	12.97	9.18	0.8266
0.1	10	34.8	37.3	5.2	9.18	-0.861
1	10	37.4	37.3	8.51	9.18	0.03444
50	10	130.3	130.3	85.73	81.33	-0.00000009512

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-168.9305	5	347.861
A2	-125.9302	8	267.8604
A3	-127.4788	6	266.9576
R	-182.2661	2	368.5321
5	-130.5029	6	273.0058

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	112.7	6	<0.0001
Test 2	86	3	<0.0001
Test 3	3.097	2	0.2125
Test 7a	6.048	0	N/A

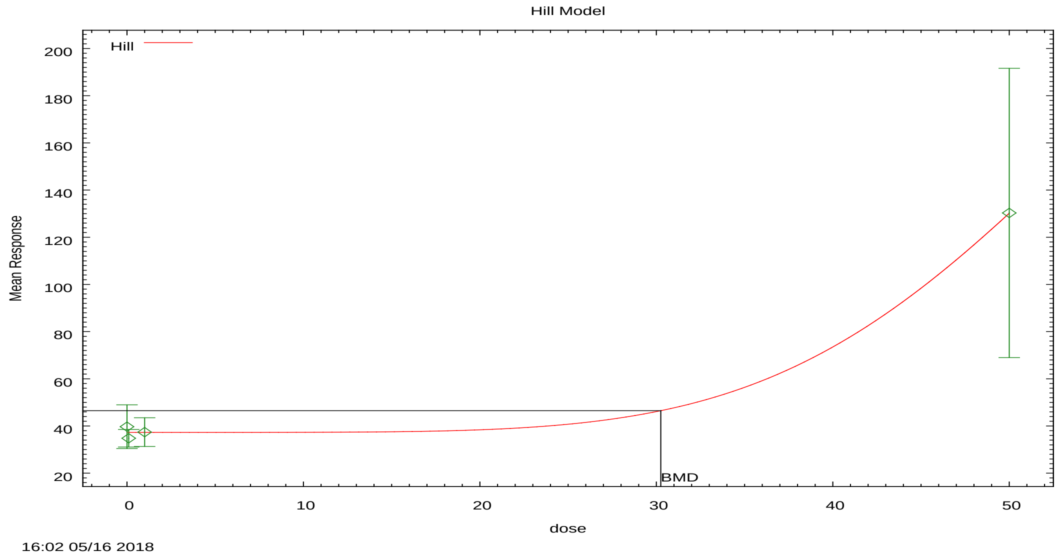

Figure 167. Plot of mean response by dose with fitted curve for Hill model with modeled variance for Alanine Aminotransferase in males at 12 months (2-year rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A modeled variance is fit

THE MODEL HAS PROBABLY NOT CONVERGED!!!

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 30.2517

BMDL at the 95% confidence level = error

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-8.18733	7.55188
rho	3.48767	0
intercept	37.3	39.7

v	316.418	90.6
n	5.24194	1
k	59.0994	73.8934

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	39.7	37.3	13	9.18	0.827
0.1	10	34.8	37.3	5.2	9.18	-0.861
1	10	37.4	37.3	8.51	9.18	0.0344
50	10	130	130	85.7	81.3	-0.000000189

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-168.930484	5	347.860968
A2	-125.930214	8	267.860427
A3	-127.47881	6	266.95762
fitted	-130.502905	6	273.00581
R	-182.266066	2	368.532131

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	112.672	6	<0.0001
Test 2	86.0005	3	<0.0001
Test 3	3.09719	2	0.2125
Test 4	6.04819	0	N/A

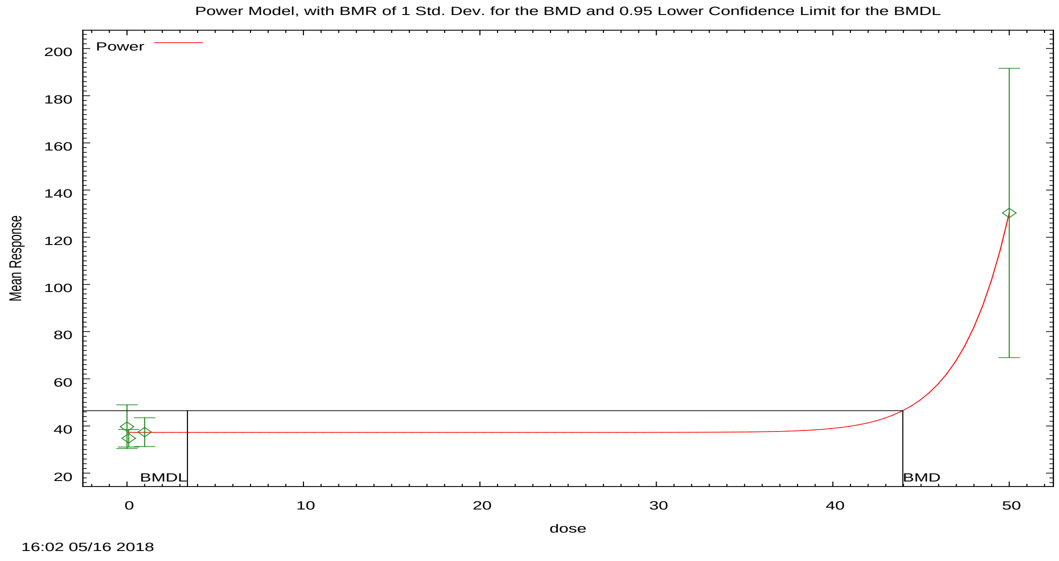

Figure 168. Plot of mean response by dose with fitted curve for Power model with modeled variance for Alanine Aminotransferase in males at 12 months (2-year rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 43.965

BMDL at the 95% confidence level = 3.42661

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-8.18733	7.55188
rho	3.48767	0
control	37.3	34.8
slope	2.43794E-29	2.6

power	18	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	39.7	37.3	13	9.18	0.827
0.1	10	34.8	37.3	5.2	9.18	-0.861
1	10	37.4	37.3	8.51	9.18	0.0344
50	10	130	130	85.7	81.3	0.000000496

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-168.930484	5	347.860968
A2	-125.930214	8	267.860427
A3	-127.47881	6	266.95762
fitted	-130.502905	4	269.00581
R	-182.266066	2	368.532131

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	112.672	6	<0.0001
Test 2	86.0005	3	<0.0001
Test 3	3.09719	2	0.2125
Test 4	6.04819	2	0.0486

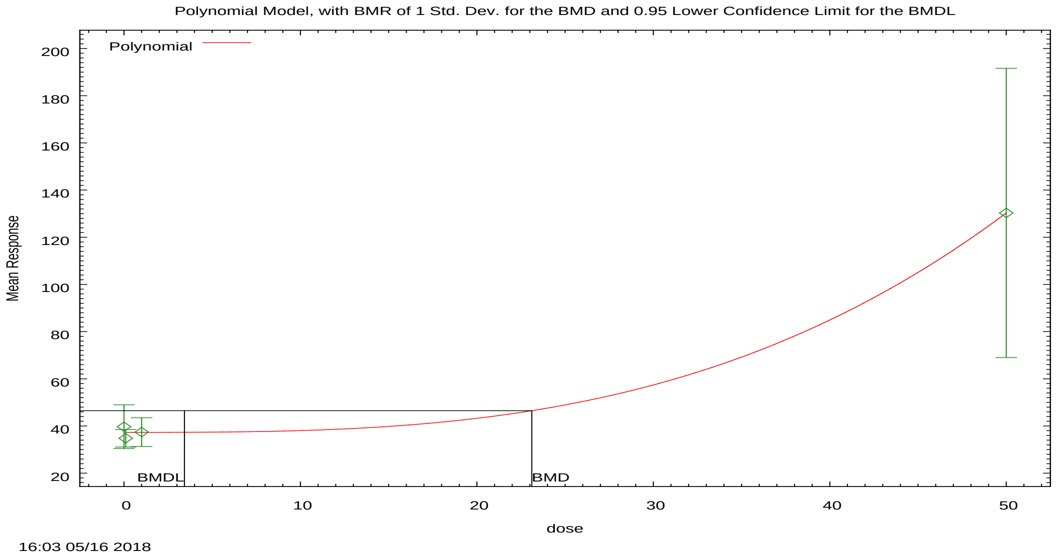

Figure 169. Plot of mean response by dose with fitted curve for Polynomial 3° model with modeled variance for Alanine Aminotransferase in males at 12 months (2-year rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 23.1094

BMDL at the 95% confidence level = 3.42656

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-8.18731	7.55188
rho	3.48766	0
beta_0	37.2998	39.7
beta_1	0	0

beta_2	1.25456E-22	0
beta_3	0.000744001	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	39.7	37.3	13	9.18	0.827
0.1	10	34.8	37.3	5.2	9.18	-0.861
1	10	37.4	37.3	8.51	9.18	0.0343
50	10	130	130	85.7	81.3	0.00000633

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-168.930484	5	347.860968
A2	-125.930214	8	267.860427
A3	-127.47881	6	266.95762
fitted	-130.502975	4	269.005951
R	-182.266066	2	368.532131

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	112.672	6	<0.0001
Test 2	86.0005	3	<0.0001
Test 3	3.09719	2	0.2125
Test 4	6.04833	2	0.0486

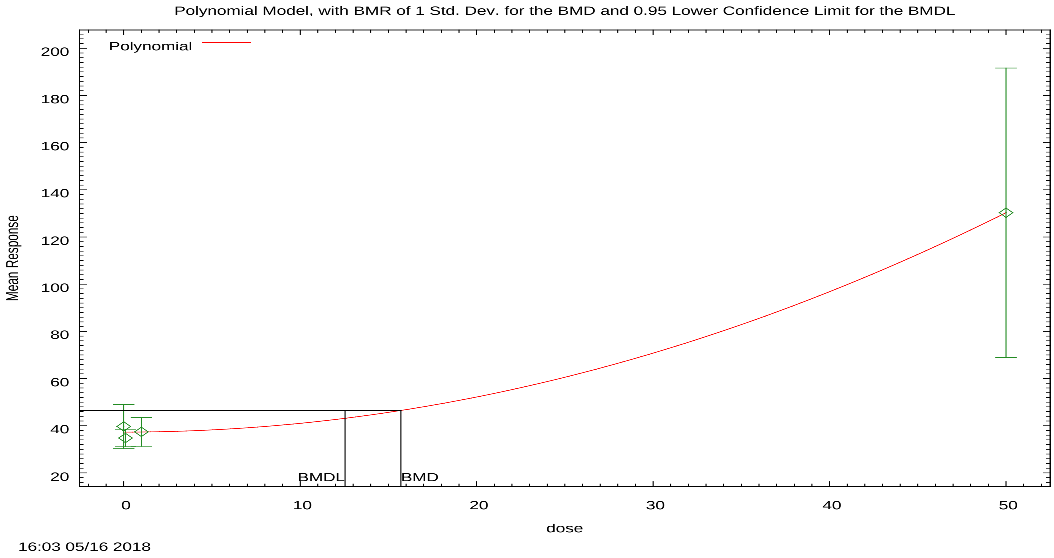

Figure 170. Plot of mean response by dose with fitted curve for Polynomial 2° model with modeled variance for Alanine Aminotransferase in males at 12 months (2-year rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 15.7074

BMDL at the 95% confidence level = 12.5405

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-8.18644	7.55188
rho	3.48751	0
beta_0	37.2876	37.3954
beta_1	6.93845E-23	0

beta_2	0.0372006	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	39.7	37.3	13	9.18	0.831
0.1	10	34.8	37.3	5.2	9.18	-0.857
1	10	37.4	37.3	8.51	9.19	0.0259
50	10	130	130	85.7	81.3	0.000424

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-168.930484	5	347.860968
A2	-125.930214	8	267.860427
A3	-127.47881	6	266.95762
fitted	-130.506701	4	269.013402
R	-182.266066	2	368.532131

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	112.672	6	<0.0001
Test 2	86.0005	3	<0.0001
Test 3	3.09719	2	0.2125
Test 4	6.05578	2	0.04842

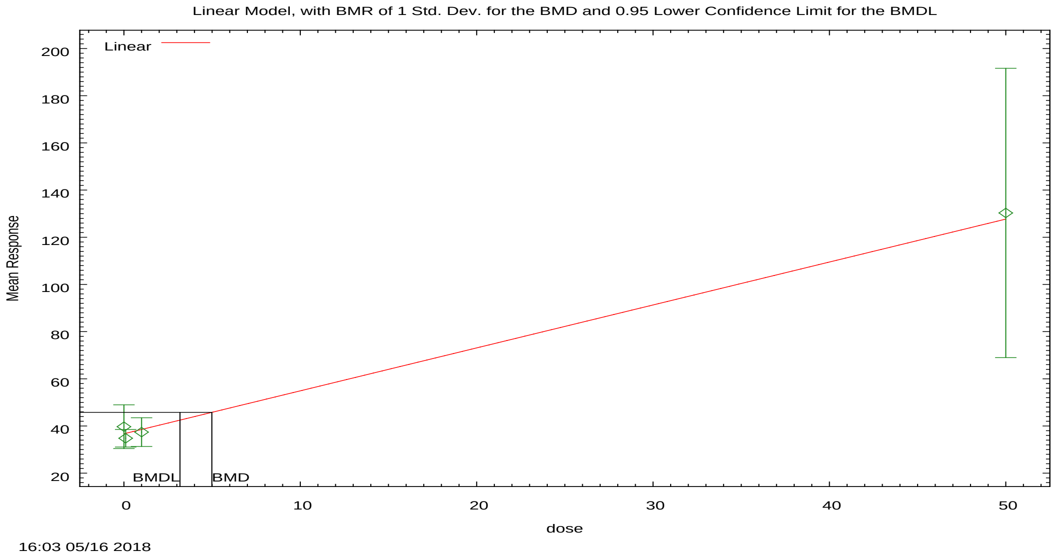

Figure 171. Plot of mean response by dose with fitted curve for Linear model with modeled variance for Alanine Aminotransferase in males at 12 months (2-year rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 4.98735

BMDL at the 95% confidence level = 3.17816

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-8.26958	7.55188
rho	3.51757	0
beta_0	36.7276	36.6219
beta_1	1.8151	1.87304

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	39.7	36.7	13	9.05	1.04
0.1	10	34.8	36.9	5.2	9.13	-0.73
1	10	37.4	38.5	8.51	9.85	-0.367
50	10	130	127	85.7	80.8	0.11

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-168.930484	5	347.860968
A2	-125.930214	8	267.860427
A3	-127.47881	6	266.95762
fitted	-130.944168	4	269.888336
R	-182.266066	2	368.532131

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	112.672	6	<0.0001
Test 2	86.0005	3	<0.0001
Test 3	3.09719	2	0.2125
Test 4	6.93072	2	0.03126

BMDS WIZARD OUTPUT REPORT

BMDS Summary of 28-Day Oral (Gavage) Toxicity Study of H-28397 in Mice with a 28-day Recovery – Aspartate Aminotransferase (U/L) in Males

1.20. BMDS Summary of Aspartate Aminotransferase (U/L) (28 Day Mice GenX)

Table 20. Summary of BMD Modeling Results for Aspartate Aminotransferase in Males (28-Day Mice); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD$_{1SD}$ (mg/kg/day)	BMDL$_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2) Exponential (M3)[b]	0.229	341.37	4.22	3.31	1.27	BMDLs from models that met model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values > 2.0; appropriate variance (continuous data only)) were compared. Selected BMDL is from model with lowest AIC and lowest BMDL.
Exponential (M4)	0.538	340.80	1.69	1.18	1.44	
Exponential (M5)	N/A[c]	342.60	2.01	1.02	1.97	
Hill	N/A[c]	342.53	2.76	error[d]	error	
Power	0.657	340.61	1.99	1.19	1.67	
Polynomial 3°[e] Polynomial 2°	0.638	340.64	1.93	1.19	1.62	
Linear	**0.827**	**338.80**	**1.69**	**1.18**	**1.44**	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = <0.0001), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 3, and 30 mg/kg/day were 0.43, 0.24, -1.08, 0.56, respectively.

[b] For the Exponential (M3) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M2) model.

[c] No available degrees of freedom to calculate a goodness of fit value.

[d] BMD or BMDL computation failed for this model.

[e] For the Polynomial 3° model, the b3 coefficient estimates was 0 (boundary of parameters space). The models in this row reduced to the Polynomial 2° model.

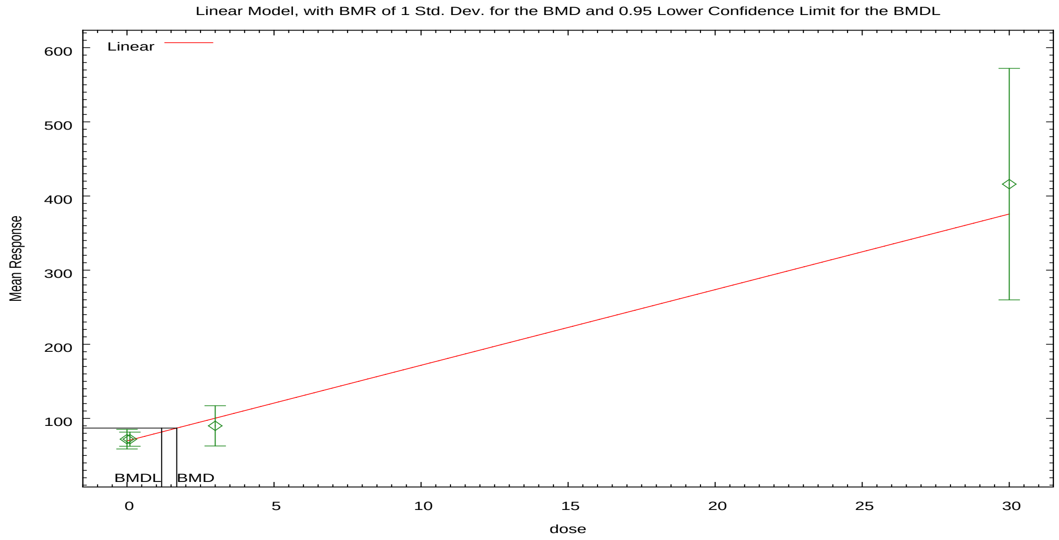

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Figure 172. Plot of mean response by dose with fitted curve for Linear model with modeled variance for Aspartate Aminotransferase in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 1.69171

BMDL at the 95% confidence level = 1.17843

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-7.18857	9.42582
rho	3.03741	0
beta_0	69.653	66.364
beta_1	10.223	11.6176

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	72	69.7	18.5	17.3	0.429
0.1	10	72	70.7	13.3	17.7	0.237
3	10	90	100	38	30.1	-1.08
30	10	416	376	218	224	0.559

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-206.409094	5	422.818187
A2	-163.182702	8	342.365403

A3	-165.208319	6	342.416637
fitted	-165.397938	4	338.795876
R	-227.865145	2	459.73029

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	129.365	6	<0.0001
Test 2	86.4528	3	<0.0001
Test 3	4.05123	2	0.1319
Test 4	0.379239	2	0.8273

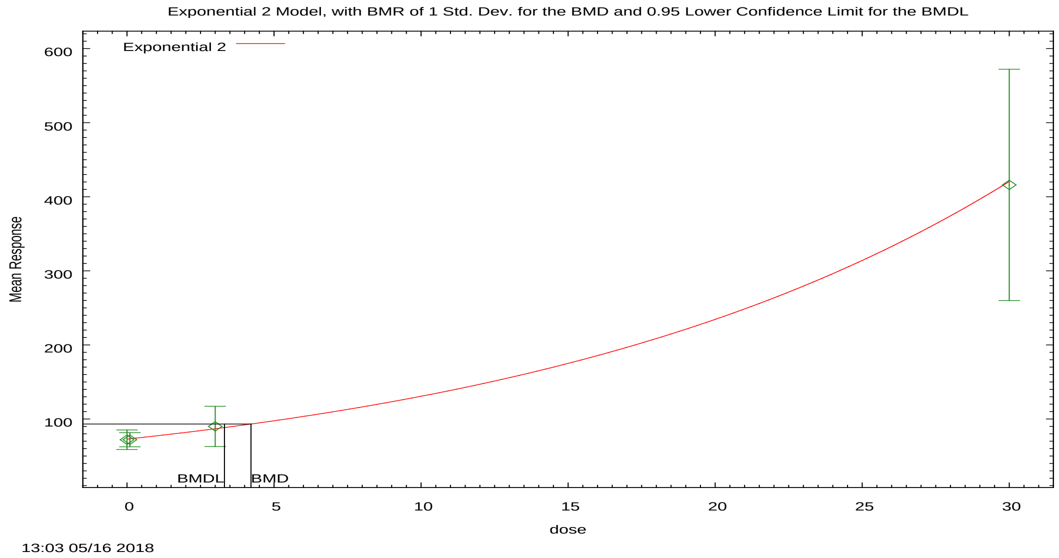

Figure 173. Plot of mean response by dose with fitted curve for Exponential (M2) model with modeled variance for Aspartate Aminotransferase in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 4.21632

BMDL at the 95% confidence level = 3.31493

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-5.56675	-6.39771
rho	2.70341	2.86362
a	72.8571	72.9518
b	0.0584388	0.058146
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	72	72.86	18.5	20.36	-0.1331
0.1	10	72	73.28	13.3	20.52	-0.1979
3	10	90	86.82	38	25.8	0.39
30	10	416	420.6	218.3	217.7	-0.06671

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-206.4091	5	422.8182
A2	-163.1827	8	342.3654
A3	-165.2083	6	342.4166
R	-227.8651	2	459.7303
2	-166.683	4	341.366

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	129.4	6	<0.0001
Test 2	86.45	3	<0.0001

Test 3	4.051	2	0.1319
Test 4	2.949	2	0.2289

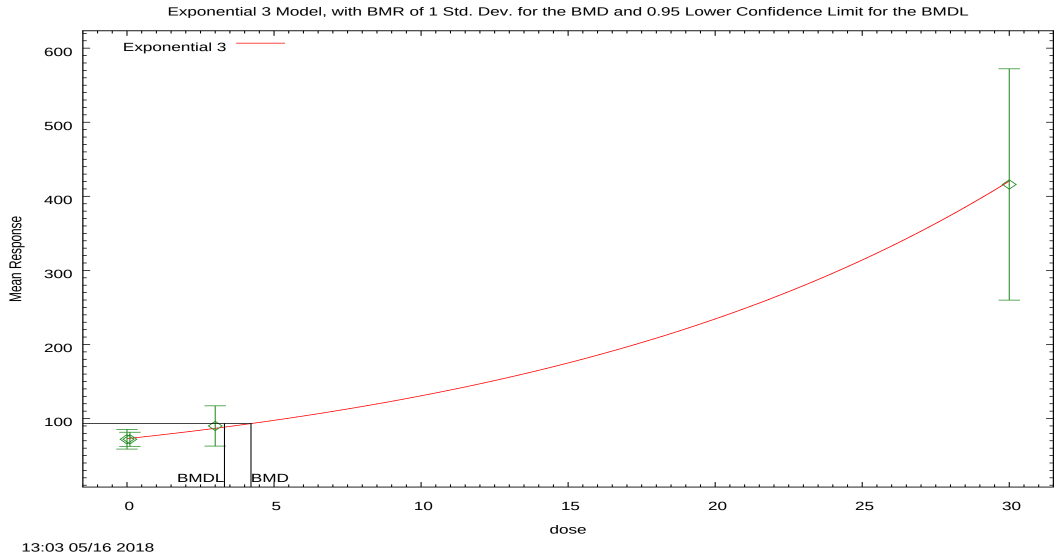

Figure 174. Plot of mean response by dose with fitted curve for Exponential (M3) model with modeled variance for Aspartate Aminotransferase in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 4.21632

BMDL at the 95% confidence level = 3.31493

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-5.56675	-6.39771

rho	2.70341	2.86362
a	72.8571	72.9518
b	0.0584388	0.058146
c	n/a	0
d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	72	72.86	18.5	20.36	-0.1331
0.1	10	72	73.28	13.3	20.52	-0.1979
3	10	90	86.82	38	25.8	0.39
30	10	416	420.6	218.3	217.7	-0.06671

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-206.4091	5	422.8182
A2	-163.1827	8	342.3654
A3	-165.2083	6	342.4166
R	-227.8651	2	459.7303
3	-166.683	4	341.366

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	129.4	6	<0.0001
Test 2	86.45	3	<0.0001
Test 3	4.051	2	0.1319
Test 5a	2.949	2	0.2289

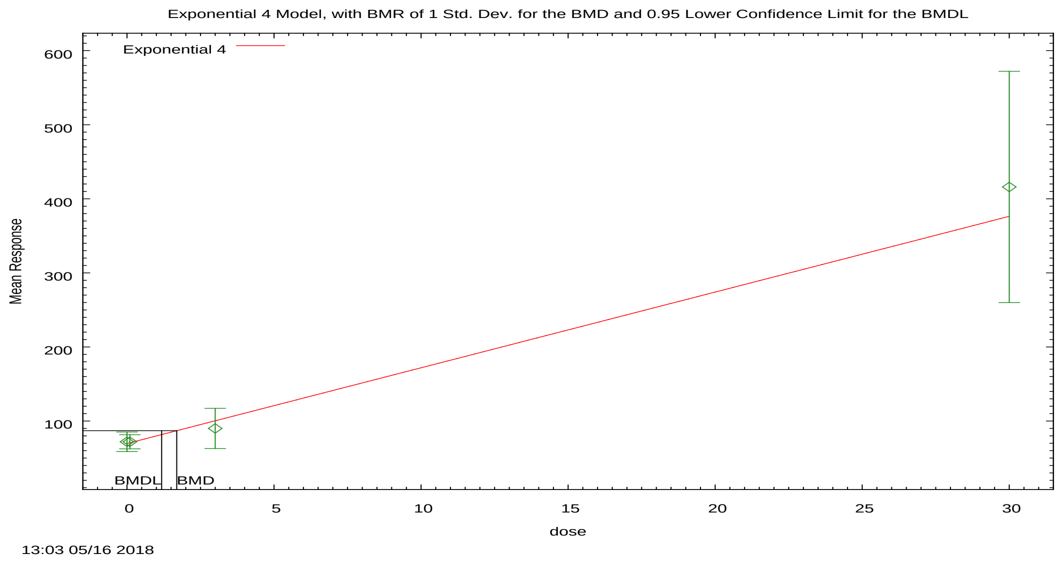

Figure 175. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Aspartate Aminotransferase in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 1.6917

BMDL at the 95% confidence level = 1.17843

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-7.18858	-6.39771
rho	3.03741	2.86362
a	69.653	68.4
b	0.000000376747	0.0000277649

c	389577	6081.87
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	72	69.65	18.5	17.29	0.4291
0.1	10	72	70.68	13.3	17.68	0.2369
3	10	90	100.3	38	30.1	-1.084
30	10	416	376.3	218.3	224.2	0.5594

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-206.4091	5	422.8182
A2	-163.1827	8	342.3654
A3	-165.2083	6	342.4166
R	-227.8651	2	459.7303
4	-165.3979	5	340.7959

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	129.4	6	<0.0001
Test 2	86.45	3	<0.0001
Test 3	4.051	2	0.1319
Test 6a	0.3792	1	0.538

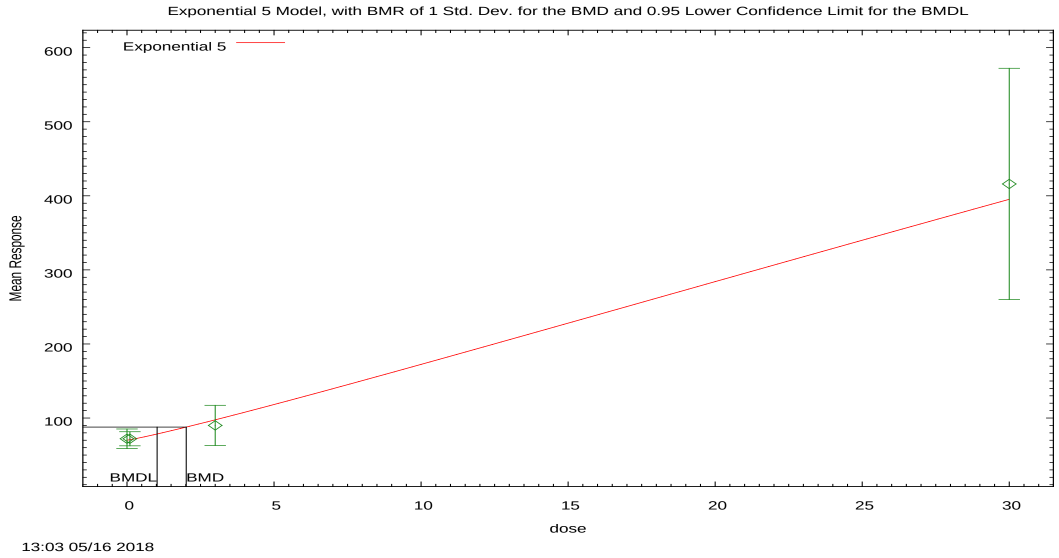

Figure 176. Plot of mean response by dose with fitted curve for Exponential (M5) model with modeled variance for Aspartate Aminotransferase in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 2.01432

BMDL at the 95% confidence level = 1.02455

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-6.63959	-6.39771
rho	2.91695	2.86362
a	70.0359	68.4
b	0.00683709	0.0000277649

c	30.1922	6081.87
d	1.10645	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	72	70.04	18.5	17.77	0.3496
0.1	10	72	70.68	13.3	18	0.232
3	10	90	97.57	38	28.82	-0.8313
30	10	416	395.3	218.3	221.7	0.295

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-206.4091	5	422.8182
A2	-163.1827	8	342.3654
A3	-165.2083	6	342.4166
R	-227.8651	2	459.7303
5	-165.3024	6	342.6049

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	129.4	6	<0.0001
Test 2	86.45	3	<0.0001
Test 3	4.051	2	0.1319
Test 7a	0.1882	0	N/A

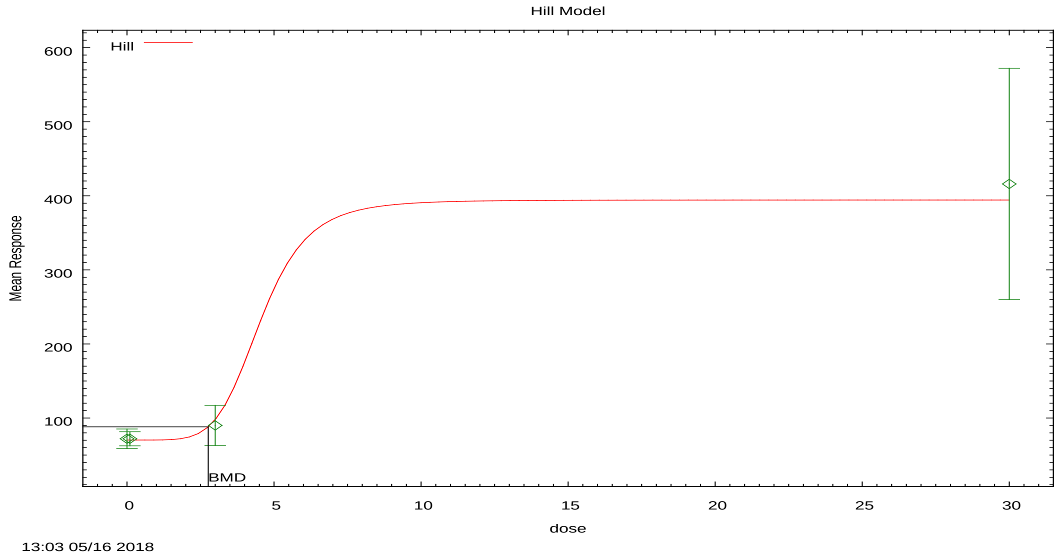

Figure 177. Plot of mean response by dose with fitted curve for Hill model with modeled variance for Aspartate Aminotransferase in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A modeled variance is fit

THE MODEL HAS PROBABLY NOT CONVERGED!!!

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 2.76269

BMDL at the 95% confidence level = error

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-6.70047	9.42582
rho	2.92962	0
intercept	70.319	72
v	323.505	344

n	5.69046	18
k	4.55306	44.2454

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	72	70.3	18.5	17.8	0.298
0.1	10	72	70.3	13.3	17.8	0.298
3	10	90	97.9	38	28.9	-0.861
30	10	416	394	218	222	0.316

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-206.409094	5	422.818187
A2	-163.182702	8	342.365403
A3	-165.208319	6	342.416637
fitted	-165.26618	6	342.532359
R	-227.865145	2	459.73029

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	129.365	6	<0.0001
Test 2	86.4528	3	<0.0001
Test 3	4.05123	2	0.1319
Test 4	0.115722	0	N/A

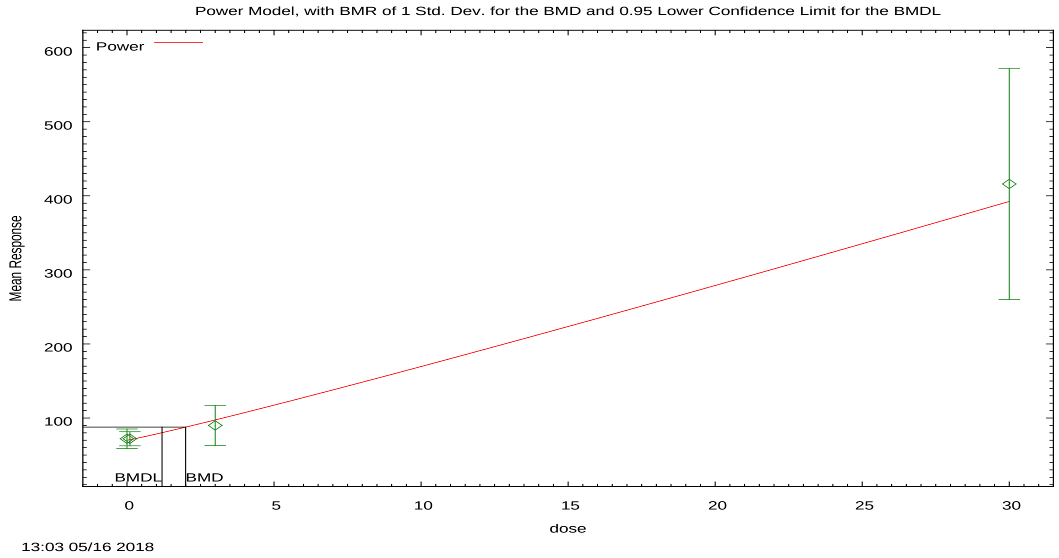

Figure 178. Plot of mean response by dose with fitted curve for Power model with modeled variance for Aspartate Aminotransferase in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 1.99497

BMDL at the 95% confidence level = 1.19209

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-6.63048	9.42582
rho	2.91504	0
control	70.0063	72
slope	8.46672	4.40498
power	1.07297	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	72	70	18.5	17.8	0.355
0.1	10	72	70.7	13.3	18	0.224
3	10	90	97.5	38	28.8	-0.826
30	10	416	396	218	222	0.292

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-206.409094	5	422.818187
A2	-163.182702	8	342.365403
A3	-165.208319	6	342.416637
fitted	-165.307186	5	340.614372
R	-227.865145	2	459.73029

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	129.365	6	<0.0001
Test 2	86.4528	3	<0.0001
Test 3	4.05123	2	0.1319
Test 4	0.197735	1	0.6566

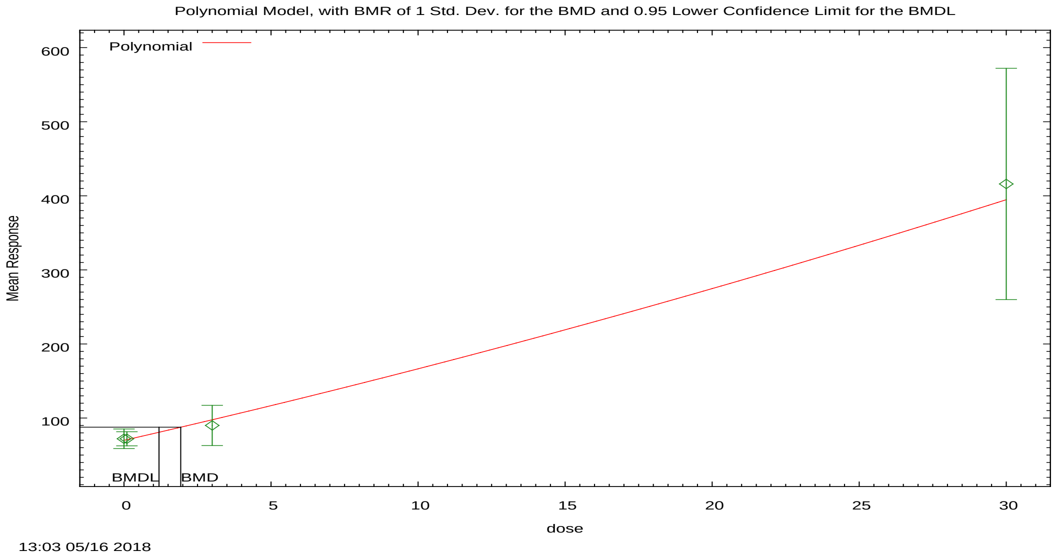

Figure 179. Plot of mean response by dose with fitted curve for Polynomial 3° model with modeled variance for Aspartate Aminotransferase in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 1.92984

BMDL at the 95% confidence level = 1.19025

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-6.64847	9.42582
rho	2.91913	0
beta_0	69.9046	72
beta_1	9.06936	0

beta_2	0.0585628	2.26248
beta_3	0	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	72	69.9	18.5	17.7	0.374
0.1	10	72	70.8	13.3	18.1	0.208
3	10	90	97.6	38	28.9	-0.837
30	10	416	395	218	222	0.304

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-206.409094	5	422.818187
A2	-163.182702	8	342.365403
A3	-165.208319	6	342.416637
fitted	-165.319127	5	340.638255
R	-227.865145	2	459.73029

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	129.365	6	<0.0001
Test 2	86.4528	3	<0.0001
Test 3	4.05123	2	0.1319
Test 4	0.221618	1	0.6378

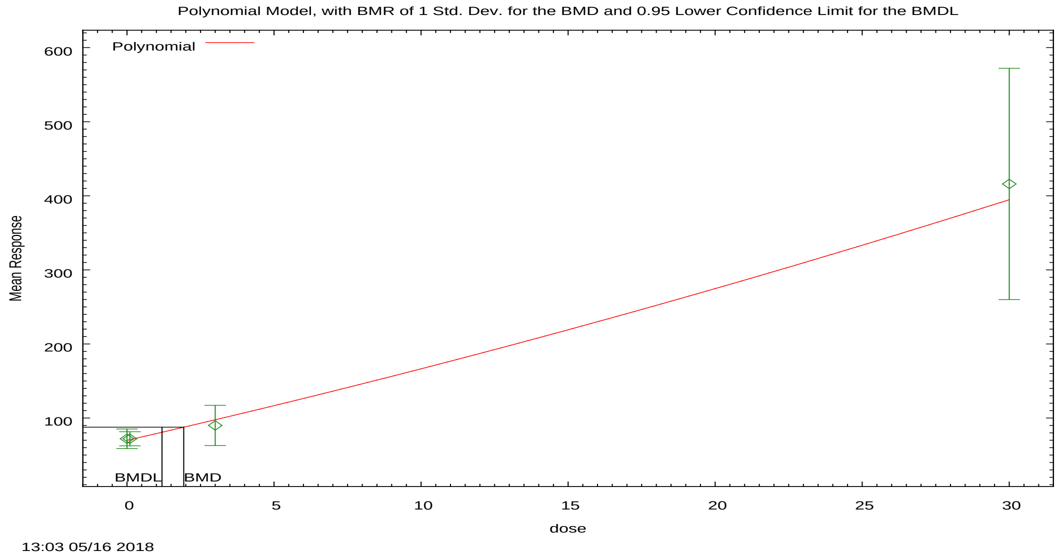

Figure 180. Plot of mean response by dose with fitted curve for Polynomial 2° model with modeled variance for Aspartate Aminotransferase in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + …

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 1.92984

BMDL at the 95% confidence level = 1.19025

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-6.64847	9.42582
rho	2.91913	0
beta_0	69.9045	71.7297
beta_1	9.06937	5.48785

beta_2	0.0585626	0.199594

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	72	69.9	18.5	17.7	0.374
0.1	10	72	70.8	13.3	18.1	0.208
3	10	90	97.6	38	28.9	-0.837
30	10	416	395	218	222	0.304

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-206.409094	5	422.818187
A2	-163.182702	8	342.365403
A3	-165.208319	6	342.416637
fitted	-165.319127	5	340.638255
R	-227.865145	2	459.73029

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	129.365	6	<0.0001
Test 2	86.4528	3	<0.0001
Test 3	4.05123	2	0.1319
Test 4	0.221618	1	0.6378

BMDS WIZARD OUTPUT REPORT

BMDS Summary of H-28548: Subchronic Toxicity 90-Day Gavage Study in Mice – Aspartate Aminotransferase (U/L) in Males

1.21. BMDS Summary of Aspartate Aminotransferase (U/L) Males (90 Day Mice GenX)

Table 21. Summary of BMD Modeling Results for Aspartate Aminotransferase in Males (90-Day Mice); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD$_{1SD}$ (mg/kg/day)	BMDL$_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2)[b]	0.0397	309.68	1.63	1.07	1.52	BMDLs from models that met model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values > 2.0; appropriate variance (continuous data only)) were compared. BMDLs from included models were sufficiently close (< 3-fold difference), so the BMDL from the model with the lowest AIC was selected.
Exponential (M3)[c]	0.0397	309.68	1.63	1.07	1.52	
Exponential (M4) Exponential (M5)[d]	0.244	306.59	0.325	0.141	2.31	
Hill	**0.264**	**306.48**	**0.303**	**0.169**	**1.80**	
Power[e] Polynomial 3°[f] Polynomial 2°[g] Linear	0.0816	308.24	1.06	0.579	1.83	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = <0.0001), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 0.5, and 5 mg/kg/day were -0.08, -0.02, 0.23, -0.16, respectively.

[b] The Exponential (M2) model may appear equivalent to the Exponential (M3) model, however differences exist in digits not displayed in the table.

[c] The Exponential (M3) model may appear equivalent to the Exponential (M2) model, however differences exist in digits not displayed in the table.

[d] For the Exponential (M5) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M4) model.

[e] For the Power model, the power parameter estimate was 1. The models in this row reduced to the Linear model.

[f] For the Polynomial 3° model, the b3 coefficient estimates was 0 (boundary of parameters space). The models in this row reduced to the Polynomial 2° model. For the Polynomial 3° model, the b3 and b2 coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Linear model.

[g] For the Polynomial 2° model, the b2 coefficient estimate was 0 (boundary of parameters space). The models in this row reduced to the Linear model.

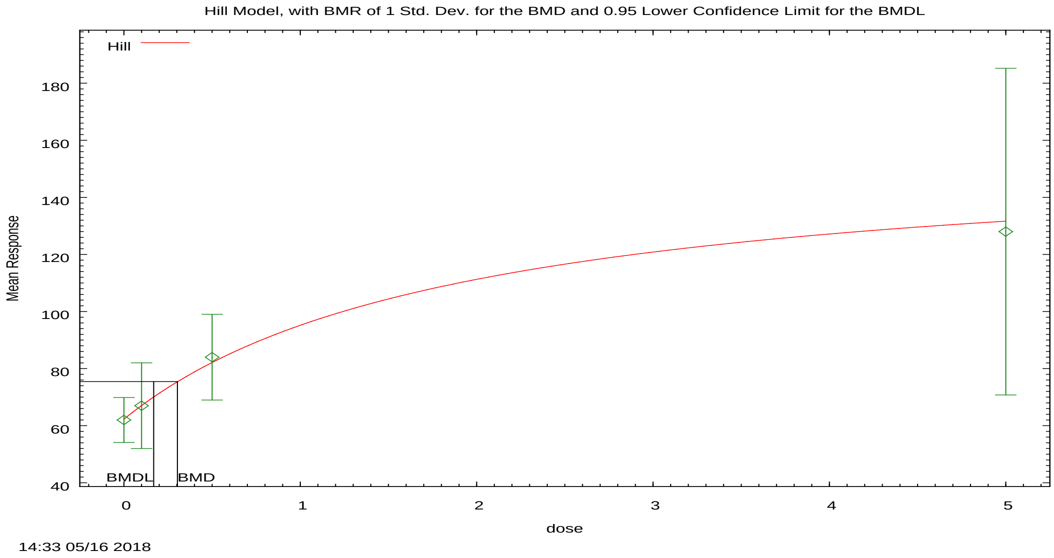

Figure 181. Plot of mean response by dose with fitted curve for Hill model with modeled variance for Aspartate Aminotransferase in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 0.303154

BMDL at the 95% confidence level = 0.168638

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-13.9353	7.52335
rho	4.61691	0
intercept	62.3436	62
v	95.9827	66

n	1	0.405435
k	1.9185	8.375

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	62	62.3	11	13.1	-0.083
0.1	10	67	67.1	21	15.5	-0.0201
0.5	10	84	82.2	21	24.8	0.231
5	10	128	132	80	73.6	-0.159

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-168.359715	5	346.719429
A2	-146.582458	8	309.164915
A3	-147.613821	6	307.227642
fitted	-148.237838	5	306.475676
R	-175.169766	2	354.339532

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	57.1746	6	<0.0001
Test 2	43.5545	3	<0.0001
Test 3	2.06273	2	0.3565
Test 4	1.24803	1	0.2639

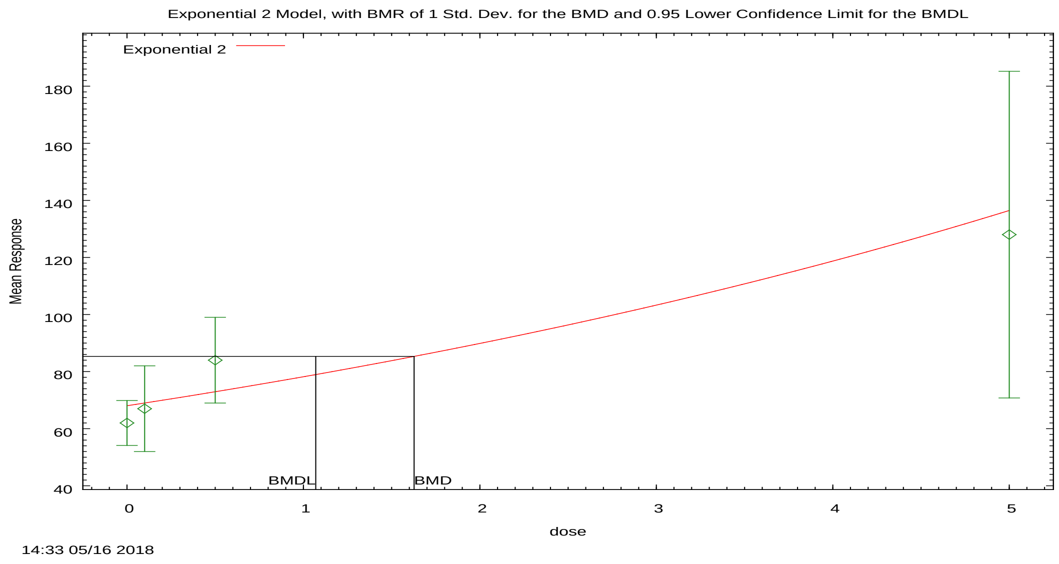

Figure 182. Plot of mean response by dose with fitted curve for Exponential (M2) model with modeled variance for Aspartate Aminotransferase in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 1.6272

BMDL at the 95% confidence level = 1.06964

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-12.5205	-15.1386
rho	4.31775	4.89888
a	68.0377	68.3067
b	0.139181	0.128329

c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	62	68.04	11	17.29	-1.104
0.1	10	67	68.99	21	17.82	-0.3533
0.5	10	84	72.94	21	20.1	1.74
5	10	128	136.5	80	77.69	-0.344

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-168.3597	5	346.7194
A2	-146.5825	8	309.1649
A3	-147.6138	6	307.2276
R	-175.1698	2	354.3395
2	-150.8395	4	309.679

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	57.17	6	<0.0001
Test 2	43.55	3	<0.0001
Test 3	2.063	2	0.3565
Test 4	6.451	2	0.03973

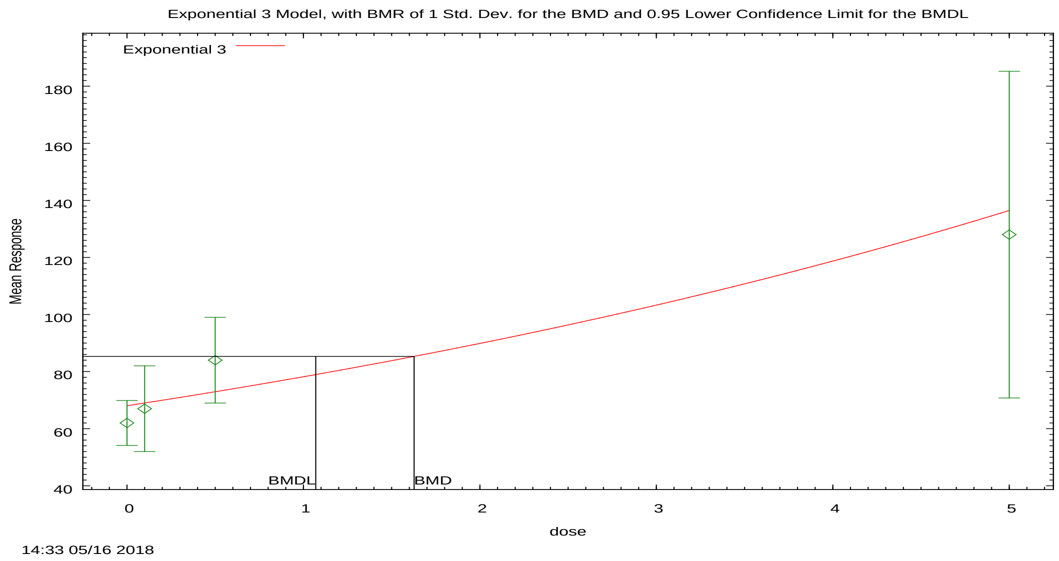

Figure 183. Plot of mean response by dose with fitted curve for Exponential (M3) model with modeled variance for Aspartate Aminotransferase in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 1.62721

BMDL at the 95% confidence level = 1.06964

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-12.5206	-15.1386
rho	4.31776	4.89888
a	68.0377	68.3067
b	0.139181	0.128329

c	n/a	0
d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	62	68.04	11	17.29	-1.104
0.1	10	67	68.99	21	17.82	-0.3533
0.5	10	84	72.94	21	20.1	1.74
5	10	128	136.5	80	77.69	-0.344

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-168.3597	5	346.7194
A2	-146.5825	8	309.1649
A3	-147.6138	6	307.2276
R	-175.1698	2	354.3395
3	-150.8395	4	309.679

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	57.17	6	<0.0001
Test 2	43.55	3	<0.0001
Test 3	2.063	2	0.3565
Test 5a	6.451	2	0.03973

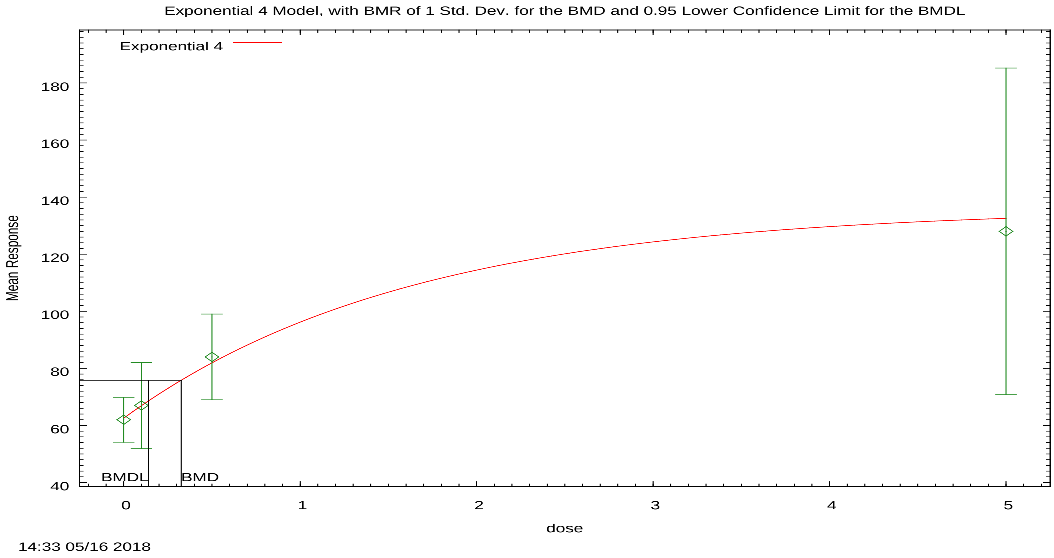

Figure 184. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Aspartate Aminotransferase in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 0.325386

BMDL at the 95% confidence level = 0.141103

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-13.715	-15.1386
rho	4.56656	4.89888
a	62.5469	58.9
b	0.61274	0.496936

c	2.17427	2.28183
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	62	62.55	11	13.28	-0.1303
0.1	10	67	66.91	21	15.49	0.01793
0.5	10	84	81.93	21	24.59	0.2664
5	10	128	132.6	80	73.78	-0.1956

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-168.3597	5	346.7194
A2	-146.5825	8	309.1649
A3	-147.6138	6	307.2276
R	-175.1698	2	354.3395
4	-148.293	5	306.586

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	57.17	6	<0.0001
Test 2	43.55	3	<0.0001
Test 3	2.063	2	0.3565
Test 6a	1.358	1	0.2438

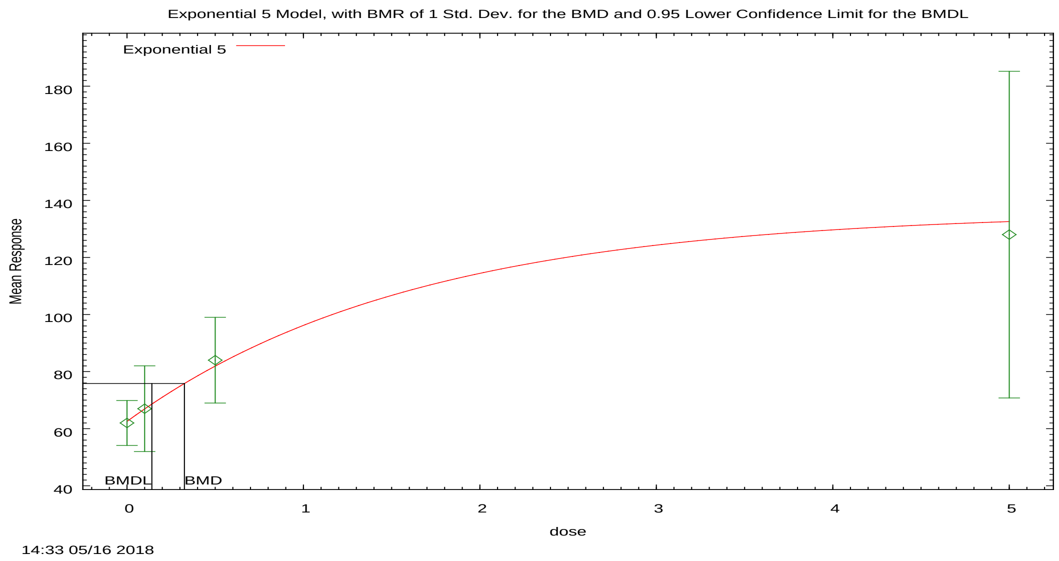

Figure 185. Plot of mean response by dose with fitted curve for Exponential (M5) model with modeled variance for Aspartate Aminotransferase in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 0.325386

BMDL at the 95% confidence level = 0.141103

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-13.7149	-15.1386
rho	4.56655	4.89888
a	62.5469	58.9
b	0.612739	0.496936

c	2.17427	2.28183
d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	62	62.55	11	13.28	-0.1303
0.1	10	67	66.91	21	15.49	0.01793
0.5	10	84	81.93	21	24.59	0.2664
5	10	128	132.6	80	73.78	-0.1956

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-168.3597	5	346.7194
A2	-146.5825	8	309.1649
A3	-147.6138	6	307.2276
R	-175.1698	2	354.3395
5	-148.293	5	306.586

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	57.17	6	<0.0001
Test 2	43.55	3	<0.0001
Test 3	2.063	2	0.3565
Test 7a	1.358	1	0.2438

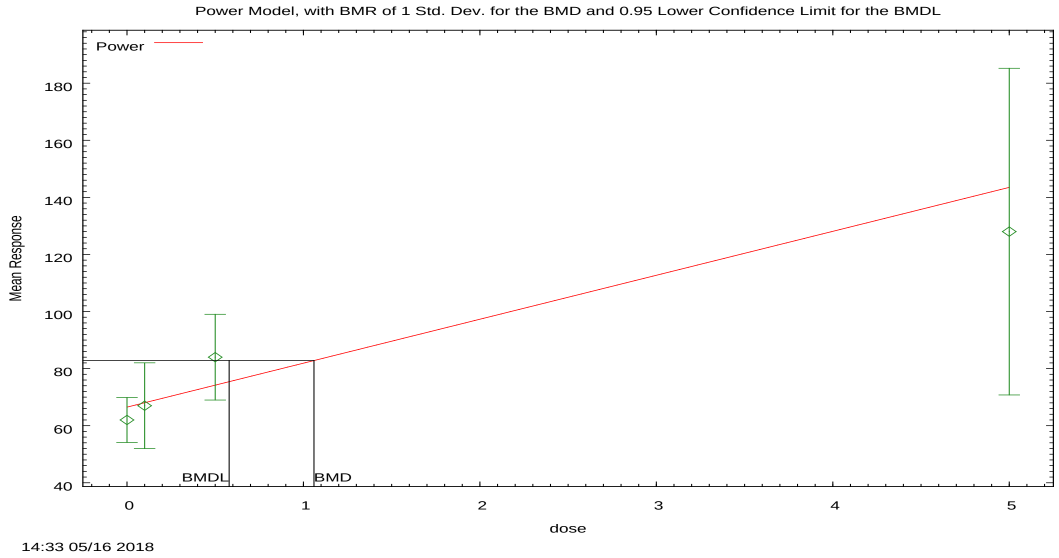

Figure 186. Plot of mean response by dose with fitted curve for Power model with modeled variance for Aspartate Aminotransferase in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 1.05967

BMDL at the 95% confidence level = 0.579048

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-11.6677	7.52335
rho	4.10907	0
control	66.539	62
slope	15.3746	23.2973
power	1	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	62	66.5	11	16.3	-0.881
0.1	10	67	68.1	21	17.1	-0.199
0.5	10	84	74.2	21	20.4	1.52
5	10	128	143	80	78.9	-0.618

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-168.359715	5	346.719429
A2	-146.582458	8	309.164915
A3	-147.613821	6	307.227642
fitted	-150.119997	4	308.239995
R	-175.169766	2	354.339532

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	57.1746	6	<0.0001
Test 2	43.5545	3	<0.0001
Test 3	2.06273	2	0.3565
Test 4	5.01235	2	0.08158

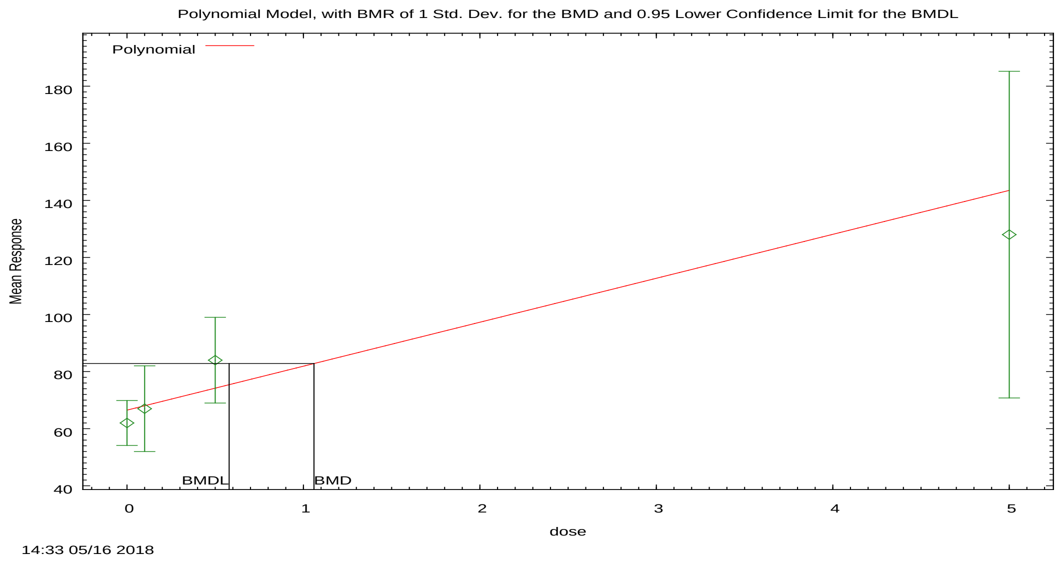

Figure 187. Plot of mean response by dose with fitted curve for Polynomial 3° model with modeled variance for Aspartate Aminotransferase in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 1.05967

BMDL at the 95% confidence level = 0.579048

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-11.6677	7.52335
rho	4.10908	0
beta_0	66.539	62
beta_1	15.3746	51.5832

beta_2	0	0
beta_3	0	1.6644

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	62	66.5	11	16.3	-0.881
0.1	10	67	68.1	21	17.1	-0.199
0.5	10	84	74.2	21	20.4	1.52
5	10	128	143	80	78.9	-0.618

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-168.359715	5	346.719429
A2	-146.582458	8	309.164915
A3	-147.613821	6	307.227642
fitted	-150.119997	4	308.239995
R	-175.169766	2	354.339532

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	57.1746	6	<0.0001
Test 2	43.5545	3	<0.0001
Test 3	2.06273	2	0.3565
Test 4	5.01235	2	0.08158

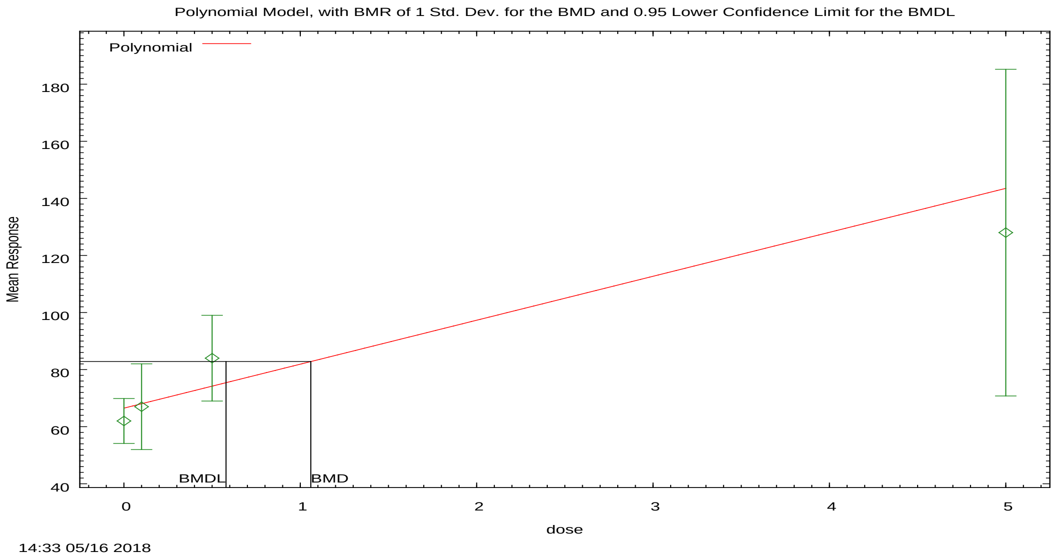

Figure 188. Plot of mean response by dose with fitted curve for Polynomial 2° model with modeled variance for Aspartate Aminotransferase in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 1.05967

BMDL at the 95% confidence level = 0.579048

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-11.6676	7.52335
rho	4.10907	0
beta_0	66.539	62.1539
beta_1	15.3746	47.1787

beta_2	0	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	62	66.5	11	16.3	-0.881
0.1	10	67	68.1	21	17.1	-0.199
0.5	10	84	74.2	21	20.4	1.52
5	10	128	143	80	78.9	-0.618

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-168.359715	5	346.719429
A2	-146.582458	8	309.164915
A3	-147.613821	6	307.227642
fitted	-150.119997	4	308.239995
R	-175.169766	2	354.339532

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	57.1746	6	<0.0001
Test 2	43.5545	3	<0.0001
Test 3	2.06273	2	0.3565
Test 4	5.01235	2	0.08158

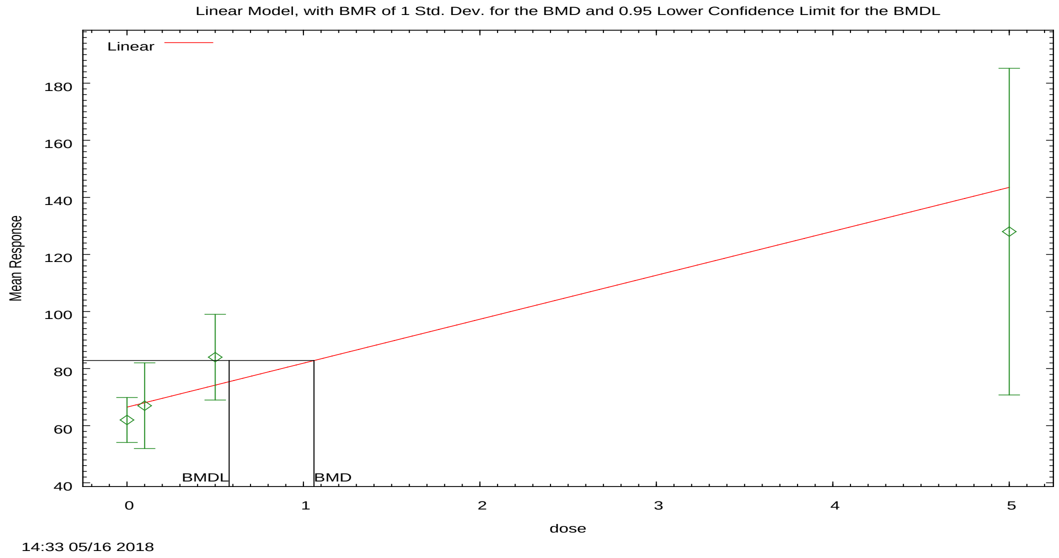

Figure 189. Plot of mean response by dose with fitted curve for Linear model with modeled variance for Aspartate Aminotransferase in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 1.05967

BMDL at the 95% confidence level = 0.579048

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-11.6677	7.52335
rho	4.10907	0
beta_0	66.539	68.2684
beta_1	15.3746	12.1297

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	62	66.5	11	16.3	-0.881
0.1	10	67	68.1	21	17.1	-0.199
0.5	10	84	74.2	21	20.4	1.52
5	10	128	143	80	78.9	-0.618

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-168.359715	5	346.719429
A2	-146.582458	8	309.164915
A3	-147.613821	6	307.227642
fitted	-150.119997	4	308.239995
R	-175.169766	2	354.339532

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	57.1746	6	<0.0001
Test 2	43.5545	3	<0.0001
Test 3	2.06273	2	0.3565
Test 4	5.01235	2	0.08158

BMDS WIZARD OUTPUT REPORT

Summary of 28-Day Oral (Gavage) Toxicity Study of H-28397 in Mice with a 28-day Recovery – Sorbitol Dehydrogenase (U/L) in Females

1.22. BMDS Summary of Sorbitol Dehydrogenase (U/L) Females (28 Day Mice GenX)

Table 22. Summary of BMD Modeling Results for Sorbitol Dehydrogenase in Females (28-Day Mice); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD_{1SD} (mg/kg/day)	$BMDL_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2)	**0.760**	**202.94**	**8.38**	**6.29**	1.33	BMDLs from models that met model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values > 2.0; appropriate variance (continuous data only)) were compared. BMDLs from included models were sufficiently close (< 3-fold difference), so the BMDL from the model with the lowest AIC was selected.
Exponential (M3)	0.493	204.86	10.2	6.32	1.61	
Exponential (M4)	0.290	205.51	5.77	3.81	1.51	
Exponential (M5)	N/A[b]	206.87	9.20	3.18	2.89	
Hill	N/A[b]	206.87	9.18	error[c]	error	
Power	0.490	204.87	9.20	4.00	2.30	
Polynomial 3°	0.499	204.85	11.6	4.01	2.89	
Polynomial 2°	0.497	204.85	10.1	4.01	2.53	
Linear	0.571	203.51	5.77	3.81	1.51	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = <0.0001), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 3, and 30 mg/kg/day were -0.56, 0.75, -0.22, 0.03, respectively.
[b] No available degrees of freedom to calculate a goodness of fit value.
[c] BMD or BMDL computation failed for this model.

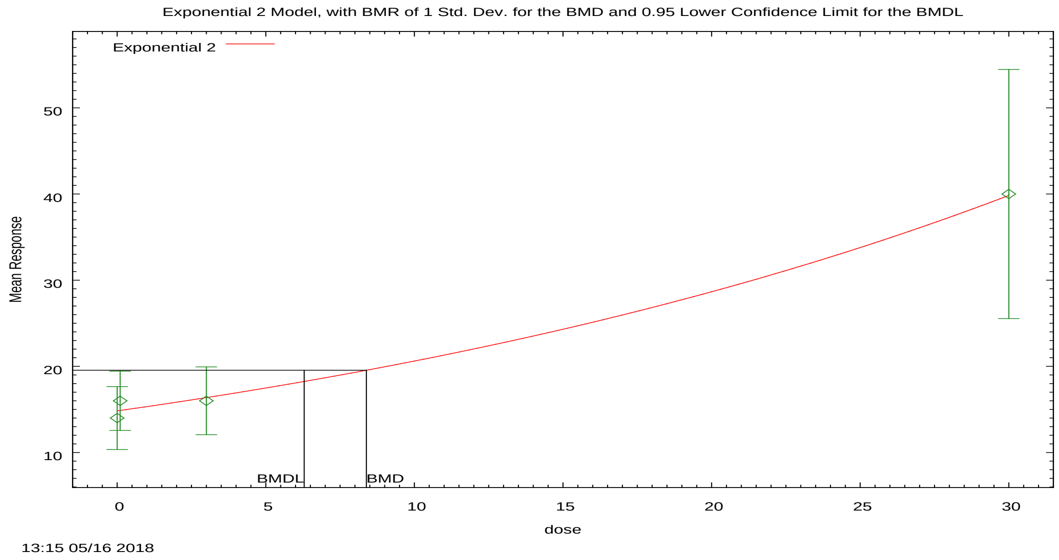

Figure 190. Plot of mean response by dose with fitted curve for Exponential (M2) model with modeled variance for Sorbitol Dehydrogenase in Females

(28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 8.38417

BMDL at the 95% confidence level = 6.29287

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-4.53233	-4.38245
rho	2.83099	2.80856
a	14.831	14.7983
b	0.0329331	0.0330832
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	14	14.83	5.1	4.72	-0.5572
0.1	10	16	14.88	4.8	4.74	0.7475
3	10	16	16.37	5.5	5.42	-0.2163
30	10	40	39.83	20.2	19.1	0.02755

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-113.9461	5	237.8923

A2	-96.97566	8	209.9513
A3	-97.19629	6	206.3926
R	-128.2687	2	260.5375
2	-97.47089	4	202.9418

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	62.59	6	<0.0001
Test 2	33.94	3	<0.0001
Test 3	0.4413	2	0.802
Test 4	0.5492	2	0.7599

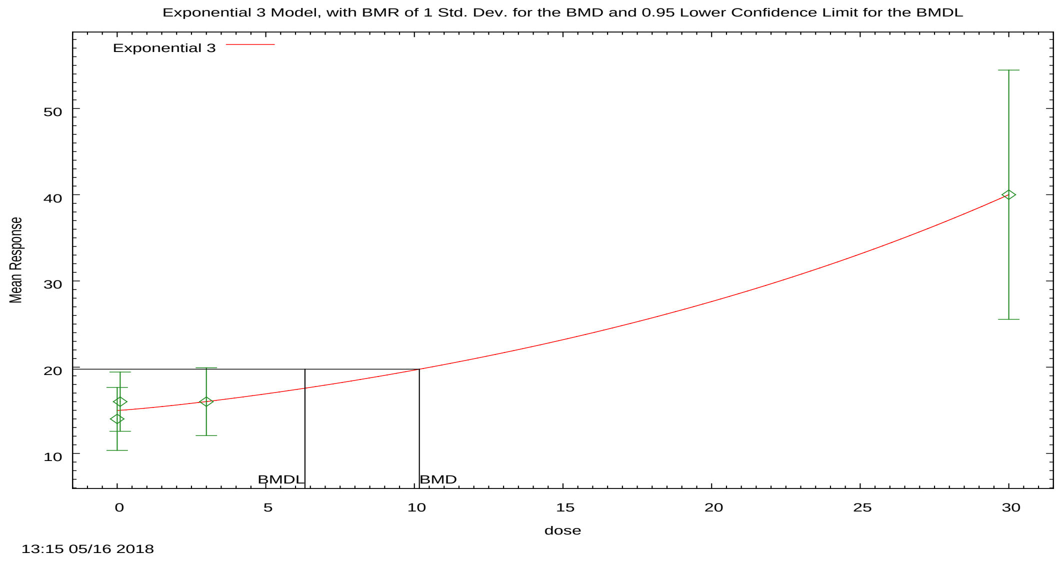

Figure 191. Plot of mean response by dose with fitted curve for Exponential (M3) model with modeled variance for Sorbitol Dehydrogenase in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 10.1665

BMDL at the 95% confidence level = 6.31813

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-4.51977	-4.38245
rho	2.82595	2.80856
a	14.9835	14.7983
b	0.0328197	0.0330832
c	n/a	0
d	1.16951	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	14	14.98	5.1	4.78	-0.6503
0.1	10	16	15	4.8	4.79	0.6587
3	10	16	16.01	5.5	5.25	-0.007944
30	10	40	40	20.2	19.15	-0.0004674

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-113.9461	5	237.8923
A2	-96.97566	8	209.9513
A3	-97.19629	6	206.3926
R	-128.2687	2	260.5375
3	-97.4308	5	204.8616

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value

Test 1	62.59	6	<0.0001
Test 2	33.94	3	<0.0001
Test 3	0.4413	2	0.802
Test 5a	0.469	1	0.4934

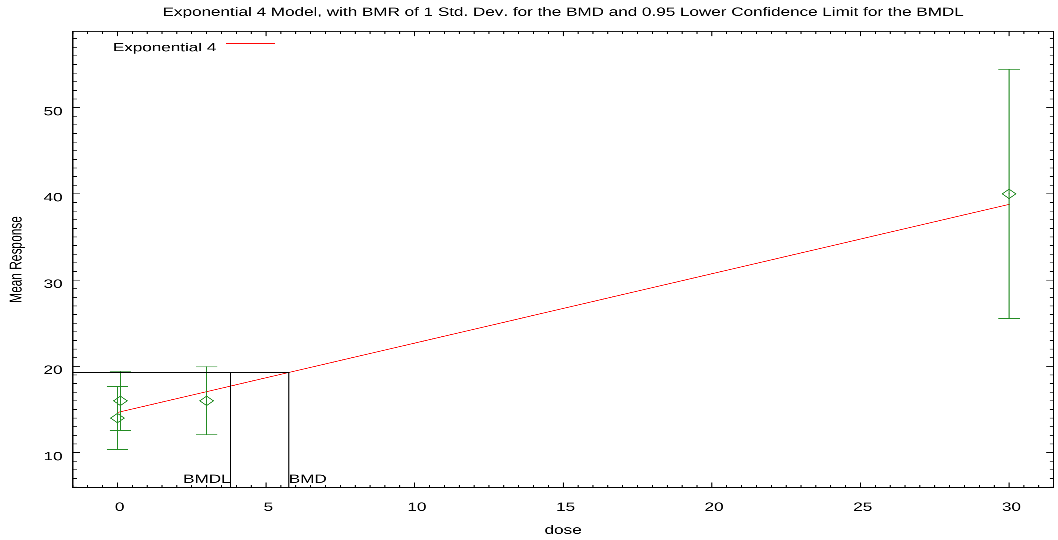

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Figure 192. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Sorbitol Dehydrogenase in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 5.76843

BMDL at the 95% confidence level = 3.80958

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-4.70037	-4.38245
rho	2.89424	2.80856
a	14.6511	13.3
b	0.00000048235	0.000224083
c	113815	300.752
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	14	14.65	5.1	4.64	-0.4438
0.1	10	16	14.73	4.8	4.68	0.8577
3	10	16	17.06	5.5	5.78	-0.5817
30	10	40	38.78	20.2	18.98	0.2032

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-113.9461	5	237.8923
A2	-96.97566	8	209.9513
A3	-97.19629	6	206.3926
R	-128.2687	2	260.5375
4	-97.75732	5	205.5146

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	62.59	6	<0.0001
Test 2	33.94	3	<0.0001
Test 3	0.4413	2	0.802
Test 6a	1.122	1	0.2895

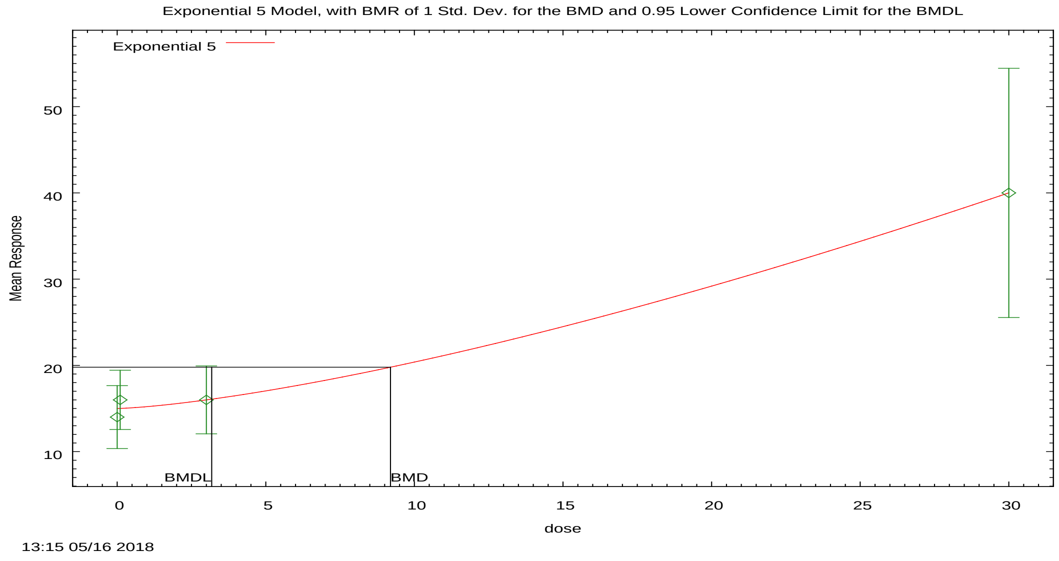

Figure 193. Plot of mean response by dose with fitted curve for Exponential (M5) model with modeled variance for Sorbitol Dehydrogenase in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 9.19545

BMDL at the 95% confidence level = 3.17978

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-4.52007	-4.38245
rho	2.82611	2.80856
a	14.9966	13.3
b	0.000536969	0.000224083

c	538.921	300.752
d	1.39883	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	14	15	5.1	4.79	-0.6581
0.1	10	16	15.01	4.8	4.79	0.6564
3	10	16	16	5.5	5.25	0.002225
30	10	40	40	20.2	19.16	-0.0004013

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-113.9461	5	237.8923
A2	-96.97566	8	209.9513
A3	-97.19629	6	206.3926
R	-128.2687	2	260.5375
5	-97.43429	6	206.8686

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	62.59	6	<0.0001
Test 2	33.94	3	<0.0001
Test 3	0.4413	2	0.802
Test 7a	0.476	0	N/A

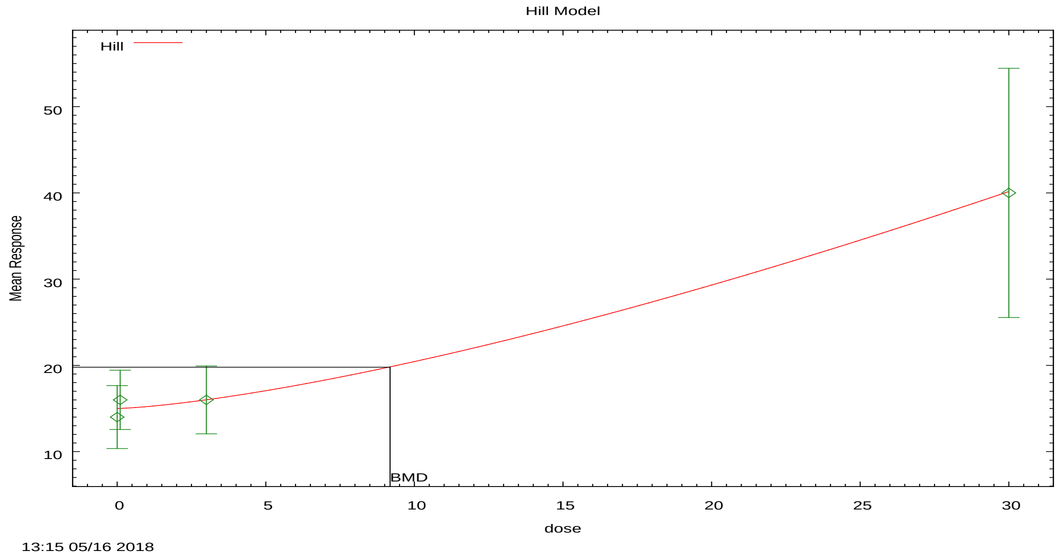

Figure 194. Plot of mean response by dose with fitted curve for Hill model with modeled variance for Sorbitol Dehydrogenase in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 9.18221

BMDL at the 95% confidence level = error

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-4.52007	4.80267
rho	2.82611	0
intercept	14.9967	14
v	2989.43	26
n	1.40179	0.663874

k	904.87	44.625

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	14	15	5.1	4.79	-0.658
0.1	10	16	15	4.8	4.79	0.656
3	10	16	16	5.5	5.25	0.00231
30	10	40	40	20.2	19.2	-0.000401

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-113.946143	5	237.892286
A2	-96.975661	8	209.951322
A3	-97.196287	6	206.392573
fitted	-97.434324	6	206.868648
R	-128.268737	2	260.537474

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	62.5862	6	<0.0001
Test 2	33.941	3	<0.0001
Test 3	0.441251	2	0.802
Test 4	0.476075	0	N/A

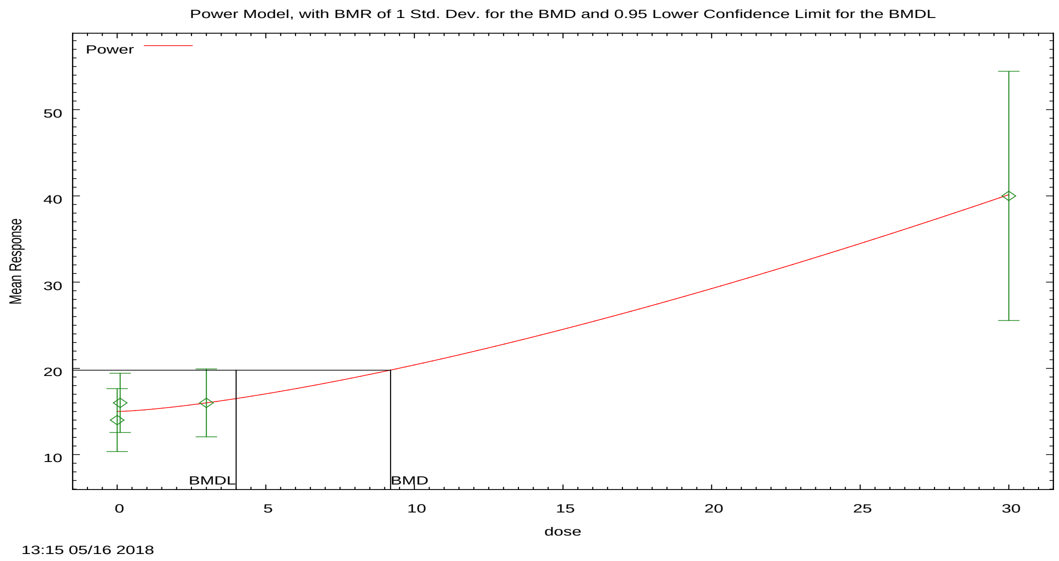

Figure 195. Plot of mean response by dose with fitted curve for Power model with modeled variance for Sorbitol Dehydrogenase in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 9.1984

BMDL at the 95% confidence level = 4.00238

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-4.52007	4.80267
rho	2.82611	0
control	14.9966	14
slope	0.215183	6.32358
power	1.39815	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	14	15	5.1	4.79	-0.658
0.1	10	16	15	4.8	4.79	0.656
3	10	16	16	5.5	5.25	0.0022
30	10	40	40	20.2	19.2	-0.000401

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-113.946143	5	237.892286
A2	-96.975661	8	209.951322
A3	-97.196287	6	206.392573
fitted	-97.434286	5	204.868572
R	-128.268737	2	260.537474

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	62.5862	6	<0.0001
Test 2	33.941	3	<0.0001
Test 3	0.441251	2	0.802
Test 4	0.475999	1	0.4902

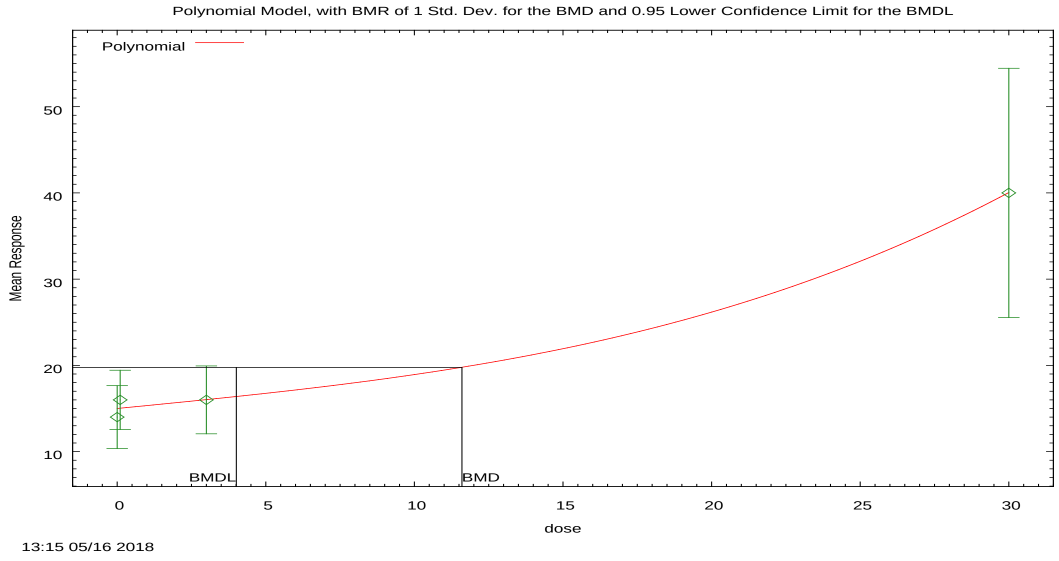

Figure 196. Plot of mean response by dose with fitted curve for Polynomial 3° model with modeled variance for Sorbitol Dehydrogenase in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 11.5999

BMDL at the 95% confidence level = 4.00852

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-4.51875	4.80267
rho	2.82552	0
beta_0	14.9776	14
beta_1	0.337764	20.7336
beta_2	0	0

beta_3	0.000551898	0.223213

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	14	15	5.1	4.78	-0.647
0.1	10	16	15	4.8	4.79	0.652
3	10	16	16	5.5	5.25	-0.00346
30	10	40	40	20.2	19.2	-0.00194

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-113.946143	5	237.892286
A2	-96.975661	8	209.951322
A3	-97.196287	6	206.392573
fitted	-97.425014	5	204.850029
R	-128.268737	2	260.537474

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	62.5862	6	<0.0001
Test 2	33.941	3	<0.0001
Test 3	0.441251	2	0.802
Test 4	0.457455	1	0.4988

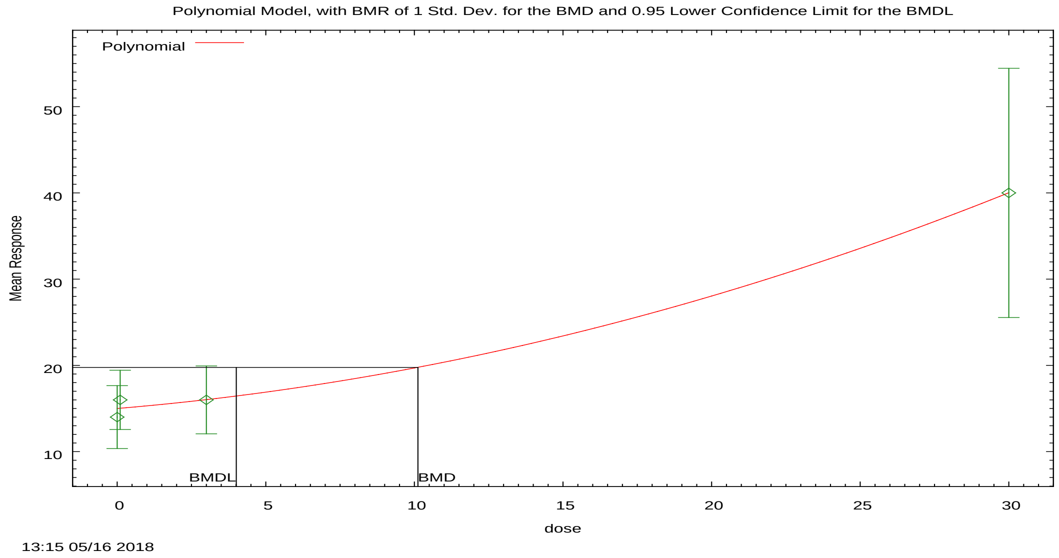

Figure 197. Plot of mean response by dose with fitted curve for Polynomial 2° model with modeled variance for Sorbitol Dehydrogenase in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 10.1185

BMDL at the 95% confidence level = 4.00732

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-4.51944	4.80267
rho	2.82578	0
beta_0	14.9795	14.9664
beta_1	0.288303	0.303817
beta_2	0.0181987	0.0176875

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	14	15	5.1	4.78	-0.648
0.1	10	16	15	4.8	4.79	0.654
3	10	16	16	5.5	5.25	-0.00494
30	10	40	40	20.2	19.2	-0.00122

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-113.946143	5	237.892286
A2	-96.975661	8	209.951322
A3	-97.196287	6	206.392573
fitted	-97.426827	5	204.853653
R	-128.268737	2	260.537474

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	62.5862	6	<0.0001
Test 2	33.941	3	<0.0001
Test 3	0.441251	2	0.802
Test 4	0.46108	1	0.4971

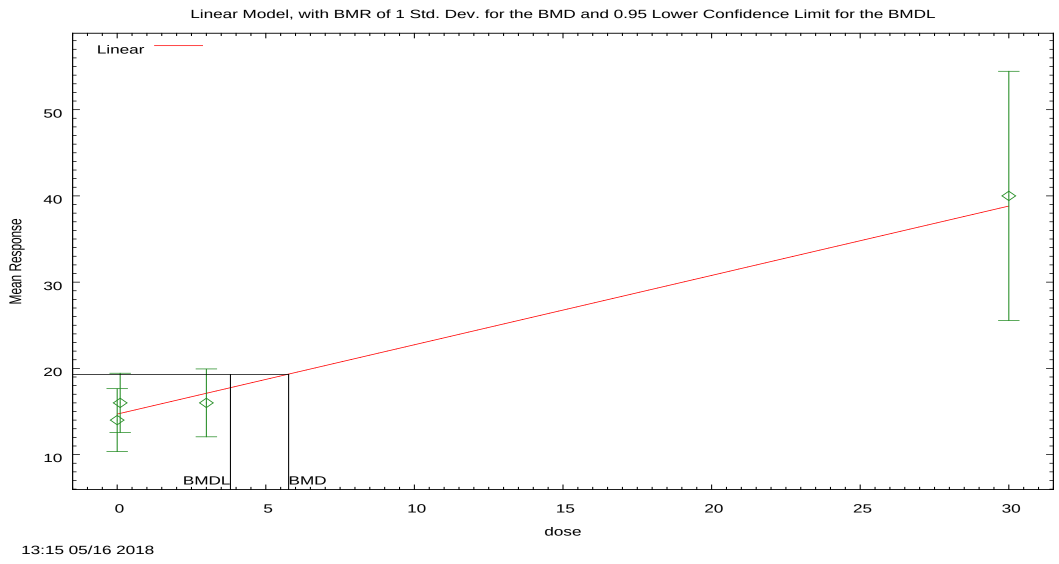

Figure 198. Plot of mean response by dose with fitted curve for Linear model with modeled variance for Sorbitol Dehydrogenase in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 5.76847

BMDL at the 95% confidence level = 3.8096

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-4.70038	4.80267
rho	2.89425	0
beta_0	14.6511	14.4909
beta_1	0.804312	0.847022

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	14	14.7	5.1	4.64	-0.444
0.1	10	16	14.7	4.8	4.68	0.858
3	10	16	17.1	5.5	5.78	-0.582
30	10	40	38.8	20.2	19	0.203

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-113.946143	5	237.892286
A2	-96.975661	8	209.951322
A3	-97.196287	6	206.392573
fitted	-97.757311	4	203.514621
R	-128.268737	2	260.537474

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	62.5862	6	<0.0001
Test 2	33.941	3	<0.0001
Test 3	0.441251	2	0.802
Test 4	1.12205	2	0.5706

BMDS WIZARD OUTPUT REPORT

BMDS Summary of H-28548: Subchronic Toxicity 90-Day Gavage Study in Mice – Sorbitol Dehydrogenase (U/L) in Females

1.23. BMDS Summary of Sorbitol Dehydrogenase (U/L) Females (90 Day Mice GenX)

Table 23. Summary of BMD Modeling Results for Sorbitol Dehydrogenase in Females (90-day Mice); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD_{1SD} (mg/kg/day)	$BMDL_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2)	<0.0001	194.11	3.87	2.56	1.51	No models met all model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). No BMDL was selected.
Exponential (M3)	<0.0001	195.56	4.77	2.67	1.79	
Exponential (M4)	<0.0001	205.81	error[b]	0	error	
Exponential (M5)	N/A[c]	207.81	error[b]	0	error	
Hill	N/A[c]	197.56	4.79	error[b]	error	
Power	<0.0001	195.56	4.83	2.42	2.00	
Polynomial 3°	<0.0001	193.56	4.53	3.35	1.35	
Polynomial 2°	<0.0001	193.61	4.31	3.34	1.29	
Linear	<0.0001	194.21	3.74	2.28	1.64	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = <0.0001, BMDS Test 3 *p*-value = 0.135), no model was selected as a best-fitting model.
[b] BMD or BMDL computation failed for this model.
[c] No available degrees of freedom to calculate a goodness of fit value.

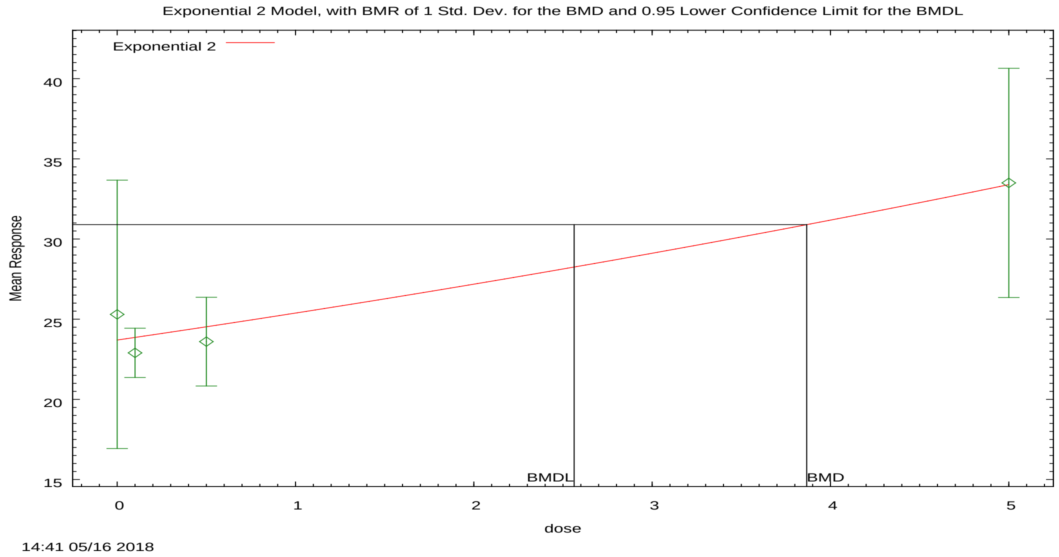

Figure 199. Plot of mean response by dose with fitted curve for Exponential (M2) model with modeled variance for Sorbitol Dehydrogenase in Females (90-day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 3.86673

BMDL at the 95% confidence level = 2.56258

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	1.13752	-16.9882
rho	0.887614	6.23567
a	23.6987	23.6811
b	0.0685802	0.0684587
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	25.3	23.7	11.7	7.2	0.7037
0.1	9	22.9	23.86	2	7.22	-0.3997
0.5	9	23.6	24.53	3.6	7.31	-0.3799
5	9	33.5	33.39	9.3	8.38	0.03863

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-92.85805	5	195.7161

A2	-78.81587	8	173.6317
A3	-80.8164	6	173.6328
R	-97.90648	2	199.813
2	-93.05697	4	194.1139

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	38.18	6	<0.0001
Test 2	28.08	3	<0.0001
Test 3	4.001	2	0.1353
Test 4	24.48	2	<0.0001

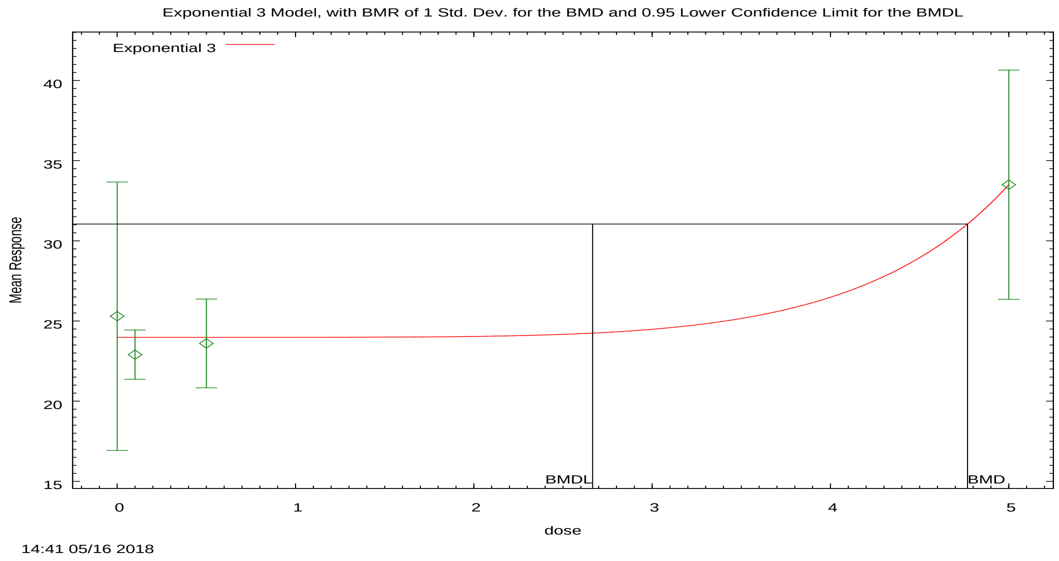

Figure 200. Plot of mean response by dose with fitted curve for Exponential (M3) model with modeled variance for Sorbitol Dehydrogenase in Females (90-day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 4.76845

BMDL at the 95% confidence level = 2.66627

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-0.200899	-16.9882
rho	1.29377	6.23567
a	23.9821	23.6811
b	0.16356	0.0684587
c	n/a	0
d	5.44847	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	25.3	23.98	11.7	7.06	0.59
0.1	9	22.9	23.98	2	7.06	-0.4596
0.5	9	23.6	23.98	3.6	7.06	-0.1623
5	9	33.5	33.5	9.3	8.77	-0.000003461

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-92.85805	5	195.7161
A2	-78.81587	8	173.6317
A3	-80.8164	6	173.6328
R	-97.90648	2	199.813
3	-92.77751	5	195.555

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value

Test 1	38.18	6	<0.0001
Test 2	28.08	3	<0.0001
Test 3	4.001	2	0.1353
Test 5a	23.92	1	<0.0001

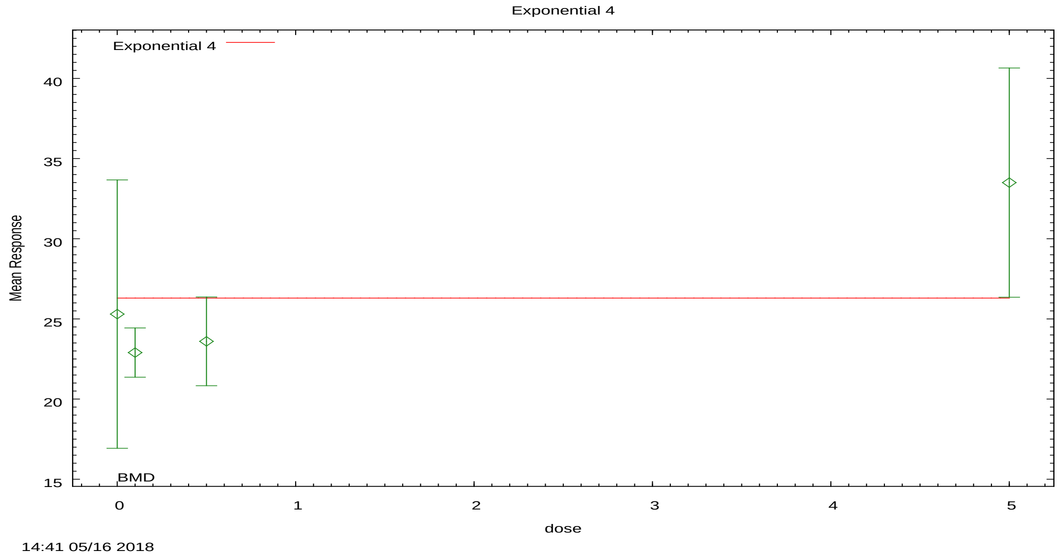

Figure 201. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Sorbitol Dehydrogenase in Females (90-day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = error

BMDL at the 95% confidence level = 0

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	51.292	-16.9882
rho	-14.3754	6.23567
a	26.2973	21.755
b	0.0742061	0.0604162
c	1	3.07975
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	25.3	26.3	11.7	8.55	-0.3688
0.1	9	22.9	26.3	2	8.55	-1.192
0.5	9	23.6	26.3	3.6	8.55	-0.9462
5	9	33.5	26.3	9.3	8.55	2.527

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-92.85805	5	195.7161
A2	-78.81587	8	173.6317
A3	-80.8164	6	173.6328
R	-97.90648	2	199.813
4	-97.90648	5	205.813

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	38.18	6	<0.0001
Test 2	28.08	3	<0.0001
Test 3	4.001	2	0.1353
Test 6a	34.18	1	<0.0001

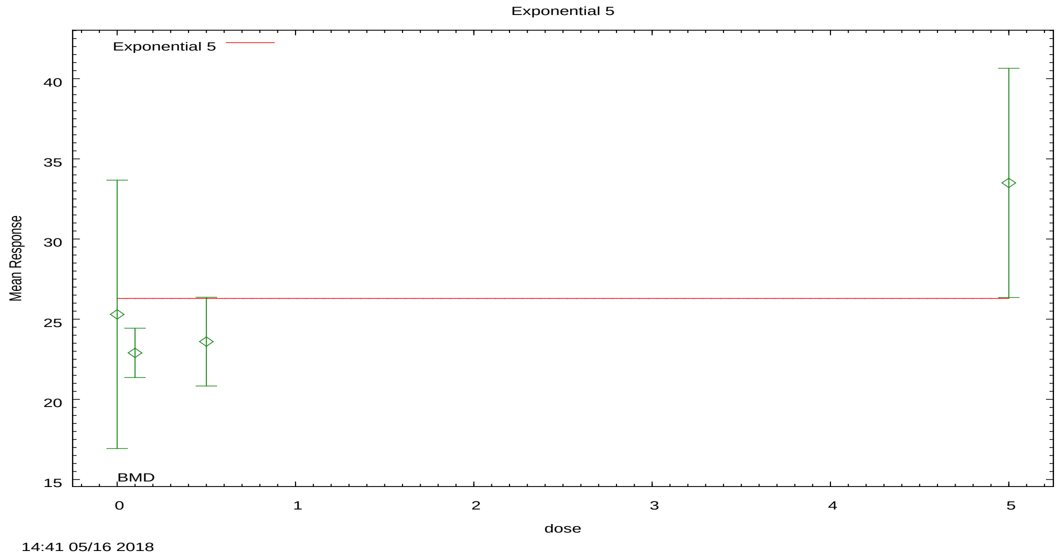

Figure 202. Plot of mean response by dose with fitted curve for Exponential (M5) model with modeled variance for Sorbitol Dehydrogenase in Females (90-day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = error

BMDL at the 95% confidence level = 0

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	47.8211	-16.9882
rho	-13.3138	6.23567
a	26.2973	21.755
b	0.0298942	0.0604162

c	1	3.07975
d	1.00001	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	25.3	26.3	11.7	8.55	-0.3688
0.1	9	22.9	26.3	2	8.55	-1.192
0.5	9	23.6	26.3	3.6	8.55	-0.9462
5	9	33.5	26.3	9.3	8.55	2.527

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-92.85805	5	195.7161
A2	-78.81587	8	173.6317
A3	-80.8164	6	173.6328
R	-97.90648	2	199.813
5	-97.90648	6	207.813

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	38.18	6	<0.0001
Test 2	28.08	3	<0.0001
Test 3	4.001	2	0.1353
Test 7a	34.18	0	N/A

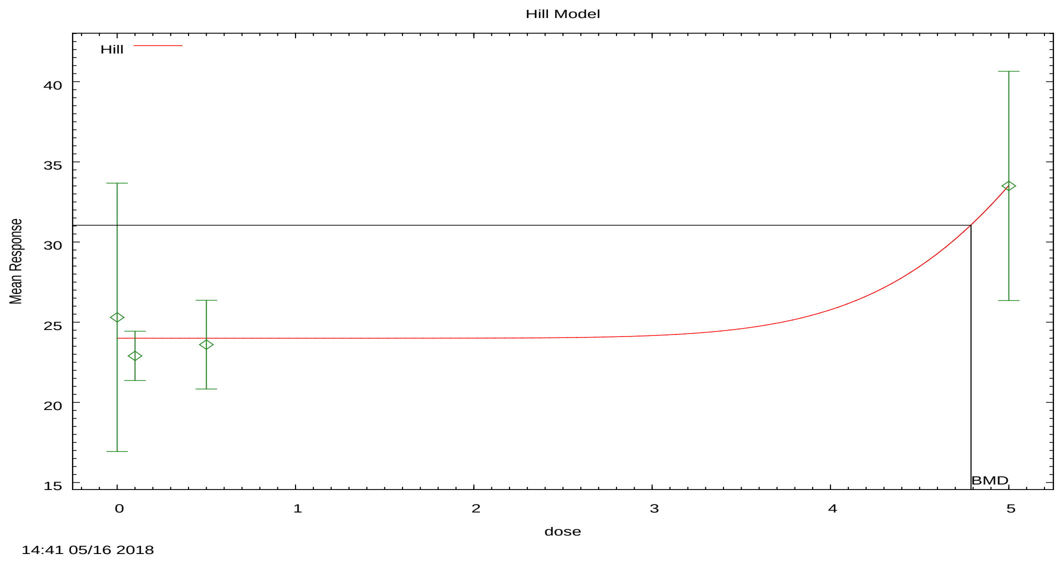

Figure 203. Plot of mean response by dose with fitted curve for Hill model with modeled variance for Sorbitol Dehydrogenase in Females (90-day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A modeled variance is fit

THE MODEL HAS PROBABLY NOT CONVERGED!!!

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 4.78804

BMDL at the 95% confidence level = error

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-0.200962	4.13376
rho	1.29379	0
intercept	23.9821	25.3
v	46.0799	8.2

n	8.38549	1
k	5.87047	6.86364

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	25.3	24	11.7	7.06	0.59
0.1	9	22.9	24	2	7.06	-0.46
0.5	9	23.6	24	3.6	7.06	-0.162
5	9	33.5	33.5	9.3	8.77	0.00000092

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-92.858049	5	195.716098
A2	-78.815874	8	173.631747
A3	-80.816402	6	173.632804
fitted	-92.777505	6	197.555009
R	-97.906482	2	199.812964

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	38.1812	6	<0.0001
Test 2	28.0844	3	<0.0001
Test 3	4.00106	2	0.1353
Test 4	23.9222	0	N/A

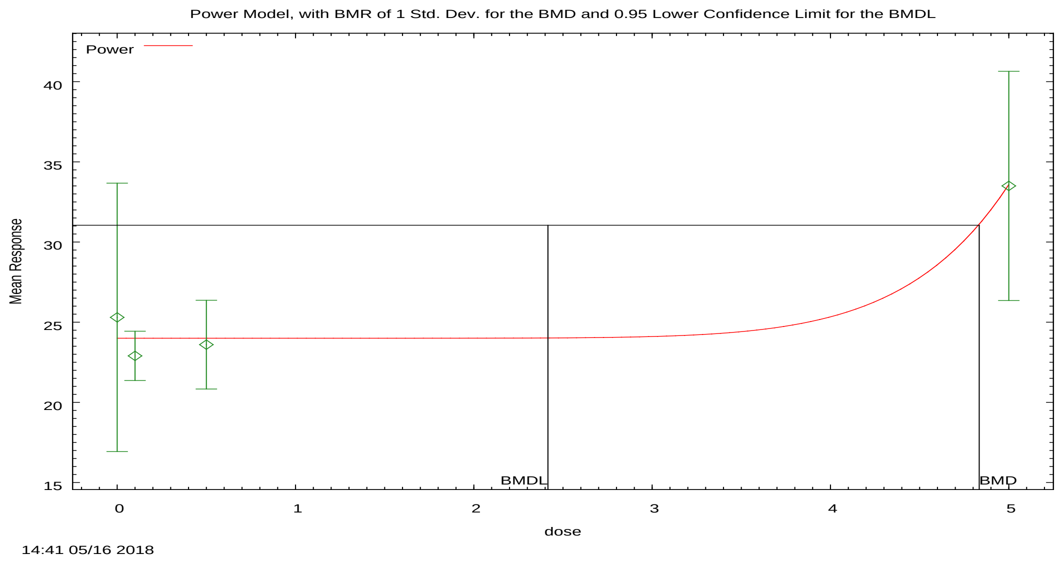

Figure 204. Plot of mean response by dose with fitted curve for Power model with modeled variance for Sorbitol Dehydrogenase in Females (90-day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A modeled variance is fit

THE MODEL HAS PROBABLY NOT CONVERGED!!!

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 4.83404

BMDL at the 95% confidence level = 2.4156

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-0.200961	4.13376
rho	1.29379	0
control	23.9821	22.9
slope	0.00000634556	1.58627

power	8.83596	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	25.3	24	11.7	7.06	0.59
0.1	9	22.9	24	2	7.06	-0.46
0.5	9	23.6	24	3.6	7.06	-0.162
5	9	33.5	33.5	9.3	8.77	-0.00000231

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-92.858049	5	195.716098
A2	-78.815874	8	173.631747
A3	-80.816402	6	173.632804
fitted	-92.777505	5	195.555009
R	-97.906482	2	199.812964

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	38.1812	6	<0.0001
Test 2	28.0844	3	<0.0001
Test 3	4.00106	2	0.1353
Test 4	23.9222	1	<0.0001

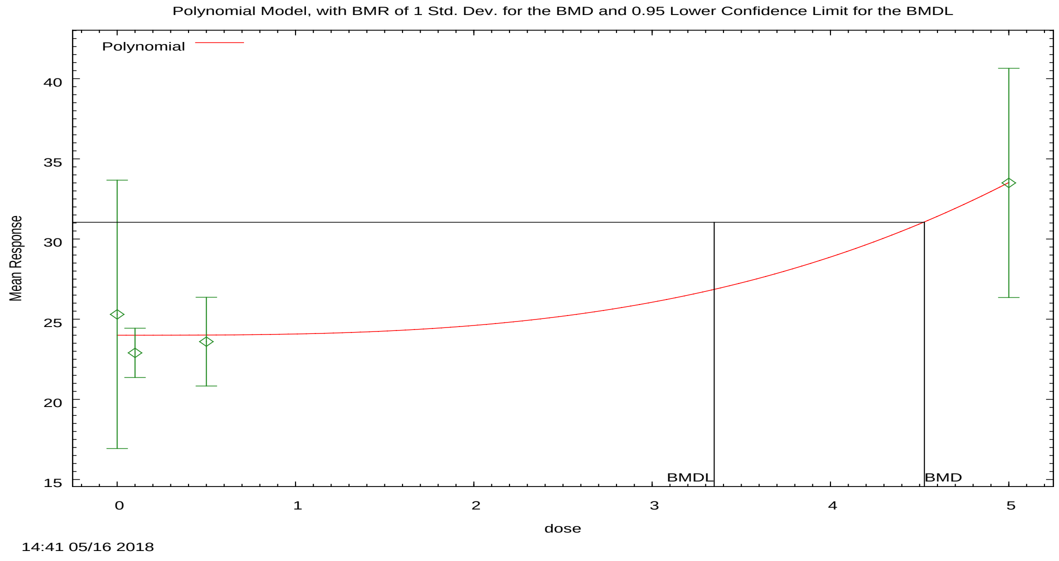

Figure 205. Plot of mean response by dose with fitted curve for Polynomial 3° model with modeled variance for Sorbitol Dehydrogenase in Females (90-day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 4.52672

BMDL at the 95% confidence level = 3.34784

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-0.187752	4.13376
rho	1.28978	0
beta_0	23.9793	25.3
beta_1	4.79108E-22	0
beta_2	0	0

beta_3	0.0761586	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	25.3	24	11.7	7.06	0.591
0.1	9	22.9	24	2	7.06	-0.458
0.5	9	23.6	24	3.6	7.07	-0.165
5	9	33.5	33.5	9.3	8.76	0.000291

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-92.858049	5	195.716098
A2	-78.815874	8	173.631747
A3	-80.816402	6	173.632804
fitted	-92.779965	4	193.559931
R	-97.906482	2	199.812964

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	38.1812	6	<0.0001
Test 2	28.0844	3	<0.0001
Test 3	4.00106	2	0.1353
Test 4	23.9271	2	<0.0001

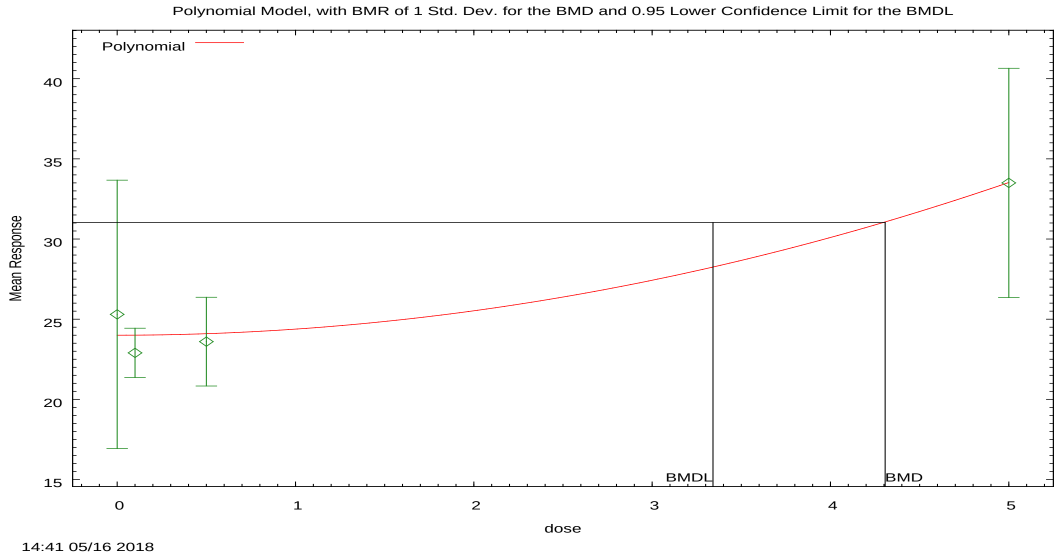

Figure 206. Plot of mean response by dose with fitted curve for Polynomial 2° model with modeled variance for Sorbitol Dehydrogenase in Females (90-day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 4.30648

BMDL at the 95% confidence level = 3.34112

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-0.0644155	4.13376
rho	1.25231	0
beta_0	23.9533	24.3494
beta_1	2.52909E-21	0
beta_2	0.381475	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	25.3	24	11.7	7.07	0.602
0.1	9	22.9	24	2	7.08	-0.448
0.5	9	23.6	24	3.6	7.09	-0.19
5	9	33.5	33.5	9.3	8.73	0.00337

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-92.858049	5	195.716098
A2	-78.815874	8	173.631747
A3	-80.816402	6	173.632804
fitted	-92.803595	4	193.60719
R	-97.906482	2	199.812964

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	38.1812	6	<0.0001
Test 2	28.0844	3	<0.0001
Test 3	4.00106	2	0.1353
Test 4	23.9744	2	<0.0001

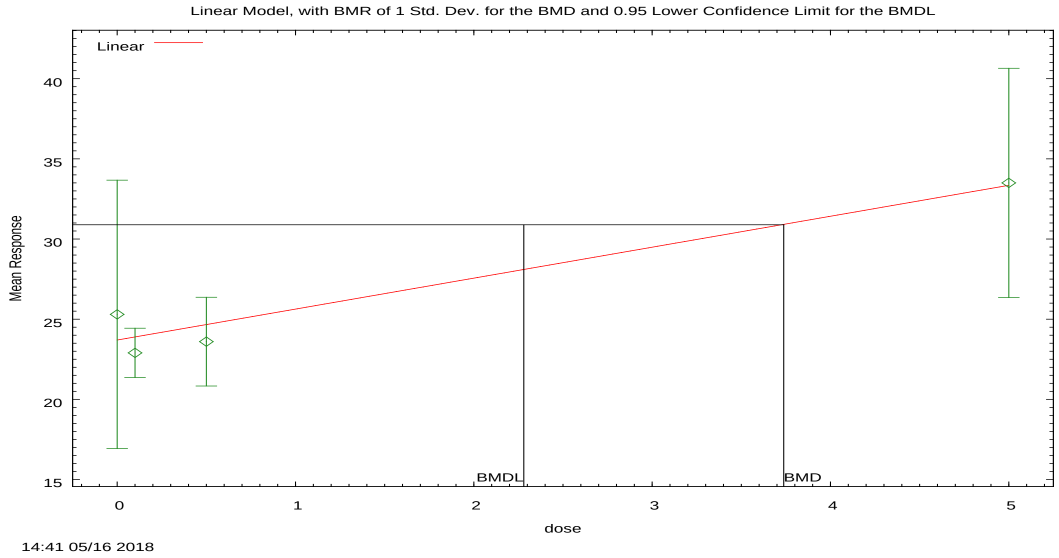

Figure 207. Plot of mean response by dose with fitted curve for Linear model with modeled variance for Sorbitol Dehydrogenase in Females (90-day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 3.7379

BMDL at the 95% confidence level = 2.28009

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	1.34146	4.13376
rho	0.825818	0
beta_0	23.6658	23.5788
beta_1	1.93221	1.96154

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	25.3	23.7	11.7	7.22	0.716
0.1	9	22.9	23.9	2	7.25	-0.397
0.5	9	23.6	24.6	3.6	7.34	-0.422
5	9	33.5	33.3	9.3	8.32	0.0624

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-92.858049	5	195.716098
A2	-78.815874	8	173.631747
A3	-80.816402	6	173.632804
fitted	-93.107064	4	194.214128
R	-97.906482	2	199.812964

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	38.1812	6	<0.0001
Test 2	28.0844	3	<0.0001
Test 3	4.00106	2	0.1353
Test 4	24.5813	2	<0.0001

BMDS WIZARD OUTPUT REPORT

Summary of H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats – Sorbitol Dehydrogenase (U/L) at 12-month timepoint in Males

1.24. BMDS Summary of Sorbitol Dehydrogenase (U/L) Males 12 months (2 Year Rats GenX)

Table 24. Summary of BMD Modeling Results for Sorbitol Dehydrogenase in Males at 12 months (2-Year Rats); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD$_{1SD}$ (mg/kg/day)	BMDL$_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2) Exponential (M3)[b]	0.738	206.75	17.6	11.6	1.52	BMDLs from models that met model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values > 2.0; appropriate variance (continuous data only)) were compared. BMDLs from included models were not sufficiently close (> 3-fold difference), so the lowest BMDL was selected.
Exponential (M4)	**0.497**	**208.60**	**6.60**	**1.21**	**5.47**	
Exponential (M5)	N/A[c]	210.53	1.32	1.01	1.31	
Hill	N/A[c]	210.53	1.42	error[d]	error	
Power[e] Polynomial 3°[f] Polynomial 2°[g] Linear	0.761	206.68	13.0	6.95	1.87	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = <0.0001), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 1, and 50 mg/kg/day were -0.57, 0.16, 0.47, -0.07, respectively.

[b] For the Exponential (M3) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M2) model.

[c] No available degrees of freedom to calculate a goodness of fit value.

[d] BMD or BMDL computation failed for this model.

[e] For the Power model, the power parameter estimate was 1. The models in this row reduced to the Linear model.

[f] For the Polynomial 3° model, the b3 coefficient estimates was 0 (boundary of parameters space). The models in this row reduced to the Polynomial 2° model. For the Polynomial 3° model, the b3 and b2 coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Linear model.

[g] For the Polynomial 2° model, the b2 coefficient estimate was 0 (boundary of parameters space). The models in this row reduced to the Linear model.

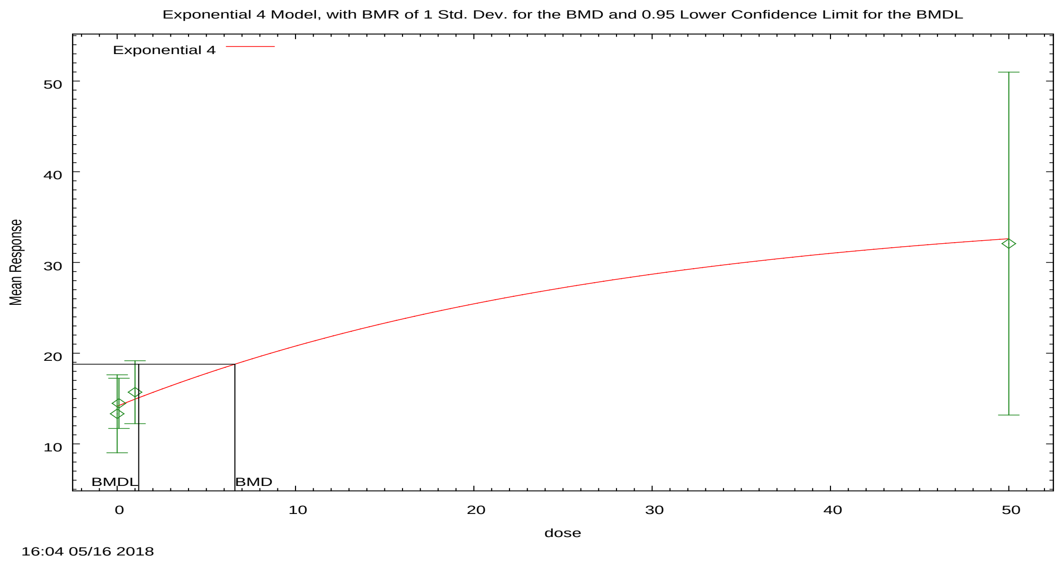

Figure 208. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Sorbitol Dehydrogenase in Males at 12 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 6.59887

BMDL at the 95% confidence level = 1.20614

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-7.62202	-7.70134
rho	4.03212	4.07591
a	14.1592	12.654
b	0.0353009	0.0515144
c	2.57315	2.66193
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	13.32	14.16	6.01	4.63	-0.5734
0.1	10	14.47	14.24	3.87	4.68	0.1569
1	10	15.7	14.93	4.85	5.15	0.4715
50	10	32.08	32.62	26.42	24.9	-0.06869

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-123.1674	5	256.3348
A2	-97.88906	8	211.7781
A3	-99.06893	6	210.1379
R	-128.9829	2	261.9658
4	-99.29957	5	208.5991

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	62.19	6	<0.0001
Test 2	50.56	3	<0.0001
Test 3	2.36	2	0.3073
Test 6a	0.4613	1	0.497

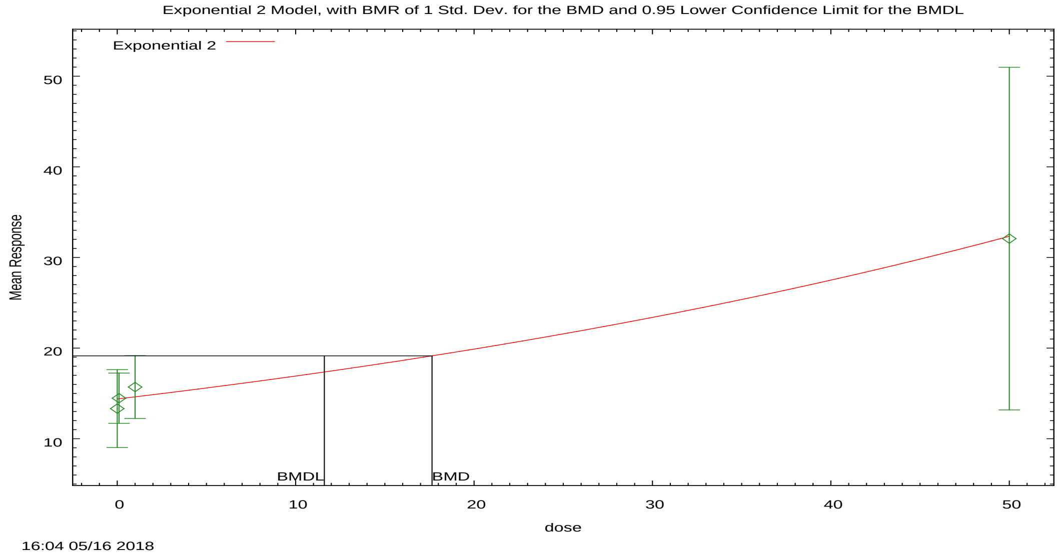

Figure 209. Plot of mean response by dose with fitted curve for Exponential (M2) model with modeled variance for Sorbitol Dehydrogenase in Males at 12 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 17.6448

BMDL at the 95% confidence level = 11.6067

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-7.81223	-7.70134
rho	4.10029	4.07591
a	14.386	14.372
b	0.0161975	0.0160881
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	13.32	14.39	6.01	4.76	-0.7083
0.1	10	14.47	14.41	3.87	4.78	0.04019
1	10	15.7	14.62	4.85	4.92	0.6936
50	10	32.08	32.33	26.42	25.04	-0.03211

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-123.1674	5	256.3348
A2	-97.88906	8	211.7781
A3	-99.06893	6	210.1379
R	-128.9829	2	261.9658
2	-99.37282	4	206.7456

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	62.19	6	<0.0001
Test 2	50.56	3	<0.0001
Test 3	2.36	2	0.3073
Test 4	0.6078	2	0.7379

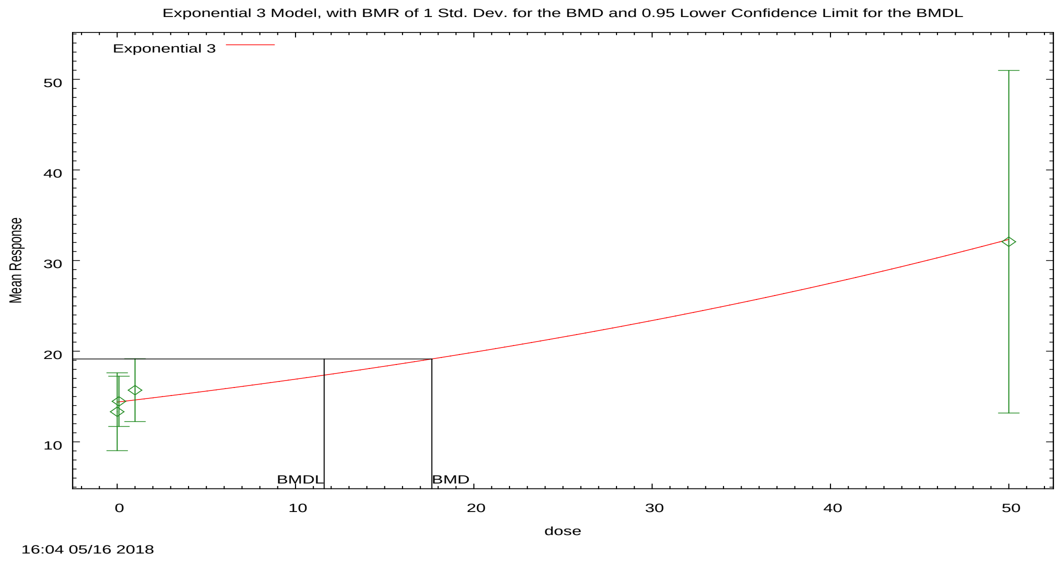

Figure 210. Plot of mean response by dose with fitted curve for Exponential (M3) model with modeled variance for Sorbitol Dehydrogenase in Males at 12 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 17.6448

BMDL at the 95% confidence level = 11.6067

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-7.81223	-7.70134
rho	4.10029	4.07591
a	14.386	14.372
b	0.0161975	0.0160881
c	n/a	0
d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	13.32	14.39	6.01	4.76	-0.7083
0.1	10	14.47	14.41	3.87	4.78	0.04019
1	10	15.7	14.62	4.85	4.92	0.6936
50	10	32.08	32.33	26.42	25.04	-0.03211

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-123.1674	5	256.3348
A2	-97.88906	8	211.7781
A3	-99.06893	6	210.1379
R	-128.9829	2	261.9658
3	-99.37282	4	206.7456

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	62.19	6	<0.0001
Test 2	50.56	3	<0.0001
Test 3	2.36	2	0.3073
Test 5a	0.6078	2	0.7379

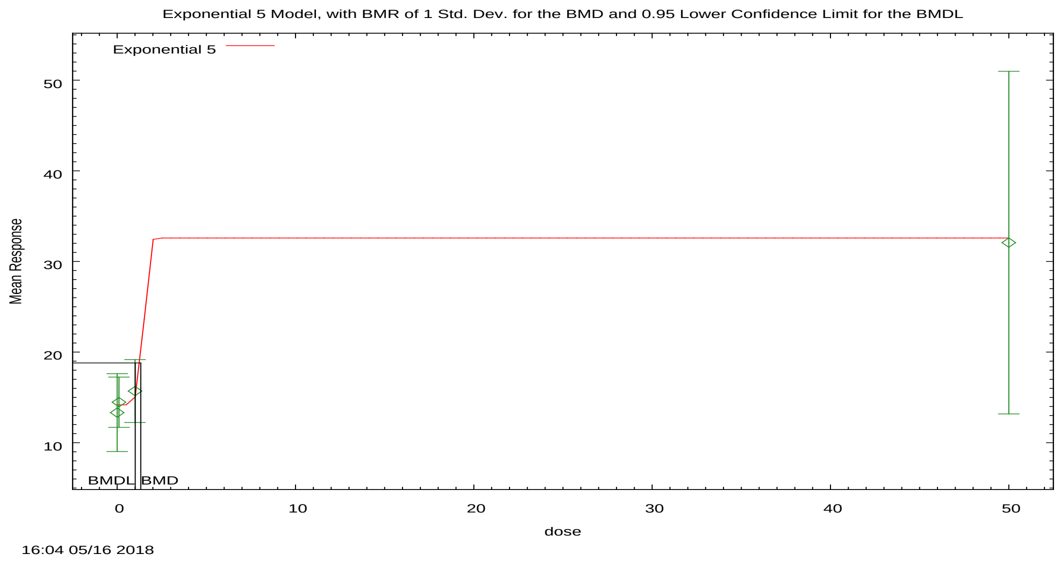

Figure 211. Plot of mean response by dose with fitted curve for Exponential (M5) model with modeled variance for Sorbitol Dehydrogenase in Males at 12 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 1.32183

BMDL at the 95% confidence level = 1.01222

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-7.65183	-7.70134
rho	4.04211	4.07591
a	14.1732	12.654
b	0.627627	0.0515144

c	2.29918	2.66193
d	6.63396	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	13.32	14.17	6.01	4.63	-0.5827
0.1	10	14.47	14.17	3.87	4.63	0.2027
1	10	15.7	14.99	4.85	5.19	0.4315
50	10	32.08	32.59	26.42	24.91	-0.06433

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-123.1674	5	256.3348
A2	-97.88906	8	211.7781
A3	-99.06893	6	210.1379
R	-128.9829	2	261.9658
5	-99.26642	6	210.5328

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	62.19	6	<0.0001
Test 2	50.56	3	<0.0001
Test 3	2.36	2	0.3073
Test 7a	0.395	0	N/A

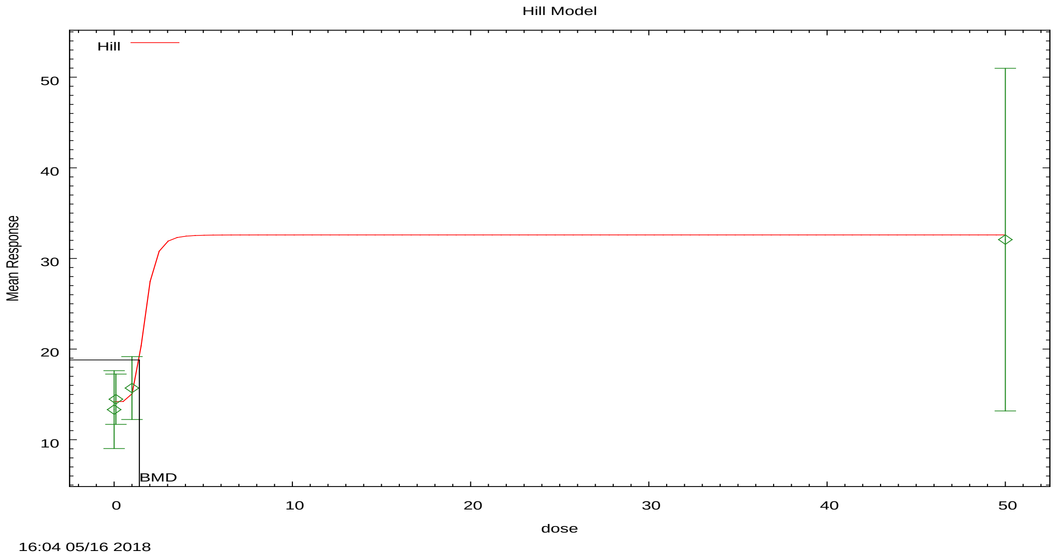

Figure 212. Plot of mean response by dose with fitted curve for Hill model with modeled variance for Sorbitol Dehydrogenase in Males at 12 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 1.41525

BMDL at the 95% confidence level = error

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-7.65188	5.26373
rho	4.04213	0
intercept	14.1732	13.32
v	18.4135	18.76

n	5.69094	0.426195
k	1.71426	78.0598

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	13.3	14.2	6.01	4.63	-0.583
0.1	10	14.5	14.2	3.87	4.63	0.203
1	10	15.7	15	4.85	5.19	0.432
50	10	32.1	32.6	26.4	24.9	-0.0643

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-123.167387	5	256.334774
A2	-97.889063	8	211.778126
A3	-99.068928	6	210.137855
fitted	-99.266423	6	210.532847
R	-128.982884	2	261.965768

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	62.1876	6	<0.0001
Test 2	50.5566	3	<0.0001
Test 3	2.35973	2	0.3073
Test 4	0.394991	0	N/A

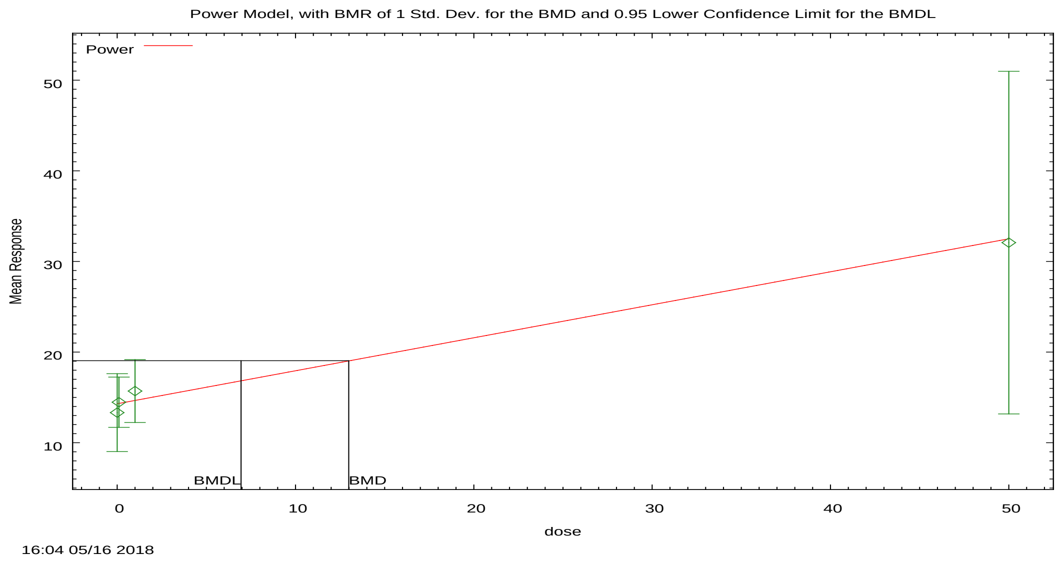

Figure 213. Plot of mean response by dose with fitted curve for Power model with modeled variance for Sorbitol Dehydrogenase in Males at 12 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 12.9849

BMDL at the 95% confidence level = 6.94645

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-7.71947	5.26373
rho	4.0664	0
control	14.3262	13.32
slope	0.36387	3.13168

power	1	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	13.3	14.3	6.01	4.72	-0.673
0.1	10	14.5	14.4	3.87	4.75	0.0715
1	10	15.7	14.7	4.85	4.97	0.642
50	10	32.1	32.5	26.4	25	-0.0556

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-123.167387	5	256.334774
A2	-97.889063	8	211.778126
A3	-99.068928	6	210.137855
fitted	-99.341825	4	206.68365
R	-128.982884	2	261.965768

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	62.1876	6	<0.0001
Test 2	50.5566	3	<0.0001
Test 3	2.35973	2	0.3073
Test 4	0.545795	2	0.7612

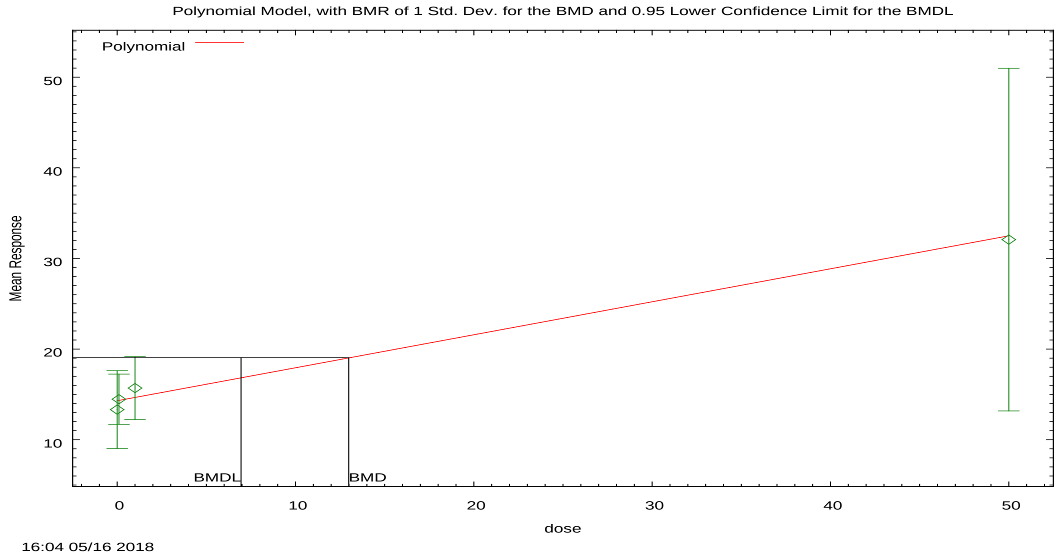

Figure 214. Plot of mean response by dose with fitted curve for Polynomial 3° model with modeled variance for Sorbitol Dehydrogenase in Males at 12 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 12.9849

BMDL at the 95% confidence level = 6.94645

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-7.71947	5.26373
rho	4.0664	0
beta_0	14.3262	13.32
beta_1	0.36387	12.5336

beta_2	7.95E-14	0
beta_3	1.59E-15	0.202253

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	13.3	14.3	6.01	4.72	-0.673
0.1	10	14.5	14.4	3.87	4.75	0.0715
1	10	15.7	14.7	4.85	4.97	0.642
50	10	32.1	32.5	26.4	25	-0.0556

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-123.167387	5	256.334774
A2	-97.889063	8	211.778126
A3	-99.068928	6	210.137855
fitted	-99.341825	4	206.68365
R	-128.982884	2	261.965768

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	62.1876	6	<0.0001
Test 2	50.5566	3	<0.0001
Test 3	2.35973	2	0.3073
Test 4	0.545795	2	0.7612

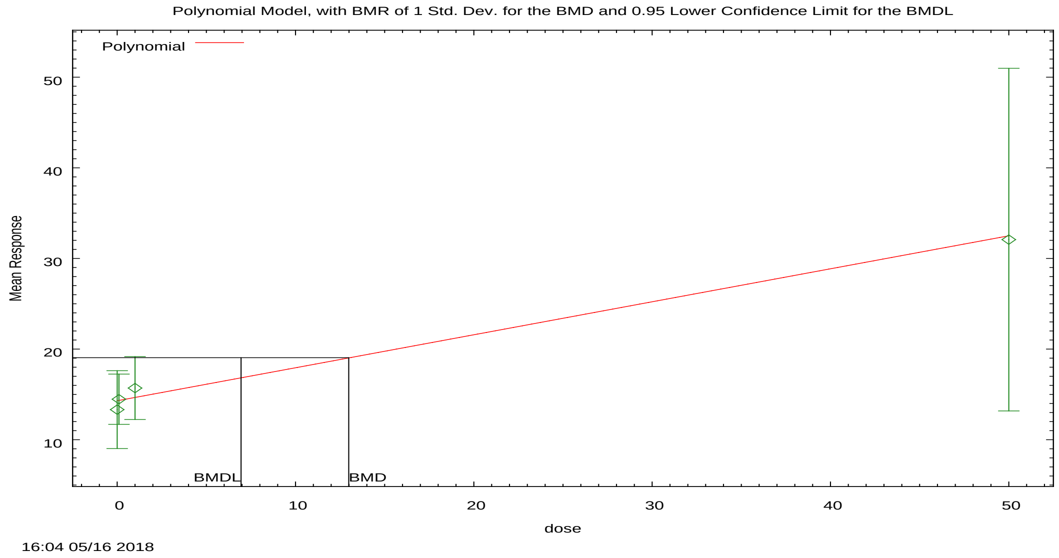

Figure 215. Plot of mean response by dose with fitted curve for Polynomial 2° model with modeled variance for Sorbitol Dehydrogenase in Males at 12 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 12.9849

BMDL at the 95% confidence level = 6.94645

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-7.71947	5.26373
rho	4.0664	0
beta_0	14.3262	13.769
beta_1	0.36387	2.0149

beta_2	0	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	13.3	14.3	6.01	4.72	-0.673
0.1	10	14.5	14.4	3.87	4.75	0.0715
1	10	15.7	14.7	4.85	4.97	0.642
50	10	32.1	32.5	26.4	25	-0.0556

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-123.167387	5	256.334774
A2	-97.889063	8	211.778126
A3	-99.068928	6	210.137855
fitted	-99.341825	4	206.68365
R	-128.982884	2	261.965768

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	62.1876	6	<0.0001
Test 2	50.5566	3	<0.0001
Test 3	2.35973	2	0.3073
Test 4	0.545795	2	0.7612

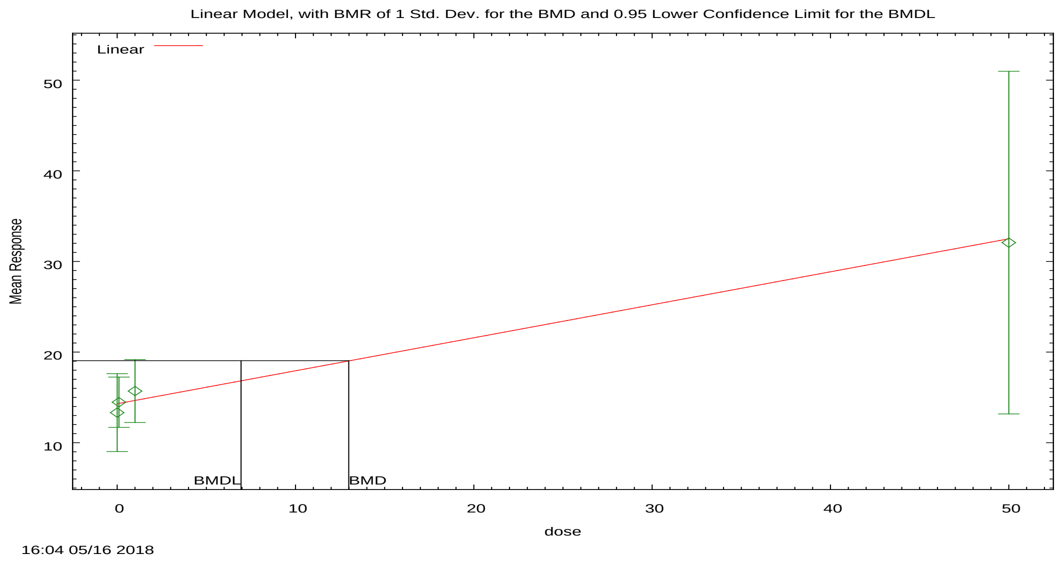

Figure 216. Plot of mean response by dose with fitted curve for Linear model with modeled variance for Sorbitol Dehydrogenase in Males at 12 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 12.9849

BMDL at the 95% confidence level = 6.94645

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-7.71949	5.26373
rho	4.06641	0
beta_0	14.3262	14.36
beta_1	0.363869	0.354798

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	13.3	14.3	6.01	4.72	-0.673
0.1	10	14.5	14.4	3.87	4.75	0.0715
1	10	15.7	14.7	4.85	4.97	0.642
50	10	32.1	32.5	26.4	25	-0.0556

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-123.167387	5	256.334774
A2	-97.889063	8	211.778126
A3	-99.068928	6	210.137855
fitted	-99.341825	4	206.68365
R	-128.982884	2	261.965768

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	62.1876	6	<0.0001
Test 2	50.5566	3	<0.0001
Test 3	2.35973	2	0.3073
Test 4	0.545795	2	0.7612

BMDS WIZARD OUTPUT REPORT

BMDS Summary of 28-Day Oral (Gavage) Toxicity Study of H-28397 in Mice with a 28-day Recovery – Single Cell Hepatocellular Necrosis in Males

1.25. BMDS Summary of Liver Necrosis, Single Cell Male (28 Day Mice GenX)

Table 25. Summary of BMD Modeling Results for Single Cell Hepatocellular Necrosis in Males (28-Day Mice)

Model[a]	Goodness of fit		BMD_{10Pct} (mg/kg/day)	$BMDL_{10Pct}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Gamma	1.000	17.460	1.88	0.323	5.80	BMDLs from models that met model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values > 2.0; appropriate variance (continuous data only)) were compared. BMDLs from included models were not sufficiently close (> 3-fold difference), so the lowest BMDL was selected.
Dichotomous-Hill[b]	1.000	17.460	2.42	0.343	7.06	
Logistic	1.000	17.460	2.72	1.16	2.34	
LogLogistic[c]	1.000	17.460	2.42	0.343	7.06	
Probit	1.000	17.460	2.45	1.04	2.37	
LogProbit	**1.000**	**17.460**	**2.01**	**0.299**	**6.72**	
Weibull	1.000	17.460	1.96	0.323	6.05	
Multistage 3°	0.998	17.469	1.45	0.323	4.48	
Multistage 2°	1.000	15.472	1.36	0.323	4.23	
Quantal-Linear	0.972	15.918	0.603	0.305	1.97	

[a] Selected model in bold; scaled residuals for selected model for doses 0, 0.1, 3, and 30 mg/kg/day were 0, 0, 0, 0, respectively.
[b] The Dichotomous-Hill model may appear equivalent to the LogLogistic model, however differences exist in digits not displayed in the table.
[c] The LogLogistic model may appear equivalent to the Dichotomous-Hill model, however differences exist in digits not displayed in the table.

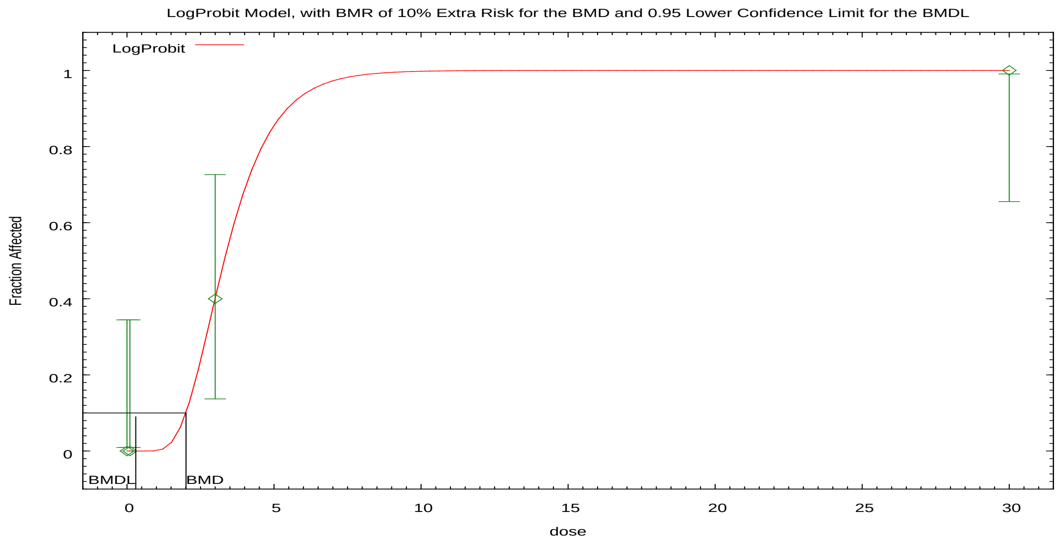

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Figure 217. Plot of incidence rate by dose with fitted curve for LogProbit model for Single Cell Hepatocellular Necrosis in Males (28-Day Mice); dose shown in mg/kg/day.

Probit Model. (Version: 3.4; Date: 5/21/2017)

The form of the probability function is: P[response] = Background + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)),where CumNorm(.) is the cumulative normal distribution function

Slope parameter is not restricted

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 2.0069

BMDL at the 95% confidence level = 0.298834

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
background	0	0
intercept	-3.0632E+00	-5.0920E-01
slope	2.5576	0.579932

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-6.73	4			
Fitted model	-6.73	2	0.000000174299	2	1
Reduced model	-25.9	1	38.3355	3	<.0001

AIC: = 17.4602

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.1	0	0	0	10	0
3	0.4	4	4	10	0
30	1	10	10	10	0

Chi^2 = 0 d.f = 2 P-value = 1

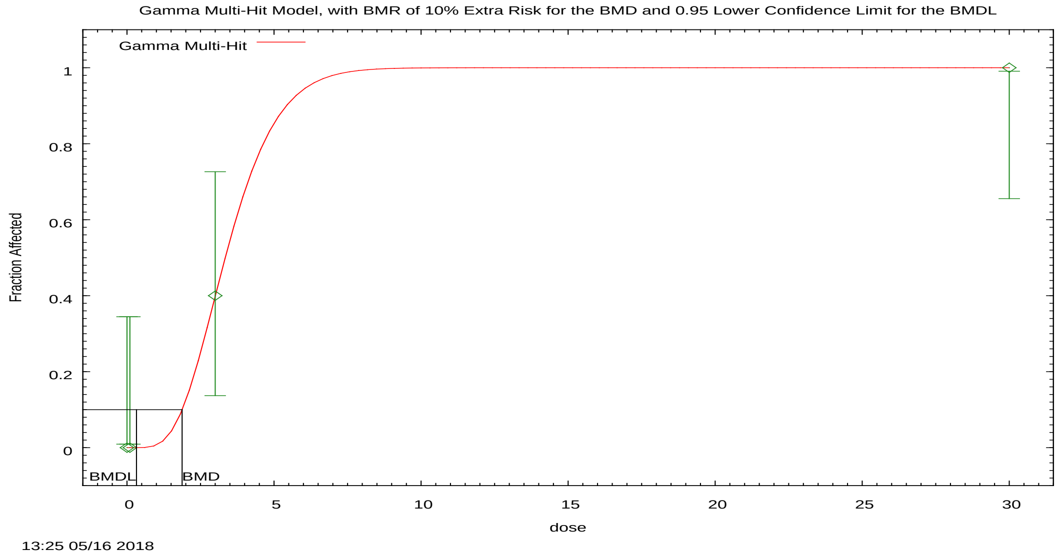

Figure 218. Plot of incidence rate by dose with fitted curve for Gamma model for Single Cell Hepatocellular Necrosis in Males (28-Day Mice); dose shown in mg/kg/day.

Gamma Model. (Version: 2.17; Date: 6/22/2017)

The form of the probability function is: P[response]= background+(1-background)*CumGamma[slope*dose,power], where CumGamma(.) is the cumulative Gamma distribution function

Power parameter is restricted as power >=1

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 1.87505

BMDL at the 95% confidence level = 0.323065

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0	0.0833333
Slope	1.76301	0.117349
Power	6.20943	1.3

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-6.73	4			
Fitted model	-6.73	2	0.000000373996	2	1
Reduced model	-25.9	1	38.3355	3	<.0001

AIC: = 17.4602

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.1	0	0	0	10	0
3	0.4	4	4	10	0
30	1	10	10	10	0

Chi^2 = 0   d.f = 2   P-value = 1

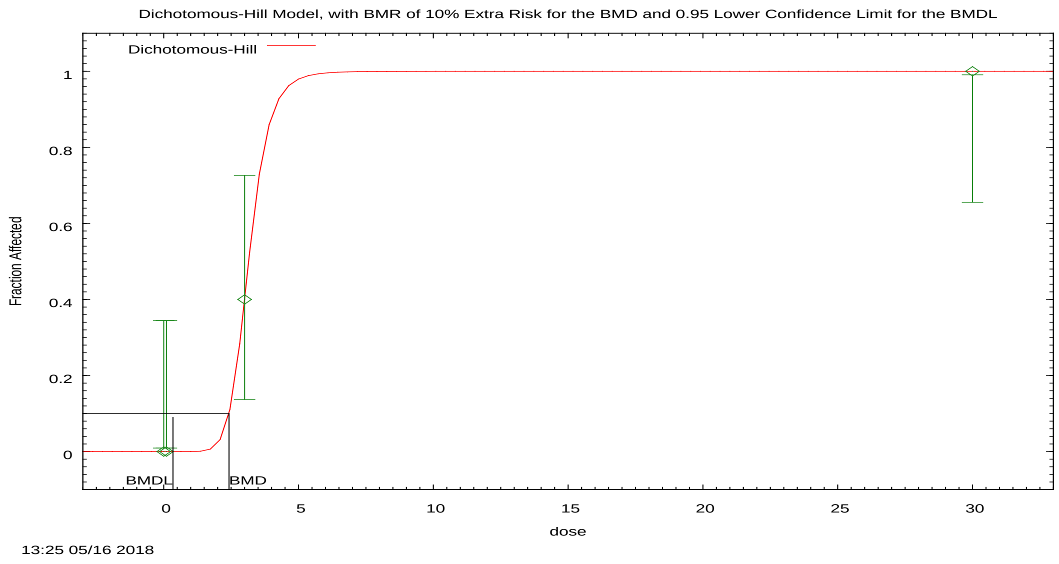

Figure 219. Plot of incidence rate by dose with fitted curve for Dichotomous-Hill model for Single Cell Hepatocellular Necrosis in Males (28-Day Mice); dose shown in mg/kg/day.

Dichotomous Hill Model. (Version: 1.3; Date: 02/28/2013)

The form of the probability function is: P[response] = v*g +(v-v*g)/[1+EXP(-intercept-slope*Log(dose))]

Slope parameter is restricted as slope >= 1

THE MODEL HAS PROBABLY NOT CONVERGED!!!

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 2.42168

BMDL at the 95% confidence level = 0.343163

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
v	1	1
g	0	0

intercept	-9.5974E+00	-9.0088E-01
slope	8.36688	1.04549

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-6.73	4			
Fitted model	-6.73	2	0.000000128904	2	1
Reduced model	-25.9	1	38.3355	3	<.0001

AIC: = 17.4602

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.1	0	0	0	10	0
3	0.4	4	4	10	0
30	1	10	10	10	0

Chi^2 = 0 d.f = 2 P-value = 1

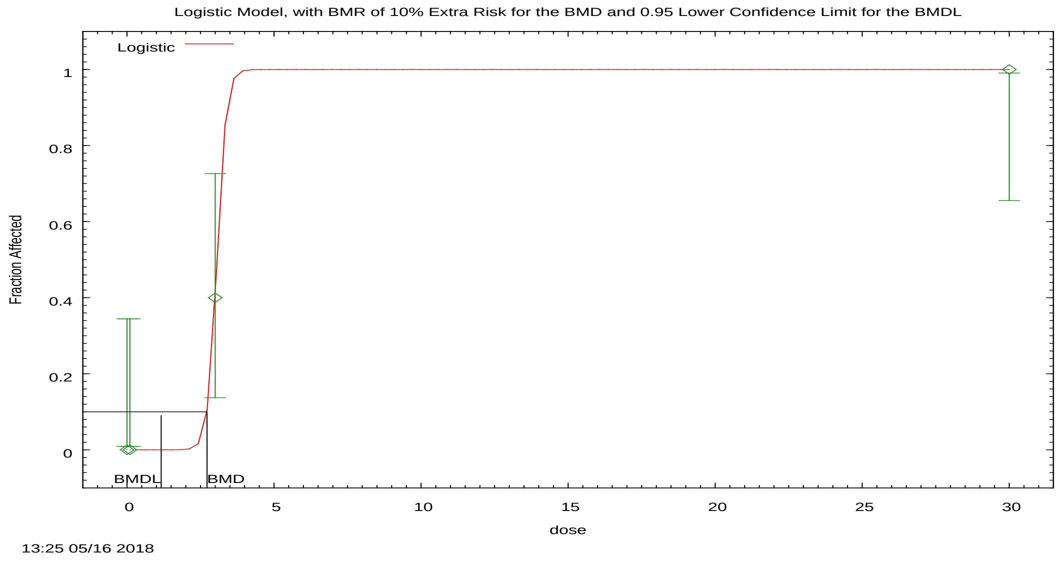

Figure 220. Plot of incidence rate by dose with fitted curve for Logistic model for Single Cell Hepatocellular Necrosis in Males (28-Day Mice); dose shown in mg/kg/day.

Logistic Model. (Version: 2.15; Date: 3/20/2017)

The form of the probability function is: P[response] = 1/[1+EXP(-intercept-slope*dose)]

Slope parameter is not restricted

THE MODEL HAS PROBABLY NOT CONVERGED!!!

Warning: BMDU computation is at best imprecise for these data

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 2.72165

BMDL at the 95% confidence level = 1.16321

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
background	n/a	0
intercept	-1.9717E+01	-2.3927E+00
slope	6.43701	0.186054

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-6.73	4			
Fitted model	-6.73	2	0.000000158926	2	1
Reduced model	-25.9	1	38.3355	3	<.0001

AIC: = 17.4602

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.1	0	0	0	10	0
3	0.4	4	4	10	0
30	1	10	10	10	0

Chi^2 = 0 d.f = 2 P-value = 1

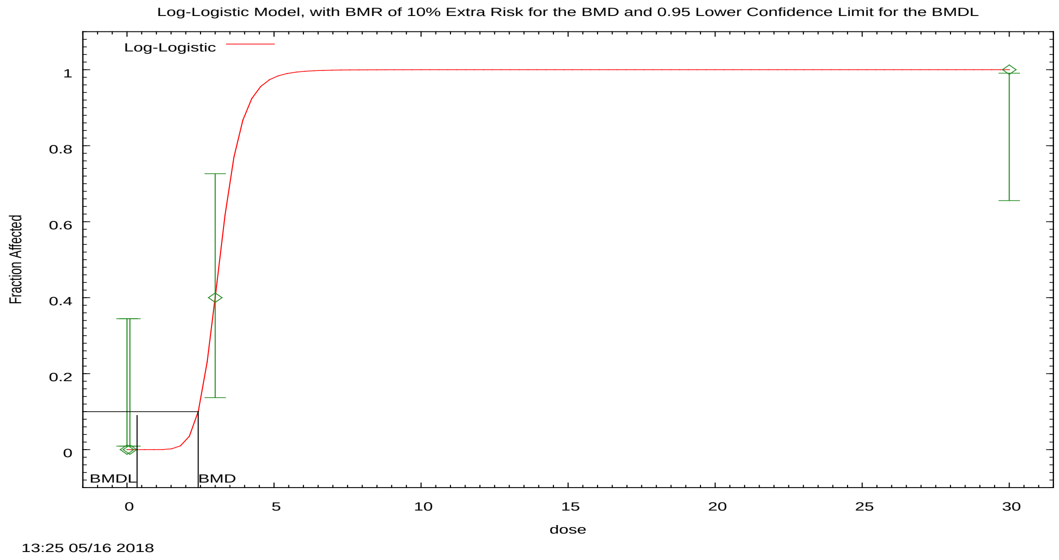

Figure 221. Plot of incidence rate by dose with fitted curve for LogLogistic model for Single Cell Hepatocellular Necrosis in Males (28-Day Mice); dose shown in mg/kg/day.

Logistic Model. (Version: 2.15; Date: 3/20/2017)

The form of the probability function is: P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]

Slope parameter is restricted as slope >= 1

THE MODEL HAS PROBABLY NOT CONVERGED!!!

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 2.42169

BMDL at the 95% confidence level = 0.343163

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
background	0	0
intercept	-9.5975E+00	-9.0088E-01
slope	8.36697	1.04549

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-6.73	4			
Fitted model	-6.73	2	0.000000128876	2	1
Reduced model	-25.9	1	38.3355	3	<.0001

AIC: = 17.4602

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.1	0	0	0	10	0
3	0.4	4	4	10	0
30	1	10	10	10	0

Chi^2 = 0   d.f = 2   P-value = 1

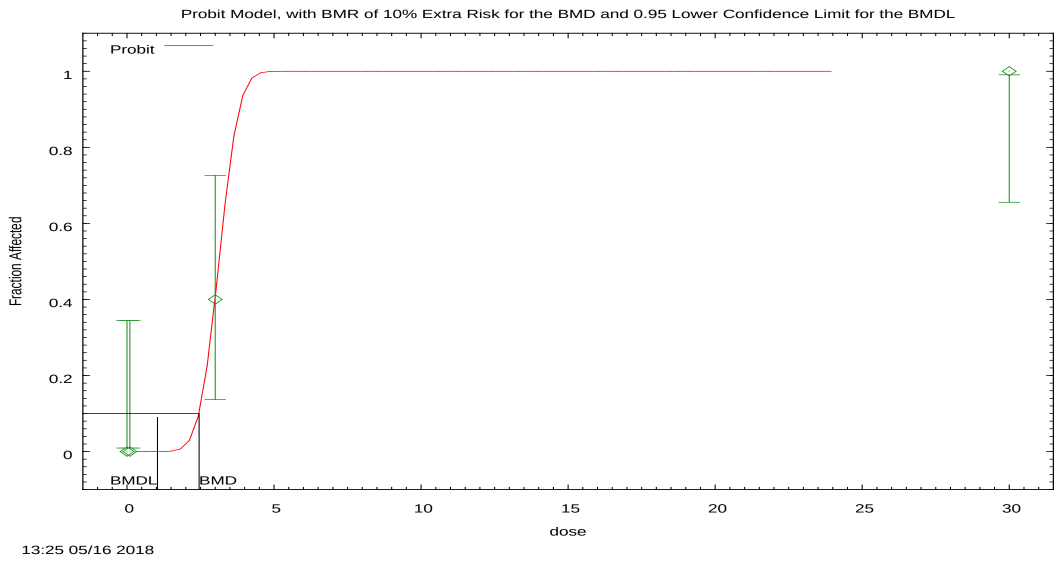

Figure 222. Plot of incidence rate by dose with fitted curve for Probit model for Single Cell Hepatocellular Necrosis in Males (28-Day Mice); dose shown in mg/kg/day.

Probit Model. (Version: 3.4; Date: 5/21/2017)

The form of the probability function is: P[response] = CumNorm(Intercept+Slope*Dose), where CumNorm(.) is the cumulative normal distribution function

Slope parameter is not restricted

Warning: BMDU computation is at best imprecise for these data

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 2.45186

BMDL at the 95% confidence level = 1.03642

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
background	n/a	0
intercept	-5.8808E+00	-1.6482E+00

slope	1.87582	0.123523

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-6.73	4			
Fitted model	-6.73	2	0.000000165492	2	1
Reduced model	-25.9	1	38.3355	3	<.0001

AIC: = 17.4602

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.1	0	0	0	10	0
3	0.4	4	4	10	0
30	1	10	10	10	0

Chi^2 = 0 d.f = 2 P-value = 1

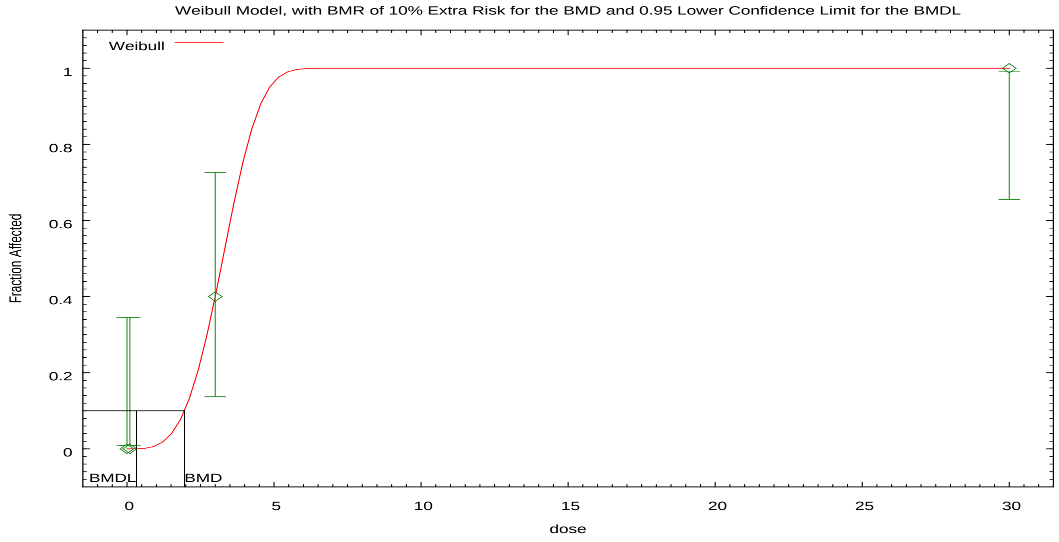

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Figure 223. Plot of incidence rate by dose with fitted curve for Weibull model for Single Cell Hepatocellular Necrosis in Males (28-Day Mice); dose shown in mg/kg/day.

Weibull Model using Weibull Model (Version: 2.17; Date: 6/23/2017)

The form of the probability function is: P[response] = background + (1-background)*[1-EXP(-slope*dose^power)]

Power parameter is restricted as power >=1

Warning: BMDU computation is at best imprecise for these data

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 1.95584

BMDL at the 95% confidence level = 0.323064

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0	0.0833333
Slope	0.0088635	0.0799298
Power	3.69018	1

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-6.73	4			
Fitted model	-6.73	2	0.0000361794	2	1
Reduced model	-25.9	1	38.3355	3	<.0001

AIC: = 17.4603

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.1	0	0	0	10	0
3	0.4	4	4	10	0
30	1	10	10	10	0

Chi^2 = 0   d.f = 2   P-value = 1

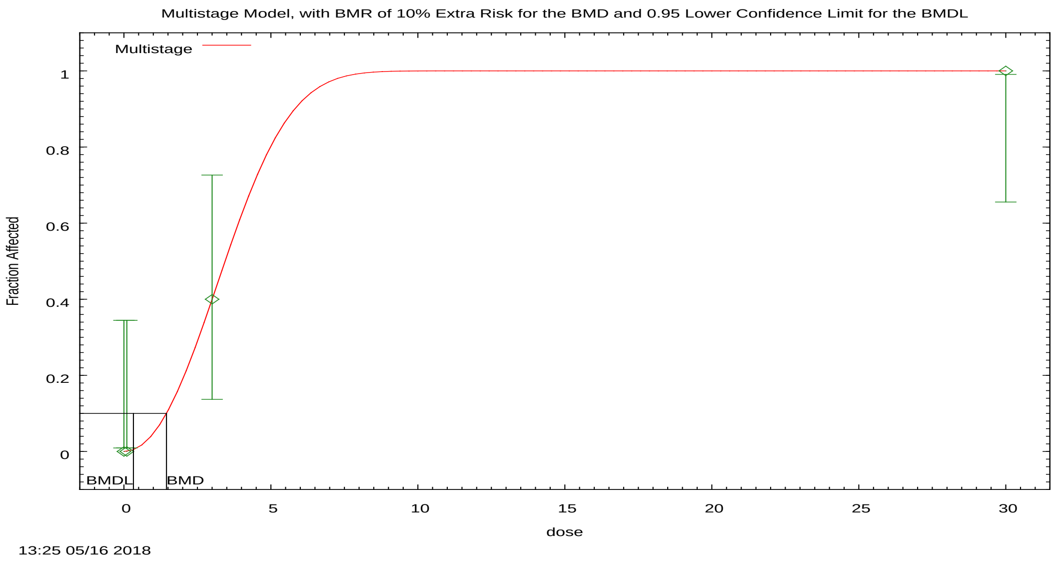

Figure 224. Plot of incidence rate by dose with fitted curve for Multistage 3° model for Single Cell Hepatocellular Necrosis in Males (28-Day Mice); dose shown in mg/kg/day.

Multistage Model. (Version: 3.4; Date: 05/02/2014)

The form of the probability function is: P[response] = background + (1-background)*[1-EXP(-beta1*dose^1-beta2*dose^2...)]

THE MODEL HAS PROBABLY NOT CONVERGED!!!

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 1.44721

BMDL at the 95% confidence level = 0.322688

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0	0
Beta(1)	0	0
Beta(2)	0.0443672	0
Beta(3)	0.00410304	3.7049E+15

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-6.73	4			
Fitted model	-6.73	2	0.00896369	2	1
Reduced model	-25.9	1	38.3355	3	<.0001

AIC: = 17.4692

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.1	0.0004	0.004	0	10	-0.07
3	0.3996	3.996	4	10	0
30	1	10	10	10	0

Chi^2 = 0   d.f = 2   P-value = 0.9978

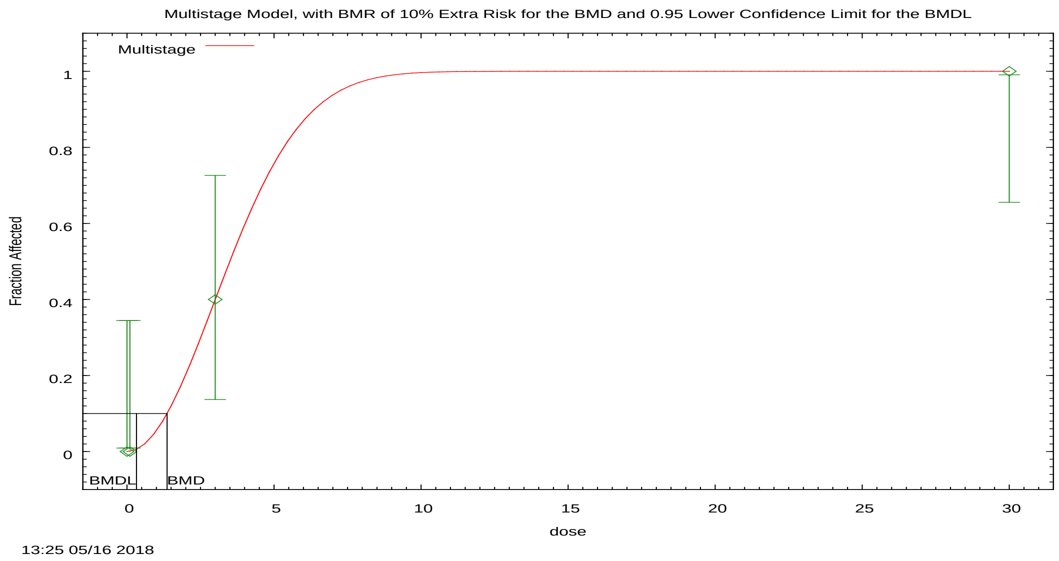

Figure 225. Plot of incidence rate by dose with fitted curve for Multistage 2° model for Single Cell Hepatocellular Necrosis in Males (28-Day Mice); dose shown in mg/kg/day.

Multistage Model. (Version: 3.4; Date: 05/02/2014)

The form of the probability function is: P[response] = background + (1-background)*[1-EXP(-beta1*dose^1-beta2*dose^2...)]

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 1.36345

BMDL at the 95% confidence level = 0.322588

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0	0
Beta(1)	0	0
Beta(2)	0.0566762	1.1147E+17

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-6.73	4			
Fitted model	-6.74	1	0.0113435	3	1
Reduced model	-25.9	1	38.3355	3	<.0001

AIC: = 15.4716

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.1	0.0006	0.006	0	10	-0.08
3	0.3996	3.996	4	10	0
30	1	10	10	10	0

Chi^2 = 0.01 d.f = 3 P-value = 0.9999

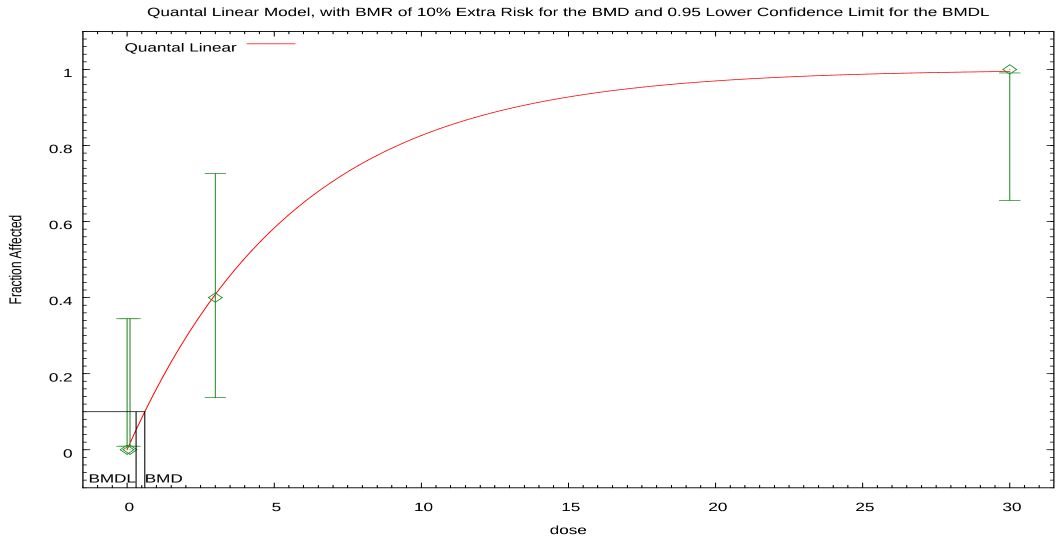

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Figure 226. Plot of incidence rate by dose with fitted curve for Quantal-Linear model for Single Cell Hepatocellular Necrosis in Males (28-Day Mice); dose shown in mg/kg/day.

Quantal Linear Model using Weibull Model (Version: 2.17; Date: 6/23/2017)

The form of the probability function is: P[response] = background + (1-background)*[1-EXP(-slope*dose)]

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 0.602799

BMDL at the 95% confidence level = 0.305305

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0	0.0833333
Slope	0.174785	0.0799298
Power	n/a	1

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-6.73	4			
Fitted model	-6.96	1	0.458177	3	0.93
Reduced model	-25.9	1	38.3355	3	<.0001

AIC: = 15.9184

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid

0	0	0	0	10	0
0.1	0.0173	0.173	0	10	-0.42
3	0.4081	4.081	4	10	-0.05
30	0.9947	9.947	10	10	0.23

Chi^2 = 0.23 d.f = 3 P-value = 0.9722

BMDS WIZARD OUTPUT REPORT

BMDS Summary of 28-Day Oral (Gavage) Toxicity Study of H-28397 in Rats with a 28-day Recovery – Hepatocellular Necrosis in Males

1.26. BMDS Summary of Hepatocellular Necrosis Males (28 Day Rats GenX)

Table 26. Summary of BMD Modeling Results for Hepatocellular Necrosis in Males (28-Day Rats)

Model[a]	Goodness of fit		BMD_{10Pct} (mg/kg/day)	$BMDL_{10Pct}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Gamma	1.000	16.217	22.8	4.89	4.67	BMDLs from models that met model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values > 2.0; appropriate variance (continuous data only)) were compared. BMDLs from included models were not sufficiently close (> 3-fold difference), so the lowest BMDL was selected.
Dichotomous-Hill	1.000	18.217	24.9	2.72	9.14	
Logistic	1.000	16.217	28.0	14.6	1.91	
LogLogistic	1.000	16.217	25.3	4.05	6.25	
Probit	1.000	16.217	26.1	13.1	1.99	
LogProbit	**1.000**	**16.217**	**21.5**	**2.70**	**7.98**	
Weibull	1.000	16.217	25.7	4.89	5.25	
Multistage 3°	1.000	14.224	20.0	4.89	4.09	
Multistage 2°	0.998	14.289	16.4	4.84	3.39	
Quantal-Linear	0.941	14.954	10.0	4.39	2.28	

[a] Selected model in bold; scaled residuals for selected model for doses 0, 0.3, 3, and 30 mg/kg/day were 0, 0, 0, 0, respectively.

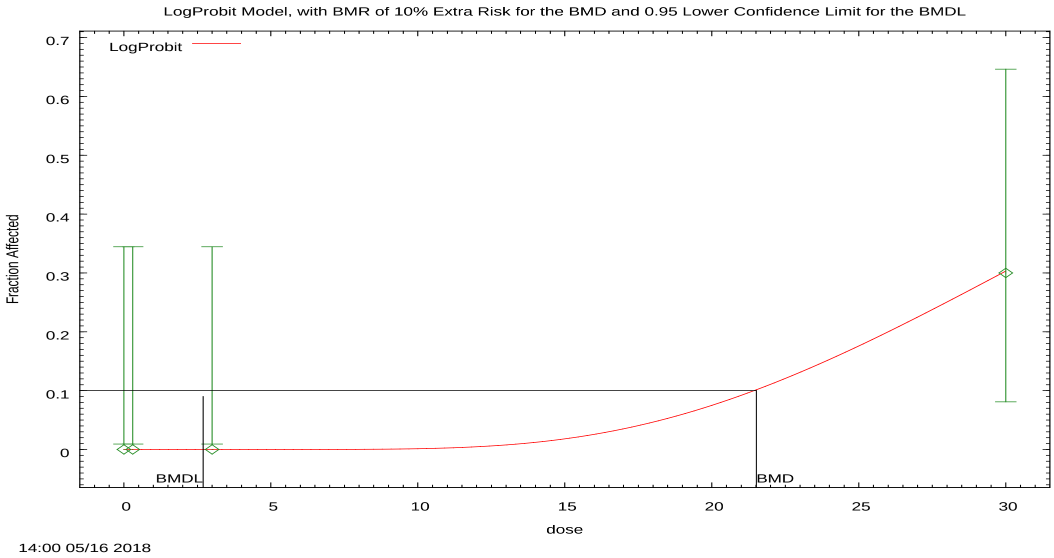

Figure 227. Plot of incidence rate by dose with fitted curve for LogProbit model for Hepatocellular Necrosis in Males (28-Day Rats); dose shown in mg/kg/day.

Probit Model. (Version: 3.4; Date: 5/21/2017)

The form of the probability function is: P[response] = Background + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)),where CumNorm(.) is the cumulative normal distribution function

Slope parameter is not restricted

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 21.5145

BMDL at the 95% confidence level = 2.69529

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
background	0	0
intercept	-8.2701E+00	-1.5801E+00
slope	2.27735	0.253242

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-6.11	4			
Fitted model	-6.11	2	0.0000000801219	2	1
Reduced model	-10.66	1	9.09347	3	0.03

AIC: = 16.2173

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid

0	0	0	0	10	0
0.3	0	0	0	10	0
3	0	0	0	10	0
30	0.3	3	3	10	0

Chi^2 = 0   d.f = 2   P-value = 1

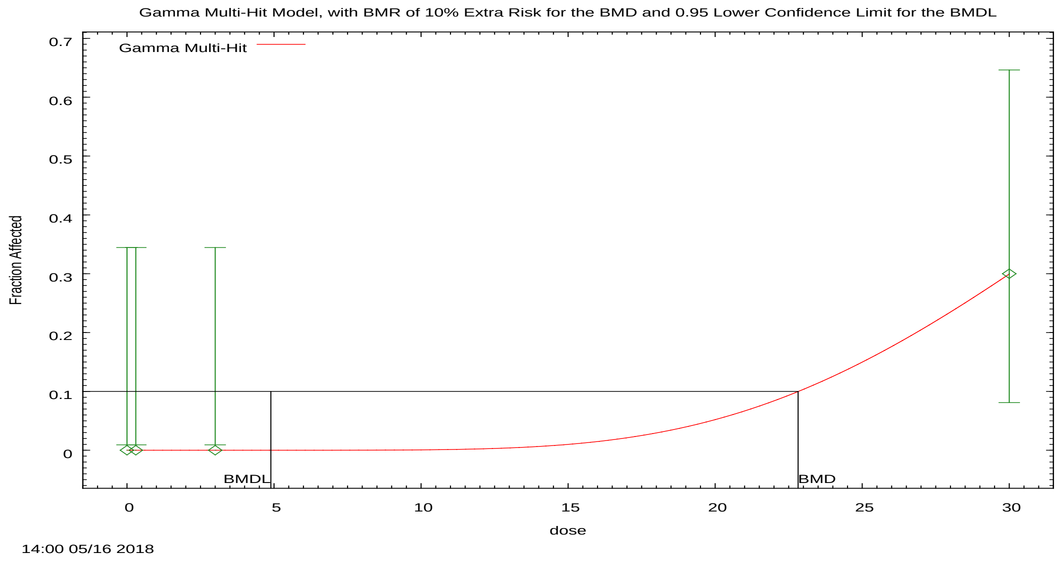

Figure 228. Plot of incidence rate by dose with fitted curve for Gamma model for Hepatocellular Necrosis in Males (28-Day Rats); dose shown in mg/kg/day.

Gamma Model. (Version: 2.17; Date: 6/22/2017)

The form of the probability function is: P[response]= background+(1-background)*CumGamma[slope*dose,power], where CumGamma(.) is the cumulative Gamma distribution function

Power parameter is restricted as power >=1

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 22.8198

BMDL at the 95% confidence level = 4.89143

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0	0.0833333
Slope	0.260092	0.0194895
Power	9.63903	1.40183

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-6.11	4			
Fitted model	-6.11	2	0.000000582716	2	1
Reduced model	-10.66	1	9.09347	3	0.03

AIC: = 16.2173

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.3	0	0	0	10	0
3	0	0	0	10	0
30	0.3	3	3	10	0

Chi^2 = 0   d.f = 2   P-value = 1

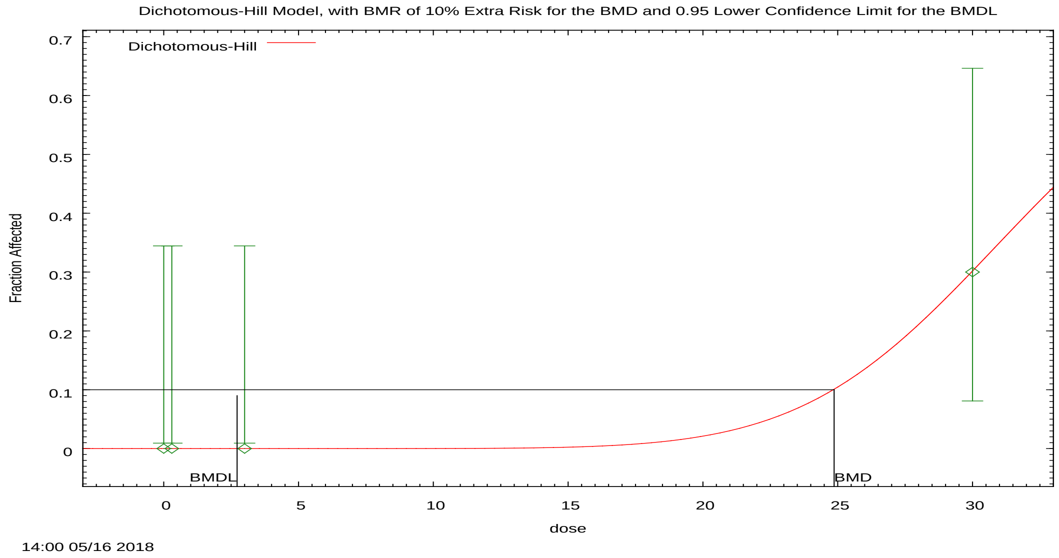

Figure 229. Plot of incidence rate by dose with fitted curve for Dichotomous-Hill model for Hepatocellular Necrosis in Males (28-Day Rats); dose shown in mg/kg/day.

Dichotomous Hill Model. (Version: 1.3; Date: 02/28/2013)

The form of the probability function is: P[response] = v*g +(v-v*g)/[1+EXP(-intercept-slope*Log(dose))]

Slope parameter is restricted as slope >= 1

Warning: BMDL computation is at best imprecise for these data

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 24.8662

BMDL at the 95% confidence level = 2.72083

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
v	0.789447	1
g	0	0

intercept	-2.6606E+01	-4.2523E+00
slope	7.67852	1

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-6.11	4			
Fitted model	-6.11	3	0.000000207435	1	1
Reduced model	-10.66	1	9.09347	3	0.03

AIC: = 18.2173

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.3	0	0	0	10	0
3	0	0	0	10	0
30	0.3	3	3	10	0

Chi^2 = 0 d.f = 1 P-value = 0.9997

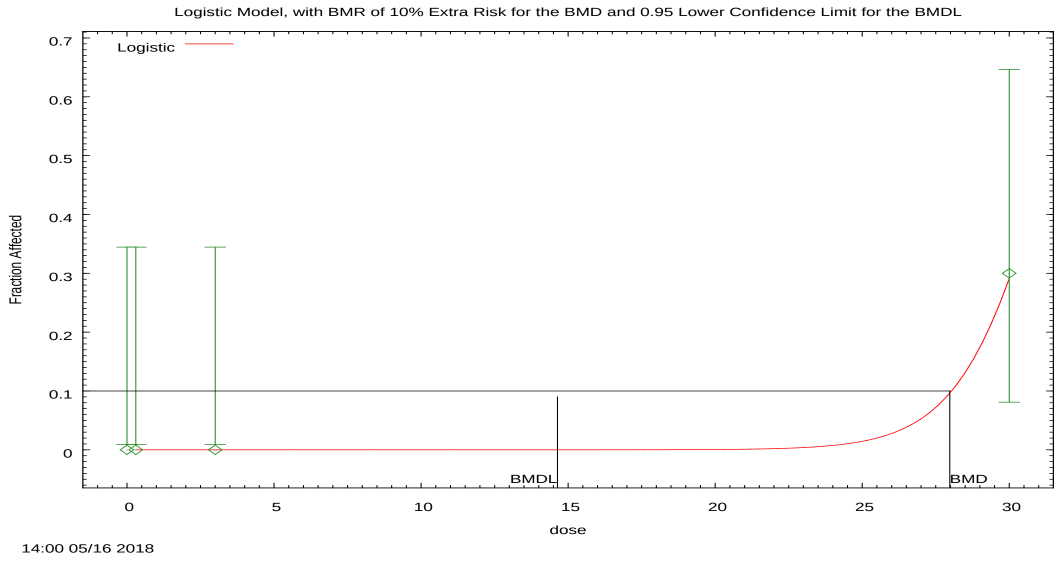

Figure 230. Plot of incidence rate by dose with fitted curve for Logistic model for Hepatocellular Necrosis in Males (28-Day Rats); dose shown in mg/kg/day.

Logistic Model. (Version: 2.15; Date: 3/20/2017)

The form of the probability function is: P[response] = 1/[1+EXP(-intercept-slope*dose)]

Slope parameter is not restricted

THE MODEL HAS PROBABLY NOT CONVERGED!!!

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 27.9773

BMDL at the 95% confidence level = 14.6373

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
background	n/a	0
intercept	-2.0869E+01	-3.1257E+00
slope	0.66738	0.0782927

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-6.11	4			
Fitted model	-6.11	2	0.000000166474	2	1
Reduced model	-10.66	1	9.09347	3	0.03

AIC: = 16.2173

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.3	0	0	0	10	0
3	0	0	0	10	0
30	0.3	3	3	10	0

Chi^2 = 0   d.f = 2   P-value = 1

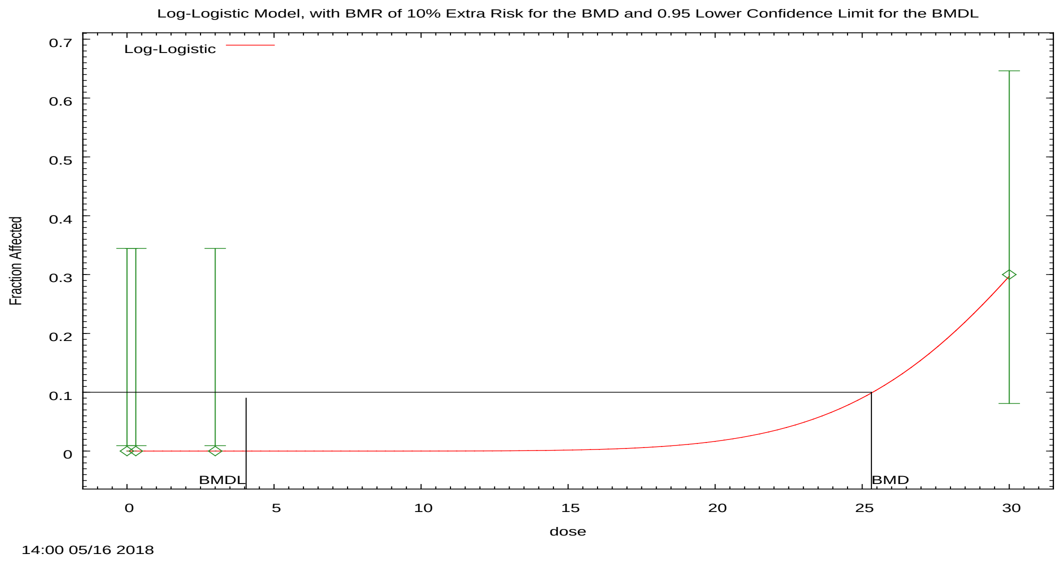

Figure 231. Plot of incidence rate by dose with fitted curve for LogLogistic model for Hepatocellular Necrosis in Males (28-Day Rats); dose shown in mg/kg/day.

Logistic Model. (Version: 2.15; Date: 3/20/2017)

The form of the probability function is: P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]

Slope parameter is restricted as slope >= 1

THE MODEL HAS PROBABLY NOT CONVERGED!!!

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 25.3124

BMDL at the 95% confidence level = 4.05137

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
background	0	0
intercept	-2.7871E+01	-4.2523E+00
slope	7.94535	1

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-6.11	4			
Fitted model	-6.11	2	0.0000000972086	2	1
Reduced model	-10.66	1	9.09347	3	0.03

AIC: = 16.2173

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.3	0	0	0	10	0
3	0	0	0	10	0
30	0.3	3	3	10	0

Chi^2 = 0   d.f = 2   P-value = 1

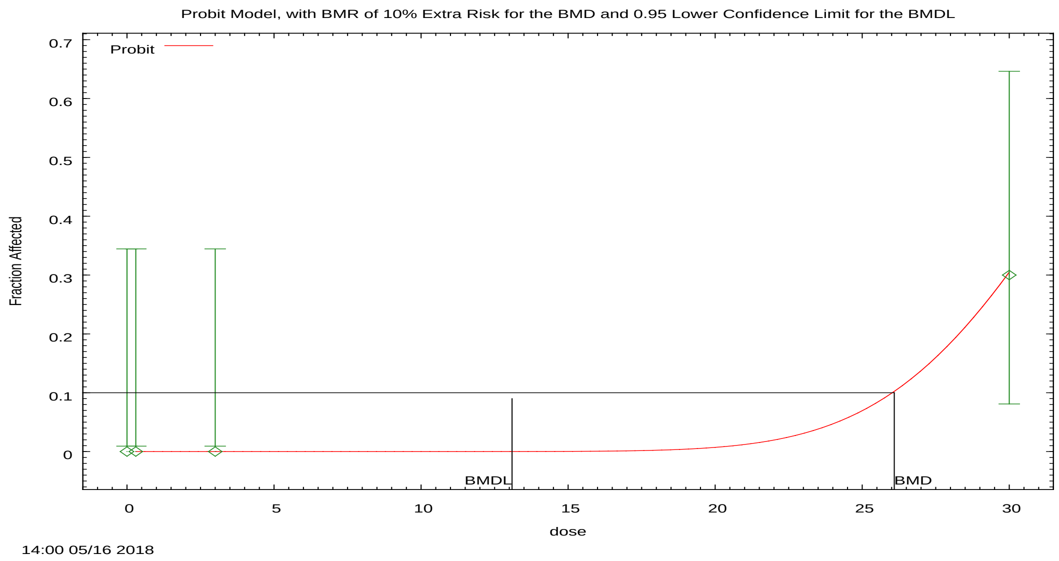

Figure 232. Plot of incidence rate by dose with fitted curve for Probit model for Hepatocellular Necrosis in Males (28-Day Rats); dose shown in mg/kg/day.

Probit Model. (Version: 3.4; Date: 5/21/2017)

The form of the probability function is: P[response] = CumNorm(Intercept+Slope*Dose), where CumNorm(.) is the cumulative normal distribution function

Slope parameter is not restricted

THE MODEL HAS PROBABLY NOT CONVERGED!!!

Warning: BMDU computation is at best imprecise for these data

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 26.0894

BMDL at the 95% confidence level = 13.0927

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
background	n/a	0

intercept	-6.3329E+00	-2.1652E+00
slope	0.193616	0.0550069

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-6.11	4			
Fitted model	-6.11	2	0.0000000940851	2	1
Reduced model	-10.66	1	9.09347	3	0.03

AIC: = 16.2173

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.3	0	0	0	10	0
3	0	0	0	10	0
30	0.3	3	3	10	0

Chi^2 = 0 d.f = 2 P-value = 1

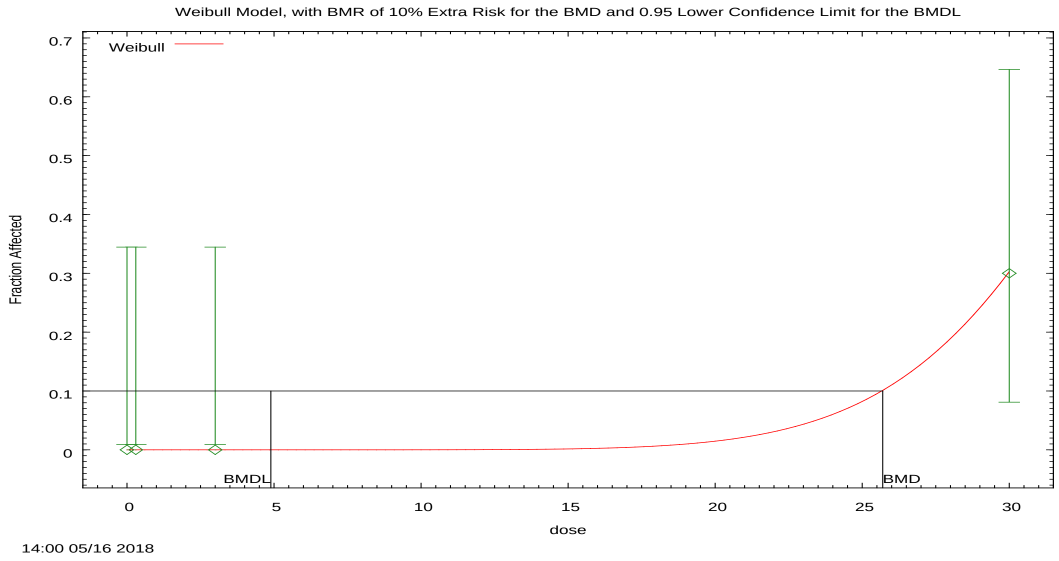

Figure 233. Plot of incidence rate by dose with fitted curve for Weibull model for Hepatocellular Necrosis in Males (28-Day Rats); dose shown in mg/kg/day.

Weibull Model using Weibull Model (Version: 2.17; Date: 6/23/2017)

The form of the probability function is: P[response] = background + (1-background)*[1-EXP(-slope*dose^power)]

Power parameter is restricted as power >=1

Warning: BMDU computation is at best imprecise for these data

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 25.6972

BMDL at the 95% confidence level = 4.89143

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0	0.0833333
Slope	8.2683E-13	0.00385791
Power	7.87671	1.29759

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-6.11	4			
Fitted model	-6.11	2	0.0000000947531	2	1
Reduced model	-10.66	1	9.09347	3	0.03

AIC: = 16.2173

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.3	0	0	0	10	0
3	0	0	0	10	0
30	0.3	3	3	10	0

Chi^2 = 0 d.f = 2 P-value = 1

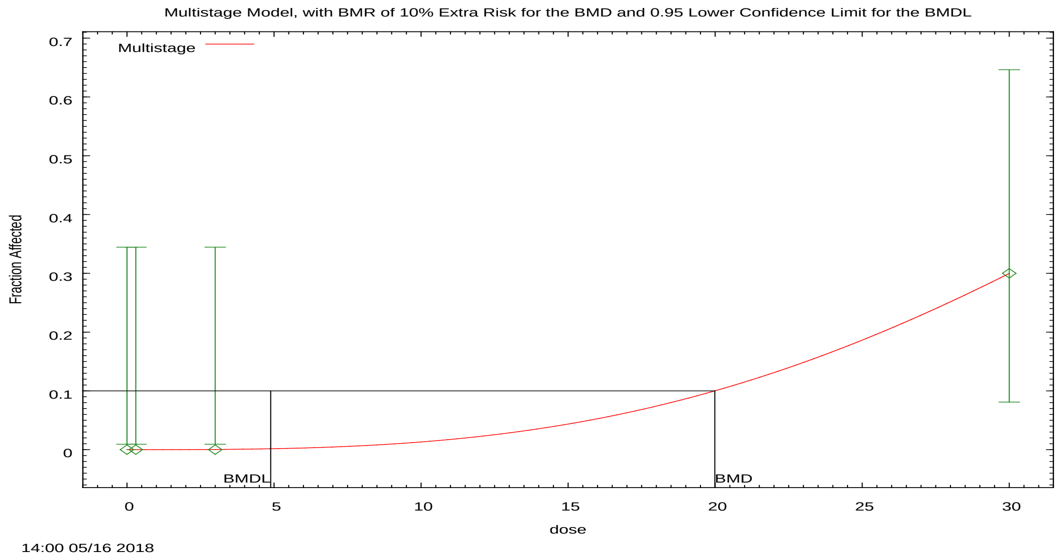

Figure 234. Plot of incidence rate by dose with fitted curve for Multistage 3° model for Hepatocellular Necrosis in Males (28-Day Rats); dose shown in mg/kg/day.

Multistage Model. (Version: 3.4; Date: 05/02/2014)

The form of the probability function is: P[response] = background + (1-background)*[1-EXP(-beta1*dose^1-beta2*dose^2...)]

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 19.9877

BMDL at the 95% confidence level = 4.88581

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0	0
Beta(1)	0	0
Beta(2)	0	0
Beta(3)	0.0000131943	0.0000132146

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-6.11	4			
Fitted model	-6.11	1	0.00713634	3	1
Reduced model	-10.66	1	9.09347	3	0.03

AIC: = 14.2244

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.3	0	0	0	10	0
3	0.0004	0.004	0	10	-0.06
30	0.2997	2.997	3	10	0

Chi^2 = 0   d.f = 3   P-value = 0.9999

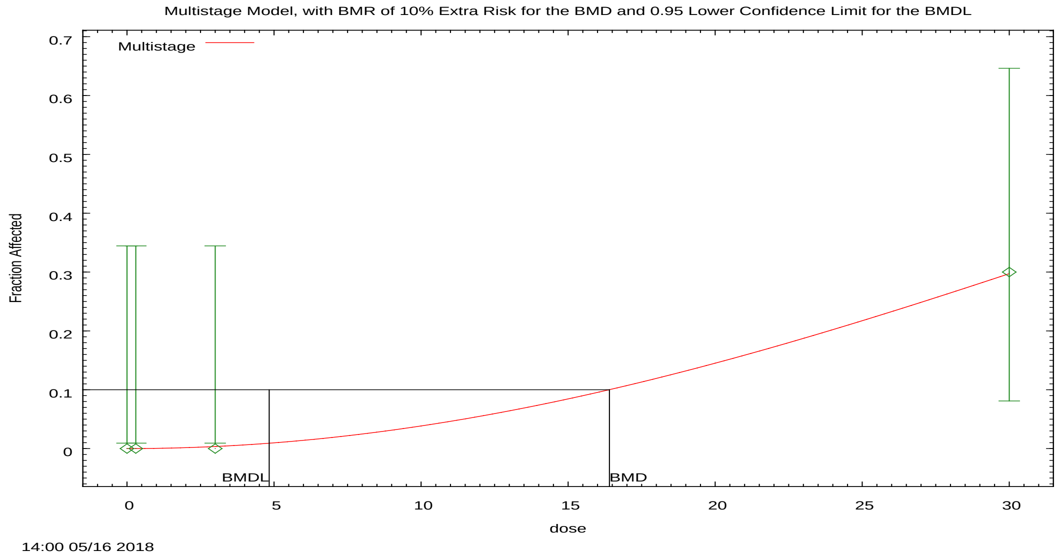

Figure 235. Plot of incidence rate by dose with fitted curve for Multistage 2° model for Hepatocellular Necrosis in Males (28-Day Rats); dose shown in mg/kg/day.

Multistage Model. (Version: 3.4; Date: 05/02/2014)

The form of the probability function is: P[response] = background + (1-background)*[1-EXP(-beta1*dose^1-beta2*dose^2...)]

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 16.4037

BMDL at the 95% confidence level = 4.83587

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0	0
Beta(1)	0	0
Beta(2)	0.000391555	0.000397609

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-6.11	4			
Fitted model	-6.14	1	0.0716147	3	1
Reduced model	-10.66	1	9.09347	3	0.03

AIC: = 14.2889

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.3	0	0	0	10	-0.02
3	0.0035	0.035	0	10	-0.19
30	0.297	2.97	3	10	0.02

Chi^2 = 0.04   d.f = 3   P-value = 0.9982

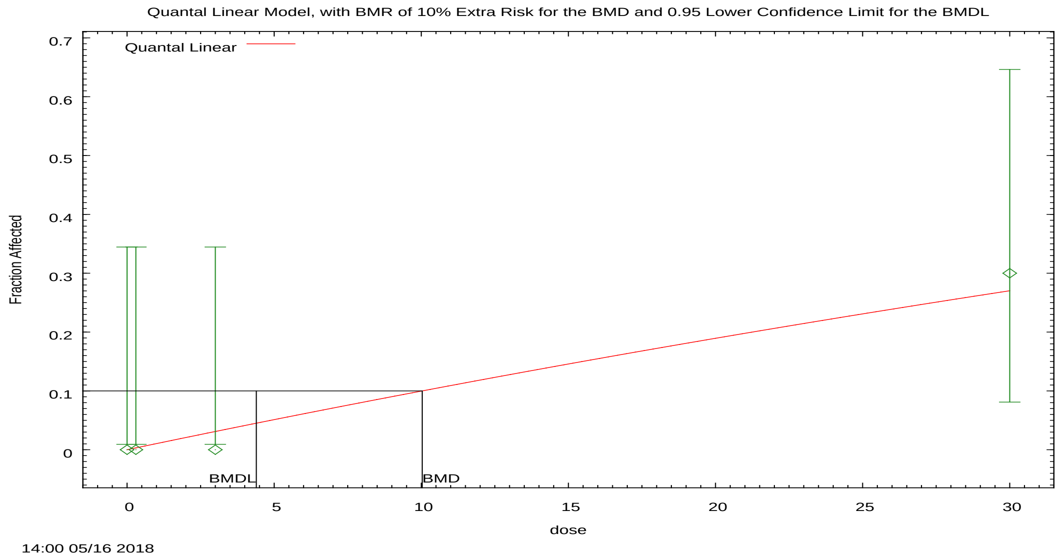

Figure 236. Plot of incidence rate by dose with fitted curve for Quantal-Linear model for Hepatocellular Necrosis in Males (28-Day Rats); dose shown in mg/kg/day.

Quantal Linear Model using Weibull Model (Version: 2.17; Date: 6/23/2017)

The form of the probability function is: P[response] = background + (1-background)*[1-EXP(-slope*dose)]

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 10.0318

BMDL at the 95% confidence level = 4.39358

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0	0.0833333
Slope	0.0105027	0.0106151
Power	n/a	1

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-6.11	4			
Fitted model	-6.48	1	0.737024	3	0.86
Reduced model	-10.66	1	9.09347	3	0.03

AIC: = 14.9543

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid

0	0	0	0	10	0
0.3	0.0031	0.031	0	10	-0.18
3	0.031	0.31	0	10	-0.57
30	0.2703	2.703	3	10	0.21

Chi^2 = 0.4 d.f = 3 P-value = 0.941

BMDS WIZARD OUTPUT REPORT

BMDS Summary of H-28548: Subchronic Toxicity 90-Day Gavage Study in Mice – Single Cell Hepatocellular Necrosis in Males

1.27. BMDS Summary of Single Cell Necrosis, Hepatocellular Male (90 Day Mice GenX)

Table 27. Summary of BMD Modeling Results for Single Cell Hepatocellular Necrosis in Males (90-Day Mice)

Model[a]	Goodness of fit		BMD_{10Pct} (mg/kg/day)	$BMDL_{10Pct}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Gamma	1.000	2.0001	1.39	0.452	3.08	BMDLs from models that met model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values > 2.0; appropriate variance (continuous data only)) were compared. BMDLs from included models were not sufficiently close (> 3-fold difference), so the lowest BMDL was selected. Note: visual inspection of the selected model shows that the fitted curve does not fit the data well, and a different model may be more appropriate.
Dichotomous-Hill[b]	1.000	2.00	1.40	0.466	3.00	
Logistic	1.000	4.00	2.64	0.477	5.53	
LogLogistic[c]	1.000	2.00	1.40	0.466	3.00	
Probit	1.000	4.00	2.34	0.470	4.98	
LogProbit	1.000	4.00	1.00	0.464	2.16	
Weibull	1.000	2.00	3.61	0.449	8.04	
Multistage 3°	0.994	2.1593	1.24	0.437	2.84	
Multistage 2°	0.899	3.1588	0.759	0.349	2.17	
Quantal-Linear	**0.245**	**9.6272**	**0.236**	**0.126**	**1.87**	

[a] Selected model in bold; scaled residuals for selected model for doses 0, 0.1, 0.5, and 5 mg/kg/day were 0, -0.68, -1.58, 1.1, respectively.

[b] The Dichotomous-Hill model may appear equivalent to the LogLogistic model, however differences exist in digits not displayed in the table.

[c] The LogLogistic model may appear equivalent to the Dichotomous-Hill model, however differences exist in digits not displayed in the table.

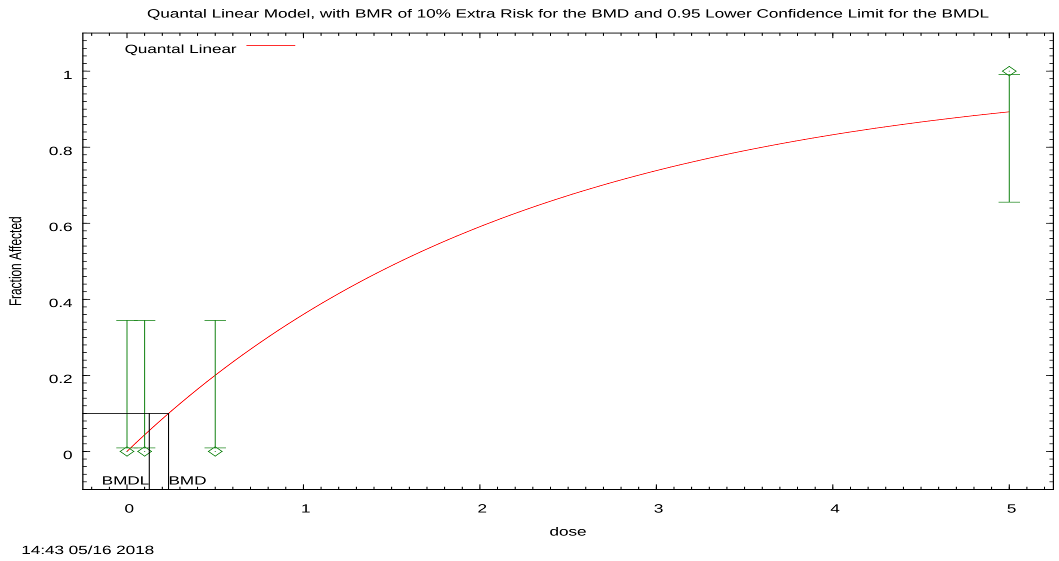

Figure 237. Plot of incidence rate by dose with fitted curve for Quantal-Linear model for Single Cell Hepatocellular Necrosis in Males (90-Day Mice); dose shown in mg/kg/day.

Quantal Linear Model using Weibull Model (Version: 2.17; Date: 6/23/2017)

The form of the probability function is: P[response] = background + (1-background)*[1-EXP(-slope*dose)]

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 0.235854

BMDL at the 95% confidence level = 0.126139

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0	0.0833333
Slope	0.446718	0.479579
Power	n/a	1

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	0	4			
Fitted model	-3.81	1	7.6272	3	0.05
Reduced model	-22.49	1	44.9868	3	<.0001

AIC: = 9.6272

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.1	0.0437	0.437	0	10	-0.68
0.5	0.2002	2.002	0	10	-1.58
5	0.8929	8.929	10	10	1.1

Chi^2 = 4.16   d.f = 3   P-value = 0.2447

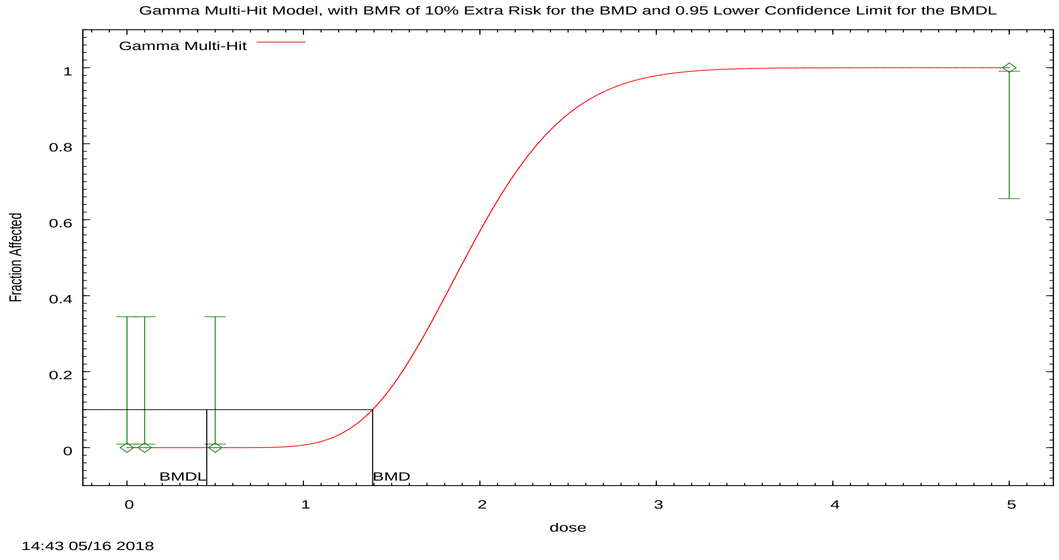

Figure 238. Plot of incidence rate by dose with fitted curve for Gamma model for Single Cell Hepatocellular Necrosis in Males (90-Day Mice); dose shown in mg/kg/day.

Gamma Model. (Version: 2.17; Date: 6/22/2017)

The form of the probability function is: P[response]= background+(1-background)*CumGamma[slope*dose,power], where CumGamma(.) is the cumulative Gamma distribution function

Power parameter is restricted as power >=1

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 1.39209

BMDL at the 95% confidence level = 0.45197

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0	0.0833333
Slope	9.21034	1.6901
Power	18	5.22392

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	0	4			
Fitted model	0	1	0.0000521053	3	1
Reduced model	-22.49	1	44.9868	3	<.0001

AIC: = 2.00005

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.1	0	0	0	10	0
0.5	0	0	0	10	0
5	1	10	10	10	0

Chi^2 = 0 d.f = 3 P-value = 1

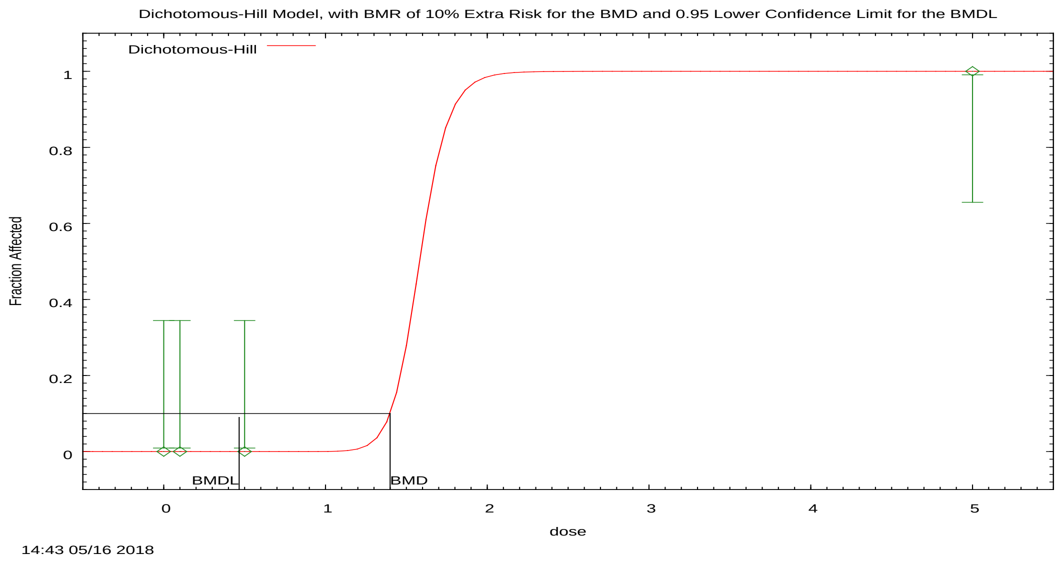

Figure 239. Plot of incidence rate by dose with fitted curve for Dichotomous-Hill model for Single Cell Hepatocellular Necrosis in Males (90-Day Mice); dose shown in mg/kg/day.

Dichotomous Hill Model. (Version: 1.3; Date: 02/28/2013)

The form of the probability function is: P[response] = v*g +(v-v*g)/[1+EXP(-intercept-slope*Log(dose))]

Slope parameter is restricted as slope >= 1

THE MODEL HAS PROBABLY NOT CONVERGED!!!

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 1.39943

BMDL at the 95% confidence level = 0.466176

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
v	1	1
g	0	0

intercept	-8.2464E+00	-2.6100E-01
slope	18	1.63135

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	0	4			
Fitted model	0	1	0.00000004	3	1
Reduced model	-22.49	1	44.9868	3	<.0001

AIC: = 2

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.1	0	0	0	10	0
0.5	0	0	0	10	0
5	1	10	10	10	0

Chi^2 = 0 d.f = 3 P-value = 1

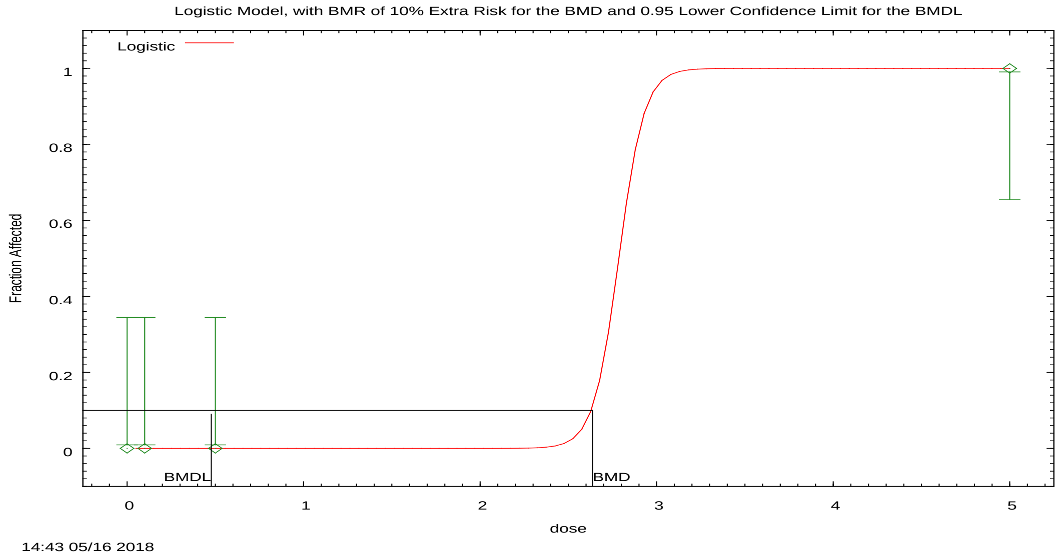

Figure 240. Plot of incidence rate by dose with fitted curve for Logistic model for Single Cell Hepatocellular Necrosis in Males (90-Day Mice); dose shown in mg/kg/day.

Logistic Model. (Version: 2.15; Date: 3/20/2017)

The form of the probability function is: P[response] = 1/[1+EXP(-intercept-slope*dose)]

Slope parameter is not restricted

THE MODEL HAS PROBABLY NOT CONVERGED!!!

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 2.63733

BMDL at the 95% confidence level = 0.476972

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
background	n/a	0
intercept	-3.9049E+01	-3.2840E+00
slope	13.9732	1.25836

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	0	4			
Fitted model	0	2	1.06359E-12	2	1
Reduced model	-22.49	1	44.9868	3	<.0001

AIC: = 4

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid

0	0	0	0	10	0
0.1	0	0	0	10	0
0.5	0	0	0	10	0
5	1	10	10	10	0

Chi^2 = 0   d.f = 2   P-value = 1

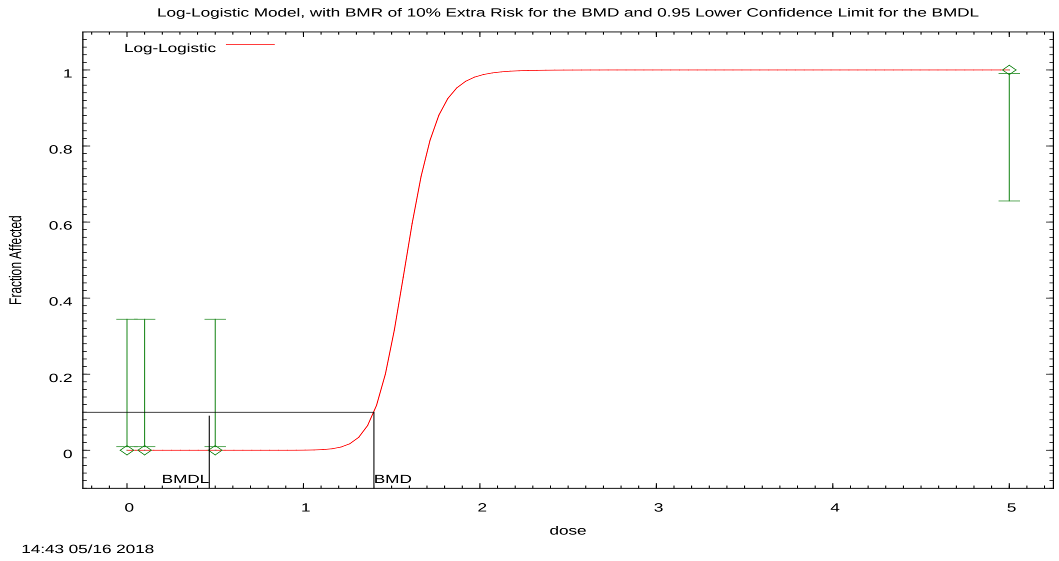

Figure 241. Plot of incidence rate by dose with fitted curve for LogLogistic model for Single Cell Hepatocellular Necrosis in Males (90-Day Mice); dose shown in mg/kg/day.

Logistic Model. (Version: 2.15; Date: 3/20/2017)

The form of the probability function is: P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]

Slope parameter is restricted as slope >= 1

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 1.39944

BMDL at the 95% confidence level = 0.466176

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
background	0	0
intercept	-8.2466E+00	-2.6100E-01
slope	18	1.63135

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	0	4			
Fitted model	0	1	0.00000004	3	1
Reduced model	-22.49	1	44.9868	3	<.0001

AIC: = 2

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.1	0	0	0	10	0
0.5	0	0	0	10	0
5	1	10	10	10	0

Chi^2 = 0 d.f = 3 P-value = 1

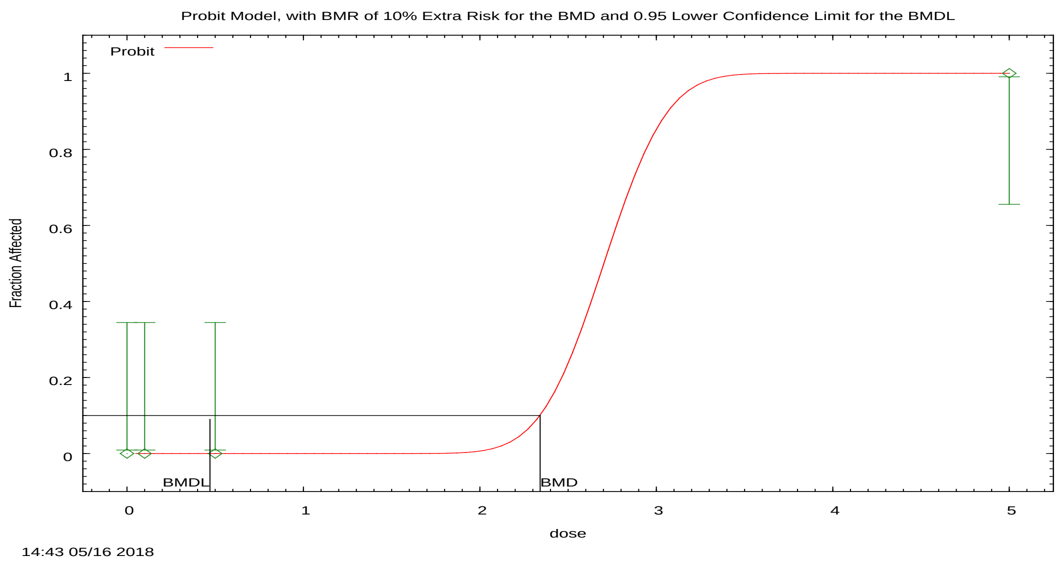

Figure 242. Plot of incidence rate by dose with fitted curve for Probit model for Single Cell Hepatocellular Necrosis in Males (90-Day Mice); dose shown in mg/kg/day.

Probit Model. (Version: 3.4; Date: 5/21/2017)

The form of the probability function is: P[response] = CumNorm(Intercept+Slope*Dose), where CumNorm(.) is the cumulative normal distribution function

Slope parameter is not restricted

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 2.34148

BMDL at the 95% confidence level = 0.470268

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
background	n/a	0
intercept	-9.5416E+00	-2.2679E+00
slope	3.52773	0.839812

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	0	4			
Fitted model	0	2	7.99361E-14	2	1
Reduced model	-22.49	1	44.9868	3	<.0001

AIC: = 4

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.1	0	0	0	10	0
0.5	0	0	0	10	0
5	1	10	10	10	0

Chi^2 = 0   d.f = 2   P-value = 1

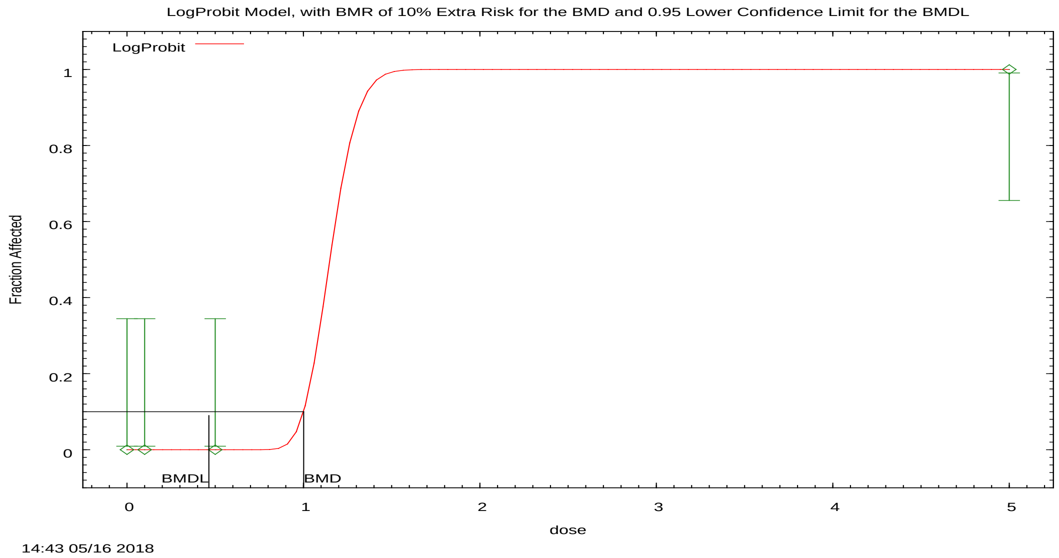

Figure 243. Plot of incidence rate by dose with fitted curve for LogProbit model for Single Cell Hepatocellular Necrosis in Males (90-Day Mice); dose shown in mg/kg/day.

Probit Model. (Version: 3.4; Date: 5/21/2017)

The form of the probability function is: P[response] = Background + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)),where CumNorm(.) is the cumulative normal distribution function

Slope parameter is not restricted

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 1.00134

BMDL at the 95% confidence level = 0.464193

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
background	0	0
intercept	-1.2939E+00	-1.4493E-01
slope	9.24923	0.905889

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	0	4			
Fitted model	0	2	1.31006E-13	2	1
Reduced model	-22.49	1	44.9868	3	<.0001

AIC: = 4

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.1	0	0	0	10	0
0.5	0	0	0	10	0
5	1	10	10	10	0

Chi^2 = 0 d.f = 2 P-value = 1

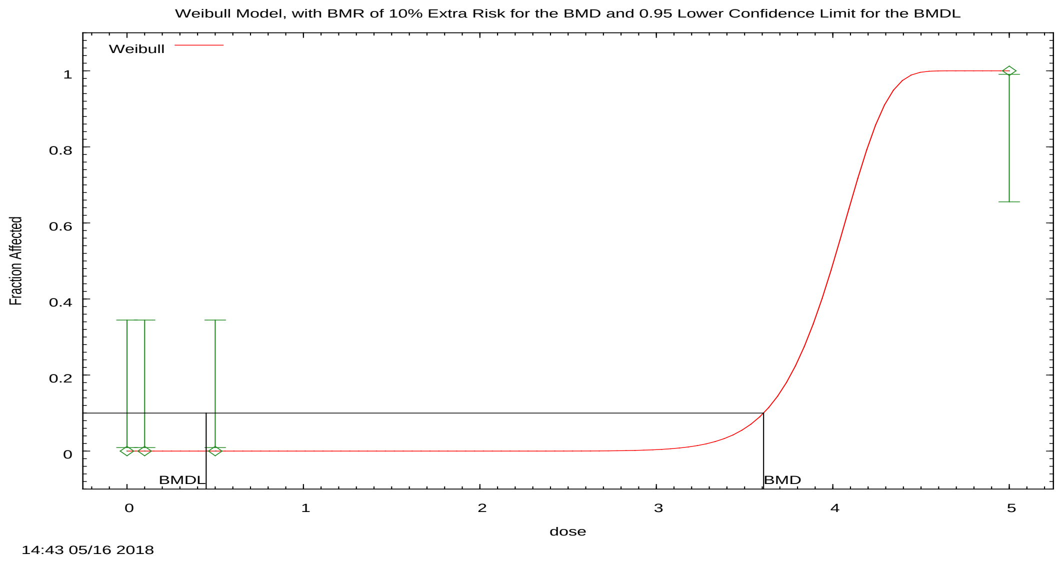

Figure 244. Plot of incidence rate by dose with fitted curve for Weibull model for Single Cell Hepatocellular Necrosis in Males (90-Day Mice); dose shown in mg/kg/day.

Weibull Model using Weibull Model (Version: 2.17; Date: 6/23/2017)

The form of the probability function is: P[response] = background + (1-background)*[1-EXP(-slope*dose^power)]

Power parameter is restricted as power >=1

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 3.60768

BMDL at the 95% confidence level = 0.448866

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0	0.0833333
Slope	9.8305E-12	0.0591487
Power	18	2.30036

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	0	4			
Fitted model	0	1	0	3	1
Reduced model	-22.49	1	44.9868	3	<.0001

AIC: = 2

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.1	0	0	0	10	0
0.5	0	0	0	10	0
5	1	10	10	10	0

Chi^2 = 0 d.f = 3 P-value = 1

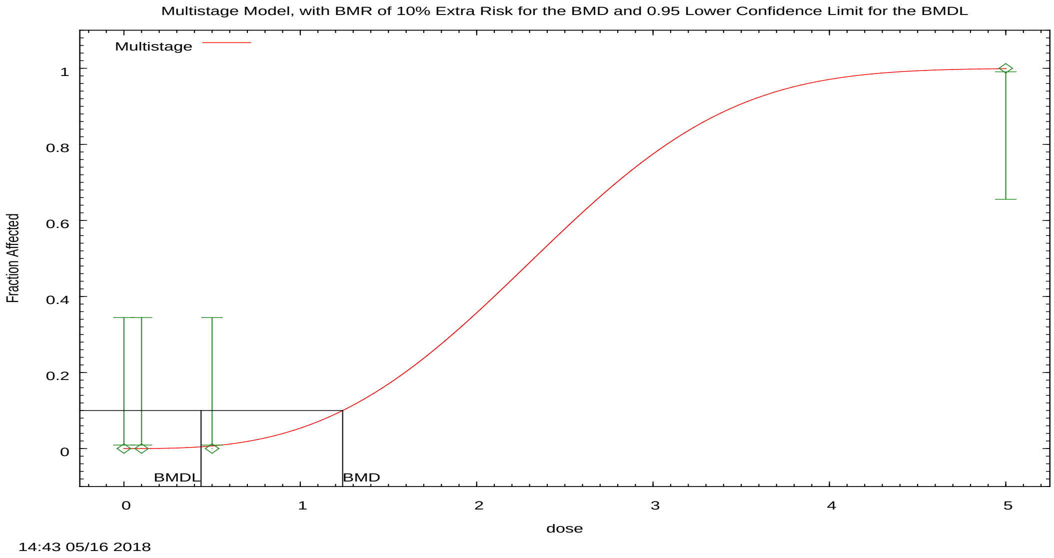

Figure 245. Plot of incidence rate by dose with fitted curve for Multistage 3° model for Single Cell Hepatocellular Necrosis in Males (90-Day Mice); dose shown in mg/kg/day.

Multistage Model. (Version: 3.4; Date: 05/02/2014)

The form of the probability function is: P[response] = background + (1-background)*[1-EXP(-beta1*dose^1-beta2*dose^2...)]

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 1.24024

BMDL at the 95% confidence level = 0.437315

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0	0
Beta(1)	0	0
Beta(2)	0	0

Beta(3)	0.0552283	8.0027E+17

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	0	4			
Fitted model	-0.08	1	0.15927	3	0.98
Reduced model	-22.49	1	44.9868	3	<.0001

AIC: = 2.15927

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.1	0.0001	0.001	0	10	-0.02
0.5	0.0069	0.069	0	10	-0.26
5	0.999	9.99	10	10	0.1

Chi^2 = 0.08 d.f = 3 P-value = 0.9941

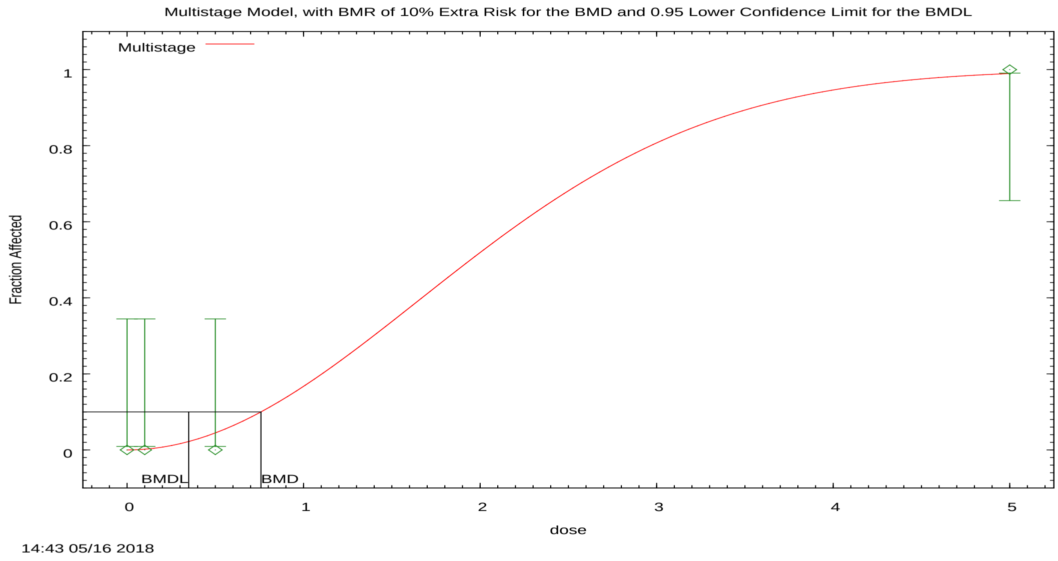

Figure 246. Plot of incidence rate by dose with fitted curve for Multistage 2° model for Single Cell Hepatocellular Necrosis in Males (90-Day Mice); dose shown in mg/kg/day.

Multistage Model. (Version: 3.4; Date: 05/02/2014)

The form of the probability function is: P[response] = background + (1-background)*[1-EXP(-beta1*dose^1-beta2*dose^2...)]

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 0.758655

BMDL at the 95% confidence level = 0.349241

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0	0
Beta(1)	0	0
Beta(2)	0.183058	4.0136E+18

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	0	4			
Fitted model	-0.58	1	1.1588	3	0.76
Reduced model	-22.49	1	44.9868	3	<.0001

AIC: = 3.1588

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid

0	0	0	0	10	0
0.1	0.0018	0.018	0	10	-0.14
0.5	0.0447	0.447	0	10	-0.68
5	0.9897	9.897	10	10	0.32

Chi^2 = 0.59   d.f = 3   P-value = 0.8986

BMDS WIZARD OUTPUT REPORT

BMDS Summary for Oral (Gavage) Reproduction/Developmental Toxicity Screening Study of H-28548 in Mice – Single Cell Hepatocellular Necrosis in Males

1.28. BMDS Summary of Liver - necrosis, single cell Males (Reproductive Mice GenX)

Table 28. Summary of BMD Modeling Results for Single Cell Hepatocellular Necrosis in Males (Reproductive Mice)

Model[a]	Goodness of fit		BMD_{10Pct} (mg/kg/day)	$BMDL_{10Pct}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Gamma	0.992	47.275	0.399	0.172	2.32	BMDLs from models that met model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values > 2.0; appropriate variance (continuous data only)) were compared. BMDLs from included models were sufficiently close (< 3-fold difference), so the BMDL from the model with the lowest AIC was selected.
Dichotomous-Hill LogLogistic	0.977	47.275	0.464	0.253	1.83	
Logistic	0.969	45.337	0.362	0.253	1.43	
Probit	0.960	45.358	0.349	0.236	1.48	
LogProbit	0.977	47.275	0.443	0.248	1.79	
Weibull	1.000	47.275	0.407	0.166	2.45	
Multistage 3°	1.000	47.275	0.408	0.145	2.81	
Multistage 2°	**0.995**	**45.285**	**0.368**	**0.151**	**2.43**	
Quantal-Linear	0.261	48.991	0.162	0.106	1.53	

[a] Selected model in bold; scaled residuals for selected model for doses 0, 0.1, 0.5, and 5 mg/kg/day were 0.07, -0.08, 0.01, 0, respectively.

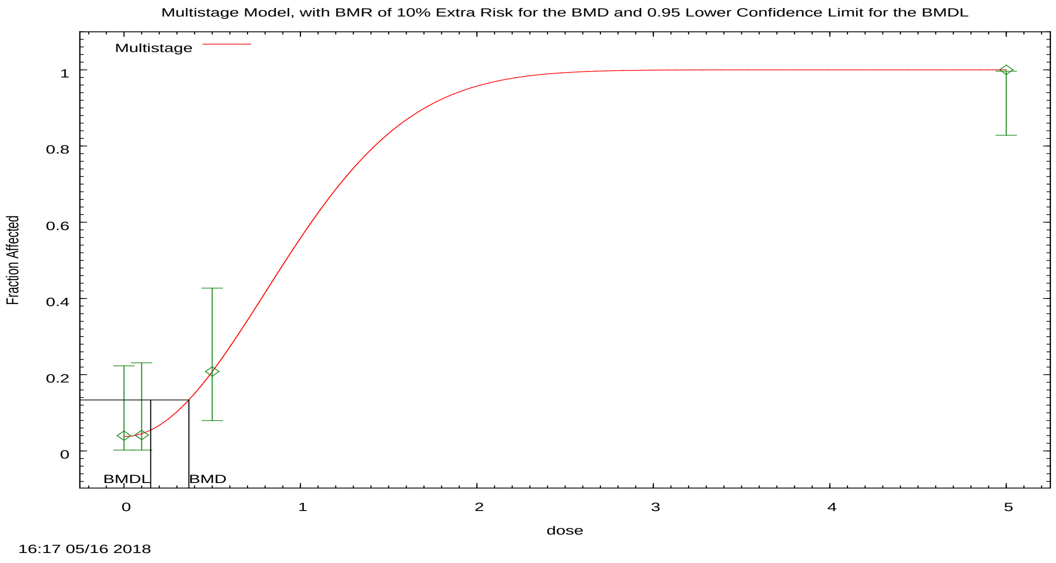

Figure 247. Plot of incidence rate by dose with fitted curve for Multistage 2° model for Single Cell Hepatocellular Necrosis in Males (Reproductive Mice); dose shown in mg/kg/day.

Multistage Model. (Version: 3.4; Date: 05/02/2014)

The form of the probability function is: P[response] = background + (1-background)*[1-EXP(-beta1*dose^1-beta2*dose^2...)]

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 0.36786

BMDL at the 95% confidence level = 0.151378

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0.0374803	0
Beta(1)	0	0
Beta(2)	0.778596	4.0136E+18

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-20.64	4			
Fitted model	-20.64	2	0.0105166	2	0.99
Reduced model	-60.78	1	80.2777	3	<.0001

AIC: = 45.2851

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0.0375	0.937	1	25	0.07
0.1	0.0449	1.079	1	24	-0.08
0.5	0.2077	4.985	5	24	0.01

5	1	24	24	24	0

Chi^2 = 0.01 d.f = 2 P-value = 0.9948

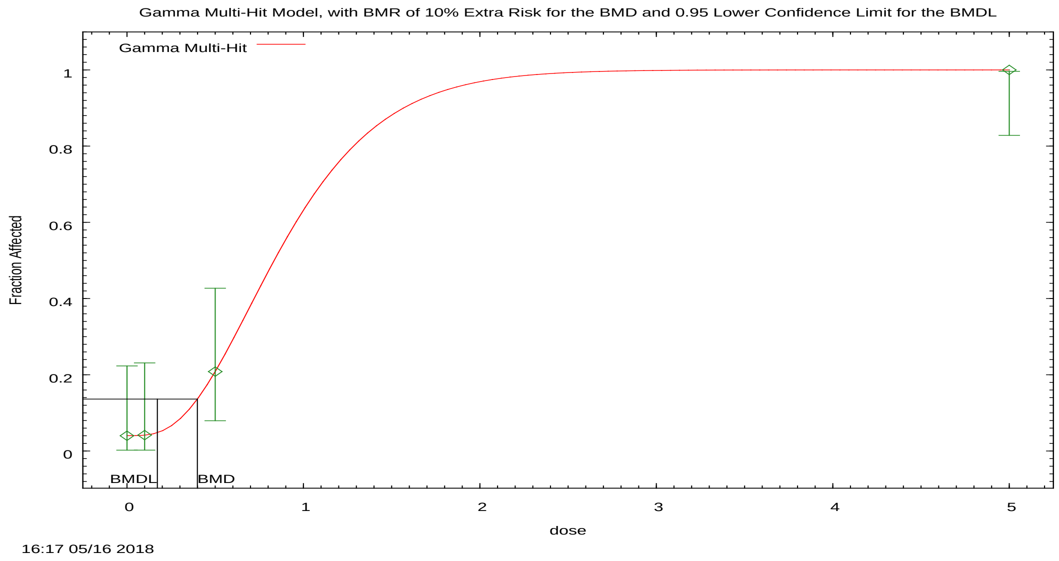

Figure 248. Plot of incidence rate by dose with fitted curve for Gamma model for Single Cell Hepatocellular Necrosis in Males (Reproductive Mice); dose shown in mg/kg/day.

Gamma Model. (Version: 2.17; Date: 6/22/2017)

The form of the probability function is: P[response]= background+(1-background)*CumGamma[slope*dose,power], where CumGamma(.) is the cumulative Gamma distribution function

Power parameter is restricted as power >=1

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 0.398912

BMDL at the 95% confidence level = 0.172112

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0.0402031	0.0740741
Slope	4.06483	1.66473
Power	3.81438	4.20395

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-20.64	4			
Fitted model	-20.64	3	0.000137835	1	0.99
Reduced model	-60.78	1	80.2777	3	<.0001

AIC: = 47.2747

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0.0402	1.005	1	25	0
0.1	0.0414	0.995	1	24	0.01
0.5	0.2084	5	5	24	0
5	1	24	24	24	0.01

Chi^2 = 0   d.f = 1   P-value = 0.9921

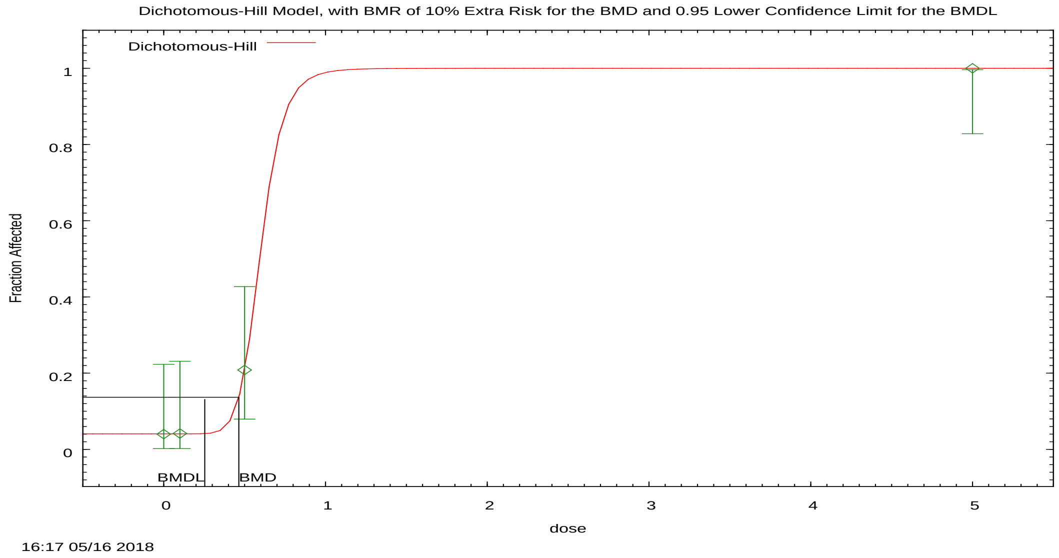

Figure 249. Plot of incidence rate by dose with fitted curve for Dichotomous-Hill model for Single Cell Hepatocellular Necrosis in Males (Reproductive Mice); dose shown in mg/kg/day.

Dichotomous Hill Model. (Version: 1.3; Date: 02/28/2013)

The form of the probability function is: P[response] = v*g +(v-v*g)/[1+EXP(-intercept-slope*Log(dose))]

Slope parameter is restricted as slope >= 1

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 0.464183

BMDL at the 95% confidence level = 0.253434

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
v	1	1
g	0.0408163	0.04
intercept	4.45404	-1.3477E-01
slope	8.66641	2.6015

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-20.64	4			
Fitted model	-20.64	3	0.000868905	1	0.98
Reduced model	-60.78	1	80.2777	3	<.0001

AIC: = 47.2754

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0.0408	1.02	1	25	-0.02
0.1	0.0408	0.98	1	24	0.02
0.5	0.2083	5	5	24	0
5	1	24	24	24	0

Chi^2 = 0   d.f = 1   P-value = 0.9765

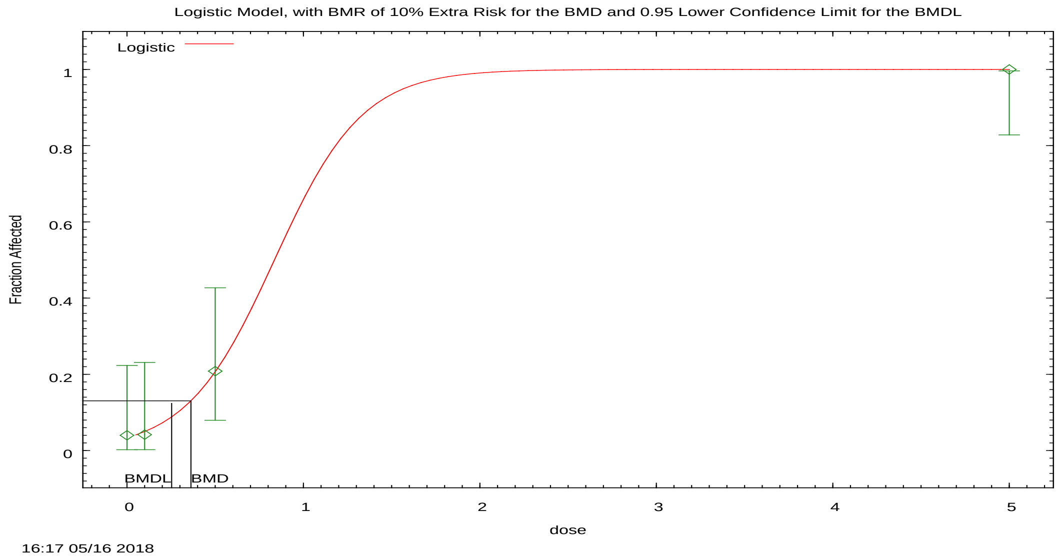

Figure 250. Plot of incidence rate by dose with fitted curve for Logistic model for Single Cell Hepatocellular Necrosis in Males (Reproductive Mice); dose shown in mg/kg/day.

Logistic Model. (Version: 2.15; Date: 3/20/2017)

The form of the probability function is: P[response] = 1/[1+EXP(-intercept-slope*dose)]

Slope parameter is not restricted

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 0.362437

BMDL at the 95% confidence level = 0.253091

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
background	n/a	0
intercept	-3.3521E+00	-2.5489E+00
slope	4.01471	1.29949

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-20.64	4			
Fitted model	-20.67	2	0.062635	2	0.97
Reduced model	-60.78	1	80.2777	3	<.0001

AIC: = 45.3372

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0.0338	0.846	1	25	0.17

0.1	0.0497	1.193	1	24	-0.18
0.5	0.2067	4.961	5	24	0.02
5	1	24	24	24	0

Chi^2 = 0.06 d.f = 2 P-value = 0.9693

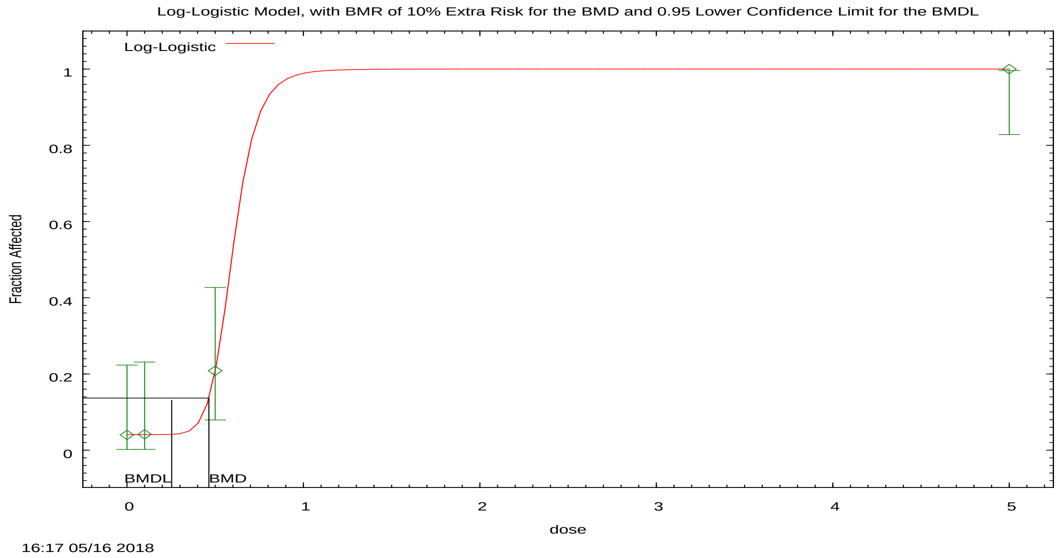

Figure 251. Plot of incidence rate by dose with fitted curve for LogLogistic model for Single Cell Hepatocellular Necrosis in Males (Reproductive Mice); dose shown in mg/kg/day.

Logistic Model. (Version: 2.15; Date: 3/20/2017)

The form of the probability function is: P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]

Slope parameter is restricted as slope >= 1

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 0.464183

BMDL at the 95% confidence level = 0.253434

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
background	0.0408163	0.04
intercept	4.45403	-1.3477E-01
slope	8.66639	2.6015

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-20.64	4			
Fitted model	-20.64	3	0.000868905	1	0.98
Reduced model	-60.78	1	80.2777	3	<.0001

AIC: = 47.2754

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0.0408	1.02	1	25	-0.02
0.1	0.0408	0.98	1	24	0.02
0.5	0.2083	5	5	24	0
5	1	24	24	24	0

Chi^2 = 0 d.f = 1 P-value = 0.9765

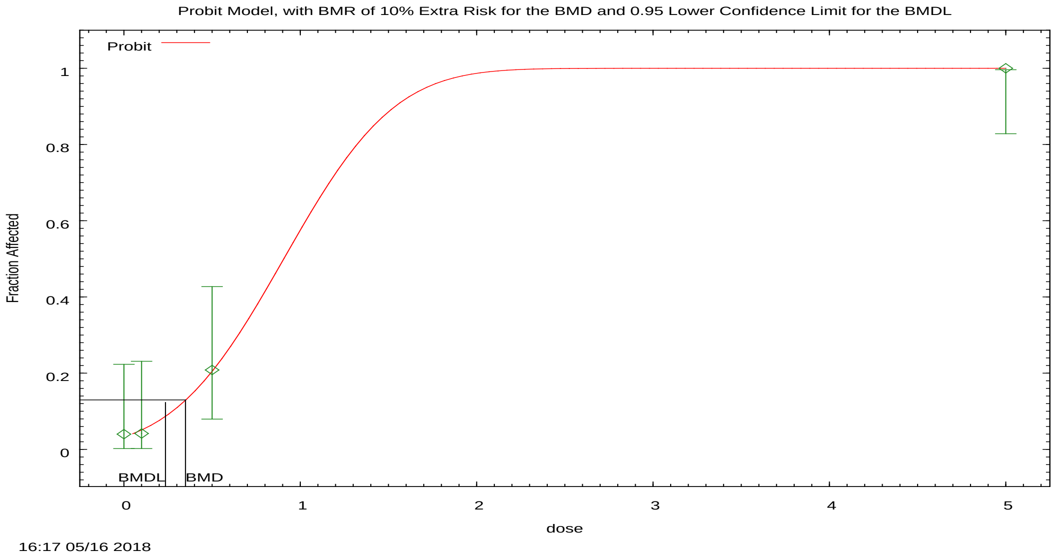

Figure 252. Plot of incidence rate by dose with fitted curve for Probit model for Single Cell Hepatocellular Necrosis in Males (Reproductive Mice); dose shown in mg/kg/day.

Probit Model. (Version: 3.4; Date: 5/21/2017)

The form of the probability function is: P[response] = CumNorm(Intercept+Slope*Dose), where CumNorm(.) is the cumulative normal distribution function

Slope parameter is not restricted

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 0.34906

BMDL at the 95% confidence level = 0.235626

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
background	n/a	0
intercept	-1.8366E+00	-1.5650E+00
slope	2.03222	0.78084

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-20.64	4			
Fitted model	-20.68	2	0.0831399	2	0.96
Reduced model	-60.78	1	80.2777	3	<.0001

AIC: = 45.3577

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0.0331	0.828	1	25	0.19
0.1	0.0512	1.229	1	24	-0.21
0.5	0.206	4.943	5	24	0.03
5	1	24	24	24	0

Chi^2 = 0.08 d.f = 2 P-value = 0.9596

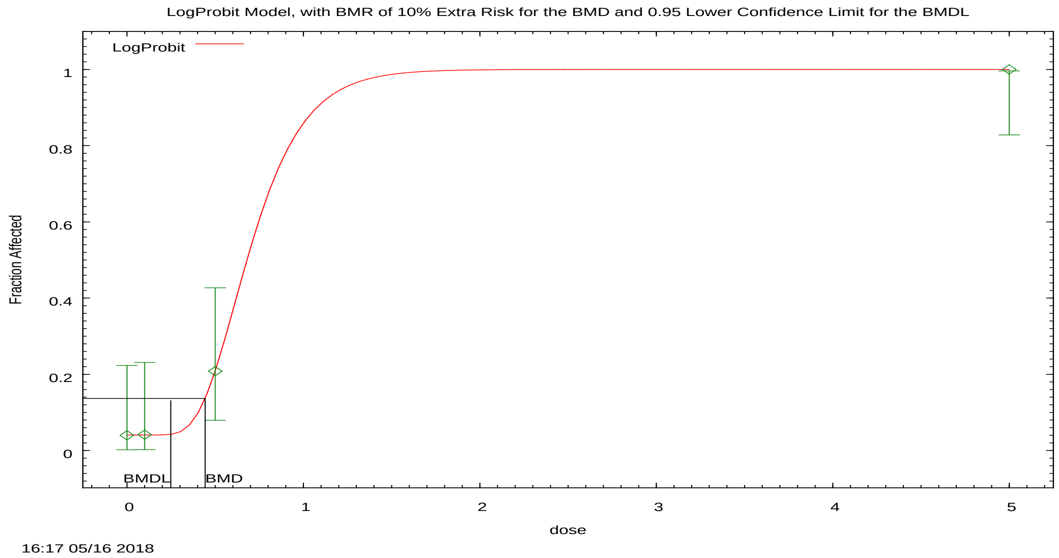

Figure 253. Plot of incidence rate by dose with fitted curve for LogProbit model for Single Cell Hepatocellular Necrosis in Males (Reproductive Mice); dose shown in mg/kg/day.

Probit Model. (Version: 3.4; Date: 5/21/2017)

The form of the probability function is: P[response] = Background + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)),where CumNorm(.) is the cumulative normal distribution function

Slope parameter is not restricted

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 0.44311

BMDL at the 95% confidence level = 0.248138

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
background	0.0408136	0.04
intercept	1.04702	-1.2059E-02
slope	2.86087	1.27378

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-20.64	4			
Fitted model	-20.64	3	0.000868989	1	0.98
Reduced model	-60.78	1	80.2777	3	<.0001

AIC: = 47.2754

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0.0408	1.02	1	25	-0.02
0.1	0.0408	0.98	1	24	0.02
0.5	0.2083	5	5	24	0
5	1	24	24	24	0

Chi^2 = 0   d.f = 1   P-value = 0.9765

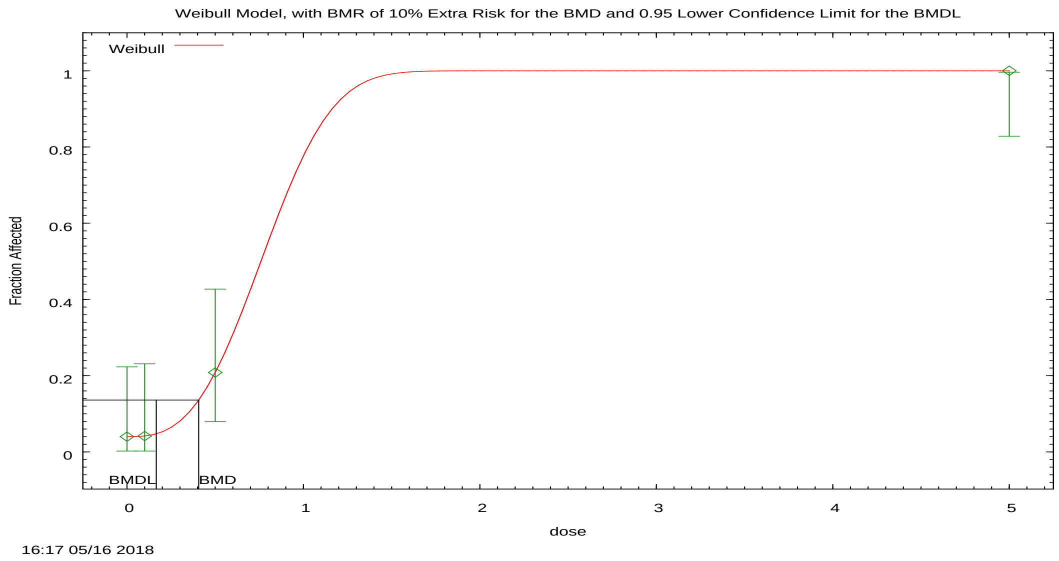

Figure 254. Plot of incidence rate by dose with fitted curve for Weibull model for Single Cell Hepatocellular Necrosis in Males (Reproductive Mice); dose shown in mg/kg/day.

Weibull Model using Weibull Model (Version: 2.17; Date: 6/23/2017)

The form of the probability function is: P[response] = background + (1-background)*[1-EXP(-slope*dose^power)]

Power parameter is restricted as power >=1

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 0.406554

BMDL at the 95% confidence level = 0.166046

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0.0399917	0.0740741
Slope	1.45834	0.126527
Power	2.9195	2.00352

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-20.64	4			
Fitted model	-20.64	3	0.000000310824	1	1
Reduced model	-60.78	1	80.2777	3	<.0001

AIC: = 47.2746

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0.04	1	1	25	0
0.1	0.0417	1	1	24	0
0.5	0.2083	4.999	5	24	0
5	1	24	24	24	0

Chi^2 = 0 d.f = 1 P-value = 0.9996

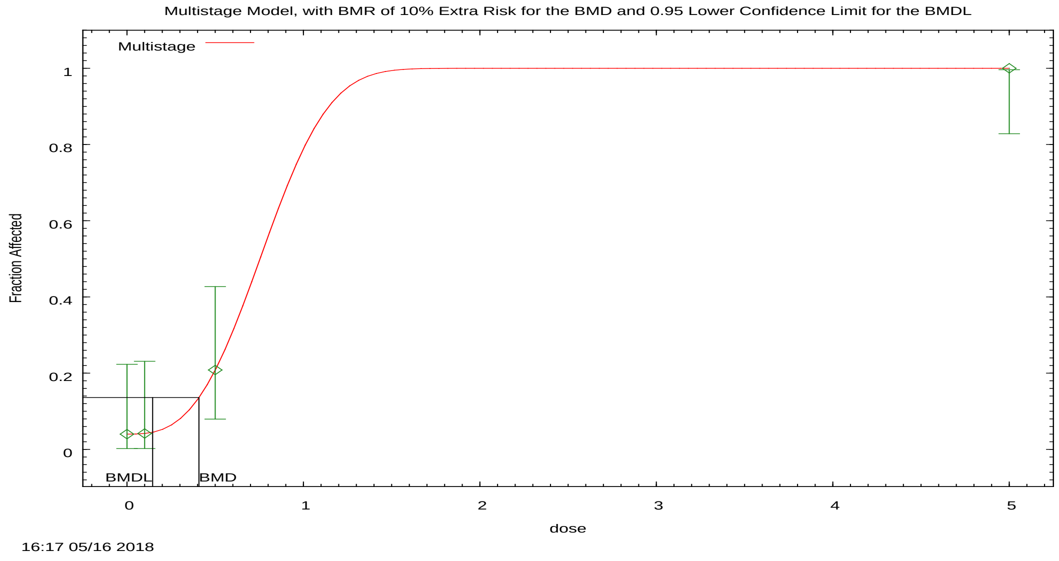

Figure 255. Plot of incidence rate by dose with fitted curve for Multistage 3° model for Single Cell Hepatocellular Necrosis in Males (Reproductive Mice); dose shown in mg/kg/day.

Multistage Model. (Version: 3.4; Date: 05/02/2014)

The form of the probability function is: P[response] = background + (1-background)*[1-EXP(-beta1*dose^1-beta2*dose^2...)]

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 0.407818

BMDL at the 95% confidence level = 0.14537

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0.04	0
Beta(1)	0	0
Beta(2)	0.0244097	0

Beta(3)	1.49352	8.0027E+17

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-20.64	4			
Fitted model	-20.64	3	1.42109E-14	1	1
Reduced model	-60.78	1	80.2777	3	<.0001

AIC: = 47.2746

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0.04	1	1	25	0
0.1	0.0417	1	1	24	0
0.5	0.2083	5	5	24	0
5	1	24	24	24	0

Chi^2 = 0 d.f = 1 P-value = 1

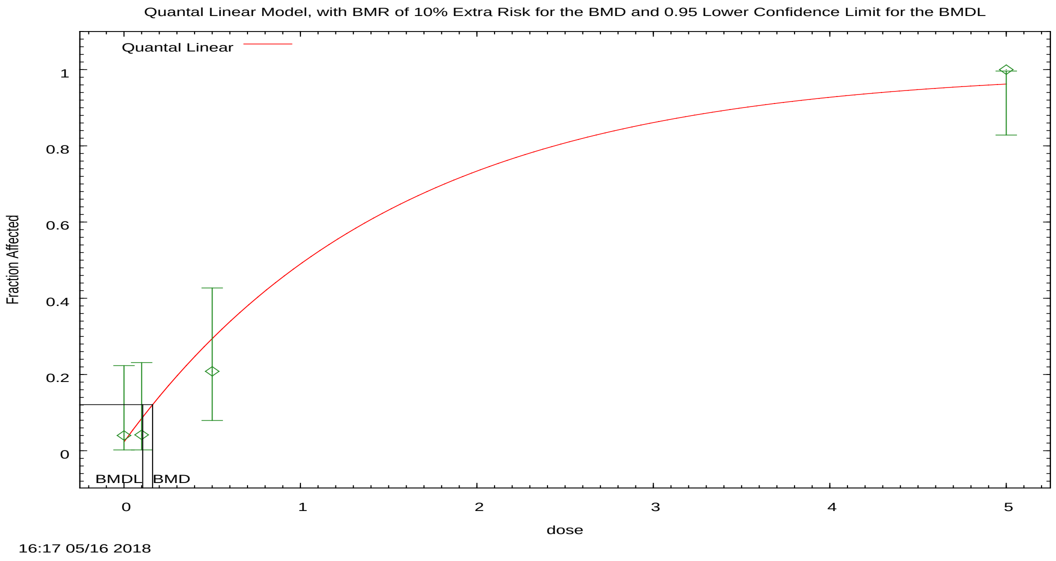

Figure 256. Plot of incidence rate by dose with fitted curve for Quantal-Linear model for Single Cell Hepatocellular Necrosis in Males (Reproductive Mice); dose shown in mg/kg/day.

Quantal Linear Model using Weibull Model (Version: 2.17; Date: 6/23/2017)

The form of the probability function is: P[response] = background + (1-background)*[1-EXP(-slope*dose)]

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 0.162062

BMDL at the 95% confidence level = 0.106106

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0.0231249	0.0740741
Slope	0.650123	0.636227
Power	n/a	1

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-20.64	4			
Fitted model	-22.5	2	3.71609	2	0.16
Reduced model	-60.78	1	80.2777	3	<.0001

AIC: = 48.9907

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid

0	0.0231	0.578	1	25	0.56
0.1	0.0846	2.031	1	24	-0.76
0.5	0.2942	7.061	5	24	-0.92
5	0.9621	23.091	24	24	0.97

Chi^2 = 2.68 d.f = 2 P-value = 0.2614

BMDS WIZARD OUTPUT REPORT

BMDS Summary of 28-Day Oral (Gavage) Toxicity Study of H-28397 in Mice with a 28-day Recovery – Liver Weight to Brain Weight (g/100g) in Males

1.29. BMDS Summary of Liver weight to brain weight (g/100g brain) Males (28 Day Mice GenX)

Table 29. Summary of BMD Modeling Results for Liver Weight to Brain Weight in Males (28-Day Mice); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD_{1SD} (mg/kg/day)	$BMDL_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2) Exponential (M3)[b]	<0.0001	442.40	8.93	6.93	1.29	Only one model met model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). Selected BMDL is from this model.
Exponential (M4) **Exponential (M5)[c]**	**0.726**	**392.82**	**0.296**	**0.194**	**1.53**	
Hill	0.871	392.73	0.238	error[d]	error	
Power[e] Linear	<0.0001	437.54	5.13	2.88	1.78	
Polynomial 3°[f] Polynomial 2°	<0.0001	435.43	0.554	0.368	1.50	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = <0.0001), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 3, and 30 mg/kg/day were -0.21, 0.31, -0.31, 0.23, respectively.
[b] For the Exponential (M3) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M2) model.
[c] For the Exponential (M5) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M4) model.
[d] BMD or BMDL computation failed for this model.
[e] For the Power model, the power parameter estimate was 1. The models in this row reduced to the Linear model.
[f] For the Polynomial 3° model, the b3 coefficient estimates was 0 (boundary of parameters space). The models in this row reduced to the Polynomial 2° model.

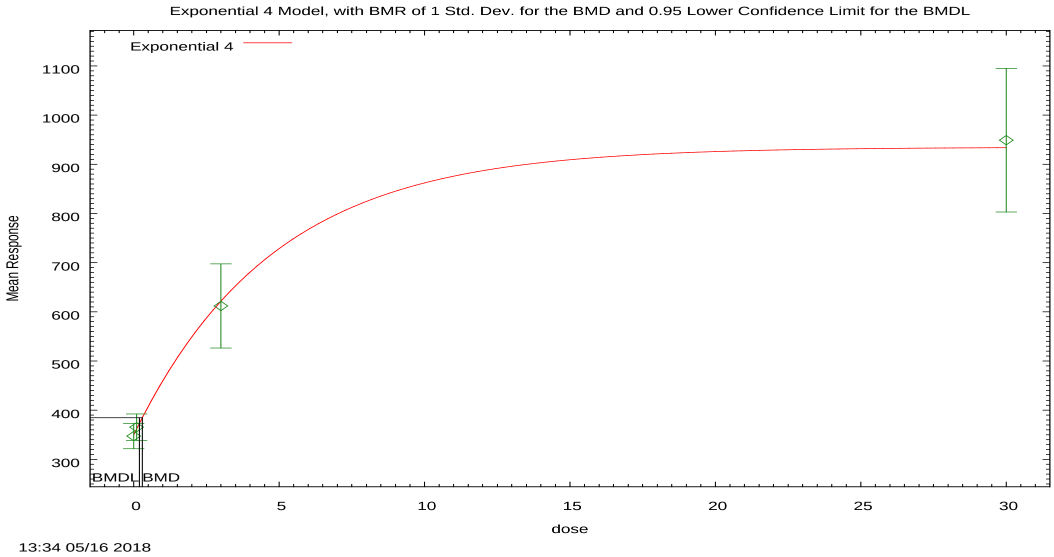

Figure 257. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Liver Weight to Brain Weight in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 0.295612

BMDL at the 95% confidence level = 0.193746

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-14.3917	-13.9147
rho	3.67106	3.60787
a	349.675	329.948
b	0.208529	0.0890268
c	2.67347	3.01988
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	347.3	349.7	35.93	34.98	-0.2134
0.1	10	365.4	361.8	37.57	37.23	0.3138
3	10	612	621.8	119.7	100.6	-0.3098
30	10	949	933.7	204.1	212.2	0.227

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-209.757	5	429.5139
A2	-191.0033	8	398.0066
A3	-191.3498	6	394.6996
R	-243.798	2	491.596
4	-191.4114	5	392.8228

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	105.6	6	<0.0001
Test 2	37.51	3	<0.0001
Test 3	0.693	2	0.7072
Test 6a	0.1232	1	0.7256

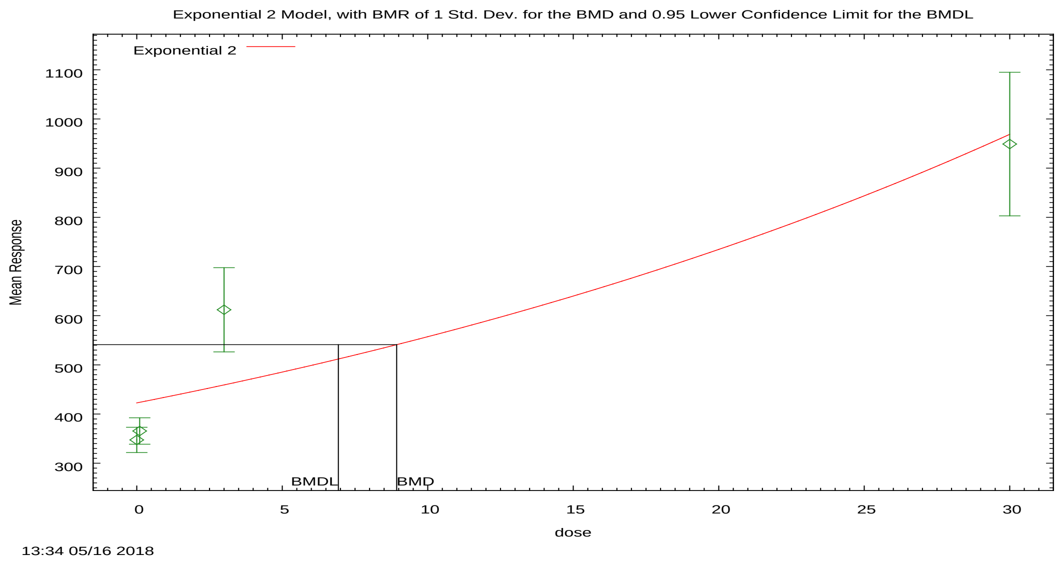

Figure 258. Plot of mean response by dose with fitted curve for Exponential (M2) model with modeled variance for Liver Weight to Brain Weight in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 8.93061

BMDL at the 95% confidence level = 6.92769

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	1.29827	-13.9147
rho	1.36434	3.60787
a	422.623	409.803
b	0.0276507	0.0290228
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	347.3	422.6	35.93	118.4	-2.012
0.1	10	365.4	423.8	37.57	118.6	-1.556
3	10	612	459.2	119.7	125.3	3.857
30	10	949	968.7	204.1	208.5	-0.3002

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-209.757	5	429.5139
A2	-191.0033	8	398.0066
A3	-191.3498	6	394.6996
R	-243.798	2	491.596
2	-217.1983	4	442.3966

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	105.6	6	<0.0001
Test 2	37.51	3	<0.0001
Test 3	0.693	2	0.7072
Test 4	51.7	2	<0.0001

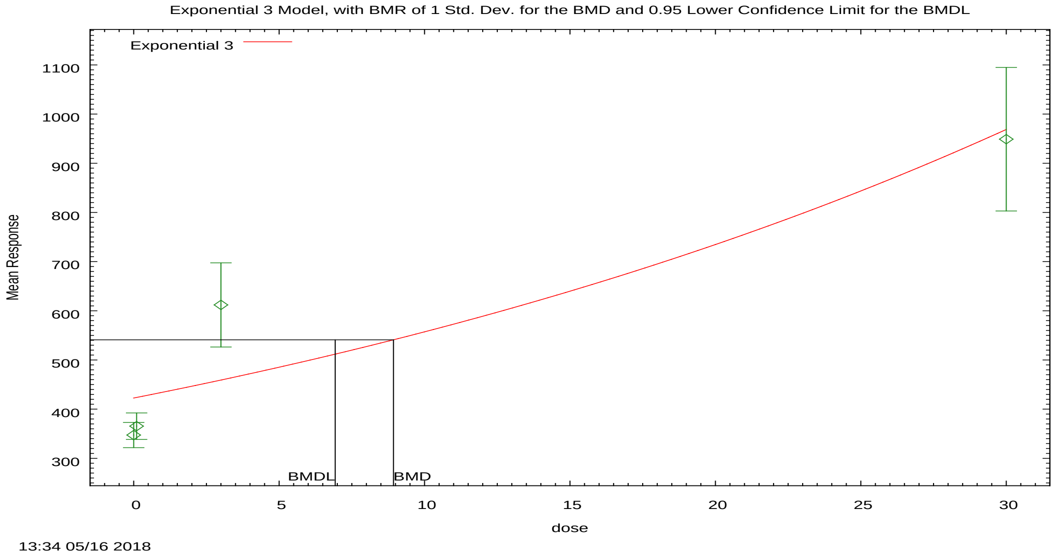

Figure 259. Plot of mean response by dose with fitted curve for Exponential (M3) model with modeled variance for Liver Weight to Brain Weight in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 8.93061

BMDL at the 95% confidence level = 6.92769

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	1.29827	-13.9147
rho	1.36434	3.60787
a	422.623	409.803
b	0.0276507	0.0290228
c	n/a	0
d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	347.3	422.6	35.93	118.4	-2.012
0.1	10	365.4	423.8	37.57	118.6	-1.556
3	10	612	459.2	119.7	125.3	3.857
30	10	949	968.7	204.1	208.5	-0.3002

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-209.757	5	429.5139
A2	-191.0033	8	398.0066
A3	-191.3498	6	394.6996
R	-243.798	2	491.596
3	-217.1983	4	442.3966

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	105.6	6	<0.0001
Test 2	37.51	3	<0.0001
Test 3	0.693	2	0.7072
Test 5a	51.7	2	<0.0001

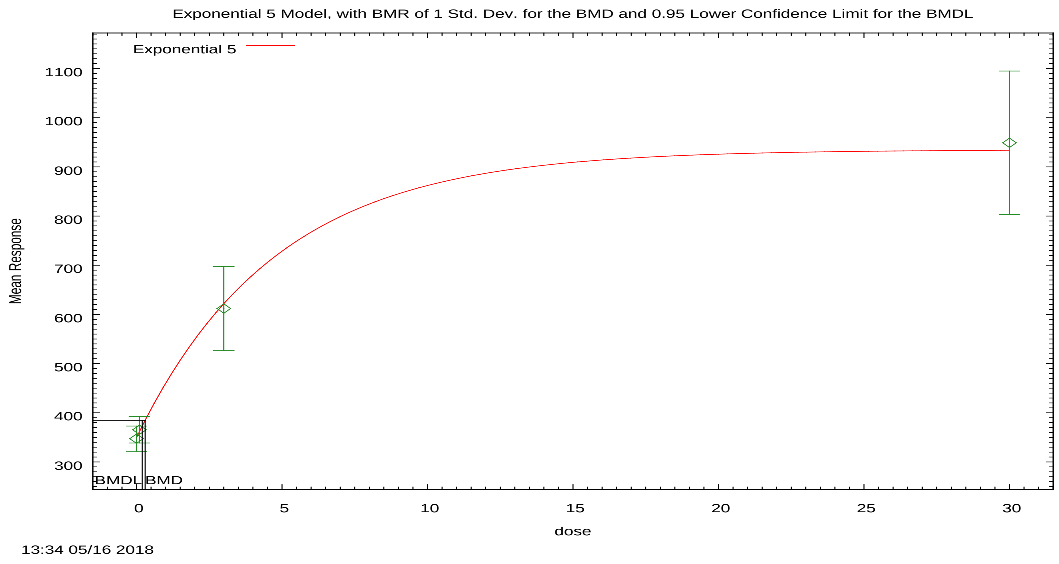

Figure 260. Plot of mean response by dose with fitted curve for Exponential (M5) model with modeled variance for Liver Weight to Brain Weight in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 0.295612

BMDL at the 95% confidence level = 0.193746

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-14.3917	-13.9147
rho	3.67106	3.60787
a	349.675	329.948
b	0.208529	0.0890268

c	2.67347	3.01988
d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	347.3	349.7	35.93	34.98	-0.2134
0.1	10	365.4	361.8	37.57	37.23	0.3138
3	10	612	621.8	119.7	100.6	-0.3098
30	10	949	933.7	204.1	212.2	0.227

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-209.757	5	429.5139
A2	-191.0033	8	398.0066
A3	-191.3498	6	394.6996
R	-243.798	2	491.596
5	-191.4114	5	392.8228

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	105.6	6	<0.0001
Test 2	37.51	3	<0.0001
Test 3	0.693	2	0.7072
Test 7a	0.1232	1	0.7256

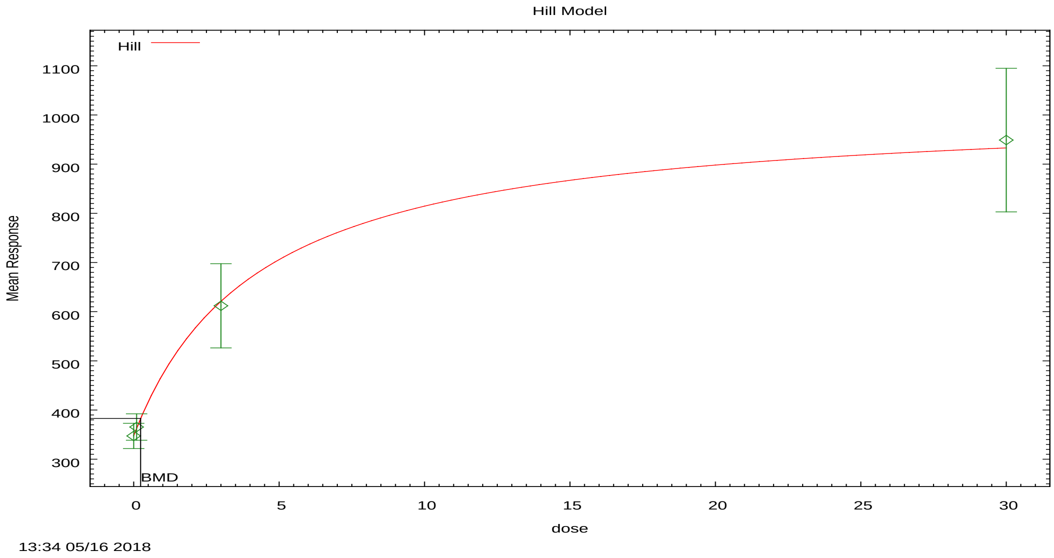

Figure 261. Plot of mean response by dose with fitted curve for Hill model with modeled variance for Liver Weight to Brain Weight in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 0.237536

BMDL at the 95% confidence level = error

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-14.4381	9.59321
rho	3.67815	0
intercept	348.287	347.314
v	670.126	601.642
n	1	0.211723

k	4.35726	54.101

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	347	348	35.9	34.6	-0.0888
0.1	10	365	363	37.6	37.4	0.179
3	10	612	622	120	101	-0.302
30	10	949	933	204	212	0.231

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-209.756967	5	429.513934
A2	-191.003314	8	398.006627
A3	-191.349795	6	394.699591
fitted	-191.362956	5	392.725912
R	-243.798014	2	491.596028

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	105.589	6	<0.0001
Test 2	37.5073	3	<0.0001
Test 3	0.692963	2	0.7072
Test 4	0.0263214	1	0.8711

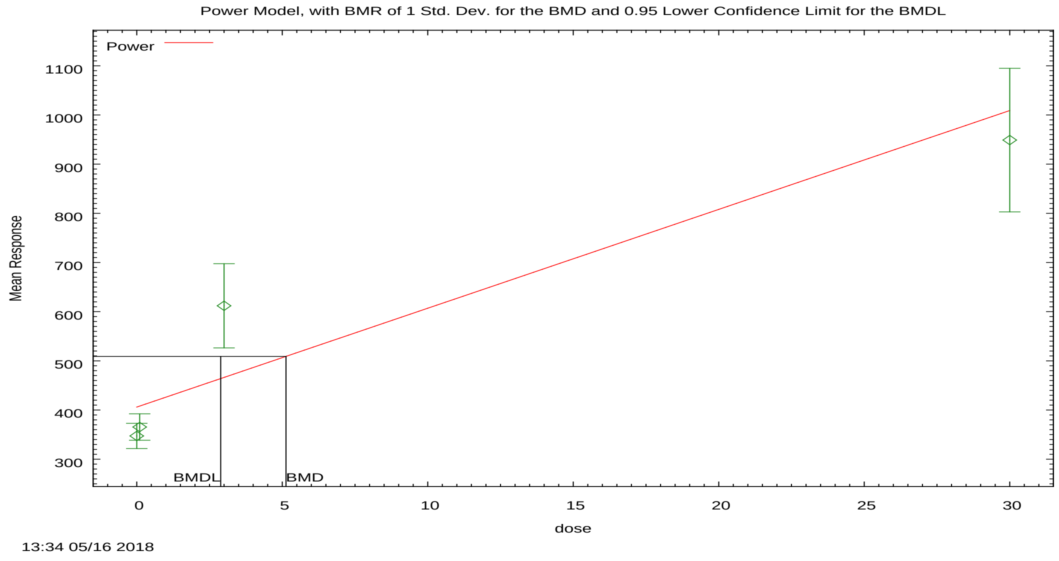

Figure 262. Plot of mean response by dose with fitted curve for Power model with modeled variance for Liver Weight to Brain Weight in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 5.12748

BMDL at the 95% confidence level = 2.884

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-1.3227	9.59321
rho	1.7642	0
control	405.867	347.314
slope	20.125	71.279
power	1	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	347	406	35.9	103	-1.79
0.1	10	365	408	37.6	104	-1.29
3	10	612	466	120	117	3.95
30	10	949	1010	204	231	-0.832

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-209.756967	5	429.513934
A2	-191.003314	8	398.006627
A3	-191.349795	6	394.699591
fitted	-214.768715	4	437.537431
R	-243.798014	2	491.596028

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	105.589	6	<0.0001
Test 2	37.5073	3	<0.0001
Test 3	0.692963	2	0.7072
Test 4	46.8378	2	<0.0001

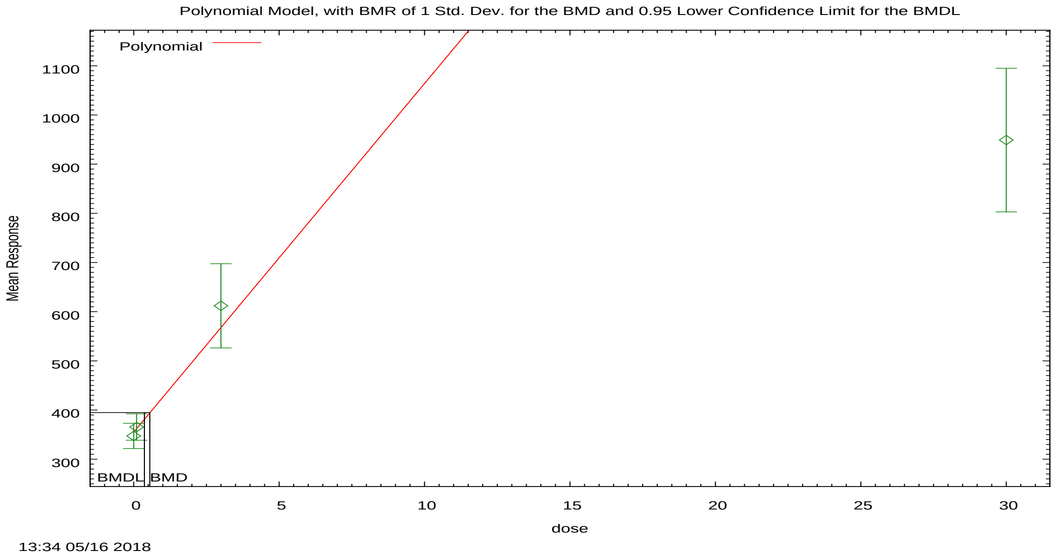

Figure 263. Plot of mean response by dose with fitted curve for Polynomial 3° model with modeled variance for Liver Weight to Brain Weight in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 0.554052

BMDL at the 95% confidence level = 0.368145

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-15.2937	9.59321
rho	3.85388	0
beta_0	355.495	347.314
beta_1	70.9191	184.827

beta_2	0	0
beta_3	0	0.989356

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	347	355	35.9	39.3	-0.658
0.1	10	365	363	37.6	40.8	0.222
3	10	612	568	120	97	1.42
30	10	949	2480	204	1660	-2.92

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-209.756967	5	429.513934
A2	-191.003314	8	398.006627
A3	-191.349795	6	394.699591
fitted	-213.715421	4	435.430842
R	-243.798014	2	491.596028

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	105.589	6	<0.0001
Test 2	37.5073	3	<0.0001
Test 3	0.692963	2	0.7072
Test 4	44.7313	2	<0.0001

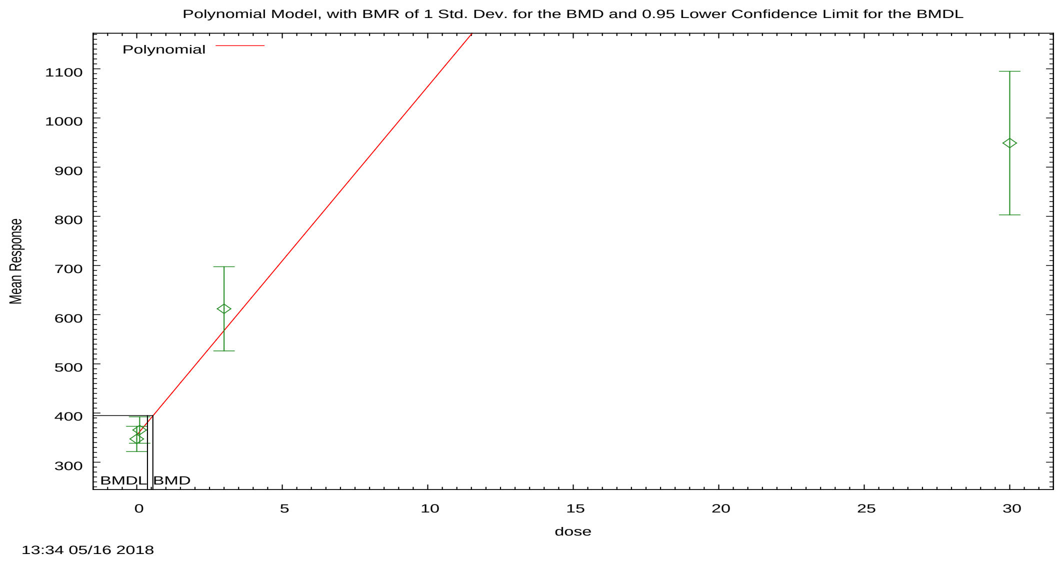

Figure 264. Plot of mean response by dose with fitted curve for Polynomial 2° model with modeled variance for Liver Weight to Brain Weight in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + …

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 0.554052

BMDL at the 95% confidence level = 0.368145

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-15.2937	9.59321
rho	3.85388	0
beta_0	355.495	351.597
beta_1	70.9191	94.2756

beta_2	0	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	347	355	35.9	39.3	-0.658
0.1	10	365	363	37.6	40.8	0.222
3	10	612	568	120	97	1.42
30	10	949	2480	204	1660	-2.92

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-209.756967	5	429.513934
A2	-191.003314	8	398.006627
A3	-191.349795	6	394.699591
fitted	-213.715421	4	435.430842
R	-243.798014	2	491.596028

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	105.589	6	<0.0001
Test 2	37.5073	3	<0.0001
Test 3	0.692963	2	0.7072
Test 4	44.7313	2	<0.0001

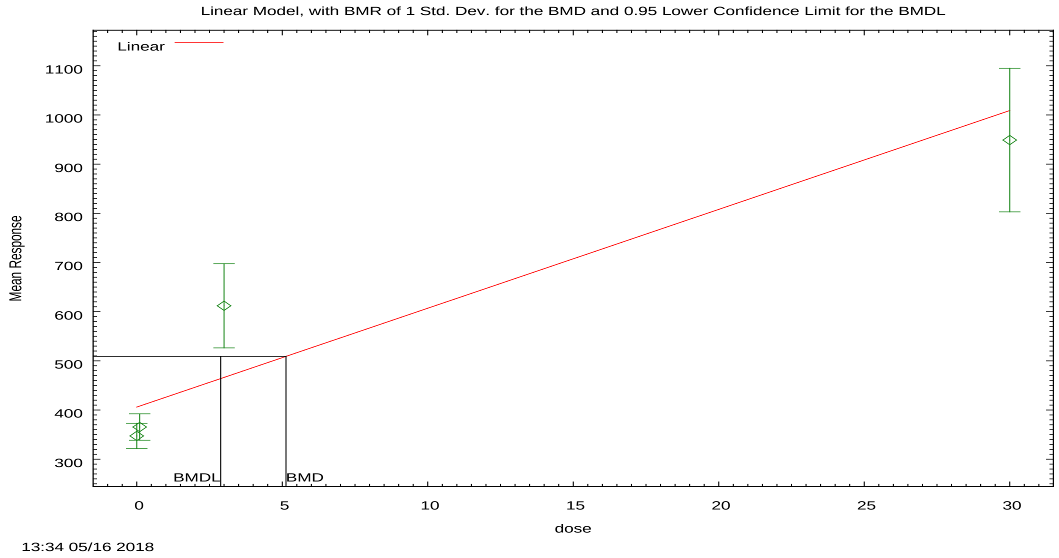

Figure 265. Plot of mean response by dose with fitted curve for Linear model with modeled variance for Liver Weight to Brain Weight in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 5.12748

BMDL at the 95% confidence level = 2.884

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-1.3227	9.59321
rho	1.76421	0
beta_0	405.867	418.235
beta_1	20.125	18.1489

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	347	406	35.9	103	-1.79
0.1	10	365	408	37.6	104	-1.29
3	10	612	466	120	117	3.95
30	10	949	1010	204	231	-0.832

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-209.756967	5	429.513934
A2	-191.003314	8	398.006627
A3	-191.349795	6	394.699591
fitted	-214.768715	4	437.537431
R	-243.798014	2	491.596028

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	105.589	6	<0.0001
Test 2	37.5073	3	<0.0001
Test 3	0.692963	2	0.7072
Test 4	46.8378	2	<0.0001

BMDS WIZARD OUTPUT REPORT

BMDS Summary of 28-Day Oral (Gavage) Toxicity Study of H-28397 in Mice with a 28-day Recovery – Liver Weight to Brain Weight (g/100g brain) in Females

1.30. BMDS Summary of Liver weight to brain weight (g/100g brain) females (28 Day Mice GenX)

Table 30. Summary of BMD Modeling Results for Liver Weight to Brain Weight in Females (28-Day Mice); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD$_{1SD}$ (mg/kg/day)	BMDL$_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2) Exponential (M3)[b]	9.00E-04	351.80	5.78	4.59	1.26	Only one model met model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). Selected BMDL is from this model.
Exponential (M4) **Exponential (M5)[c]**	**0.381**	**340.54**	**1.14**	**0.751**	**1.52**	
Hill	0.387	340.52	1.10	error[d]	error	
Power[e]	0.00434	348.65	3.99	3.02	1.32	
Polynomial 3°[f] Polynomial 2°[g] Linear[h]	0.00434	348.65	3.99	3.02	1.32	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = 0.035), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 3, and 30 mg/kg/day were -0.64, 0.66, -0.02, 0, respectively.

[b] For the Exponential (M3) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M2) model.

[c] For the Exponential (M5) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M4) model.

[d] BMD or BMDL computation failed for this model.

[e] The Power model may appear equivalent to the Polynomial 3° model, however differences exist in digits not displayed in the table. This also applies to the Polynomial 2° model. This also applies to the Linear model.

[f] For the Polynomial 3° model, the b3 coefficient estimates was 0 (boundary of parameters space). The models in this row reduced to the Polynomial 2° model. For the Polynomial 3° model, the b3 and b2 coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Linear model.

[g] For the Polynomial 2° model, the b2 coefficient estimate was 0 (boundary of parameters space). The models in this row reduced to the Linear model.

[h] The Linear model may appear equivalent to the Power model, however differences exist in digits not displayed in the table.

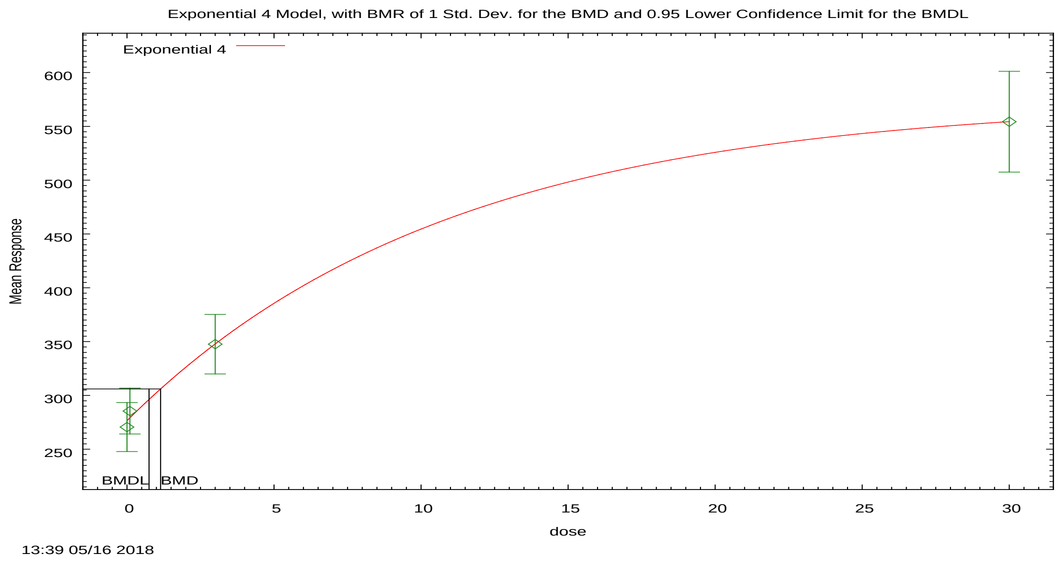

Figure 266. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Liver Weight to Brain Weight in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 1.14268

BMDL at the 95% confidence level = 0.75065

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-5.14733	-5.34291
rho	2.11933	2.16682
a	276.535	257.053
b	0.0915598	0.0823334
c	2.07363	2.26425
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	270.6	276.5	31.83	29.49	-0.6383
0.1	10	285.5	279.2	29.77	29.8	0.6611
3	10	347.6	347.8	38.68	37.61	-0.01903
30	10	554.3	554.4	65.5	61.63	-0.003785

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-169.1109	5	348.2218
A2	-164.8074	8	345.6148
A3	-164.886	6	341.772
R	-211.7408	2	427.4817
4	-165.2698	5	340.5397

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	93.87	6	<0.0001
Test 2	8.607	3	0.035
Test 3	0.1572	2	0.9244
Test 6a	0.7677	1	0.3809

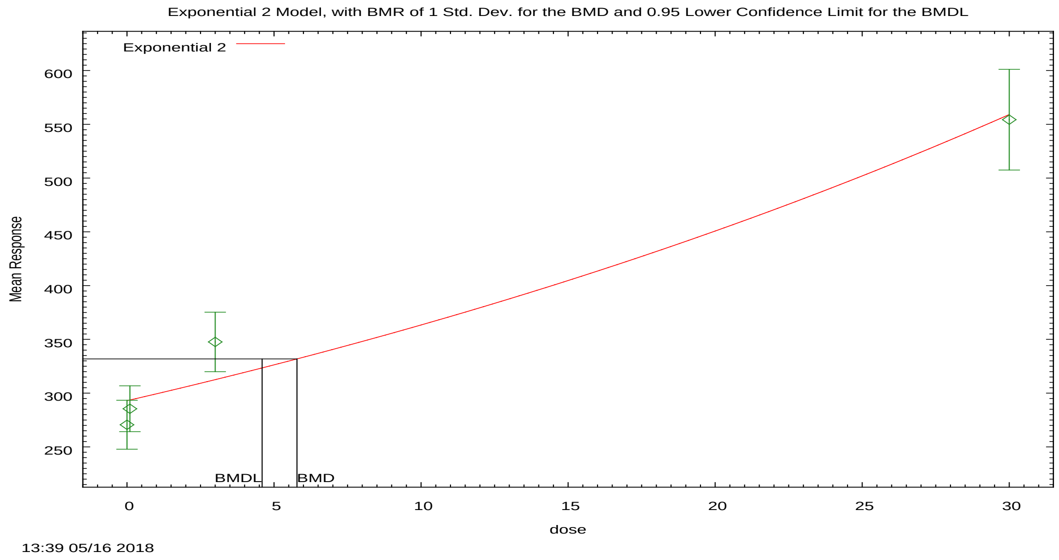

Figure 267. Plot of mean response by dose with fitted curve for Exponential (M2) model with modeled variance for Liver Weight to Brain Weight in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 5.77952

BMDL at the 95% confidence level = 4.59476

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-1.47223	-5.34291
rho	1.54775	2.16682
a	292.97	291.725
b	0.0215421	0.0217614
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	270.6	293	31.83	38.84	-1.823
0.1	10	285.5	293.6	29.77	38.91	-0.6609
3	10	347.6	312.5	38.68	40.84	2.717
30	10	554.3	559.1	65.5	64.05	-0.2363

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-169.1109	5	348.2218
A2	-164.8074	8	345.6148
A3	-164.886	6	341.772
R	-211.7408	2	427.4817
2	-171.8997	4	351.7993

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	93.87	6	<0.0001
Test 2	8.607	3	0.035
Test 3	0.1572	2	0.9244
Test 4	14.03	2	0.0008995

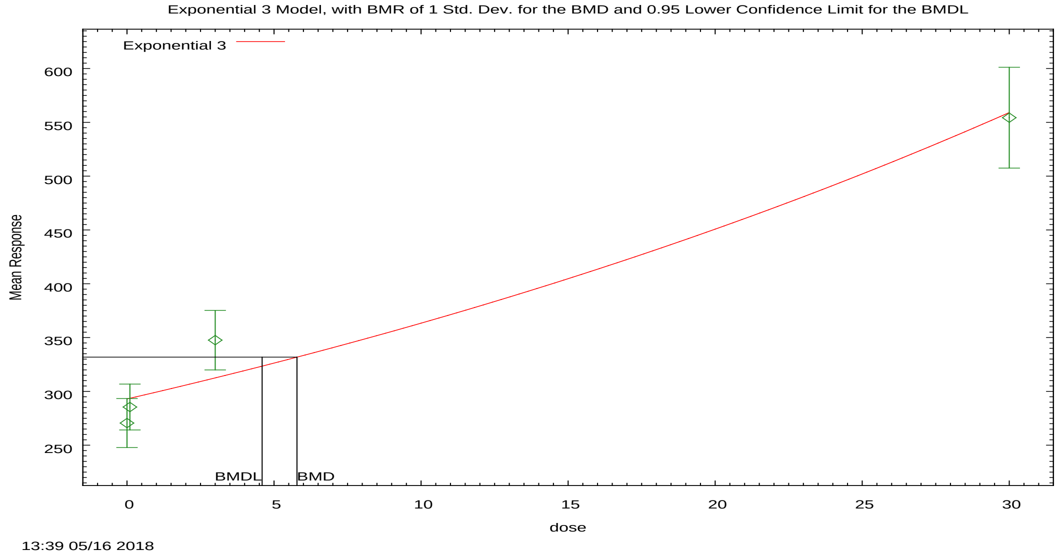

Figure 268. Plot of mean response by dose with fitted curve for Exponential (M3) model with modeled variance for Liver Weight to Brain Weight in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 5.77952

BMDL at the 95% confidence level = 4.59476

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-1.47222	-5.34291
rho	1.54775	2.16682
a	292.97	291.725

b	0.0215421	0.0217614
c	n/a	0
d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	270.6	293	31.83	38.84	-1.823
0.1	10	285.5	293.6	29.77	38.91	-0.6609
3	10	347.6	312.5	38.68	40.84	2.717
30	10	554.3	559.1	65.5	64.05	-0.2363

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-169.1109	5	348.2218
A2	-164.8074	8	345.6148
A3	-164.886	6	341.772
R	-211.7408	2	427.4817
3	-171.8997	4	351.7993

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	93.87	6	<0.0001
Test 2	8.607	3	0.035
Test 3	0.1572	2	0.9244
Test 5a	14.03	2	0.0008995

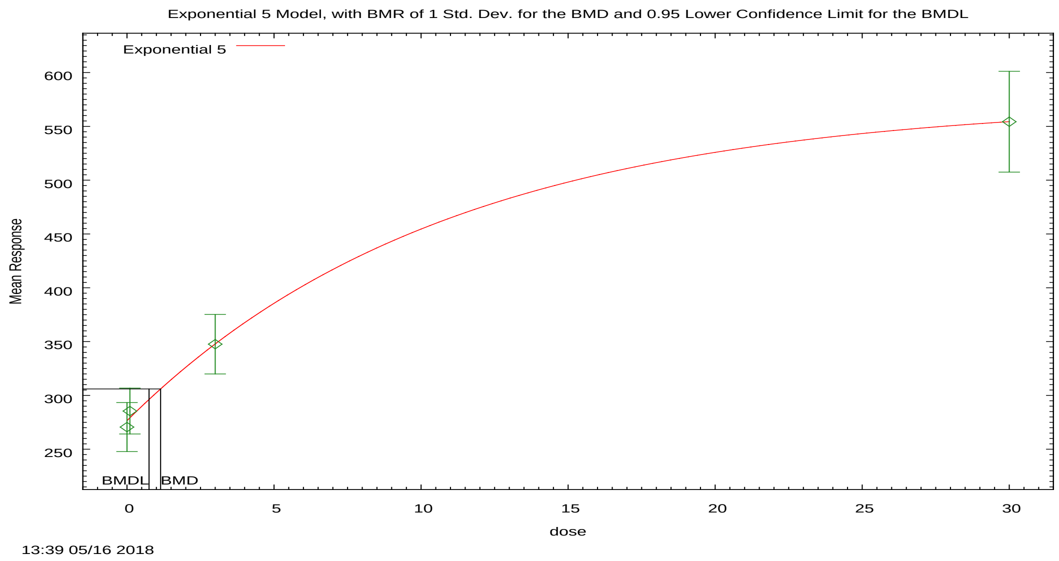

Figure 269. Plot of mean response by dose with fitted curve for Exponential (M5) model with modeled variance for Liver Weight to Brain Weight in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 1.14268

BMDL at the 95% confidence level = 0.75065

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-5.14729	-5.34291
rho	2.11933	2.16682
a	276.535	257.053
b	0.0915596	0.0823334

c	2.07363	2.26425
d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	270.6	276.5	31.83	29.49	-0.6383
0.1	10	285.5	279.2	29.77	29.8	0.6611
3	10	347.6	347.8	38.68	37.61	-0.01902
30	10	554.3	554.4	65.5	61.63	-0.003788

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-169.1109	5	348.2218
A2	-164.8074	8	345.6148
A3	-164.886	6	341.772
R	-211.7408	2	427.4817
5	-165.2698	5	340.5397

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	93.87	6	<0.0001
Test 2	8.607	3	0.035
Test 3	0.1572	2	0.9244
Test 7a	0.7677	1	0.3809

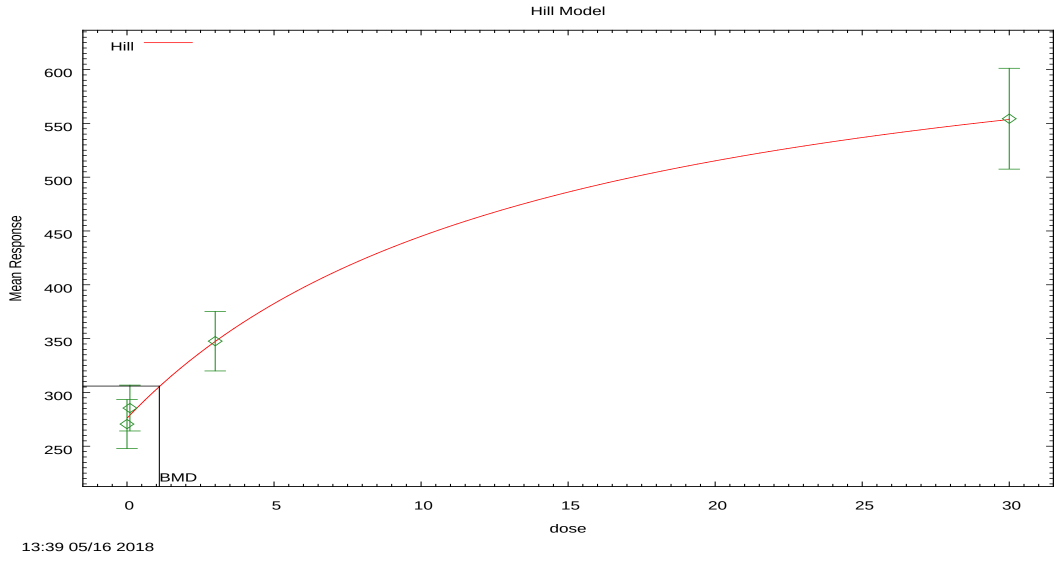

Figure 270. Plot of mean response by dose with fitted curve for Hill model with modeled variance for Liver Weight to Brain Weight in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 1.09982

BMDL at the 95% confidence level = error

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-5.15539	7.56091
rho	2.12062	0
intercept	276.432	270.582
v	409.207	283.733
n	1	0.411212

k	14.1723	48.5315

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	271	276	31.8	29.5	-0.628
0.1	10	285	279	29.8	29.8	0.655
3	10	348	348	38.7	37.6	-0.0254
30	10	554	554	65.5	61.6	-0.00171

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-169.110923	5	348.221846
A2	-164.807379	8	345.614758
A3	-164.885988	6	341.771976
fitted	-165.259533	5	340.519065
R	-211.740842	2	427.481684

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	93.8669	6	<0.0001
Test 2	8.60709	3	0.035
Test 3	0.157219	2	0.9244
Test 4	0.747089	1	0.3874

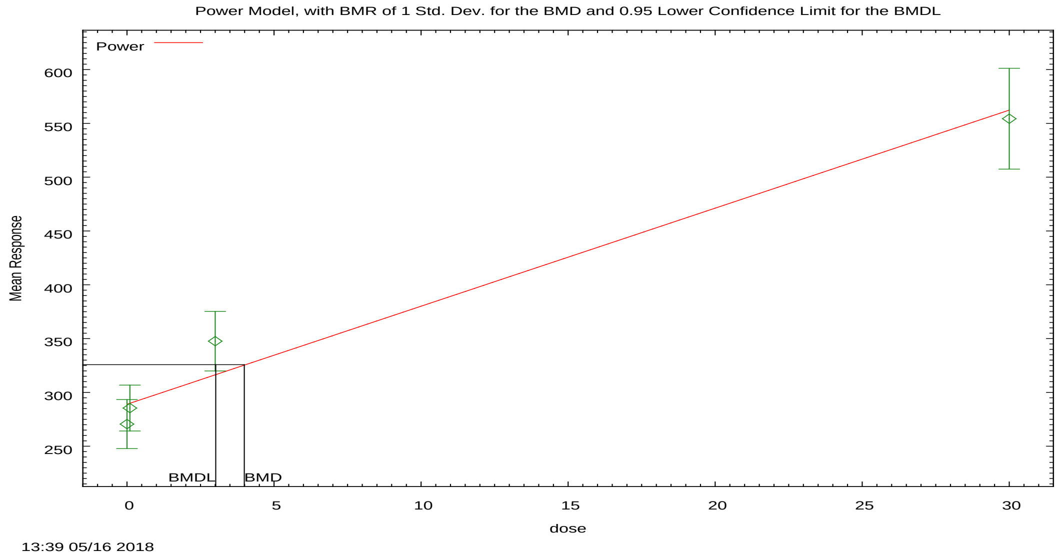

Figure 271. Plot of mean response by dose with fitted curve for Power model with modeled variance for Liver Weight to Brain Weight in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 3.98904

BMDL at the 95% confidence level = 3.01743

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-2.67787	7.56091
rho	1.74036	0
control	289.421	270.582
slope	9.11208	49.3555
power	1	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	271	289	31.8	36.3	-1.64
0.1	10	285	290	29.8	36.4	-0.422
3	10	348	317	38.7	39.3	2.48
30	10	554	563	65.5	64.8	-0.413

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-169.110923	5	348.221846
A2	-164.807379	8	345.614758
A3	-164.885988	6	341.771976
fitted	-170.325497	4	348.650994
R	-211.740842	2	427.481684

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	93.8669	6	<0.0001
Test 2	8.60709	3	0.035
Test 3	0.157219	2	0.9244
Test 4	10.879	2	0.004342

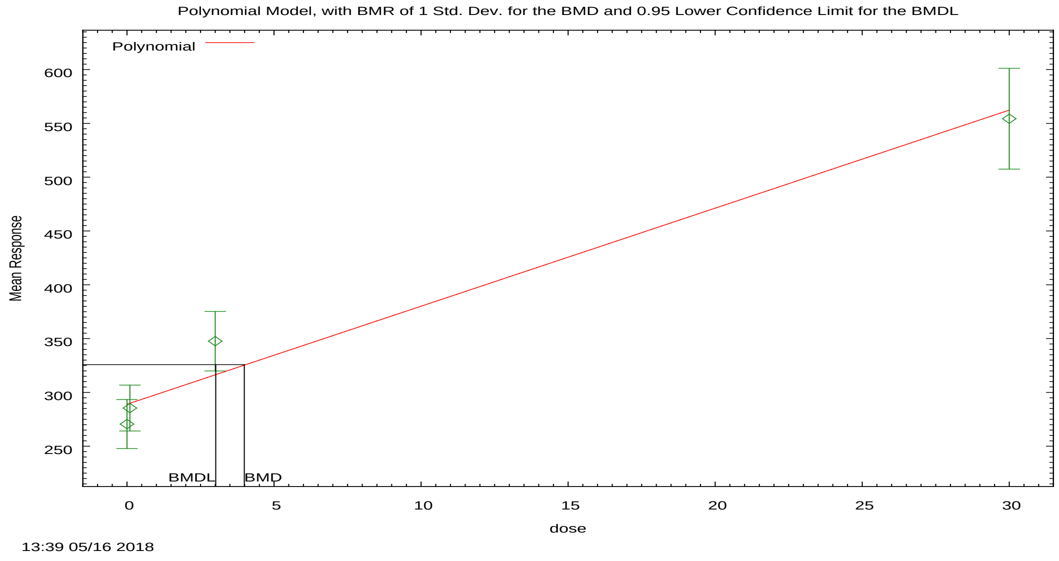

Figure 272. Plot of mean response by dose with fitted curve for Polynomial 3° model with modeled variance for Liver Weight to Brain Weight in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 3.98903

BMDL at the 95% confidence level = 3.01743

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-2.67789	7.56091
rho	1.74037	0
beta_0	289.421	270.582
beta_1	9.11208	153.549

beta_2	0	0
beta_3	0	1.40075

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	271	289	31.8	36.3	-1.64
0.1	10	285	290	29.8	36.4	-0.422
3	10	348	317	38.7	39.3	2.48
30	10	554	563	65.5	64.8	-0.413

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-169.110923	5	348.221846
A2	-164.807379	8	345.614758
A3	-164.885988	6	341.771976
fitted	-170.325497	4	348.650994
R	-211.740842	2	427.481684

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	93.8669	6	<0.0001
Test 2	8.60709	3	0.035
Test 3	0.157219	2	0.9244
Test 4	10.879	2	0.004342

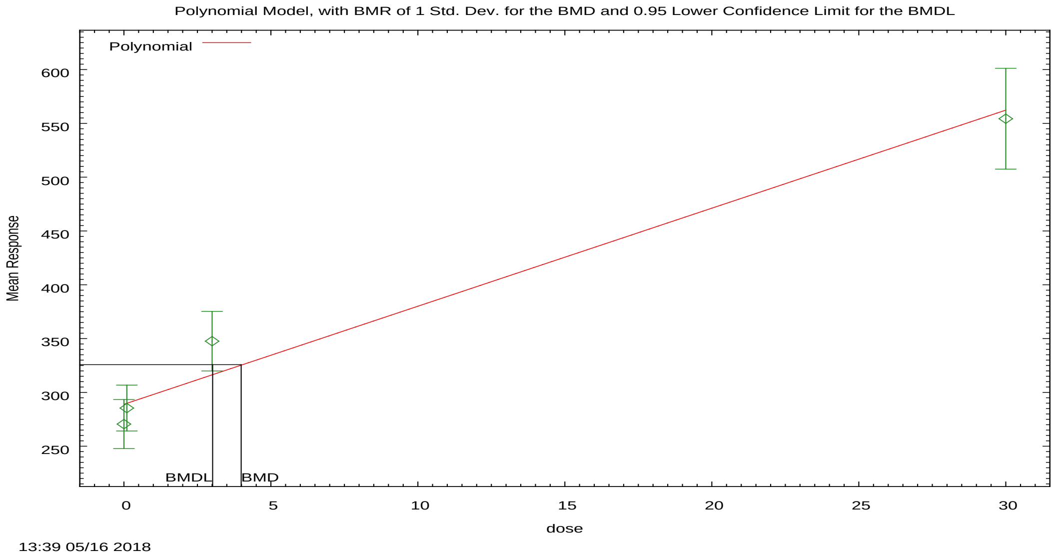

Figure 273. Plot of mean response by dose with fitted curve for Polynomial 2° model with modeled variance for Liver Weight to Brain Weight in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 3.98903

BMDL at the 95% confidence level = 3.01743

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-2.67789	7.56091
rho	1.74037	0
beta_0	289.421	276.646
beta_1	9.11208	25.3434

beta_2	0	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	271	289	31.8	36.3	-1.64
0.1	10	285	290	29.8	36.4	-0.422
3	10	348	317	38.7	39.3	2.48
30	10	554	563	65.5	64.8	-0.413

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-169.110923	5	348.221846
A2	-164.807379	8	345.614758
A3	-164.885988	6	341.771976
fitted	-170.325497	4	348.650994
R	-211.740842	2	427.481684

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	93.8669	6	<0.0001
Test 2	8.60709	3	0.035
Test 3	0.157219	2	0.9244
Test 4	10.879	2	0.004342

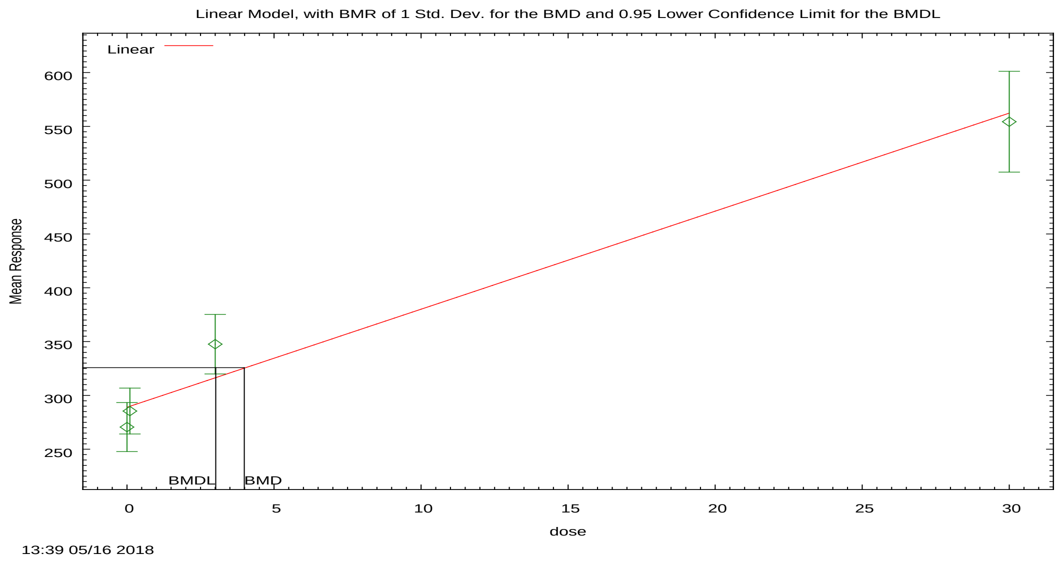

Figure 274. Plot of mean response by dose with fitted curve for Linear model with modeled variance for Liver Weight to Brain Weight in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 3.98903

BMDL at the 95% confidence level = 3.01743

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-2.67788	7.56091
rho	1.74036	0
beta_0	289.421	291.063
beta_1	9.11208	8.87413

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	271	289	31.8	36.3	-1.64
0.1	10	285	290	29.8	36.4	-0.422
3	10	348	317	38.7	39.3	2.48
30	10	554	563	65.5	64.8	-0.413

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-169.110923	5	348.221846
A2	-164.807379	8	345.614758
A3	-164.885988	6	341.771976
fitted	-170.325497	4	348.650994
R	-211.740842	2	427.481684

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	93.8669	6	<0.0001
Test 2	8.60709	3	0.035
Test 3	0.157219	2	0.9244
Test 4	10.879	2	0.004342

BMDS WIZARD OUTPUT REPORT

BMDS Summary of 28-Day Oral (Gavage) Toxicity Study of H-28397 in Rats with a 28-day Recovery – Liver Weight to Brain Weight (g/100g brain) in Males

1.31. BMDS Summary of Liver weight to brain weight (g/100g brain) Males (28 Day Rats GenX)

Table 31. Summary of BMD Modeling Results for Liver Weight to Brain Weight in Males (28-Day Rats); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD_{1SD} (mg/kg/day)	$BMDL_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2) Exponential (M3)[b]	3.82E-04	403.18	8.78	6.58	1.33	Only one model met model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). Selected BMDL is from this model.
Exponential (M4)	**0.762**	**389.53**	**1.01**	**0.611**	**1.65**	
Exponential (M5)	N/A[c]	391.44	1.27	0.616	2.06	
Hill	N/A[c]	391.44	1.20	error[d]	error	
Power[e]	7.43E-04	401.85	7.09	4.98	1.42	
Polynomial 3°[f] Polynomial 2°[g] Linear[h]	7.43E-04	401.85	7.09	4.98	1.42	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = 0.0263), selected model in bold; scaled residuals for selected model for doses 0, 0.3, 3, and 30 mg/kg/day were 0.05, -0.1, 0.1, -0.04, respectively.

[b] For the Exponential (M3) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M2) model.

[c] No available degrees of freedom to calculate a goodness of fit value.

[d] BMD or BMDL computation failed for this model.

[e] The Power model may appear equivalent to the Polynomial 3° model, however differences exist in digits not displayed in the table. This also applies to the Polynomial 2° model. This also applies to the Linear model.

[f] For the Polynomial 3° model, the b3 coefficient estimates was 0 (boundary of parameters space). The models in this row reduced to the Polynomial 2° model. For the Polynomial 3° model, the b3 and b2 coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Linear model.

[g] For the Polynomial 2° model, the b2 coefficient estimate was 0 (boundary of parameters space). The models in this row reduced to the Linear model.

[h] The Linear model may appear equivalent to the Power model, however differences exist in digits not displayed in the table.

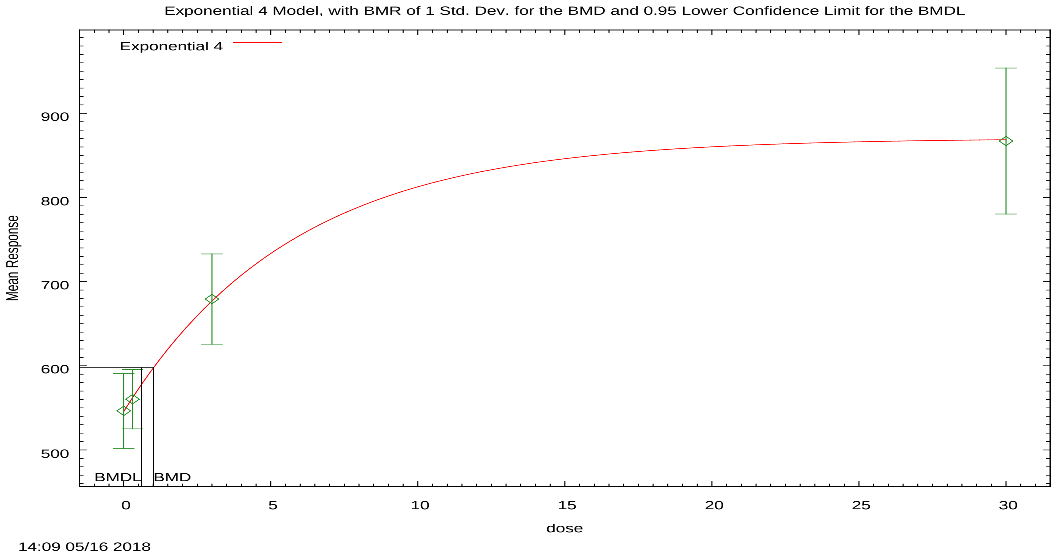

Figure 275. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Liver Weight to Brain Weight in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 1.01078

BMDL at the 95% confidence level = 0.610799

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-12.9002	-13.4573
rho	3.30092	3.39985
a	545.71	519.162

b	0.172629	0.074374
c	1.59511	1.75365
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	546.5	545.7	62.27	52	0.04719
0.3	10	560.3	562.1	49.37	54.6	-0.1024
3	10	679.3	677	74.89	74.22	0.09887
30	10	867.1	868.6	121.2	112	-0.04414

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-193.9575	5	397.915
A2	-189.3381	8	394.6761
A3	-189.7208	6	391.4416
R	-220.4231	2	444.8461
4	-189.7667	5	389.5334

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	62.17	6	<0.0001
Test 2	9.239	3	0.02628
Test 3	0.7655	2	0.682
Test 6a	0.09174	1	0.762

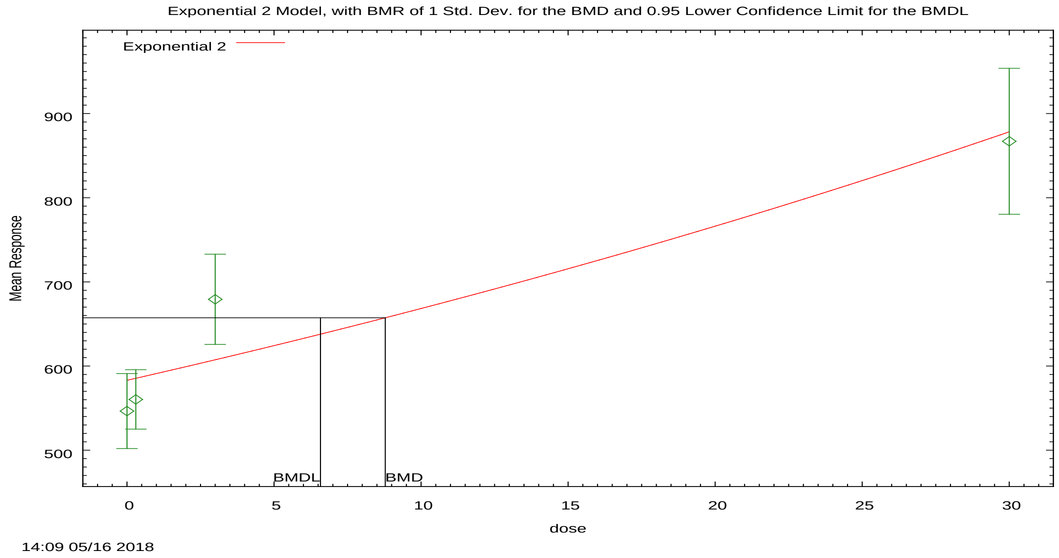

Figure 276. Plot of mean response by dose with fitted curve for Exponential (M2) model with modeled variance for Liver Weight to Brain Weight in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 8.782

BMDL at the 95% confidence level = 6.57964

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-6.13218	-13.4573
rho	2.31593	3.39985
a	583.048	581.518
b	0.0136582	0.0136837

c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	546.5	583	62.27	74.3	-1.556
0.3	10	560.3	585.4	49.37	74.65	-1.064
3	10	679.3	607.4	74.89	77.91	2.917
30	10	867.1	878.3	121.2	119.4	-0.2979

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-193.9575	5	397.915
A2	-189.3381	8	394.6761
A3	-189.7208	6	391.4416
R	-220.4231	2	444.8461
2	-197.5918	4	403.1836

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	62.17	6	<0.0001
Test 2	9.239	3	0.02628
Test 3	0.7655	2	0.682
Test 4	15.74	2	0.0003816

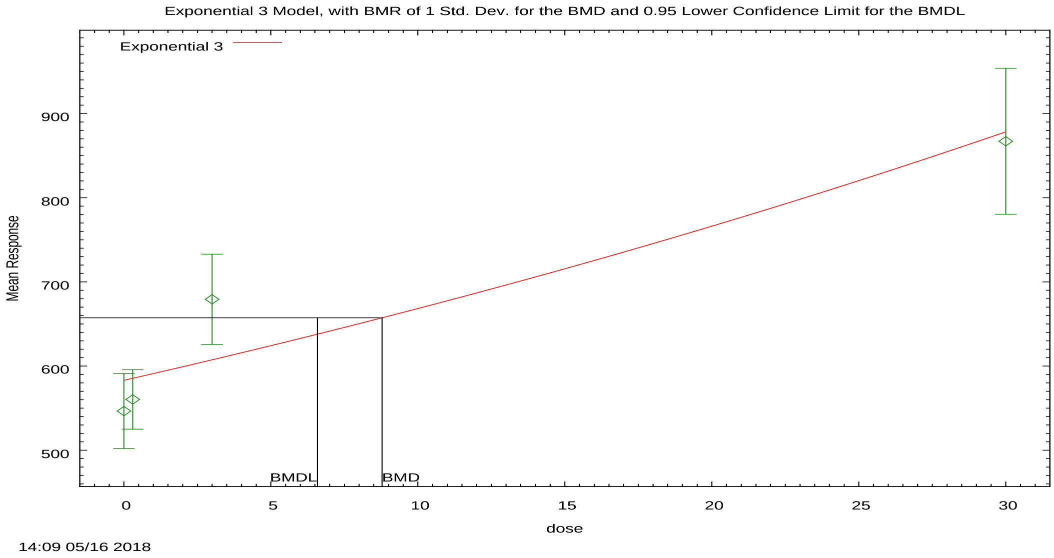

Figure 277. Plot of mean response by dose with fitted curve for Exponential (M3) model with modeled variance for Liver Weight to Brain Weight in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 8.782

BMDL at the 95% confidence level = 6.57964

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-6.13218	-13.4573
rho	2.31593	3.39985
a	583.048	581.518
b	0.0136582	0.0136837

c	n/a	0
d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	546.5	583	62.27	74.3	-1.556
0.3	10	560.3	585.4	49.37	74.65	-1.064
3	10	679.3	607.4	74.89	77.91	2.917
30	10	867.1	878.3	121.2	119.4	-0.2979

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-193.9575	5	397.915
A2	-189.3381	8	394.6761
A3	-189.7208	6	391.4416
R	-220.4231	2	444.8461
3	-197.5918	4	403.1836

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	62.17	6	<0.0001
Test 2	9.239	3	0.02628
Test 3	0.7655	2	0.682
Test 5a	15.74	2	0.0003816

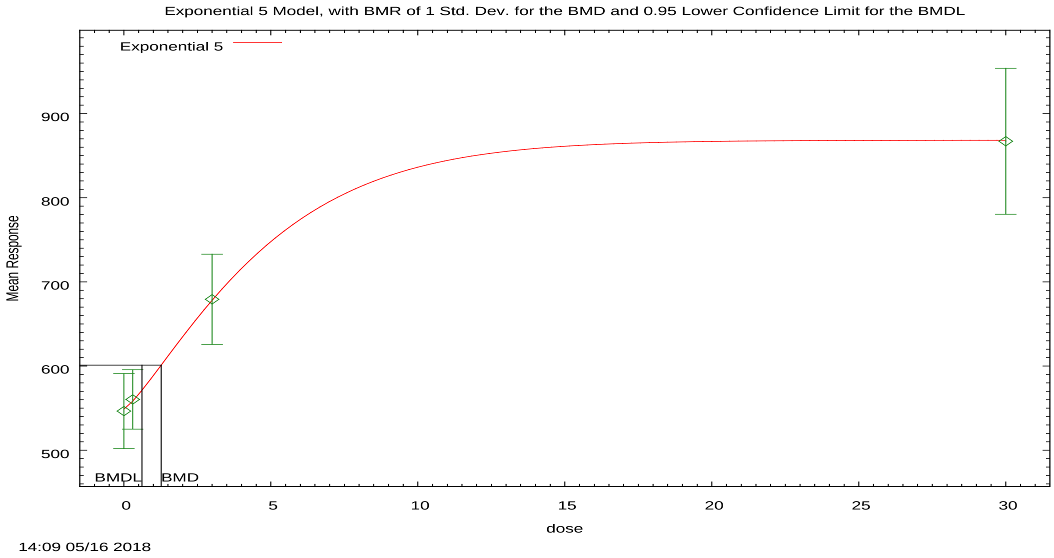

Figure 278. Plot of mean response by dose with fitted curve for Exponential (M5) model with modeled variance for Liver Weight to Brain Weight in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 1.26762

BMDL at the 95% confidence level = 0.615908

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-13.1092	-13.4573
rho	3.33281	3.39985
a	548.799	519.162
b	0.196101	0.074374

c	1.5822	1.75365
d	1.23719	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	546.5	548.8	62.27	52.28	-0.1399
0.3	10	560.3	558.3	49.37	53.79	0.1221
3	10	679.3	678.1	74.89	74.38	0.05058
30	10	867.1	868.3	121.2	112.3	-0.03361

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-193.9575	5	397.915
A2	-189.3381	8	394.6761
A3	-189.7208	6	391.4416
R	-220.4231	2	444.8461
5	-189.7208	6	391.4416

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	62.17	6	<0.0001
Test 2	9.239	3	0.02628
Test 3	0.7655	2	0.682
Test 7a	-9.663E-13	0	N/A

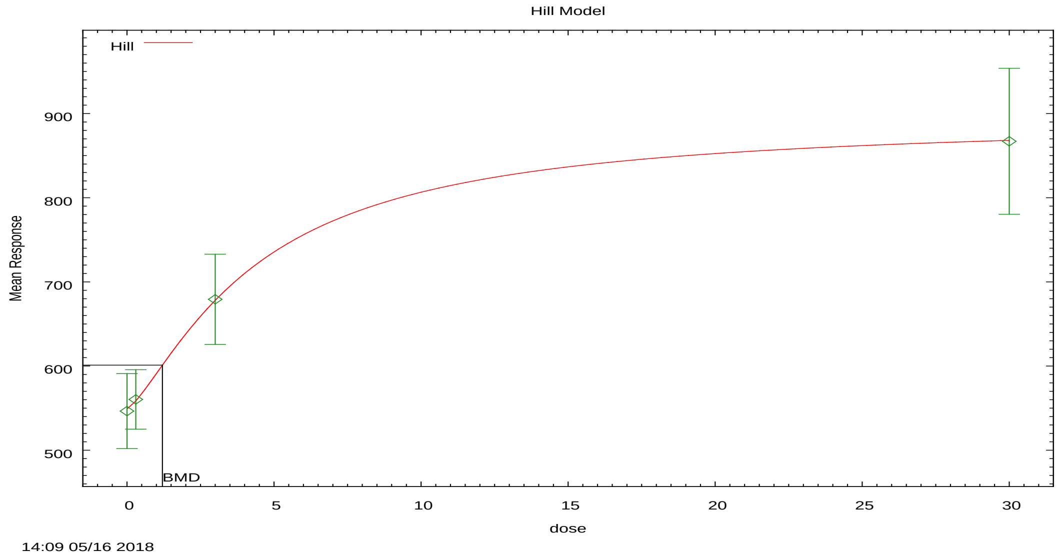

Figure 279. Plot of mean response by dose with fitted curve for Hill model with modeled variance for Liver Weight to Brain Weight in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 1.20483

BMDL at the 95% confidence level = error

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-13.1092	8.80324
rho	3.33281	0
intercept	548.799	546.486
v	344.427	320.59
n	1.32826	0.359579

k	4.40059	53.0492

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	546	549	62.3	52.3	-0.14
0.3	10	560	558	49.4	53.8	0.122
3	10	679	678	74.9	74.4	0.0506
30	10	867	868	121	112	-0.0336

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-193.957517	5	397.915035
A2	-189.338063	8	394.676127
A3	-189.72081	6	391.441621
fitted	-189.72081	6	391.441621
R	-220.423064	2	444.846129

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	62.17	6	<0.0001
Test 2	9.23891	3	0.02628
Test 3	0.765494	2	0.682
Test 4	1.63709E-11	0	N/A

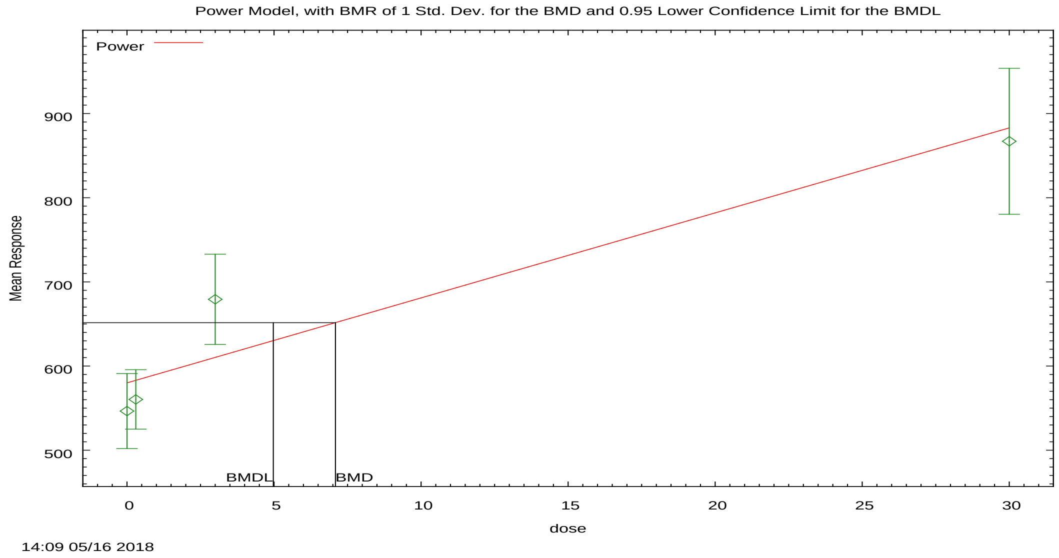

Figure 280. Plot of mean response by dose with fitted curve for Power model with modeled variance for Liver Weight to Brain Weight in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 7.08863

BMDL at the 95% confidence level = 4.97533

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-7.10734	8.80324
rho	2.46125	0
control	579.553	546.486
slope	10.1491	31.4841
power	1	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	546	580	62.3	71.9	-1.45
0.3	10	560	583	49.4	72.4	-0.972
3	10	679	610	74.9	76.6	2.86
30	10	867	884	121	121	-0.443

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-193.957517	5	397.915035
A2	-189.338063	8	394.676127
A3	-189.72081	6	391.441621
fitted	-196.925841	4	401.851681
R	-220.423064	2	444.846129

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	62.17	6	<0.0001
Test 2	9.23891	3	0.02628
Test 3	0.765494	2	0.682
Test 4	14.4101	2	0.0007428

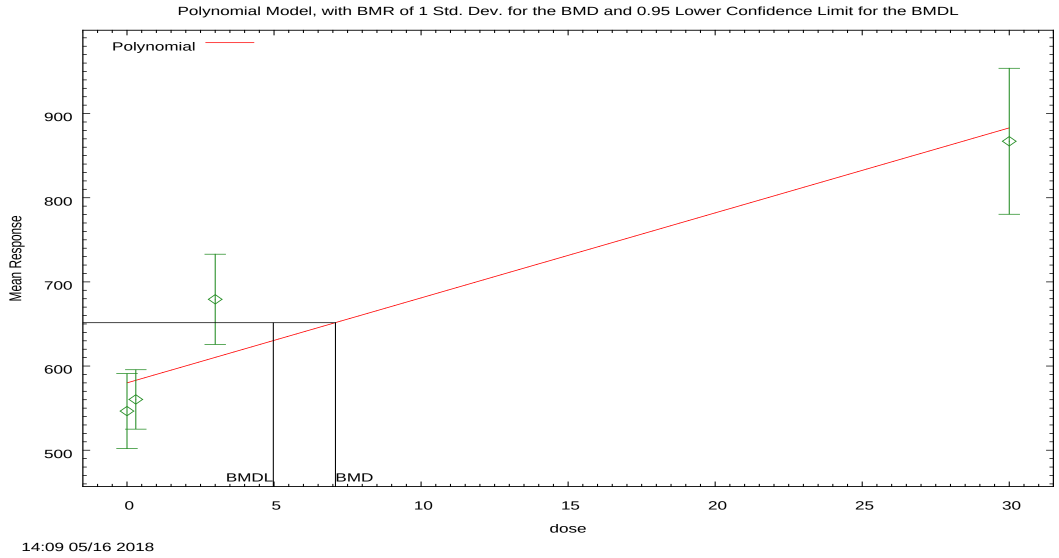

Figure 281. Plot of mean response by dose with fitted curve for Polynomial 3° model with modeled variance for Liver Weight to Brain Weight in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 7.08864

BMDL at the 95% confidence level = 4.97533

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-7.10731	8.80324
rho	2.46124	0
beta_0	579.553	546.486
beta_1	10.1491	46.3457

beta_2	0	0
beta_3	0	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	546	580	62.3	71.9	-1.45
0.3	10	560	583	49.4	72.4	-0.972
3	10	679	610	74.9	76.6	2.86
30	10	867	884	121	121	-0.443

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-193.957517	5	397.915035
A2	-189.338063	8	394.676127
A3	-189.72081	6	391.441621
fitted	-196.925841	4	401.851681
R	-220.423064	2	444.846129

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	62.17	6	<0.0001
Test 2	9.23891	3	0.02628
Test 3	0.765494	2	0.682
Test 4	14.4101	2	0.0007428

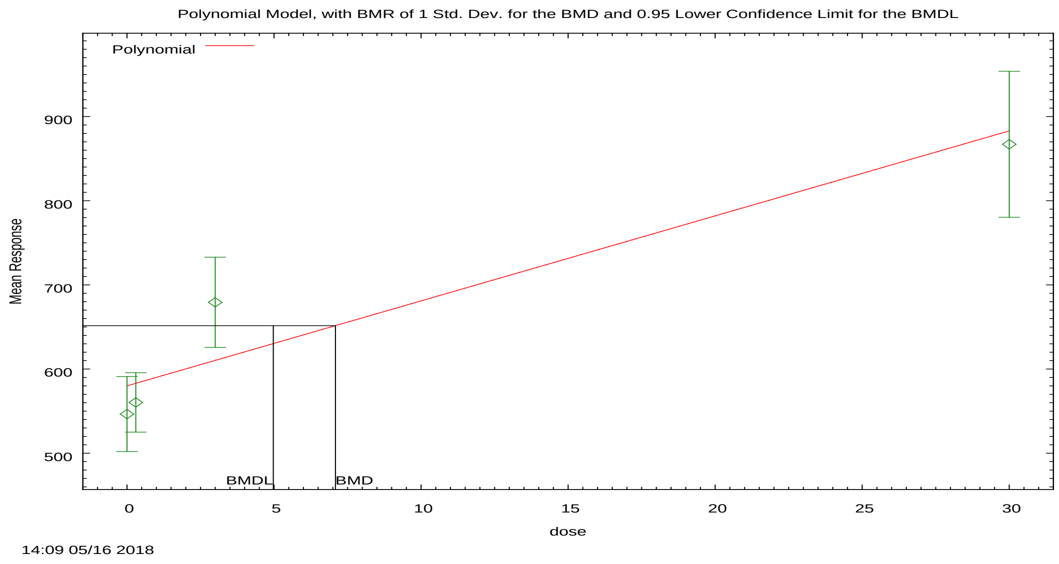

Figure 282. Plot of mean response by dose with fitted curve for Polynomial 2° model with modeled variance for Liver Weight to Brain Weight in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 7.08864

BMDL at the 95% confidence level = 4.97533

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-7.10735	8.80324
rho	2.46125	0
beta_0	579.553	546.267
beta_1	10.1491	48.0751

beta_2	0	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	546	580	62.3	71.9	-1.45
0.3	10	560	583	49.4	72.4	-0.972
3	10	679	610	74.9	76.6	2.86
30	10	867	884	121	121	-0.443

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-193.957517	5	397.915035
A2	-189.338063	8	394.676127
A3	-189.72081	6	391.441621
fitted	-196.925841	4	401.851681
R	-220.423064	2	444.846129

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	62.17	6	<0.0001
Test 2	9.23891	3	0.02628
Test 3	0.765494	2	0.682
Test 4	14.4101	2	0.0007428

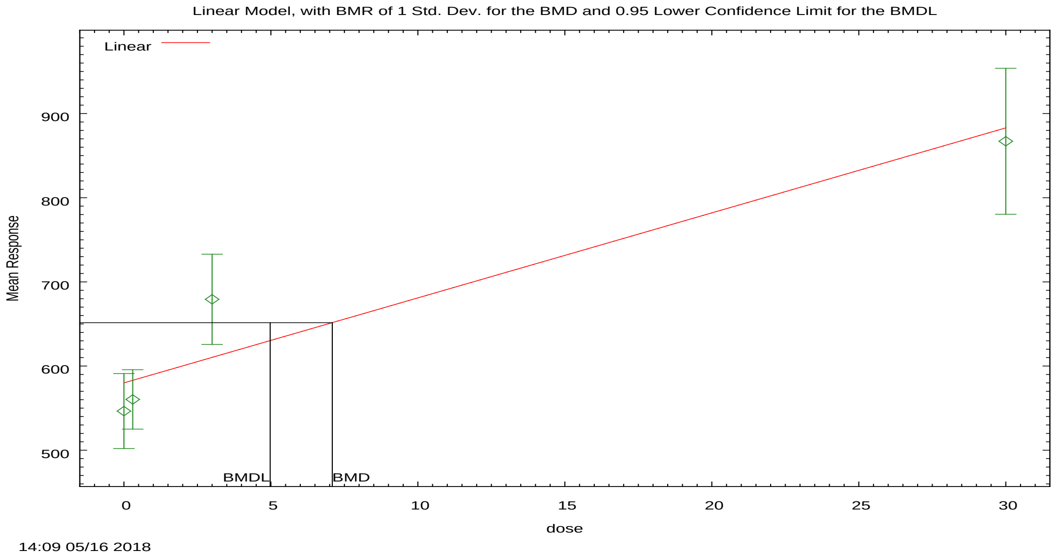

Figure 283. Plot of mean response by dose with fitted curve for Linear model with modeled variance for Liver Weight to Brain Weight in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 7.08864

BMDL at the 95% confidence level = 4.97533

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-7.10734	8.80324
rho	2.46125	0
beta_0	579.553	582.53
beta_1	10.1491	9.70205

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	546	580	62.3	71.9	-1.45
0.3	10	560	583	49.4	72.4	-0.972
3	10	679	610	74.9	76.6	2.86
30	10	867	884	121	121	-0.443

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-193.957517	5	397.915035
A2	-189.338063	8	394.676127
A3	-189.72081	6	391.441621
fitted	-196.925841	4	401.851681
R	-220.423064	2	444.846129

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	62.17	6	<0.0001
Test 2	9.23891	3	0.02628
Test 3	0.765494	2	0.682
Test 4	14.4101	2	0.0007428

BMDS WIZARD OUTPUT REPORT

BMDS Summary of H-28548: Subchronic Toxicity 90-Day Gavage Study in Mice – Liver Weight to Brain Weight (%) in Males

1.32. BMDS Summary of Liver weight to brain weight (%) Males (90 Day Mice GenX)

Table 32. Summary of BMD Modeling Results for Liver Weight to Brain Weight in Males (90-Day Mice); BMR = 1 std. dev. change from control mean

Model[a]	**Goodness of fit**		**BMD_{1SD} (mg/kg/day)**	**$BMDL_{1SD}$ (mg/kg/day)**	**BMD/BMDL**	**Basis for model selection**
	***p*-value**	**AIC**				
Exponential (M2) Exponential (M3)[b]	0.619	373.81	0.630	0.496	1.27	BMDLs from models that met model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values > 2.0; appropriate variance (continuous data only)) were compared. BMDLs from included models were sufficiently close (< 3-fold difference), so the BMDL from the model with the lowest AIC was selected.
Exponential (M4)[c]	0.747	374.96	0.395	0.210	1.88	
Exponential (M5)[d]	0.747	374.96	0.395	0.210	1.88	
Hill	0.747	374.96	0.398	error[e]	error	
Power[f] **Polynomial 3°[g]** **Polynomial 2°[h]** **Linear**	**0.949**	**372.96**	**0.400**	**0.300**	**1.34**	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = <0.0001), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 0.5, and 5 mg/kg/day were -0.19, 0.5, -0.36, 0.06, respectively.

[b] For the Exponential (M3) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M2) model.

[c] The Exponential (M4) model may appear equivalent to the Exponential (M5) model, however differences exist in digits not displayed in the table.

[d] The Exponential (M5) model may appear equivalent to the Exponential (M4) model, however differences exist in digits not displayed in the table.

[e] BMD or BMDL computation failed for this model.

[f] For the Power model, the power parameter estimate was 1. The models in this row reduced to the Linear model.

[g] For the Polynomial 3° model, the b3 coefficient estimates was 0 (boundary of parameters space). The models in this row reduced to the Polynomial 2° model. For the Polynomial 3° model, the b3 and b2 coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Linear model.

[h] For the Polynomial 2° model, the b2 coefficient estimate was 0 (boundary of parameters space). The models in this row reduced to the Linear model.

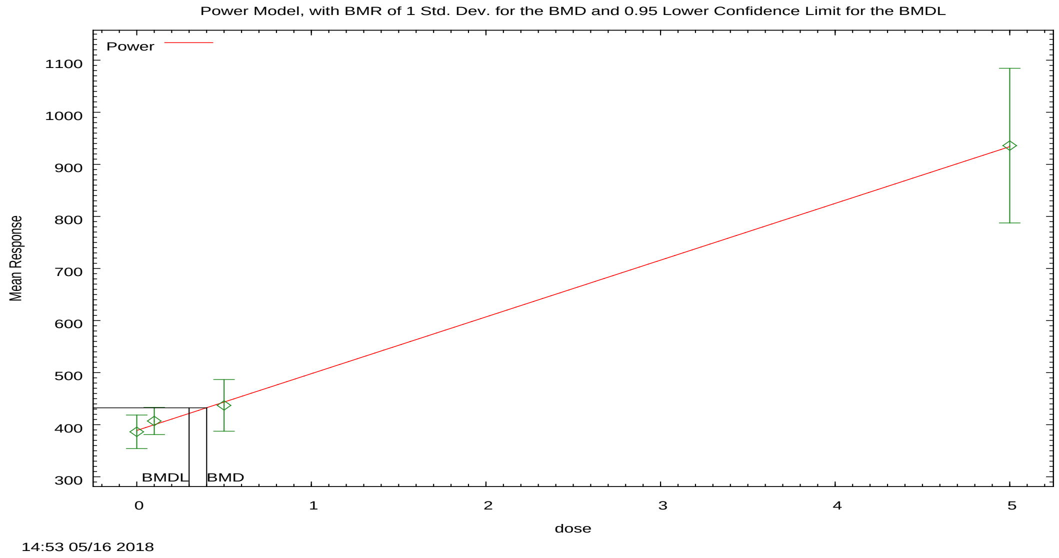

Figure 284. Plot of mean response by dose with fitted curve for Power model with modeled variance for Liver Weight to Brain Weight in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 0.400252

BMDL at the 95% confidence level = 0.299666

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-12.4949	9.2714
rho	3.3602	0
control	389.017	386.366
slope	108.602	139.636

power	1	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	386	389	45	43.5	-0.193
0.1	10	407	400	36.4	45.5	0.502
0.5	10	437	443	69.4	54.1	-0.363
5	9	936	932	193	189	0.0626

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-198.182127	5	406.364254
A2	-181.17551	8	378.351021
A3	-182.426362	6	376.852725
fitted	-182.47882	4	372.957641
R	-233.69519	2	471.39038

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	105.039	6	<0.0001
Test 2	34.0132	3	<0.0001
Test 3	2.5017	2	0.2863
Test 4	0.104916	2	0.9489

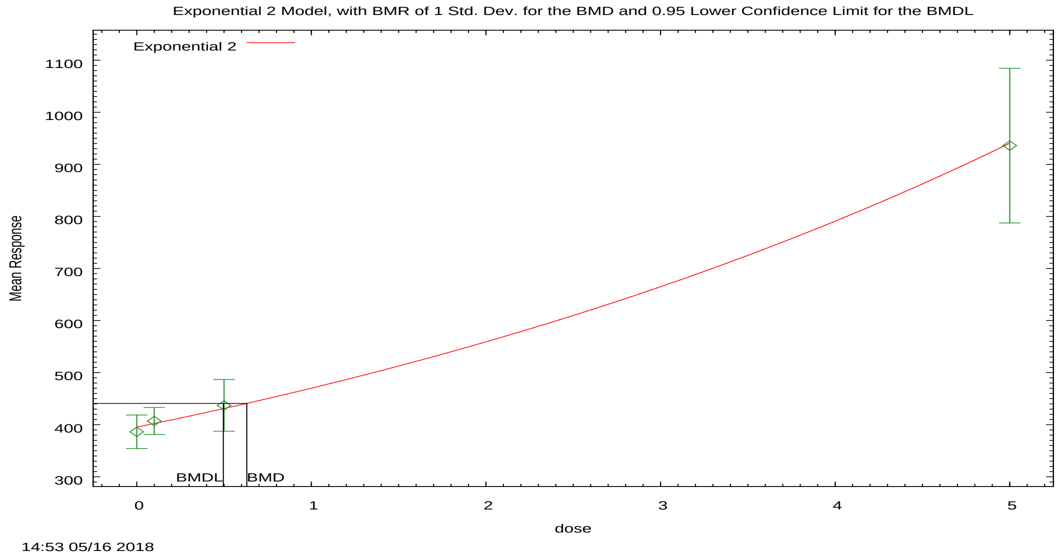

Figure 285. Plot of mean response by dose with fitted curve for Exponential (M2) model with modeled variance for Liver Weight to Brain Weight in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 0.630028

BMDL at the 95% confidence level = 0.495699

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-11.8538	-12.7752
rho	3.26009	3.41177
a	395.343	395.553
b	0.173345	0.172612

c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	386.4	395.3	45.01	45.62	-0.6223
0.1	10	407.1	402.3	36.41	46.93	0.3265
0.5	10	437.1	431.1	69.39	52.55	0.3588
5	9	936	940.6	193.2	187.4	-0.07359

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-198.1821	5	406.3643
A2	-181.1755	8	378.351
A3	-182.4264	6	376.8527
R	-233.6952	2	471.3904
2	-182.9059	4	373.8117

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	105	6	<0.0001
Test 2	34.01	3	<0.0001
Test 3	2.502	2	0.2863
Test 4	0.959	2	0.6191

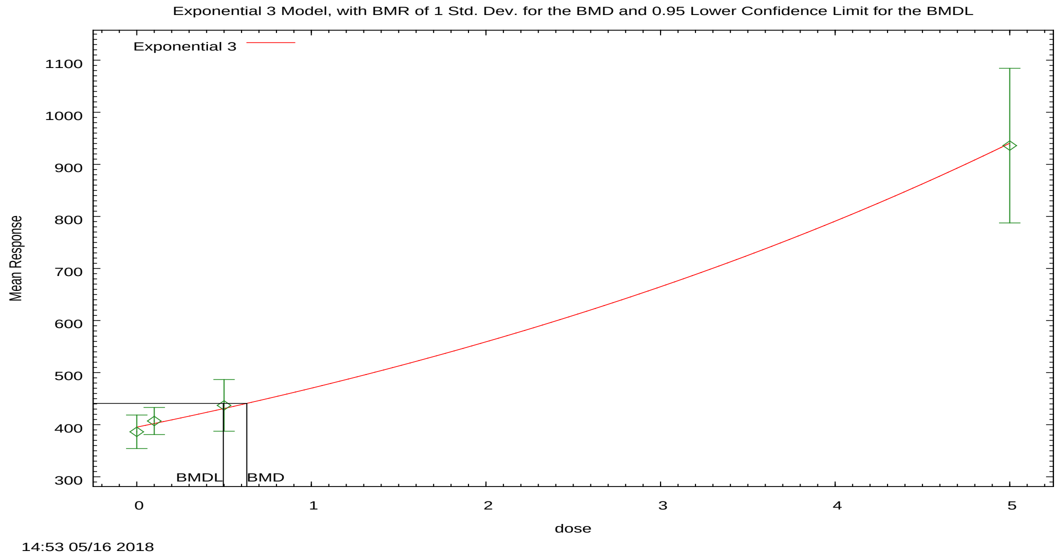

Figure 286. Plot of mean response by dose with fitted curve for Exponential (M3) model with modeled variance for Liver Weight to Brain Weight in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 0.630028

BMDL at the 95% confidence level = 0.495699

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-11.8538	-12.7752
rho	3.26009	3.41177
a	395.343	395.553
b	0.173345	0.172612

c	n/a	0
d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	386.4	395.3	45.01	45.62	-0.6223
0.1	10	407.1	402.3	36.41	46.93	0.3265
0.5	10	437.1	431.1	69.39	52.55	0.3588
5	9	936	940.6	193.2	187.4	-0.07359

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-198.1821	5	406.3643
A2	-181.1755	8	378.351
A3	-182.4264	6	376.8527
R	-233.6952	2	471.3904
3	-182.9059	4	373.8117

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	105	6	<0.0001
Test 2	34.01	3	<0.0001
Test 3	2.502	2	0.2863
Test 5a	0.959	2	0.6191

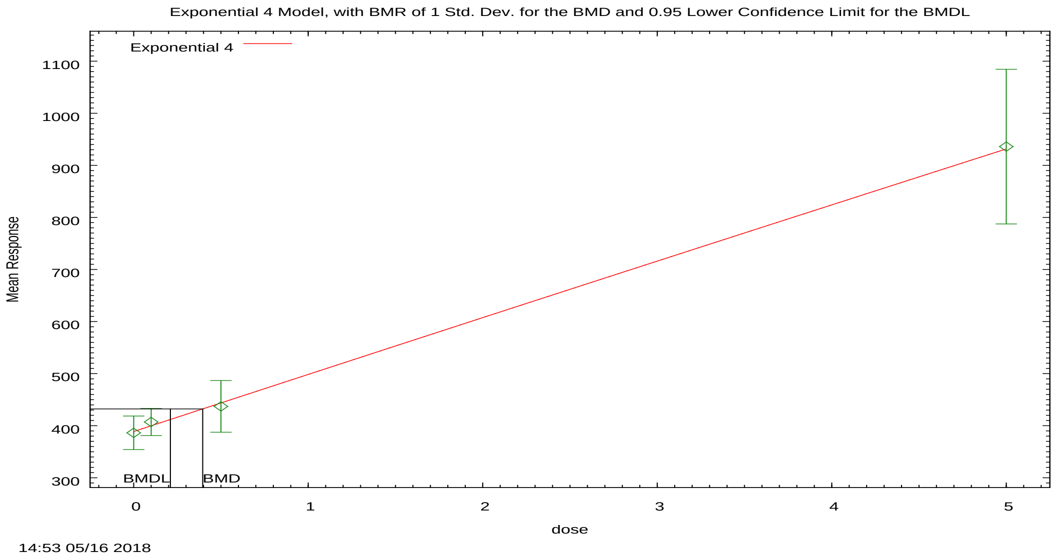

Figure 287. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Liver Weight to Brain Weight in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 0.395422

BMDL at the 95% confidence level = 0.210227

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-12.5182	-12.7752
rho	3.36398	3.41177
a	388.84	367.048
b	0.00509897	0.0950512

c	56.4368	5.09997
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	386.4	388.8	45.01	43.42	-0.1802
0.1	10	407.1	399.8	36.41	45.5	0.5054
0.5	10	437.1	443.7	69.39	54.22	-0.3865
5	9	936	931.5	193.2	188.7	0.07162

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-198.1821	5	406.3643
A2	-181.1755	8	378.351
A3	-182.4264	6	376.8527
R	-233.6952	2	471.3904
4	-182.4784	5	374.9568

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	105	6	<0.0001
Test 2	34.01	3	<0.0001
Test 3	2.502	2	0.2863
Test 6a	0.1041	1	0.747

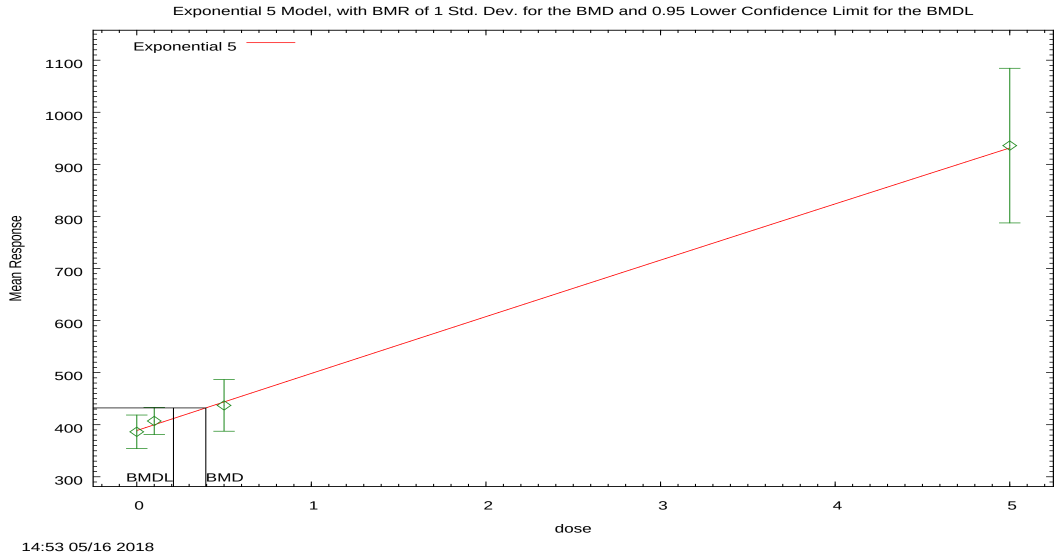

Figure 288. Plot of mean response by dose with fitted curve for Exponential (M5) model with modeled variance for Liver Weight to Brain Weight in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 0.395425

BMDL at the 95% confidence level = 0.210227

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-12.5182	-12.7752
rho	3.36397	3.41177
a	388.84	367.048
b	0.00509556	0.0950512

c	56.4734	5.09997
d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	386.4	388.8	45.01	43.42	-0.1802
0.1	10	407.1	399.8	36.41	45.5	0.5054
0.5	10	437.1	443.7	69.39	54.22	-0.3865
5	9	936	931.5	193.2	188.7	0.07161

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-198.1821	5	406.3643
A2	-181.1755	8	378.351
A3	-182.4264	6	376.8527
R	-233.6952	2	471.3904
5	-182.4784	5	374.9568

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	105	6	<0.0001
Test 2	34.01	3	<0.0001
Test 3	2.502	2	0.2863
Test 7a	0.1041	1	0.747

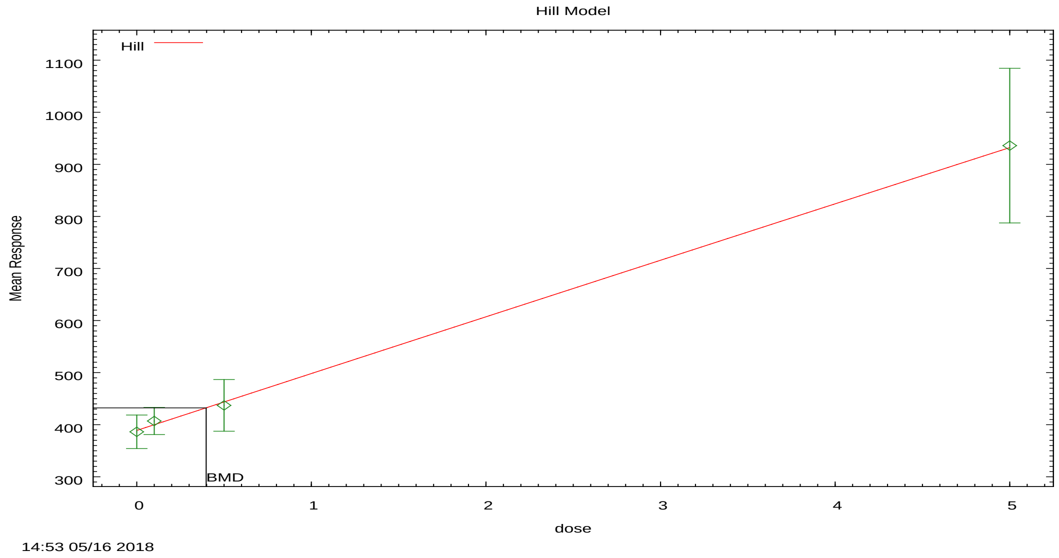

Figure 289. Plot of mean response by dose with fitted curve for Hill model with modeled variance for Liver Weight to Brain Weight in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A modeled variance is fit

THE MODEL HAS PROBABLY NOT CONVERGED!!!

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 0.397504

BMDL at the 95% confidence level = error

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-12.5081	9.2714
rho	3.36233	0
intercept	388.917	386.366
v	75472.5	549.6

n	1	0.797806
k	690.226	7.47882

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	386	389	45	43.4	-0.186
0.1	10	407	400	36.4	45.5	0.504
0.5	10	437	444	69.4	54.2	-0.376
5	9	936	932	193	189	0.0677

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-198.182127	5	406.364254
A2	-181.17551	8	378.351021
A3	-182.426362	6	376.852725
fitted	-182.478479	5	374.956959
R	-233.69519	2	471.39038

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	105.039	6	<0.0001
Test 2	34.0132	3	<0.0001
Test 3	2.5017	2	0.2863
Test 4	0.104234	1	0.7468

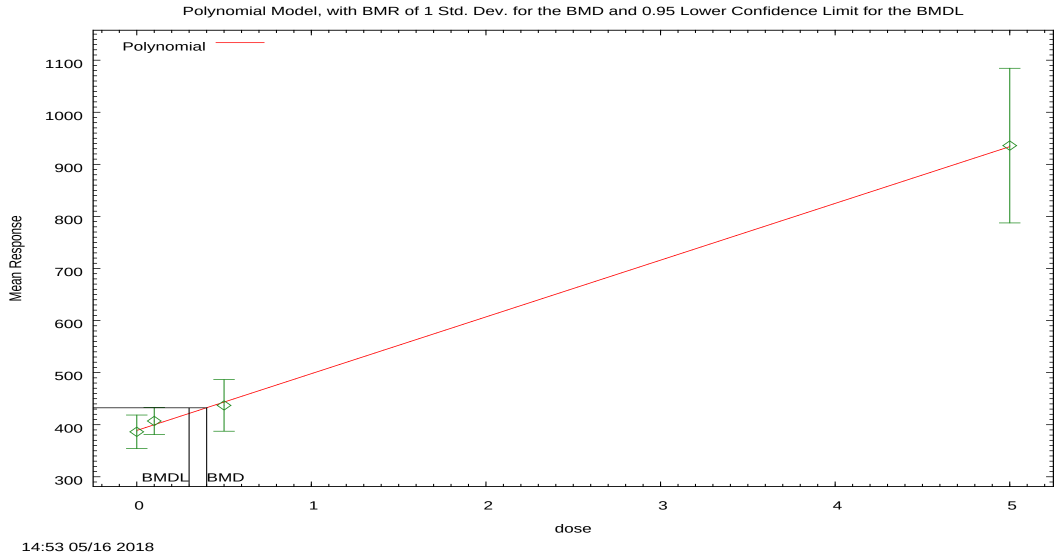

Figure 290. Plot of mean response by dose with fitted curve for Polynomial 3° model with modeled variance for Liver Weight to Brain Weight in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 0.400252

BMDL at the 95% confidence level = 0.299666

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-12.4949	9.2714
rho	3.3602	0
beta_0	389.017	386.366
beta_1	108.602	236.541

beta_2	0	0
beta_3	2.57962E-84	54.4047

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	386	389	45	43.5	-0.193
0.1	10	407	400	36.4	45.5	0.502
0.5	10	437	443	69.4	54.1	-0.363
5	9	936	932	193	189	0.0626

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-198.182127	5	406.364254
A2	-181.17551	8	378.351021
A3	-182.426362	6	376.852725
fitted	-182.47882	4	372.957641
R	-233.69519	2	471.39038

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	105.039	6	<0.0001
Test 2	34.0132	3	<0.0001
Test 3	2.5017	2	0.2863
Test 4	0.104916	2	0.9489

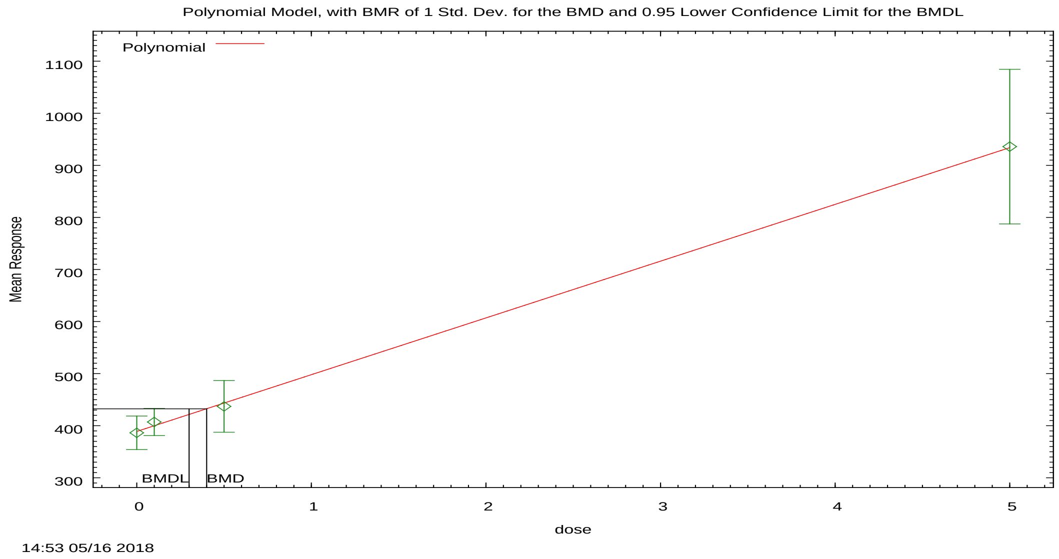

Figure 291. Plot of mean response by dose with fitted curve for Polynomial 2° model with modeled variance for Liver Weight to Brain Weight in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 0.400252

BMDL at the 95% confidence level = 0.299666

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-12.4949	9.2714
rho	3.3602	0
beta_0	389.017	391.396
beta_1	108.602	92.5683

beta_2	0	3.26869

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	386	389	45	43.5	-0.193
0.1	10	407	400	36.4	45.5	0.502
0.5	10	437	443	69.4	54.1	-0.363
5	9	936	932	193	189	0.0626

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-198.182127	5	406.364254
A2	-181.17551	8	378.351021
A3	-182.426362	6	376.852725
fitted	-182.47882	4	372.957641
R	-233.69519	2	471.39038

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	105.039	6	<0.0001
Test 2	34.0132	3	<0.0001
Test 3	2.5017	2	0.2863
Test 4	0.104916	2	0.9489

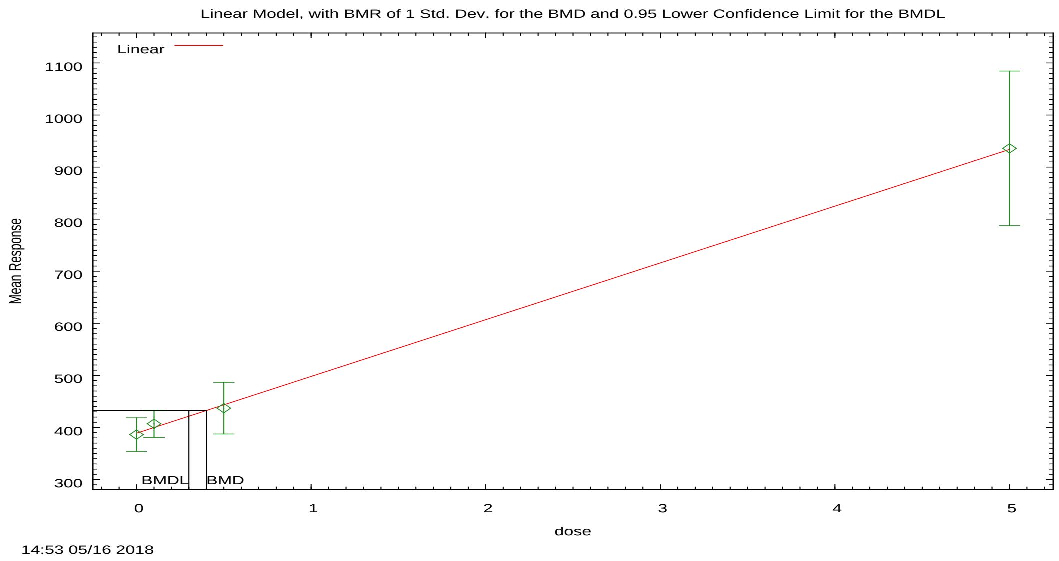

Figure 292. Plot of mean response by dose with fitted curve for Linear model with modeled variance for Liver Weight to Brain Weight in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 0.400252

BMDL at the 95% confidence level = 0.299666

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-12.4949	9.2714
rho	3.3602	0
beta_0	389.017	388.458
beta_1	108.602	109.411

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	386	389	45	43.5	-0.193
0.1	10	407	400	36.4	45.5	0.502
0.5	10	437	443	69.4	54.1	-0.363
5	9	936	932	193	189	0.0626

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-198.182127	5	406.364254
A2	-181.17551	8	378.351021
A3	-182.426362	6	376.852725
fitted	-182.47882	4	372.957641
R	-233.69519	2	471.39038

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	105.039	6	<0.0001
Test 2	34.0132	3	<0.0001
Test 3	2.5017	2	0.2863
Test 4	0.104916	2	0.9489

BMDS WIZARD OUTPUT REPORT

BMDS Summary of H-28548: Subchronic Toxicity 90-Day Gavage Study in Mice – Liver Weight to Brain Weight (%) in Females

1.33. BMDS Summary of Liver weight to brain weight (%) Females (90 Day Mice GenX)

Table 33. Summary of BMD Modeling Results for Liver Weight to Brain Weight in Females (90-Day Mice); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD_{1SD} (mg/kg/day)	BMDL_{1SD} (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2)	**0.520**	**368.12**	**1.34**	**0.929**	1.44	BMDLs from models that met model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values > 2.0; appropriate variance (continuous data only)) were compared. BMDLs from included models were sufficiently close (< 3-fold difference), so the BMDL from the model with the lowest AIC was selected.
Exponential (M3)	0.268	370.04	1.59	0.933	1.70	
Exponential (M4)	0.227	370.28	1.10	0.449	2.45	
Exponential (M5)	N/A[b]	371.77	0.555	0.469	1.18	
Hill	N/A[b]	371.77	0.564	error[c]	error	
Power	0.275	370.01	1.47	0.714	2.05	
Polynomial 3°[d] Polynomial 2°	0.261	370.08	1.57	0.709	2.21	
Linear	0.483	368.27	1.10	0.699	1.57	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = <0.0001), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 0.5, and 5 mg/kg/day were 0.05, -0.08, 0.03, 0, respectively.
[b] No available degrees of freedom to calculate a goodness of fit value.
[c] BMD or BMDL computation failed for this model.
[d] For the Polynomial 3° model, the b3 coefficient estimates was 0 (boundary of parameters space). The models in this row reduced to the Polynomial 2° model.

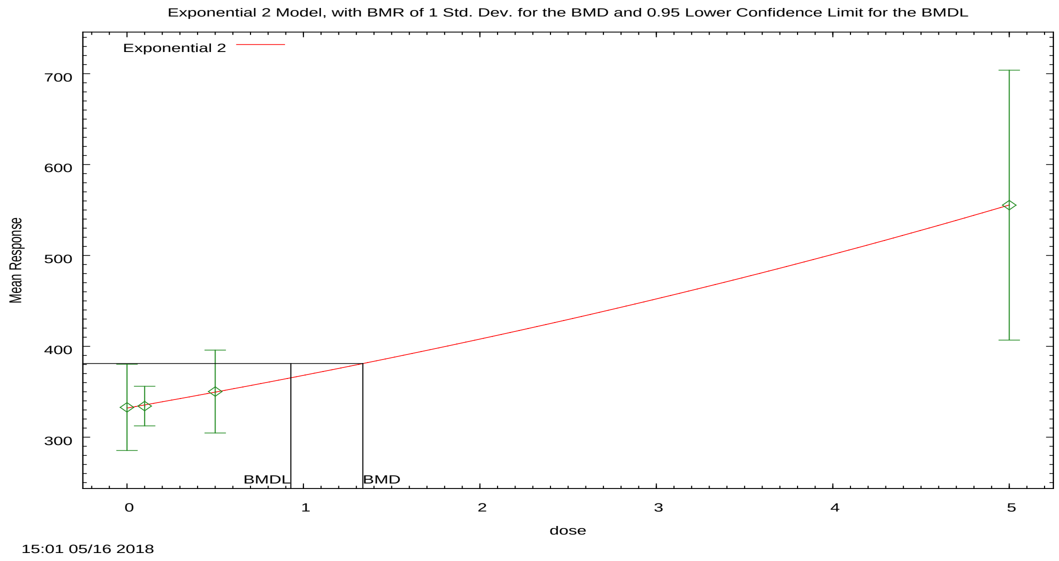

Figure 293. Plot of mean response by dose with fitted curve for Exponential (M2) model with modeled variance for Liver Weight to Brain Weight in

Females (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 1.33655

BMDL at the 95% confidence level = 0.928594

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-21.701	-24.6464
rho	5.07868	5.5678
a	332.061	332.075
b	0.102919	0.102859
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	332.8	332.1	66.34	48.97	0.04942
0.1	10	334.2	335.5	30.44	50.26	-0.07851
0.5	9	350.2	349.6	59.32	55.8	0.03335
5	9	555.3	555.5	193.2	180.9	-0.003207

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-193.7363	5	397.4727

A2	-177.1145	8	370.229
A3	-179.4087	6	370.8173
R	-205.5727	2	415.1453
2	-180.062	4	368.124

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	56.92	6	<0.0001
Test 2	33.24	3	<0.0001
Test 3	4.588	2	0.1008
Test 4	1.307	2	0.5203

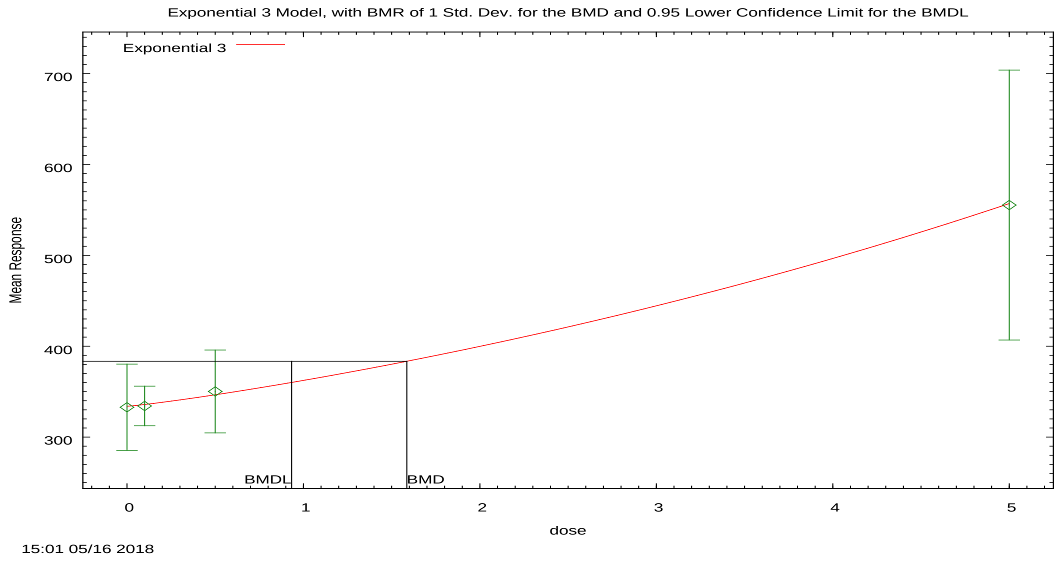

Figure 294. Plot of mean response by dose with fitted curve for Exponential (M3) model with modeled variance for Liver Weight to Brain Weight in Females (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 1.58582

BMDL at the 95% confidence level = 0.933248

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-21.7049	-24.6464
rho	5.07872	5.5678
a	333.889	332.075
b	0.111062	0.102859
c	n/a	0
d	1.13876	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	332.8	333.9	66.34	49.57	-0.06782
0.1	10	334.2	335.9	30.44	50.32	-0.1026
0.5	9	350.2	346.5	59.32	54.47	0.2026
5	9	555.3	557	193.2	181.8	-0.02782

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-193.7363	5	397.4727
A2	-177.1145	8	370.229
A3	-179.4087	6	370.8173
R	-205.5727	2	415.1453
3	-180.0222	5	370.0445

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value

Test 1	56.92	6	<0.0001
Test 2	33.24	3	<0.0001
Test 3	4.588	2	0.1008
Test 5a	1.227	1	0.268

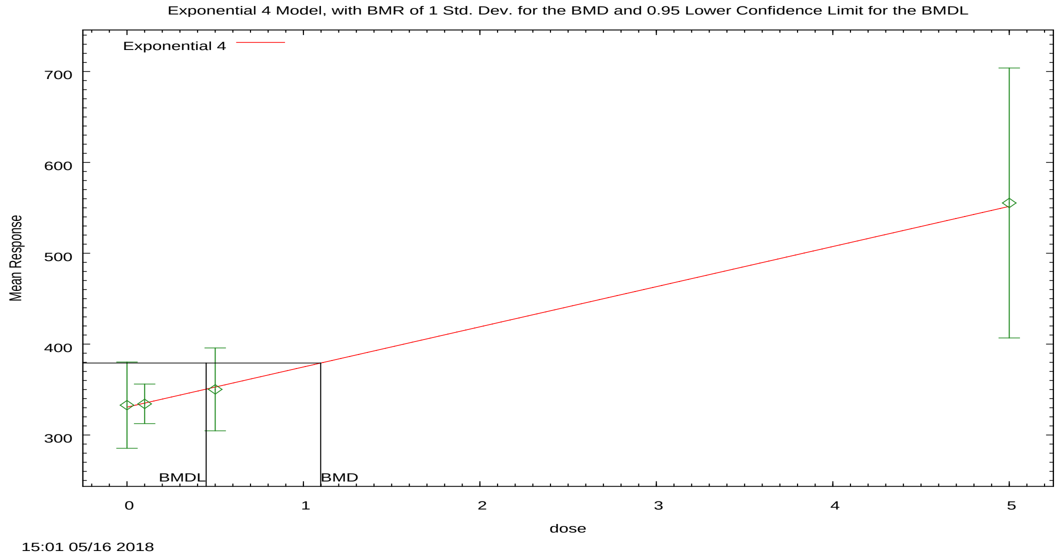

Figure 295. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Liver Weight to Brain Weight in Females (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 1.09769

BMDL at the 95% confidence level = 0.448825

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-21.9721	-24.6464
rho	5.1258	5.5678
a	330.674	316.185
b	0.0000741586	0.0718443
c	1803.04	3.51269
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	332.8	330.7	66.34	48.51	0.1403
0.1	10	334.2	335.1	30.44	50.18	-0.05327
0.5	9	350.2	352.8	59.32	57.25	-0.1338
5	9	555.3	551.6	193.2	180	0.06242

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-193.7363	5	397.4727
A2	-177.1145	8	370.229
A3	-179.4087	6	370.8173
R	-205.5727	2	415.1453
4	-180.1376	5	370.2751

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	56.92	6	<0.0001
Test 2	33.24	3	<0.0001
Test 3	4.588	2	0.1008
Test 6a	1.458	1	0.2273

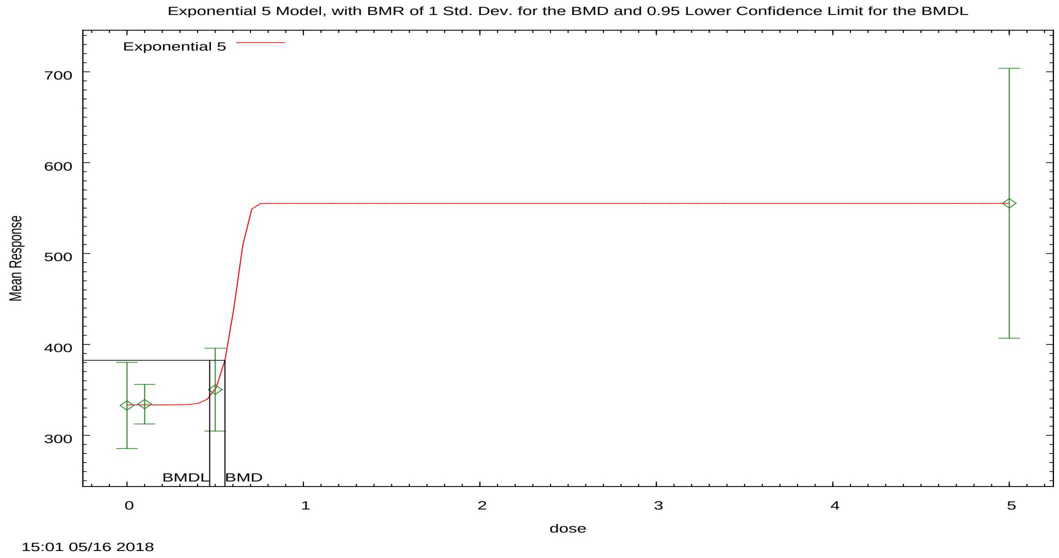

Figure 296. Plot of mean response by dose with fitted curve for Exponential (M5) model with modeled variance for Liver Weight to Brain Weight in Females (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 0.555118

BMDL at the 95% confidence level = 0.468614

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-22.1329	-24.6464
rho	5.14986	5.5678
a	333.478	316.185
b	1.58761	0.0718443

c	1.66492	3.51269
d	10.9725	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	332.8	333.5	66.34	49.05	-0.04202
0.1	10	334.2	333.5	30.44	49.05	0.04966
0.5	9	350.2	350.4	59.32	55.71	-0.009639
5	9	555.3	555.2	193.2	182.3	0.001931

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-193.7363	5	397.4727
A2	-177.1145	8	370.229
A3	-179.4087	6	370.8173
R	-205.5727	2	415.1453
5	-179.8862	6	371.7724

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	56.92	6	<0.0001
Test 2	33.24	3	<0.0001
Test 3	4.588	2	0.1008
Test 7a	0.9551	0	N/A

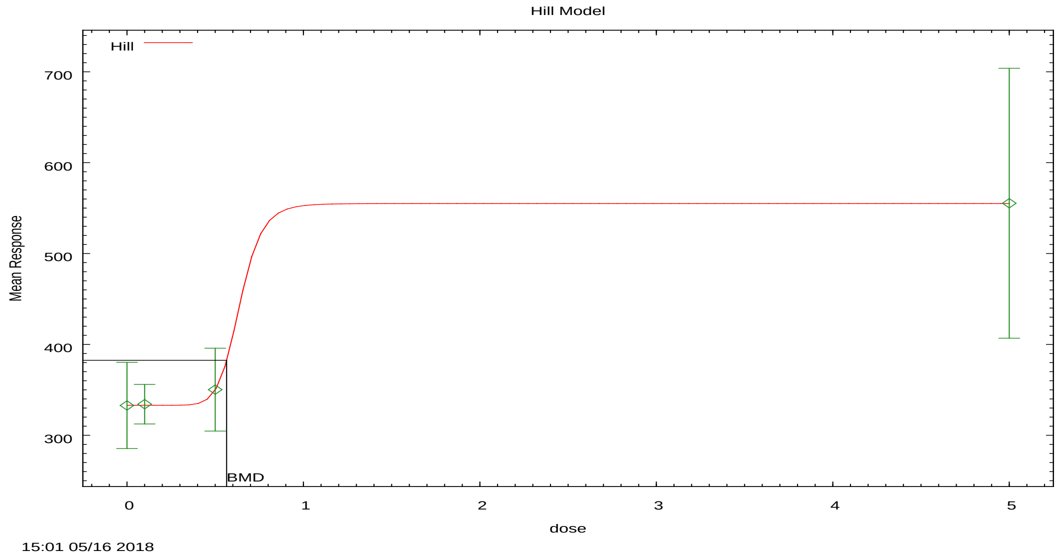

Figure 297. Plot of mean response by dose with fitted curve for Hill model with modeled variance for Liver Weight to Brain Weight in Females (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 0.564491

BMDL at the 95% confidence level = error

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-22.133	9.30788
rho	5.14986	0
intercept	333.478	332.826
v	221.735	222.504
n	10.1808	1.04245

k	0.638779	7.44076

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	333	333	66.3	49	-0.042
0.1	10	334	333	30.4	49	0.0497
0.5	9	350	350	59.3	55.7	-0.00964
5	9	555	555	193	182	0.00193

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-193.736349	5	397.472698
A2	-177.114505	8	370.229011
A3	-179.408666	6	370.817331
fitted	-179.886216	6	371.772432
R	-205.572651	2	415.145302

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	56.9163	6	<0.0001
Test 2	33.2437	3	<0.0001
Test 3	4.58832	2	0.1008
Test 4	0.9551	0	N/A

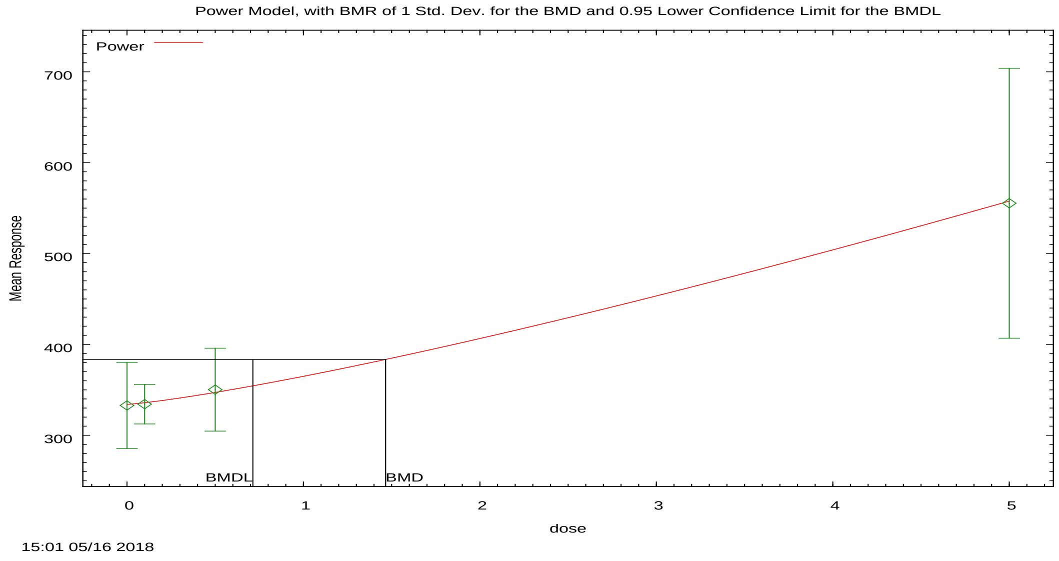

Figure 298. Plot of mean response by dose with fitted curve for Power model with modeled variance for Liver Weight to Brain Weight in Females (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 1.46578

BMDL at the 95% confidence level = 0.713574

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-21.717	9.30788
rho	5.08057	0
control	333.778	332.826
slope	30.9436	28.4057
power	1.22806	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	333	334	66.3	49.5	-0.0608
0.1	10	334	336	30.4	50.2	-0.0857
0.5	9	350	347	59.3	54.6	0.177
5	9	555	557	193	182	-0.0293

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-193.736349	5	397.472698
A2	-177.114505	8	370.229011
A3	-179.408666	6	370.817331
fitted	-180.005253	5	370.010505
R	-205.572651	2	415.145302

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	56.9163	6	<0.0001
Test 2	33.2437	3	<0.0001
Test 3	4.58832	2	0.1008
Test 4	1.19317	1	0.2747

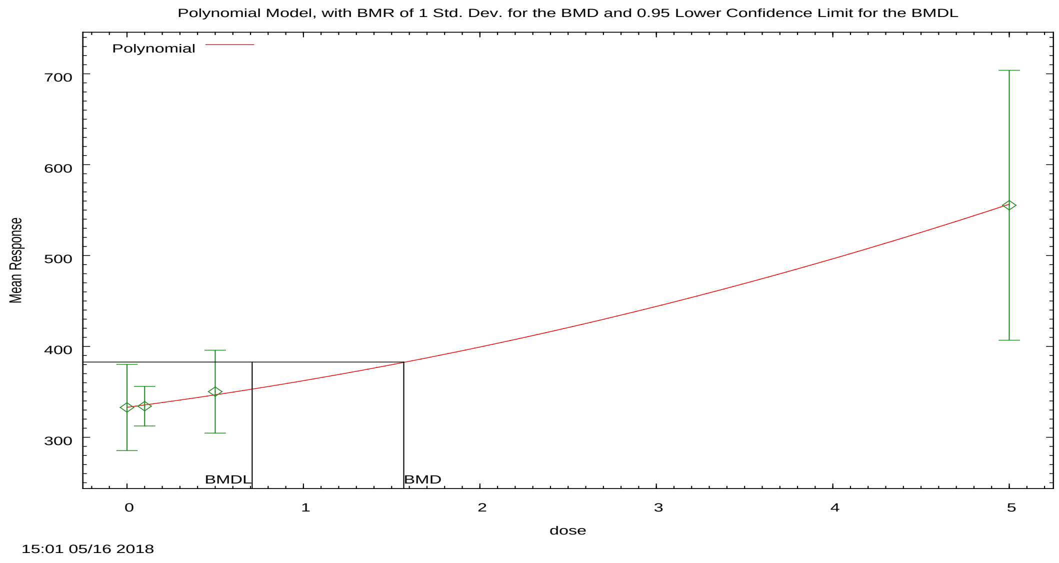

Figure 299. Plot of mean response by dose with fitted curve for Polynomial 3° model with modeled variance for Liver Weight to Brain Weight in Females (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 1.56853

BMDL at the 95% confidence level = 0.709326

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-21.6616	9.30788
rho	5.07164	0
beta_0	333.382	332.826
beta_1	25.4879	8.57755

beta_2	3.84048	57.4294
beta_3	0	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	333	333	66.3	49.4	-0.0356
0.1	10	334	336	30.4	50.4	-0.108
0.5	9	350	347	59.3	54.7	0.172
5	9	555	557	193	182	-0.0248

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-193.736349	5	397.472698
A2	-177.114505	8	370.229011
A3	-179.408666	6	370.817331
fitted	-180.041834	5	370.083668
R	-205.572651	2	415.145302

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	56.9163	6	<0.0001
Test 2	33.2437	3	<0.0001
Test 3	4.58832	2	0.1008
Test 4	1.26634	1	0.2605

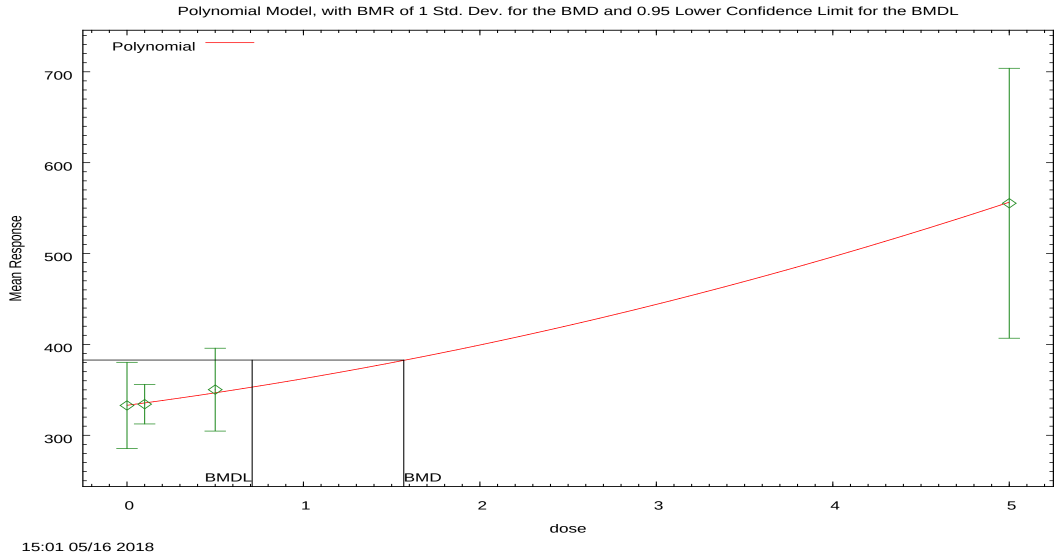

Figure 300. Plot of mean response by dose with fitted curve for Polynomial 2° model with modeled variance for Liver Weight to Brain Weight in Females (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 1.56853

BMDL at the 95% confidence level = 0.709326

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-21.6616	9.30788
rho	5.07164	0
beta_0	333.382	331.897
beta_1	25.4879	35.1703

beta_2	3.84048	1.90335

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	333	333	66.3	49.4	-0.0356
0.1	10	334	336	30.4	50.4	-0.108
0.5	9	350	347	59.3	54.7	0.172
5	9	555	557	193	182	-0.0248

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-193.736349	5	397.472698
A2	-177.114505	8	370.229011
A3	-179.408666	6	370.817331
fitted	-180.041834	5	370.083668
R	-205.572651	2	415.145302

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	56.9163	6	<0.0001
Test 2	33.2437	3	<0.0001
Test 3	4.58832	2	0.1008
Test 4	1.26634	1	0.2605

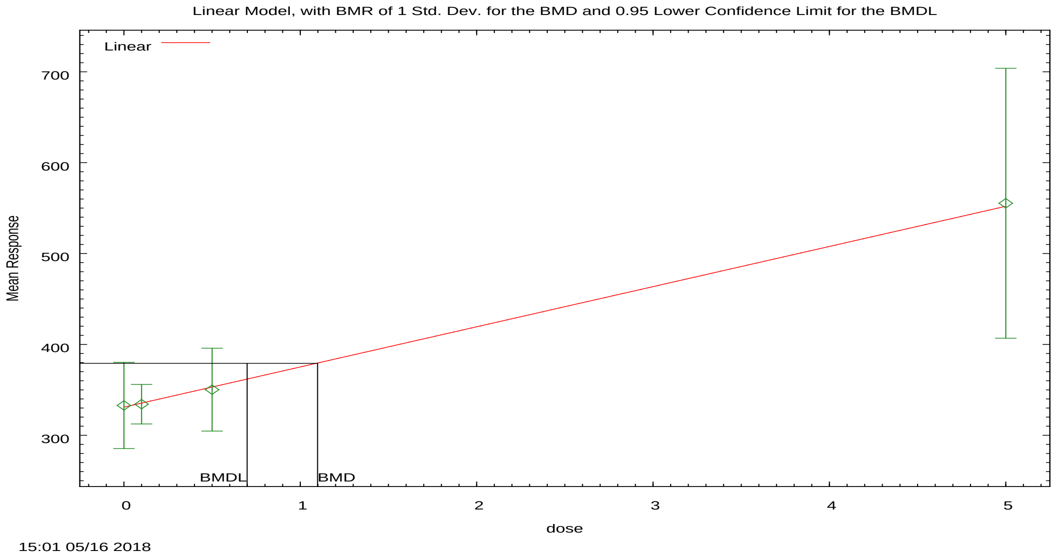

Figure 301. Plot of mean response by dose with fitted curve for Linear model with modeled variance for Liver Weight to Brain Weight in Females (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 1.09783

BMDL at the 95% confidence level = 0.698635

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-21.9718	9.30788
rho	5.12574	0
beta_0	330.675	330.186
beta_1	44.1828	44.9779

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	333	331	66.3	48.5	0.14
0.1	10	334	335	30.4	50.2	-0.0533
0.5	9	350	353	59.3	57.2	-0.134
5	9	555	552	193	180	0.0623

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-193.736349	5	397.472698
A2	-177.114505	8	370.229011
A3	-179.408666	6	370.817331
fitted	-180.137486	4	368.274971
R	-205.572651	2	415.145302

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	56.9163	6	<0.0001
Test 2	33.2437	3	<0.0001
Test 3	4.58832	2	0.1008
Test 4	1.45764	2	0.4825

BMDS WIZARD OUTPUT REPORT

BMDS Summary of Oral (Gavage) Reproduction/Developmental Toxicity Screening Study of H-28548 in Mice – Liver Weight to Brain Weight (g/100g brain) in Males

1.34. BMDS Summary of Liver weight to brain weight (g/100g brain weight) (Reproductive Mice GenX)

Table 34. Summary of BMD Modeling Results for Liver Weight to Brain Weight in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD_{1SD} (mg/kg/day)	$BMDL_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2) Exponential (M3)[b]	3.52E-04	941.07	0.774	0.662	1.17	Only one model met model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). Selected BMDL is from this model.
Exponential (M4) **Exponential (M5)[c]**	**0.570**	**927.48**	**0.232**	**0.165**	**1.40**	
Hill	0.586	927.46	0.229	error[d]	error	
Power[e] Polynomial 3°[f] Polynomial 2°[g] Linear	0.0179	933.21	0.472	0.388	1.22	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = <0.0001), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 0.5, and 5 mg/kg/day were -0.15, 0.27, -0.13, 0.02, respectively.

[b] For the Exponential (M3) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M2) model.

[c] For the Exponential (M5) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M4) model.

[d] BMD or BMDL computation failed for this model.

[e] For the Power model, the power parameter estimate was 1. The models in this row reduced to the Linear model.

[f] For the Polynomial 3° model, the b3 coefficient estimates was 0 (boundary of parameters space). The models in this row reduced to the Polynomial 2° model. For the Polynomial 3° model, the b3 and b2 coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Linear model.

[g] For the Polynomial 2° model, the b2 coefficient estimate was 0 (boundary of parameters space). The models in this row reduced to the Linear model.

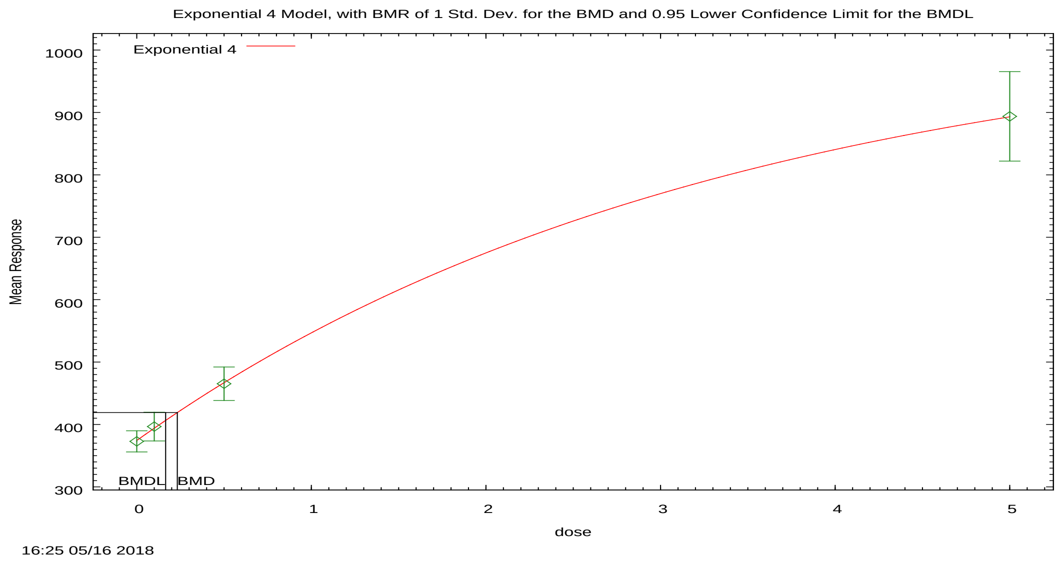

Figure 302. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Liver Weight to Brain Weight in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 0.23223

BMDL at the 95% confidence level = 0.16532

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-10.3467	-10.4607
rho	3.02939	3.05296
a	374.308	354.287
b	0.297892	0.513265
c	2.78911	2.64868
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	25	372.9	374.3	41.08	44.76	-0.1535
0.1	24	396.6	394	54.49	48.37	0.2689
0.5	24	465.3	467	63.57	62.58	-0.1333
5	24	893.7	893	169.8	167.1	0.02143

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-489.6261	5	989.2522
A2	-458.1745	8	932.349
A3	-458.5804	6	929.1608
R	-576.4866	2	1156.973
4	-458.7417	5	927.4834

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	236.6	6	<0.0001
Test 2	62.9	3	<0.0001
Test 3	0.8118	2	0.6664
Test 6a	0.3226	1	0.5701

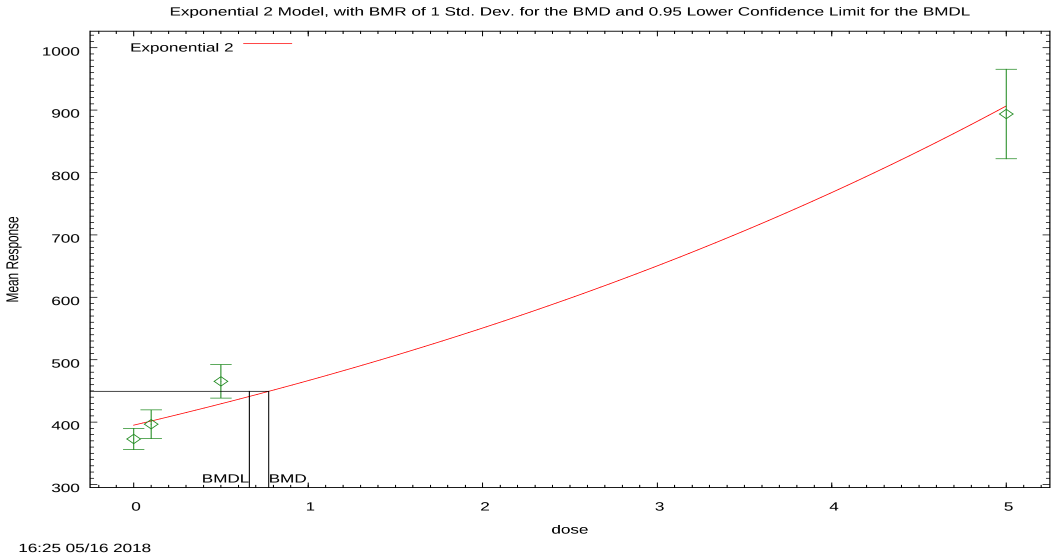

Figure 303. Plot of mean response by dose with fitted curve for Exponential (M2) model with modeled variance for Liver Weight to Brain Weight in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 0.77405

BMDL at the 95% confidence level = 0.662372

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-8.47038	-10.4607
rho	2.75225	3.05296
a	395.114	395.162
b	0.166106	0.164785
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	25	372.9	395.1	41.08	54.21	-2.046
0.1	24	396.6	401.7	54.49	55.47	-0.4516
0.5	24	465.3	429.3	63.57	60.78	2.898
5	24	893.7	906.6	169.8	170	-0.3716

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-489.6261	5	989.2522
A2	-458.1745	8	932.349
A3	-458.5804	6	929.1608
R	-576.4866	2	1156.973
2	-466.5332	4	941.0663

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	236.6	6	<0.0001
Test 2	62.9	3	<0.0001
Test 3	0.8118	2	0.6664
Test 4	15.91	2	0.0003517

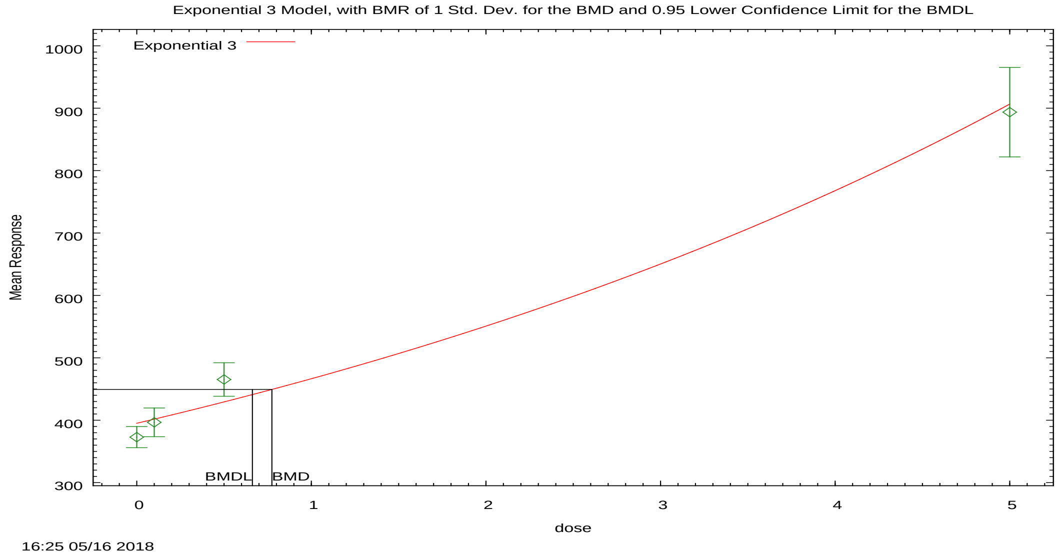

Figure 304. Plot of mean response by dose with fitted curve for Exponential (M3) model with modeled variance for Liver Weight to Brain Weight in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 0.77405

BMDL at the 95% confidence level = 0.662372

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-8.47038	-10.4607
rho	2.75225	3.05296
a	395.114	395.162
b	0.166106	0.164785
c	n/a	0
d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	25	372.9	395.1	41.08	54.21	-2.046
0.1	24	396.6	401.7	54.49	55.47	-0.4516
0.5	24	465.3	429.3	63.57	60.78	2.898
5	24	893.7	906.6	169.8	170	-0.3716

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-489.6261	5	989.2522
A2	-458.1745	8	932.349
A3	-458.5804	6	929.1608
R	-576.4866	2	1156.973
3	-466.5332	4	941.0663

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	236.6	6	<0.0001
Test 2	62.9	3	<0.0001
Test 3	0.8118	2	0.6664
Test 5a	15.91	2	0.0003517

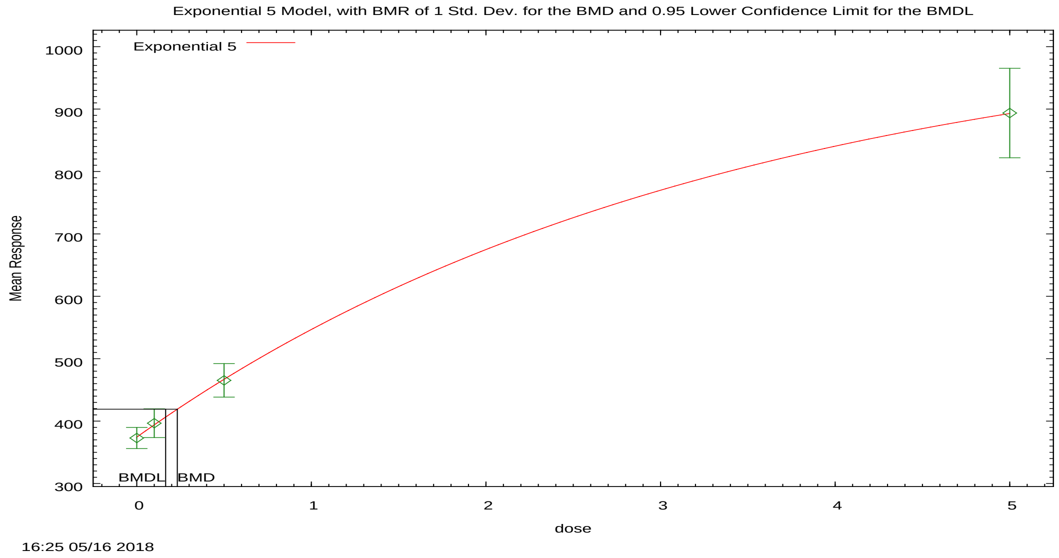

Figure 305. Plot of mean response by dose with fitted curve for Exponential (M5) model with modeled variance for Liver Weight to Brain Weight in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 0.23223

BMDL at the 95% confidence level = 0.16532

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-10.3467	-10.4607
rho	3.02939	3.05296
a	374.308	354.287
b	0.297893	0.513265

c	2.78911	2.64868
d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	25	372.9	374.3	41.08	44.76	-0.1535
0.1	24	396.6	394	54.49	48.37	0.2689
0.5	24	465.3	467	63.57	62.58	-0.1333
5	24	893.7	893	169.8	167.1	0.02143

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-489.6261	5	989.2522
A2	-458.1745	8	932.349
A3	-458.5804	6	929.1608
R	-576.4866	2	1156.973
5	-458.7417	5	927.4834

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	236.6	6	<0.0001
Test 2	62.9	3	<0.0001
Test 3	0.8118	2	0.6664
Test 7a	0.3226	1	0.5701

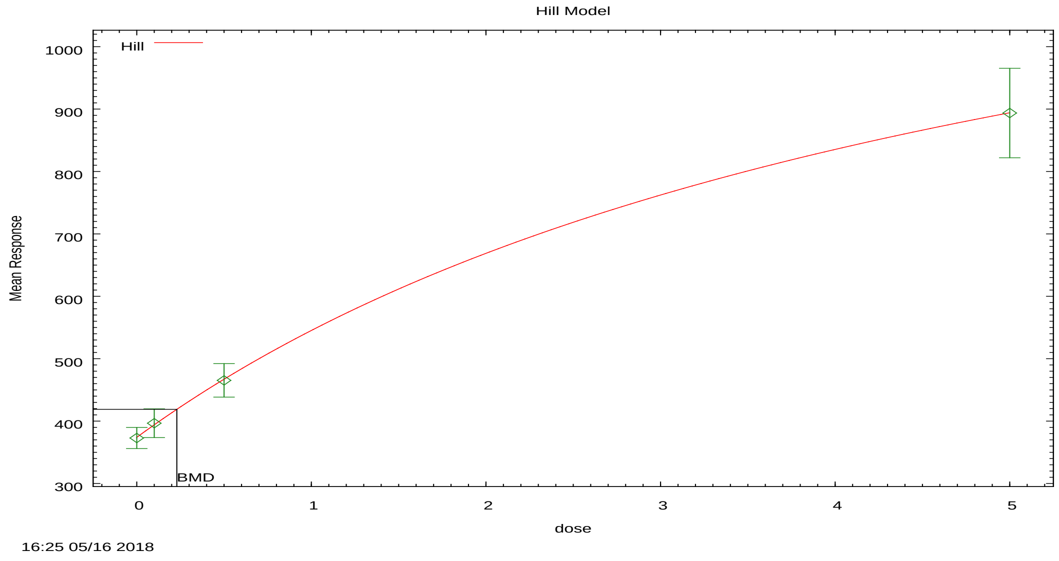

Figure 306. Plot of mean response by dose with fitted curve for Hill model with modeled variance for Liver Weight to Brain Weight in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 0.229327

BMDL at the 95% confidence level = error

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-10.355	9.1375
rho	3.03069	0
intercept	374.154	372.934
v	1057.51	520.775

n	1	0.630167
k	5.1936	7.73496

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	25	373	374	41.1	44.7	-0.136
0.1	24	397	394	54.5	48.4	0.252
0.5	24	465	467	63.6	62.6	-0.137
5	24	894	893	170	167	0.0247

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-489.626103	5	989.252206
A2	-458.17449	8	932.34898
A3	-458.580397	6	929.160793
fitted	-458.728897	5	927.457794
R	-576.486609	2	1156.973219

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	236.624	6	<0.0001
Test 2	62.9032	3	<0.0001
Test 3	0.811814	2	0.6664
Test 4	0.297001	1	0.5858

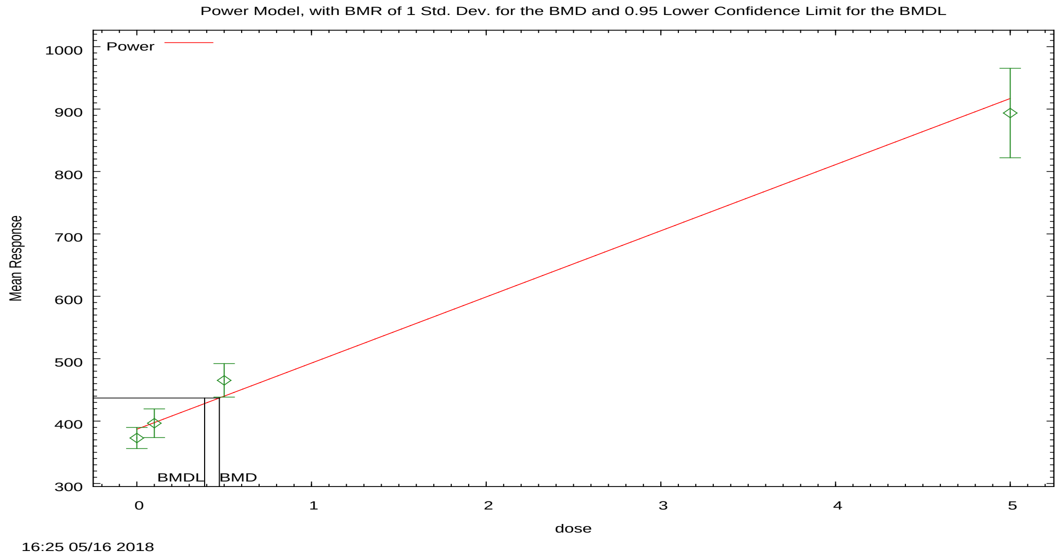

Figure 307. Plot of mean response by dose with fitted curve for Power model with modeled variance for Liver Weight to Brain Weight in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 0.472329

BMDL at the 95% confidence level = 0.388102

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-9.25889	9.1375
rho	2.86598	0
control	387.098	372.934
slope	105.57	146.664

power	1	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	25	373	387	41.1	49.9	-1.42
0.1	24	397	398	54.5	51.8	-0.098
0.5	24	465	440	63.6	59.9	2.08
5	24	894	915	170	171	-0.608

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-489.626103	5	989.252206
A2	-458.17449	8	932.34898
A3	-458.580397	6	929.160793
fitted	-462.606263	4	933.212526
R	-576.486609	2	1156.973219

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	236.624	6	<0.0001
Test 2	62.9032	3	<0.0001
Test 3	0.811814	2	0.6664
Test 4	8.05173	2	0.01785

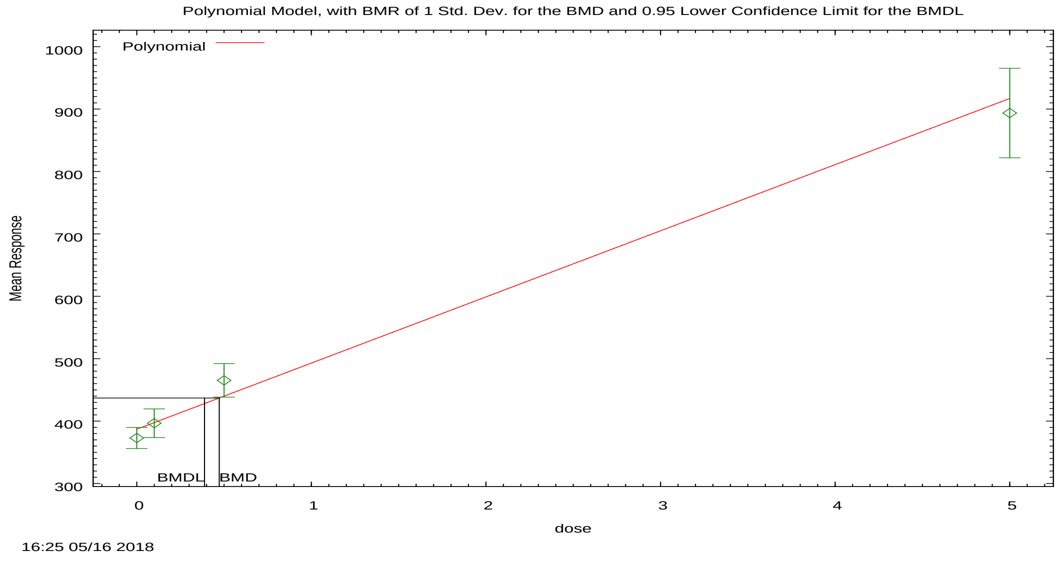

Figure 308. Plot of mean response by dose with fitted curve for Polynomial 3° model with modeled variance for Liver Weight to Brain Weight in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 0.472329

BMDL at the 95% confidence level = 0.388102

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-9.25889	9.1375
rho	2.86598	0
beta_0	387.098	372.934
beta_1	105.57	251.026

beta_2	3.92727E-92	0
beta_3	0	22.9559

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	25	373	387	41.1	49.9	-1.42
0.1	24	397	398	54.5	51.8	-0.098
0.5	24	465	440	63.6	59.9	2.08
5	24	894	915	170	171	-0.608

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-489.626103	5	989.252206
A2	-458.17449	8	932.34898
A3	-458.580397	6	929.160793
fitted	-462.606263	4	933.212526
R	-576.486609	2	1156.973219

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	236.624	6	<0.0001
Test 2	62.9032	3	<0.0001
Test 3	0.811814	2	0.6664
Test 4	8.05173	2	0.01785

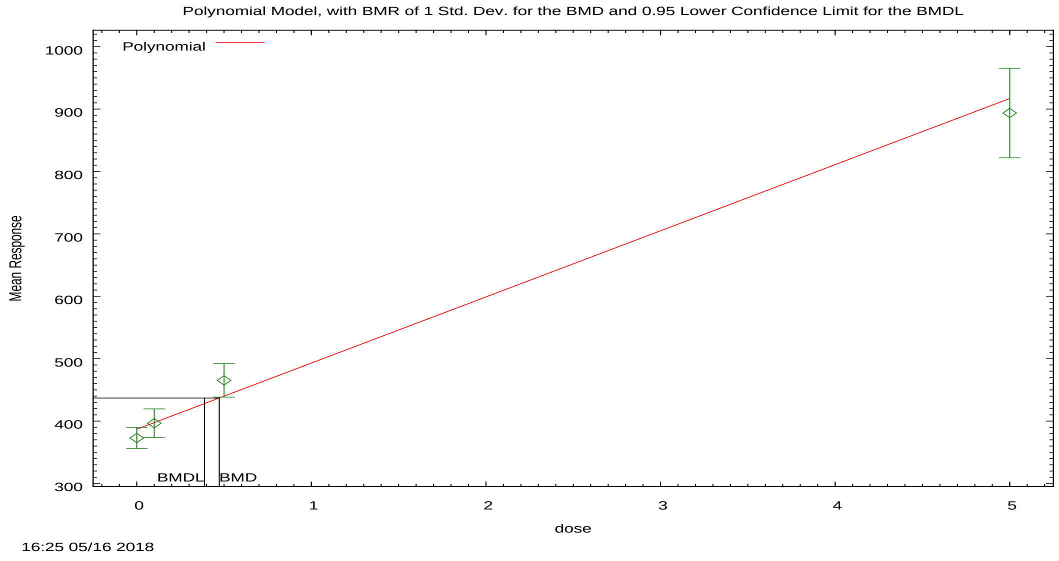

Figure 309. Plot of mean response by dose with fitted curve for Polynomial 2° model with modeled variance for Liver Weight to Brain Weight in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 0.472329

BMDL at the 95% confidence level = 0.388102

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-9.2589	9.1375
rho	2.86598	0
beta_0	387.098	375.056
beta_1	105.57	190.277

beta_2	0	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	25	373	387	41.1	49.9	-1.42
0.1	24	397	398	54.5	51.8	-0.098
0.5	24	465	440	63.6	59.9	2.08
5	24	894	915	170	171	-0.608

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-489.626103	5	989.252206
A2	-458.17449	8	932.34898
A3	-458.580397	6	929.160793
fitted	-462.606263	4	933.212526
R	-576.486609	2	1156.973219

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	236.624	6	<0.0001
Test 2	62.9032	3	<0.0001
Test 3	0.811814	2	0.6664
Test 4	8.05173	2	0.01785

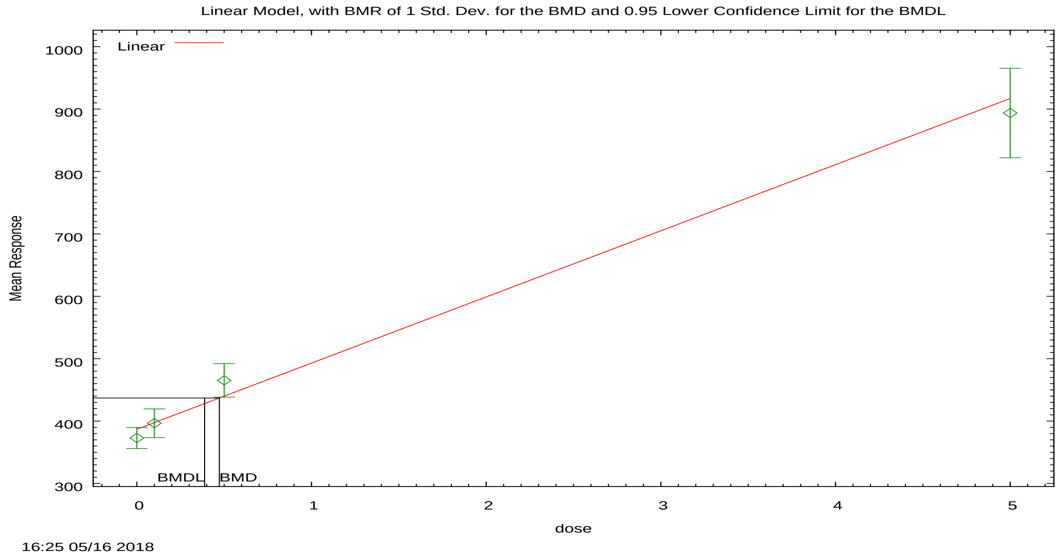

Figure 310. Plot of mean response by dose with fitted curve for Linear model with modeled variance for Liver Weight to Brain Weight in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 0.472329

BMDL at the 95% confidence level = 0.388102

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-9.2589	9.1375
rho	2.86598	0
beta_0	387.098	390.617
beta_1	105.57	101.084

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	25	373	387	41.1	49.9	-1.42
0.1	24	397	398	54.5	51.8	-0.098
0.5	24	465	440	63.6	59.9	2.08
5	24	894	915	170	171	-0.608

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-489.626103	5	989.252206
A2	-458.17449	8	932.34898
A3	-458.580397	6	929.160793
fitted	-462.606263	4	933.212526
R	-576.486609	2	1156.973219

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	236.624	6	<0.0001
Test 2	62.9032	3	<0.0001
Test 3	0.811814	2	0.6664
Test 4	8.05173	2	0.01785

BMDS WIZARD OUTPUT REPORT

BMDS Summary of Oral (Gavage) Prenatal Developmental Toxicity Study of H-28548 in Rats – Percent per Litter with Skeletal Variations

1.35. BMDS Summary of Percent per litter with skeletal variations (%) (Prenatal and Developmental Rats GenX)

Table 35. Summary of BMD Modeling Results for Percent per Litter with Skeletal Variations (Prenatal and Developmental Rats); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD_{1SD} (mg/kg/day)	BMDL_{1SD} (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2)	0.563	547.74	716	540	1.33	BMDLs from models that met model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values > 2.0; appropriate variance (continuous data only)) were compared. BMDLs from included models were sufficiently close (< 3-fold difference), so the BMDL from the model with the lowest AIC was selected.
Exponential (M3)	0.364	549.41	872	548	1.59	
Exponential (M4)	0.206	550.19	614	386	1.59	
Exponential (M5)	N/A[b]	551.41	831	107	7.75	
Hill	N/A[b]	551.41	613	error[c]	error	
Power	0.364	549.41	833	411	2.02	
Polynomial 3°	0.364	549.41	848	636	1.33	
Polynomial 2°	**0.661**	**547.42**	**805**	**635**	**1.27**	
Linear	0.450	548.19	614	386	1.59	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = <0.0001), selected model in bold; scaled residuals for selected model for doses 0, 10, 100, and 1000 mg/kg/day were -0.63, -0.23, 0.89, -0.01, respectively.

[b] No available degrees of freedom to calculate a goodness of fit value.

[c] BMD or BMDL computation failed for this model.

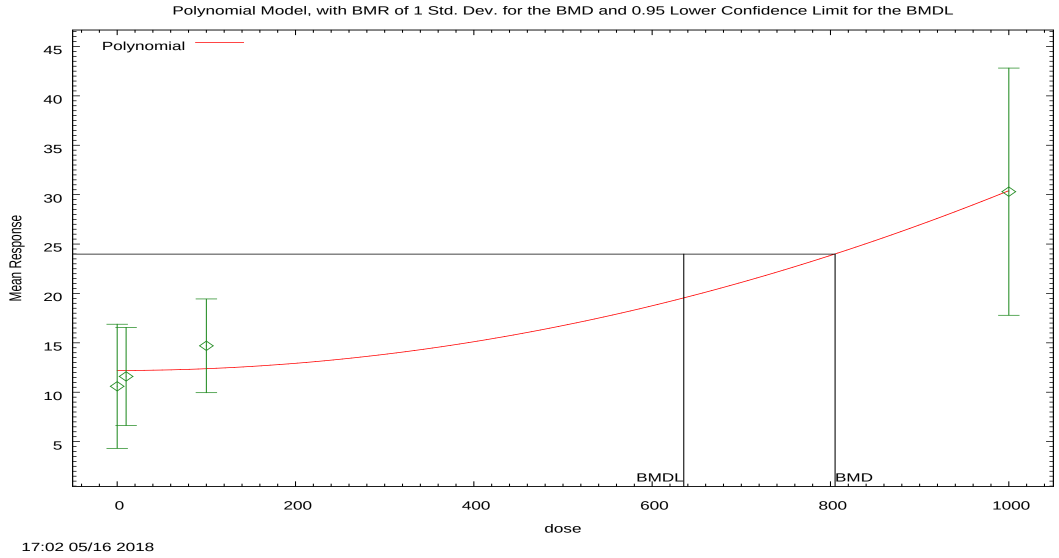

Figure 311. Plot of mean response by dose with fitted curve for Polynomial 2° model with modeled variance for Percent per Litter with Skeletal Variations (Prenatal and Developmental Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + …

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 805.163

BMDL at the 95% confidence level = 635.448

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	0.438015	5.68628
rho	1.7978	0
beta_0	12.1925	10.8806
beta_1	1.99095E-24	0.0406653
beta_2	0.0000181818	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	22	10.6	12.2	14.2	11.8	-0.634
10	21	11.6	12.2	10.9	11.8	-0.231
100	21	14.7	12.4	10.4	11.9	0.892
1000	21	30.3	30.4	27.5	26.8	-0.0127

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC

A1	-282.118145	5	574.236289
A2	-267.74874	8	551.497479
A3	-269.294095	6	550.58819
fitted	-269.707549	4	547.415099
R	-290.685425	2	585.37085

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	45.8734	6	<0.0001
Test 2	28.7388	3	<0.0001
Test 3	3.09071	2	0.2132
Test 4	0.826909	2	0.6614

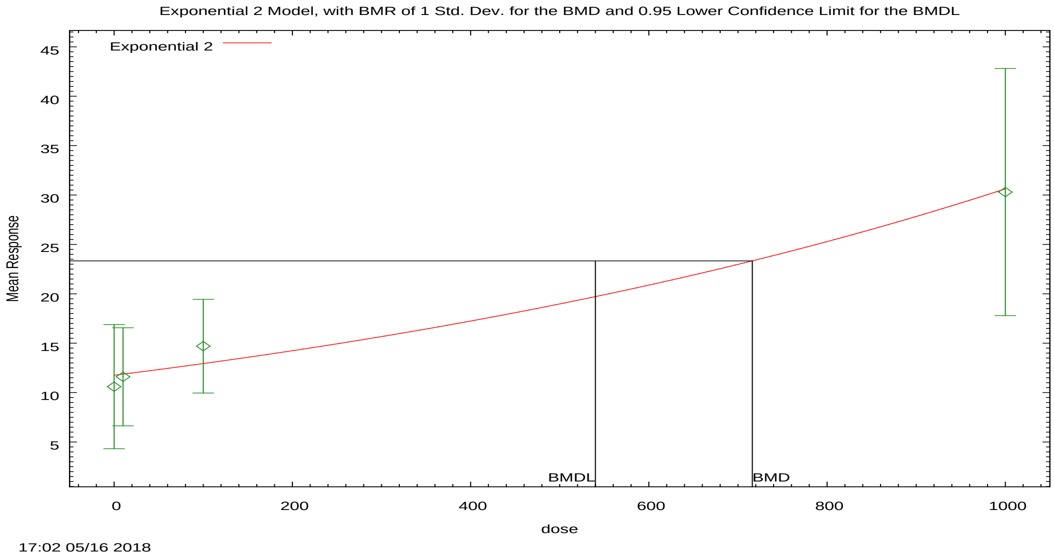

Figure 312. Plot of mean response by dose with fitted curve for Exponential (M2) model with modeled variance for Percent per Litter with Skeletal Variations (Prenatal and Developmental Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 716.091

BMDL at the 95% confidence level = 540.031

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	0.657242	1.03331
rho	1.72078	1.58206
a	11.7578	11.6882
b	0.000957211	0.000965669
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	22	10.6	11.76	14.17	11.58	-0.4691
10	21	11.6	11.87	10.9	11.67	-0.1064
100	21	14.7	12.94	10.42	12.57	0.642
1000	21	30.3	30.62	27.49	26.38	-0.05599

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-282.1181	5	574.2363
A2	-267.7487	8	551.4975
A3	-269.2941	6	550.5882
R	-290.6854	2	585.3709
2	-269.868	4	547.736

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	45.87	6	<0.0001
Test 2	28.74	3	<0.0001
Test 3	3.091	2	0.2132
Test 4	1.148	2	0.5633

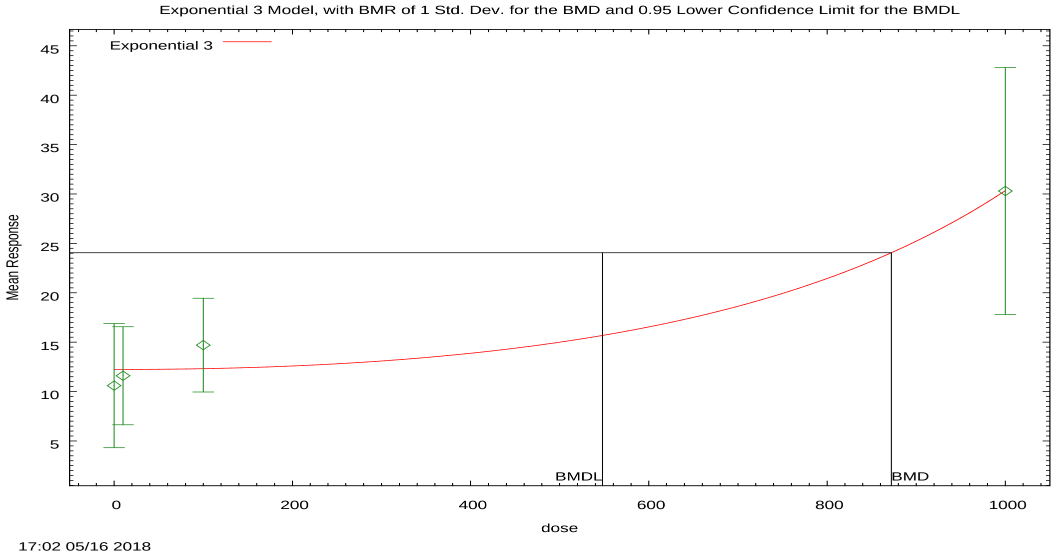

Figure 313. Plot of mean response by dose with fitted curve for Exponential (M3) model with modeled variance for Percent per Litter with Skeletal Variations (Prenatal and Developmental Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 872.124

BMDL at the 95% confidence level = 548.126

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	0.41575	1.03331
rho	1.80569	1.58206
a	12.2385	11.6882
b	0.000956119	0.000965669
c	n/a	0
d	2.15848	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	22	10.6	12.24	14.17	11.81	-0.6506
10	21	11.6	12.24	10.9	11.81	-0.2479
100	21	14.7	12.32	10.42	11.88	0.9197
1000	21	30.3	30.33	27.49	26.81	-0.00584

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-282.1181	5	574.2363
A2	-267.7487	8	551.4975
A3	-269.2941	6	550.5882
R	-290.6854	2	585.3709
3	-269.7063	5	549.4126

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	45.87	6	<0.0001
Test 2	28.74	3	<0.0001
Test 3	3.091	2	0.2132
Test 5a	0.8244	1	0.3639

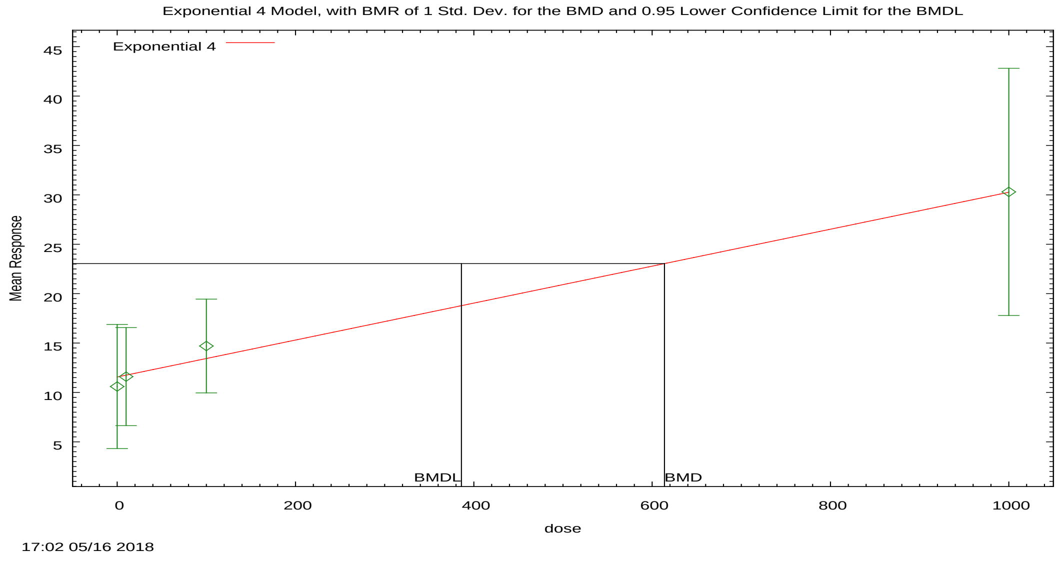

Figure 314. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Percent per Litter with Skeletal Variations (Prenatal and Developmental Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 613.794

BMDL at the 95% confidence level = 386.055

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	0.713673	1.03331
rho	1.70232	1.58206
a	11.5638	10.07
b	0.0000000754115	0.000156222

c	21444.1	15.0447
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	22	10.6	11.56	14.17	11.48	-0.3939
10	21	11.6	11.75	10.9	11.64	-0.0594
100	21	14.7	13.43	10.42	13.04	0.445
1000	21	30.3	30.26	27.49	26.03	0.00661

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-282.1181	5	574.2363
A2	-267.7487	8	551.4975
A3	-269.2941	6	550.5882
R	-290.6854	2	585.3709
4	-270.0929	5	550.1858

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	45.87	6	<0.0001
Test 2	28.74	3	<0.0001
Test 3	3.091	2	0.2132
Test 6a	1.598	1	0.2062

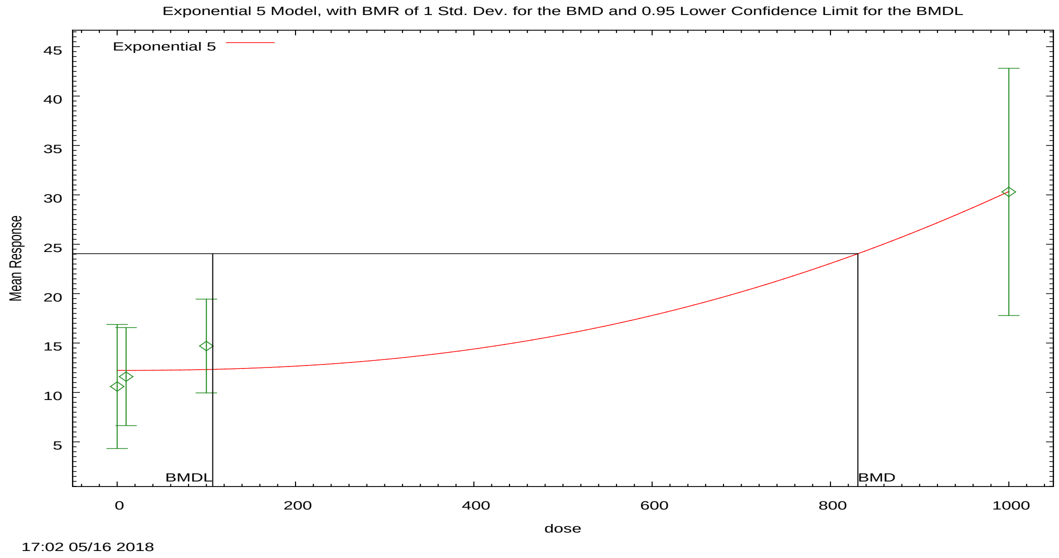

Figure 315. Plot of mean response by dose with fitted curve for Exponential (M5) model with modeled variance for Percent per Litter with Skeletal Variations (Prenatal and Developmental Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 830.717

BMDL at the 95% confidence level = 107.133

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	0.417383	1.03331
rho	1.80511	1.58206
a	12.2353	10.07
b	0.00024556	0.000156222

c	41.1806	15.0447
d	2.33795	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	22	10.6	12.24	14.17	11.81	-0.6494
10	21	11.6	12.24	10.9	11.81	-0.2466
100	21	14.7	12.32	10.42	11.88	0.9177
1000	21	30.3	30.34	27.49	26.8	-0.0064

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-282.1181	5	574.2363
A2	-267.7487	8	551.4975
A3	-269.2941	6	550.5882
R	-290.6854	2	585.3709
5	-269.7062	6	551.4124

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	45.87	6	<0.0001
Test 2	28.74	3	<0.0001
Test 3	3.091	2	0.2132
Test 7a	0.8243	0	N/A

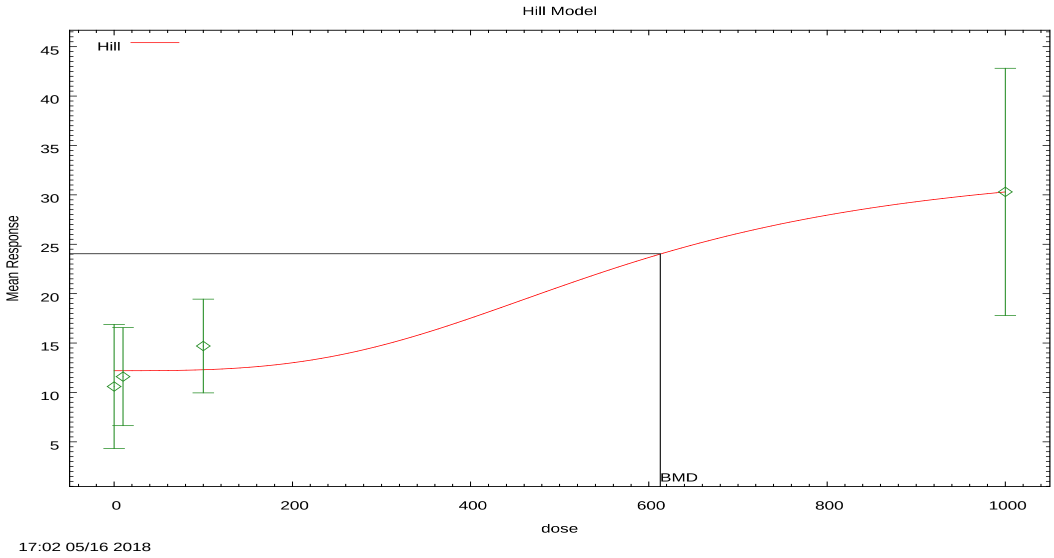

Figure 316. Plot of mean response by dose with fitted curve for Hill model with modeled variance for Percent per Litter with Skeletal Variations (Prenatal and Developmental Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A modeled variance is fit

THE MODEL HAS PROBABLY NOT CONVERGED!!!

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 612.652

BMDL at the 95% confidence level = error

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	0.419997	5.68628
rho	1.80418	0
intercept	12.2301	10.6

v	21.3148	19.7
n	3.09428	0.354929
k	571.214	1568.27

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	22	10.6	12.2	14.2	11.8	-0.648
10	21	11.6	12.2	10.9	11.8	-0.245
100	21	14.7	12.3	10.4	11.9	0.915
1000	21	30.3	30.3	27.5	26.8	-0.0073

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-282.118145	5	574.236289
A2	-267.74874	8	551.497479
A3	-269.294095	6	550.58819
fitted	-269.70608	6	551.412159
R	-290.685425	2	585.37085

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	45.8734	6	<0.0001
Test 2	28.7388	3	<0.0001
Test 3	3.09071	2	0.2132
Test 4	0.82397	0	N/A

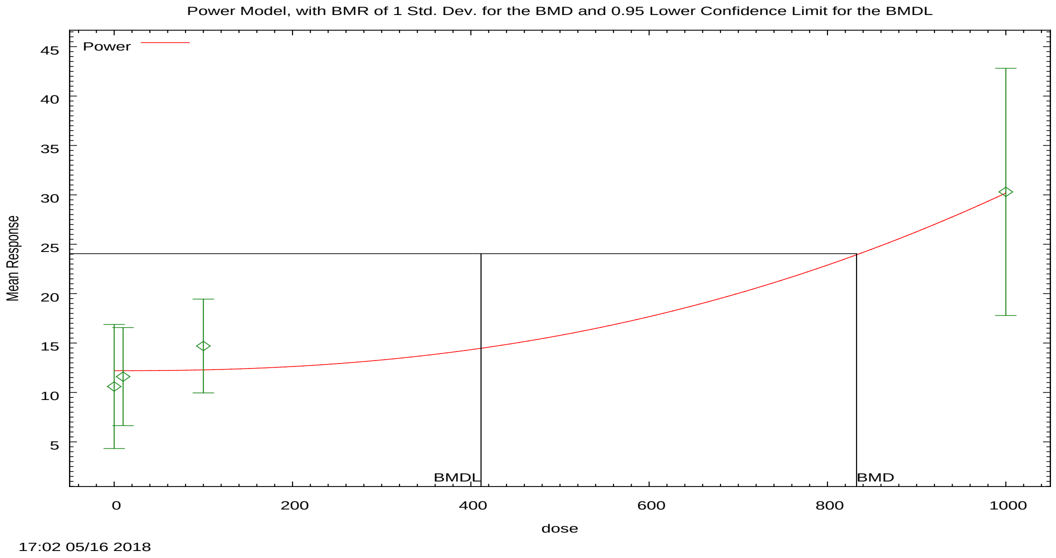

Figure 317. Plot of mean response by dose with fitted curve for Power model with modeled variance for Percent per Litter with Skeletal Variations (Prenatal and Developmental Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 832.617

BMDL at the 95% confidence level = 411.414

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	0.417329	5.68628
rho	1.80513	0
control	12.2354	10.6
slope	0.00000183768	0.225303

power	2.33115	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	22	10.6	12.2	14.2	11.8	-0.649
10	21	11.6	12.2	10.9	11.8	-0.247
100	21	14.7	12.3	10.4	11.9	0.918
1000	21	30.3	30.3	27.5	26.8	-0.00637

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-282.118145	5	574.236289
A2	-267.74874	8	551.497479
A3	-269.294095	6	550.58819
fitted	-269.706226	5	549.412452
R	-290.685425	2	585.37085

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	45.8734	6	<0.0001
Test 2	28.7388	3	<0.0001
Test 3	3.09071	2	0.2132
Test 4	0.824262	1	0.3639

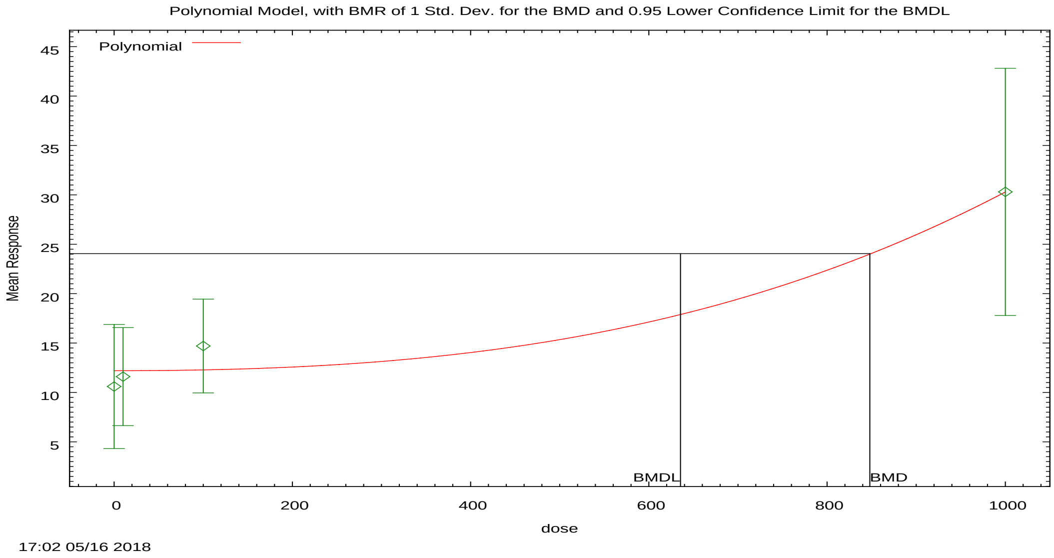

Figure 318. Plot of mean response by dose with fitted curve for Polynomial 3° model with modeled variance for Percent per Litter with Skeletal Variations (Prenatal and Developmental Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 847.968

BMDL at the 95% confidence level = 635.505

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	0.416772	5.68628
rho	1.80533	0
beta_0	12.2364	10.6
beta_1	9.13497E-23	0.107194

beta_2	0.00000709061	0
beta_3	0.0000000110091	0.000000638272

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	22	10.6	12.2	14.2	11.8	-0.65
10	21	11.6	12.2	10.9	11.8	-0.247
100	21	14.7	12.3	10.4	11.9	0.919
1000	21	30.3	30.3	27.5	26.8	-0.00618

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-282.118145	5	574.236289
A2	-267.74874	8	551.497479
A3	-269.294095	6	550.58819
fitted	-269.706361	5	549.412722
R	-290.685425	2	585.37085

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	45.8734	6	<0.0001
Test 2	28.7388	3	<0.0001
Test 3	3.09071	2	0.2132
Test 4	0.824532	1	0.3639

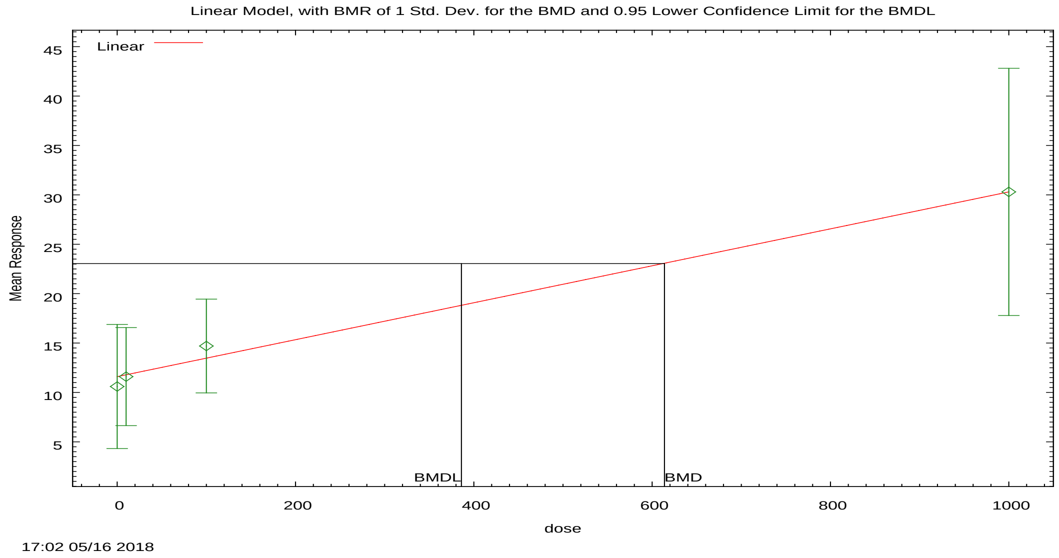

Figure 319. Plot of mean response by dose with fitted curve for Linear model with modeled variance for Percent per Litter with Skeletal Variations (Prenatal and Developmental Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 613.802

BMDL at the 95% confidence level = 386.066

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	0.713678	5.68628
rho	1.70231	0
beta_0	11.5638	11.5676
beta_1	0.0186987	0.0188555

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	22	10.6	11.6	14.2	11.5	-0.394
10	21	11.6	11.8	10.9	11.6	-0.0594
100	21	14.7	13.4	10.4	13	0.445
1000	21	30.3	30.3	27.5	26	0.0066

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-282.118145	5	574.236289
A2	-267.74874	8	551.497479
A3	-269.294095	6	550.58819
fitted	-270.092862	4	548.185724
R	-290.685425	2	585.37085

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	45.8734	6	<0.0001
Test 2	28.7388	3	<0.0001
Test 3	3.09071	2	0.2132
Test 4	1.59753	2	0.4499

BMDS WIZARD OUTPUT REPORT

BMDS Summary of Oral (Gavage) Reproduction/Developmental Toxicity Screening Study of H-28548 in Mice – Offspring Weight (g) at Postnatal Day 21 in Males

1.36. BMDS Summary of Offspring weight (litter as experimental unit) PND21 Males (Reproductive Mice GenX)

Table 36. Summary of BMD Modeling Results for Offspring Weight (litter as experimental unit) at PND21 in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD_{1SD} (mg/kg/day)	$BMDL_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2)	0.268	152.90	2.12	1.66	1.27	BMDLs from models that met model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values > 2.0; appropriate variance (continuous data only)) were compared. BMDLs from included models were sufficiently close (< 3-fold difference), so the BMDL from the model with the lowest AIC was selected.
Exponential (M3)	0.416	152.92	4.52	1.86	2.43	
Exponential (M4)	0.268	152.90	2.12	1.25	1.70	
Exponential (M5)	N/A[b]	154.92	3.66	0.540	6.77	
Hill	N/A[b]	154.92	4.21	error[c]	error	
Power	0.416	152.92	4.57	1.99	2.30	
Polynomial 3°	**0.715**	**150.93**	**3.87**	**3.06**	**1.26**	
Polynomial 2°	0.681	151.03	3.40	3.06	1.11	
Linear	0.312	152.59	2.28	1.84	1.24	

[a] Constant variance case presented (BMDS Test 2 *p*-value = 0.233), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 0.5, and 5 mg/kg/day were -0.64, 0.16, 0.48, 0, respectively.

[b] No available degrees of freedom to calculate a goodness of fit value.

[c] BMD or BMDL computation failed for this model.

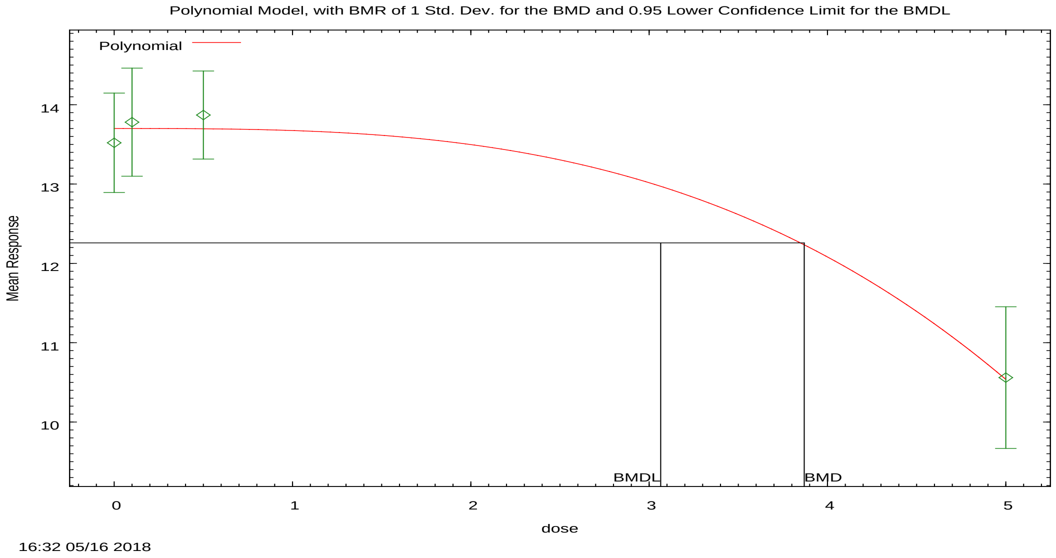

Figure 320. Plot of mean response by dose with fitted curve for Polynomial 3° model with constant variance for Offspring Weight (litter as experimental unit) at PND21 in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + …

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 3.86966

BMDL at the 95% confidence level = 3.06466

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	2.15434	2.24633
rho	n/a	0
beta_0	13.7264	13.52
beta_1	-7.86983E-23	0
beta_2	0	-5.29648
beta_3	-0.0253302	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	13.5	13.7	1.38	1.47	-0.645
0.1	18	13.8	13.7	1.37	1.47	0.155
0.5	23	13.9	13.7	1.28	1.47	0.479
5	20	10.6	10.6	1.91	1.47	-0.000515

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-72.130858	5	154.261716
A2	-69.989194	8	155.978389
A3	-72.130858	5	154.261716
fitted	-72.46686	3	150.933721
R	-97.85625	2	199.712499

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	55.7341	6	<0.0001
Test 2	4.28333	3	0.2325
Test 3	4.28333	3	0.2325
Test 4	0.672005	2	0.7146

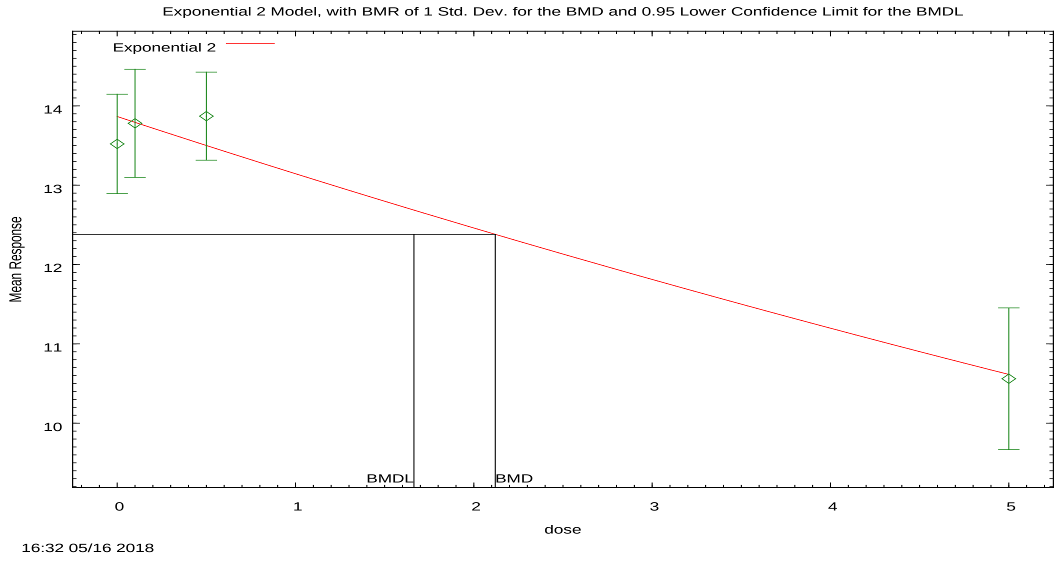

Figure 321. Plot of mean response by dose with fitted curve for Exponential (M2) model with constant variance for Offspring Weight (litter as experimental unit) at PND21 in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 2.12008

BMDL at the 95% confidence level = 1.66414

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	0.791404	0.759289
rho	n/a	0
a	13.8655	11.9502
b	0.0534487	0.0539212
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	13.52	13.87	1.38	1.48	-1.066
0.1	18	13.78	13.79	1.37	1.48	-0.03315
0.5	23	13.87	13.5	1.28	1.48	1.195
5	20	10.56	10.61	1.91	1.48	-0.1622

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-72.13086	5	154.2617
A2	-69.98919	8	155.9784
A3	-72.13086	5	154.2617
R	-97.85625	2	199.7125
2	-73.44756	3	152.8951

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	55.73	6	<0.0001
Test 2	4.283	3	0.2325
Test 3	4.283	3	0.2325
Test 4	2.633	2	0.268

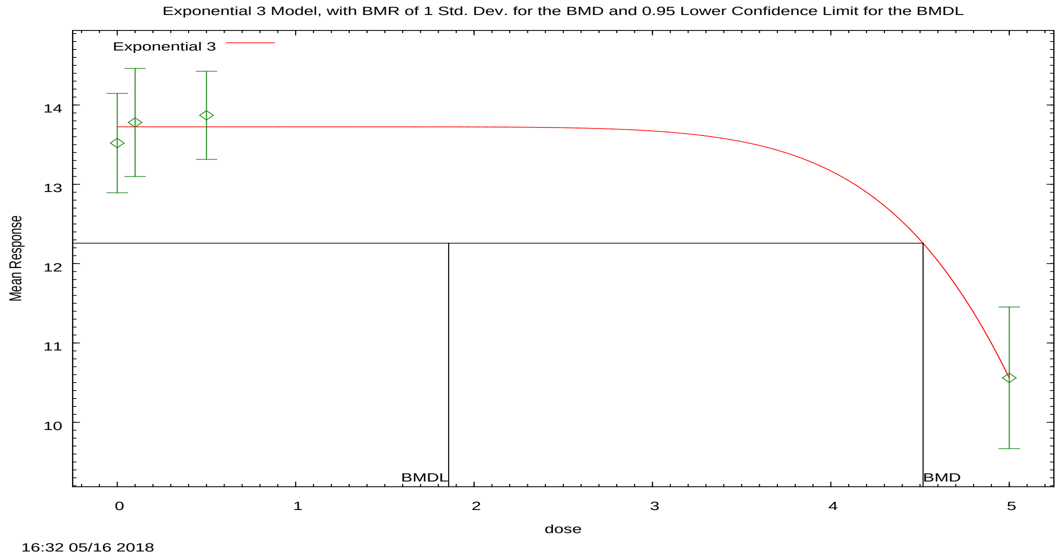

Figure 322. Plot of mean response by dose with fitted curve for Exponential (M3) model with constant variance for Offspring Weight (litter as experimental unit) at PND21 in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 4.51681

BMDL at the 95% confidence level = 1.85773

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	0.767364	0.759289
rho	n/a	0
a	13.7253	11.9502
b	0.170118	0.0539212
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	13.52	13.73	1.38	1.47	-0.6411
0.1	18	13.78	13.73	1.37	1.47	0.1581
0.5	23	13.87	13.73	1.28	1.47	0.4728
5	20	10.56	10.56	1.91	1.47	-0.000000008943

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-72.13086	5	154.2617
A2	-69.98919	8	155.9784
A3	-72.13086	5	154.2617
R	-97.85625	2	199.7125
3	-72.46192	4	152.9238

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	55.73	6	<0.0001
Test 2	4.283	3	0.2325
Test 3	4.283	3	0.2325
Test 5a	0.6621	1	0.4158

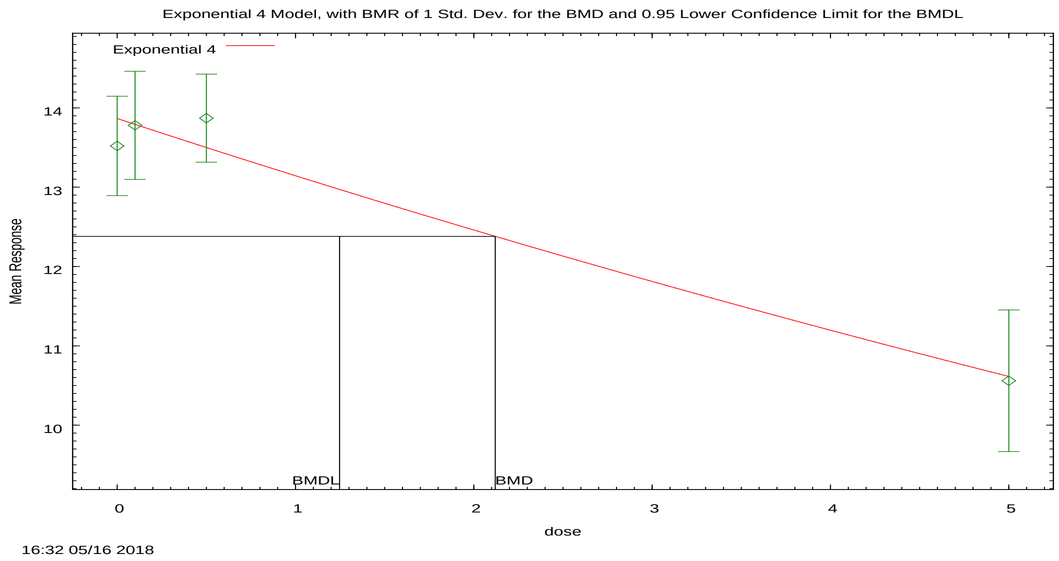

Figure 323. Plot of mean response by dose with fitted curve for Exponential (M4) model with constant variance for Offspring Weight (litter as experimental unit) at PND21 in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 2.12008

BMDL at the 95% confidence level = 1.24698

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	0.791404	0.759289
rho	n/a	0
a	13.8655	14.5635
b	0.0534487	0.438137

c	0	0.690572
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	13.52	13.87	1.38	1.48	-1.066
0.1	18	13.78	13.79	1.37	1.48	-0.03315
0.5	23	13.87	13.5	1.28	1.48	1.195
5	20	10.56	10.61	1.91	1.48	-0.1622

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-72.13086	5	154.2617
A2	-69.98919	8	155.9784
A3	-72.13086	5	154.2617
R	-97.85625	2	199.7125
4	-73.44756	3	152.8951

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	55.73	6	<0.0001
Test 2	4.283	3	0.2325
Test 3	4.283	3	0.2325
Test 6a	2.633	2	0.268

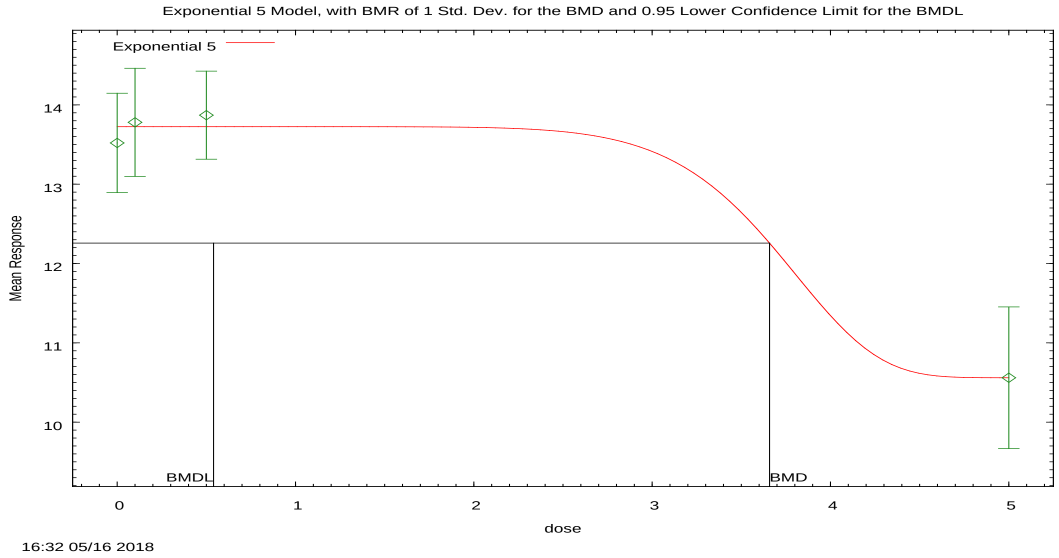

Figure 324. Plot of mean response by dose with fitted curve for Exponential (M5) model with constant variance for Offspring Weight (litter as experimental unit) at PND21 in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 3.65823

BMDL at the 95% confidence level = 0.540376

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	0.767364	0.759289
rho	n/a	0
a	13.7253	14.5635
b	0.25941	0.438137

c	0.769374	0.690572
d	9.03662	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	13.52	13.73	1.38	1.47	-0.6411
0.1	18	13.78	13.73	1.37	1.47	0.1581
0.5	23	13.87	13.73	1.28	1.47	0.4728
5	20	10.56	10.56	1.91	1.47	-0.0000000894

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-72.13086	5	154.2617
A2	-69.98919	8	155.9784
A3	-72.13086	5	154.2617
R	-97.85625	2	199.7125
5	-72.46192	5	154.9238

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	55.73	6	<0.0001
Test 2	4.283	3	0.2325
Test 3	4.283	3	0.2325
Test 7a	0.6621	0	N/A

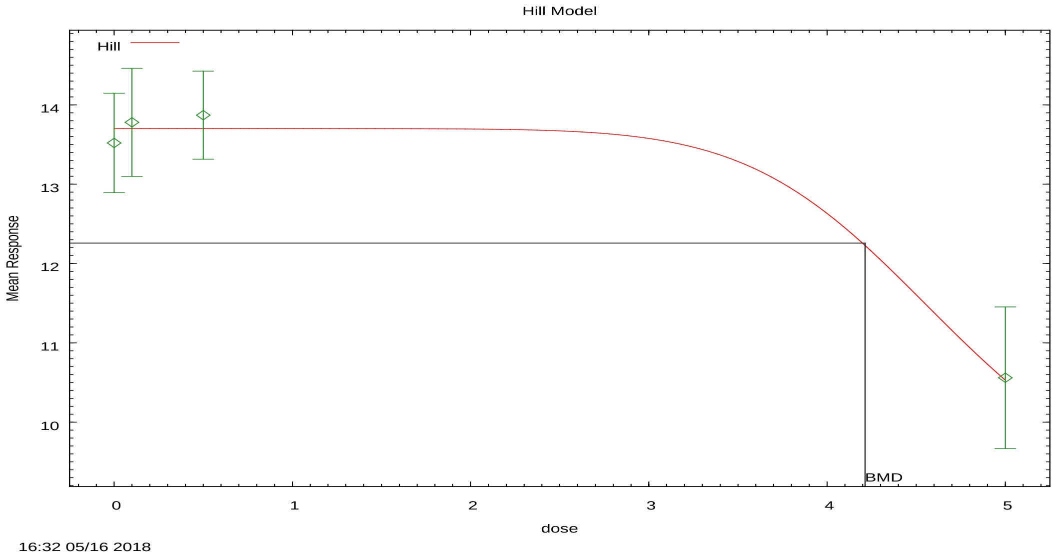

Figure 325. Plot of mean response by dose with fitted curve for Hill model with constant variance for Offspring Weight (litter as experimental unit) at PND21 in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A constant variance model is fit

THE MODEL HAS PROBABLY NOT CONVERGED!!!

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 4.21281

BMDL at the 95% confidence level = error

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	2.15408	2.24633
rho	n/a	0
intercept	13.7253	13.52

v	-5.0422	-2.96
n	8.24712	1
k	4.69297	2.98792

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	13.5	13.7	1.38	1.47	-0.641
0.1	18	13.8	13.7	1.37	1.47	0.158
0.5	23	13.9	13.7	1.28	1.47	0.473
5	20	10.6	10.6	1.91	1.47	0.000000118

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-72.130858	5	154.261716
A2	-69.989194	8	155.978389
A3	-72.130858	5	154.261716
fitted	-72.461924	5	154.923849
R	-97.85625	2	199.712499

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	55.7341	6	<0.0001
Test 2	4.28333	3	0.2325
Test 3	4.28333	3	0.2325
Test 4	0.662133	0	N/A

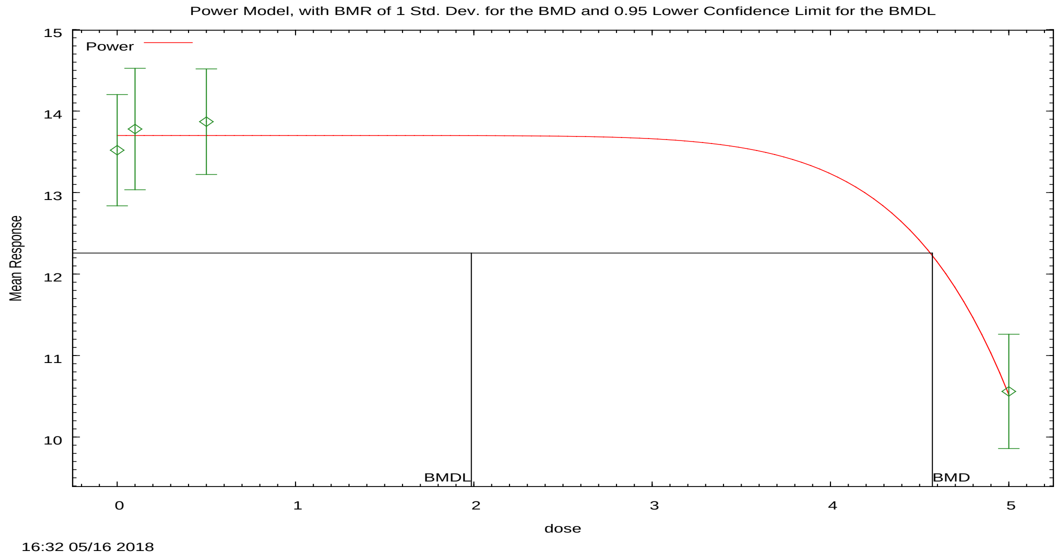

Figure 326. Plot of mean response by dose with fitted curve for Power model with constant variance for Offspring Weight (litter as experimental unit) at PND21 in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A constant variance model is fit

THE MODEL HAS PROBABLY NOT CONVERGED!!!

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 4.57146

BMDL at the 95% confidence level = 1.98598

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	2.15408	2.24633
rho	n/a	0
control	13.7253	10.56

slope	-0.00000319984	3.34953
power	8.57732	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	13.5	13.7	1.38	1.47	-0.641
0.1	18	13.8	13.7	1.37	1.47	0.158
0.5	23	13.9	13.7	1.28	1.47	0.473
5	20	10.6	10.6	1.91	1.47	0.0000000353

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-72.130858	5	154.261716
A2	-69.989194	8	155.978389
A3	-72.130858	5	154.261716
fitted	-72.461924	4	152.923849
R	-97.85625	2	199.712499

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	55.7341	6	<0.0001
Test 2	4.28333	3	0.2325
Test 3	4.28333	3	0.2325
Test 4	0.662132	1	0.4158

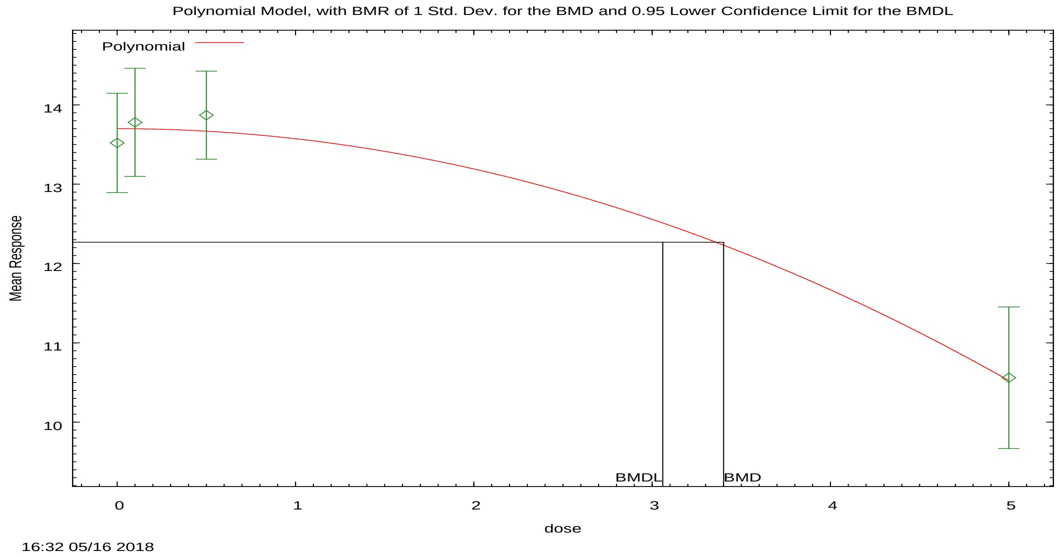

Figure 327. Plot of mean response by dose with fitted curve for Polynomial 2° model with constant variance for Offspring Weight (litter as experimental unit) at PND21 in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 3.40062

BMDL at the 95% confidence level = 3.05942

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	2.15686	2.24633
rho	n/a	0
beta_0	13.7369	13.6042
beta_1	-2.69168E-23	0

beta_2	-0.126998	-0.263833

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	13.5	13.7	1.38	1.47	-0.677
0.1	18	13.8	13.7	1.37	1.47	0.128
0.5	23	13.9	13.7	1.28	1.47	0.538
5	20	10.6	10.6	1.91	1.47	-0.00582

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-72.130858	5	154.261716
A2	-69.989194	8	155.978389
A3	-72.130858	5	154.261716
fitted	-72.514804	3	151.029608
R	-97.85625	2	199.712499

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	55.7341	6	<0.0001
Test 2	4.28333	3	0.2325
Test 3	4.28333	3	0.2325
Test 4	0.767891	2	0.6812

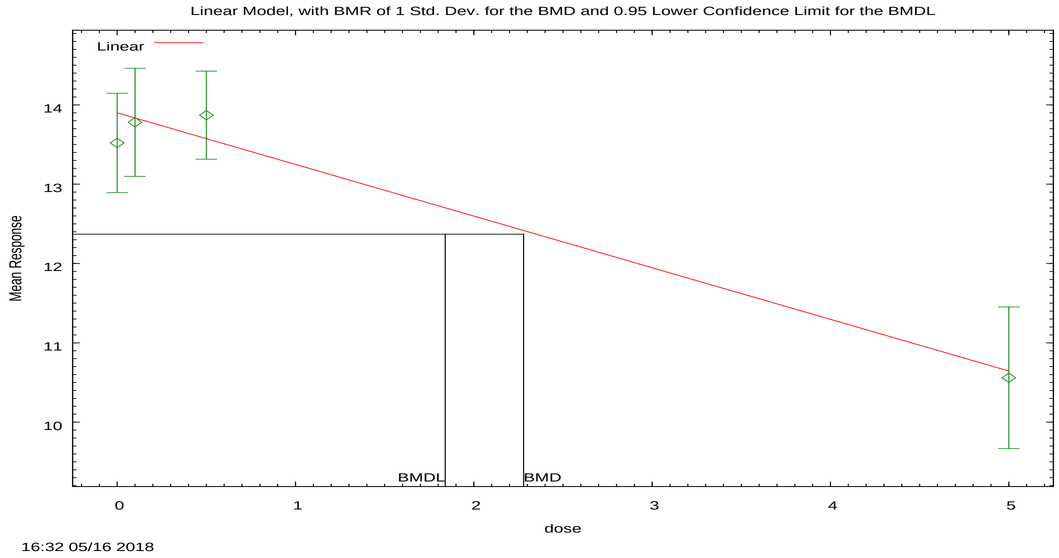

Figure 328. Plot of mean response by dose with fitted curve for Linear model with constant variance for Offspring Weight (litter as experimental unit) at PND21 in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 2.27908

BMDL at the 95% confidence level = 1.83952

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	2.19842	2.24633
rho	n/a	0
beta_0	13.8522	13.8414
beta_1	-0.650574	-0.649196

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	13.5	13.9	1.38	1.48	-1.03
0.1	18	13.8	13.8	1.37	1.48	-0.0204
0.5	23	13.9	13.5	1.28	1.48	1.11
5	20	10.6	10.6	1.91	1.48	-0.119

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-72.130858	5	154.261716
A2	-69.989194	8	155.978389
A3	-72.130858	5	154.261716
fitted	-73.297359	3	152.594717
R	-97.85625	2	199.712499

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	55.7341	6	<0.0001
Test 2	4.28333	3	0.2325
Test 3	4.28333	3	0.2325
Test 4	2.333	2	0.3115

BMDS WIZARD OUTPUT REPORT

BMDS Summary of Oral (Gavage) Reproduction/Developmental Toxicity Screening Study of H-28548 in Mice – Offspring Weight (g) at Postnatal Day 21 in Females

1.37. BMDS Summary of Offspring weight (litter as experimental unit) PND 21 Females (Reproductive Mice GenX)

Table 37. Summary of BMD Modeling Results for Offspring Weight (litter as experimental unit) at PND 21 in Females (Reproductive Mice); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD$_{1SD}$ (mg/kg/day)	BMDL$_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2)	0.169	123.03	2.33	1.80	1.29	BMDLs from models that met model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values > 2.0; appropriate variance (continuous data only)) were compared. BMDLs from included models were sufficiently close (< 3-fold difference), so the BMDL from the model with the lowest AIC was selected.
Exponential (M3)	0.270	122.69	4.56	2.10	2.17	
Exponential (M4)	0.169	123.03	2.33	1.41	1.65	
Exponential (M5)	N/A[b]	124.69	4.37	0.548	7.98	
Hill	N/A[b]	124.69	4.19	error[c]	error	
Power	0.270	122.69	4.67	2.18	2.14	
Polynomial 3°	**0.541**	**120.71**	**3.95**	**3.66**	**1.08**	
Polynomial 2°	0.503	120.85	3.51	2.15	1.63	
Linear	0.193	122.76	2.45	1.95	1.26	

[a] Constant variance case presented (BMDS Test 2 *p*-value = 0.486), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 0.5, and 5 mg/kg/day were -0.76, -0.09, 0.8, 0, respectively.

[b] No available degrees of freedom to calculate a goodness of fit value.

[c] BMD or BMDL computation failed for this model.

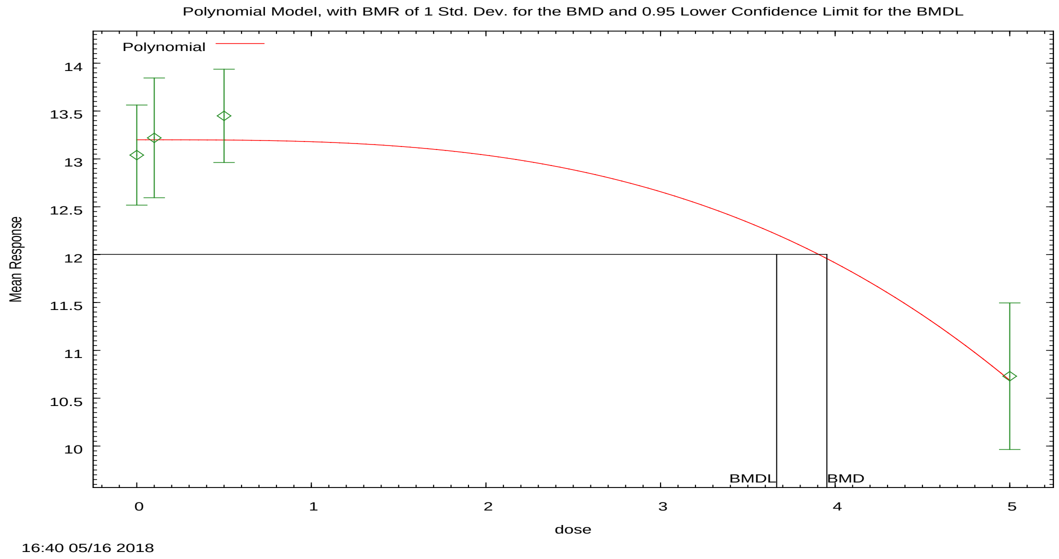

Figure 329. Plot of mean response by dose with fitted curve for Polynomial 3° model with constant variance for Offspring Weight (litter as experimental unit) at PND 21 in Females (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 3.9524

BMDL at the 95% confidence level = 3.66495

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	1.54315	1.59957
rho	n/a	0
beta_0	13.2452	13.04
beta_1	-2.55441E-24	0
beta_2	-2.52457E-26	-2.71512
beta_3	-0.0201196	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	13	13.2	1.15	1.24	-0.757
0.1	18	13.2	13.2	1.26	1.24	-0.0861
0.5	23	13.4	13.2	1.13	1.24	0.8
5	18	10.7	10.7	1.54	1.24	-0.000904

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-56.737769	5	123.475538
A2	-55.517751	8	127.035503
A3	-56.737769	5	123.475538
fitted	-57.352978	3	120.705956
R	-78.910547	2	161.821093

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	46.7856	6	<0.0001
Test 2	2.44004	3	0.4862
Test 3	2.44004	3	0.4862
Test 4	1.23042	2	0.5405

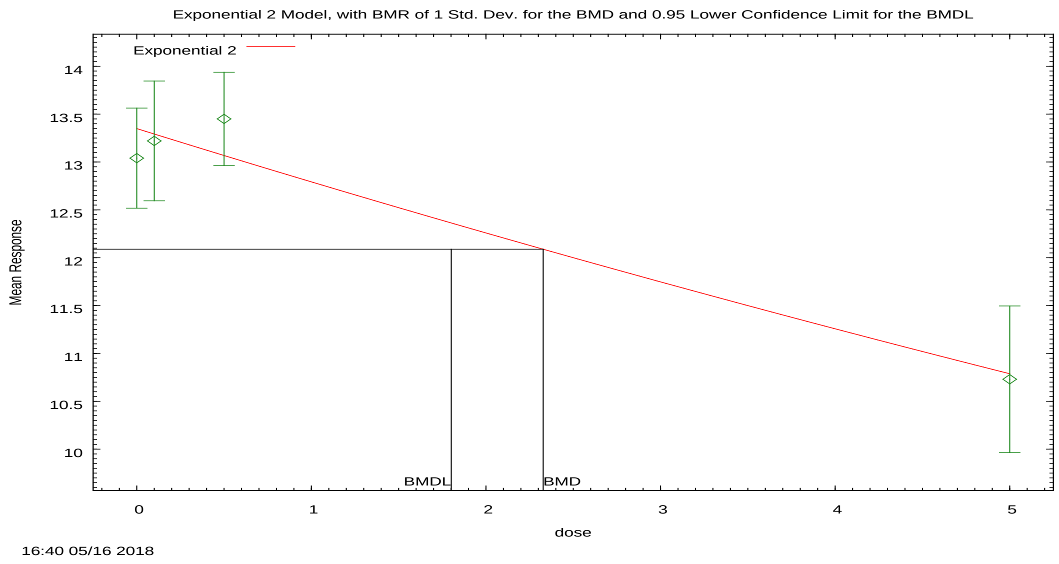

Figure 330. Plot of mean response by dose with fitted curve for Exponential (M2) model with constant variance for Offspring Weight (litter as experimental unit) at PND 21 in Females (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 2.32766

BMDL at the 95% confidence level = 1.80118

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	0.462864	0.418444
rho	n/a	0
a	13.3488	11.9484
b	0.0426095	0.043013
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	13.04	13.35	1.15	1.26	-1.123
0.1	18	13.22	13.29	1.26	1.26	-0.2426
0.5	23	13.45	13.07	1.13	1.26	1.456
5	18	10.73	10.79	1.54	1.26	-0.1933

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-56.73777	5	123.4755
A2	-55.51775	8	127.0355
A3	-56.73777	5	123.4755
R	-78.91055	2	161.8211
2	-58.51457	3	123.0291

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	46.79	6	<0.0001
Test 2	2.44	3	0.4862
Test 3	2.44	3	0.4862
Test 4	3.554	2	0.1692

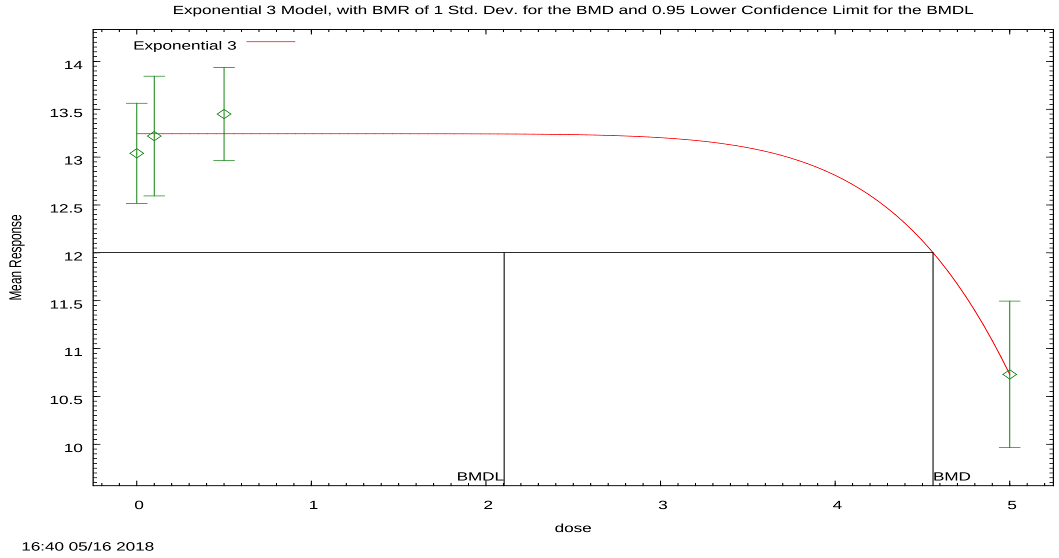

Figure 331. Plot of mean response by dose with fitted curve for Exponential (M3) model with constant variance for Offspring Weight (litter as experimental unit) at PND 21 in Females (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 4.56068

BMDL at the 95% confidence level = 2.10402

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	0.433631	0.418444
rho	n/a	0
a	13.2444	11.9484
b	0.165623	0.043013
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	13.04	13.24	1.15	1.24	-0.7539
0.1	18	13.22	13.24	1.26	1.24	-0.08319
0.5	23	13.45	13.24	1.13	1.24	0.794
5	18	10.73	10.73	1.54	1.24	0.00001304

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-56.73777	5	123.4755
A2	-55.51775	8	127.0355
A3	-56.73777	5	123.4755
R	-78.91055	2	161.8211
3	-57.34524	4	122.6905

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	46.79	6	<0.0001
Test 2	2.44	3	0.4862
Test 3	2.44	3	0.4862
Test 5a	1.215	1	0.2704

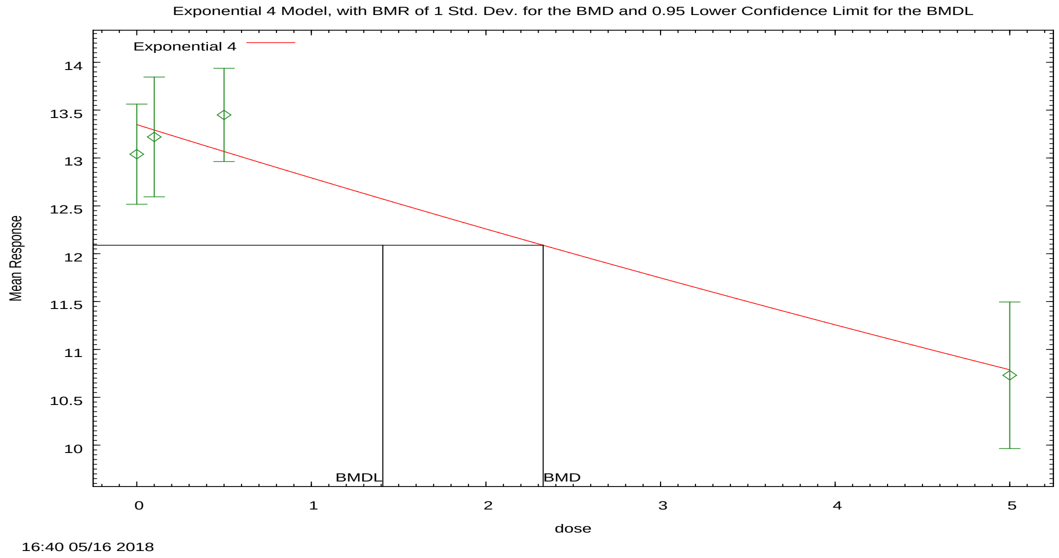

Figure 332. Plot of mean response by dose with fitted curve for Exponential (M4) model with constant variance for Offspring Weight (litter as experimental unit) at PND 21 in Females (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 2.32766

BMDL at the 95% confidence level = 1.40916

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	0.462864	0.418444
rho	n/a	0
a	13.3488	14.1225
b	0.0426095	0.407266

c	0	0.7236
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	13.04	13.35	1.15	1.26	-1.123
0.1	18	13.22	13.29	1.26	1.26	-0.2426
0.5	23	13.45	13.07	1.13	1.26	1.456
5	18	10.73	10.79	1.54	1.26	-0.1933

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-56.73777	5	123.4755
A2	-55.51775	8	127.0355
A3	-56.73777	5	123.4755
R	-78.91055	2	161.8211
4	-58.51457	3	123.0291

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	46.79	6	<0.0001
Test 2	2.44	3	0.4862
Test 3	2.44	3	0.4862
Test 6a	3.554	2	0.1692

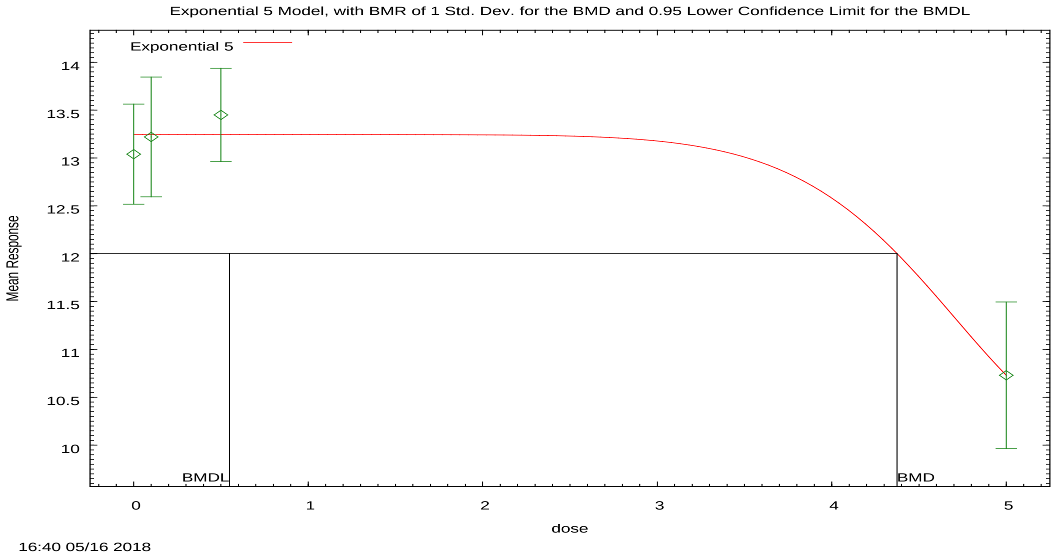

Figure 333. Plot of mean response by dose with fitted curve for Exponential (M5) model with constant variance for Offspring Weight (litter as experimental unit) at PND 21 in Females (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 4.3739

BMDL at the 95% confidence level = 0.548167

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	0.433631	0.418444
rho	n/a	0
a	13.2444	14.1225
b	0.209141	0.407266

c	0.752134	0.7236
d	8.34611	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	13.04	13.24	1.15	1.24	-0.7539
0.1	18	13.22	13.24	1.26	1.24	-0.08319
0.5	23	13.45	13.24	1.13	1.24	0.794
5	18	10.73	10.73	1.54	1.24	-0.00000003966

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-56.73777	5	123.4755
A2	-55.51775	8	127.0355
A3	-56.73777	5	123.4755
R	-78.91055	2	161.8211
5	-57.34524	5	124.6905

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	46.79	6	<0.0001
Test 2	2.44	3	0.4862
Test 3	2.44	3	0.4862
Test 7a	1.215	0	N/A

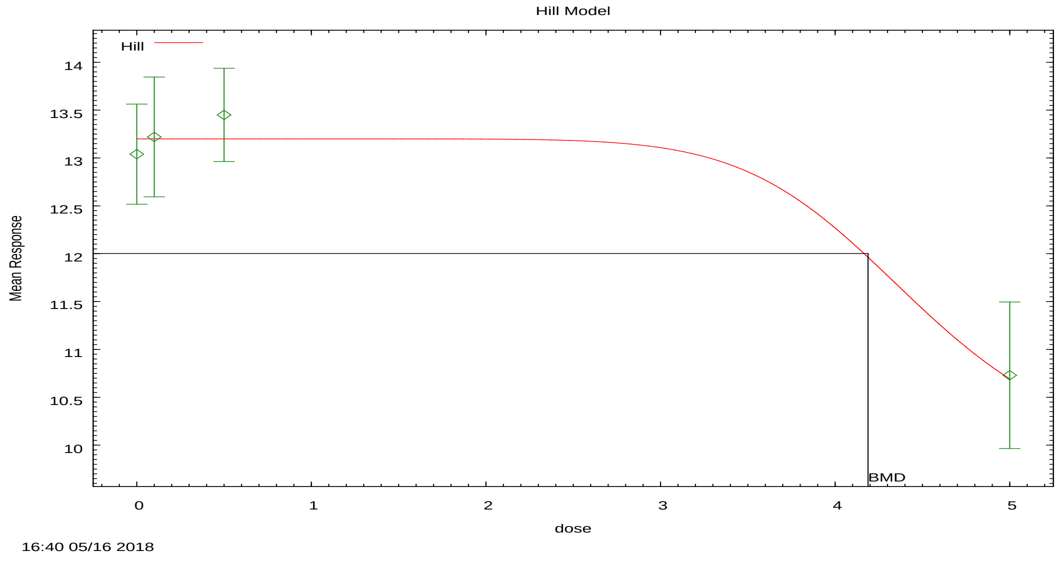

Figure 334. Plot of mean response by dose with fitted curve for Hill model with constant variance for Offspring Weight (litter as experimental unit) at PND 21 in Females (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 4.18842

BMDL at the 95% confidence level = error

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	1.54285	1.59957
rho	n/a	0
intercept	13.2444	13.04
v	-3.38304	-2.31

n	9.0745	1
k	4.4474	3.08915

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	13	13.2	1.15	1.24	-0.754
0.1	18	13.2	13.2	1.26	1.24	-0.0832
0.5	23	13.4	13.2	1.13	1.24	0.794
5	18	10.7	10.7	1.54	1.24	-0.0000000356

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-56.737769	5	123.475538
A2	-55.517751	8	127.035503
A3	-56.737769	5	123.475538
fitted	-57.345245	5	124.690489
R	-78.910547	2	161.821093

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	46.7856	6	<0.0001
Test 2	2.44004	3	0.4862
Test 3	2.44004	3	0.4862
Test 4	1.21495	0	N/A

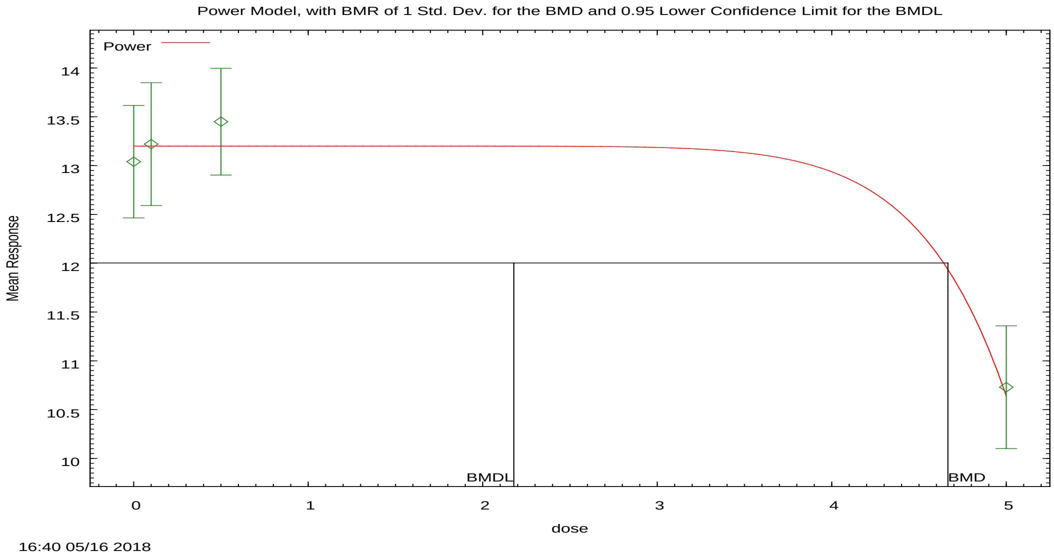

Figure 335. Plot of mean response by dose with fitted curve for Power model with constant variance for Offspring Weight (litter as experimental unit) at PND 21 in Females (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 4.66568

BMDL at the 95% confidence level = 2.17825

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	1.54285	1.59957
rho	n/a	0
control	13.2444	10.73
slope	-0.000000189638	2.82549

power	10.19	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	13	13.2	1.15	1.24	-0.754
0.1	18	13.2	13.2	1.26	1.24	-0.0832
0.5	23	13.4	13.2	1.13	1.24	0.794
5	18	10.7	10.7	1.54	1.24	-0.00000000209

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-56.737769	5	123.475538
A2	-55.517751	8	127.035503
A3	-56.737769	5	123.475538
fitted	-57.345245	4	122.690489
R	-78.910547	2	161.821093

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	46.7856	6	<0.0001
Test 2	2.44004	3	0.4862
Test 3	2.44004	3	0.4862
Test 4	1.21495	1	0.2704

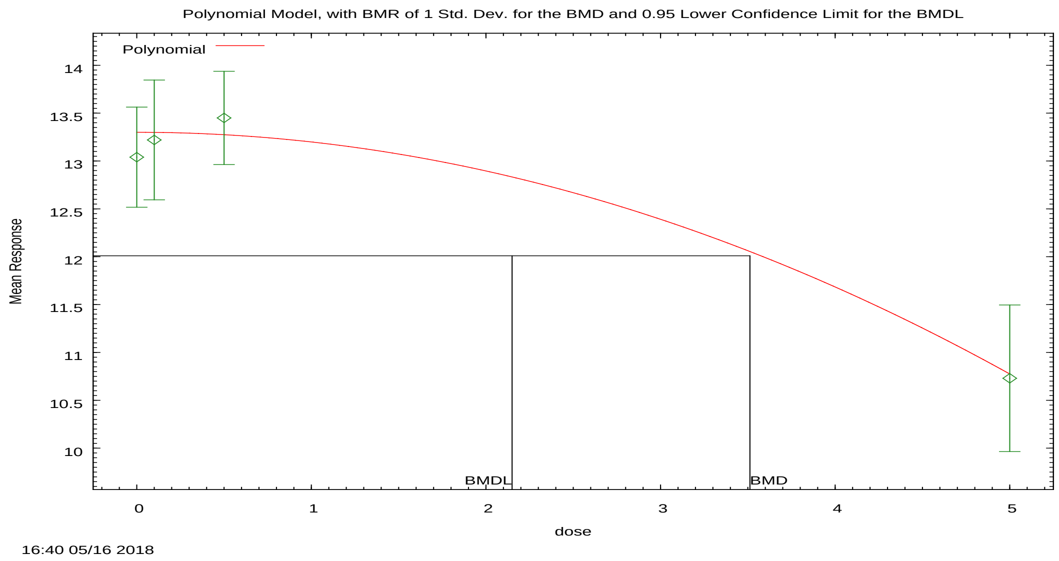

Figure 336. Plot of mean response by dose with fitted curve for Polynomial 2° model with constant variance for Offspring Weight (litter as experimental unit) at PND 21 in Females (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + …

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 3.51186

BMDL at the 95% confidence level = 2.14962

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	1.54593	1.59957
rho	n/a	0
beta_0	13.2532	13.0809
beta_1	0	0

beta_2	-0.100814	-0.273596

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	13	13.3	1.15	1.24	-0.786
0.1	18	13.2	13.3	1.26	1.24	-0.11
0.5	23	13.4	13.2	1.13	1.24	0.856
5	18	10.7	10.7	1.54	1.24	-0.00964

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-56.737769	5	123.475538
A2	-55.517751	8	127.035503
A3	-56.737769	5	123.475538
fitted	-57.425076	3	120.850152
R	-78.910547	2	161.821093

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	46.7856	6	<0.0001
Test 2	2.44004	3	0.4862
Test 3	2.44004	3	0.4862
Test 4	1.37461	2	0.5029

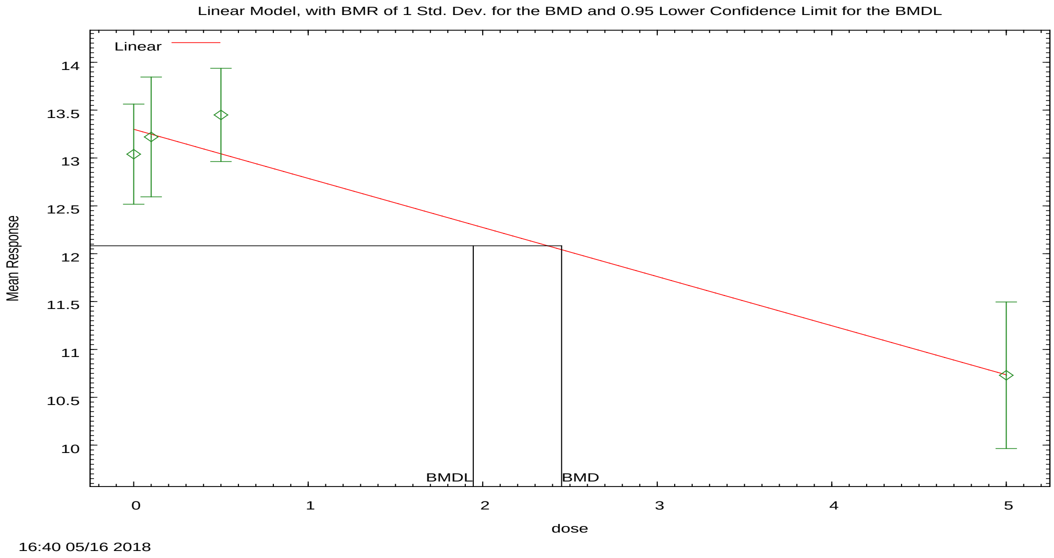

Figure 337. Plot of mean response by dose with fitted curve for Linear model with constant variance for Offspring Weight (litter as experimental unit) at PND 21 in Females (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 2.45188

BMDL at the 95% confidence level = 1.94563

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	1.58335	1.59957
rho	n/a	0
beta_0	13.3413	13.3268
beta_1	-0.513204	-0.511998

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	13	13.3	1.15	1.26	-1.1
0.1	18	13.2	13.3	1.26	1.26	-0.236
0.5	23	13.4	13.1	1.13	1.26	1.39
5	18	10.7	10.8	1.54	1.26	-0.153

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-56.737769	5	123.475538
A2	-55.517751	8	127.035503
A3	-56.737769	5	123.475538
fitted	-58.381829	3	122.763658
R	-78.910547	2	161.821093

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	46.7856	6	<0.0001
Test 2	2.44004	3	0.4862
Test 3	2.44004	3	0.4862
Test 4	3.28812	2	0.1932

BMDS WIZARD OUTPUT REPORT

BMDS Summary of Oral (Gavage) Reproduction/Developmental Toxicity Screening Study of H-28548 in Mice – Offspring Weight (g) at Postnatal Day 40 in Males

1.38. BMDS Summary of F1 Body weight PND40 (g) Males (Reproductive Mice GenX)

Table 38. Summary of BMD Modeling Results for Offspring Body weight at PND40 in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD_{1SD} (mg/kg/day)	$BMDL_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2)	0.657	235.51	4.68	3.18	1.47	BMDLs from models that met model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values > 2.0; appropriate variance (continuous data only)) were compared. BMDLs from included models were sufficiently close (< 3-fold difference), so the BMDL from the model with the lowest AIC was selected.
Exponential (M3)	0.595	236.95	4.97	3.30	1.51	
Exponential (M4)	0.657	235.51	4.68	2.01	2.33	
Exponential (M5)	N/A[b]	238.95	4.89	0.549	8.89	
Hill	N/A[b]	238.95	4.94	error[c]	error	
Power	0.595	236.95	4.97	3.36	1.48	
Polynomial 3°	**0.866**	**234.96**	**4.93**	**3.36**	**1.47**	
Polynomial 2°	0.851	234.99	4.88	4.08	1.20	
Linear	0.667	235.48	4.69	3.26	1.44	

[a] Constant variance case presented (BMDS Test 2 *p*-value = 0.423), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 0.5, and 5 mg/kg/day were -0.38, -0.01, 0.38, 0, respectively.

[b] No available degrees of freedom to calculate a goodness of fit value.

[c] BMD or BMDL computation failed for this model.

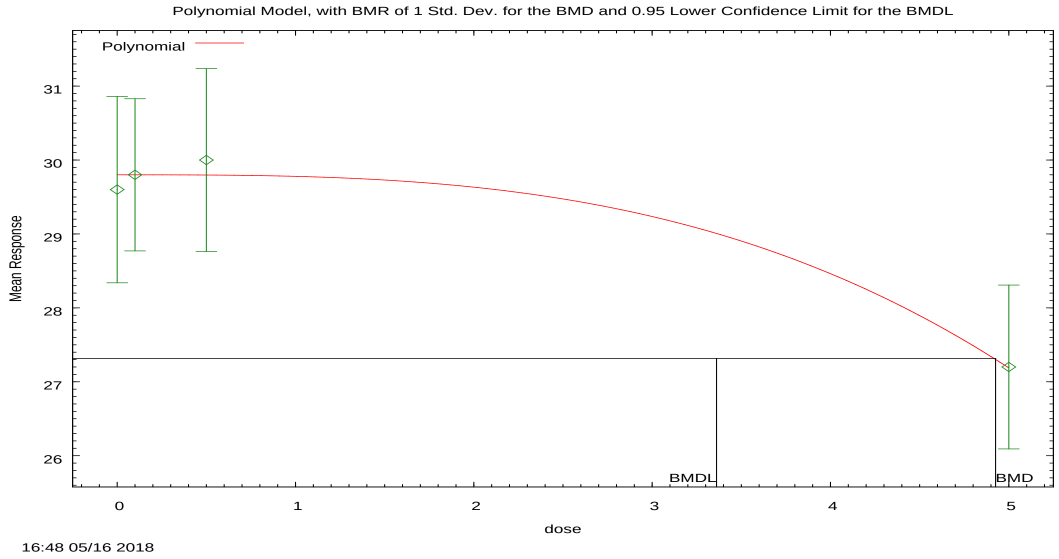

Figure 338. Plot of mean response by dose with fitted curve for Polynomial 3° model with constant variance for Offspring Body weight at PND40 in Males

(Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + …

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 4.92569

BMDL at the 95% confidence level = 3.36106

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	6.213	6.51263
rho	n/a	0
beta_0	29.8074	29.6
beta_1	0	0
beta_2	0	-3.33252
beta_3	-0.0208569	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	29.6	29.8	2.77	2.49	-0.381
0.1	18	29.8	29.8	2.07	2.49	-0.0125
0.5	23	30	29.8	2.86	2.49	0.376
5	19	27.2	27.2	2.3	2.49	-0.000413

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-114.335534	5	238.671069
A2	-112.934283	8	241.868566

A3	-114.335534	5	238.671069
fitted	-114.479095	3	234.95819
R	-121.737289	2	247.474579

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	17.606	6	0.007296
Test 2	2.8025	3	0.4231
Test 3	2.8025	3	0.4231
Test 4	0.287121	2	0.8663

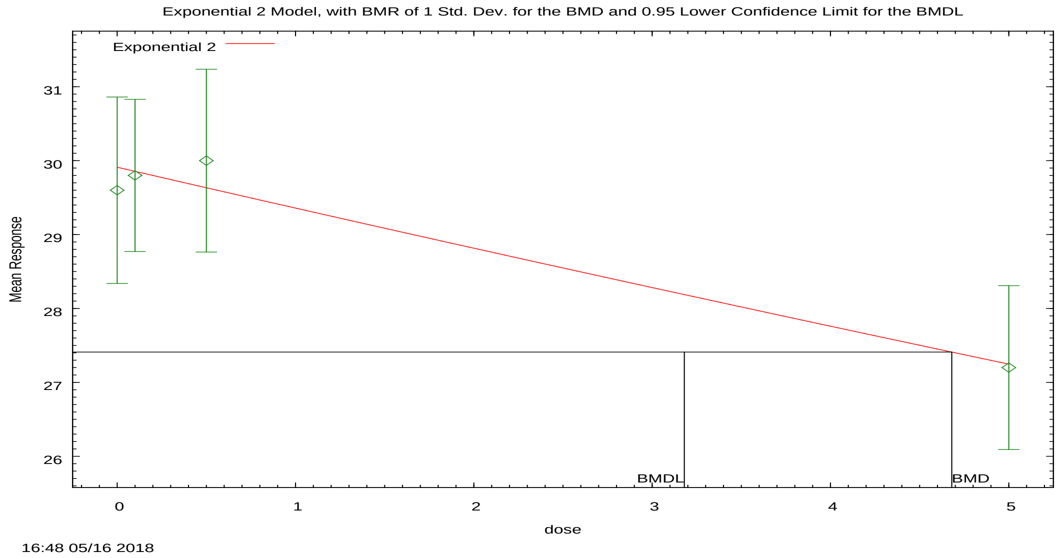

Figure 339. Plot of mean response by dose with fitted curve for Exponential (M2) model with constant variance for Offspring Body weight at PND40 in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 4.68011

BMDL at the 95% confidence level = 3.18036

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	1.83346	1.8231
rho	n/a	0
a	29.9113	28.4519
b	0.0186579	0.0187227
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	29.6	29.91	2.77	2.5	-0.5704
0.1	18	29.8	29.86	2.07	2.5	-0.09421
0.5	23	30	29.63	2.86	2.5	0.7027
5	19	27.2	27.25	2.3	2.5	-0.08207

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-114.3355	5	238.6711
A2	-112.9343	8	241.8686
A3	-114.3355	5	238.6711
R	-121.7373	2	247.4746
2	-114.755	3	235.5101

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	17.61	6	0.007296
Test 2	2.803	3	0.4231

Test 3	2.803	3	0.4231
Test 4	0.839	2	0.6574

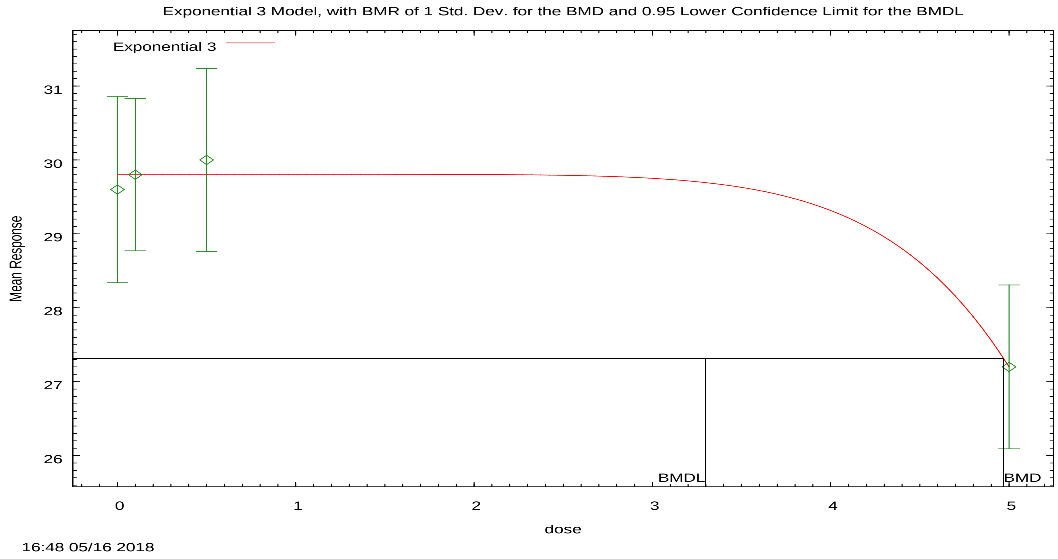

Figure 340. Plot of mean response by dose with fitted curve for Exponential (M3) model with constant variance for Offspring Body weight at PND40 in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 4.96956

BMDL at the 95% confidence level = 3.29703

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	1.8266	1.8231

rho	n/a	0
a	29.8065	28.4519
b	0.14635	0.0187227
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	29.6	29.81	2.77	2.49	-0.3796
0.1	18	29.8	29.81	2.07	2.49	-0.01098
0.5	23	30	29.81	2.86	2.49	0.3724
5	19	27.2	27.2	2.3	2.49	0.0000001374

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-114.3355	5	238.6711
A2	-112.9343	8	241.8686
A3	-114.3355	5	238.6711
R	-121.7373	2	247.4746
3	-114.4772	4	236.9544

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	17.61	6	0.007296
Test 2	2.803	3	0.4231
Test 3	2.803	3	0.4231
Test 5a	0.2834	1	0.5945

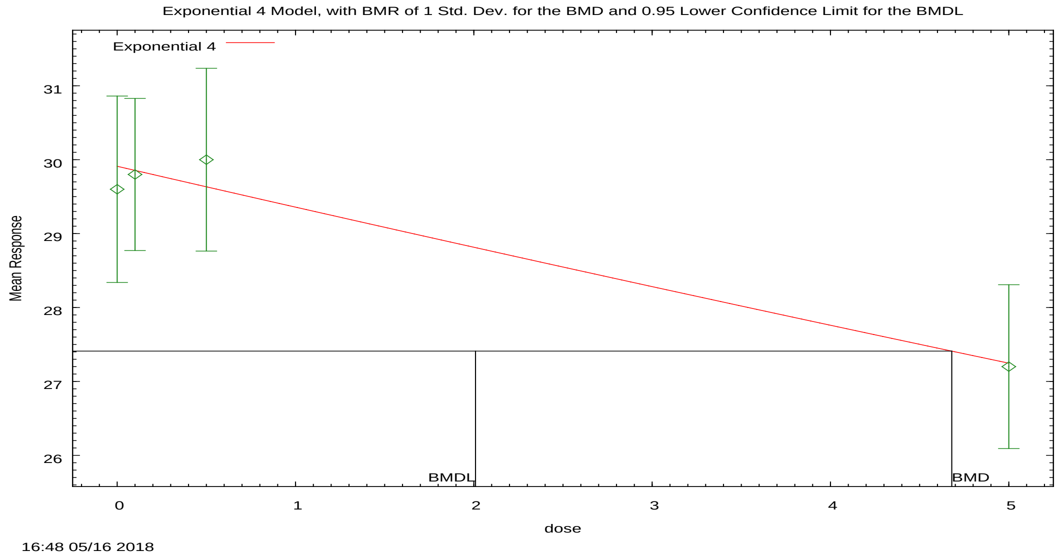

Figure 341. Plot of mean response by dose with fitted curve for Exponential (M4) model with constant variance for Offspring Body weight at PND40 in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 4.68011

BMDL at the 95% confidence level = 2.00942

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	1.83346	1.8231
rho	n/a	0
a	29.9113	31.5
b	0.0186579	0.297243

c	0	0.822373
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	29.6	29.91	2.77	2.5	-0.5704
0.1	18	29.8	29.86	2.07	2.5	-0.09421
0.5	23	30	29.63	2.86	2.5	0.7027
5	19	27.2	27.25	2.3	2.5	-0.08207

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-114.3355	5	238.6711
A2	-112.9343	8	241.8686
A3	-114.3355	5	238.6711
R	-121.7373	2	247.4746
4	-114.755	3	235.5101

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	17.61	6	0.007296
Test 2	2.803	3	0.4231
Test 3	2.803	3	0.4231
Test 6a	0.839	2	0.6574

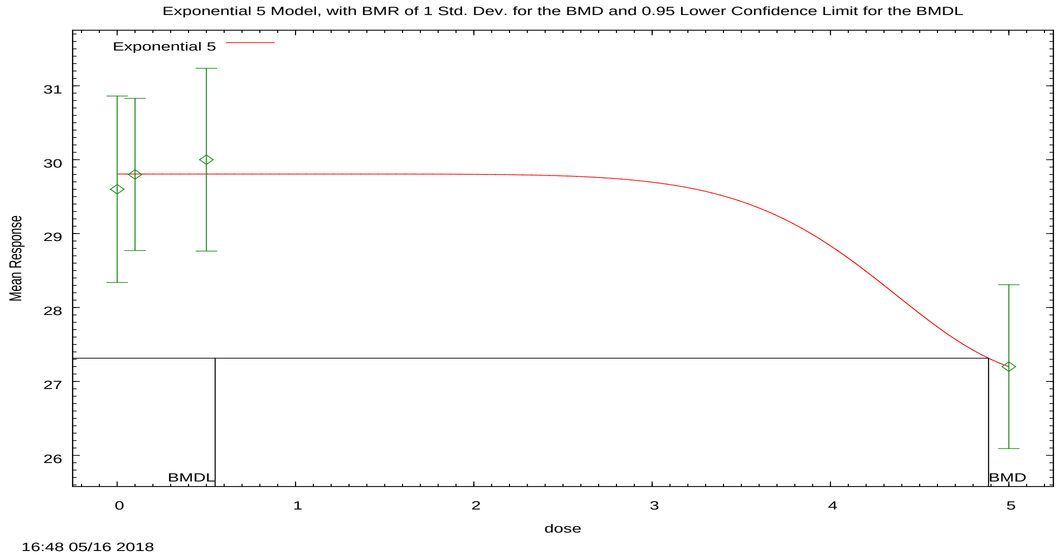

Figure 342. Plot of mean response by dose with fitted curve for Exponential (M5) model with constant variance for Offspring Body weight at PND40 in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 4.88638

BMDL at the 95% confidence level = 0.549447

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	1.8266	1.8231
rho	n/a	0
a	29.8065	31.5
b	0.225278	0.297243

c	0.905956	0.822373
d	8.21077	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	29.6	29.81	2.77	2.49	-0.3796
0.1	18	29.8	29.81	2.07	2.49	-0.01098
0.5	23	30	29.81	2.86	2.49	0.3724
5	19	27.2	27.2	2.3	2.49	-0.0000001035

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-114.3355	5	238.6711
A2	-112.9343	8	241.8686
A3	-114.3355	5	238.6711
R	-121.7373	2	247.4746
5	-114.4772	5	238.9544

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	17.61	6	0.007296
Test 2	2.803	3	0.4231
Test 3	2.803	3	0.4231
Test 7a	0.2834	0	N/A

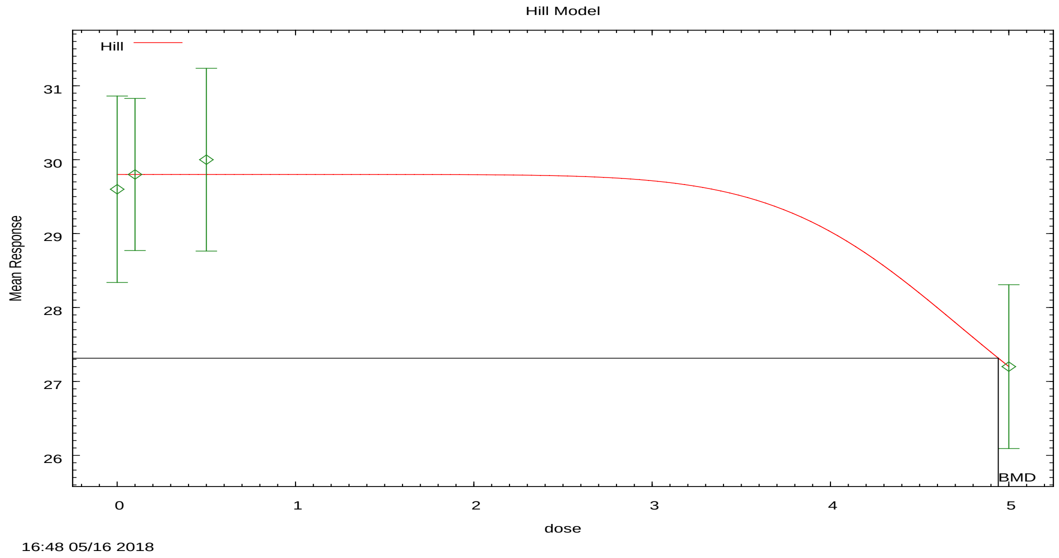

Figure 343. Plot of mean response by dose with fitted curve for Hill model with constant variance for Offspring Body weight at PND40 in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 4.94093

BMDL at the 95% confidence level = error

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	6.21272	6.51263
rho	n/a	0
intercept	29.8065	29.6
v	-4.69177	-2.4

n	8.2367	1
k	4.86641	3.07143

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	29.6	29.8	2.77	2.49	-0.38
0.1	18	29.8	29.8	2.07	2.49	-0.011
0.5	23	30	29.8	2.86	2.49	0.372
5	19	27.2	27.2	2.3	2.49	-0.00000031

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-114.335534	5	238.671069
A2	-112.934283	8	241.868566
A3	-114.335534	5	238.671069
fitted	-114.477219	5	238.954439
R	-121.737289	2	247.474579

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	17.606	6	0.007296
Test 2	2.8025	3	0.4231
Test 3	2.8025	3	0.4231
Test 4	0.28337	0	N/A

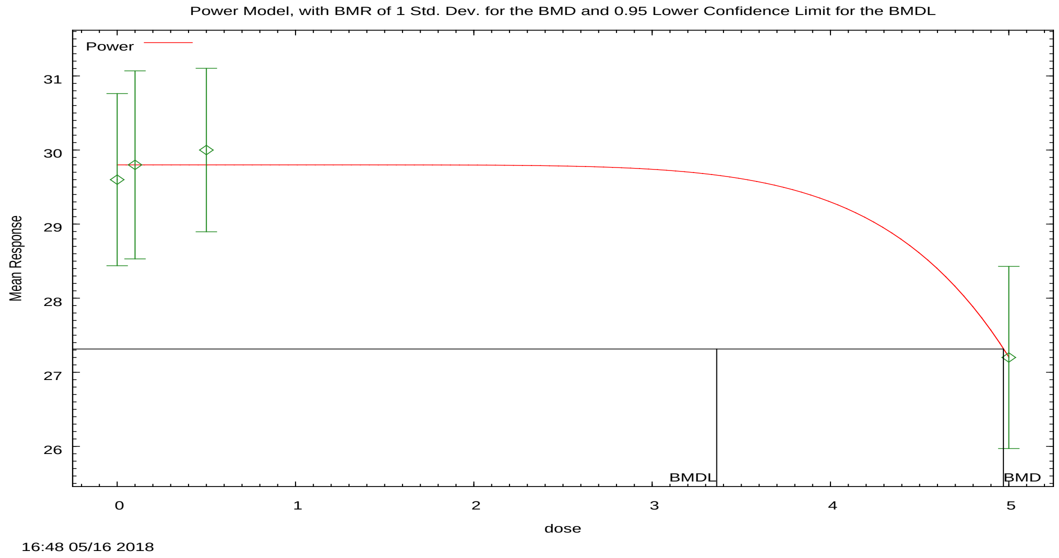

Figure 344. Plot of mean response by dose with fitted curve for Power model with constant variance for Offspring Body weight at PND40 in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 4.96979

BMDL at the 95% confidence level = 3.36188

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	6.21272	6.51263
rho	n/a	0
control	29.8065	27.2
slope	-0.0000182645	2.89081

power	7.37434	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	29.6	29.8	2.77	2.49	-0.38
0.1	18	29.8	29.8	2.07	2.49	-0.011
0.5	23	30	29.8	2.86	2.49	0.372
5	19	27.2	27.2	2.3	2.49	-0.0000000173

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-114.335534	5	238.671069
A2	-112.934283	8	241.868566
A3	-114.335534	5	238.671069
fitted	-114.477219	4	236.954439
R	-121.737289	2	247.474579

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	17.606	6	0.007296
Test 2	2.8025	3	0.4231
Test 3	2.8025	3	0.4231
Test 4	0.28337	1	0.5945

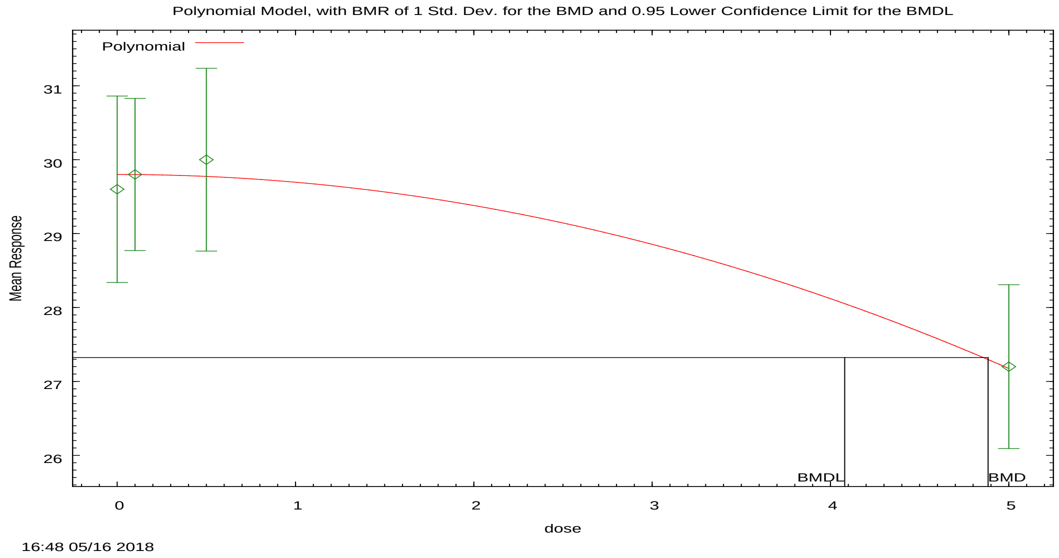

Figure 345. Plot of mean response by dose with fitted curve for Polynomial 2° model with constant variance for Offspring Body weight at PND40 in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 4.88385

BMDL at the 95% confidence level = 4.07971

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	6.2157	6.51263
rho	n/a	0
beta_0	29.8157	29.6512
beta_1	-1.88555E-23	0

beta_2	-0.104525	-0.27028

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	29.6	29.8	2.77	2.49	-0.396
0.1	18	29.8	29.8	2.07	2.49	-0.0249
0.5	23	30	29.8	2.86	2.49	0.405
5	19	27.2	27.2	2.3	2.49	-0.00444

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-114.335534	5	238.671069
A2	-112.934283	8	241.868566
A3	-114.335534	5	238.671069
fitted	-114.496699	3	234.993397
R	-121.737289	2	247.474579

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	17.606	6	0.007296
Test 2	2.8025	3	0.4231
Test 3	2.8025	3	0.4231
Test 4	0.322329	2	0.8512

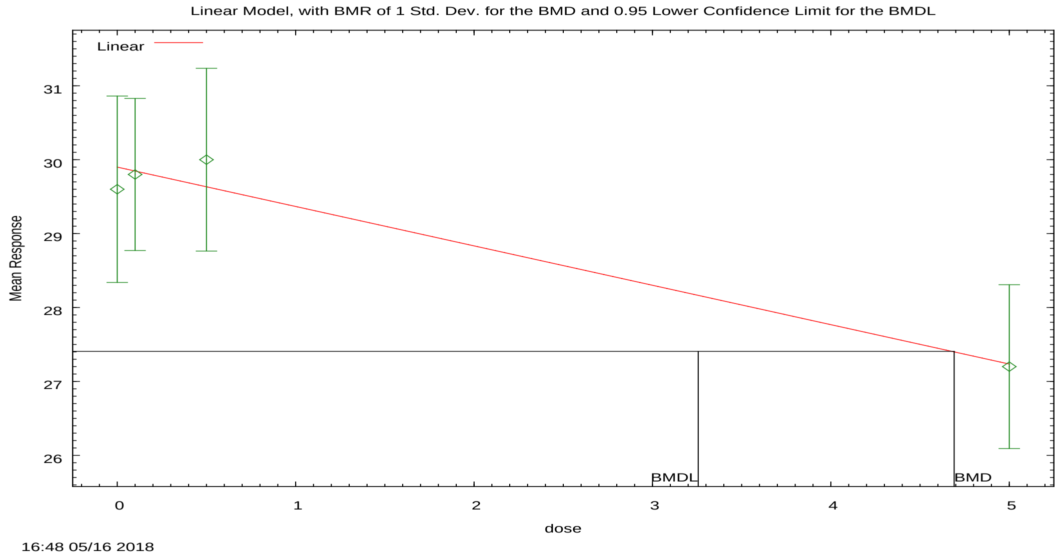

Figure 346. Plot of mean response by dose with fitted curve for Linear model with constant variance for Offspring Body weight at PND40 in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 4.69089

BMDL at the 95% confidence level = 3.25646

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	6.2532	6.51263
rho	n/a	0
beta_0	29.9078	29.8942
beta_1	-0.533085	-0.531573

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	29.6	29.9	2.77	2.5	-0.564
0.1	18	29.8	29.9	2.07	2.5	-0.0925
0.5	23	30	29.6	2.86	2.5	0.688
5	19	27.2	27.2	2.3	2.5	-0.0739

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-114.335534	5	238.671069
A2	-112.934283	8	241.868566
A3	-114.335534	5	238.671069
fitted	-114.740315	3	235.480629
R	-121.737289	2	247.474579

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	17.606	6	0.007296
Test 2	2.8025	3	0.4231
Test 3	2.8025	3	0.4231
Test 4	0.809561	2	0.6671