BENCHMARK DOSE MODELING REPORT FOR GENX

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Prepared for:
North Carolina Secretaries' Science Advisory Board

May 26, 2018

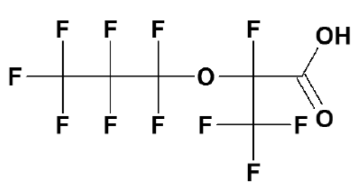
Contents

Purpose

This report was prepared by staff in the Occupational and Environmental Epidemiology Branch (OEEB) of the North Carolina Division of Public Health (DPH), Department of Health and Human Services (DHHS). The purpose of this report is to provide the Secretaries' Science Advisory Board (SAB) with the results of benchmark dose modeling of certain priority endpoints for GenX in a timely and succinct manner. This report was created in response to a request from the North Carolina SAB during their review of the DHHS provisional health goal for GenX in drinking water. Benchmark dose modeling was requested to help refine the point of departure for calculating reference doses. This report is not intended to provide a comprehensive review of all scientific information available for GenX, but rather to provide the SAB with a matrix of BMDL values to consider when making recommendations regarding health or regulatory levels for GenX in the state of North Carolina.

Background

In June 2017, the N.C. DHHS was notified of a chemical called GenX found in drinking water sourced from the lower Cape Fear River. GenX refers to the hexafluoropropylene oxide dimer acid (CASRN 13252-13-6) and its ammonium salt (CASRN 62037-80-3) (Figure 1). In solution, both dissociate into the same anion.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CASRN 13252-13-6

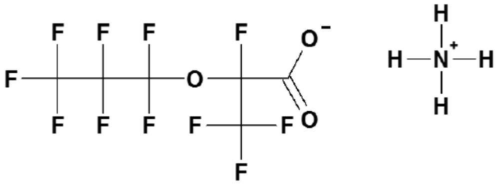
HFPO dimer acid, ammonium salt
CASRN 62037-80-3

Figure 1. Chemical structure of the GenX chemicals.

In response to reports of this and other per- and polyfluoroalkyl substances in the Cape Fear River, N.C. DHHS began to compile and review available toxicological information and consult with federal partners such as the U.S. Environmental Protection Agency (EPA). In July 2017, N.C. DHHS issued a provisional health goal for GenX in drinking water of 140 nanograms per liter (ng/L, or parts per trillion (ppt)). The provisional health goal was based on a point of departure from a No Observed Adverse Effects Level (NOAEL) of 0.1 mg/kg/day from two sub-chronic studies in mice provided by the chemical manufacturer (a 28-day repeat oral dose study and a reproductive and developmental toxicity screen). Sensitive adverse effects observed at doses higher than 0.1 mg/kg/day included liver effects such as single cell hepatocellular necrosis.

In the fall of 2017, the provisional health goal was brought before the SAB for their review. The SAB recommended benchmark dose modeling using the EPA's Benchmark Dose Software to better refine the point of departure. The following report presents the efforts of OEEB staff to conduct benchmark dose modeling for SAB consideration in their review of GenX in North Carolina.

Toxicity Study and Endpoint Selection

OEEB focused on studies provided by the registrant (i.e. the chemical manufacturer) because the reports provided sufficient information on dosing levels (controls + 3 treated dose levels) and responses (incidence numbers or means and standard deviations). Currently, there is limited information in the published peer-reviewed literature regarding the toxicity of GenX that provides the level of detail necessary for benchmark dose modeling[1]. Full reports of the studies provided by the registrant are available online in the N.C. Department of Environmental Quality electronic document repository[2].

The registrant provided seven repeat oral dose studies in rodents with exposure durations of 28-days or longer. These studies are as follows:

- 28-Day Oral (Gavage) Toxicity Study of H-28397 in Mice with a 28-day Recovery (28-day mice)
- 28-Day Oral (Gavage) Toxicity Study of H-28397 in Rats with a 28-day Recovery (28-day rats)
- H-28548: Subchronic Toxicity 90-Day Gavage Study in Mice (90-day mice)
- 90-Day Oral (Gavage) Toxicity Study of H-28548 in Rats with a 28-Day Recovery (90-day rats)
- H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats (2-year rats)
- Oral (Gavage) Reproduction/Developmental Toxicity Screening Study of H-28548 in Mice (Reproductive screen mice)
- Oral (Gavage) Prenatal Developmental Toxicity Study of H-28548 in Rats (Prenatal and developmental rats)

OEEB first compiled all dose-response data for endpoints that showed a statistically significant response between the control and treated animals in all seven studies (OEEB 2018). OEEB relied on the registrant's statistical analysis in compiling these endpoints. Additionally, endpoints for which no statistical analysis was performed (i.e. pathology data) were included if an apparent dose-response trend existed. Some of these endpoints were deemed by the registrant to be either non-adverse or not considered related to the test substance. OEEB considered all statistically significant endpoints in its review, regardless of registrant determinations of relevance.

OEEB then reviewed the previously compiled data for the following to narrow down the endpoints to be modeled:

- an apparent dose-response trend,
- sensitivity and adversity of the endpoint,
- the endpoint's relevance to human health,
- the magnitude of response for each endpoint, and;
- consistency in the response for each endpoint across studies.

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[1] Primary literature on toxic effects of GenX that are not based on data provided in the seven registrant studies include Wang et al 2017, Rushing et al 2017, and Sheng et al 2018. Wang et al 2017 only used one dose group, which is insufficient for benchmark dose modeling. Sheng et al 2018 is an in vitro study and chemical specific information to translate in vitro exposure levels to external doses for modeling is unavailable. Rushing et al 2017 uses three dose groups plus a control group, but the identified NOAEL for liver effects from that study is 1 mg/kg/day, which is an order of magnitude higher than the most sensitive effects seen in the registrant provided literature. Rushing et al 2017 also looked at immune effects, with a NOAEL of 10 mg/kg/day for these effects.

[2] https://edocs.deq.nc.gov/WaterResources/Browse.aspx?dbid=0&startid=624254&row=1&cr=1

During this process, OEEB consulted with a member of the SAB and partners at the U.S. Environmental Protection Agency (EPA) regarding interpretation of toxic endpoints, relevance of endpoints to human health, and benchmark dose guidance.

This detailed review led OEEB to further narrow its modeling efforts to a subset of hepatic, hematological, and developmental endpoints. Hepatic and hematological endpoints were chosen because these effects were consistently observed at similar dose levels across studies, and often at lower doses than other endpoints. Hepatic effects chosen for modeling include hepatocellular necrosis and increases in liver enzymes and liver weights. Hematological effects chosen for modeling include changes in red blood cell parameters such as decreases in hemoglobin and hematocrit. Developmental endpoints were included in modeling to address concerns about the potential for GenX to cause adverse developmental effects in exposed infants and children. This age group is considered to be a sensitive population due to physiological and behavioral differences from adults. Developmental effects chosen for modeling include decreased offspring weight and an increase in skeletal variations in offspring exposed to high doses of GenX in utero.

A few other considerations were taken into account for narrowing the endpoints to be modeled. For endpoints where clear sex-specific differences were observed, response data for the more sensitive sex was used for modeling. Sex-specific differences were considered to be present if statistically significant effects were seen in only one sex, or if the effect was seen at lower doses in one sex. Additionally, in the two-year rat study some endpoints were measured at multiple time points throughout the study. Only the latest time point with a statistically significant difference between the control and treatment animals was used in modeling to be more representative of long term exposure. In the two-year rat study, some hematological effects appeared to be transient, in that they appeared significant at earlier timepoints but not at later timepoints. In these cases, the latest timepoint with statically significant changes was used for modeling. Appendix A includes data tables for all modeled data.

It is worth noting that other adverse effects were observed in toxicity studies but not selected for modeling in this analysis. Hepatocellular hypertrophy was not modeled because single cell hepatocellular necrosis was chosen as a more representative adverse effect on the liver. Other liver histopathology endpoints, such as focal hepatocellular necrosis, were not observed consistently across studies and therefore were not modeled. Increased kidney weight was observed in several studies, but this was not modeled because increased liver weight was observed at lower doses in those studies and was determined to be a more sensitive endpoint. Histopathology changes in the kidney and increased adrenal gland weight were only observed in one study and therefore were not modeled.

Benchmark Dose Modeling Methods

Staff from OEEB used EPA's Benchmark Dose Software (BMDS), version 2.7.0.4, which is available for free download at https://www.epa.gov/bmds. The BMDS Wizard is available as part of this download. The BMDS Wizard is an Excel-based tool that allows for multiple modeling session to be run in BMDS at one time. The BMDS Wizard (version 1.11) was used for all modeling and analysis and to create the output reports presented in Appendix B. The standard benchmark response (BMR) was chosen for each endpoint based on guidance from the SAB and the EPA BMDS guidance document (EPA 2012). For dichotomous data, the standard BMR is 10% extra risk. For continuous data, the standard BMR is a one standard deviation change from the control mean. The benchmark dose lower bound (BMDL) is the lower end of a one-sided confidence limit on the benchmark dose, with the standard confidence level of 95%. OEEB did not alter any model parameters in the BMDS Wizard.

To review the BMDS Wizard results, OEEB used the BMD decision tree (Figure 2) found in the EPA Benchmark Dose Technical Guidance (EPA 2012).

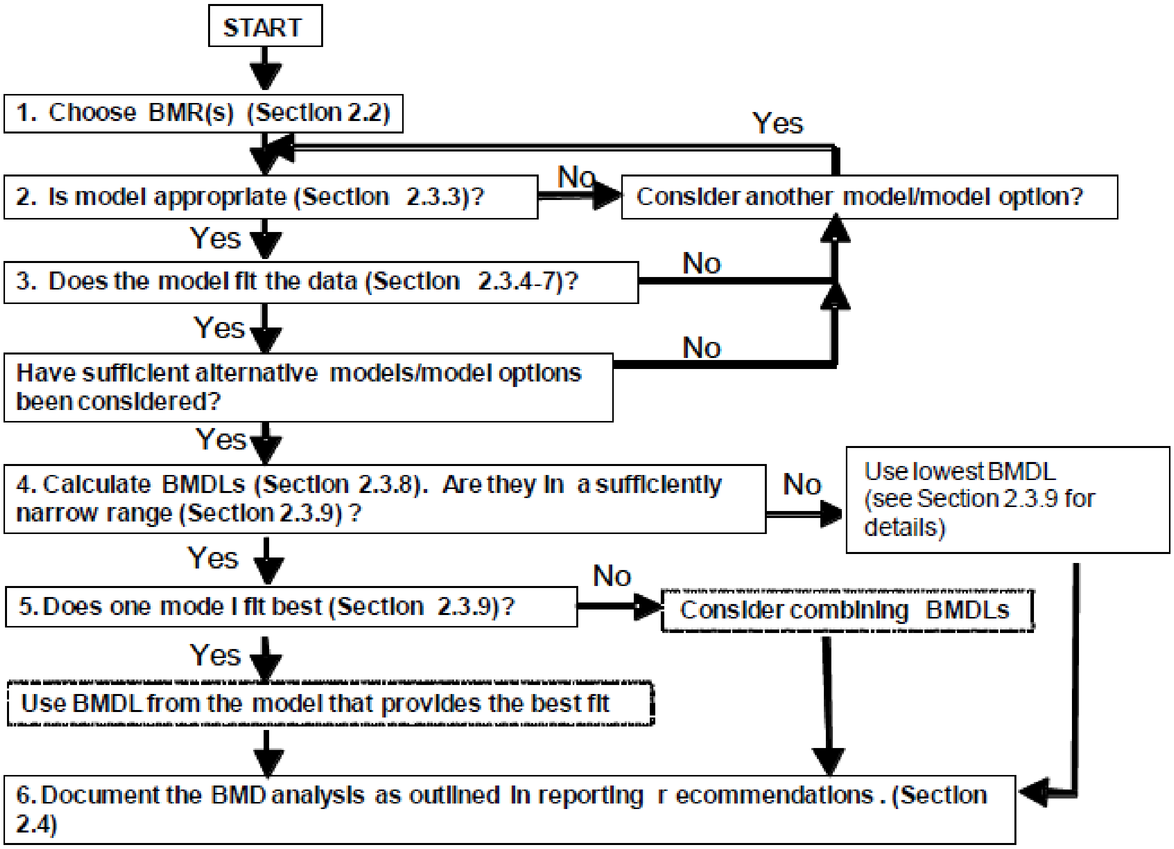

Figure 2. EPA Benchmark Dose Technical Guidance Decision Tree (EPA 2012)

When reviewing model fit, OEEB looked at the following criteria per the BMD technical guidance:

- Goodness-of-fit p-value: models with a goodness-of-fit p-value <0.1 were discarded
- Local measurement: Models with scaled residuals with absolute values > 2.0 were discarded
- Variance modeling (continuous data only):
    - If the Test 2 p-value > 0.1, then the variance of the data is constant and models using constant variance were chosen.
    - If the Test 2 p-value is <0.1 and the Test 3 p-value is >0.1, then the variance of the data is not constant and models using modeled variance were chosen.
    - If the Test 2 p-value is <0.1 and the Test 3 p-value is <0.1, then OEEB determined the data was not adequate for modeling and no BMDL could be calculated.
- Visual inspection of the model results

Only models meeting all model fit criteria were included for selection of the BMDL. The models included in the output reports in Appendix B are only those meeting the above model fit criteria. All models that fit the data were then compared to select a BMDL for each endpoint modeled. If the BMDLs from each model were sufficiently close (< 3-fold difference), then the BMDL from the least complex model, or model with the lowest Akaike's Information Criterion (AIC), was selected. If the BMDLs were not sufficiently close (> 3-fold difference), then the lowest BMDL was selected.

Output reports were created using the report function in the BMDS Wizard. BMD-to-BMDL ratios were added to these reports to illustrate the size of the confidence intervals. A large BMD-to-BMDL ratio may indicate poor data quality for modeling purposes.

Benchmark Dose Modeling Results

Table 1 below summarizes the selected BMDLs for modeled endpoints across all seven studies with NOAELs for each endpoint included for comparison. BMDs, BMD-to-BMDL ratio, and model visualizations for each modeled endpoint can be found in the Wizard output reports in Appendix B. BMDLs from selected endpoints ranged from 0.00589 to 635 mg/kg/day across studies and endpoints. It is important to note that several endpoints, including the three endpoints with the lowest BMDLs, have very large BMD-to-BMDL ratios, indicating a large confidence interval on the BMD and perhaps inadequate data for modeling these endpoints. The BMDS Wizard automatically flags any BMDL that has a BMD-to-BMDL ratio greater than five.

For hematological effects, BMDLs ranged from 0.00589 to 25.3 mg/kg/day across studies. Decreased hematocrit in males from the 28-day mice study resulted in the lowest BMDL of 0.00589 mg/kg/day, but the BMD-to-BMDL ratio for this endpoint from this study is 20.7. The lowest hematological BMDL without a flag is 0.357 mg/kg/day for decreased hematocrit in males from the 28-day rat study.

BMDLs for hepatic effects ranged from 0.0741 to 5.55 mg/kg/day across studies. The BMDL of 0.0741 mg/kg/day for increased albumin to globulin ratio in males from the 90-day rat study was the lowest for hepatic endpoints but had a BMD-to-BMDL ratio of 45.8. The lowest hepatic BMDL without a flag is 0.151 mg/kg/day for single cell hepatocellular necrosis in males from the reproductive study in mice.

Finally, BMDLs for developmental effects ranged from 3.06 to 635 mg/kg/day across studies. The lowest developmental BMDL was for decreased offspring weight on postnatal day 21 in male offspring from the reproductive study in mice.

Table 1. No observed adverse effects levels (NOAELs) and proposed benchmark dose lower bound (BMDL) for selected endpoints from seven repeat oral dose studies in rodents dosed with GenX. BMDS Wizard output reports, which include BMD, BMD-to-BMDL ratio, and model visualizations for each modeled endpoint, can be found in Appendix B.

	28-day Mice		**28-day Rats**		**90-day Mice**		**90-day Rats**	
Study dose groups (mg/kg/day)	**0, 0.1, 3, 30**		**M - 0, 0.3, 3, 30 F - 0, 3, 30, 300**		**0, 0.1, 0.5, 5**		**M - 0, 0.1, 10, 100 F - 0, 10, 100, 1000**	
	NOAEL (mg/kg/day)	**Proposed BMDL (mg/kg/day)**	**NOAEL (mg/kg/day)**	**Proposed BMDL (mg/kg/day)**	**NOAEL (mg/kg/day)**	**Proposed BMDL (mg/kg/day)**	**NOAEL (mg/kg/day)**	**Proposed BMDL (mg/kg/day)**
Hematology								
Hemoglobin	0.1 (M)	0.0492*	0.3 (M)	1.19	NS		0.1 (M)	2.12
Hematocrit	0.1 (M)	0.00589*	0.3 (M)	0.357	NS		0.1 (M)	--
Hepatotoxicity								
Albumin/Globulin ratio	0.1 (M&F)	0.464 (M); 0.595 (F)	0.3 (M)	0.945	NS		0.1 (M)	0.0741*
Alkaline Phosphatase	3 (M&F)	-- (M); 5.55 (F)	NS		0.5 (M&F)	0.480 (M); 0.859* (F)	10 (M)	1.43
Alanine Aminotransferase	3 (M)	--	NS		0.5 (M&F)	-- (M&F)	NS	
Aspartate Aminotransferase	3 (M)	1.18	NS		0.5 (M)	0.169	NS	
Sorbitol dehydrogenase	3 (M&F)	-- (M); 6.29 (F)	NS		0.5 (M&F)	-- (M&F)	NS	
Hepatocellular necrosis (single cell)	0.1 (M)^	0.299*	3 (M)^	2.70*	0.5 (M)^	0.126#		
Liver weight to brain weight	0.1 (M&F)	0.194 (M); 0.751 (F)	0.3 (M)	0.611	0.5 (M&F)	0.300 (M); 0.929 (F)	0.1 (M)	--
Developmental								
Combined fetal weights								
Skeletal variations								
Offspring weight PND 21								
F1 body weight PND 40								

* = BMD-to-BMDL ratio > 5 for the selected model, indicating the data may be of poor quality for modeling purposes
\# = selected model has a questionable visual fit
^ = NOAEL estimated based on visual inspection of data, no statistical analysis provided
-- = No models met all criteria for model fit, so no BMDL was selected
NOAEL = No Observed Adverse Effect Level
BMDL = Benchmark Dose Lower Bound

mg/kg/day = milligrams of GenX per kilogram of body weight per day
M = Males
F = Females
NS = effect not statistically significant in the study
mo = months
PND = postnatal day
Cells shaded dark grey denote that the endpoint was not measured in that study

Table 1 Continued. No observed adverse effects levels (NOAELs) and proposed benchmark dose lower bound (BMDL) for selected endpoints from seven repeat oral dose studies in rodents dosed with GenX. BMDS Wizard output reports, which include BMD, BMD-to-BMDL ratio, and model visualizations for each modeled endpoint, can be found in Appendix B.

	2-year Rats		**Reproductive Screen Mice**		**Prenatal and Developmental Rats**	
Study dose groups (mg/kg/day)	**M - 0, 0.1, 1, 50** **F - 0, 1, 50, 500**		**0, 0.1, 0.5, 5**		**0, 10, 100, 1000**	
	NOAEL (mg/kg/day)	**Proposed BMDL (mg/kg/day)**	**NOAEL (mg/kg/day)**	**Proposed BMDL (mg/kg/day)**	**NOAEL (mg/kg/day)**	**Proposed BMDL (mg/kg/day)**
Hematology						
Hemoglobin	1 (M 3&6mo)	3.55*# (6mo)				
Hematocrit	1 (M 3 and 6 mo)	25.3 (6mo)				
Hepatotoxicity						
Albumin/Globulin ratio	0.1 (M 3&12mo)	-- (12 mo)				
Alkaline Phosphatase	1 (M 3,6,12mo)	-- (12 mo)				
Alanine Aminotransferase	1 (M 12mo)	-- (12 mo)				
Aspartate Aminotransferase	NS					
Sorbitol dehydrogenase	1 (M 12mo)	1.21* (12mo)				
Hepatocellular necrosis (single cell)	50 (F)	Not modeled (high NOAEL)	0.1 (M)^	0.151		
Liver weight to brain weight	50 (F)	Not modeled (high NOAEL)	0.1 (M&F)	0.165 (M); -- (F)		
Developmental						
Combined fetal weights					10	--
Skeletal variations					100	635
Offspring weight PND 21			0.5 (M&F)	3.06 (M); 3.66 (F)		
F1 body weight PND 40			0.5 (M)	3.36 (M)		

* = BMD-to-BMDL ratio > 5 for the selected model, indicating the data may be of poor quality for modeling purposes
# = selected model has a questionable visual fit
^ = NOAEL estimated based on visual inspection of data, no statistical analysis provided
-- = No models met all criteria for model fit, so no BMDL was selected
NOAEL = No Observed Adverse Effect Level
BMDL = Benchmark Dose Lower Bound

mg/kg/day = milligrams of GenX per kilogram of body weight per day
M = Males
F = Females
NS = effect not statistically significant in the study
mo = months
PND = postnatal day
Cells shaded dark grey denote that the endpoint was not measured in that study

Limitations

This report is not intended as a comprehensive review of all scientific information available for GenX. Not all statistically significant endpoints were modeled for this report. Rather, this report focuses on those endpoints that were seen at the lowest doses and observed consistently across studies, as well as developmental endpoints given the special concerns for exposure to infants and children. This report does not address the factors used to calculate a provisional health goal for drinking water, such as uncertainty factors or exposure parameters.

Conclusions

This report provides the results of benchmark dose modeling of certain priority endpoints for GenX in response to a request from the North Carolina SAB made during their review of the DHHS provisional health goal for GenX in drinking water. OEEB has completed benchmark dose modeling on select hematological, hepatic, and developmental endpoints from seven repeat oral dose studies in rodents. NOAELs from these endpoints range from 0.1 to 100 mg/kg/day, and proposed BMDLs for these endpoints range from 0.00589 to 635 mg/kg/day. N.C. DHHS asks that the SAB consider this information when making recommendations regarding health or regulatory levels for GenX in the state of North Carolina.

References

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Appendix A

Data Tables for Endpoints Selected for Benchmark Dose Modeling

Contents

Introduction

Data tables for all statistically significant endpoints from all seven repeat oral dose studies can be found in a separate document previously provided to the North Carolina Secretaries' Science Advisory Board (OEEB 2018). Data tables presented here are for endpoints selected for benchmark dose modeling.

The following tables are organized by endpoint. For endpoints where clear sex-specific differences were observed, the more sensitive sex was used for modeling, and only that data is shown here. For endpoints that were measured at multiple time points in the same study, the latest time point with a statistically significant difference between the control and treatment animals was used to be more representative of long term exposure, and only that data is shown here.

Table A-1. Hemoglobin data from repeat oral dose studies used for benchmark dose modeling.

Hemoglobin (g/dL)					
28-Day Oral (Gavage) Toxicity Study of H-28397 in Mice with a 28-day Recovery					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	9	14.1	0.53	
	0.1	8	13.8	0.45	
	3	8	13.4	0.46	significant at p=0.05
	30	9	13.1	0.53	significant at p=0.01
28-Day Oral (Gavage) Toxicity Study of H-28397 in Rats with a 28-day Recovery					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	16.3	0.36	
	0.3	10	16.3	0.47	
	3	10	15.8	0.42	significant at p=0.05
	30	10	15.2	0.61	significant at p=0.01
90-Day Oral (Gavage) Toxicity Study of H-28548 in Rats with a 28-Day Recovery					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	16.4	0.59	
	0.1	10	16.3	0.81	
	10	10	15.3	0.94	significant at p=0.01
	100	10	14.3	0.56	significant at p=0.01
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats 6-month timepoint					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	15.99	0.645	
	0.1	10	15.76	1.082	
	1	10	16.22	0.587	
	50	10	14.86	1.064	significant at p=0.05

Table A-2. Hematocrit data from repeat oral dose studies used for benchmark dose modeling.

Hematocrit (%)					
28-Day Oral (Gavage) Toxicity Study of H-28397 in Mice with a 28-day Recovery					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	9	40.1	1.72	
	0.1	8	38.8	1.06	
	3	8	38.1	1.36	significant at p=0.05
	30	9	37.5	1.54	significant at p=0.01
28-Day Oral (Gavage) Toxicity Study of H-28397 in Rats with a 28-day Recovery					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	45.6	1.66	
	0.3	10	44.9	1.37	
	3	10	43.4	1.4	significant at p=0.01
	30	10	42	1.6	significant at p=0.01
90-Day Oral (Gavage) Toxicity Study of H-28548 in Rats with a 28-Day Recovery					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	46.8	1.5	
	0.1	10	46.3	2.53	
	10	10	43.5	2.64	significant at p=0.01
	100	10	41.2	1.36	significant at p=0.01
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats 6-month timepoint					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	48.15	1.706	
	0.1	10	47.61	2.762	
	1	10	48.98	2.836	
	50	10	44.85	2.974	significant at p=0.05

Table A-3. Albumin to globulin ratio data from repeat oral dose studies used for benchmark dose modeling.

<table>
<tr><th colspan="6">Albumin/Globulin Ratio</th></tr>
<tr><th colspan="6">28-Day Oral (Gavage) Toxicity Study of H-28397 in Mice with a 28-day Recovery</th></tr>
<tr><th></th><th>Dose (mg/kg/day)</th><th>N</th><th>Mean</th><th>St. Dev</th><th>Notes</th></tr>
<tr><td rowspan="4">Males</td><td>0</td><td>10</td><td>1.54</td><td>0.134</td><td></td></tr>
<tr><td>0.1</td><td>10</td><td>1.56</td><td>0.128</td><td></td></tr>
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<tr><td rowspan="4">Females</td><td>0</td><td>10</td><td>1.93</td><td>0.159</td><td></td></tr>
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<tr><th colspan="6">28-Day Oral (Gavage) Toxicity Study of H-28397 in Rats with a 28-day Recovery</th></tr>
<tr><th>Sex</th><th>Dose (mg/kg/day)</th><th>N</th><th>Mean</th><th>St. Dev</th><th>Notes</th></tr>
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<tr><th>Sex</th><th>Dose (mg/kg/day)</th><th>N</th><th>Mean</th><th>St. Dev</th><th>Notes</th></tr>
<tr><td rowspan="4">Males</td><td>0</td><td>10</td><td>1.64</td><td>0.179</td><td></td></tr>
<tr><td>0.1</td><td>10</td><td>1.73</td><td>0.195</td><td></td></tr>
<tr><td>10</td><td>10</td><td>2.06</td><td>0.289</td><td>significant at p=0.01</td></tr>
<tr><td>100</td><td>10</td><td>2.22</td><td>0.357</td><td>significant at p=0.01</td></tr>
<tr><th colspan="6">H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats 12-month timepoint</th></tr>
<tr><th>Sex</th><th>Dose (mg/kg/day)</th><th>N</th><th>Mean</th><th>St. Dev</th><th>Notes</th></tr>
<tr><td rowspan="4">Males</td><td>0</td><td>10</td><td>0.88</td><td>0.063</td><td></td></tr>
<tr><td>0.1</td><td>10</td><td>0.94</td><td>0.135</td><td></td></tr>
<tr><td>1</td><td>10</td><td>1.02</td><td>0.092</td><td>significant at p=0.05</td></tr>
<tr><td>50</td><td>10</td><td>1.13</td><td>0.125</td><td>significant at p=0.01</td></tr>
</table>

Table A-4. Alkaline phosphatase data from repeat oral dose studies used for benchmark dose modeling.

Alkaline Phosphatase (U/L)					
28-Day Oral (Gavage) Toxicity Study of H-28397 in Mice with a 28-day Recovery					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	88	29.5	
	0.1	10	73	18.2	
	3	10	144	51.2	
	30	10	1163	682.4	significant at p=0.01
Females	0	10	90	21.9	
	0.1	10	97	22.1	
	3	10	96	19.7	
	30	10	216	51.3	significant at p=0.01
H-28548: Subchronic Toxicity 90-Day Gavage Study in Mice					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	50	12	
	0.1	10	55	22	
	0.5	10	70	30	
	5	10	617	339	significant at p=0.05
Females	0	10	65	19	
	0.1	10	77	25	
	0.5	9	72	18	
	5	9	158	38	significant at p=0.05
90-Day Oral (Gavage) Toxicity Study of H-28548 in Rats with a 28-Day Recovery					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	80	12.9	
	0.1	10	79	15.4	
	10	10	118	30.9	
	100	10	165	41.5	significant at p=0.01
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats 12-month timepoint					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	73	15.06	
	0.1	10	93.5	26.22	
	1	10	107	31.7	
	50	10	204.7	67.12	significant at p=0.01

Table A-5. Alanine aminotransferase data from repeat oral dose studies used for benchmark dose modeling.

Alanine Aminotransferase (U/L)					
28-Day Oral (Gavage) Toxicity Study of H-28397 in Mice with a 28-day Recovery					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	52	37.2	
	0.1	10	38	11	
	3	10	82	30.8	
	30	10	704	311.9	significant at p=0.01
H-28548: Subchronic Toxicity 90-Day Gavage Study in Mice					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	49	16	
	0.1	10	62	22	
	0.5	10	66	48	
	5	10	255	114	significant at p=0.05
Females	0	10	36	12	
	0.1	10	36	8	
	0.5	9	32	6	
	5	9	51	20	significant at p=0.05
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats 12-month timepoint					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	39.7	12.97	
	0.1	10	34.8	5.2	
	1	10	37.4	8.51	
	50	10	130.3	85.73	significant at p=0.05

Table A-6. Aspartate aminotransferase data from repeat oral dose studies used for benchmark dose modeling.

Aspartate Aminotransferase (U/L)					
28-Day Oral (Gavage) Toxicity Study of H-28397 in Mice with a 28-day Recovery					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	72	18.5	
	0.1	10	72	13.3	
	3	10	90	38	
	30	10	416	218.3	significant at p=0.01
H-28548: Subchronic Toxicity 90-Day Gavage Study in Mice					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	62	11	
	0.1	10	67	21	
	0.5	10	84	21	
	5	10	128	80	significant at p=0.05

Table A-7. Sorbitol dehydrogenase data from repeat oral dose studies used for benchmark dose modeling.

Sorbitol Dehydrogenase (U/L)					
28-Day Oral (Gavage) Toxicity Study of H-28397 in Mice with a 28-day Recovery					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	24	5.4	
	0.1	10	22	3.4	
	3	10	46	20.4	
	30	9	456	225.2	significant at p=0.01
Females	0	10	14	5.1	
	0.1	10	16	4.8	
	3	10	16	5.5	
	30	10	40	20.2	significant at p=0.01
H-28548: Subchronic Toxicity 90-Day Gavage Study in Mice					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	26.6	2.5	
	0.1	10	26	2.4	
	0.5	10	25.8	5.4	
	5	10	108.5	47.2	significant at p=0.05
Females	0	10	25.3	11.7	
	0.1	9	22.9	2	
	0.5	9	23.6	3.6	
	5	9	33.5	9.3	significant at p=0.05
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats 12-month timepoint					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	13.32	6.006	
	0.1	10	14.47	3.873	
	1	10	15.7	4.848	
	50	10	32.08	26.424	significant at p=0.05

Table A-8. Single cell hepatocellular necrosis data from repeat oral dose studies used for benchmark dose modeling.

<table>
<tr><th colspan="5">Liver Necrosis, Single Cell</th></tr>
<tr><th colspan="5">28-Day Oral (Gavage) Toxicity Study of H-28397 in Mice with a 28-day Recovery</th></tr>
<tr><th>Sex</th><th>Dose (mg/kg/day)</th><th>N</th><th>Incidence (#)</th><th>Notes</th></tr>
<tr><td rowspan="4">Males</td><td>0</td><td>10</td><td>0</td><td></td></tr>
<tr><td>0.1</td><td>10</td><td>0</td><td></td></tr>
<tr><td>3</td><td>10</td><td>4</td><td>4 minimal</td></tr>
<tr><td>30</td><td>10</td><td>10</td><td>10 minimal</td></tr>
<tr><td rowspan="4">Females</td><td>0</td><td>10</td><td>0</td><td></td></tr>
<tr><td>0.1</td><td>10</td><td>0</td><td></td></tr>
<tr><td>3</td><td>10</td><td>0</td><td></td></tr>
<tr><td>30</td><td>10</td><td>4</td><td>4 minimal</td></tr>
<tr><th colspan="5">28-Day Oral (Gavage) Toxicity Study of H-28397 in Rats with a 28-day Recovery</th></tr>
<tr><th>Sex</th><th>Dose (mg/kg/day)</th><th>N</th><th>Incidence #</th><th>Notes</th></tr>
<tr><td rowspan="4">Males</td><td>0</td><td>10</td><td>0</td><td></td></tr>
<tr><td>0.3</td><td>10</td><td>0</td><td></td></tr>
<tr><td>3</td><td>10</td><td>0</td><td></td></tr>
<tr><td>30</td><td>10</td><td>3</td><td>3 minimal</td></tr>
<tr><th colspan="5">H-28548: Subchronic Toxicity 90-Day Gavage Study in Mice</th></tr>
<tr><th>Sex</th><th>Dose (mg/kg/day)</th><th>N</th><th>Incidence (#)</th><th>Notes</th></tr>
<tr><td rowspan="4">Males</td><td>0</td><td>10</td><td>0</td><td></td></tr>
<tr><td>0.1</td><td>10</td><td>0</td><td></td></tr>
<tr><td>0.5</td><td>10</td><td>0</td><td></td></tr>
<tr><td>5</td><td>10</td><td>10</td><td>10 minimal</td></tr>
<tr><th colspan="5">Oral (Gavage) Reproduction/Developmental Toxicity Screening Study of H-28548 in Mice</th></tr>
<tr><th>Sex</th><th>Dose (mg/kg/day)</th><th>N</th><th>Incidence (#)</th><th>Notes</th></tr>
<tr><td rowspan="4">Males</td><td>0</td><td>25</td><td>1</td><td>1 minimal</td></tr>
<tr><td>0.1</td><td>24</td><td>1</td><td>1 minimal</td></tr>
<tr><td>0.5</td><td>24</td><td>5</td><td>5 minimal</td></tr>
<tr><td>5</td><td>24</td><td>24</td><td>4 minimal, 17 mild, 3 moderate</td></tr>
</table>

Table A-9. Liver weight to brain weight data from repeat oral dose studies used for benchmark dose modeling.

Liver Weight to Brain Weight (g/100g brain)					
28-Day Oral (Gavage) Toxicity Study of H-28397 in Mice with a 28-day Recovery					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	347.314	35.9339	
	0.1	10	365.446	37.5748	
	3	10	611.951	119.6603	significant at p=0.01
	30	10	948.956	204.0532	significant at p=0.01
Females	0	10	270.582	31.8333	
	0.1	10	285.47	29.77	
	3	10	347.618	38.6819	significant at p=0.01
	30	10	554.315	65.5015	significant at p=0.01
28-Day Oral (Gavage) Toxicity Study of H-28397 in Rats with a 28-day Recovery					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	546.486	62.2678	
	0.3	10	560.332	49.3673	
	3	10	679.305	74.8864	significant at p=0.01
	30	10	867.076	121.2461	significant at p=0.01
H-28548: Subchronic Toxicity 90-Day Gavage Study in Mice					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	386.366	45.011	
	0.1	10	407.101	36.407	
	0.5	10	437.1	69.385	
	5	9	935.966	193.179	significant at p=0.05
Females	0	10	332.826	66.34	
	0.1	10	334.248	30.441	
	0.5	9	350.216	59.323	
	5	9	555.33	193.239	significant at p=0.05
90-Day Oral (Gavage) Toxicity Study of H-28548 in Rats with a 28-Day Recovery					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	657.943	47.9593	
	0.1	10	682.492	66.4246	
	10	10	825.582	161.3767	significant at p=0.01
	100	10	1060.36	136.53	significant at p=0.01

Table A-9 continued. Liver weight to brain weight data from repeat oral dose studies used for benchmark dose modeling.

Liver Weight to Brain Weight (g/100g brain)					
Oral (Gavage) Reproduction/Developmental Toxicity Screening Study of H-28548 in Mice					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	25	372.934	41.0786	
	0.1	24	396.618	54.4874	
	0.5	24	465.278	63.5695	significant at p=0.01
	5	24	893.709	169.7741	significant at p=0.01
Females	0	21	427.097	51.1989	
	0.1	18	455.91	46.8862	
	0.5	23	526.053	94.2293	significant at p=0.01
	5	20	863.983	93.4767	significant at p=0.01

Table A-10. Offspring weight postnatal day 21 data from the Oral (Gavage) Reproduction/Developmental Toxicity Screening Study of H-28548 in Mice study used for benchmark dose modeling.

Offspring Weight (litter as experimental unit) - PND21 (g)					
Oral (Gavage) Reproduction/Developmental Toxicity Screening Study of H-28548 in Mice					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	21	13.52	1.376	
	0.1	18	13.78	1.37	
	0.5	23	13.87	1.284	
	5	20	10.56	1.908	significant at p=0.01
Females	0	21	13.04	1.149	
	0.1	18	13.22	1.258	
	0.5	23	13.45	1.127	
	5	18	10.73	1.54	significant at p=0.01

Table A-11. F1 Body weight postnatal day 40 data from the Oral (Gavage) Reproduction/Developmental Toxicity Screening Study of H-28548 in Mice study used for benchmark dose modeling.

F1 Body Weight - PND40 (g)					
Oral (Gavage) Reproduction/Developmental Toxicity Screening Study of H-28548 in Mice					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	21	29.6	2.77	
	0.1	18	29.8	2.07	
	0.5	23	30	2.86	
	5	19	27.2	2.3	significant at p=0.01

Table A-12. Combined fetal weight data from the Oral (Gavage) Prenatal Developmental Toxicity Study of H-28548 in Rats study used for benchmark dose modeling.

Combined Fetal Weights (g)				
Oral (Gavage) Prenatal Developmental Toxicity Study of H-28548 in Rats				
Dose (mg/kg/day)	**N (# of litters)**	**Mean**	**St. Dev**	**Notes**
0	22	5.7	0.38	
10	21	5.6	0.24	
100	21	5.2	0.24	significant at p=0.01
1000	21	4.1	0.29	significant at p=0.01

Table A-13. Percent per litter with skeletal variations data from the Oral (Gavage) Prenatal Developmental Toxicity Study of H-28548 in Rats study used for benchmark dose modeling.

Percent Per Litter with Skeletal Variations (%)				
Oral (Gavage) Prenatal Developmental Toxicity Study of H-28548 in Rats				
Dose (mg/kg/day)	**N (# of litters)**	**Mean**	**St. Dev**	**Notes**
0	22	10.6	14.17	
10	21	11.6	10.9	
100	21	14.7	10.42	
1000	21	30.3	27.49	significant at p=0.05, 14th rudimentary rib, 7th cervical rib

Appendix B

BMDS Wizard Output Reports for Endpoints Selected for Benchmark Dose Modeling

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 in Males (28-Day Mice)

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 (M4) Exponential (M5)[b]	0.241	-8.5015	2.08	0.0607	24.2	Models that met inclusion criteria are presented (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). Selected BMDL is from model with lowest AIC and lowest BMDL.
Hill	0.287	-8.7441	0.343	0.0492	6.97	

[a] Constant variance case presented (BMDS Test 2 *p*-value = 0.933, BMDS Test 3 *p*-value = 0.933), no model was selected as a best-fitting model.

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

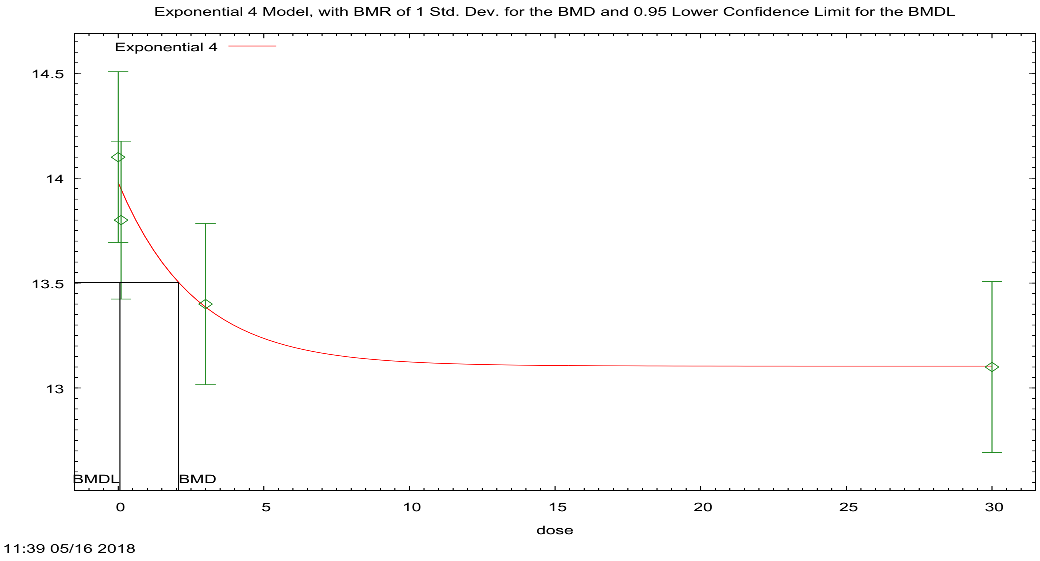

Figure 1. Plot of mean response by dose with fitted curve for Exponential (M4) model with constant variance for Hemoglobin in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

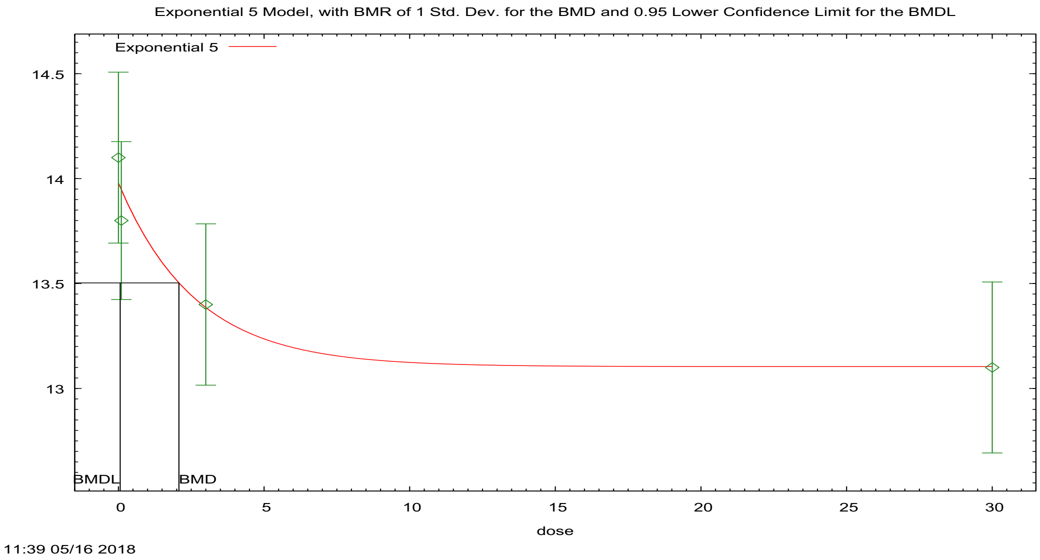

Figure 2. Plot of mean response by dose with fitted curve for Exponential (M5) model with constant variance for Hemoglobin in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

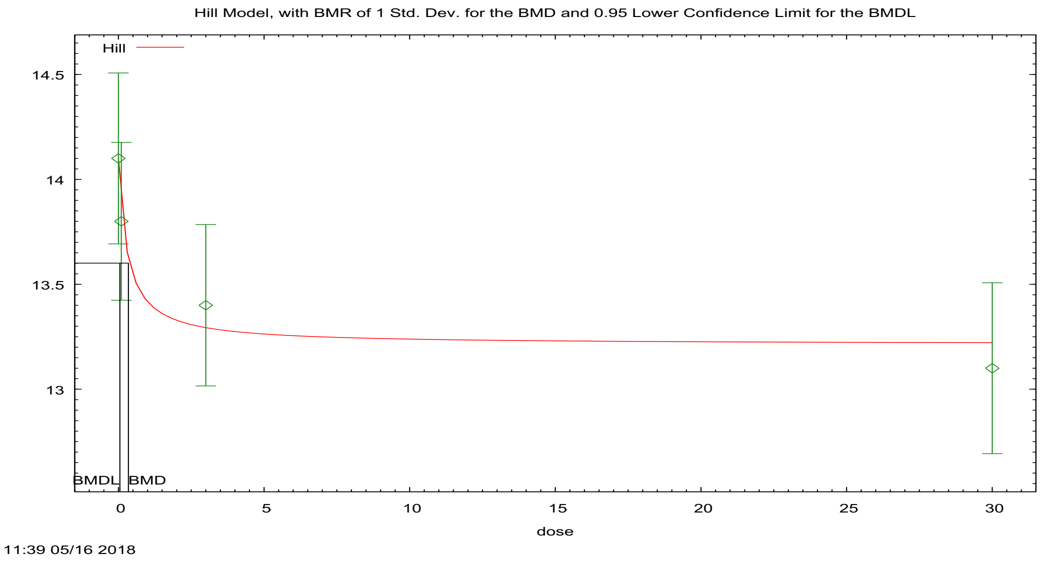

Figure 3. Plot of mean response by dose with fitted curve for Hill model with constant variance for Hemoglobin in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

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 in Males (28-Day Rats)

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 (M4)	**0.731**	**-15.807**	**2.44**	**1.19**	**2.06**	**Only one model met inclusion criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)).**

[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.

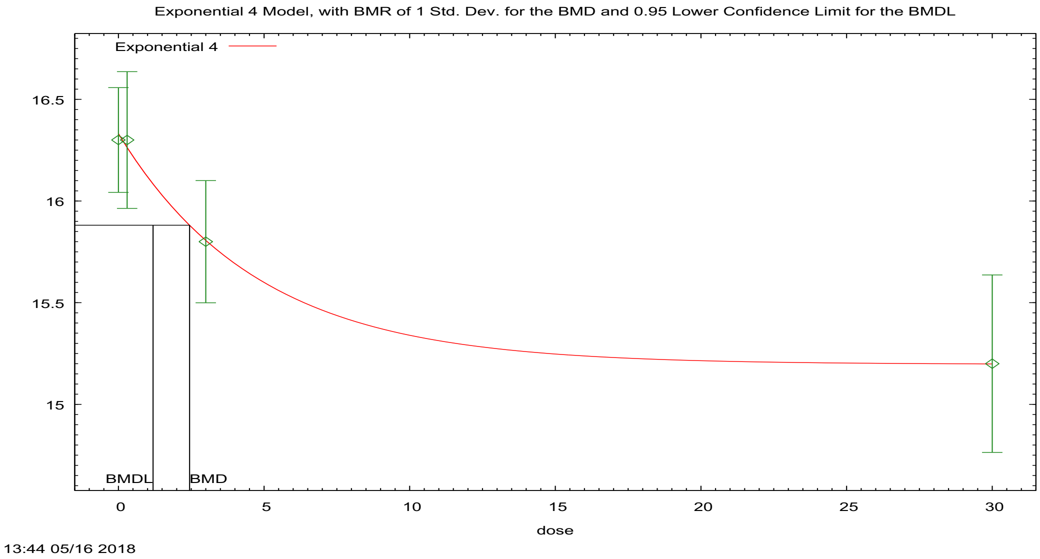

Figure 4. Plot of mean response by dose with fitted curve for Exponential (M4) model with constant variance for Hemoglobin in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

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 in Males (90-Day Rats)

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 (M4) Exponential (M5)[b]	0.787	19.971	5.80	3.23	1.80	Models that met inclusion criteria are presented (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). Selected BMDL is from model with lowest AIC and lowest BMDL.
Hill	**0.798**	**19.963**	**5.15**	**2.12**	**2.42**	

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

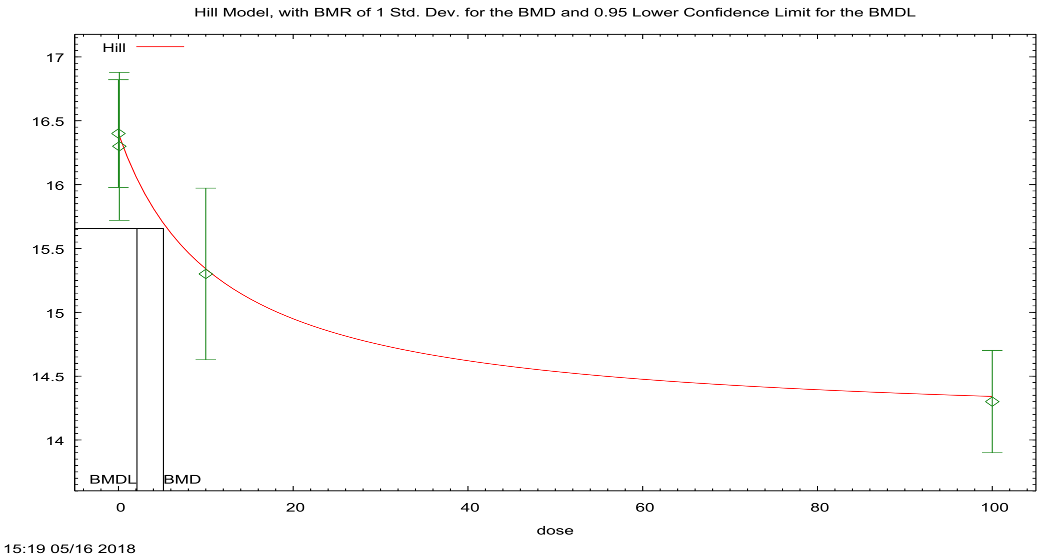

Figure 5. Plot of mean response by dose with fitted curve for Hill model with constant variance for Hemoglobin in Males (90-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

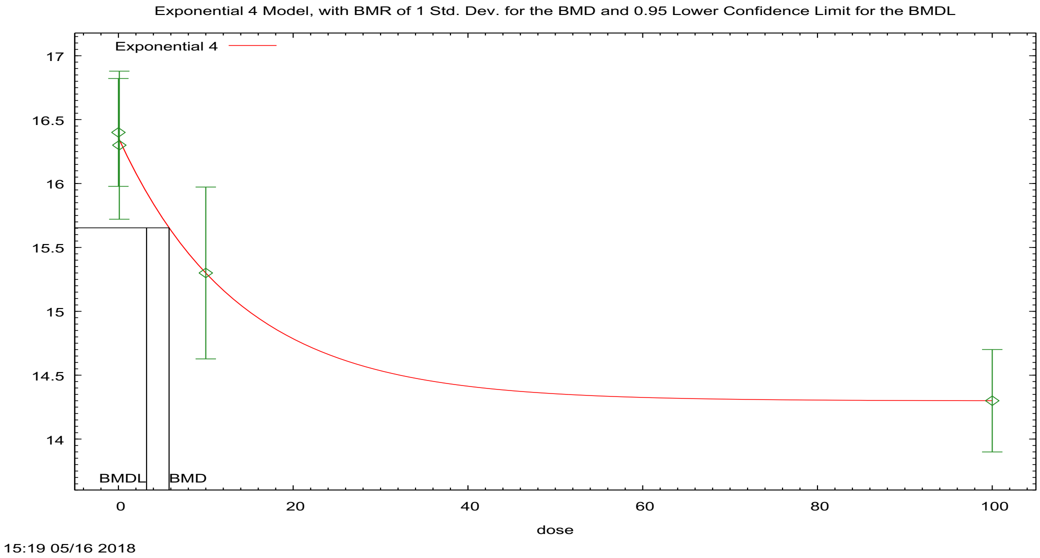

Figure 6. Plot of mean response by dose with fitted curve for Exponential (M4) model with constant variance for Hemoglobin in Males (90-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

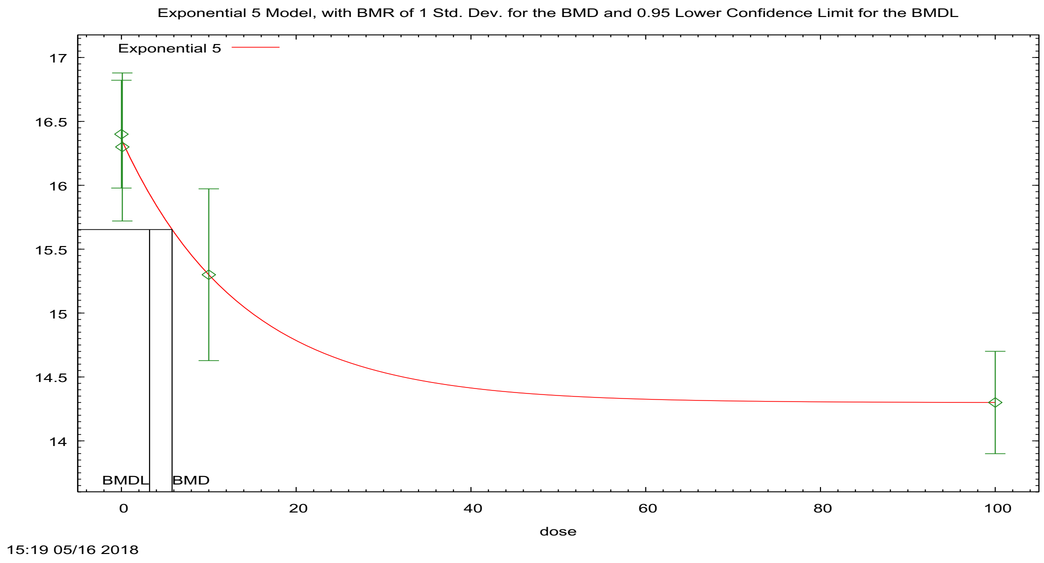

Figure 7. Plot of mean response by dose with fitted curve for Exponential (M5) model with constant variance for Hemoglobin in Males (90-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

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 in Males at 6 months (2-Year Rats)

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	Models that met inclusion criteria are presented (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). 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**	
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.

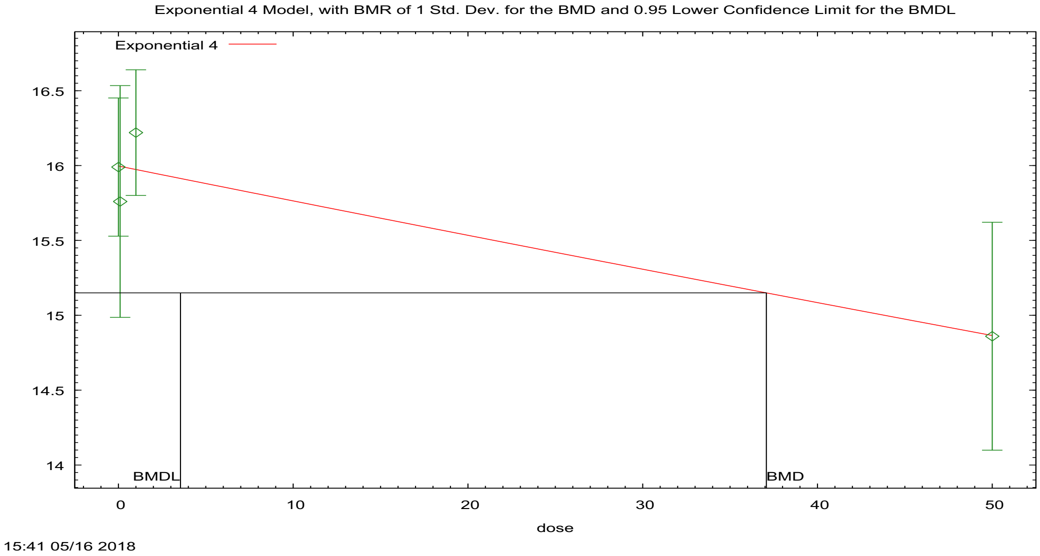

Figure 8. Plot of mean response by dose with fitted curve for Exponential (M4) model with constant variance for Hemoglobin in Males at 6 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

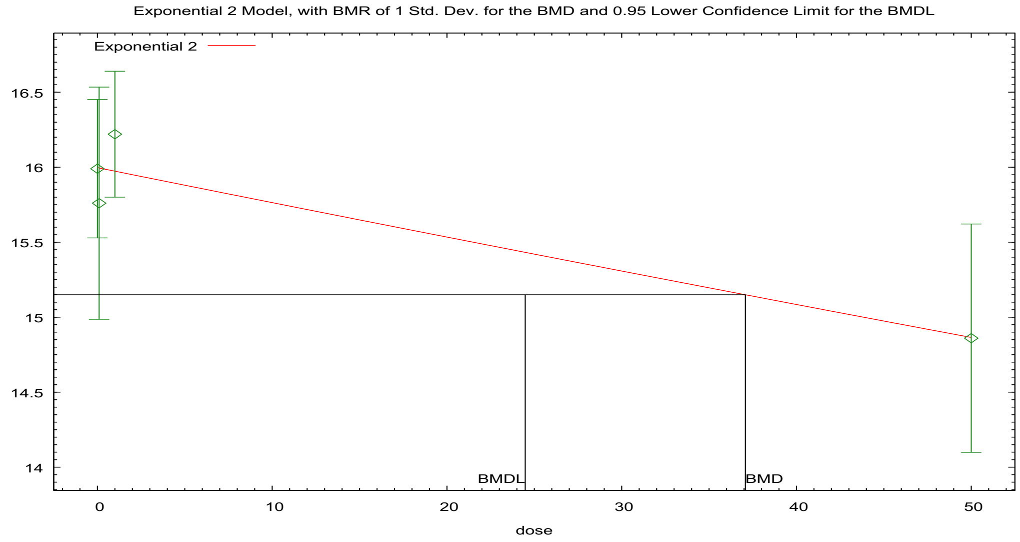

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Figure 9. Plot of mean response by dose with fitted curve for Exponential (M2) model with constant variance for Hemoglobin in Males at 6 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

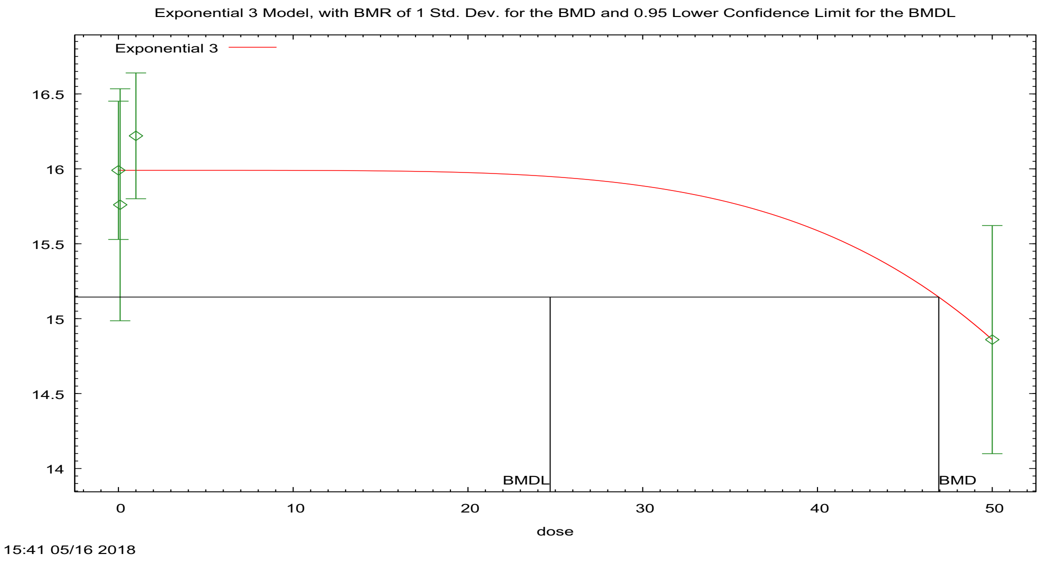

Figure 10. Plot of mean response by dose with fitted curve for Exponential (M3) model with constant variance for Hemoglobin in Males at 6 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

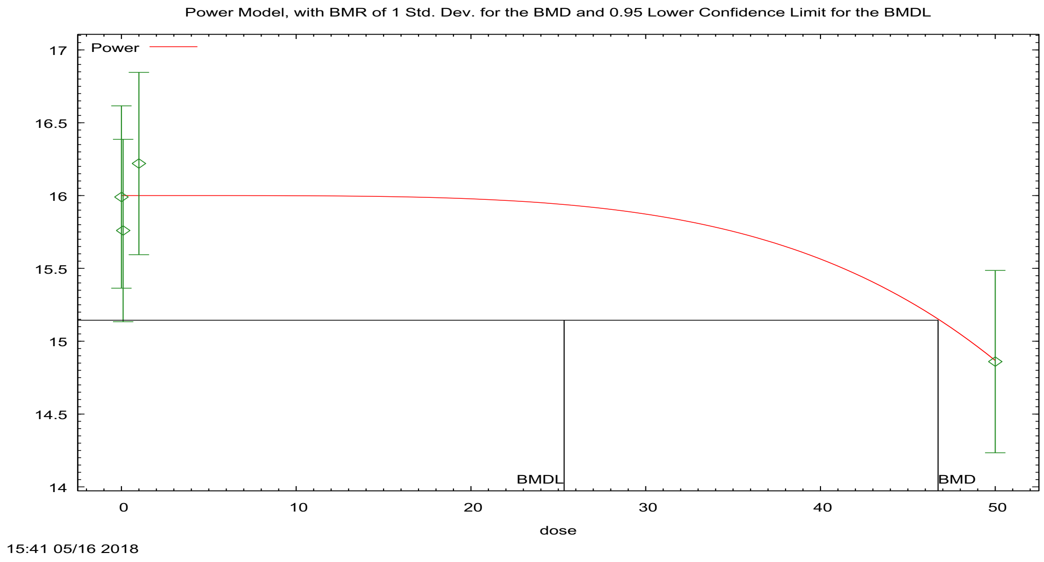

Figure 11. Plot of mean response by dose with fitted curve for Power model with constant variance for Hemoglobin in Males at 6 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

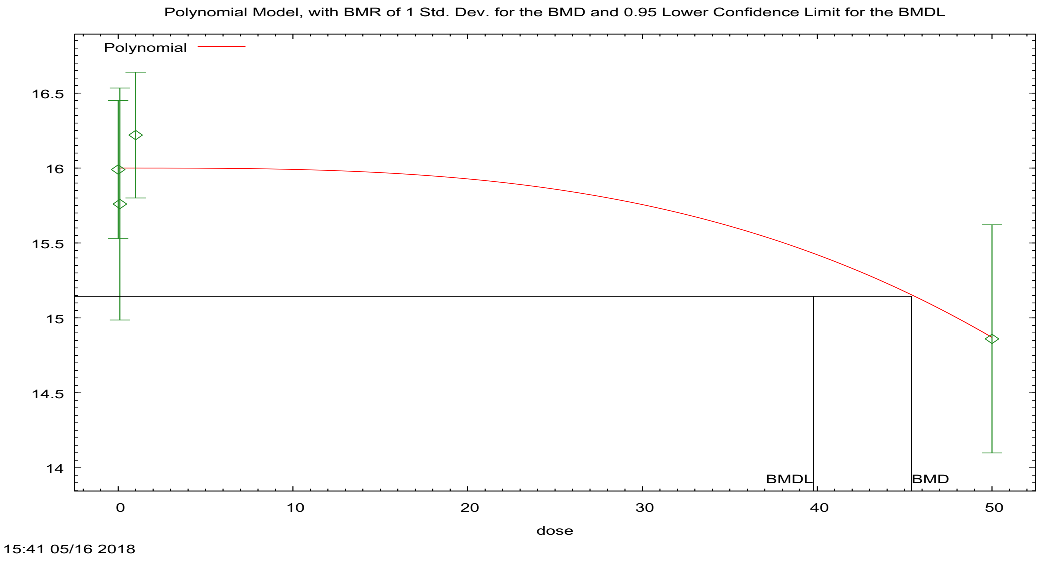

Figure 12. Plot of mean response by dose with fitted curve for Polynomial 3° model with constant variance for Hemoglobin in Males at 6 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

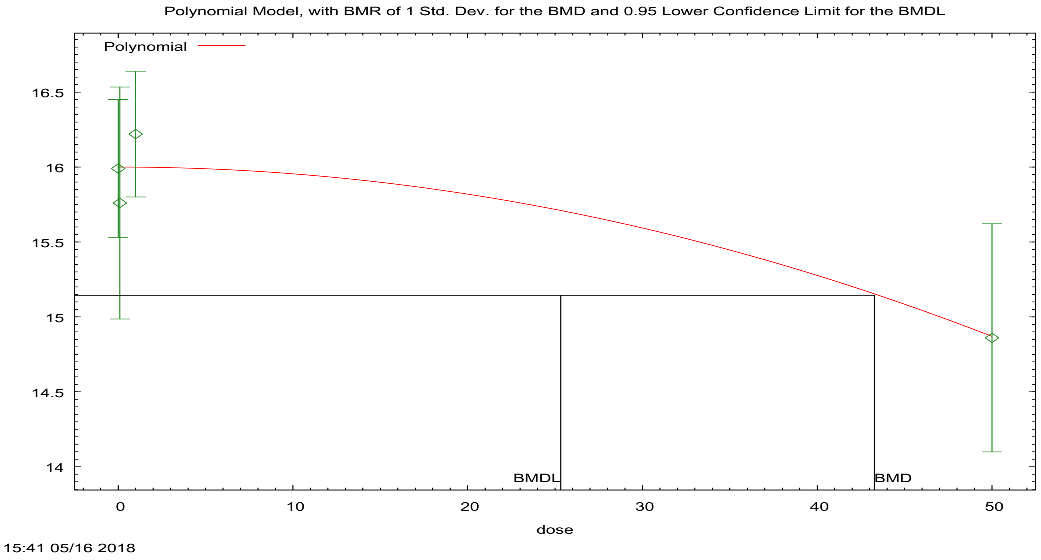

Figure 13. Plot of mean response by dose with fitted curve for Polynomial 2° model with constant variance for Hemoglobin in Males at 6 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

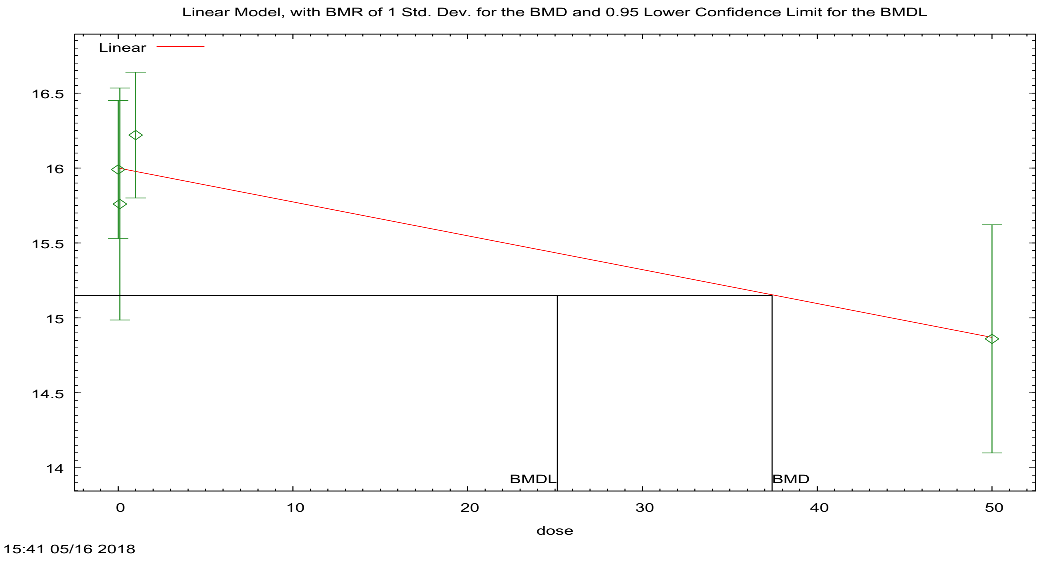

Figure 14. Plot of mean response by dose with fitted curve for Linear model with constant variance for Hemoglobin in Males at 6 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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 in Males (28-Day Mice)

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				
Hill	**0.416**	**63.876**	**0.122**	**0.00589**	**20.7**	**Only one model met inclusion criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)).**

[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.

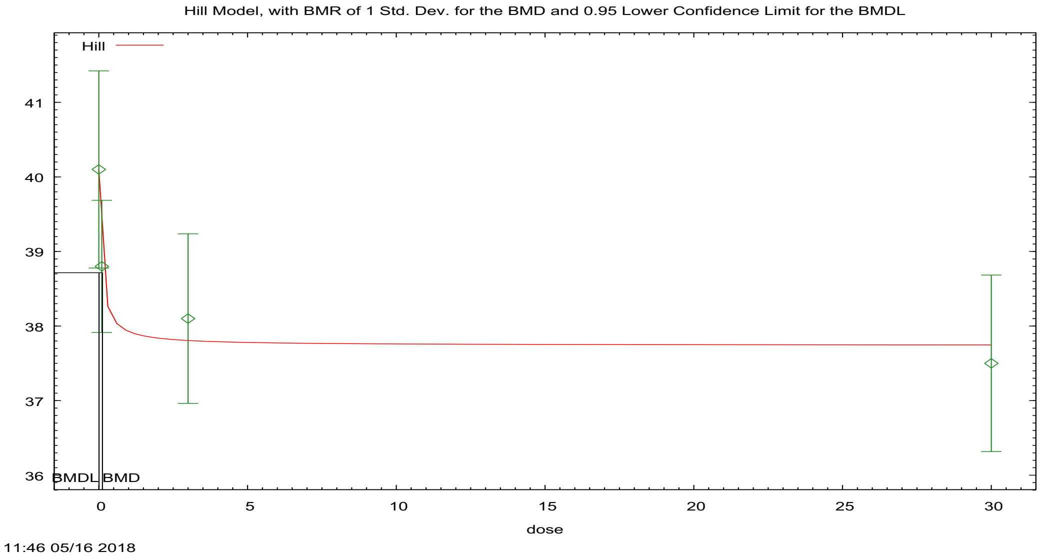
Hill Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

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Figure 15. 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

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 in Males (28-Day Rats)

Table 6. Summary of BMD Modeling Results for ; 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 (M4) Exponential (M5)[b]	0.53	77.289	1.76	0.738	2.39	Models that met inclusion criteria are presented (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). Selected BMDL is from model with lowest AIC and lowest BMDL.
Hill	**0.676**	**77.070**	**1.35**	**0.357**	**3.78**	

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

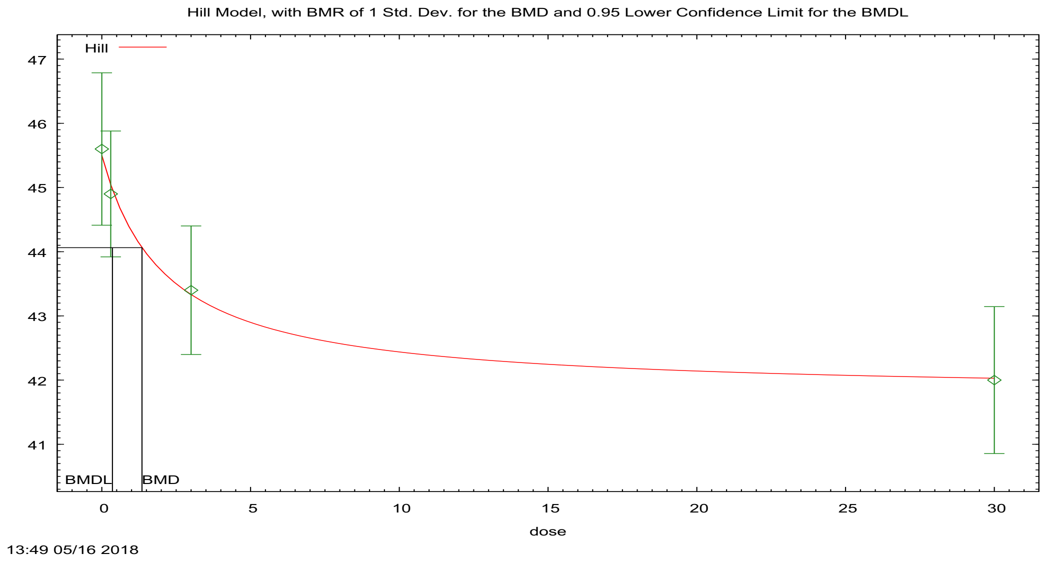

Figure 16. Plot of mean response by dose with fitted curve for Hill model with constant variance for Hematocrit in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

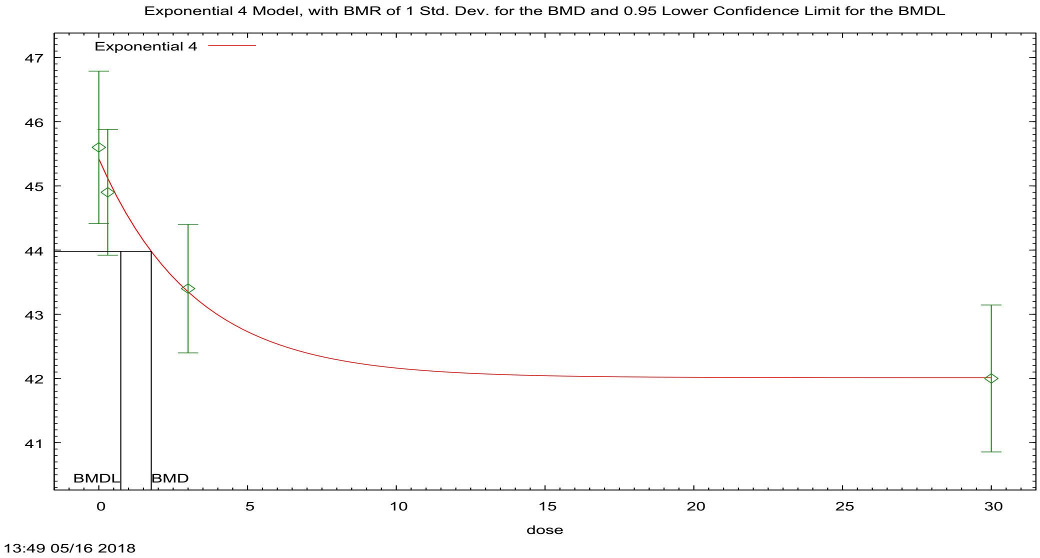

Figure 17. Plot of mean response by dose with fitted curve for Exponential (M4) model with constant variance for Hematocrit in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

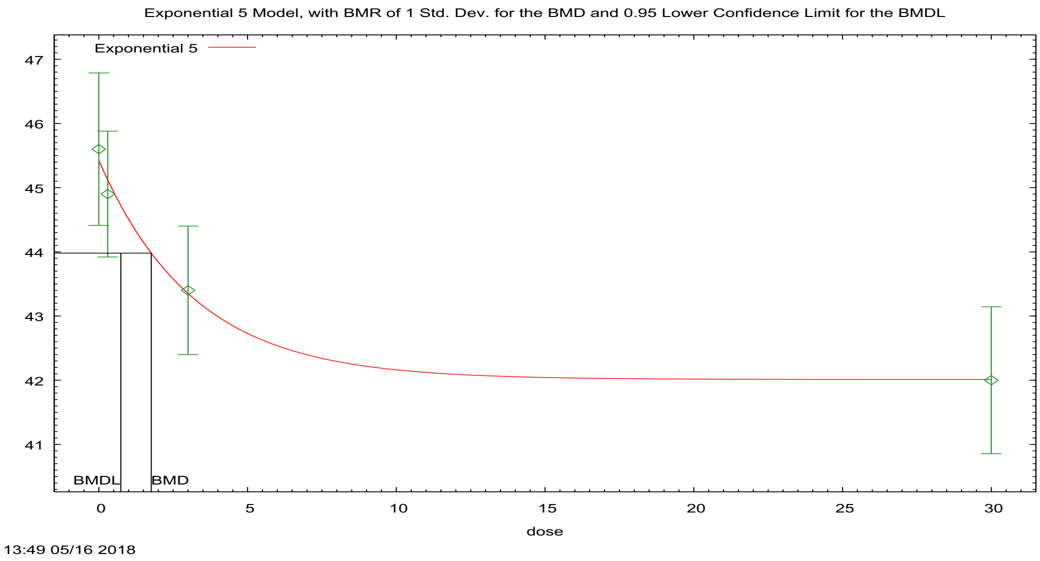

Figure 18. Plot of mean response by dose with fitted curve for Exponential (M5) model with constant variance for Hematocrit in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

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 in Males at 6 months (2-Year Rats)

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	Models that met inclusion criteria are presented (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). 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	
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.

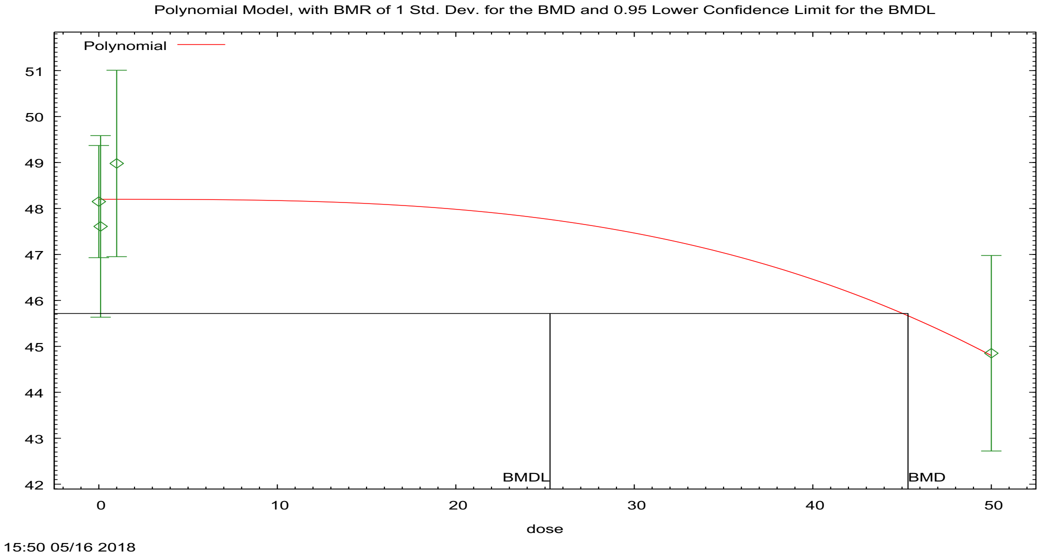

Figure 19. Plot of mean response by dose with fitted curve for Polynomial 3° model with constant variance for Hematocrit in Males at 6 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

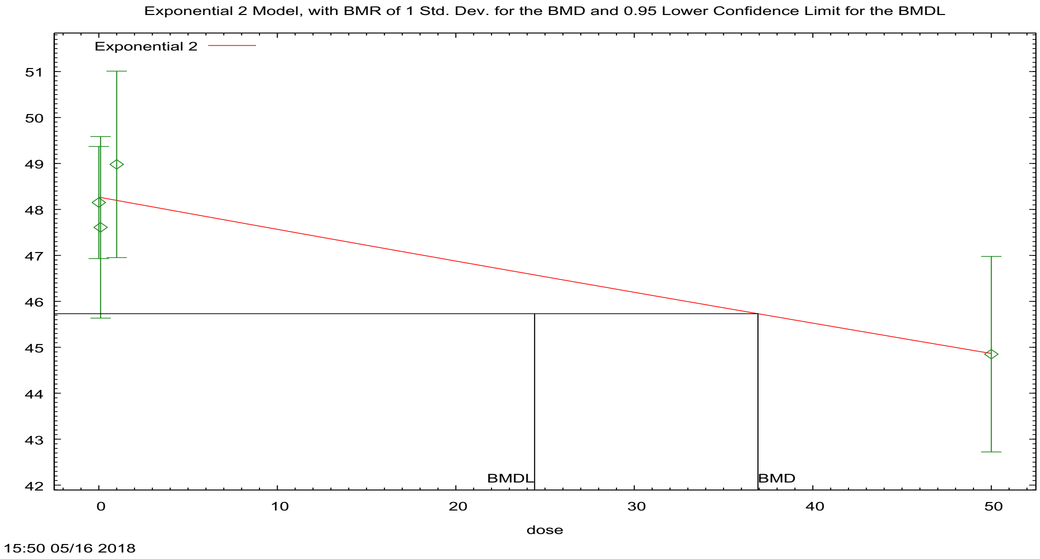

Figure 20. Plot of mean response by dose with fitted curve for Exponential (M2) model with constant variance for Hematocrit in Males at 6 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

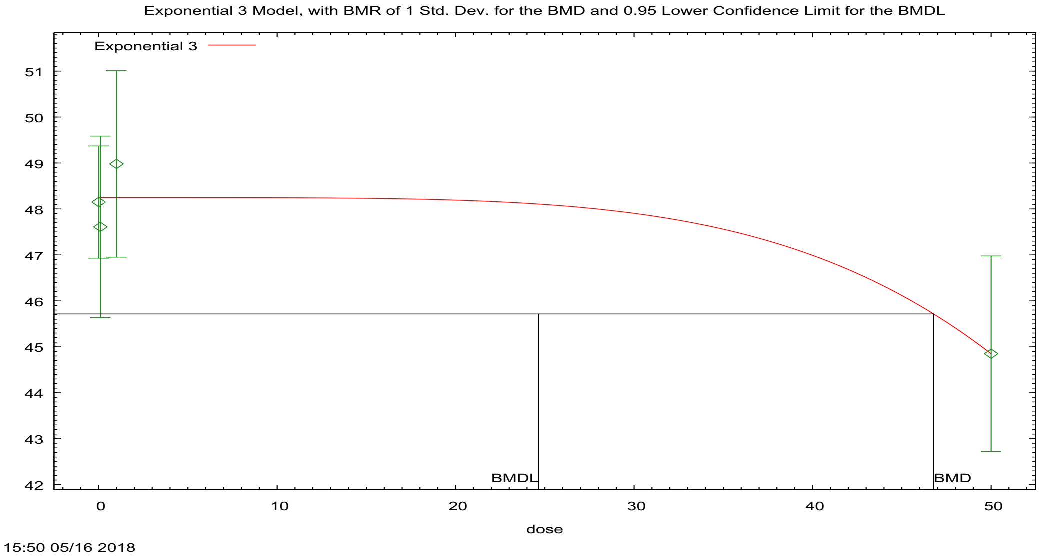

Figure 21. Plot of mean response by dose with fitted curve for Exponential (M3) model with constant variance for Hematocrit in Males at 6 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

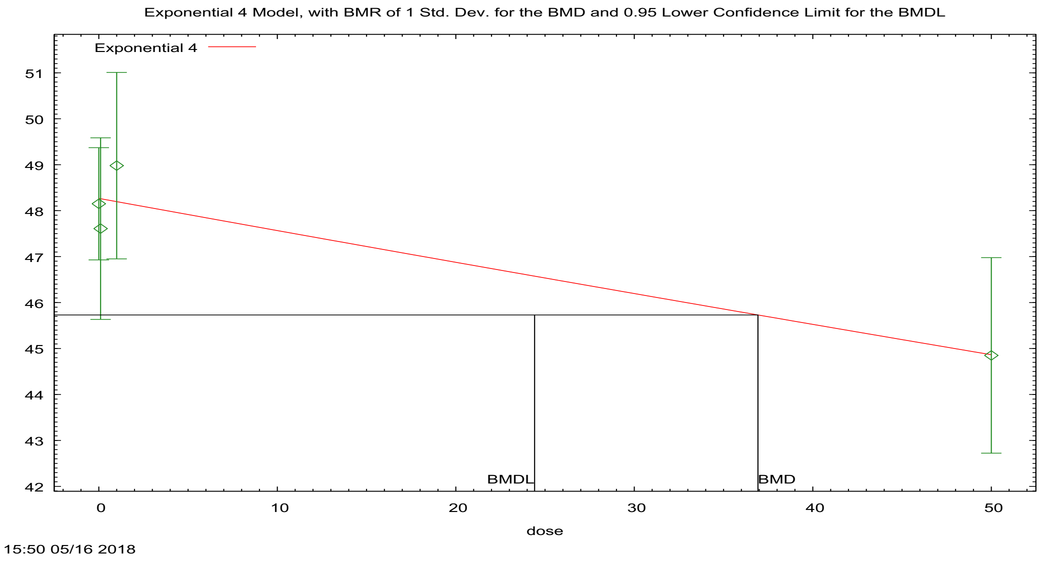

Figure 22. Plot of mean response by dose with fitted curve for Exponential (M4) model with constant variance for Hematocrit in Males at 6 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

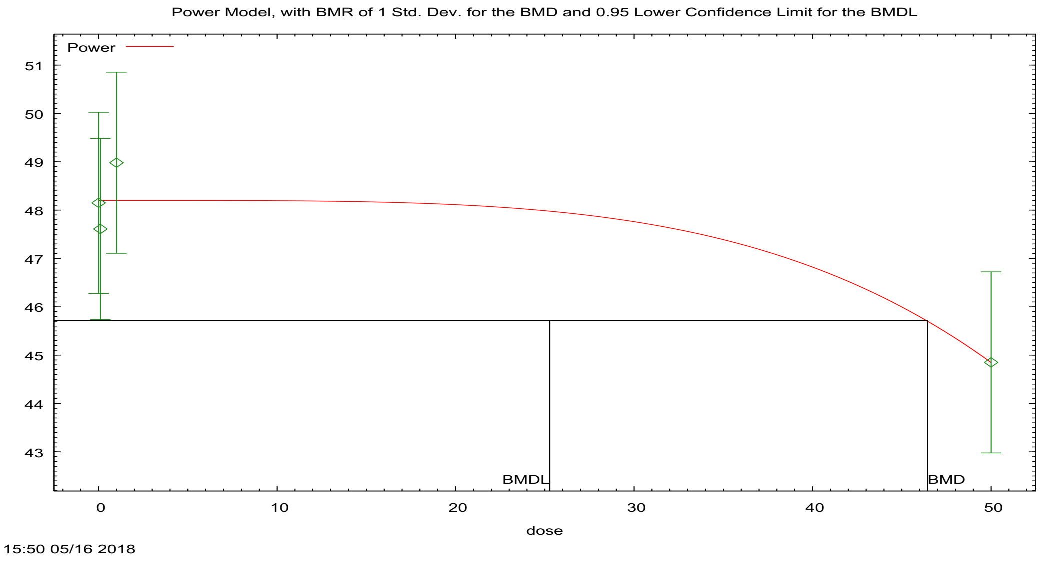

Figure 23. Plot of mean response by dose with fitted curve for Power model with constant variance for Hematocrit in Males at 6 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

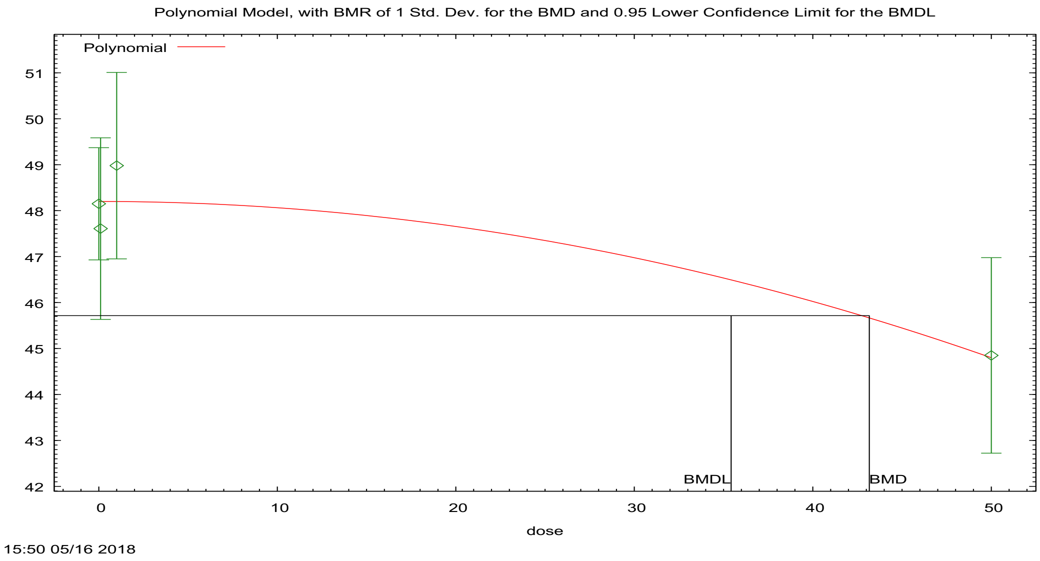

Figure 24. Plot of mean response by dose with fitted curve for Polynomial 2° model with constant variance for Hematocrit in Males at 6 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

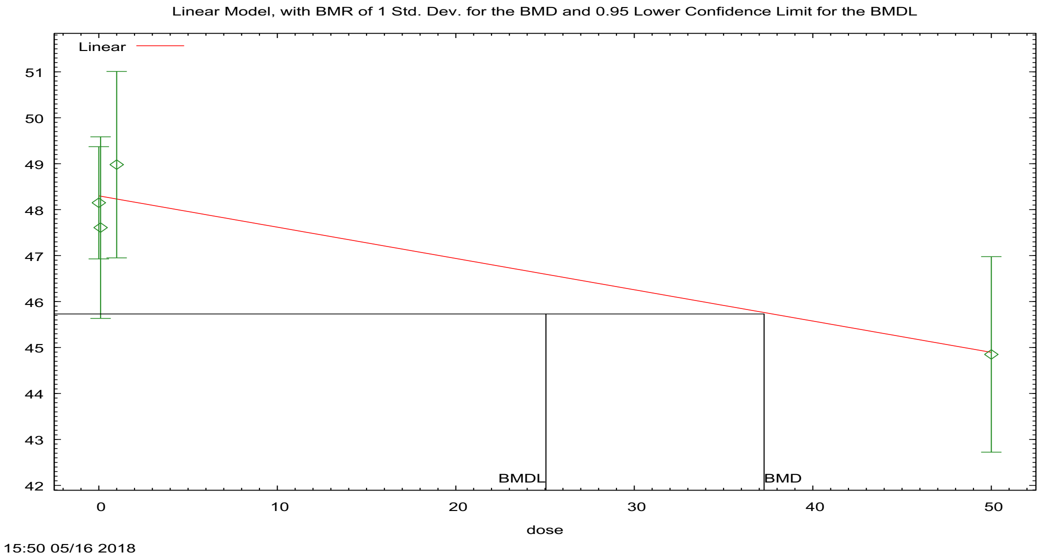

Figure 25. Plot of mean response by dose with fitted curve for Linear model with constant variance for Hematocrit in Males at 6 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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 in Males (28-Day Mice)

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 (M4) Exponential (M5)[b]	**0.999**	**-93.451**	**0.775**	**0.464**	**1.67**	**Only one model met inclusion criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)).**

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

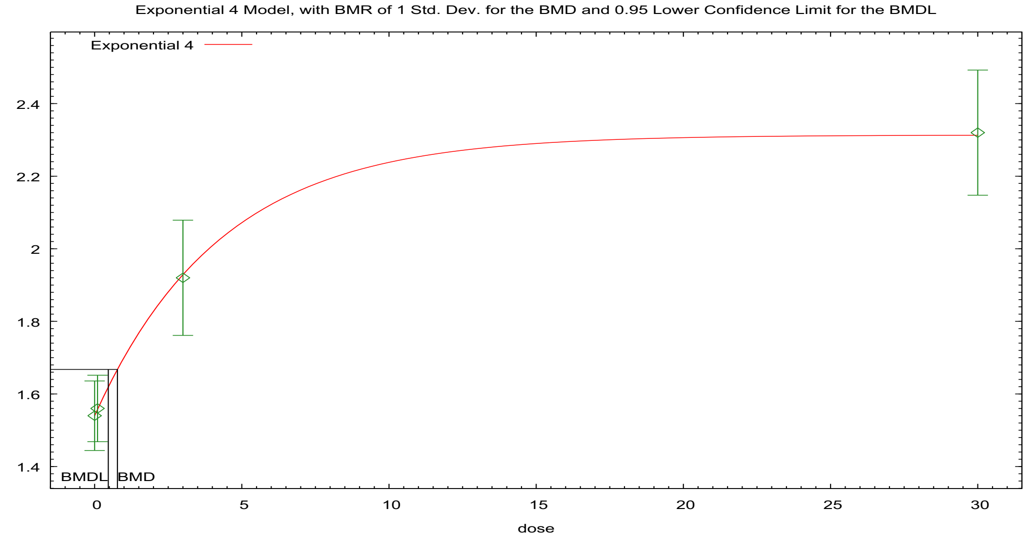

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Figure 26. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Albumin to Globulin Ratio in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

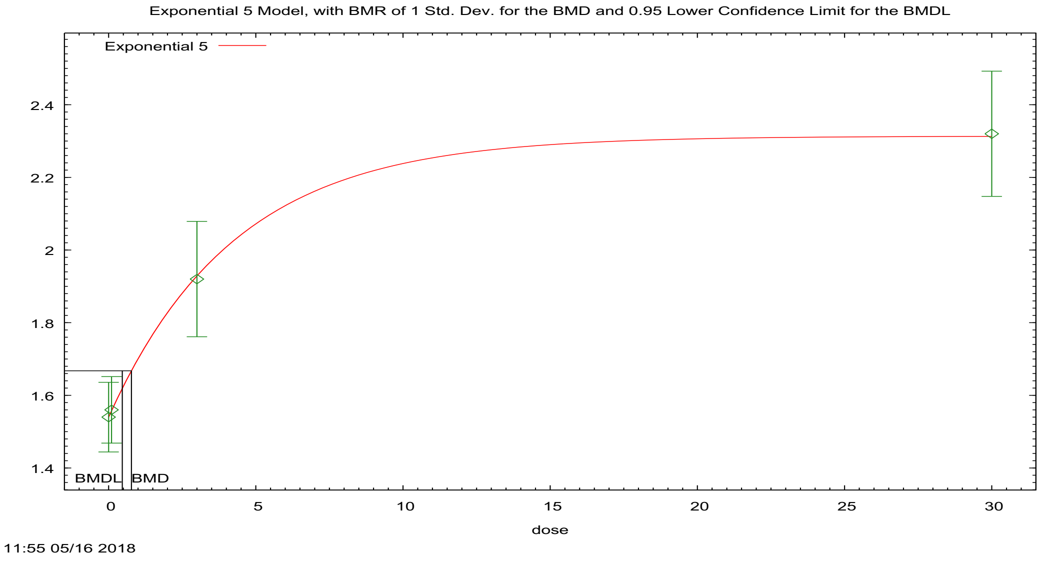

Figure 27. Plot of mean response by dose with fitted curve for Exponential (M5) model with modeled variance for Albumin to Globulin Ratio in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

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 in Females (28-Day Mice)

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 (M4) Exponential (M5)[b]	0.538	-109.00	1.42	0.863	1.64	Models that met inclusion criteria are presented (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). Selected BMDL is from model with lowest AIC and lowest BMDL.
Hill	**0.573**	**-109.07**	**1.22**	**0.595**	**2.04**	

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

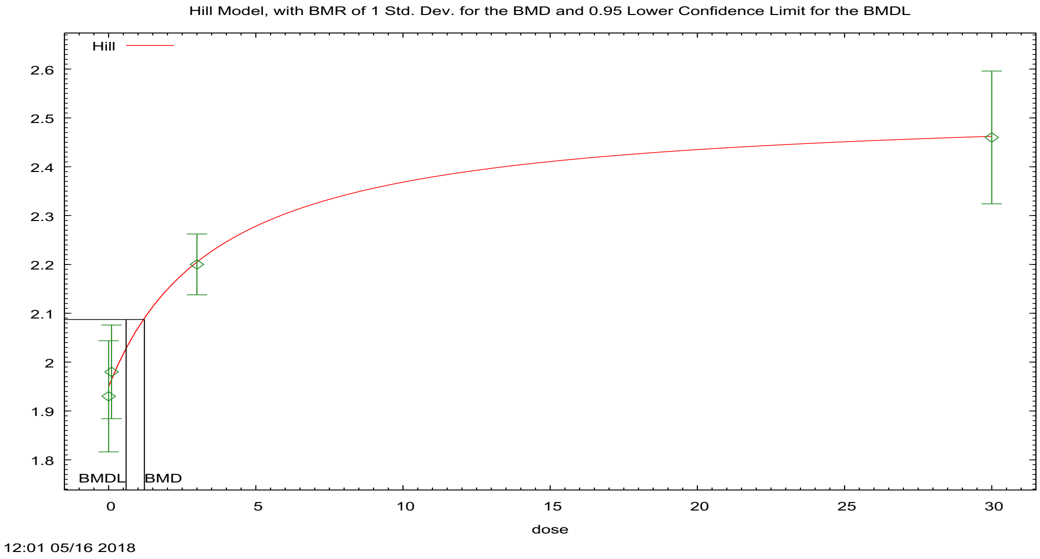

Figure 28. Plot of mean response by dose with fitted curve for Hill model with constant variance for Albumin to Globulin Ratio in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

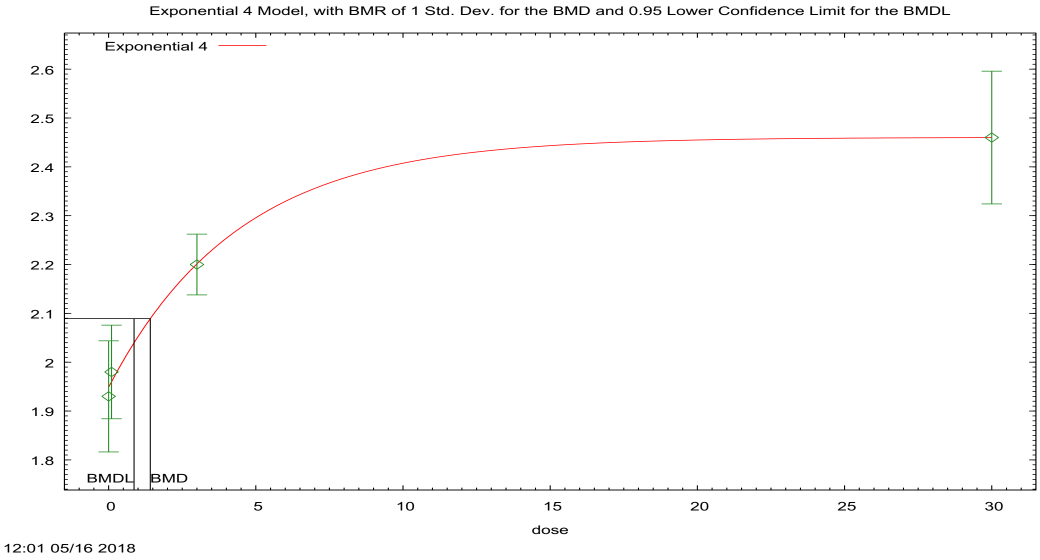

Figure 29. Plot of mean response by dose with fitted curve for Exponential (M4) model with constant variance for Albumin to Globulin Ratio in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

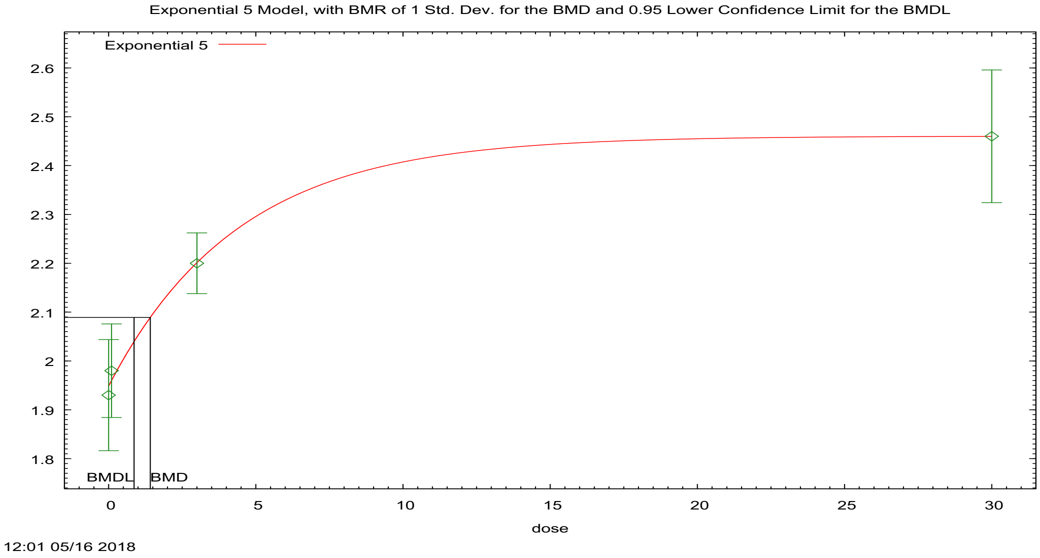

Figure 30. Plot of mean response by dose with fitted curve for Exponential (M5) model with constant variance for Albumin to Globulin Ratio in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

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 in Males (28-Day Rats)

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 (M4) Exponential (M5)[b]	0.511	-81.804	2.07	1.17	1.76	Models that met inclusion criteria are presented (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). Selected BMDL is from model with lowest AIC and lowest BMDL.
Hill	**0.544**	**-81.868**	**1.94**	**0.945**	**2.05**	

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

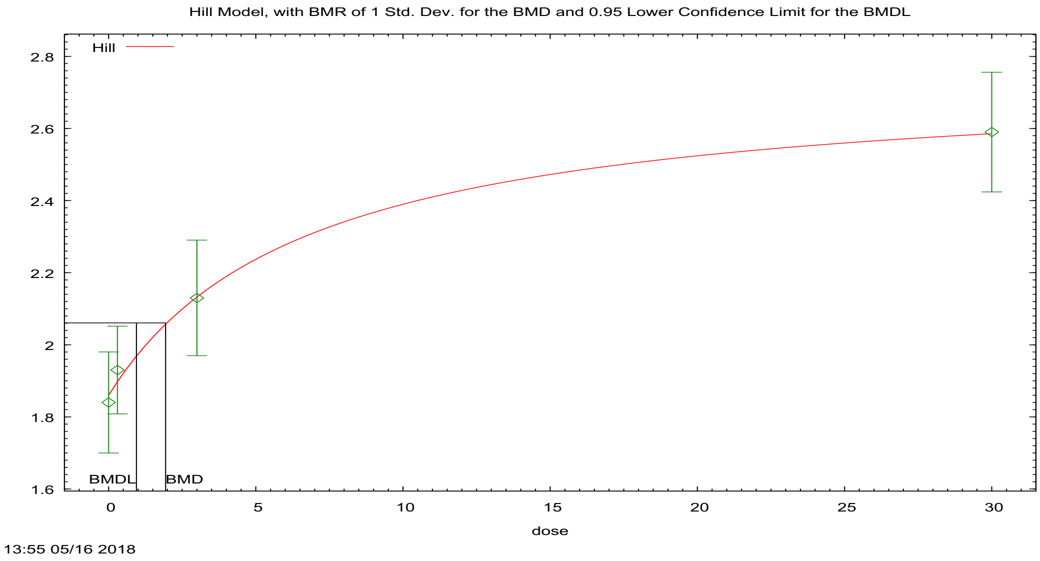

Figure 31. Plot of mean response by dose with fitted curve for Hill model with constant variance for Albumin to Globulin Ratio in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

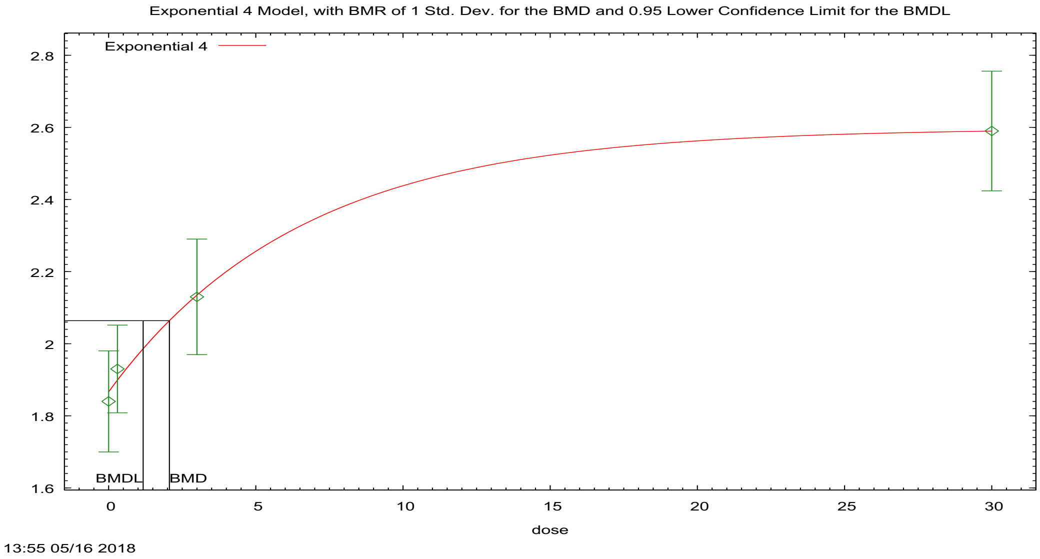

Figure 32. Plot of mean response by dose with fitted curve for Exponential (M4) model with constant variance for Albumin to Globulin Ratio in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

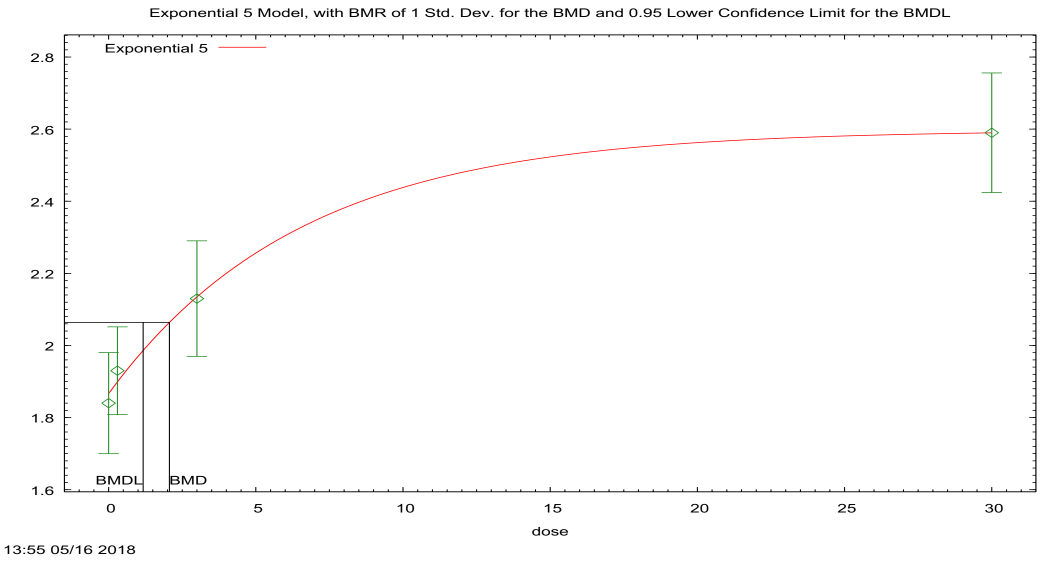

Figure 33. Plot of mean response by dose with fitted curve for Exponential (M5) model with constant variance for Albumin to Globulin Ratio in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

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 Ratio in Males (90-Day Rats)

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 (M4) **Exponential (M5)**[b]	**0.287**	**-65.584**	**3.39**	**0.0741**	**45.8**	**Only one model met inclusion criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)).**

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

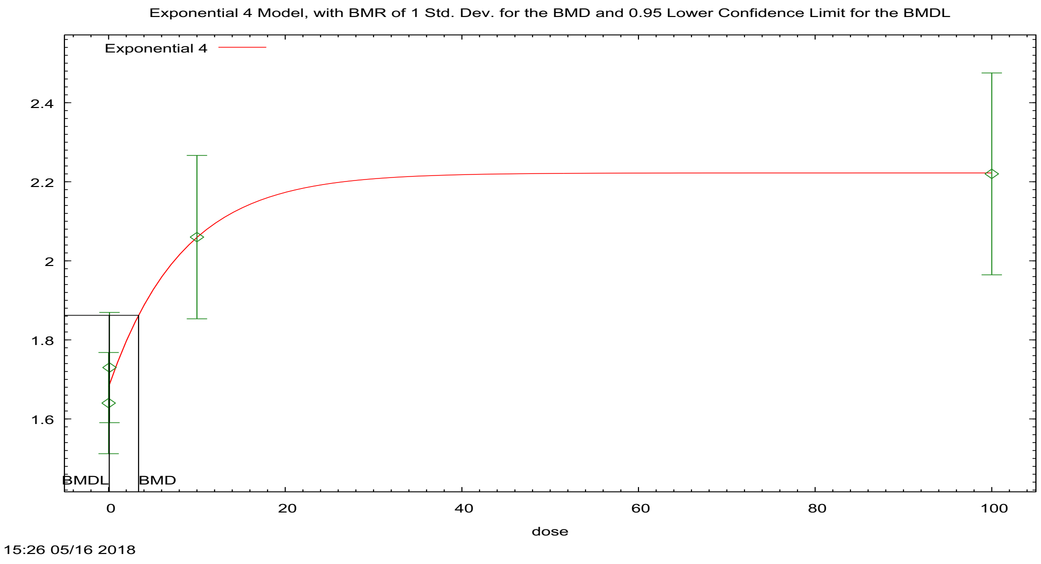

Figure 34. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Albumin to Globulin Ratio in Males (90-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

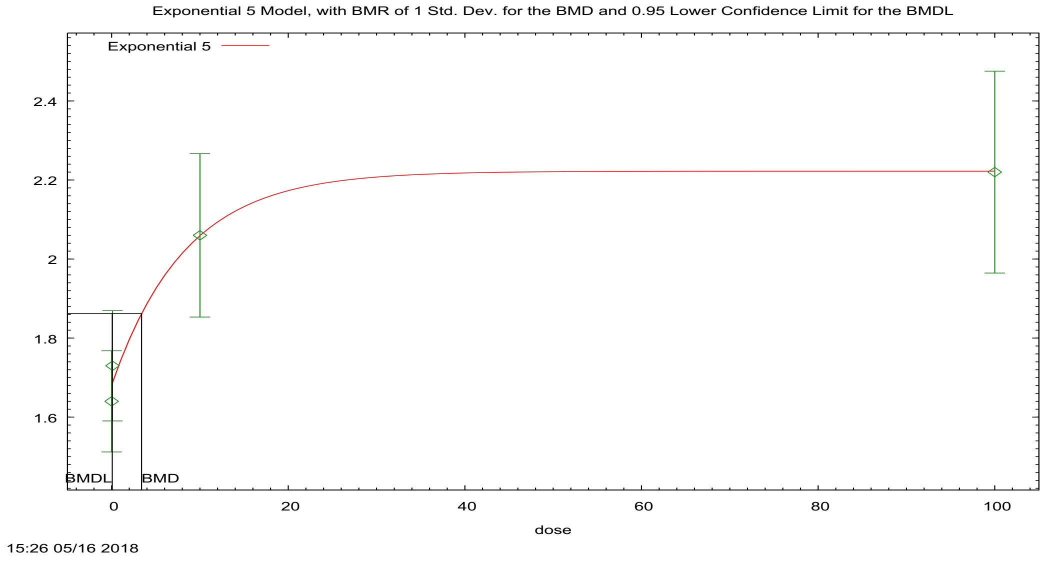

Figure 35. Plot of mean response by dose with fitted curve for Exponential (M5) model with modeled variance for Albumin to Globulin Ratio in Males (90-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

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

1.12. BMDS Summary of Alkaline Phosphatase in Females (28-Day Mice)

Table 12. 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**	**Models that met inclusion criteria are presented (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). 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	
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.

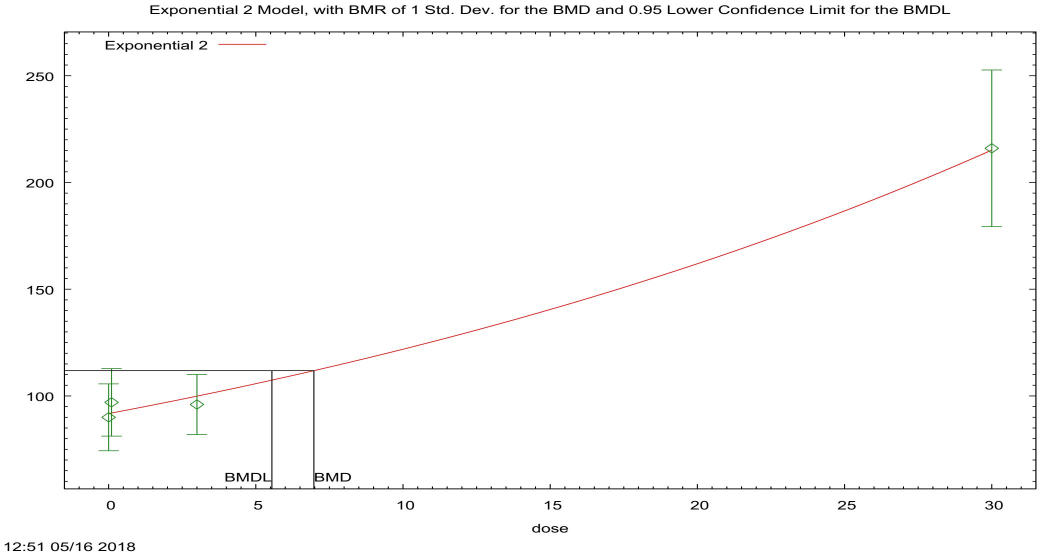

Figure 36. Plot of mean response by dose with fitted curve for Exponential (M2) model with modeled variance for Alkaline Phosphatase in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

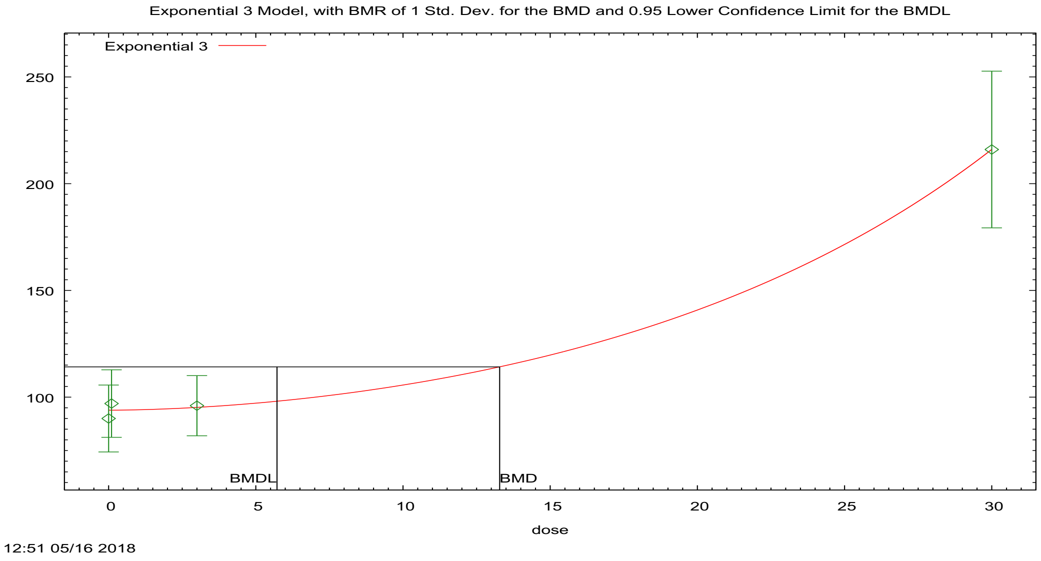

Figure 37. Plot of mean response by dose with fitted curve for Exponential (M3) model with modeled variance for Alkaline Phosphatase in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

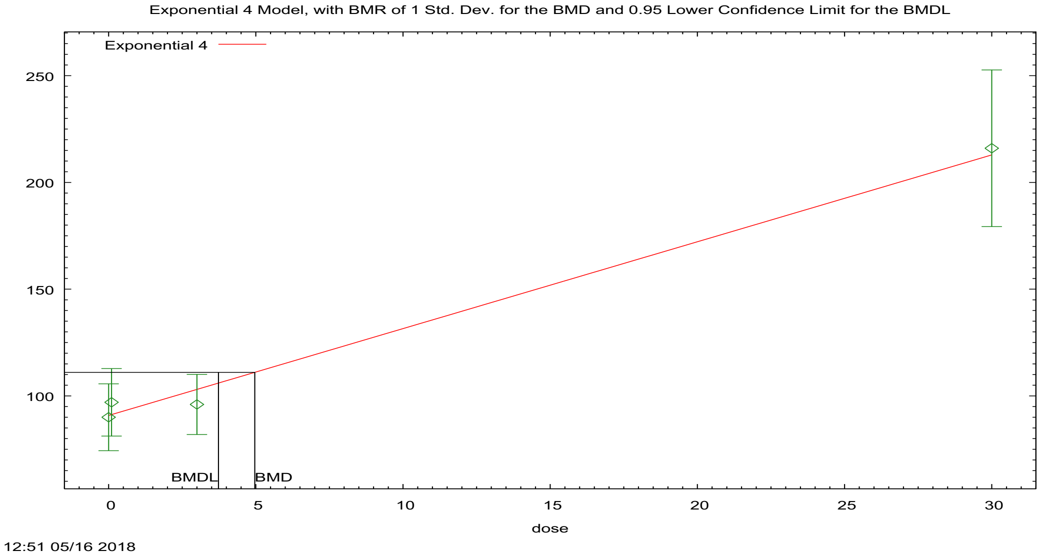

Figure 38. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Alkaline Phosphatase in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

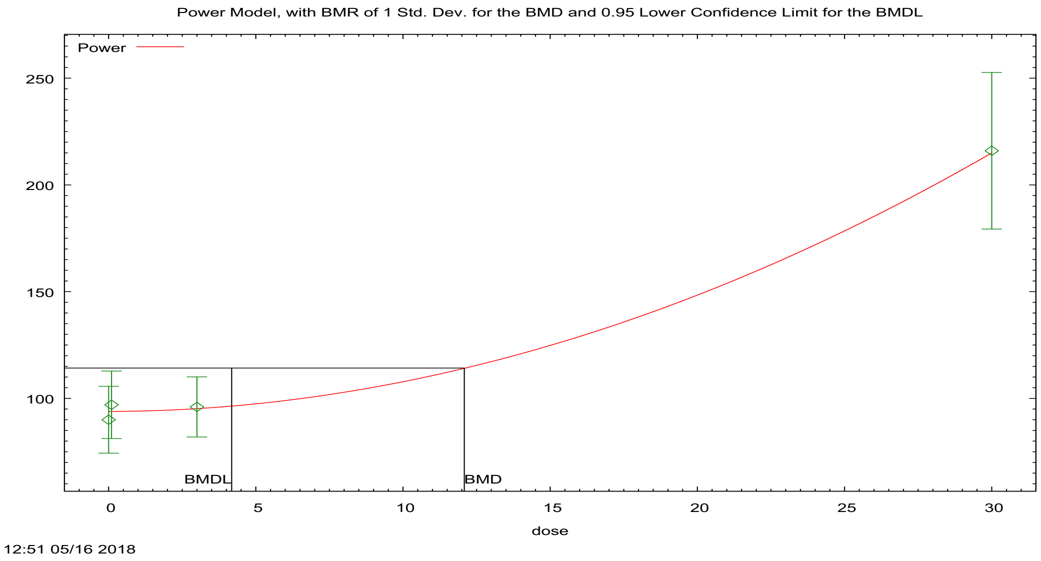

Figure 39. Plot of mean response by dose with fitted curve for Power model with modeled variance for Alkaline Phosphatase in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

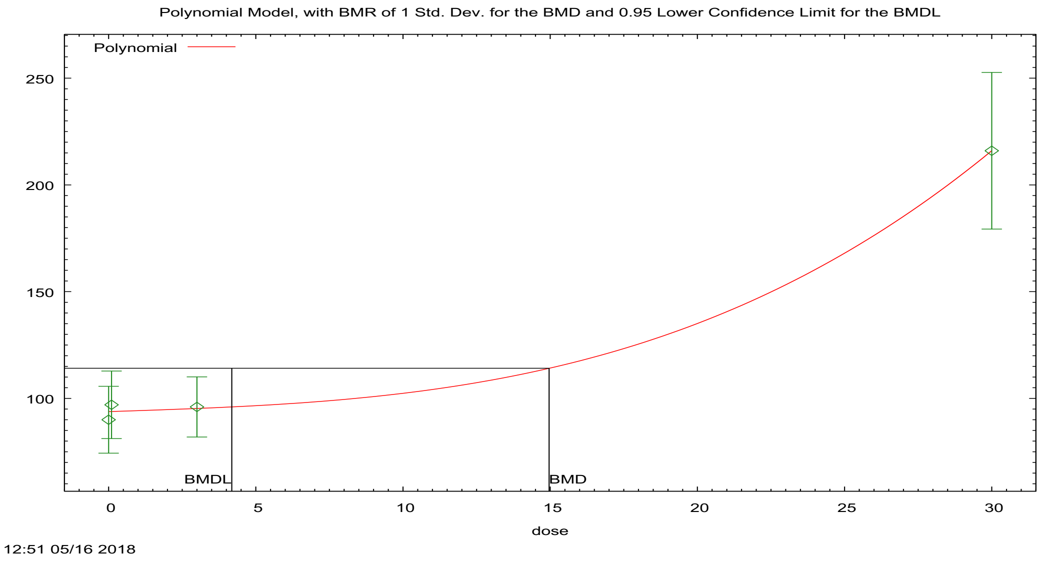

Figure 40. Plot of mean response by dose with fitted curve for Polynomial 3° model with modeled variance for Alkaline Phosphatase in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

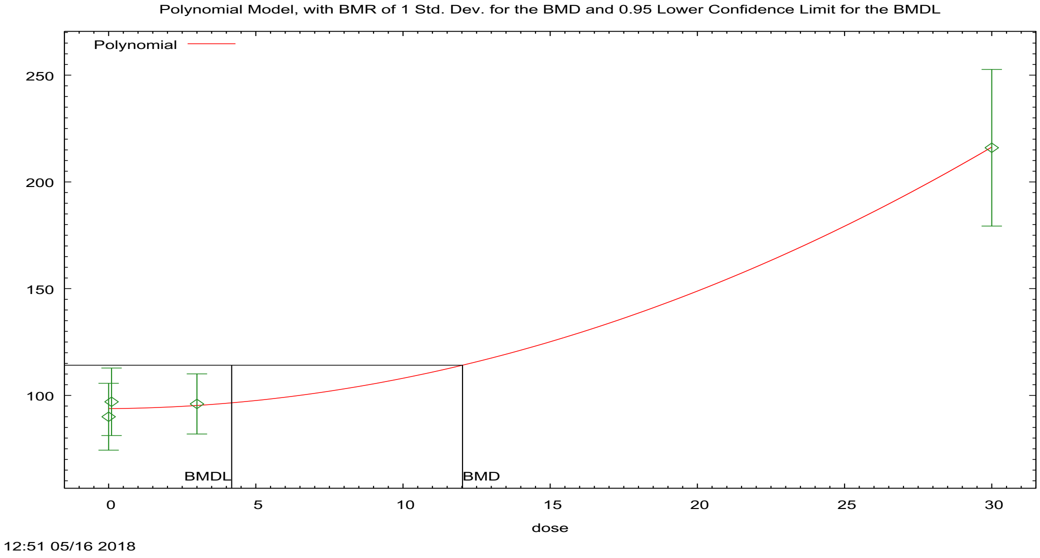

Figure 41. Plot of mean response by dose with fitted curve for Polynomial 2° model with modeled variance for Alkaline Phosphatase in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

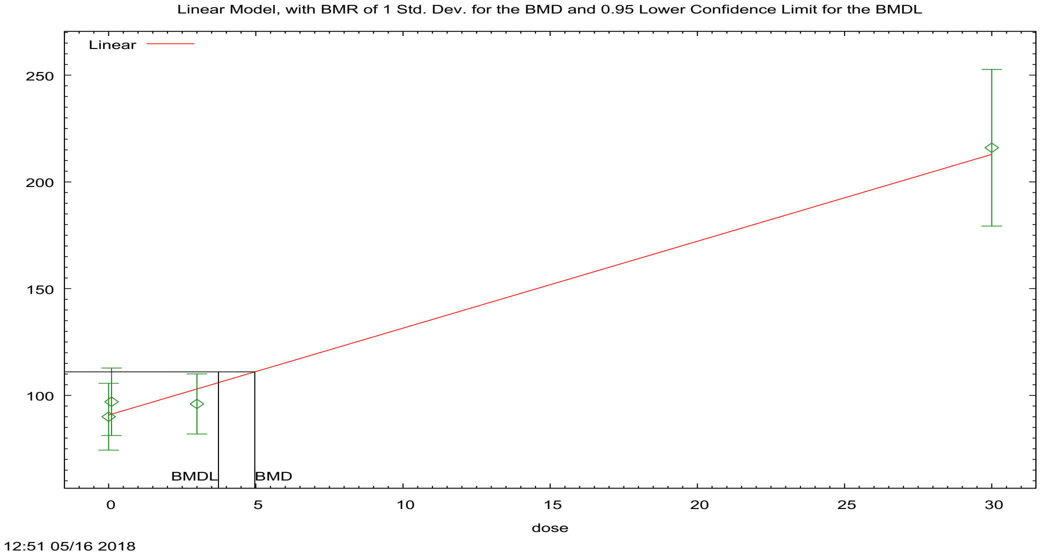

Figure 42. Plot of mean response by dose with fitted curve for Linear model with modeled variance for Alkaline Phosphatase in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

1.13. BMDS Summary of Alkaline Phosphatase in Males (90-Day Mice)

Table 13. 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**	**Models that met inclusion criteria are presented (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). BMDLs from included models were sufficiently close (< 3-fold difference), so the BMDL from the model with the lowest AIC was selected.**
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	

[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.

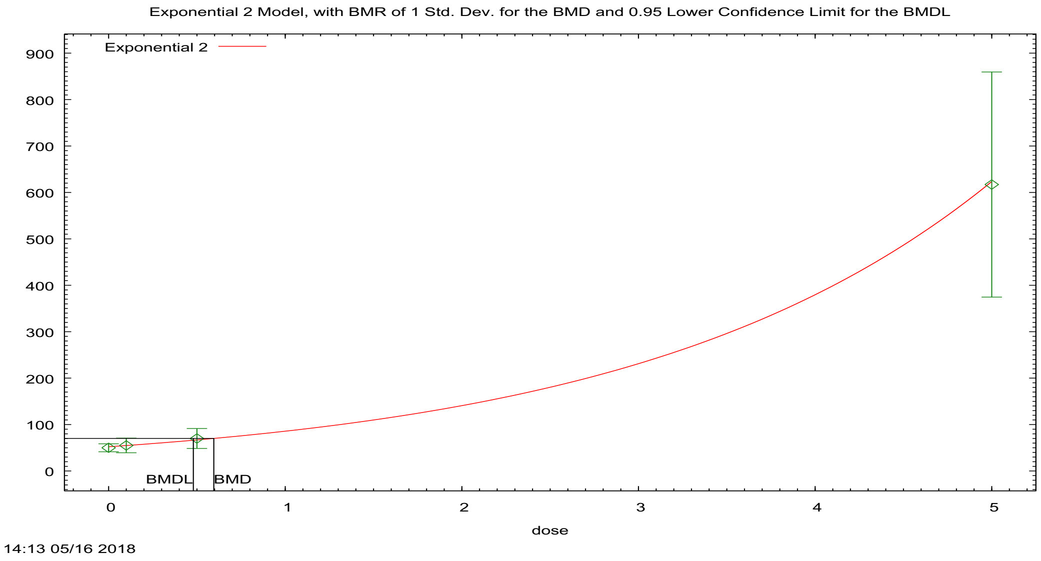

Figure 43. Plot of mean response by dose with fitted curve for Exponential (M2) model with modeled variance for Alkaline Phosphatase in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

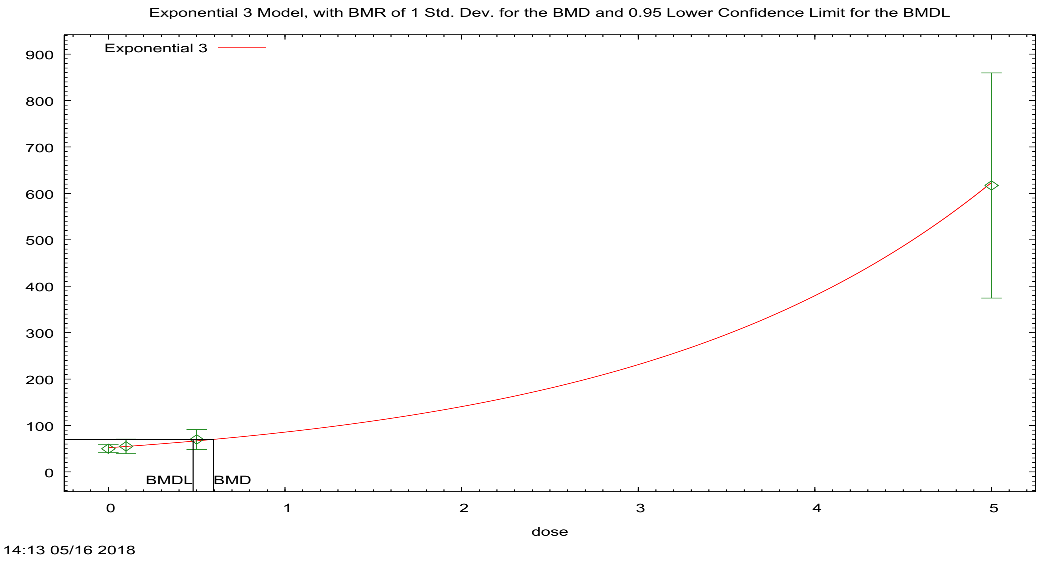

Figure 44. Plot of mean response by dose with fitted curve for Exponential (M3) model with modeled variance for Alkaline Phosphatase in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

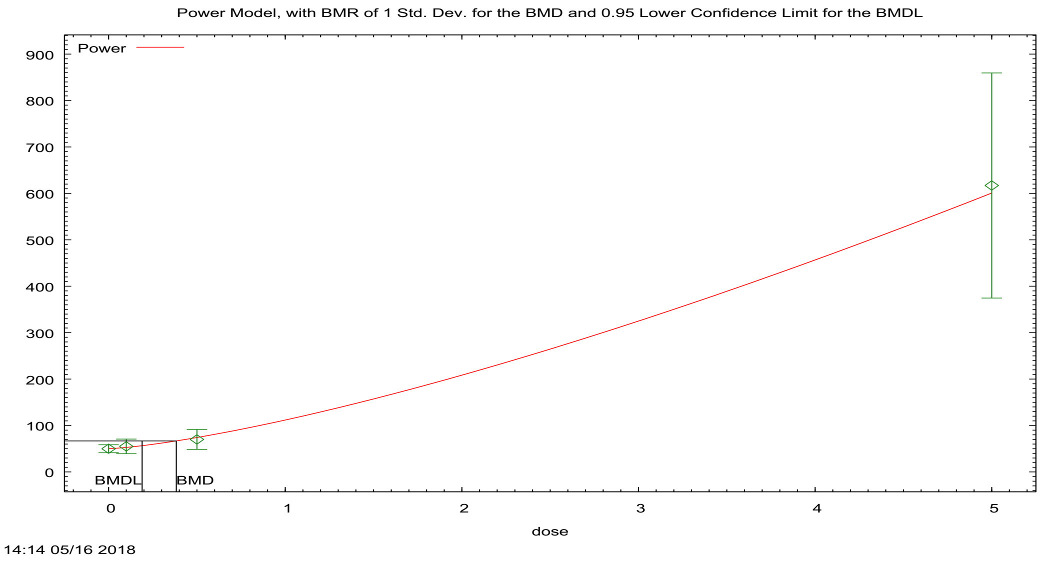

Figure 45. Plot of mean response by dose with fitted curve for Power model with modeled variance for Alkaline Phosphatase in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

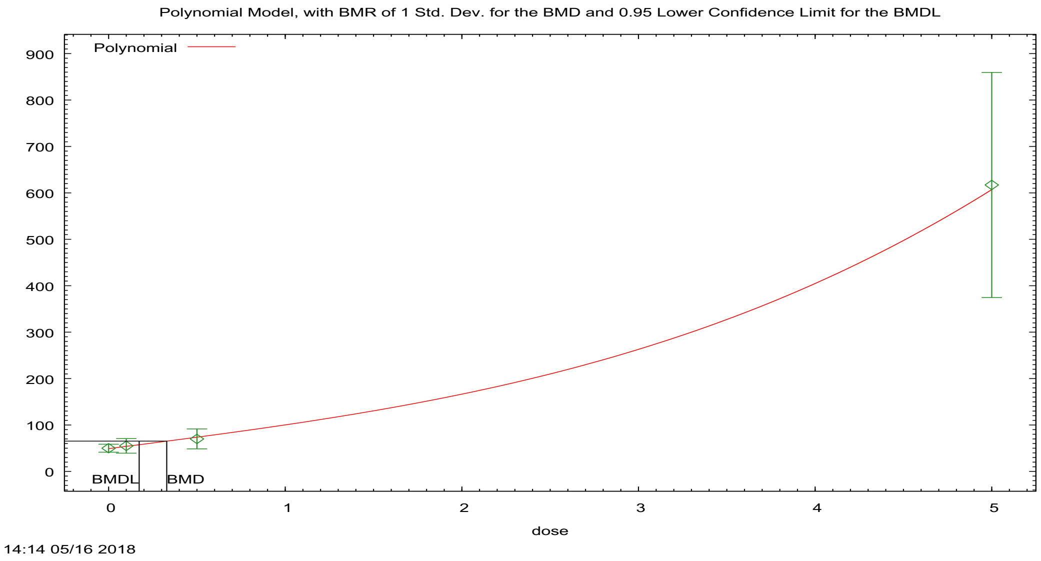

Figure 46. Plot of mean response by dose with fitted curve for Polynomial 3° model with modeled variance for Alkaline Phosphatase in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

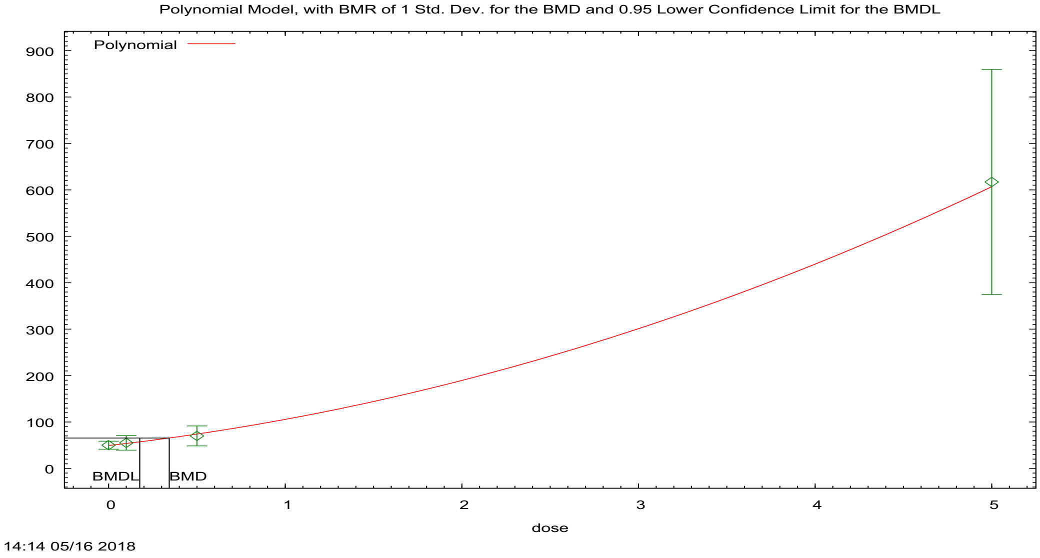

Figure 47. Plot of mean response by dose with fitted curve for Polynomial 2° model with modeled variance for Alkaline Phosphatase in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

BMDS WIZARD OUTPUT REPORT

BMDS Summary of H-28548: Subchronic Toxicity 90-Day Gavage Study in Mice – Alkaline Phosphatase (U/L) in Females

1.14. BMDS Summary of Alkaline Phosphatase in Females (90-Day Mice)

Table 14. 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	Models that met inclusion criteria are presented (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). 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	
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.

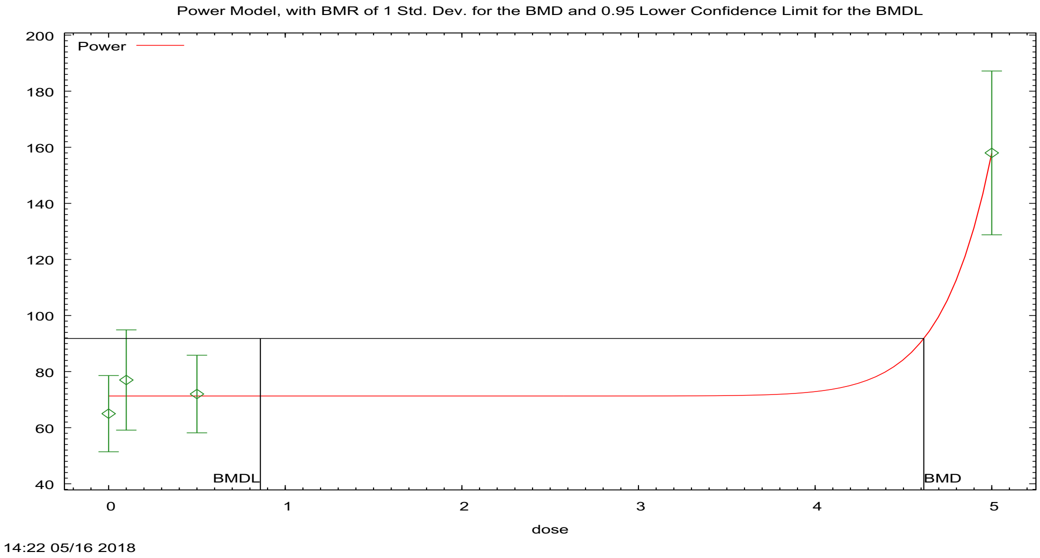

Figure 48. Plot of mean response by dose with fitted curve for Power model with modeled variance for Alkaline Phosphatase in Females (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

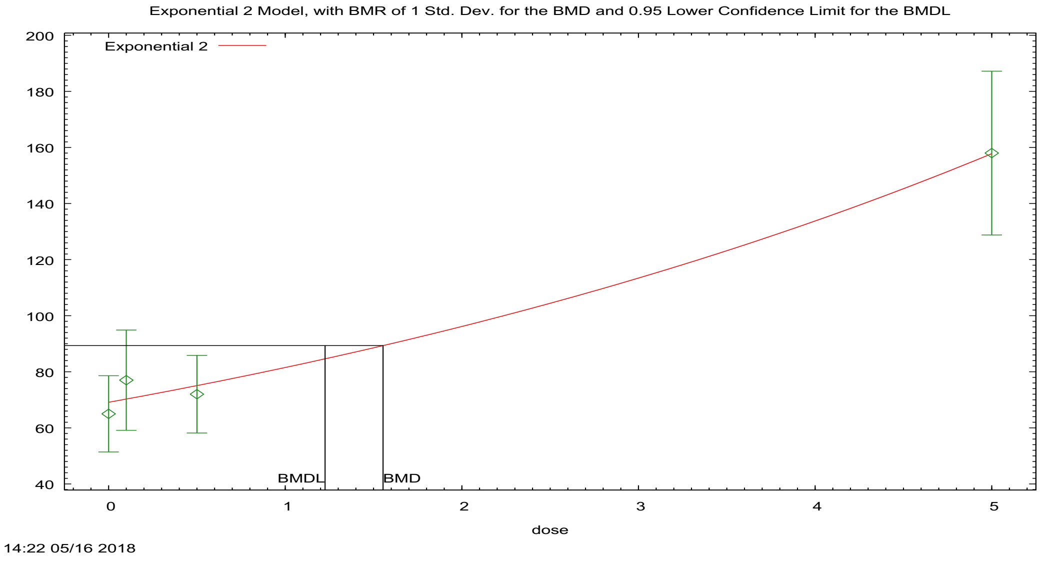

Figure 49. Plot of mean response by dose with fitted curve for Exponential (M2) model with modeled variance for Alkaline Phosphatase in Females (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

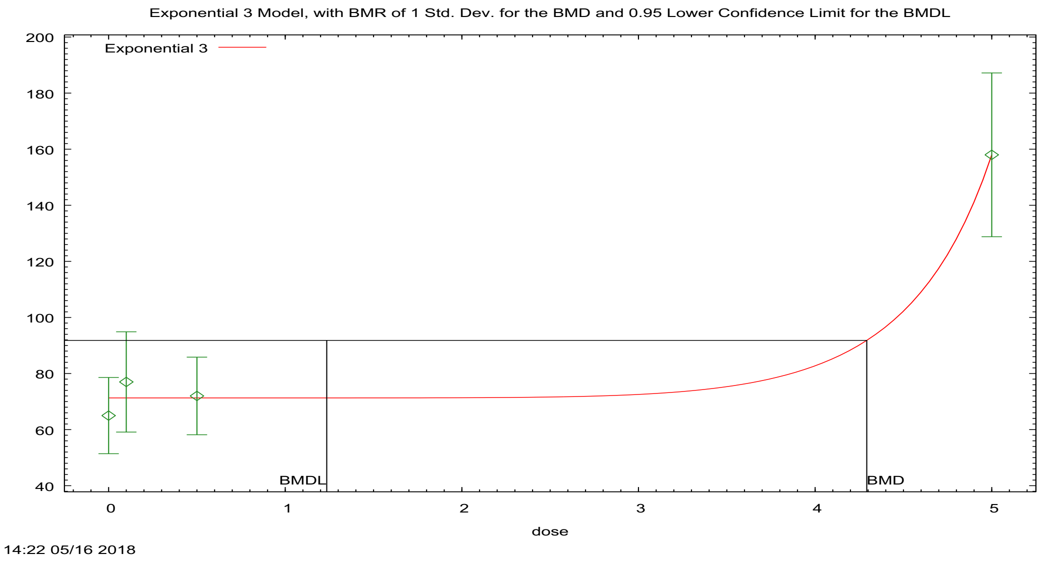

Figure 50. Plot of mean response by dose with fitted curve for Exponential (M3) model with modeled variance for Alkaline Phosphatase in Females (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

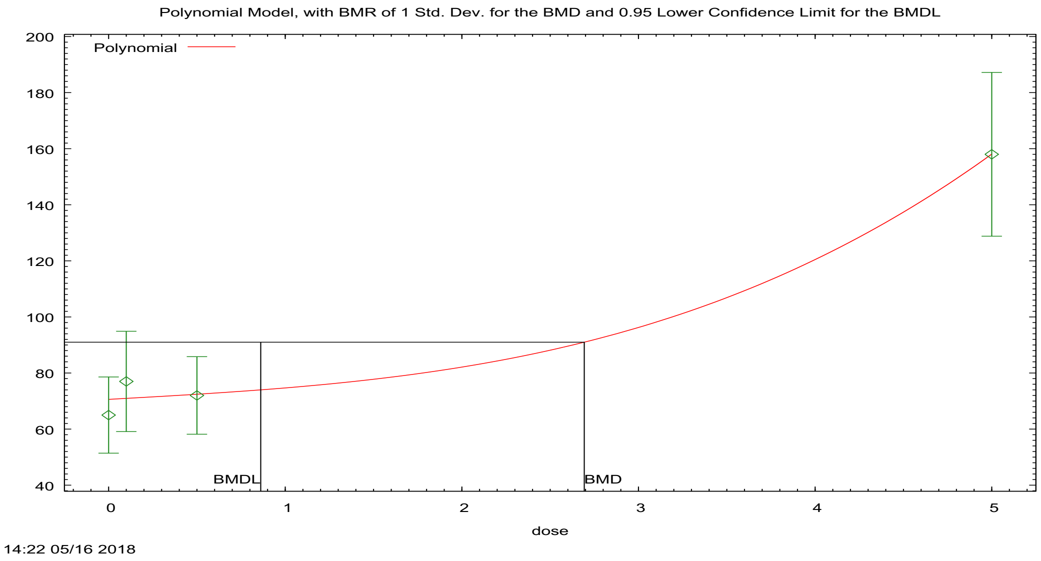

Figure 51. Plot of mean response by dose with fitted curve for Polynomial 3° model with modeled variance for Alkaline Phosphatase in Females (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

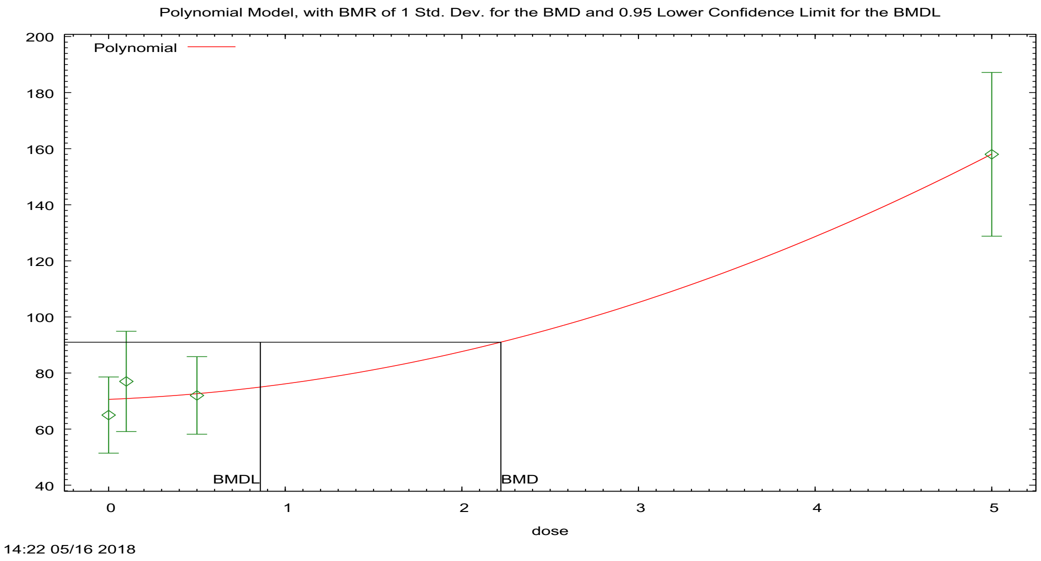

Figure 52. Plot of mean response by dose with fitted curve for Polynomial 2° model with modeled variance for Alkaline Phosphatase in Females (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

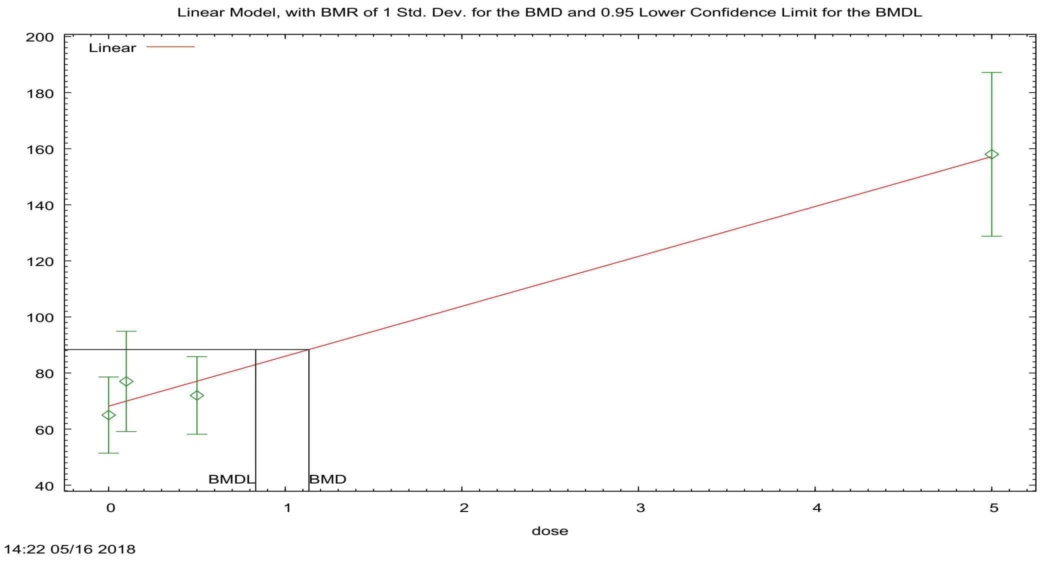

Figure 53. Plot of mean response by dose with fitted curve for Linear model with modeled variance for Alkaline Phosphatase in Females (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

1.15. BMDS Summary of Alkaline Phosphatase in Males (90-Day Rats)

Table 15. 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 (M4)	**0.952**	**295.55**	**2.66**	**1.43**	**1.86**	**Only one model met inclusion criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)).**

[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.

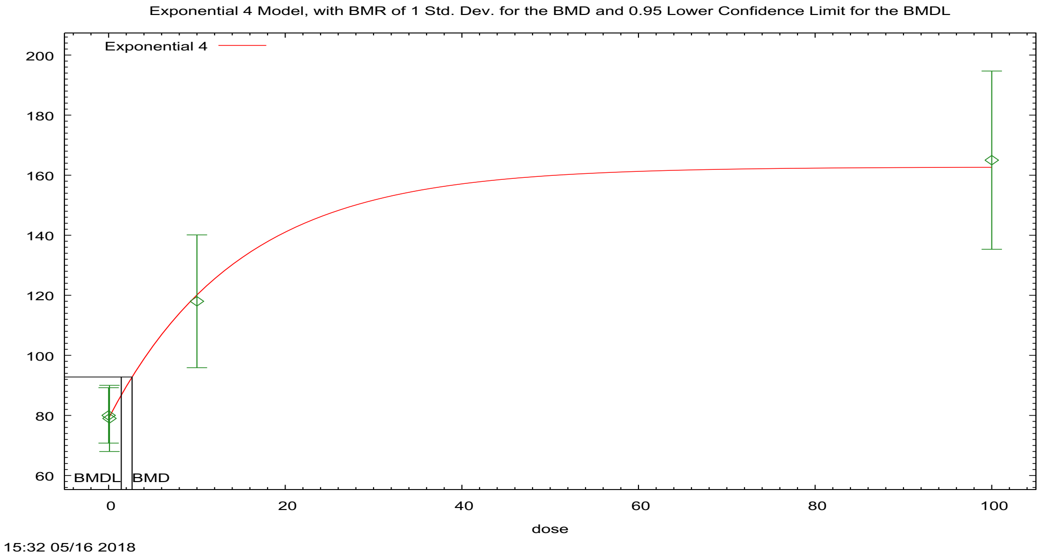

Figure 54. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Alkaline Phosphatase in Males (90-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

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

1.16. BMDS Summary of Aspartate Aminotransferase in Males (28-Day Mice)

Table 16. 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	Models that met inclusion criteria are presented (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). Selected BMDL is from model with lowest AIC and lowest BMDL.
Exponential (M4)	0.538	340.80	1.69	1.18	1.44	
Power	0.657	340.61	1.99	1.19	1.67	
Polynomial 3°[c] 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] 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.

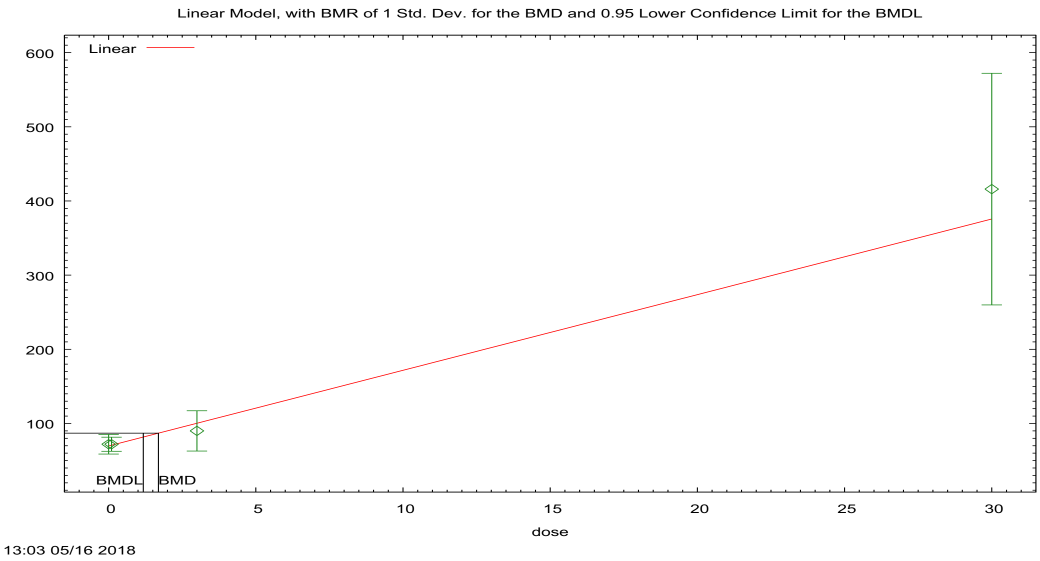

Figure 55. Plot of mean response by dose with fitted curve for Linear model with modeled variance for Aspartate Aminotransferase in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

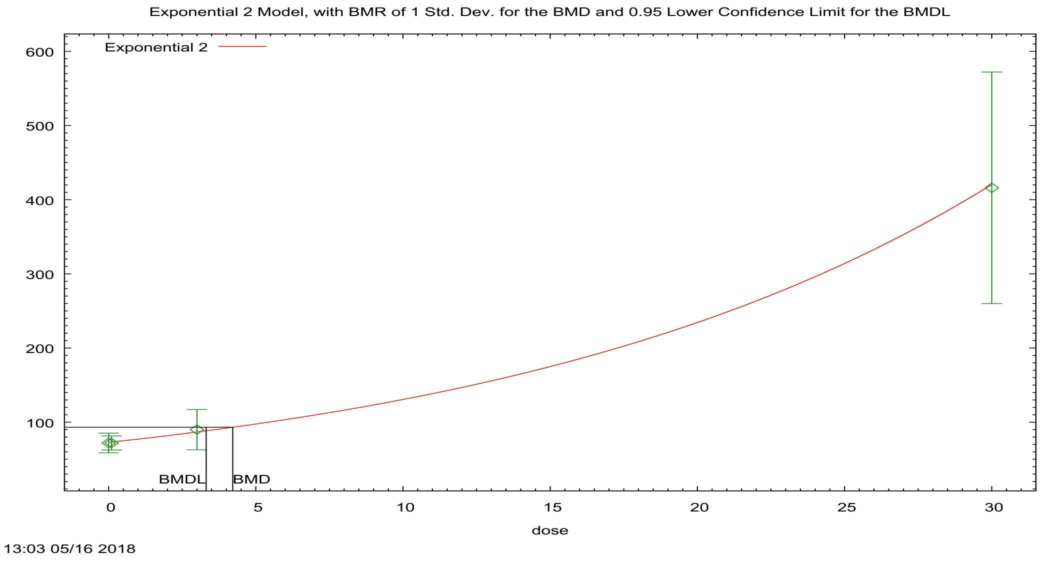

Figure 56. Plot of mean response by dose with fitted curve for Exponential (M2) model with modeled variance for Aspartate Aminotransferase in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

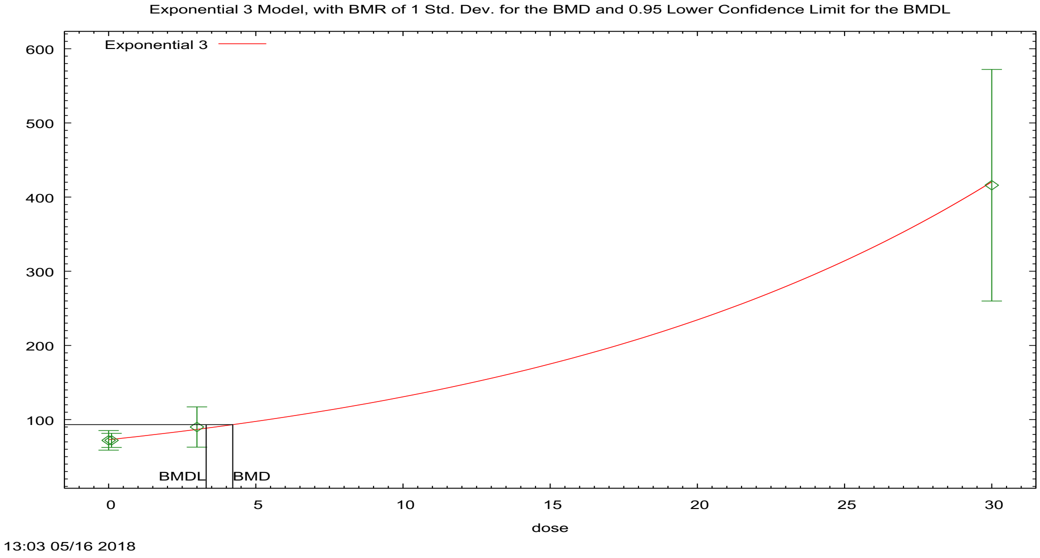

Figure 57. Plot of mean response by dose with fitted curve for Exponential (M3) model with modeled variance for Aspartate Aminotransferase in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

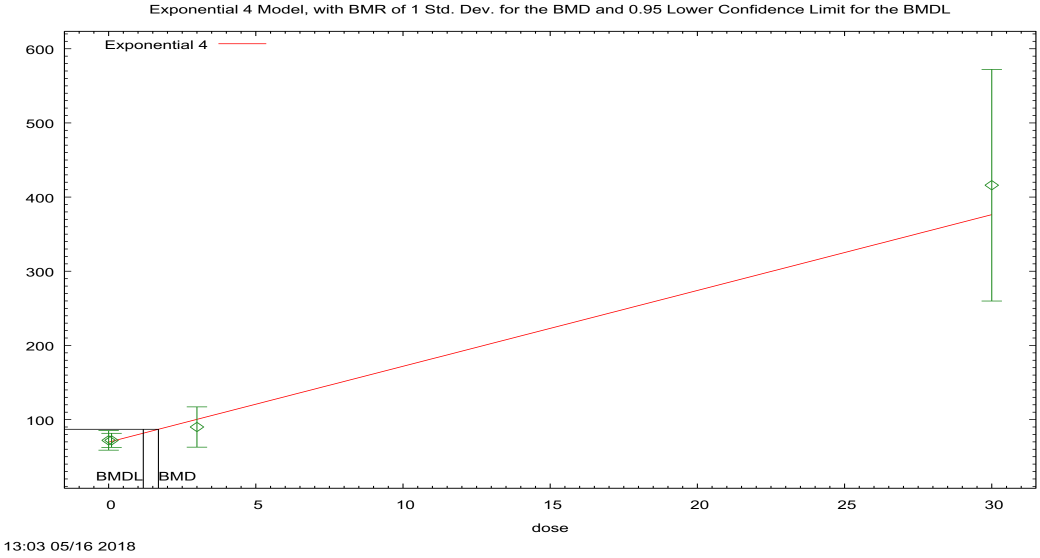

Figure 58. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Aspartate Aminotransferase in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

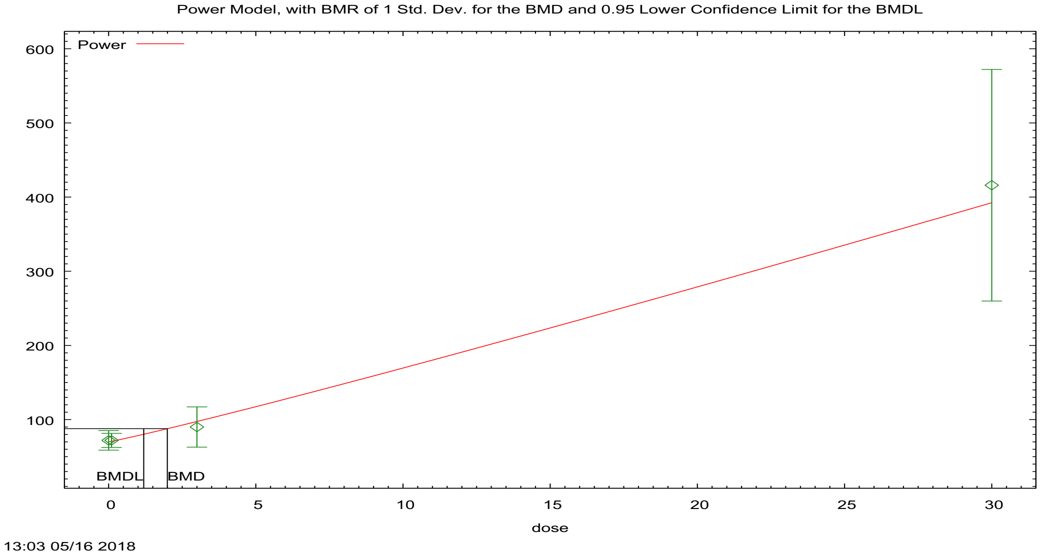

Figure 59. Plot of mean response by dose with fitted curve for Power model with modeled variance for Aspartate Aminotransferase in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

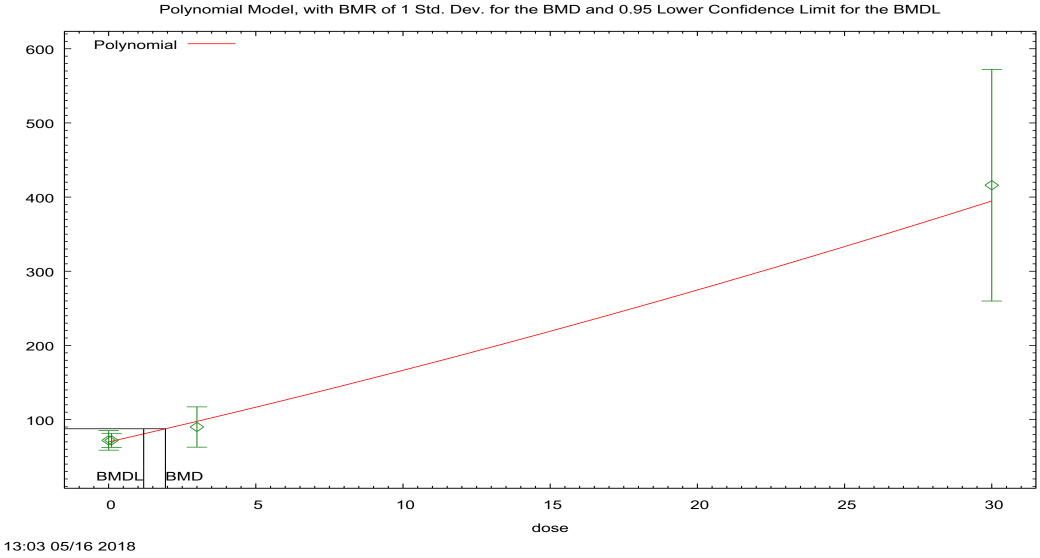

Figure 60. Plot of mean response by dose with fitted curve for Polynomial 3° model with modeled variance for Aspartate Aminotransferase in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

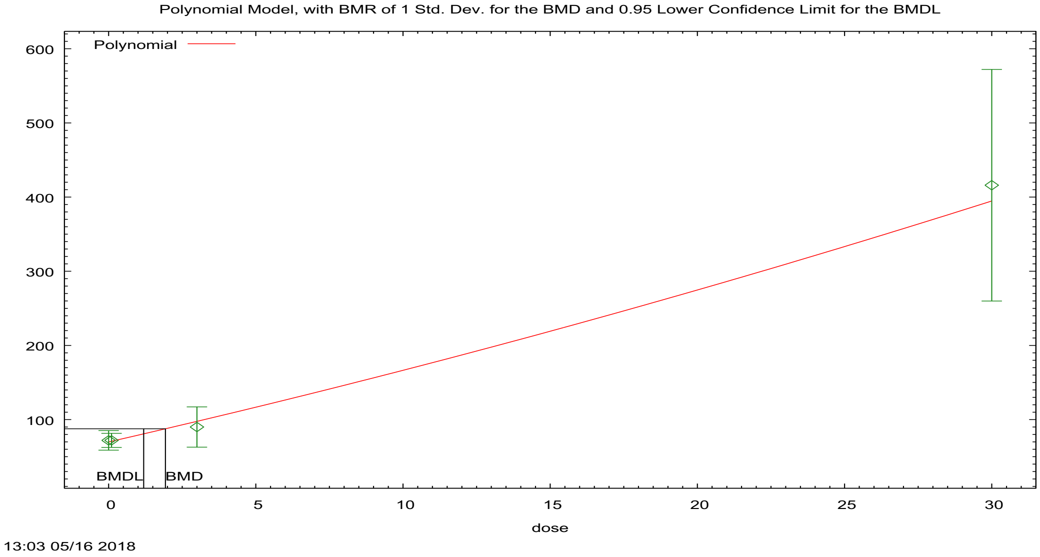

Figure 61. Plot of mean response by dose with fitted curve for Polynomial 2° model with modeled variance for Aspartate Aminotransferase in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

1.17. BMDS Summary of Aspartate Aminotransferase in Males (90-Day Mice)

Table 17. 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 (M4) Exponential (M5)[b]	0.244	306.59	0.325	0.141	2.31	Models that met inclusion criteria are presented (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). BMDLs from included models were sufficiently close (< 3-fold difference), so the BMDL from the model with the lowest AIC was selected.
Hill	**0.264**	**306.48**	**0.303**	**0.169**	**1.80**	

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

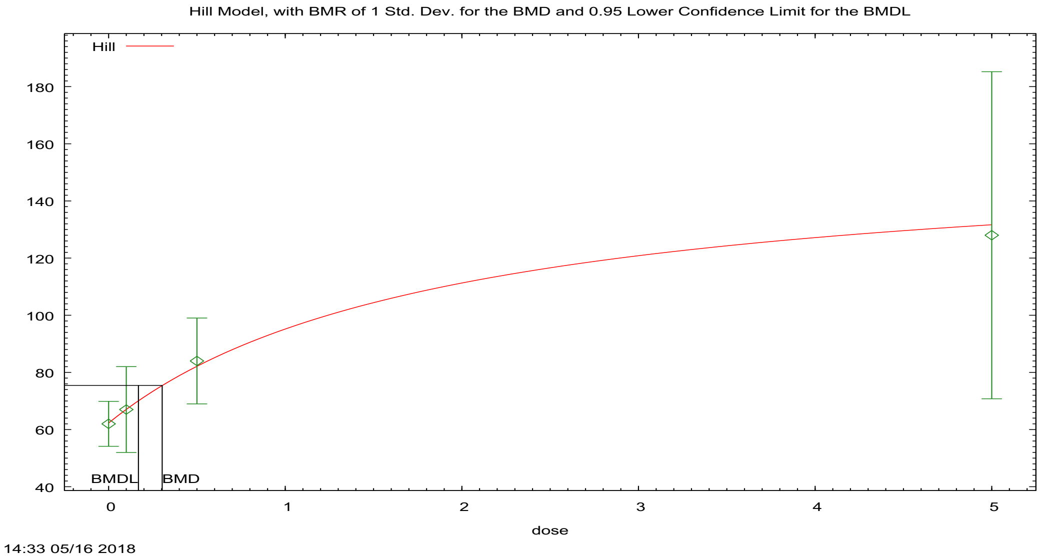

Figure 62. Plot of mean response by dose with fitted curve for Hill model with modeled variance for Aspartate Aminotransferase in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

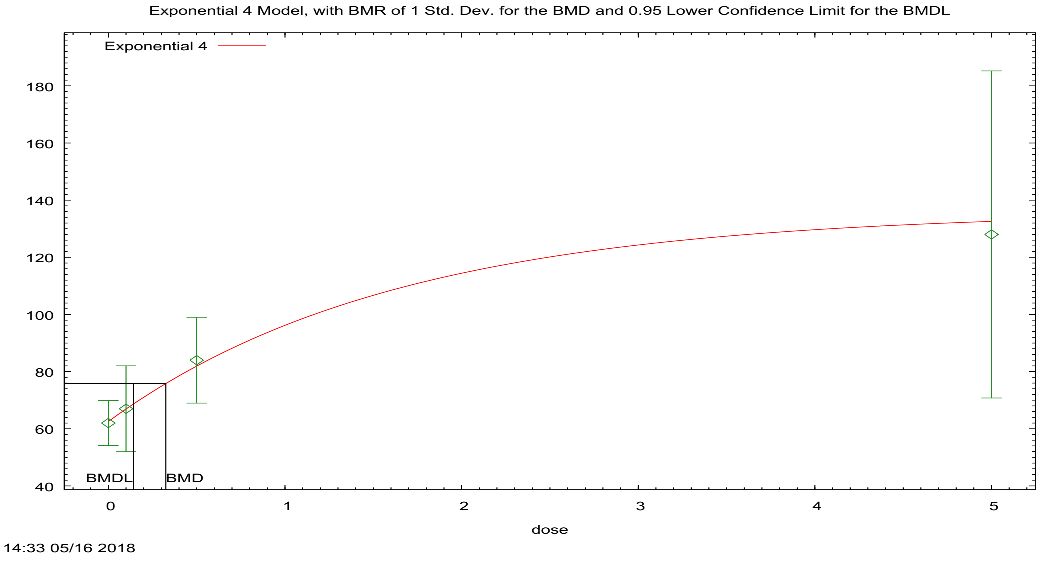

Figure 63. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Aspartate Aminotransferase in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

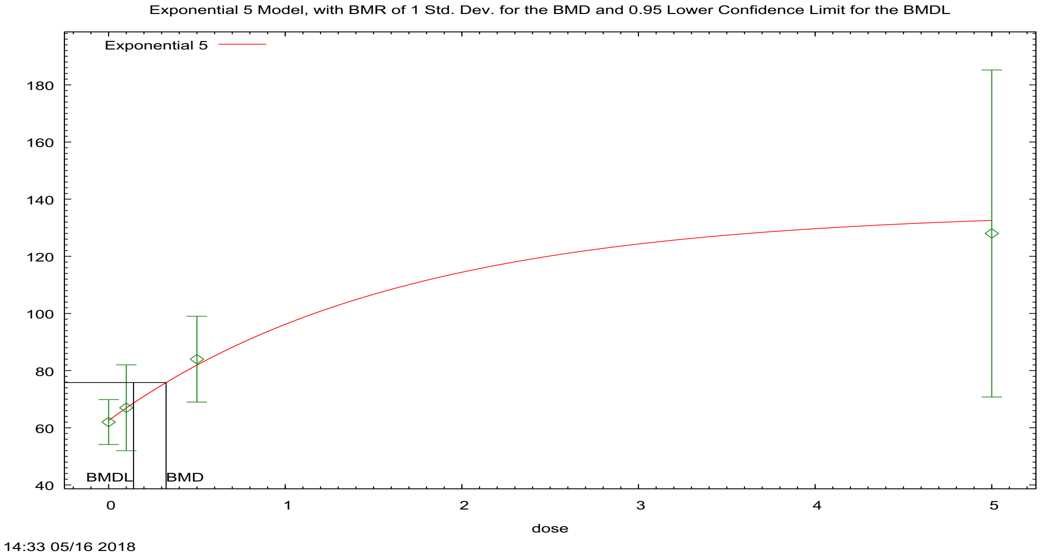

Figure 64. Plot of mean response by dose with fitted curve for Exponential (M5) model with modeled variance for Aspartate Aminotransferase in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

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

1.18. BMDS Summary of Sorbitol Dehydrogenase in Females (28-Day Mice)

Table 18. 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**	**Models that met inclusion criteria are presented (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). 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	
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.

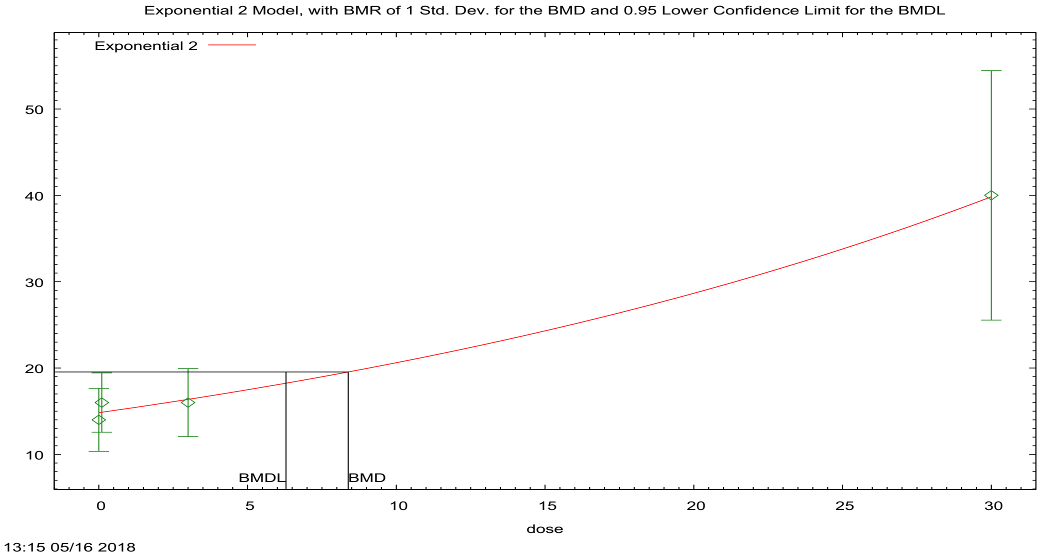

Figure 65. Plot of mean response by dose with fitted curve for Exponential (M2) model with modeled variance for Sorbitol Dehydrogenase in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

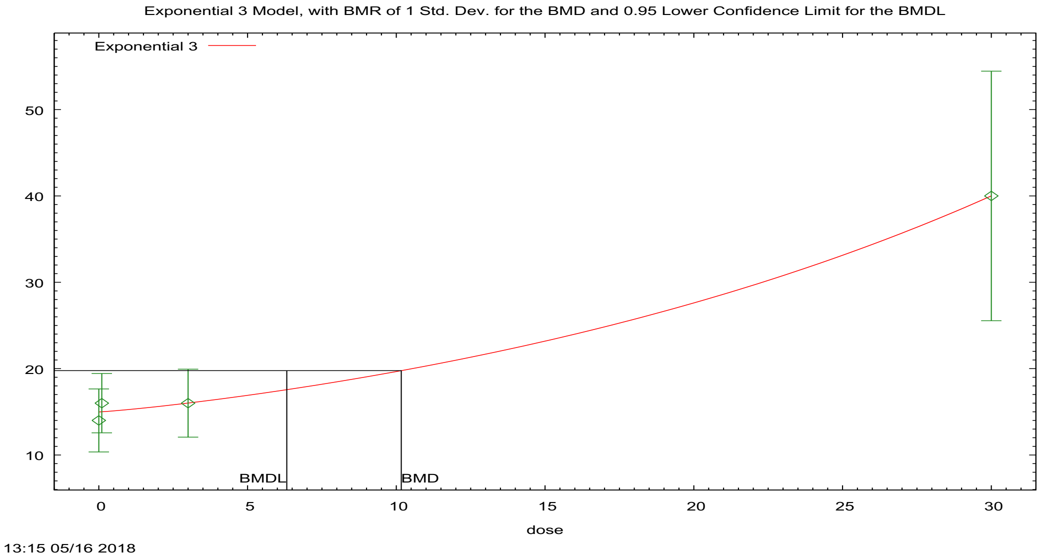

Figure 66. Plot of mean response by dose with fitted curve for Exponential (M3) model with modeled variance for Sorbitol Dehydrogenase in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

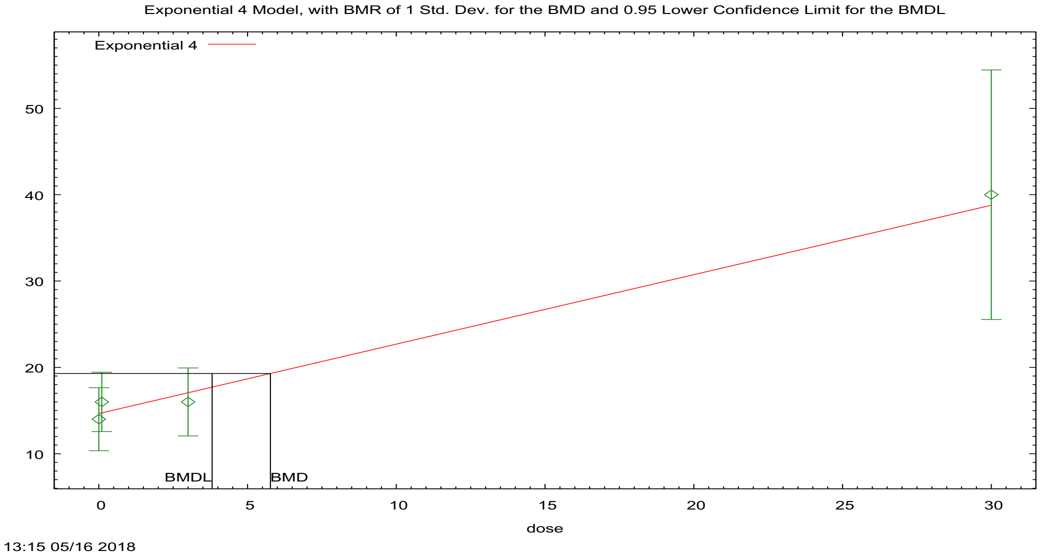

Figure 67. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Sorbitol Dehydrogenase in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

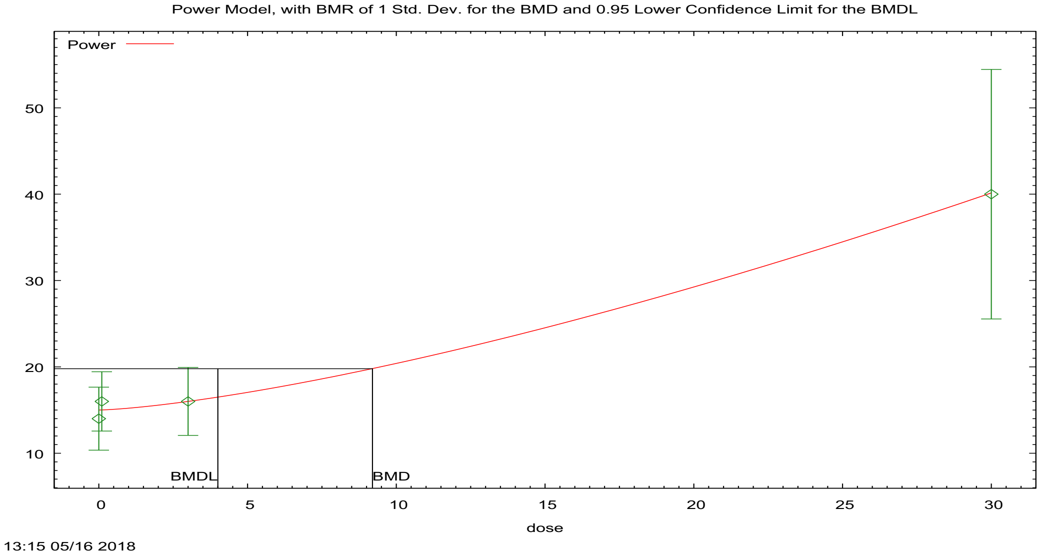

Figure 68. Plot of mean response by dose with fitted curve for Power model with modeled variance for Sorbitol Dehydrogenase in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

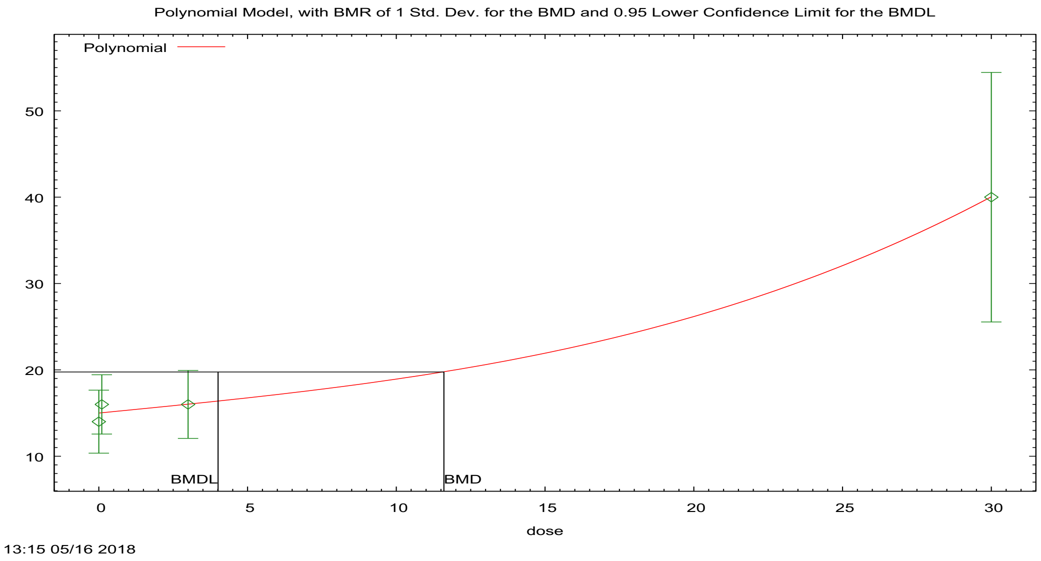

Figure 69. Plot of mean response by dose with fitted curve for Polynomial 3° model with modeled variance for Sorbitol Dehydrogenase in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

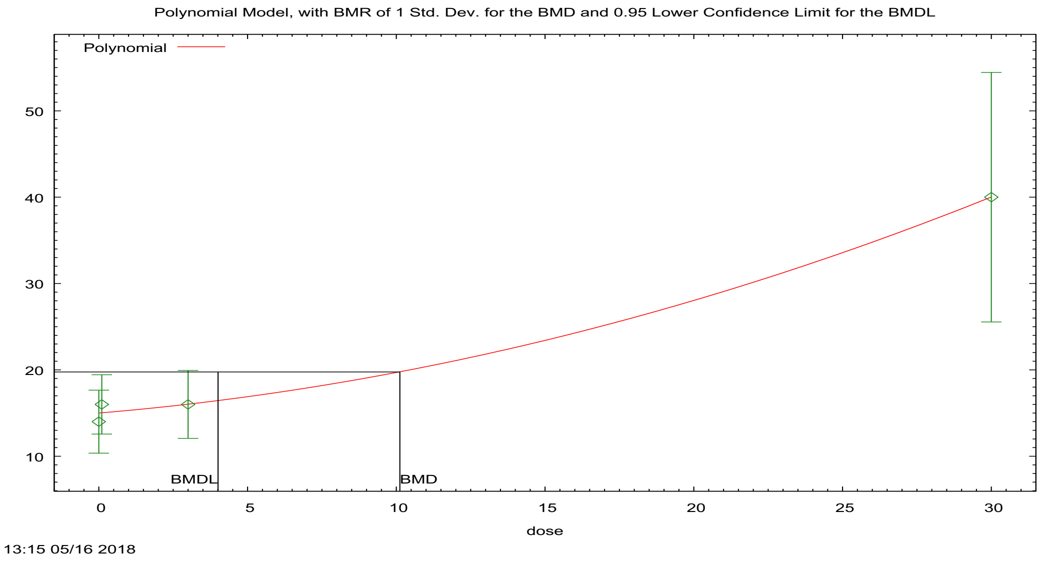

Figure 70. Plot of mean response by dose with fitted curve for Polynomial 2° model with modeled variance for Sorbitol Dehydrogenase in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

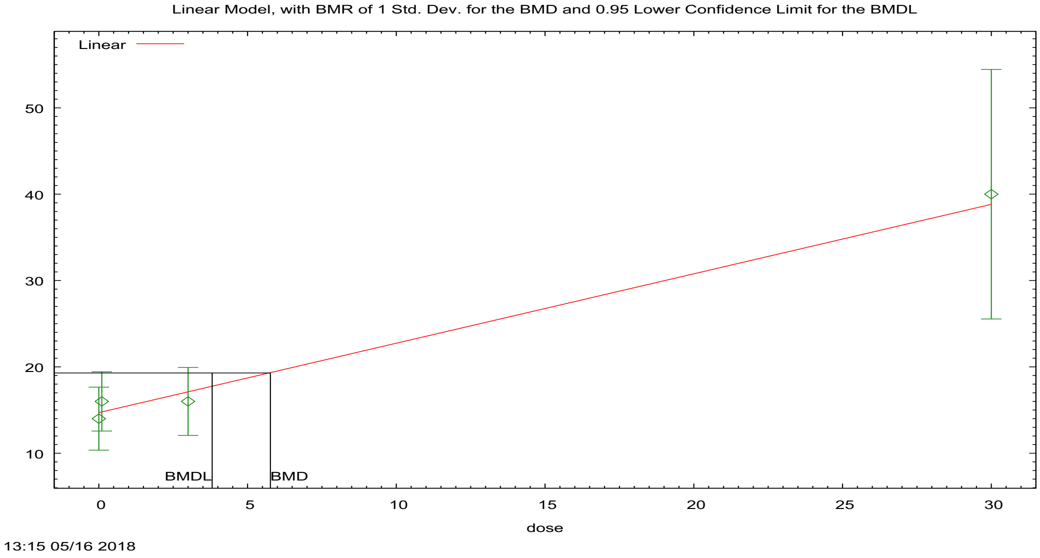

Figure 71. Plot of mean response by dose with fitted curve for Linear model with modeled variance for Sorbitol Dehydrogenase in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

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

1.19. BMDS Summary of Sorbitol Dehydrogenase in Males at 12 months (2-Year Rats)

Table 19. 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	Models that met inclusion criteria are presented (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). 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**	
Power[c] Polynomial 3°[d] Polynomial 2°[e] 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] 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.

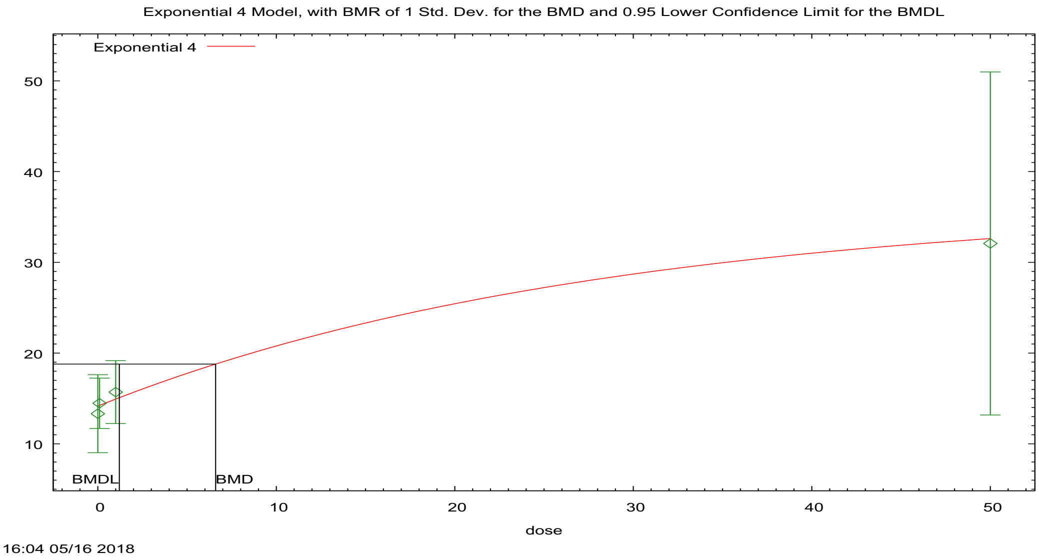

Figure 72. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Sorbitol Dehydrogenase in Males at 12 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

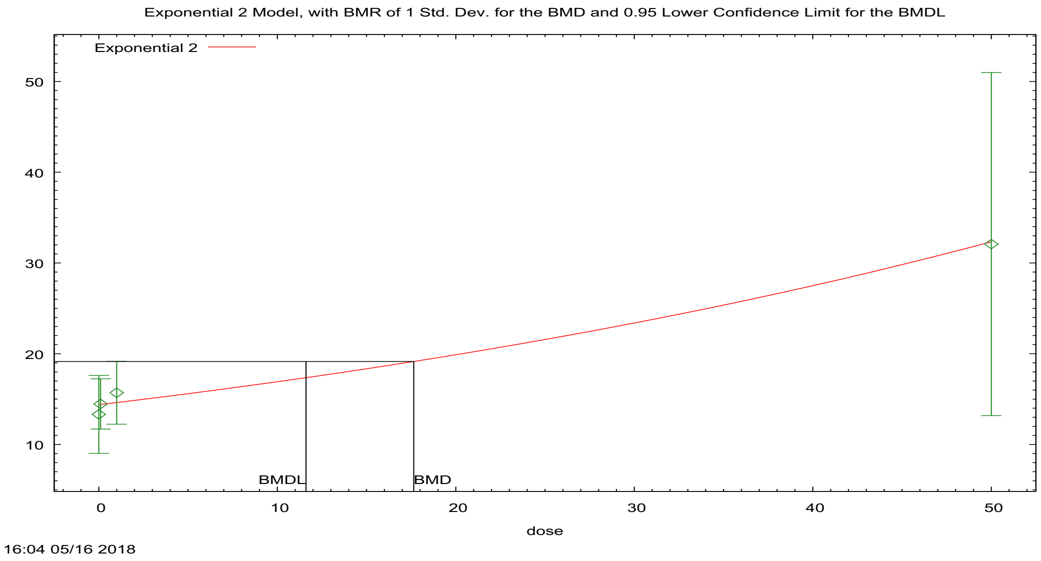

Figure 73. Plot of mean response by dose with fitted curve for Exponential (M2) model with modeled variance for Sorbitol Dehydrogenase in Males at 12 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

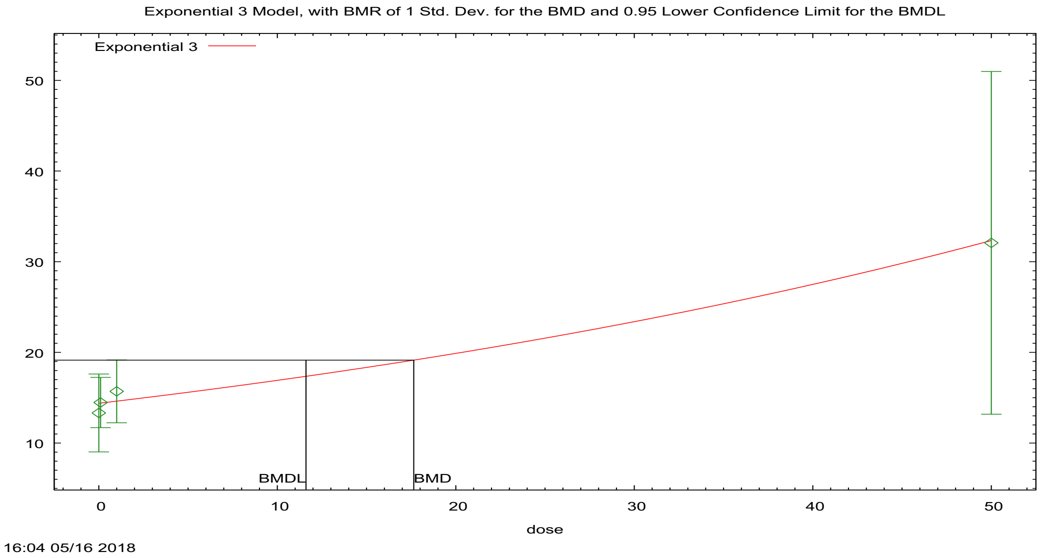

Figure 74. Plot of mean response by dose with fitted curve for Exponential (M3) model with modeled variance for Sorbitol Dehydrogenase in Males at 12 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

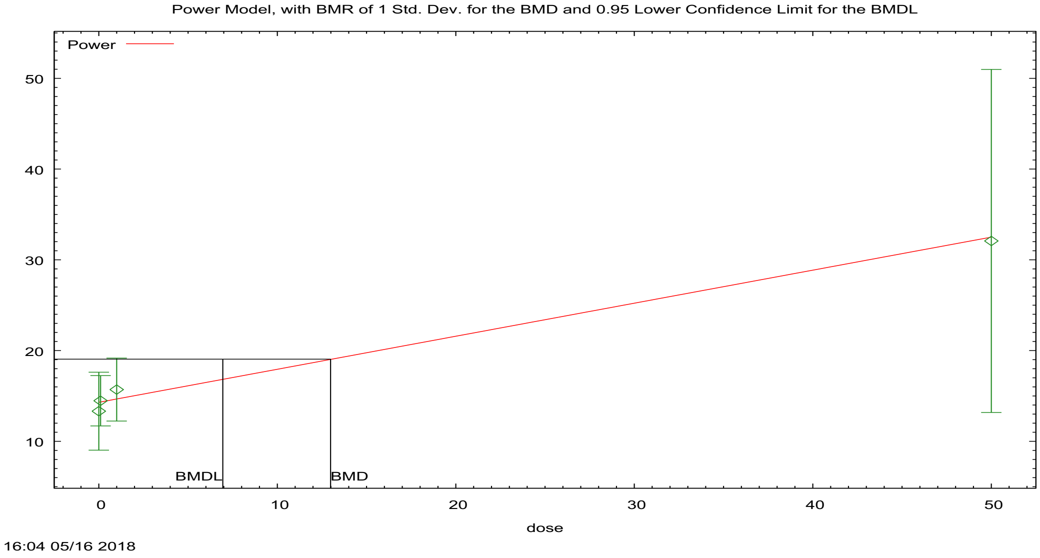

Figure 75. Plot of mean response by dose with fitted curve for Power model with modeled variance for Sorbitol Dehydrogenase in Males at 12 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

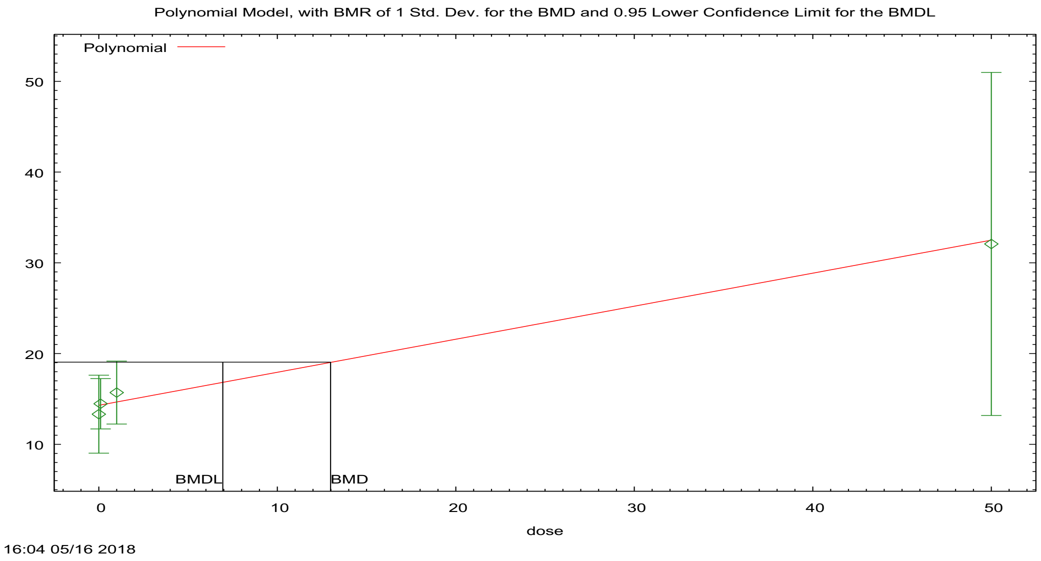

Figure 76. Plot of mean response by dose with fitted curve for Polynomial 3° model with modeled variance for Sorbitol Dehydrogenase in Males at 12 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

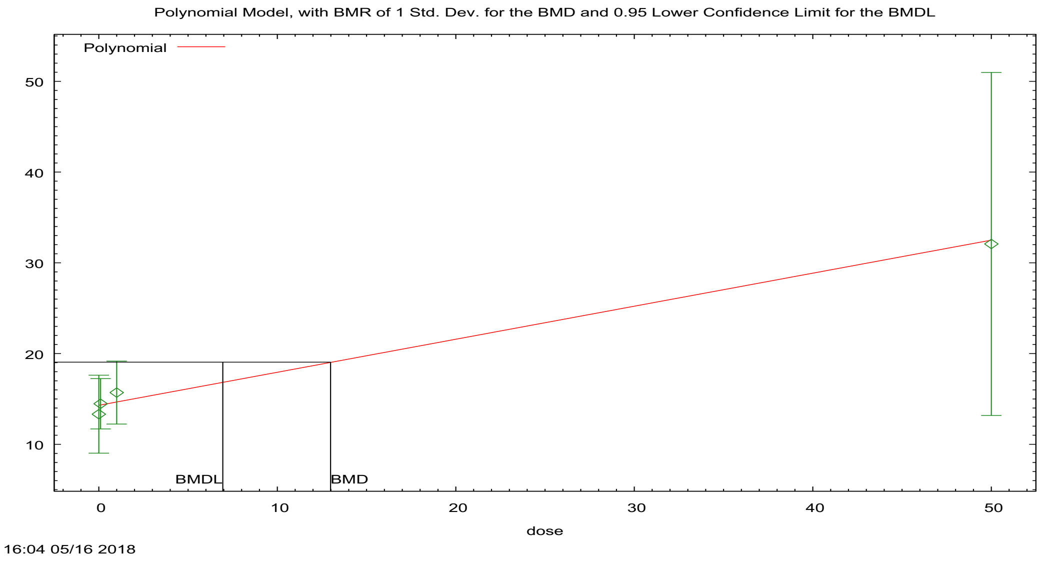

Figure 77. Plot of mean response by dose with fitted curve for Polynomial 2° model with modeled variance for Sorbitol Dehydrogenase in Males at 12 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

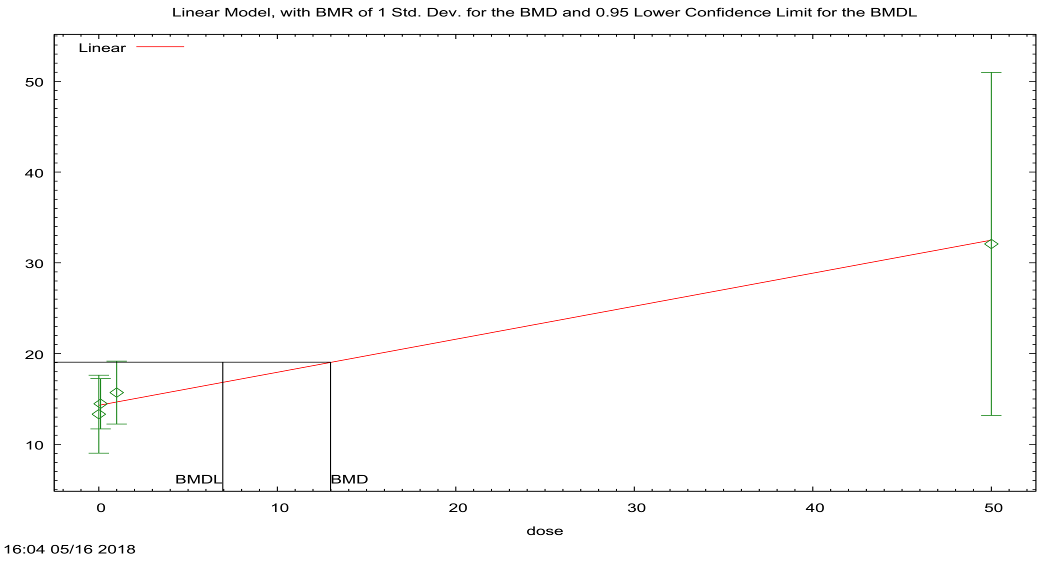

Figure 78. Plot of mean response by dose with fitted curve for Linear model with modeled variance for Sorbitol Dehydrogenase in Males at 12 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

1.20. BMDS Summary of Single Cell Hepatocellular Necrosis in Males (28-Day Mice)

Table 20. Summary of BMD Modeling Results for Single Cell Hepatocellular Necrosis in Males (28-Day Mice)

Model[a]	Goodness of fit		$\text{BMD}_{10\text{Pct}}$ (mg/kg/day)	$\text{BMDL}_{10\text{Pct}}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Gamma	1.000	17.460	1.88	0.323	5.80	Models that met inclusion criteria are presented (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). 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.

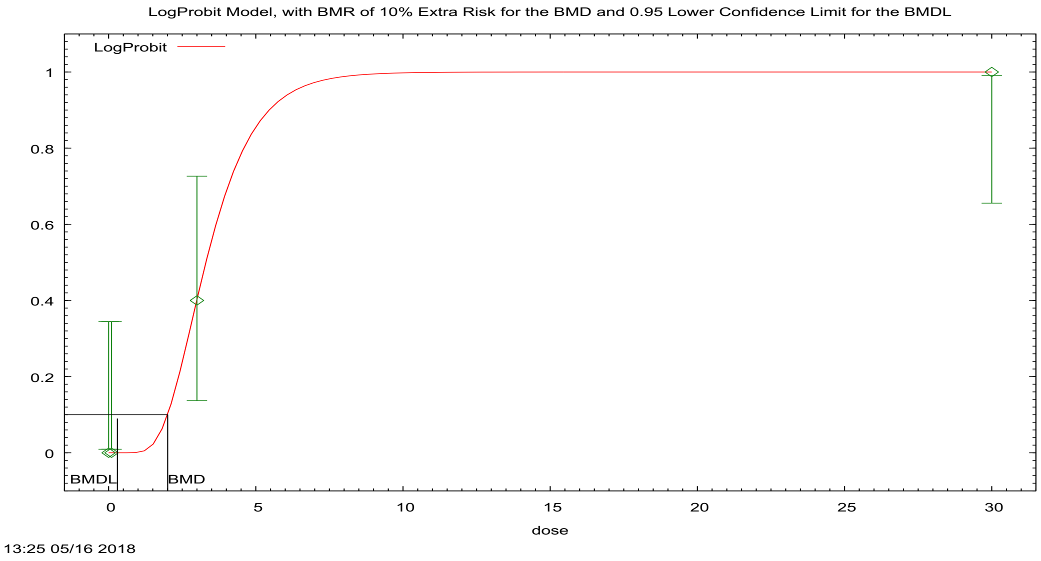

Figure 79. Plot of incidence rate by dose with fitted curve for LogProbit model for Single Cell Hepatocellular Necrosis in Males (28-Day Mice); dose shown in mg/kg/day.

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

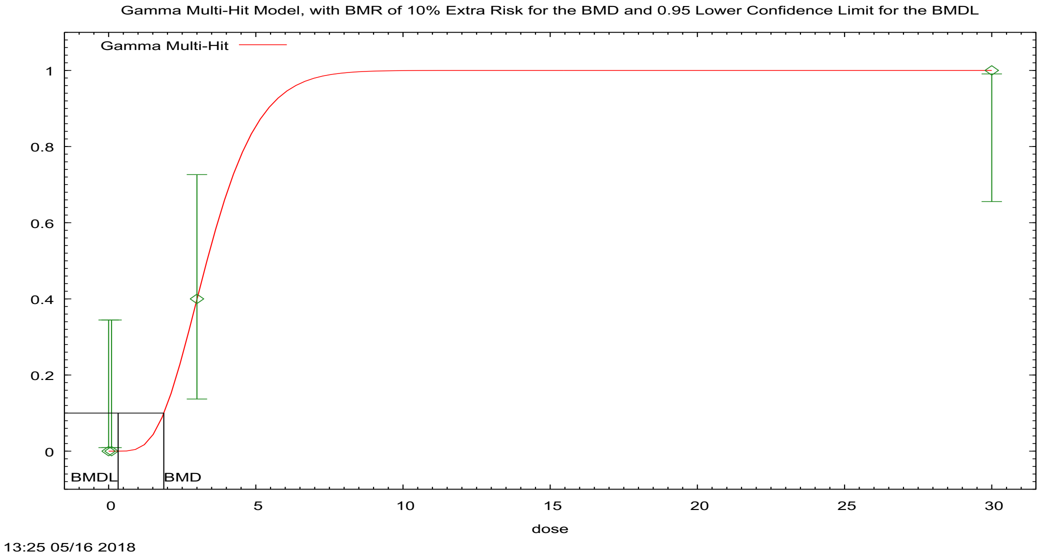

Figure 80. Plot of incidence rate by dose with fitted curve for Gamma model for Single Cell Hepatocellular Necrosis in Males (28-Day Mice); dose shown in mg/kg/day.

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

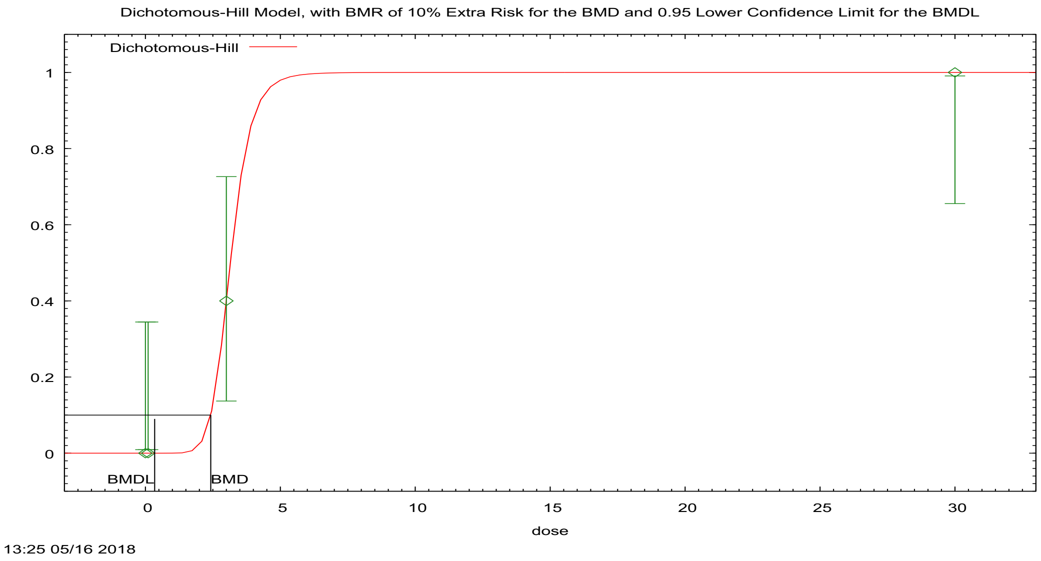

Figure 81. Plot of incidence rate by dose with fitted curve for Dichotomous-Hill model for Single Cell Hepatocellular Necrosis in Males (28-Day Mice); dose shown in mg/kg/day.

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

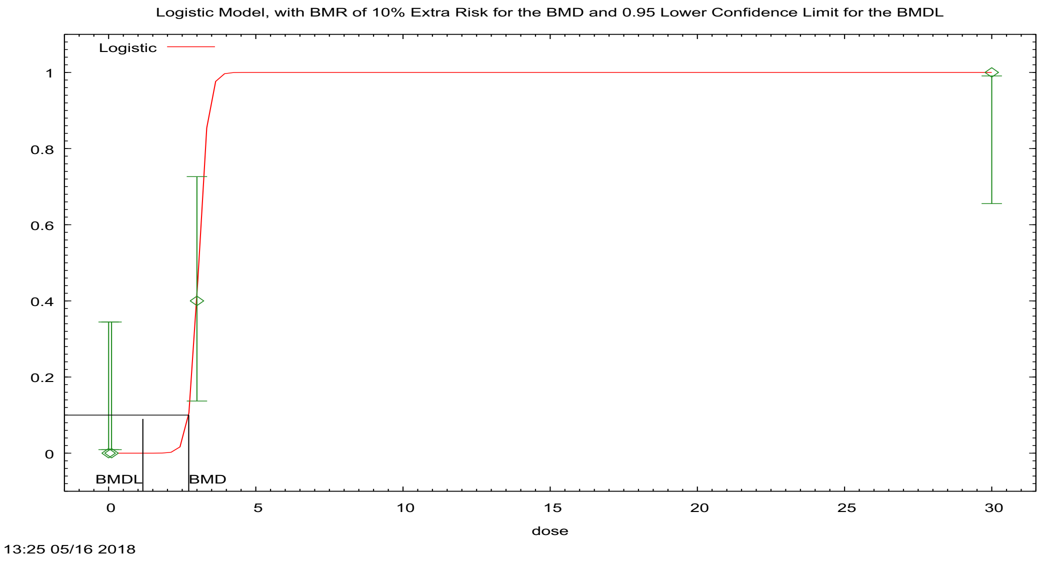

Figure 82. Plot of incidence rate by dose with fitted curve for Logistic model for Single Cell Hepatocellular Necrosis in Males (28-Day Mice); dose shown in mg/kg/day.

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

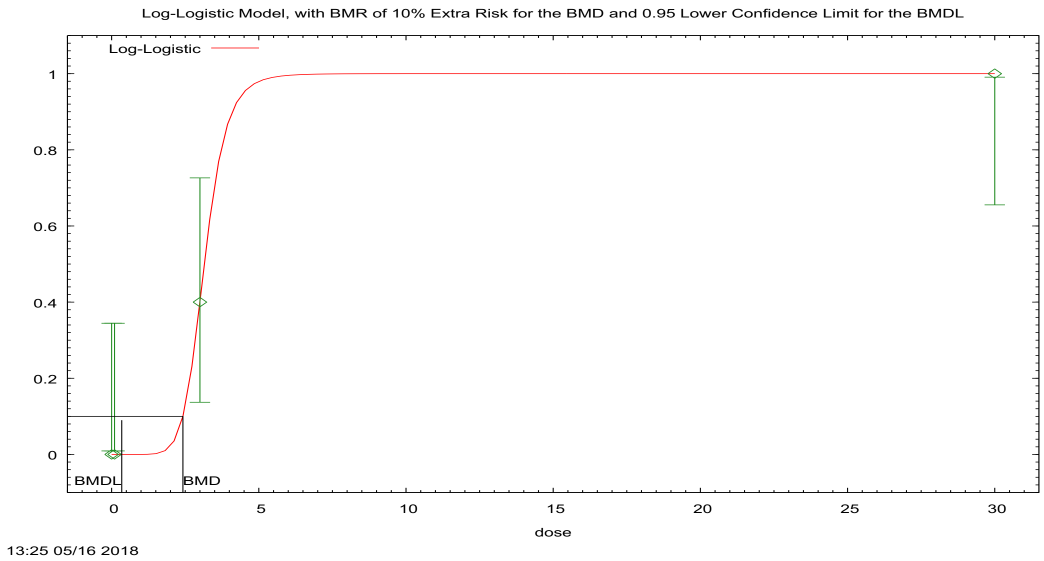

Figure 83. Plot of incidence rate by dose with fitted curve for LogLogistic model for Single Cell Hepatocellular Necrosis in Males (28-Day Mice); dose shown in mg/kg/day.

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

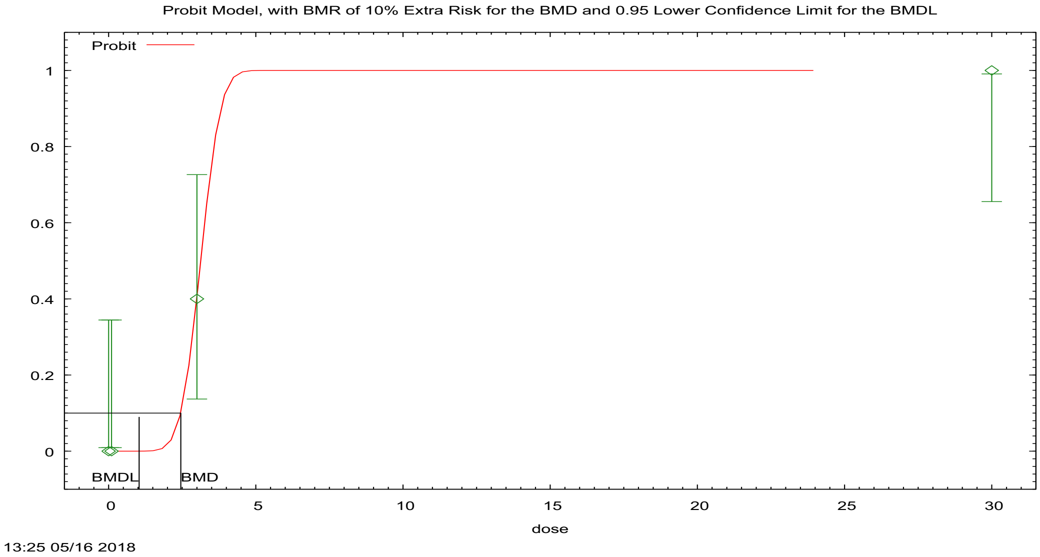

Figure 84. Plot of incidence rate by dose with fitted curve for Probit model for Single Cell Hepatocellular Necrosis in Males (28-Day Mice); dose shown in mg/kg/day.

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	0.0000001654 92	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

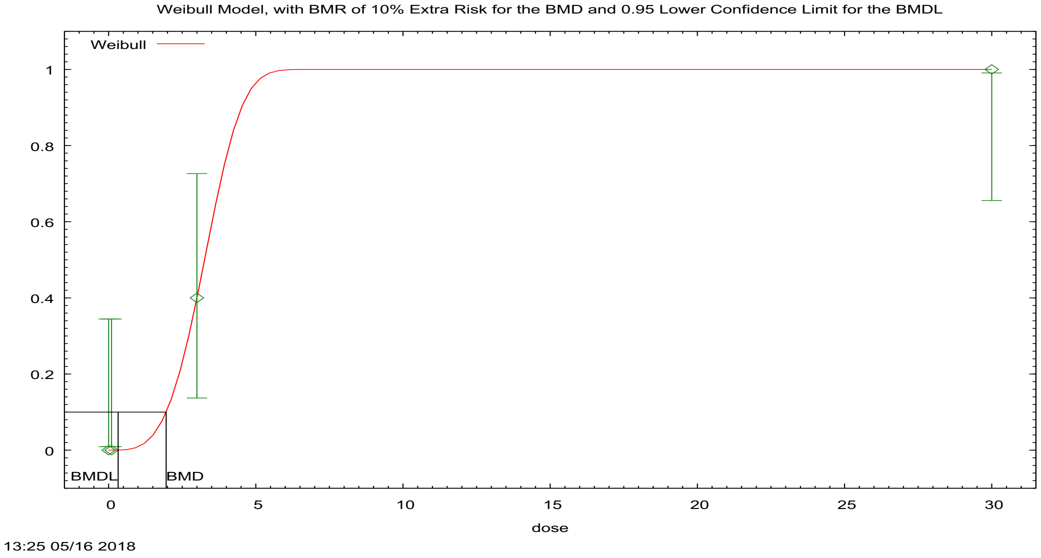

Figure 85. Plot of incidence rate by dose with fitted curve for Weibull model for Single Cell Hepatocellular Necrosis in Males (28-Day Mice); dose shown in mg/kg/day.

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

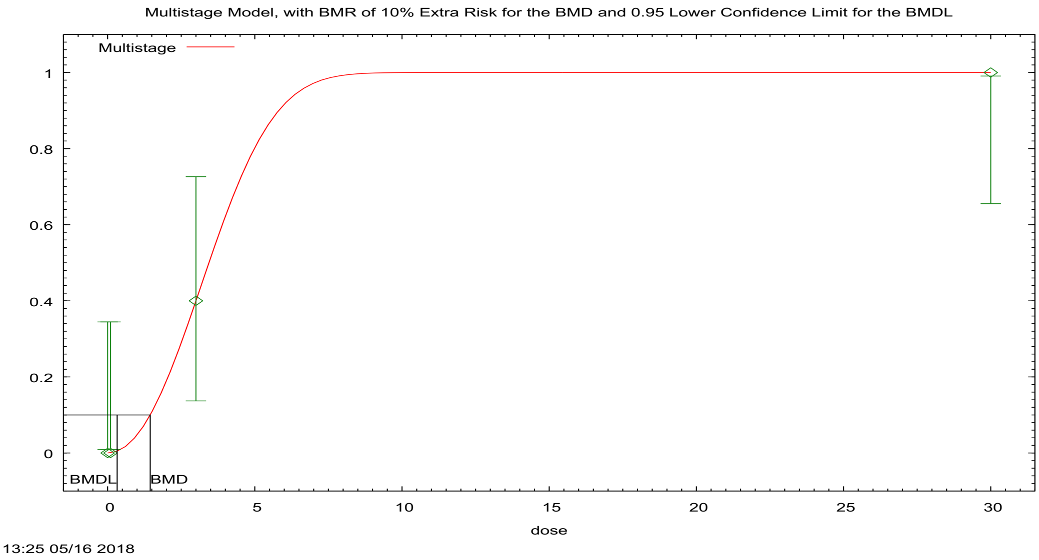

Figure 86. Plot of incidence rate by dose with fitted curve for Multistage 3° model for Single Cell Hepatocellular Necrosis in Males (28-Day Mice); dose shown in mg/kg/day.

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

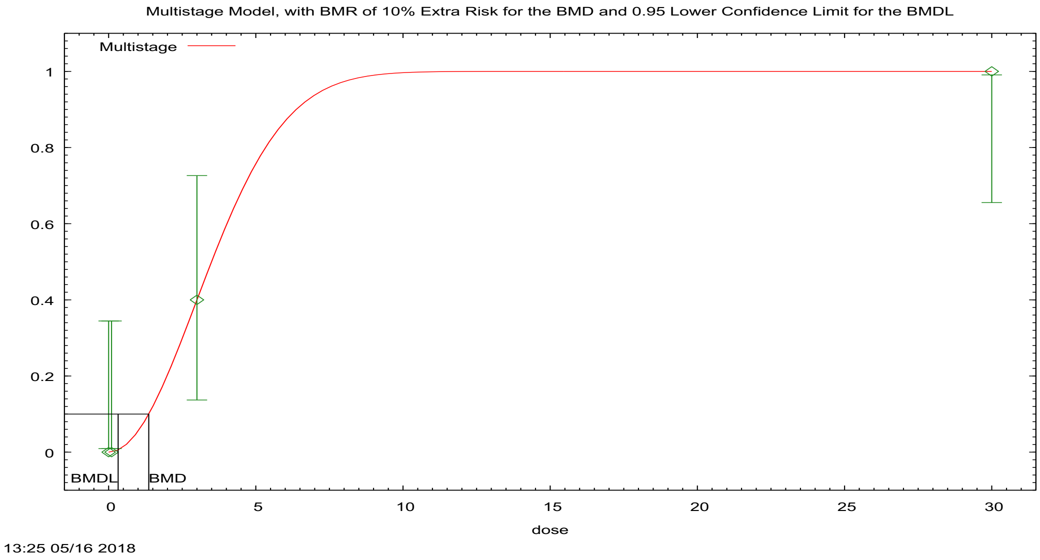

Figure 87. Plot of incidence rate by dose with fitted curve for Multistage 2° model for Single Cell Hepatocellular Necrosis in Males (28-Day Mice); dose shown in mg/kg/day.

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

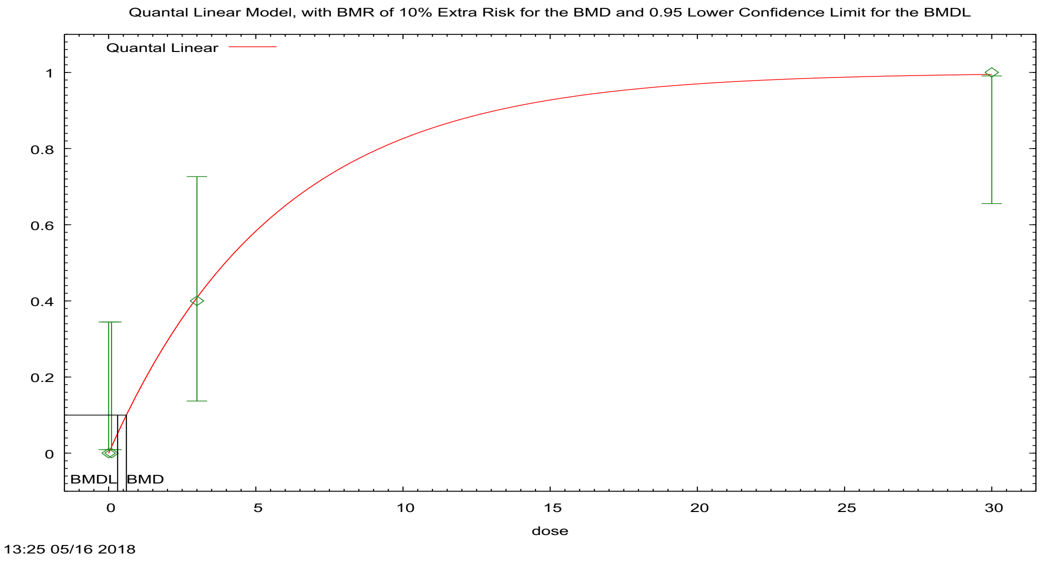

Figure 88. Plot of incidence rate by dose with fitted curve for Quantal-Linear model for Single Cell Hepatocellular Necrosis in Males (28-Day Mice); dose shown in mg/kg/day.

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

1.21. BMDS Summary of Hepatocellular Necrosis in Males (28-Day Rats)

Table 21. 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	Models that met inclusion criteria are presented (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). 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.

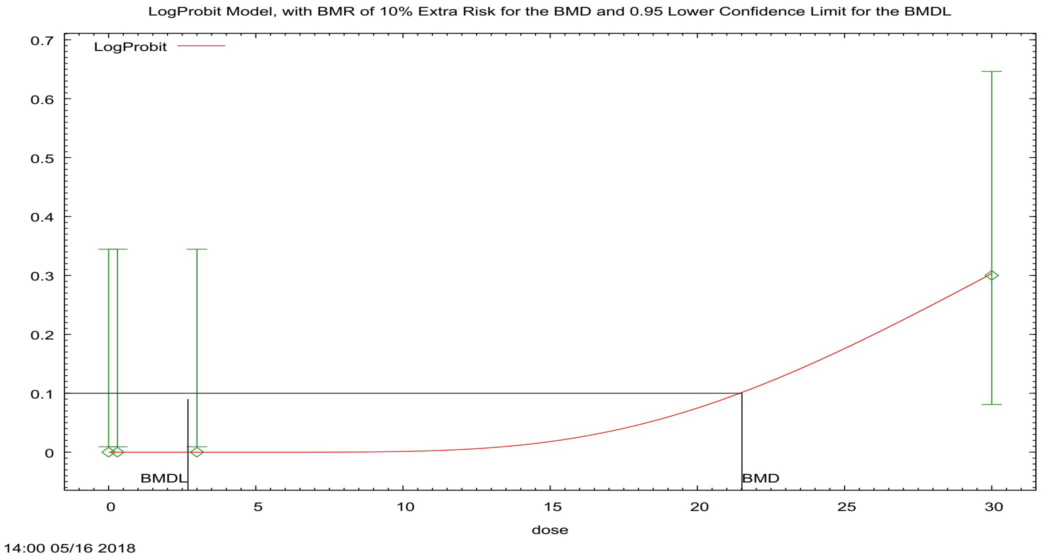

Figure 89. Plot of incidence rate by dose with fitted curve for LogProbit model for Hepatocellular Necrosis in Males (28-Day Rats); dose shown in mg/kg/day.

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

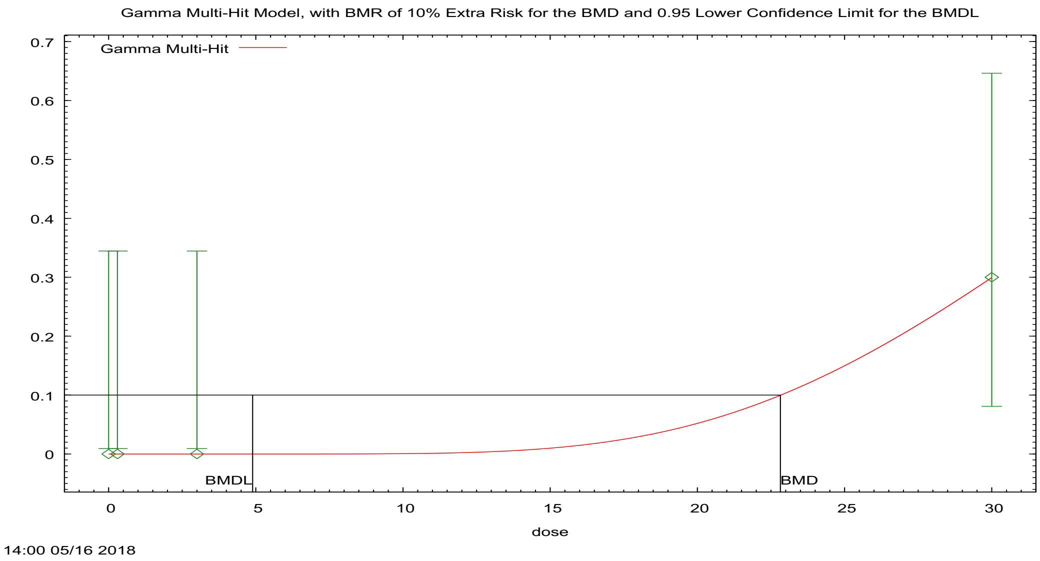

Figure 90. Plot of incidence rate by dose with fitted curve for Gamma model for Hepatocellular Necrosis in Males (28-Day Rats); dose shown in mg/kg/day.

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

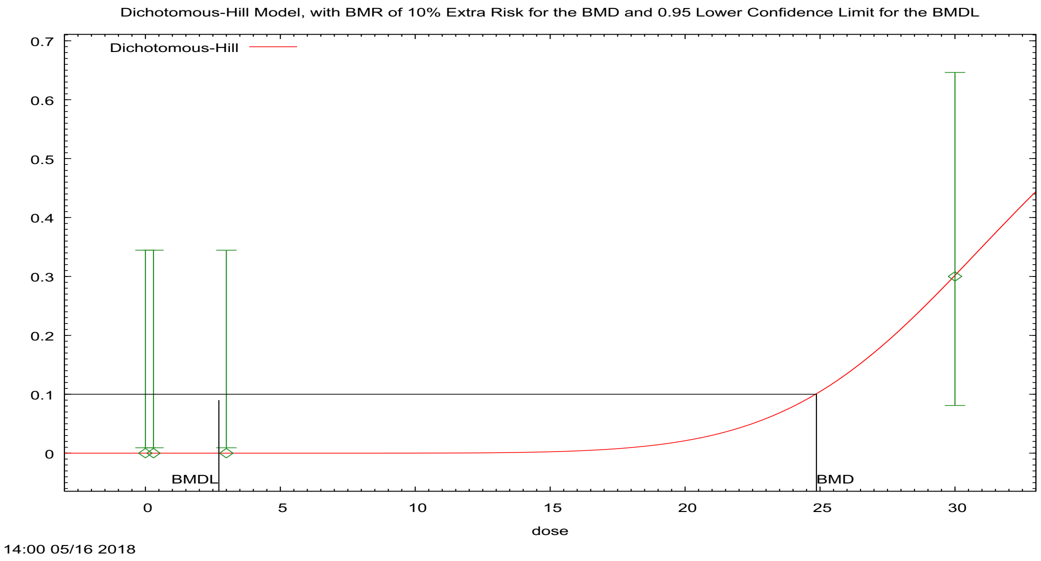

Figure 91. Plot of incidence rate by dose with fitted curve for Dichotomous-Hill model for Hepatocellular Necrosis in Males (28-Day Rats); dose shown in mg/kg/day.

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

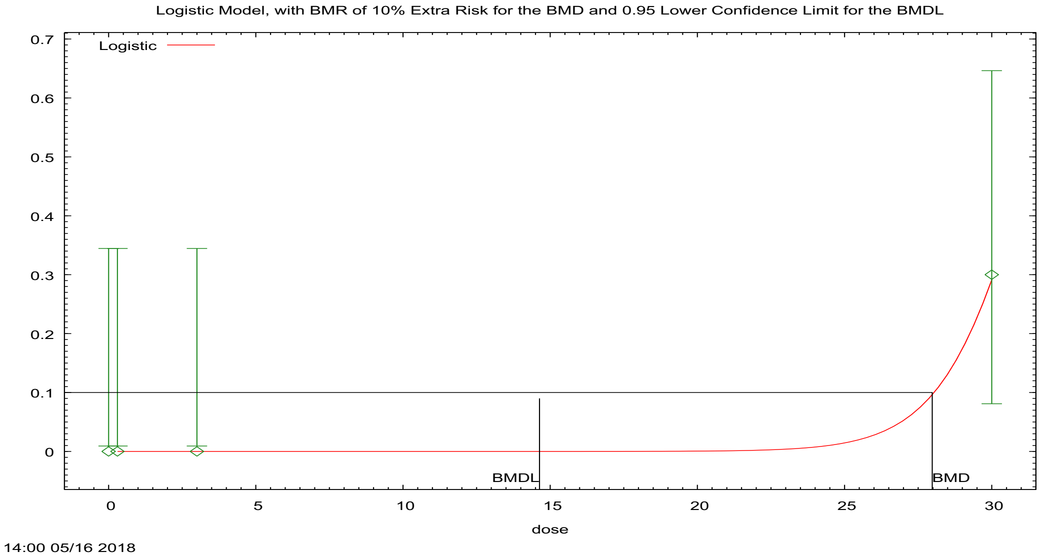

Figure 92. Plot of incidence rate by dose with fitted curve for Logistic model for Hepatocellular Necrosis in Males (28-Day Rats); dose shown in mg/kg/day.

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

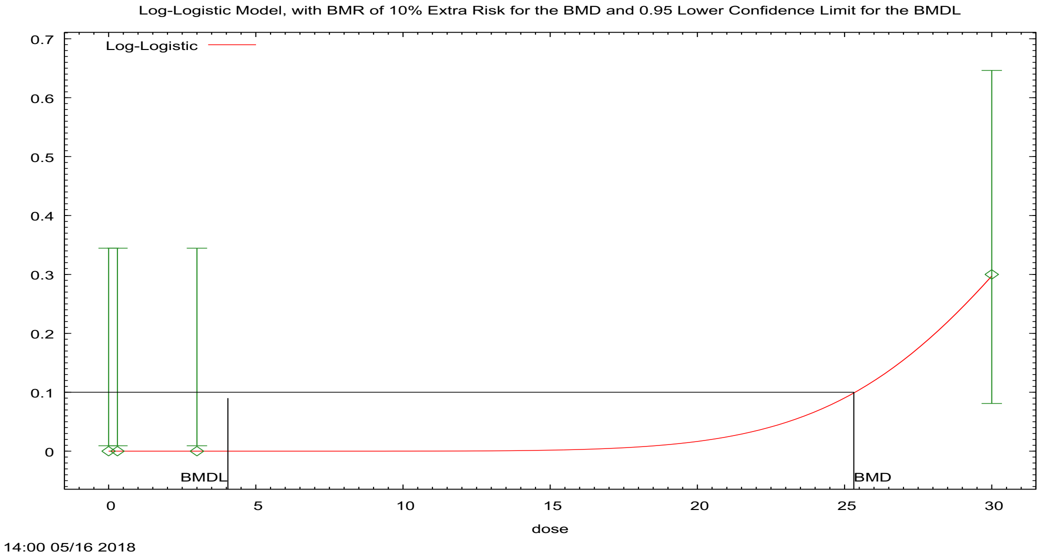

Figure 93. Plot of incidence rate by dose with fitted curve for LogLogistic model for Hepatocellular Necrosis in Males (28-Day Rats); dose shown in mg/kg/day.

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

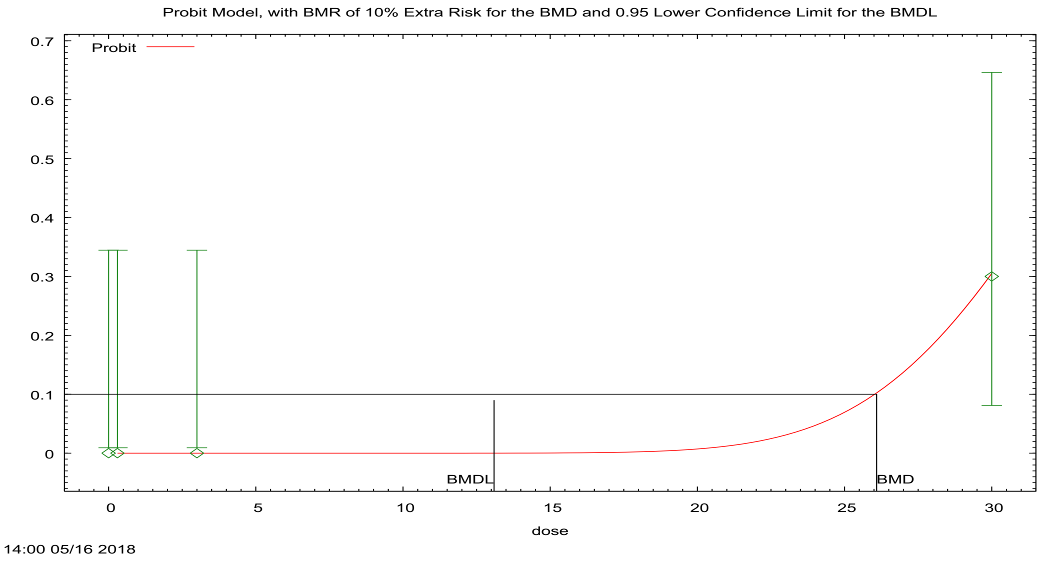

Figure 94. Plot of incidence rate by dose with fitted curve for Probit model for Hepatocellular Necrosis in Males (28-Day Rats); dose shown in mg/kg/day.

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

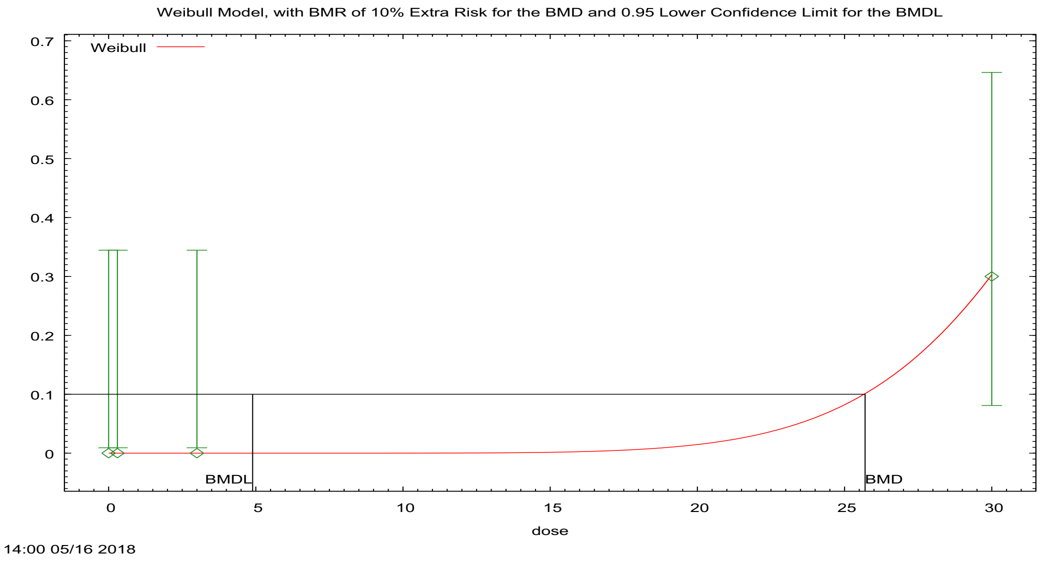

Figure 95. Plot of incidence rate by dose with fitted curve for Weibull model for Hepatocellular Necrosis in Males (28-Day Rats); dose shown in mg/kg/day.

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

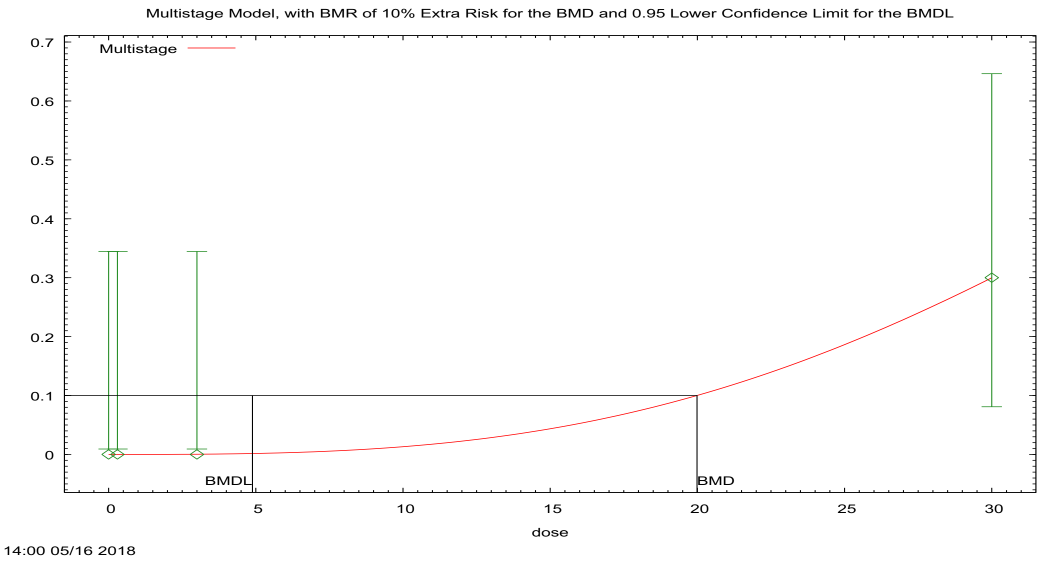

Figure 96. Plot of incidence rate by dose with fitted curve for Multistage 3° model for Hepatocellular Necrosis in Males (28-Day Rats); dose shown in mg/kg/day.

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

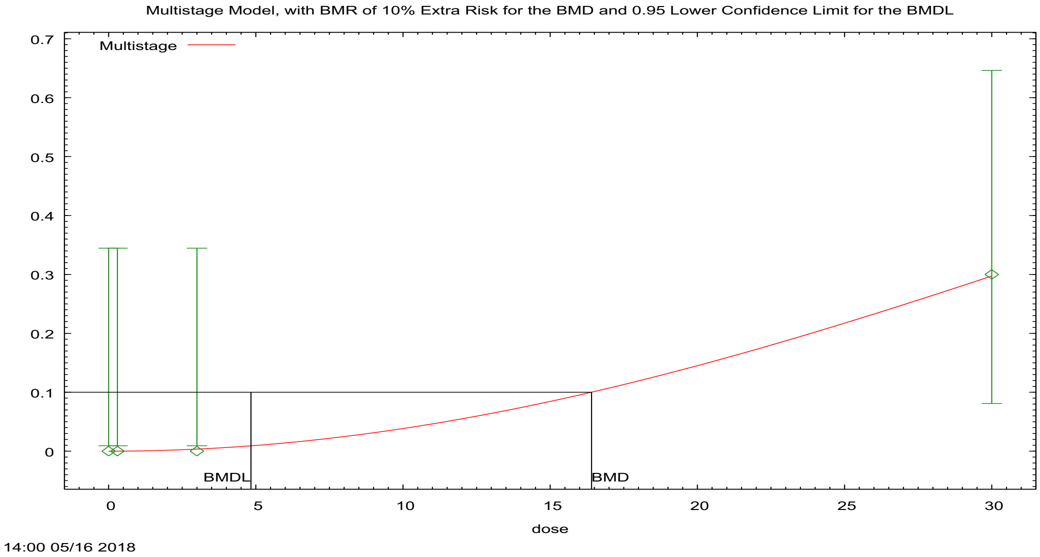

Figure 97. Plot of incidence rate by dose with fitted curve for Multistage 2° model for Hepatocellular Necrosis in Males (28-Day Rats); dose shown in mg/kg/day.

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

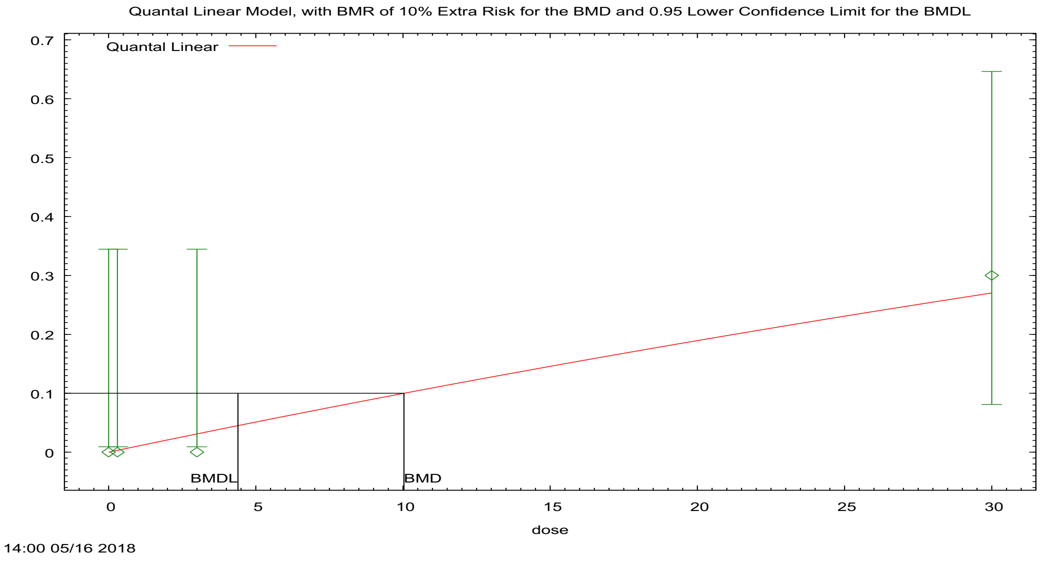

Figure 98. Plot of incidence rate by dose with fitted curve for Quantal-Linear model for Hepatocellular Necrosis in Males (28-Day Rats); dose shown in mg/kg/day.

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

1.22. BMDS Summary of Single Cell Hepatocellular Necrosis in Males (90-Day Mice)

Table 22. 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	Models that met inclusion criteria are presented (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). 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.

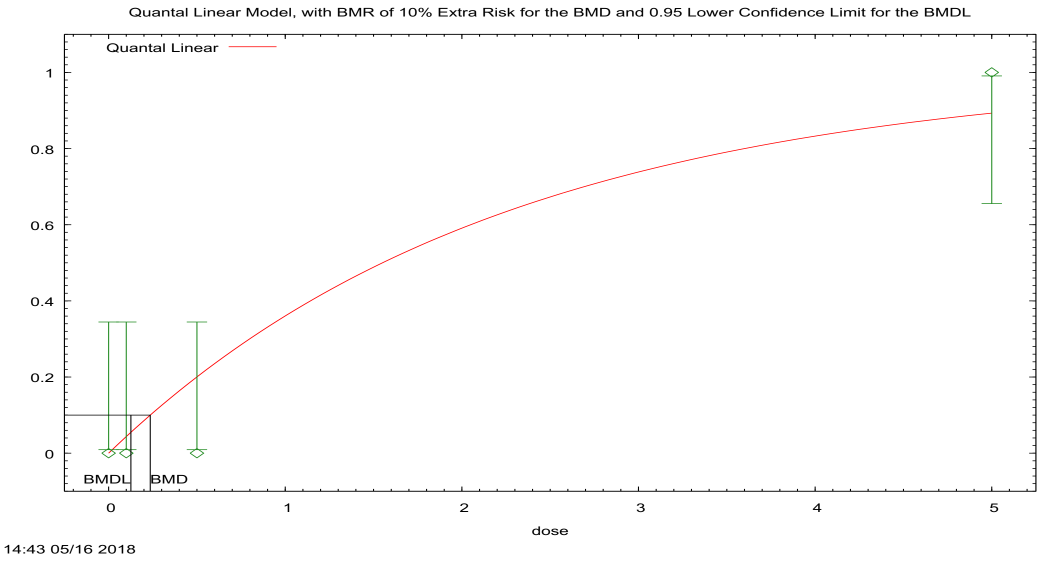

Figure 99. Plot of incidence rate by dose with fitted curve for Quantal-Linear model for Single Cell Hepatocellular Necrosis in Males (90-Day Mice); dose shown in mg/kg/day.

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

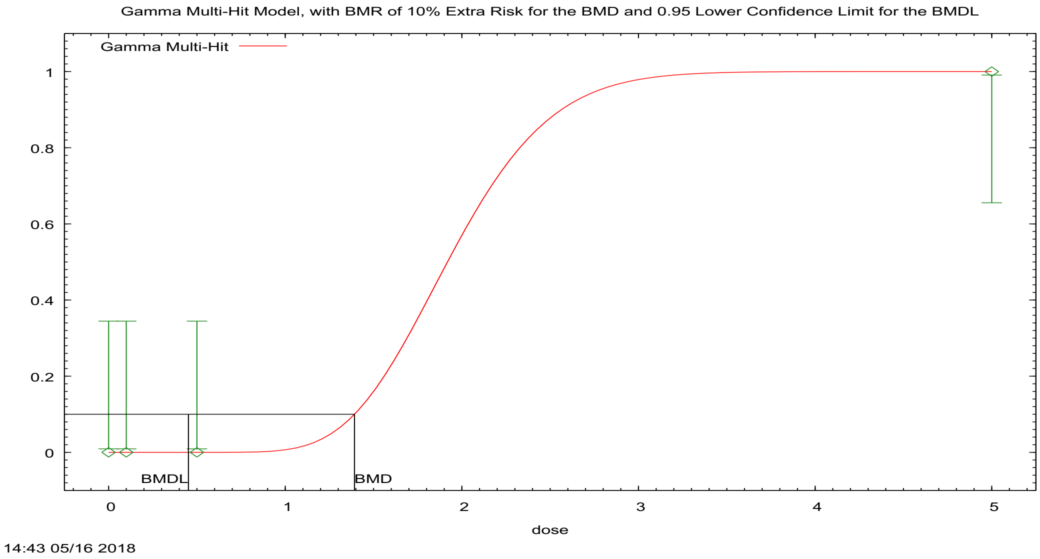

Figure 100. Plot of incidence rate by dose with fitted curve for Gamma model for Single Cell Hepatocellular Necrosis in Males (90-Day Mice); dose shown in mg/kg/day.

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

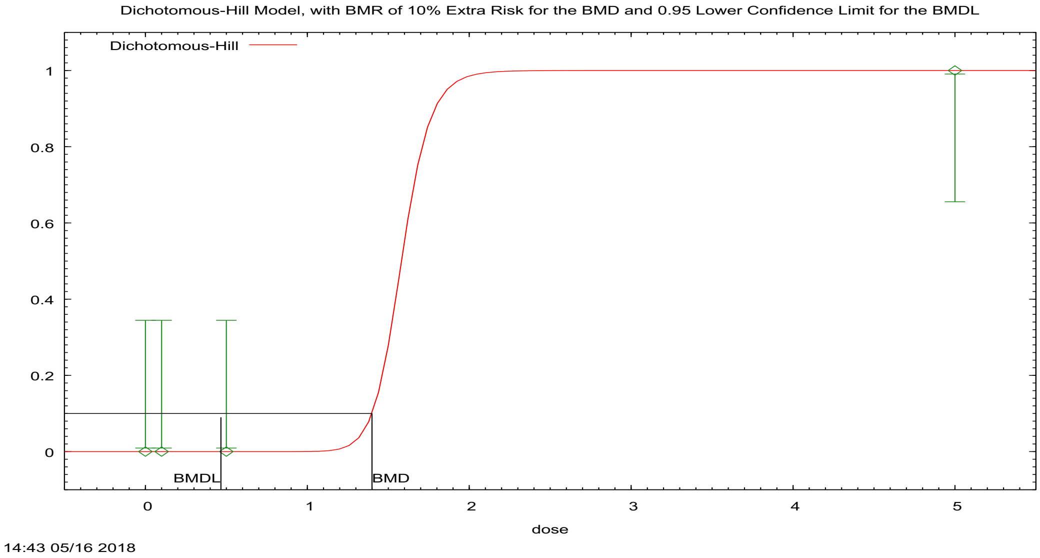

Figure 101. Plot of incidence rate by dose with fitted curve for Dichotomous-Hill model for Single Cell Hepatocellular Necrosis in Males (90-Day Mice); dose shown in mg/kg/day.

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

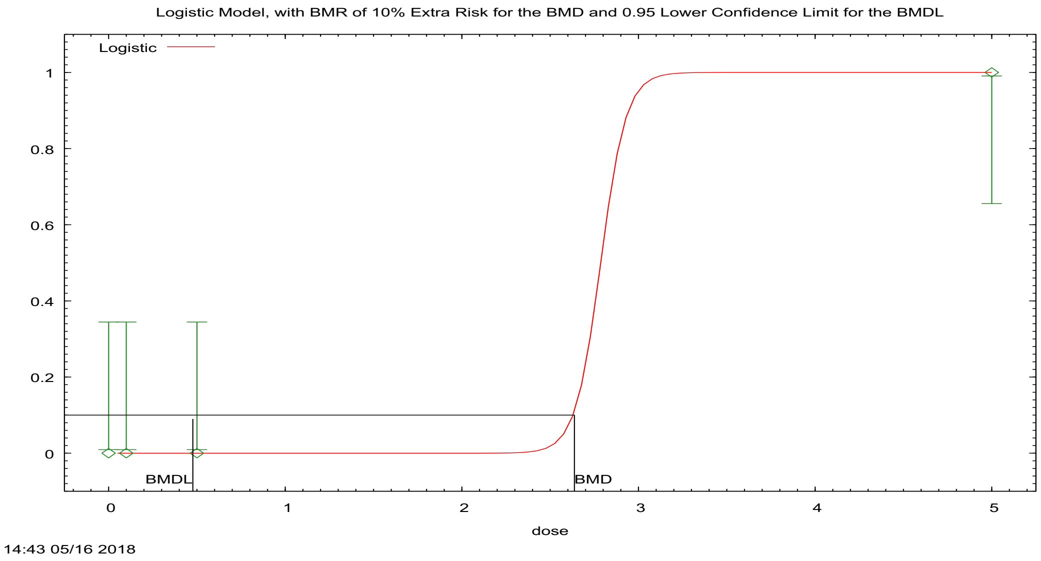

Figure 102. Plot of incidence rate by dose with fitted curve for Logistic model for Single Cell Hepatocellular Necrosis in Males (90-Day Mice); dose shown in mg/kg/day.

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

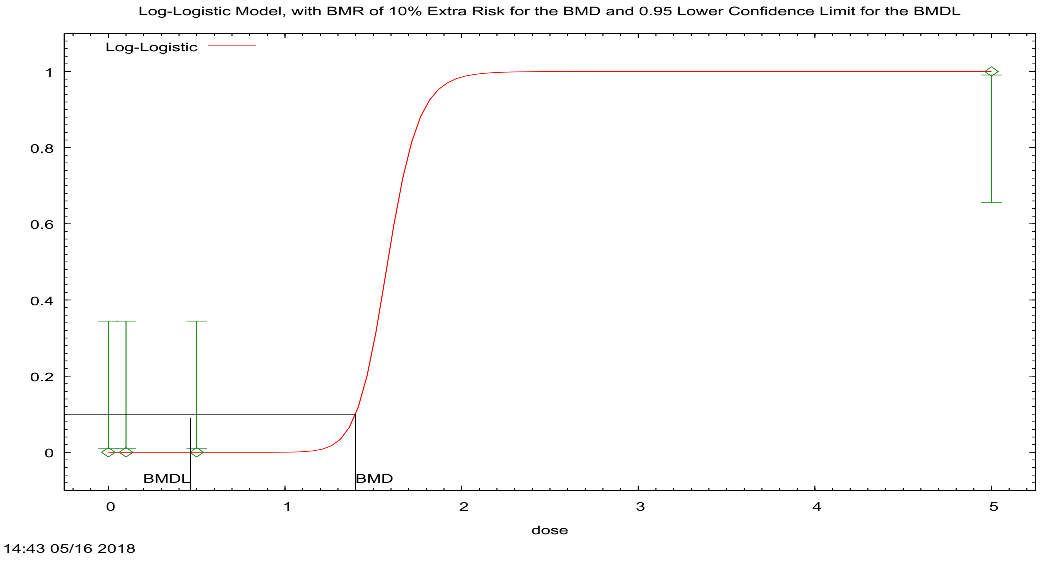

Figure 103. Plot of incidence rate by dose with fitted curve for LogLogistic model for Single Cell Hepatocellular Necrosis in Males (90-Day Mice); dose shown in mg/kg/day.

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

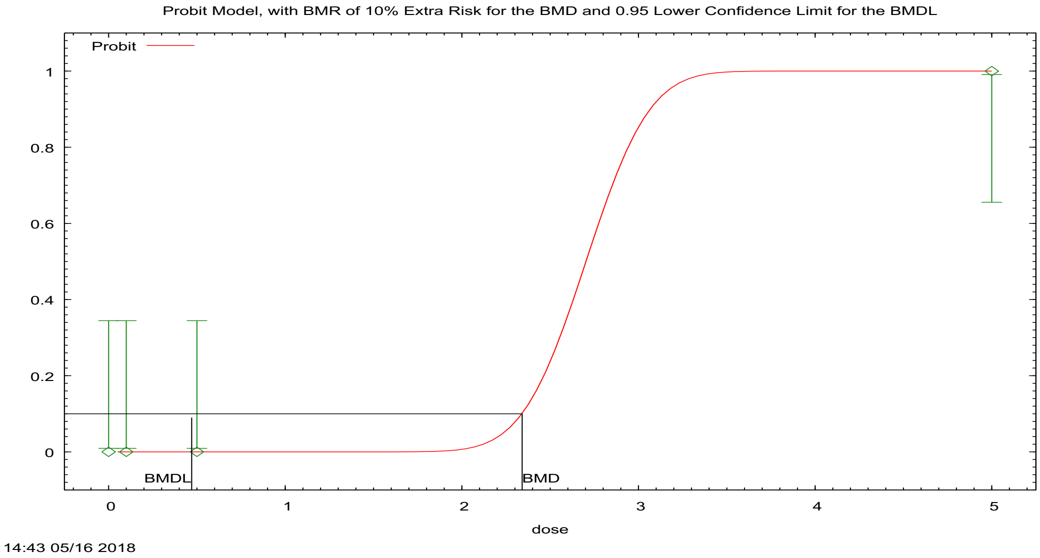

Figure 104. Plot of incidence rate by dose with fitted curve for Probit model for Single Cell Hepatocellular Necrosis in Males (90-Day Mice); dose shown in mg/kg/day.

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

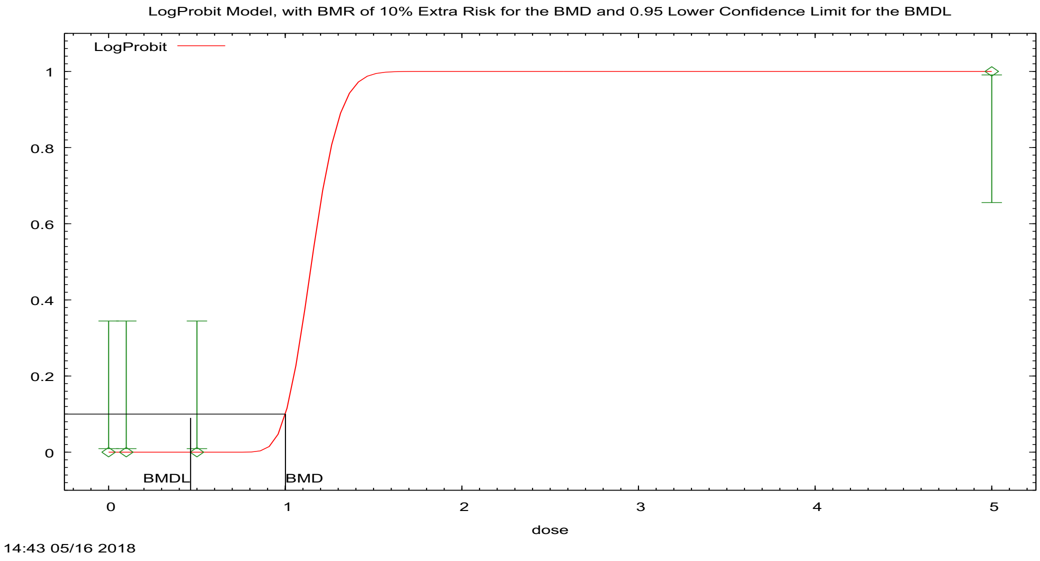

Figure 105. Plot of incidence rate by dose with fitted curve for LogProbit model for Single Cell Hepatocellular Necrosis in Males (90-Day Mice); dose shown in mg/kg/day.

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

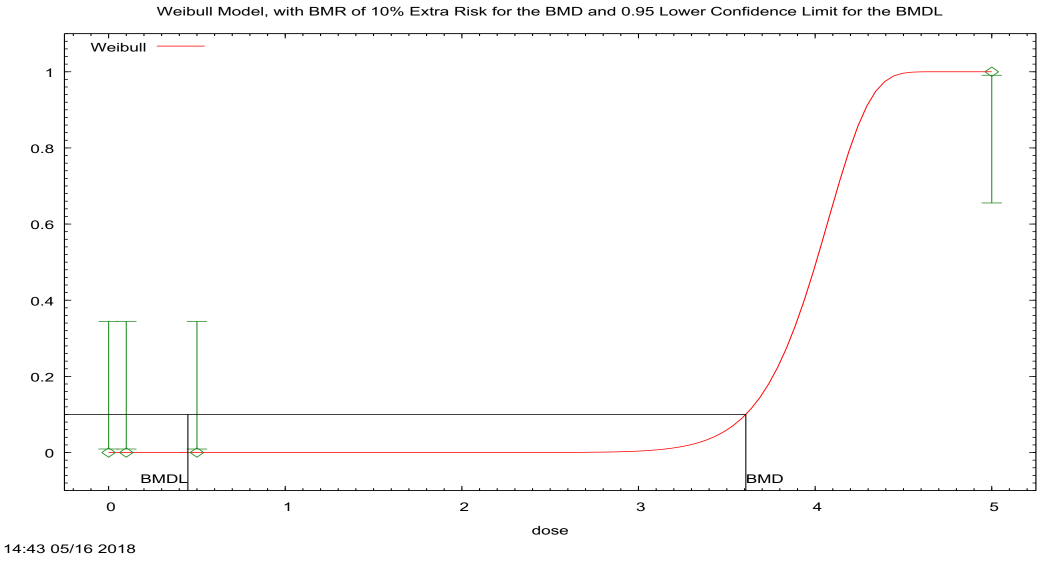

Figure 106. Plot of incidence rate by dose with fitted curve for Weibull model for Single Cell Hepatocellular Necrosis in Males (90-Day Mice); dose shown in mg/kg/day.

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

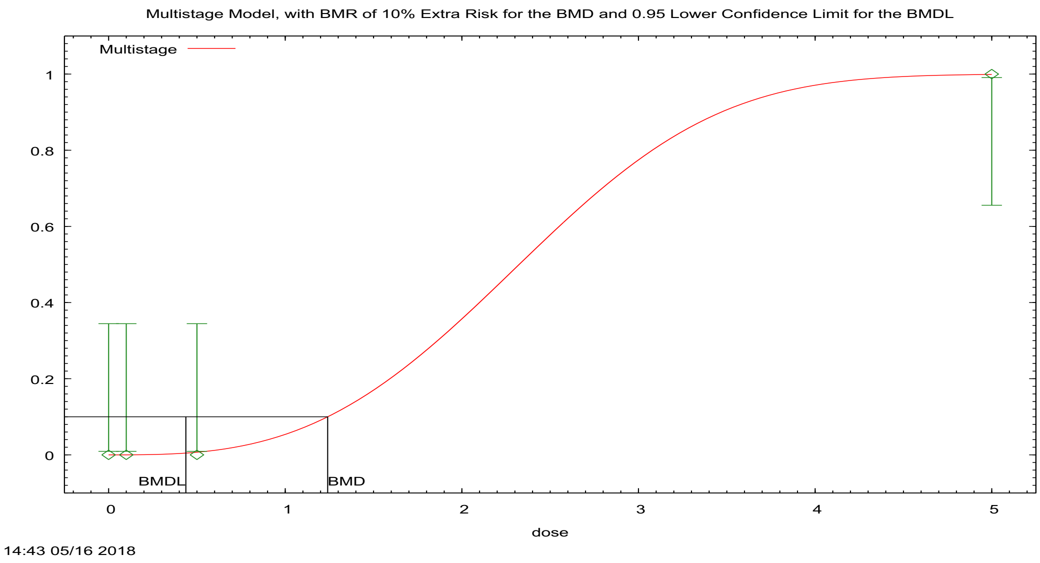

Figure 107. Plot of incidence rate by dose with fitted curve for Multistage 3° model for Single Cell Hepatocellular Necrosis in Males (90-Day Mice); dose shown in mg/kg/day.

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

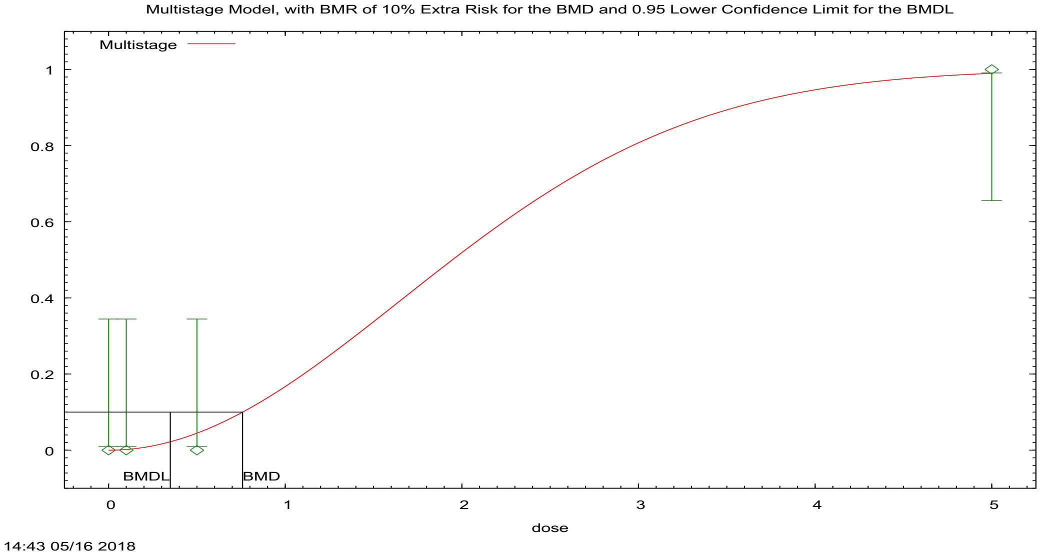

Figure 108. Plot of incidence rate by dose with fitted curve for Multistage 2° model for Single Cell Hepatocellular Necrosis in Males (90-Day Mice); dose shown in mg/kg/day.

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

1.23. BMDS Summary of Single Cell Hepatocellular Necrosis in Males (Reproductive Mice)

Table 23. 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	Models that met inclusion criteria are presented (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). 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.

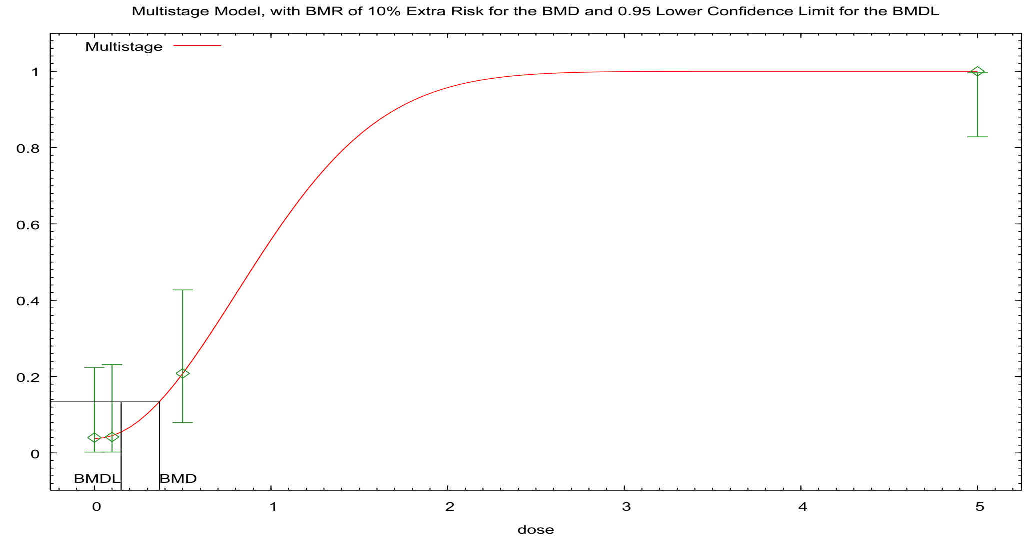

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Figure 109. Plot of incidence rate by dose with fitted curve for Multistage 2° model for Single Cell Hepatocellular Necrosis in Males (Reproductive Mice); dose shown in mg/kg/day.

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

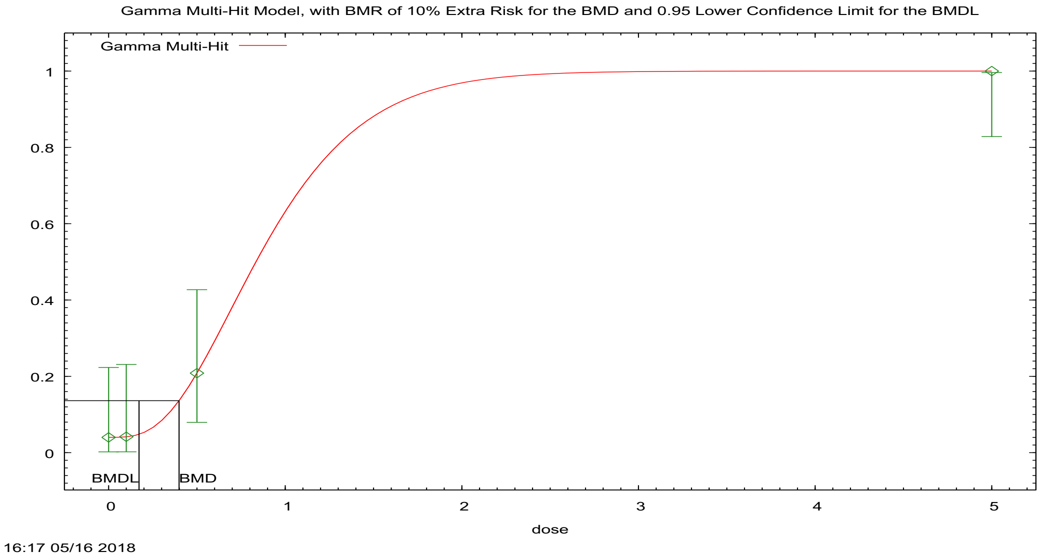

Figure 110. Plot of incidence rate by dose with fitted curve for Gamma model for Single Cell Hepatocellular Necrosis in Males (Reproductive Mice); dose shown in mg/kg/day.

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

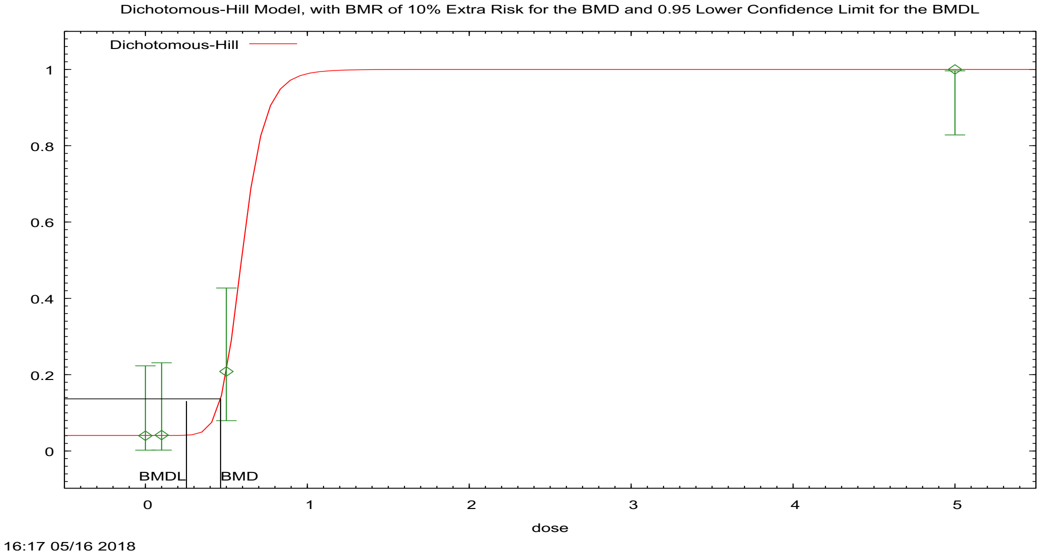

Figure 111. Plot of incidence rate by dose with fitted curve for Dichotomous-Hill model for Single Cell Hepatocellular Necrosis in Males (Reproductive Mice); dose shown in mg/kg/day.

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

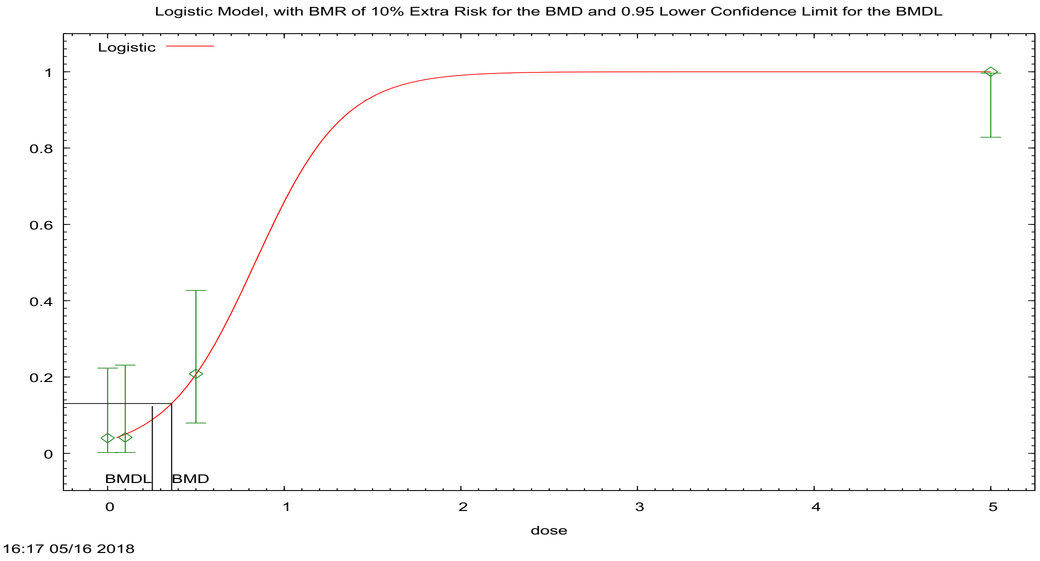

Figure 112. Plot of incidence rate by dose with fitted curve for Logistic model for Single Cell Hepatocellular Necrosis in Males (Reproductive Mice); dose shown in mg/kg/day.

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

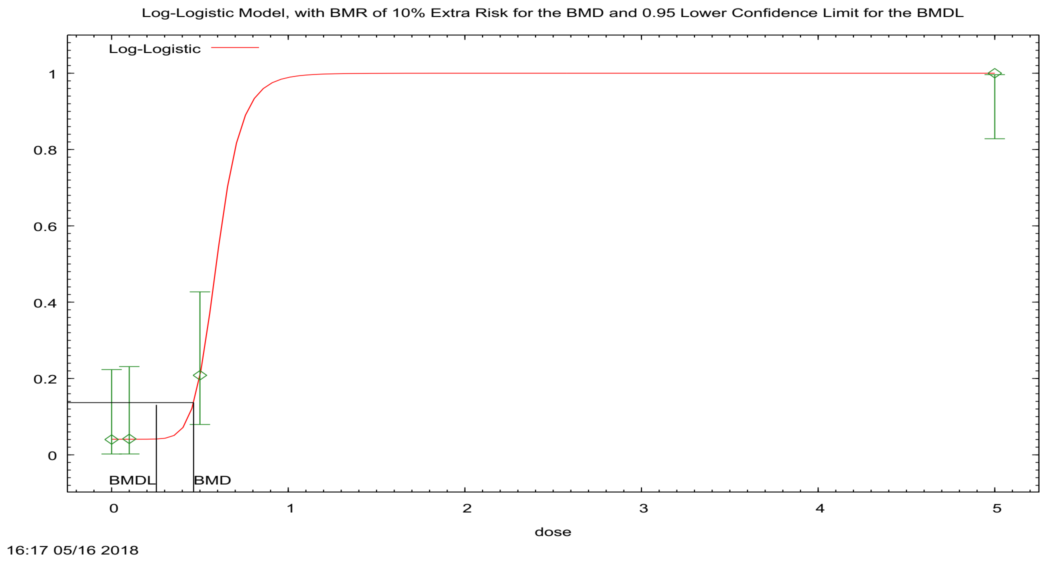

Figure 113. Plot of incidence rate by dose with fitted curve for LogLogistic model for Single Cell Hepatocellular Necrosis in Males (Reproductive Mice); dose shown in mg/kg/day.

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

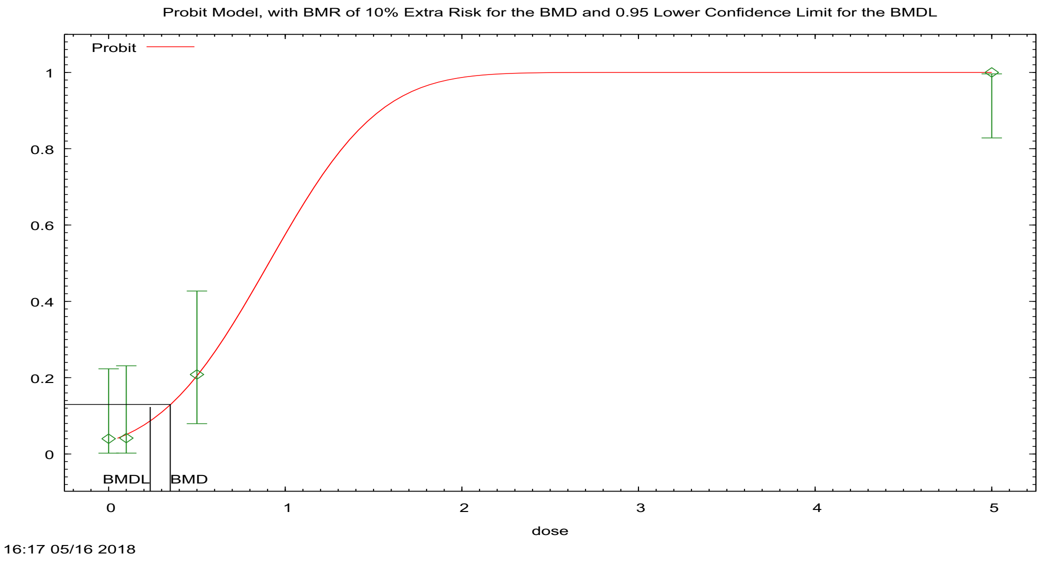

Figure 114. Plot of incidence rate by dose with fitted curve for Probit model for Single Cell Hepatocellular Necrosis in Males (Reproductive Mice); dose shown in mg/kg/day.

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

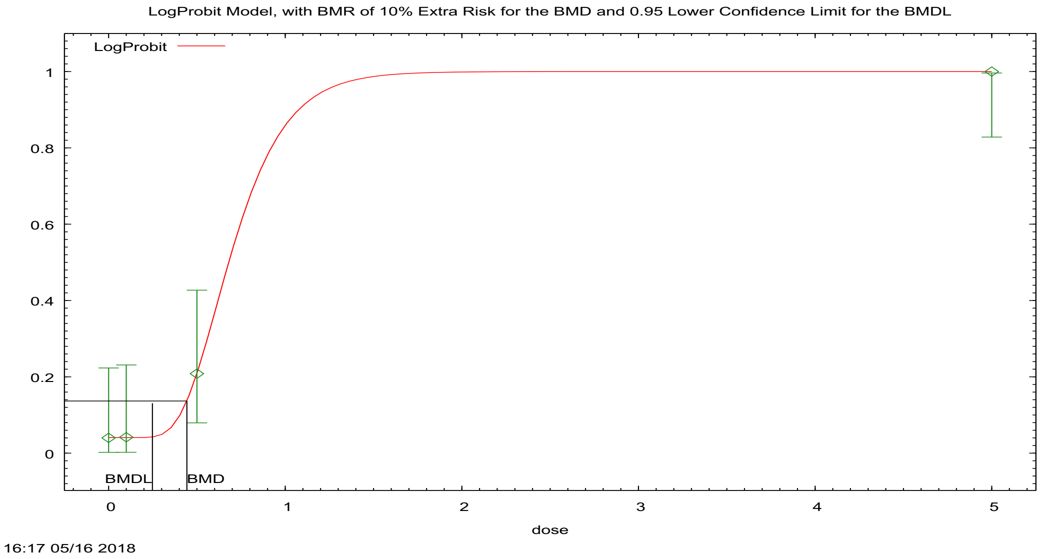

Figure 115. Plot of incidence rate by dose with fitted curve for LogProbit model for Single Cell Hepatocellular Necrosis in Males (Reproductive Mice); dose shown in mg/kg/day.

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

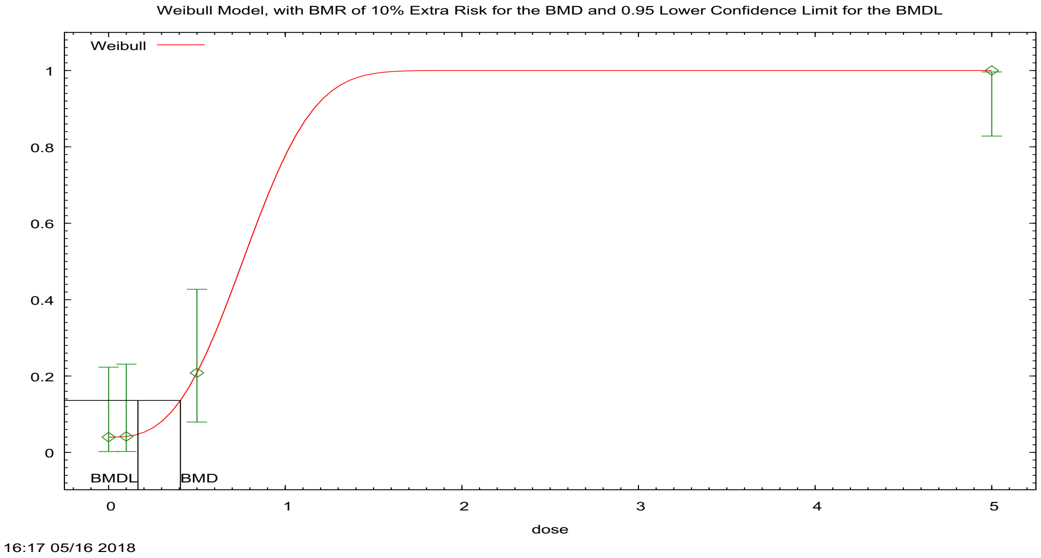

Figure 116. Plot of incidence rate by dose with fitted curve for Weibull model for Single Cell Hepatocellular Necrosis in Males (Reproductive Mice); dose shown in mg/kg/day.

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

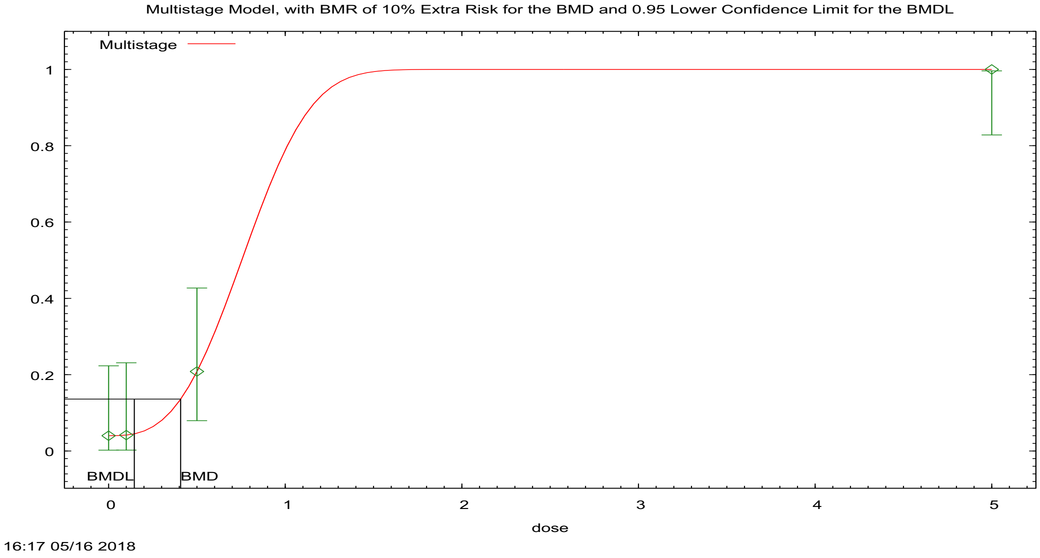

Figure 117. Plot of incidence rate by dose with fitted curve for Multistage 3° model for Single Cell Hepatocellular Necrosis in Males (Reproductive Mice); dose shown in mg/kg/day.

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

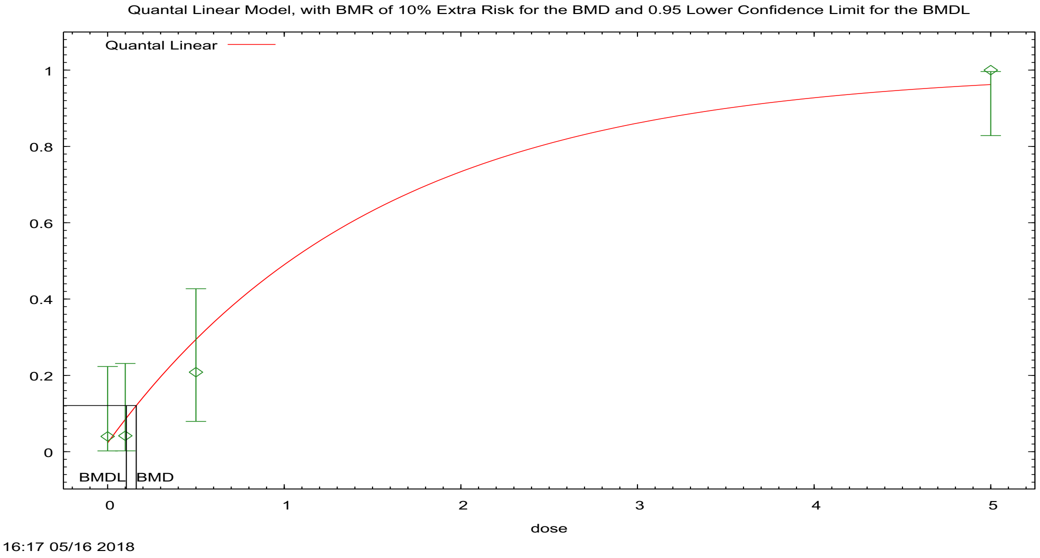

Figure 118. Plot of incidence rate by dose with fitted curve for Quantal-Linear model for Single Cell Hepatocellular Necrosis in Males (Reproductive Mice); dose shown in mg/kg/day.

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

1.24. BMDS Summary of Liver Weight to Brain Weight in Males (28-Day Mice)

Table 24. 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 (M4) **Exponential (M5)[b]**	**0.726**	**392.82**	**0.296**	**0.194**	**1.53**	**Only one model met inclusion criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)).**

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

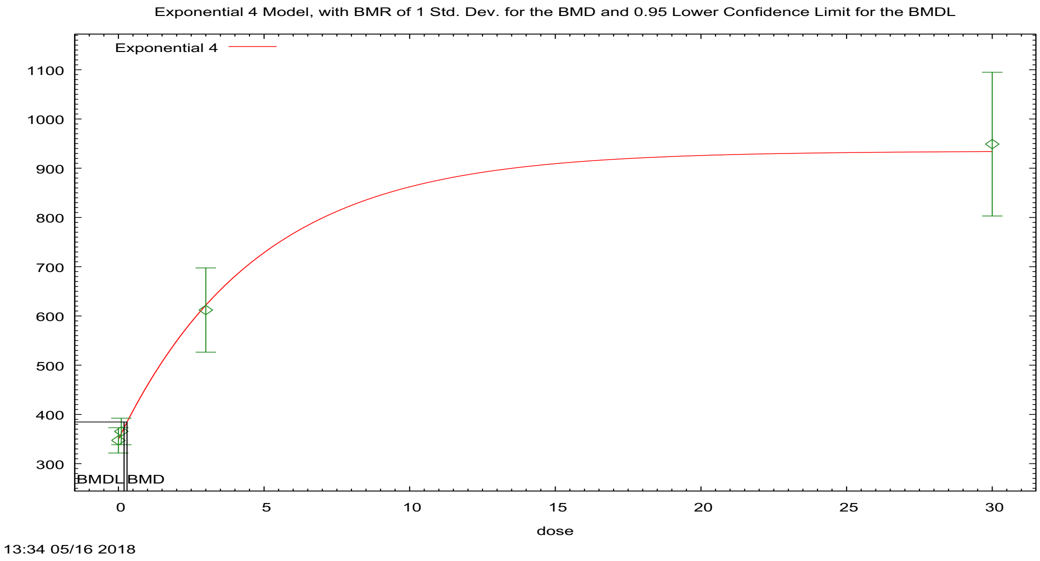

Figure 119. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Liver Weight to Brain Weight in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

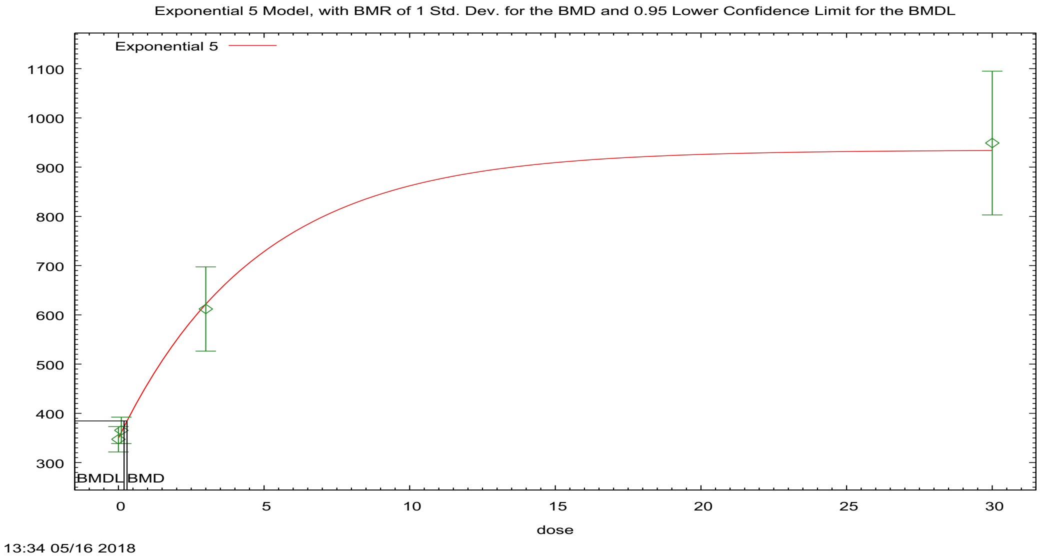

Figure 120. Plot of mean response by dose with fitted curve for Exponential (M5) model with modeled variance for Liver Weight to Brain Weight in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

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

1.25. BMDS Summary of Liver Weight to Brain Weight in Females (28-Day Mice)

Table 25. 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 (M4) **Exponential (M5)**[b]	**0.381**	**340.54**	**1.14**	**0.751**	**1.52**	**Only one model met inclusion criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)).**

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

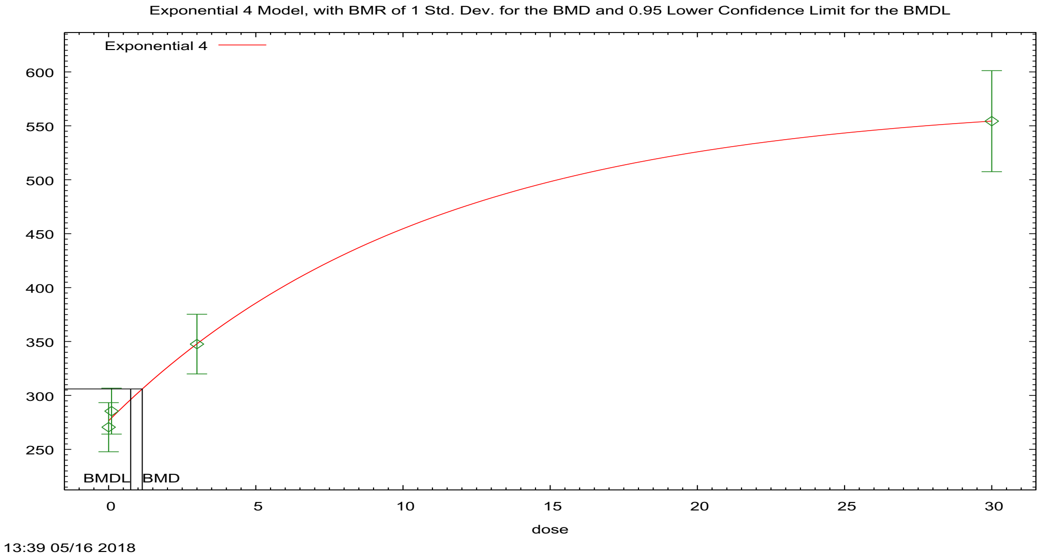

Figure 121. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Liver Weight to Brain Weight in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

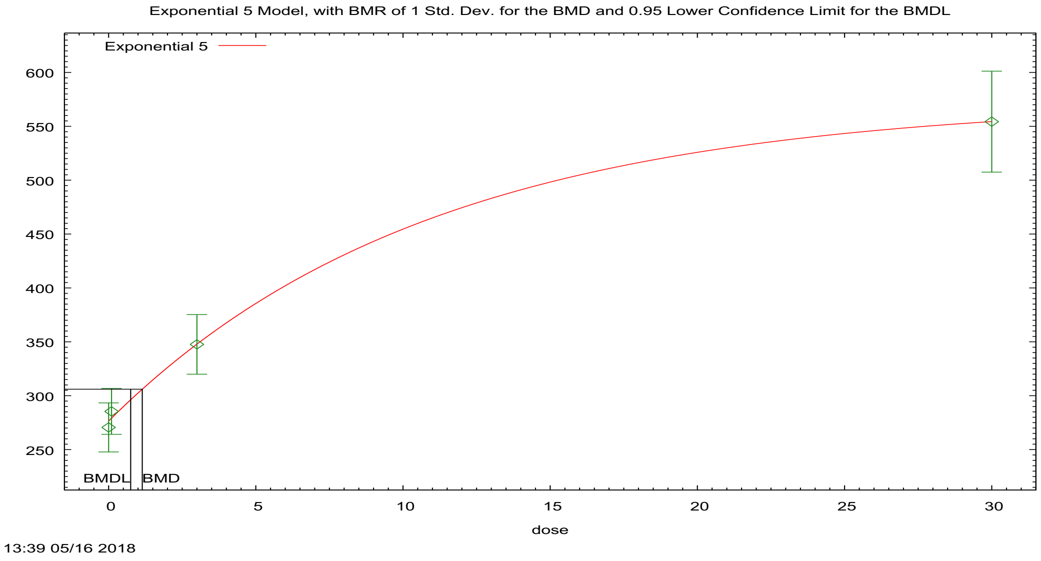

Figure 122. Plot of mean response by dose with fitted curve for Exponential (M5) model with modeled variance for Liver Weight to Brain Weight in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

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

1.26. BMDS Summary of Liver Weight to Brain Weight in Males (28-Day Rats)

Table 26. 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 (M4)	**0.762**	**389.53**	**1.01**	**0.611**	**1.65**	**Only one model met inclusion criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)).**

[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.

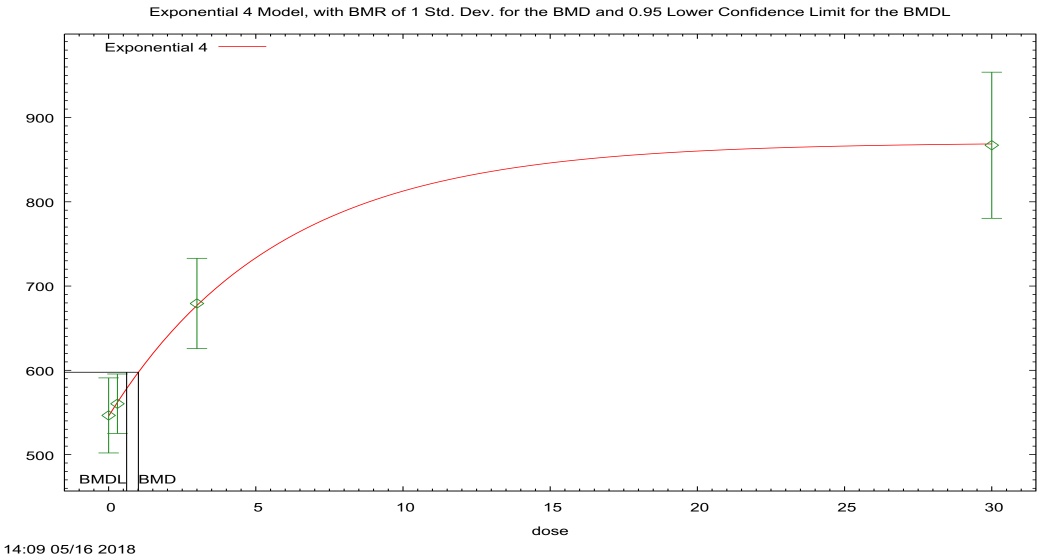

Figure 123. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Liver Weight to Brain Weight in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

BMDS WIZARD OUTPUT REPORT

BMDS Summary of H-28548: Subchronic Toxicity 90-Day Gavage Study in Mice – Liver Weight to Brain Weight (%) in Males

1.27. BMDS Summary of Liver Weight to Brain Weight in Males (90-Day Mice)

Table 27. 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	Models that met inclusion criteria are presented (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). 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	
Power[e] **Polynomial 3°**[f] **Polynomial 2°**[g] **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] 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.

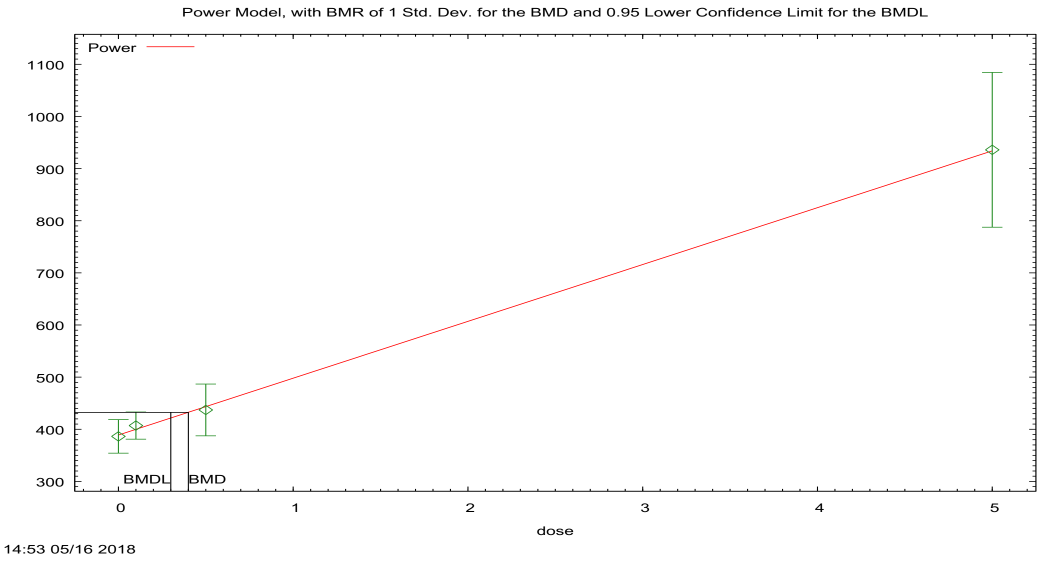

Figure 124. Plot of mean response by dose with fitted curve for Power model with modeled variance for Liver Weight to Brain Weight in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

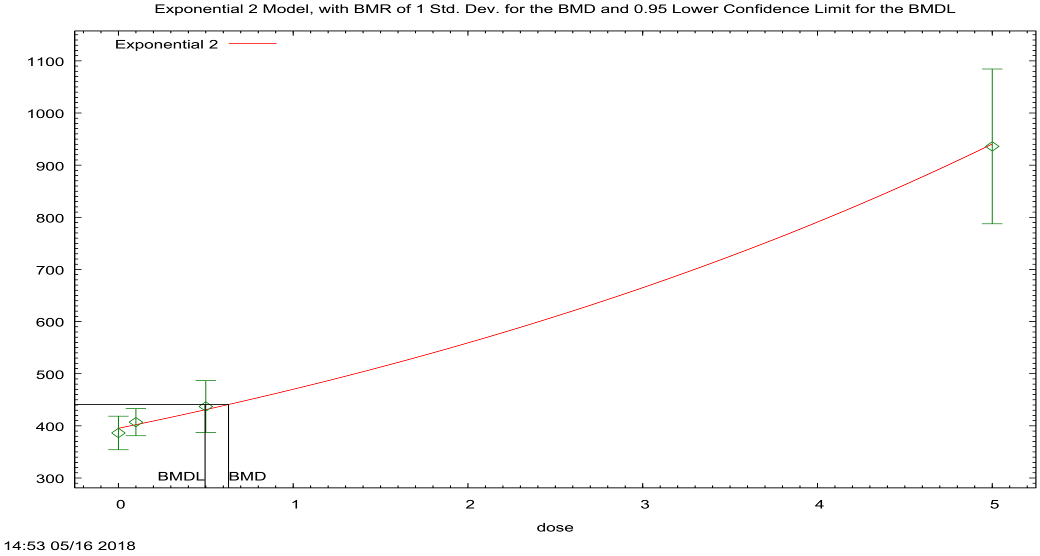

Figure 125. Plot of mean response by dose with fitted curve for Exponential (M2) model with modeled variance for Liver Weight to Brain Weight in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

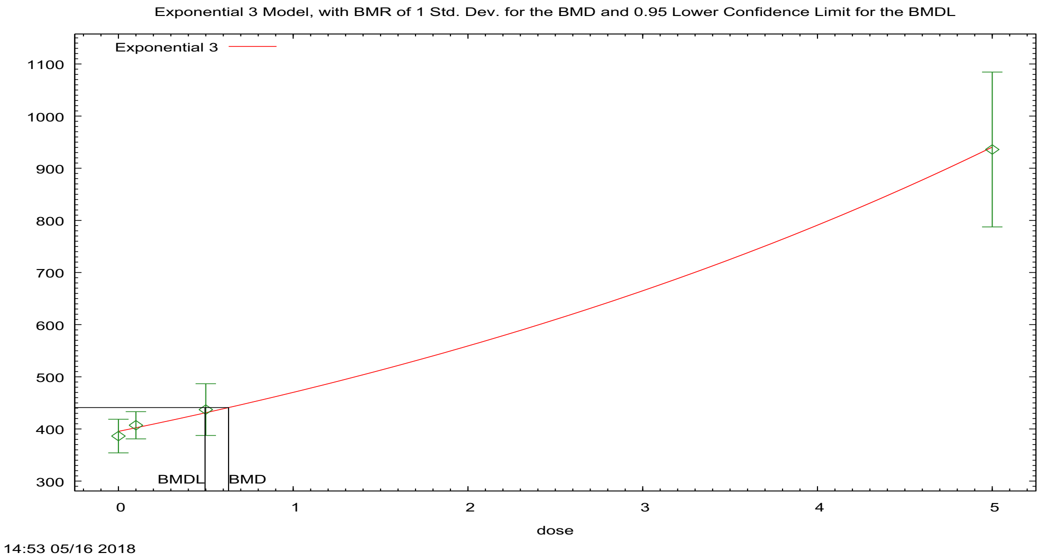

Figure 126. Plot of mean response by dose with fitted curve for Exponential (M3) model with modeled variance for Liver Weight to Brain Weight in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

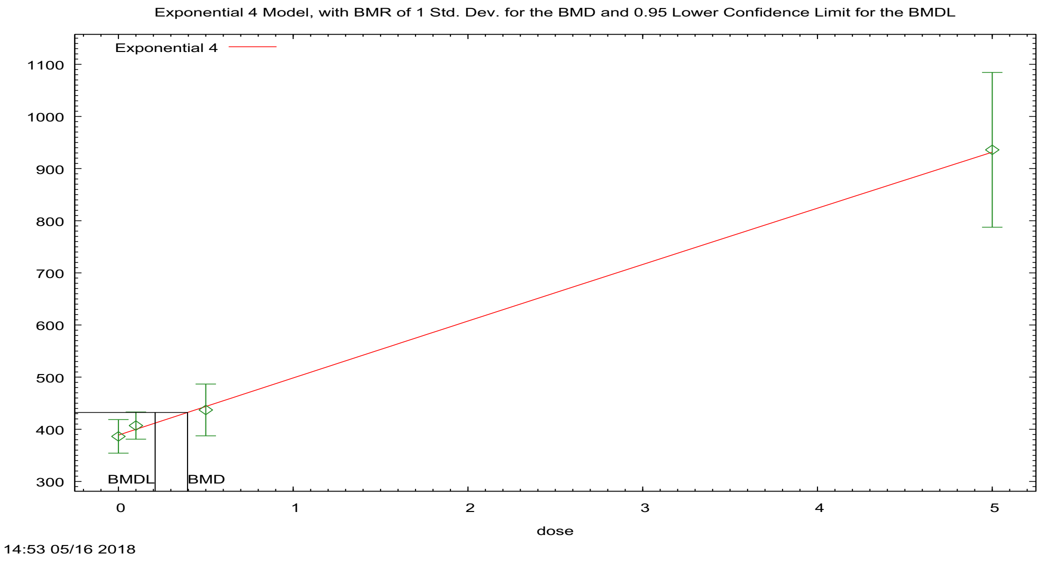

Figure 127. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Liver Weight to Brain Weight in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

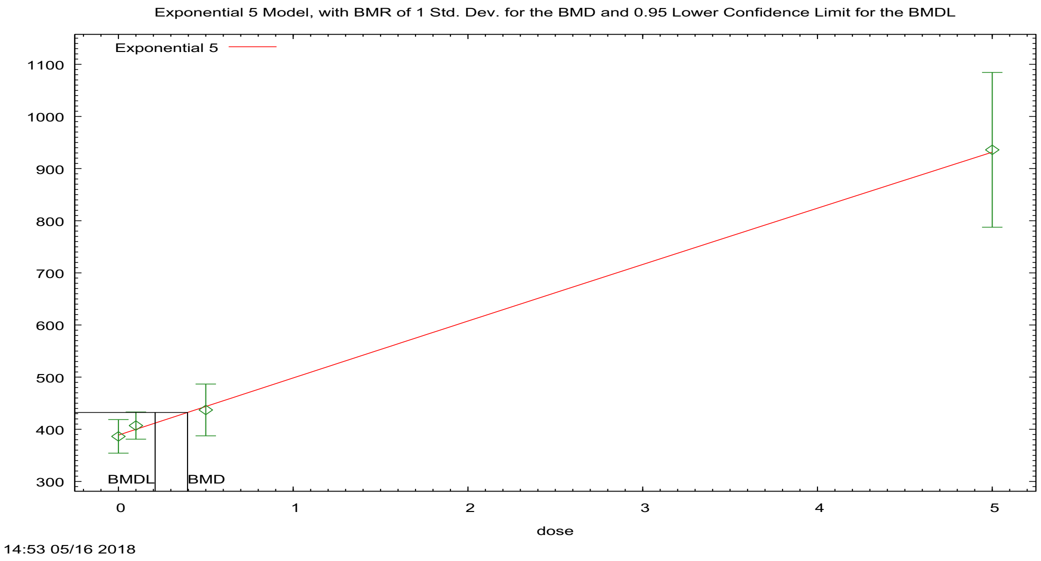

Figure 128. Plot of mean response by dose with fitted curve for Exponential (M5) model with modeled variance for Liver Weight to Brain Weight in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

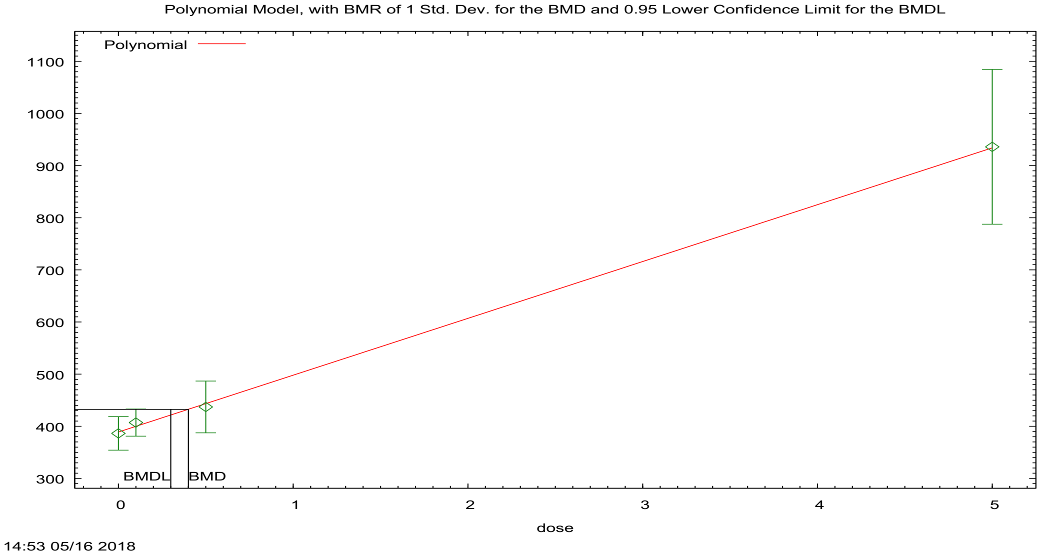

Figure 129. Plot of mean response by dose with fitted curve for Polynomial 3° model with modeled variance for Liver Weight to Brain Weight in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

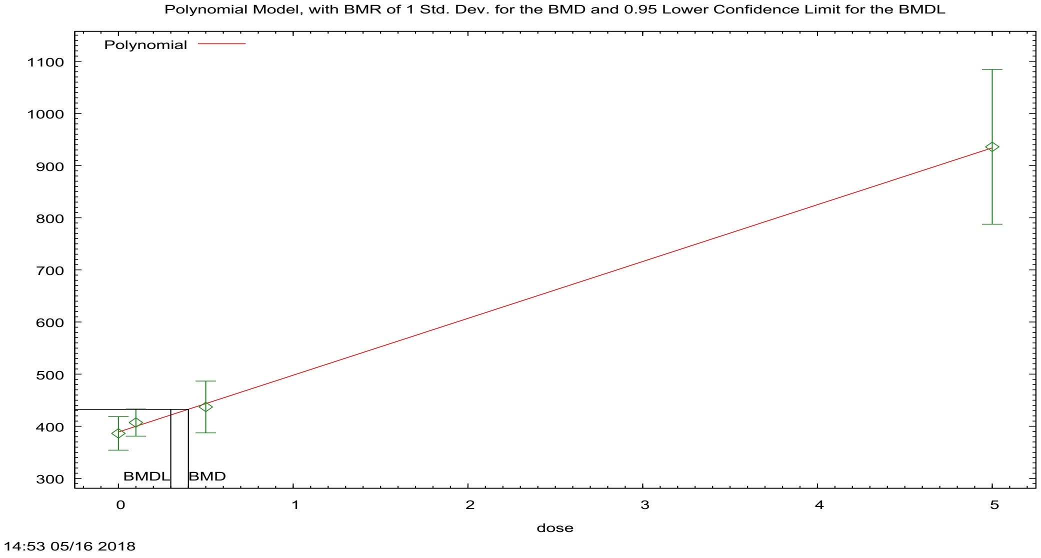

Figure 130. Plot of mean response by dose with fitted curve for Polynomial 2° model with modeled variance for Liver Weight to Brain Weight in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

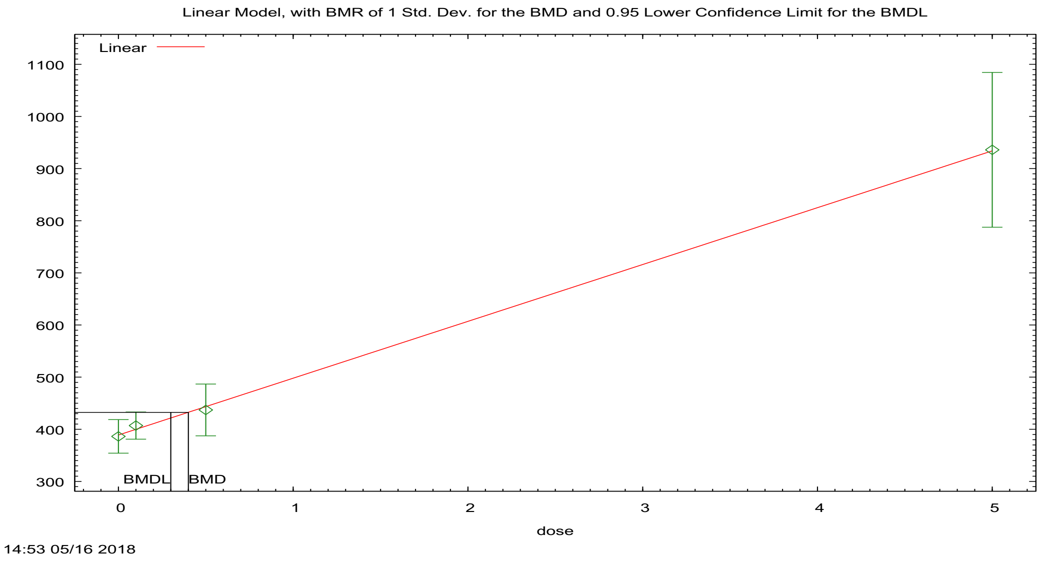

Figure 131. Plot of mean response by dose with fitted curve for Linear model with modeled variance for Liver Weight to Brain Weight in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

1.28. BMDS Summary of Liver Weight to Brain Weight in Females (90-Day Mice)

Table 28. 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**	**Models that met inclusion criteria are presented (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). 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	
Power	0.275	370.01	1.47	0.714	2.05	
Polynomial 3°[b] 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] 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.

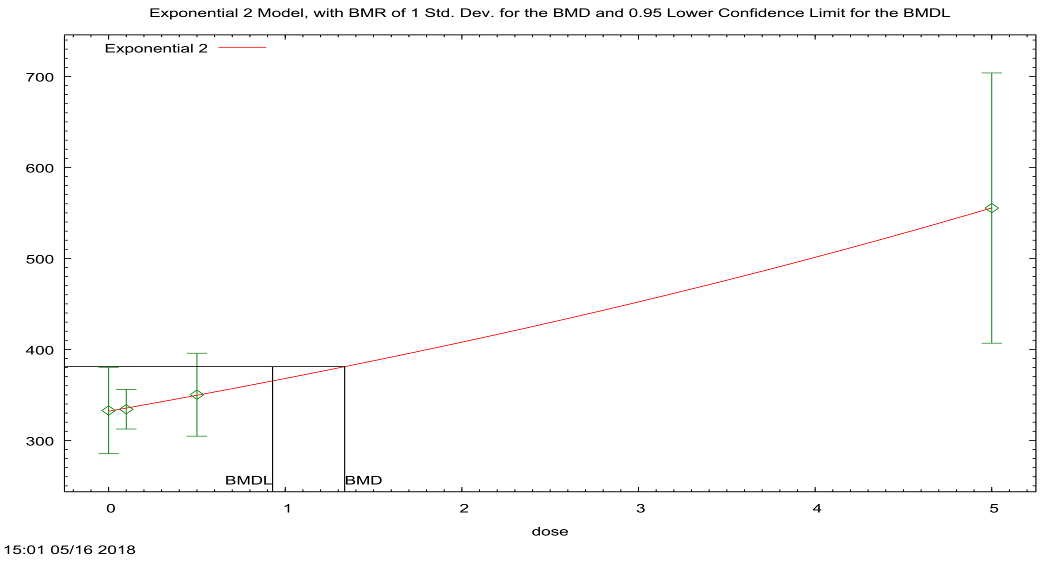

Figure 132. Plot of mean response by dose with fitted curve for Exponential (M2) model with modeled variance for Liver Weight to Brain Weight in Females (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

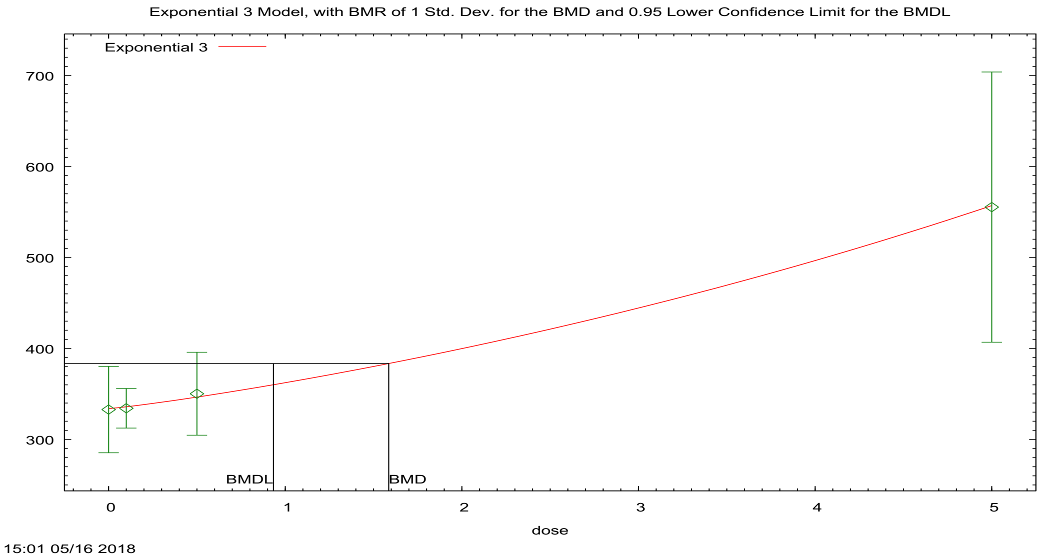

Figure 133. Plot of mean response by dose with fitted curve for Exponential (M3) model with modeled variance for Liver Weight to Brain Weight in Females (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

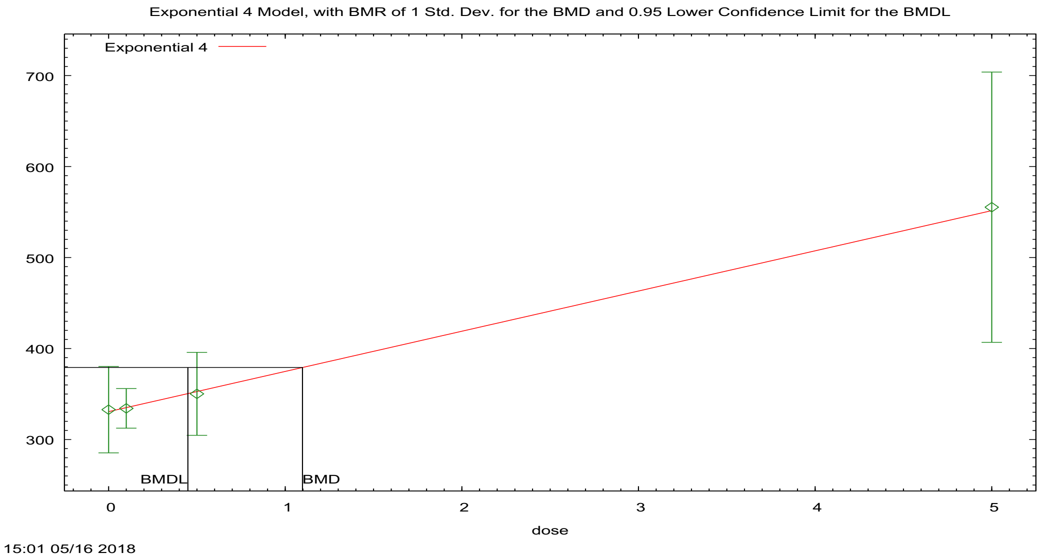

Figure 134. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Liver Weight to Brain Weight in Females (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

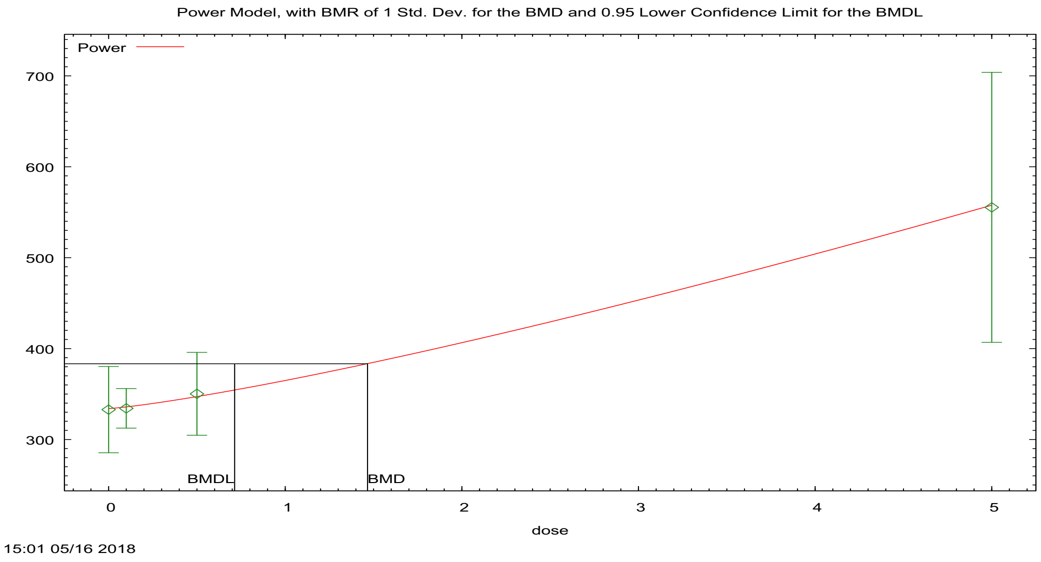

Figure 135. Plot of mean response by dose with fitted curve for Power model with modeled variance for Liver Weight to Brain Weight in Females (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

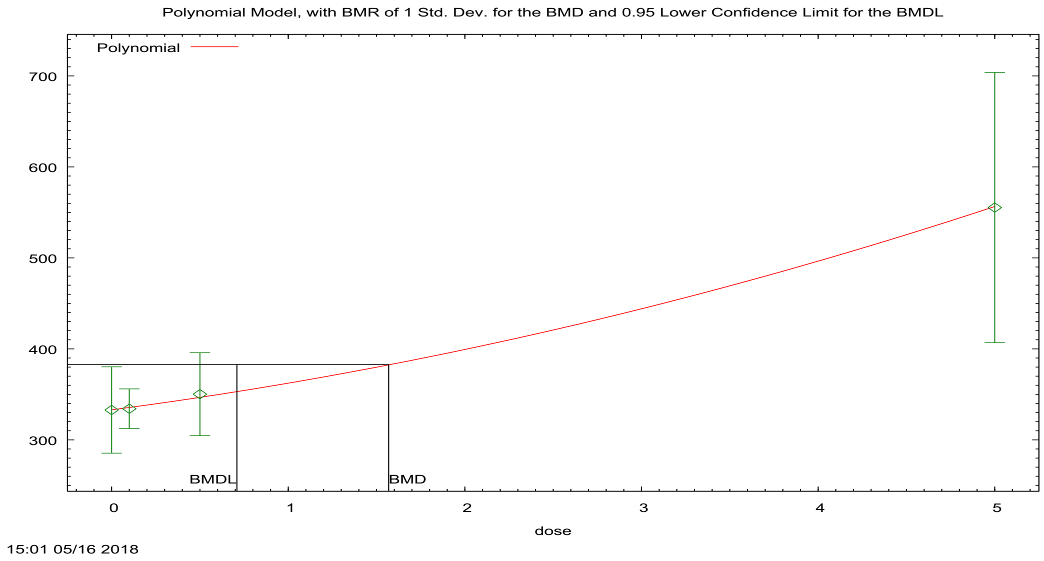

Figure 136. Plot of mean response by dose with fitted curve for Polynomial 3° model with modeled variance for Liver Weight to Brain Weight in Females (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

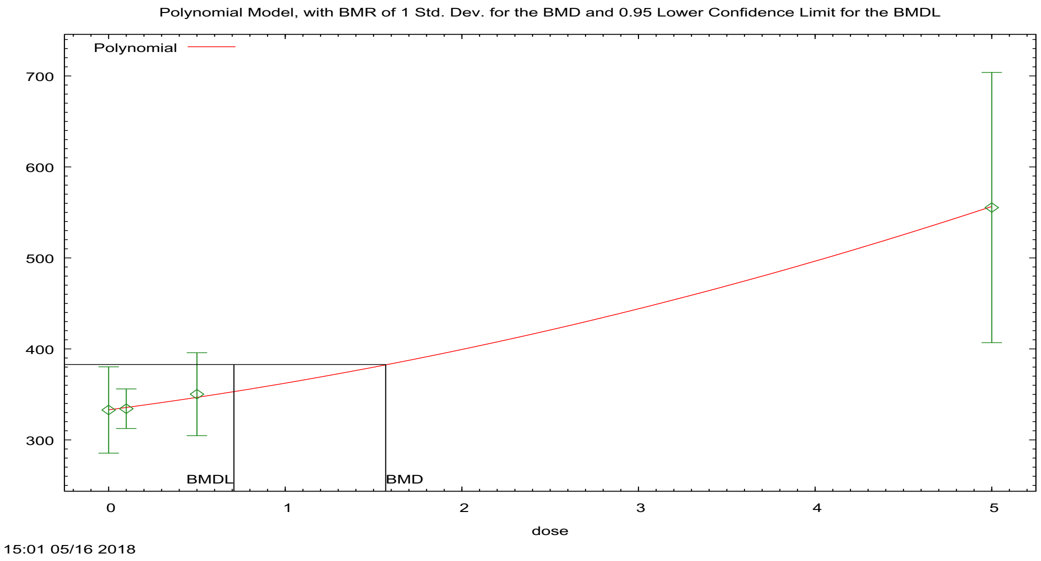

Figure 137. Plot of mean response by dose with fitted curve for Polynomial 2° model with modeled variance for Liver Weight to Brain Weight in Females (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

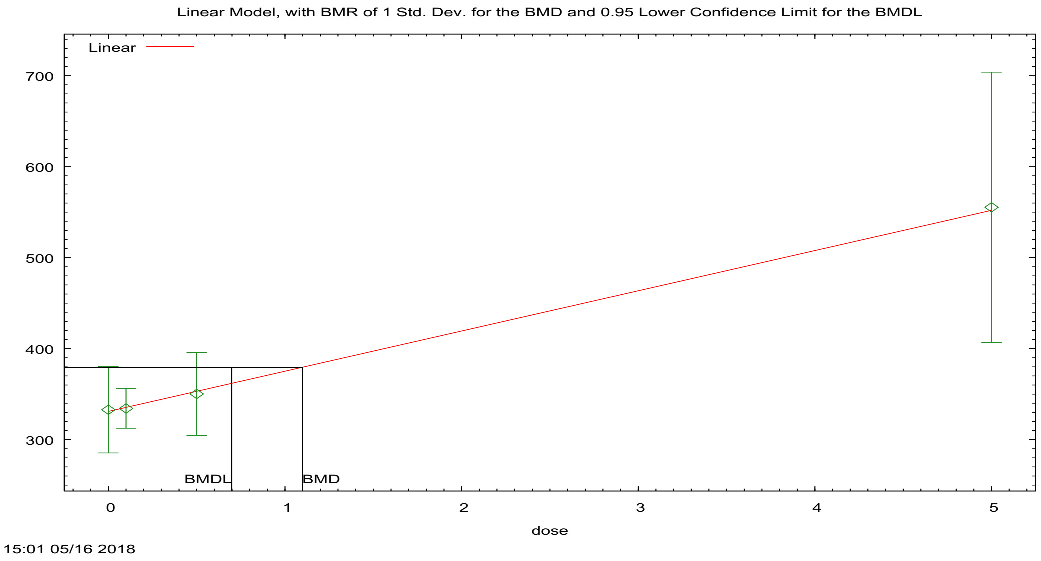

Figure 138. Plot of mean response by dose with fitted curve for Linear model with modeled variance for Liver Weight to Brain Weight in Females (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

1.29. BMDS Summary of Liver Weight to Brain Weight in Males (Reproductive Mice)

Table 29. 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 (M4) **Exponential (M5)**[b]	**0.570**	**927.48**	**0.232**	**0.165**	**1.40**	**Only one model met inclusion criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)).**

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

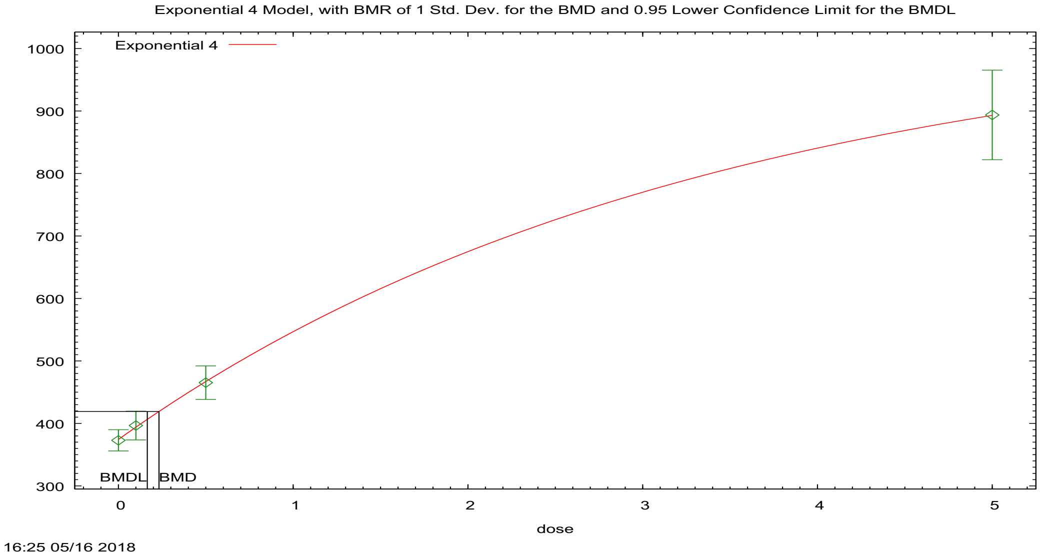

Figure 139. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Liver Weight to Brain Weight in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

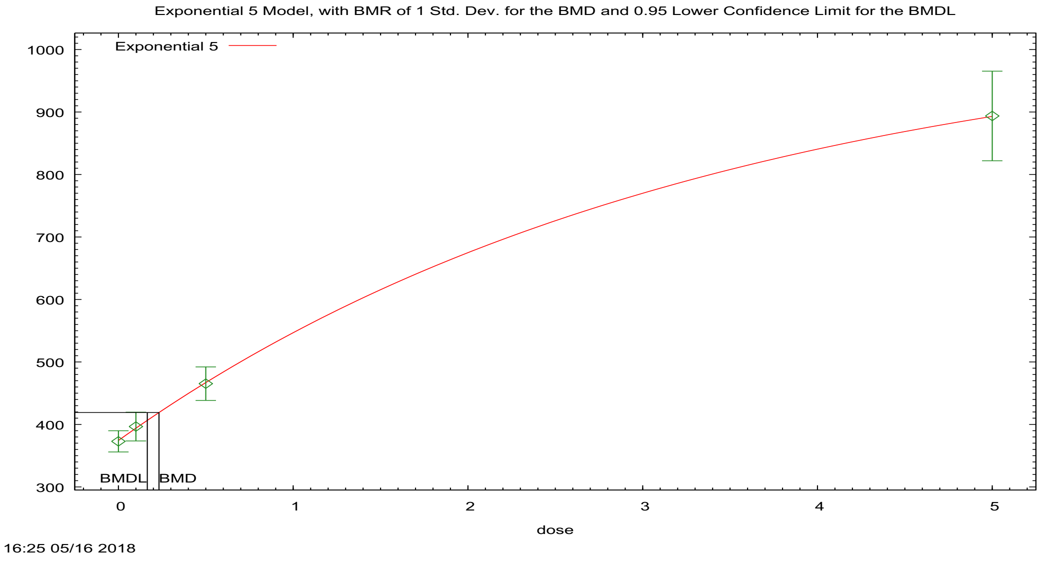

Figure 140. Plot of mean response by dose with fitted curve for Exponential (M5) model with modeled variance for Liver Weight to Brain Weight in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

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

1.30. BMDS Summary of Offspring Weight (litter as experimental unit) at PND21 in Males (Reproductive Mice)

Table 30. 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	Models that met inclusion criteria are presented (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). 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	
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.

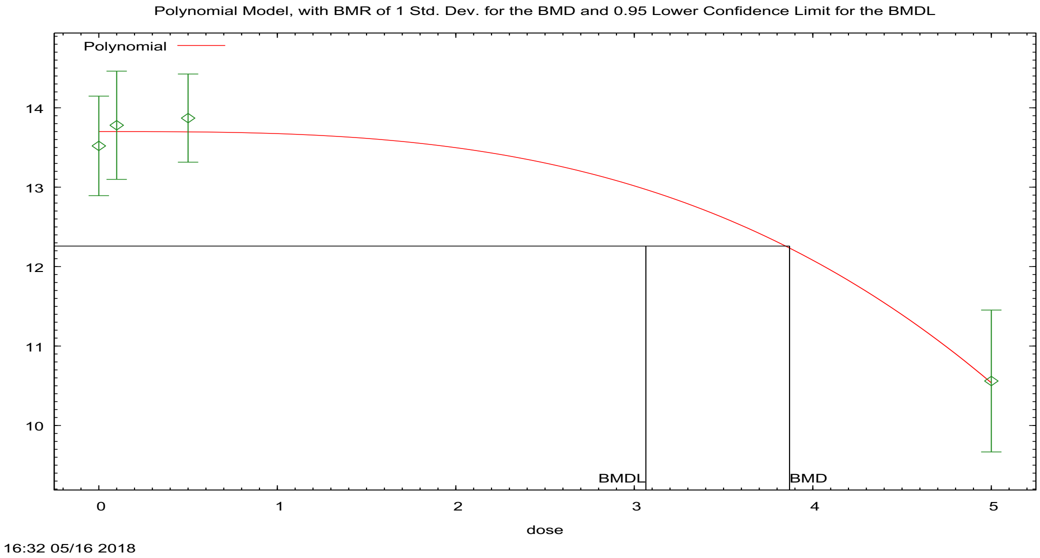

Figure 141. Plot of mean response by dose with fitted curve for Polynomial 3° model with constant variance for Offspring Weight (litter as experimental unit) at PND21 in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

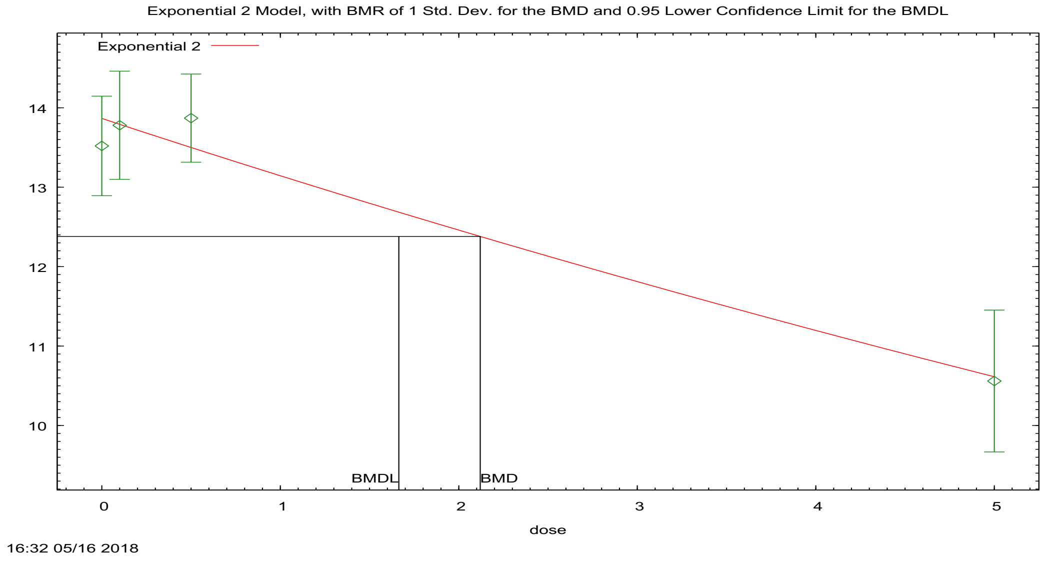

Figure 142. Plot of mean response by dose with fitted curve for Exponential (M2) model with constant variance for Offspring Weight (litter as experimental unit) at PND21 in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

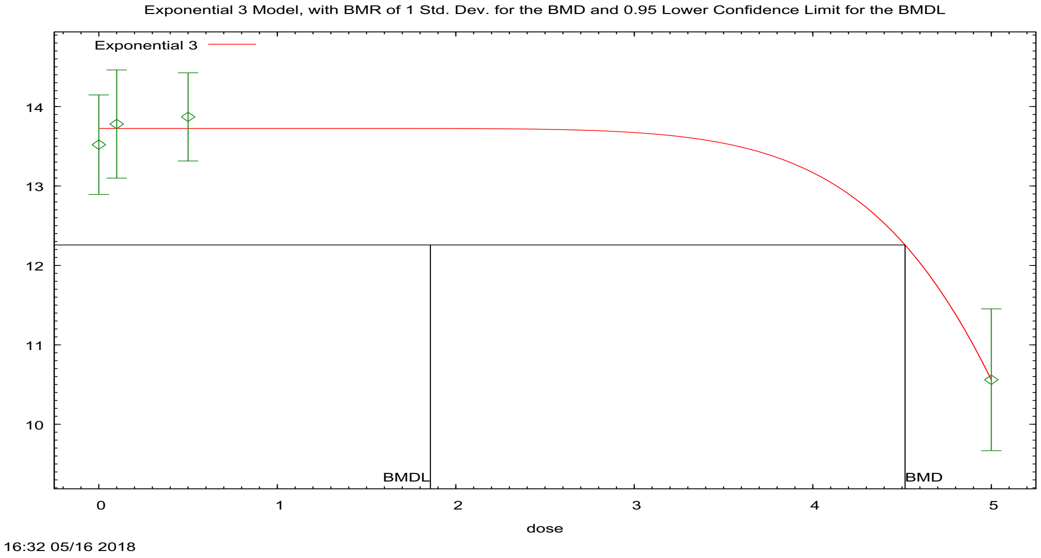

Figure 143. Plot of mean response by dose with fitted curve for Exponential (M3) model with constant variance for Offspring Weight (litter as experimental unit) at PND21 in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

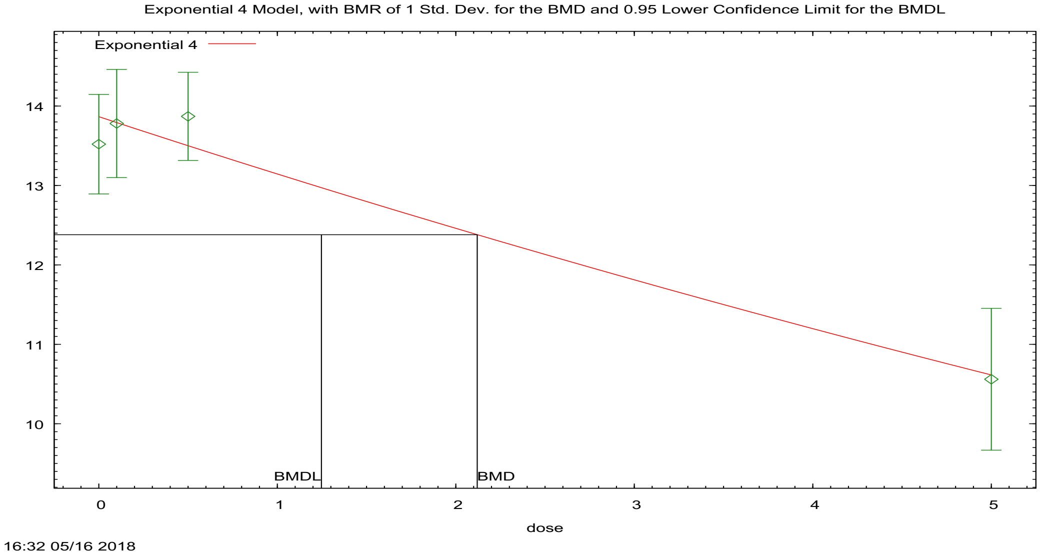

Figure 144. Plot of mean response by dose with fitted curve for Exponential (M4) model with constant variance for Offspring Weight (litter as experimental unit) at PND21 in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

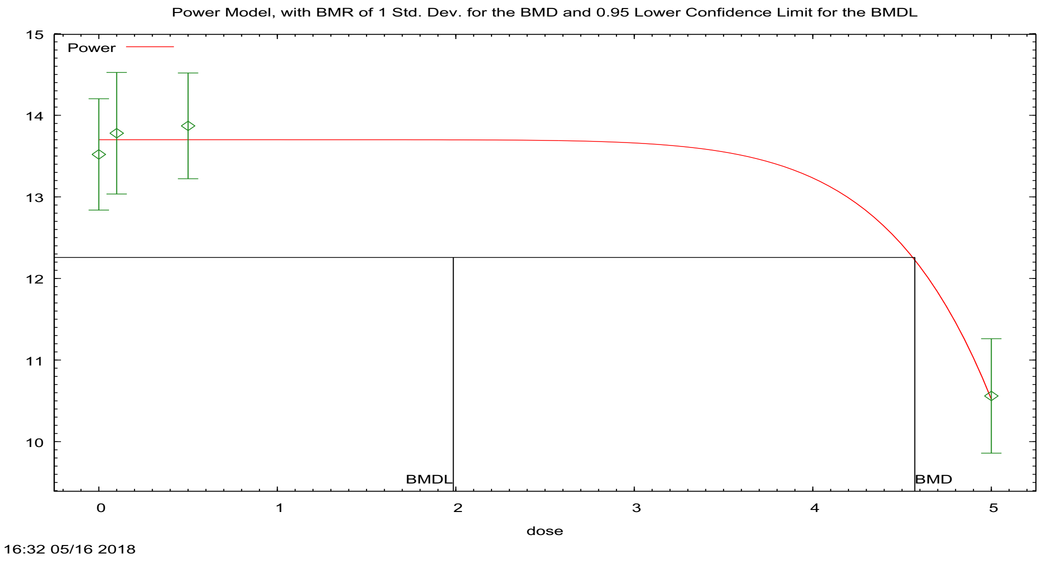

Figure 145. Plot of mean response by dose with fitted curve for Power model with constant variance for Offspring Weight (litter as experimental unit) at PND21 in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

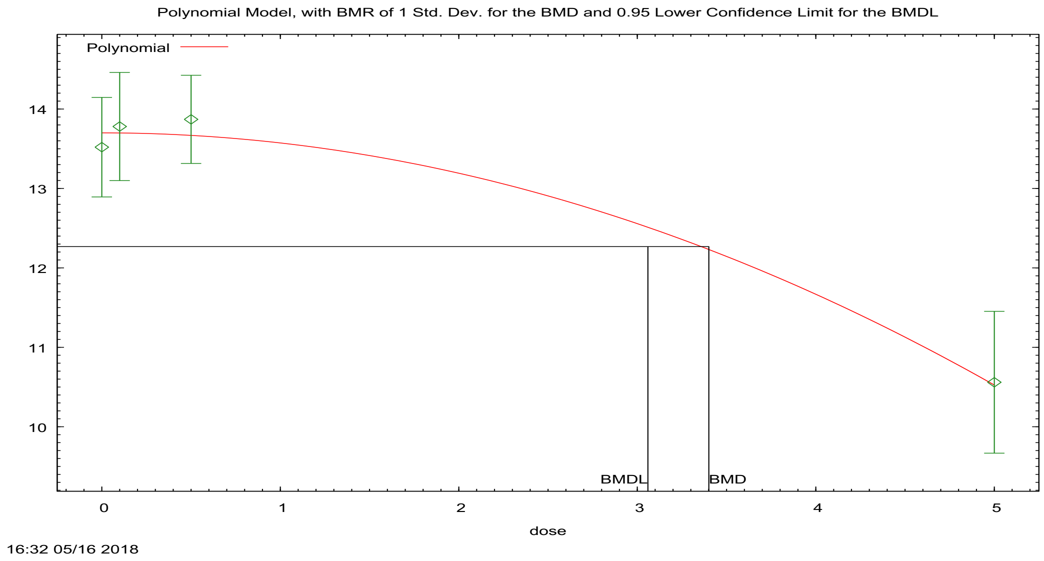

Figure 146. Plot of mean response by dose with fitted curve for Polynomial 2° model with constant variance for Offspring Weight (litter as experimental unit) at PND21 in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

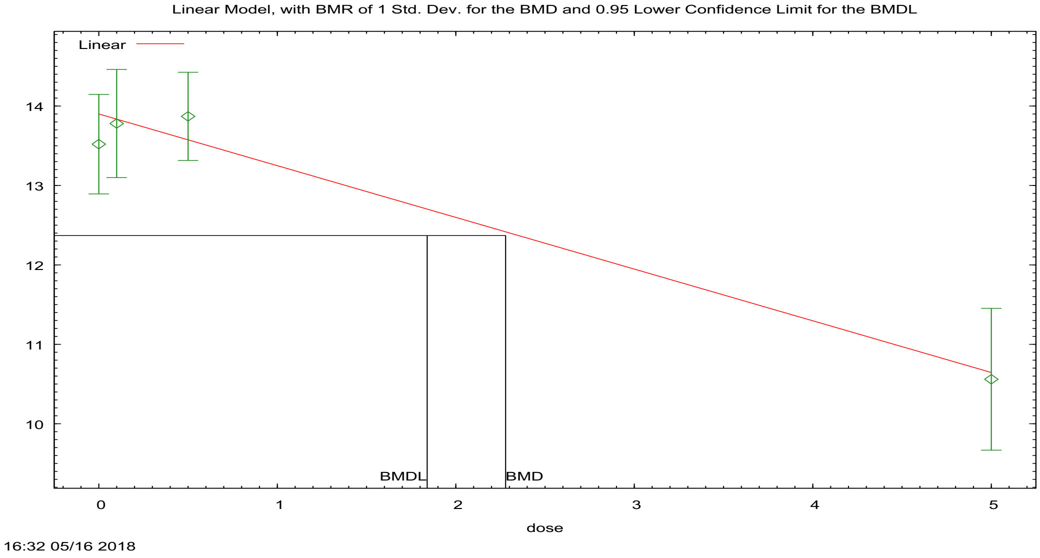

Figure 147. Plot of mean response by dose with fitted curve for Linear model with constant variance for Offspring Weight (litter as experimental unit) at PND21 in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

1.31. BMDS Summary of Offspring Weight (litter as experimental unit) at PND 21 in Females (Reproductive Mice)

Table 31. 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	Models that met inclusion criteria are presented (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). 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	
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.

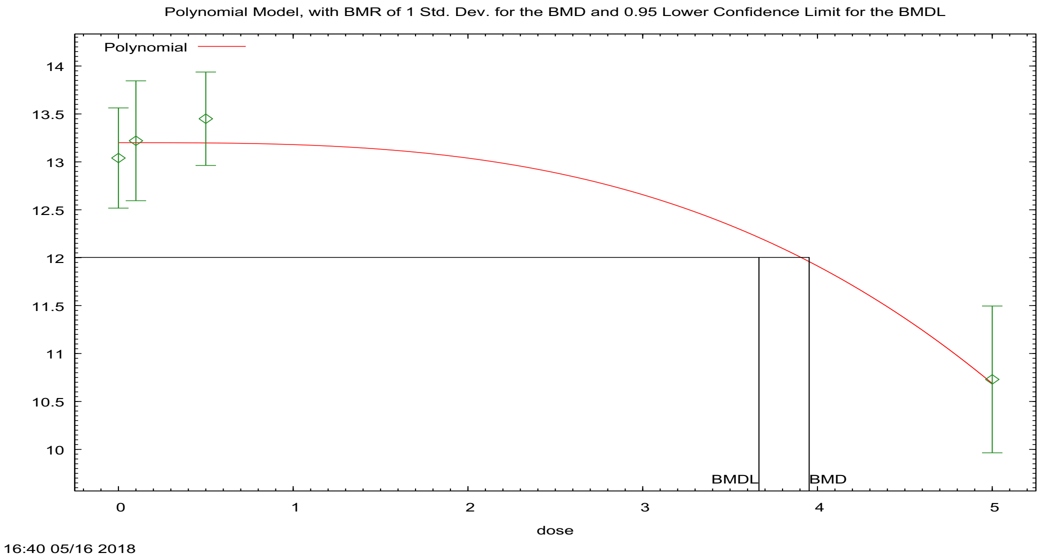

Figure 148. Plot of mean response by dose with fitted curve for Polynomial 3° model with constant variance for Offspring Weight (litter as experimental unit) at PND 21 in

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

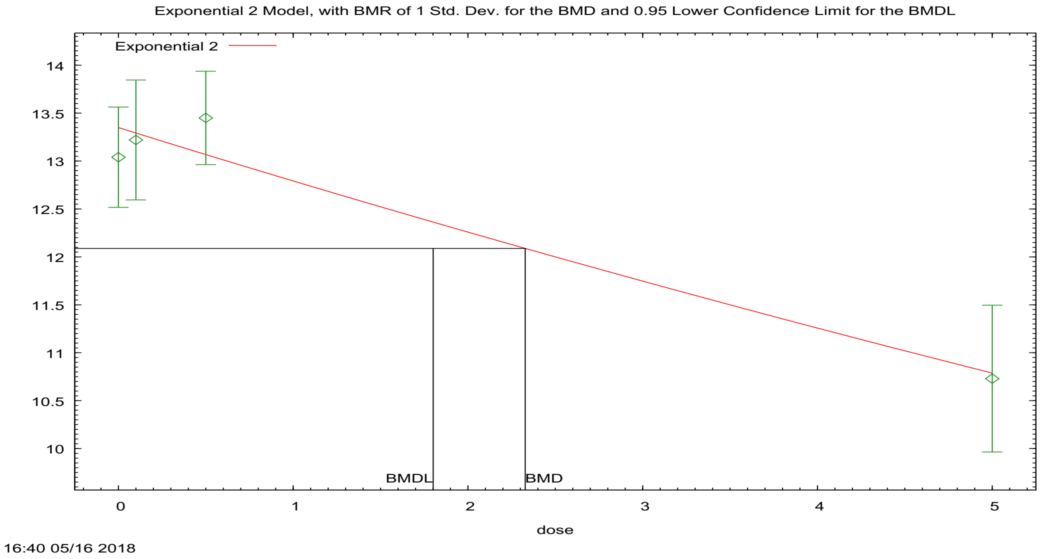

Figure 149. Plot of mean response by dose with fitted curve for Exponential (M2) model with constant variance for Offspring Weight (litter as experimental unit) at PND 21 in Females (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

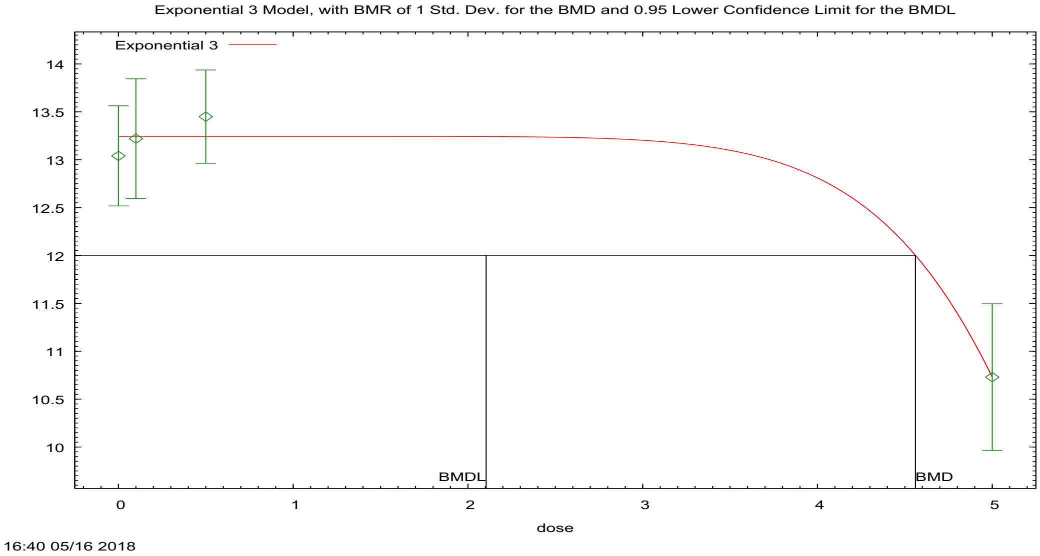

Figure 150. Plot of mean response by dose with fitted curve for Exponential (M3) model with constant variance for Offspring Weight (litter as experimental unit) at PND 21 in Females (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

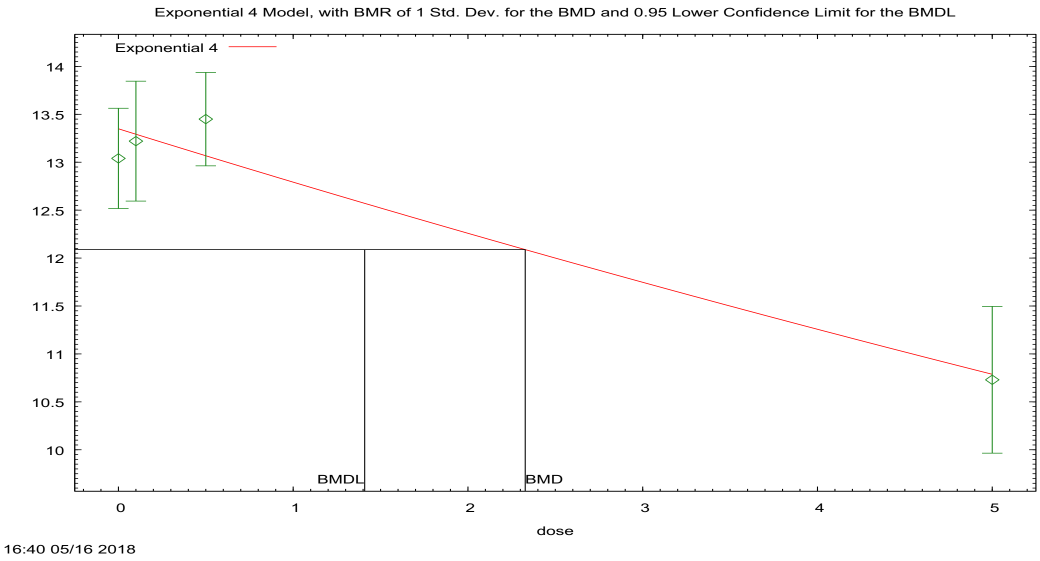

Figure 151. Plot of mean response by dose with fitted curve for Exponential (M4) model with constant variance for Offspring Weight (litter as experimental unit) at PND 21 in Females (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

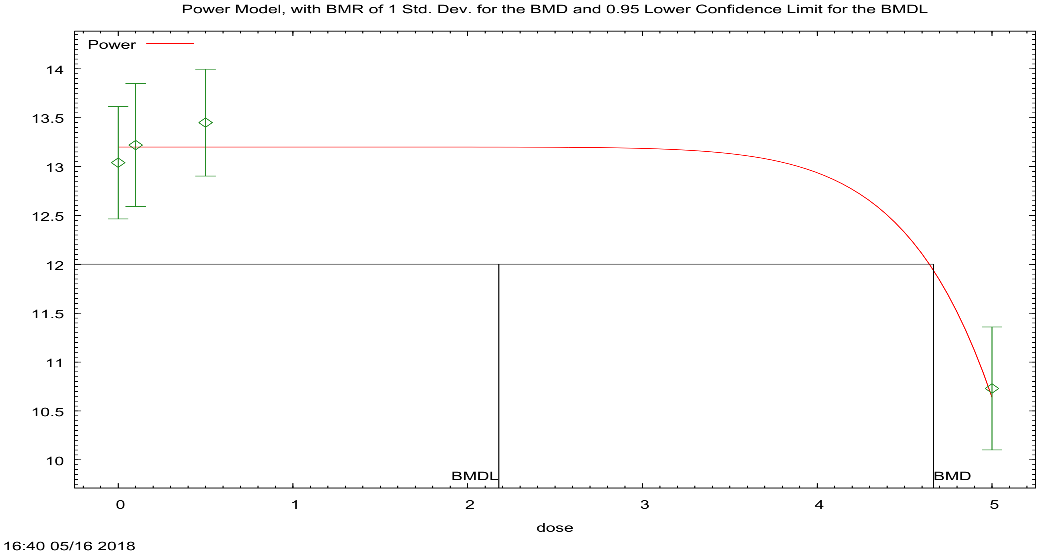

Figure 152. Plot of mean response by dose with fitted curve for Power model with constant variance for Offspring Weight (litter as experimental unit) at PND 21 in Females (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

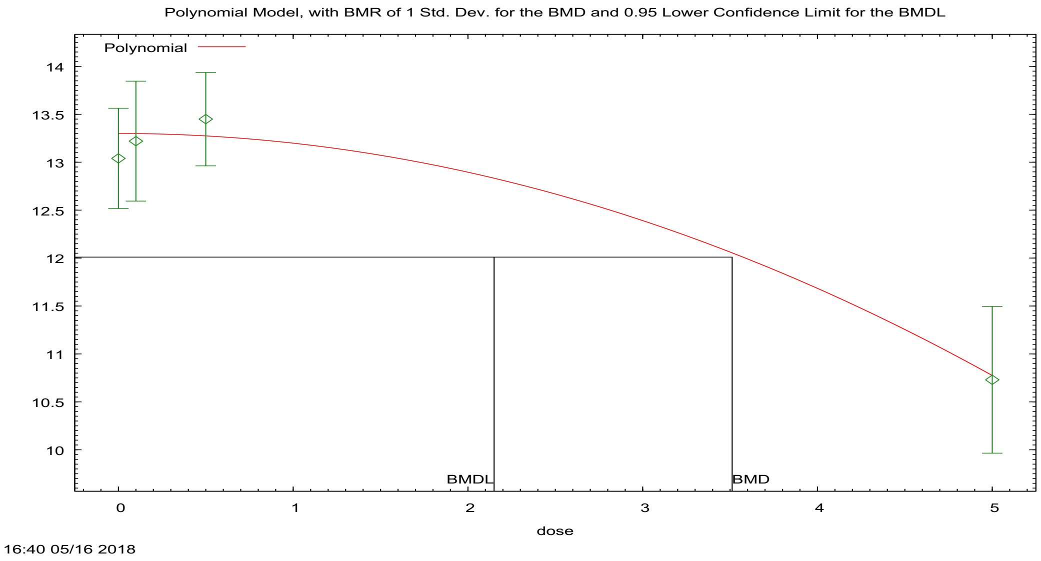

Figure 153. Plot of mean response by dose with fitted curve for Polynomial 2° model with constant variance for Offspring Weight (litter as experimental unit) at PND 21 in Females (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

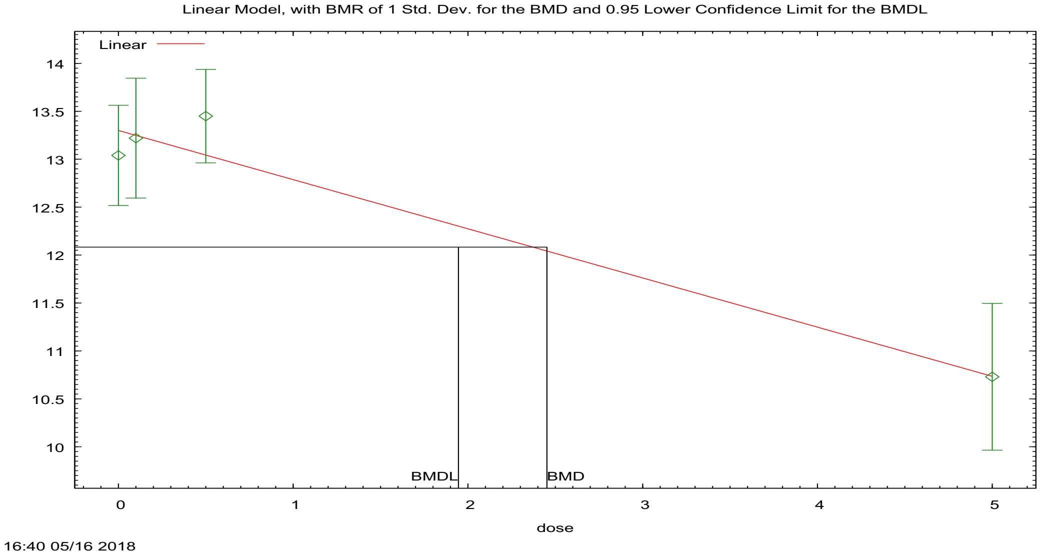

Figure 154. Plot of mean response by dose with fitted curve for Linear model with constant variance for Offspring Weight (litter as experimental unit) at PND 21 in Females (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

1.32. BMDS Summary of Offspring Body weight at PND40 in Males (Reproductive Mice)

Table 32. 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	Models that met inclusion criteria are presented (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). 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	
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.

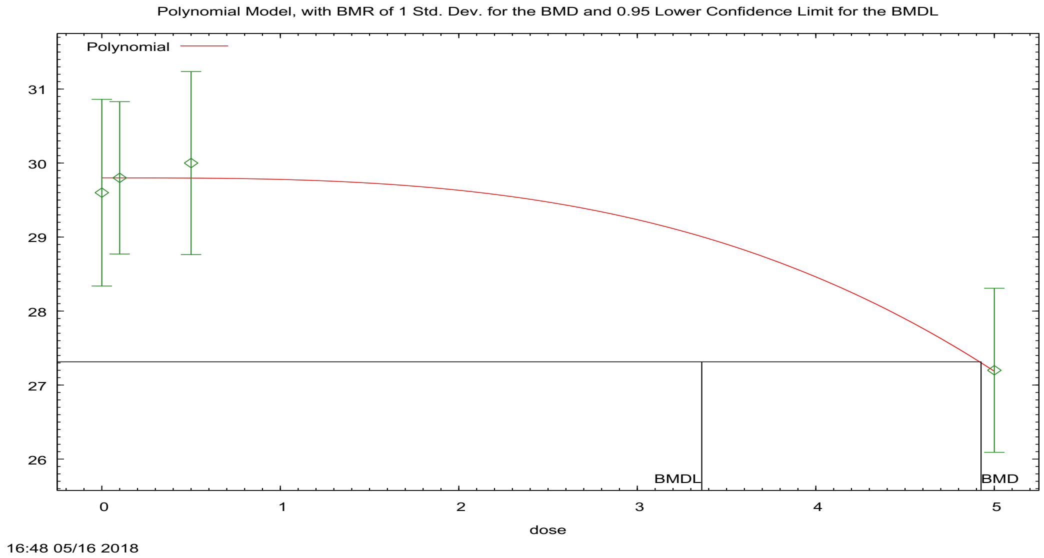

Figure 155. Plot of mean response by dose with fitted curve for Polynomial 3° model with constant variance for Offspring Body weight at PND40 in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

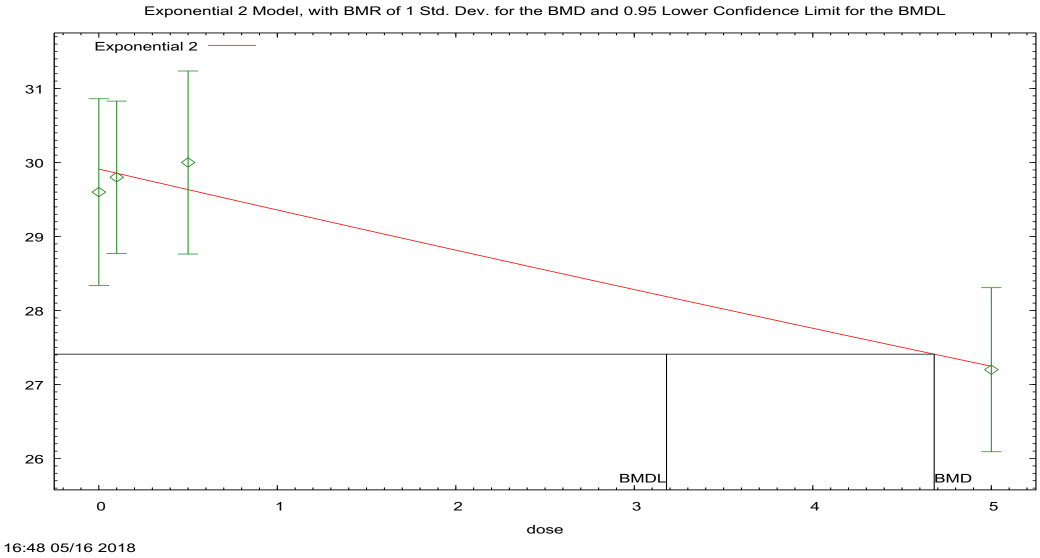

Figure 156. Plot of mean response by dose with fitted curve for Exponential (M2) model with constant variance for Offspring Body weight at PND40 in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

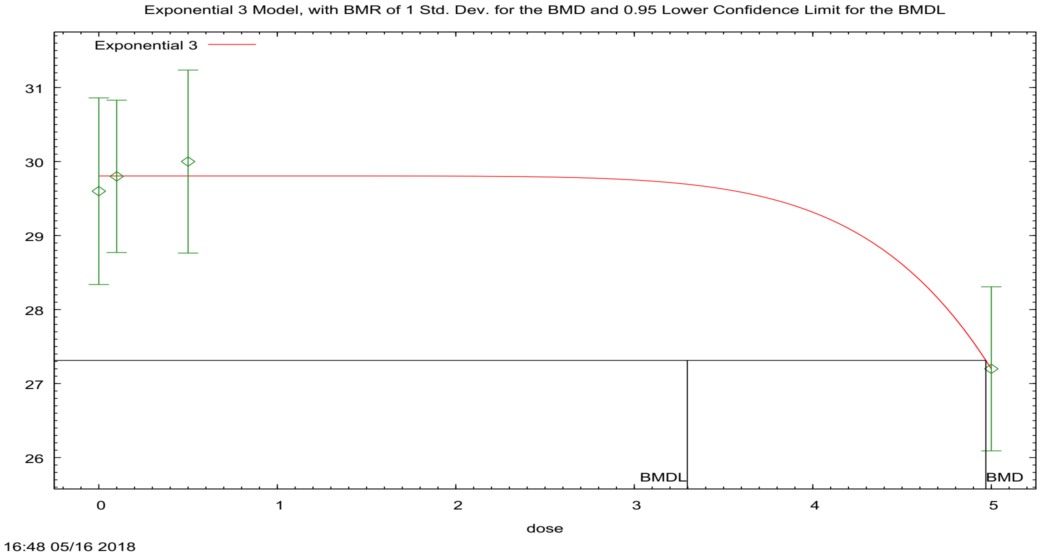

Figure 157. Plot of mean response by dose with fitted curve for Exponential (M3) model with constant variance for Offspring Body weight at PND40 in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

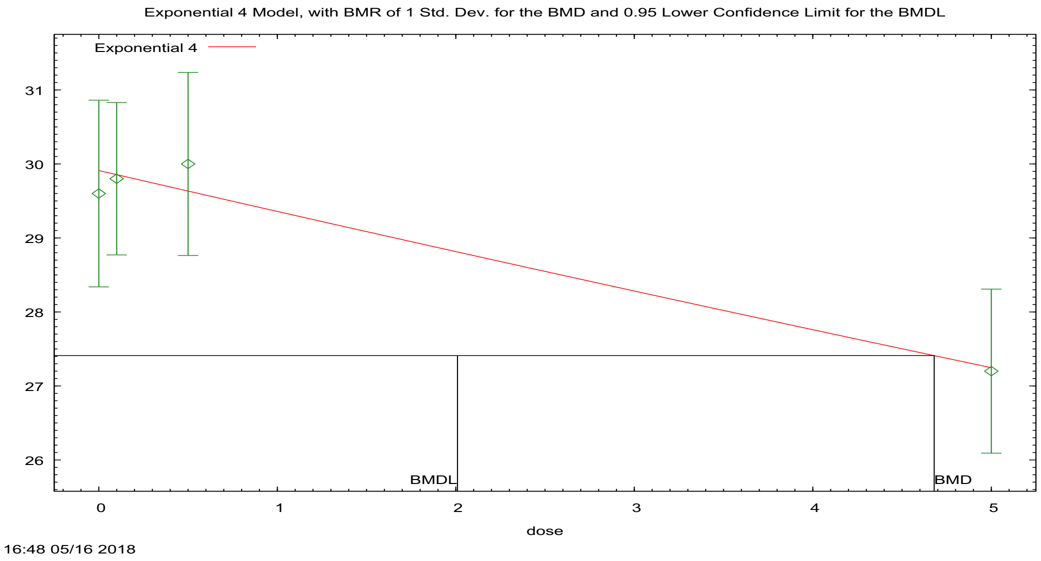

Figure 158. Plot of mean response by dose with fitted curve for Exponential (M4) model with constant variance for Offspring Body weight at PND40 in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

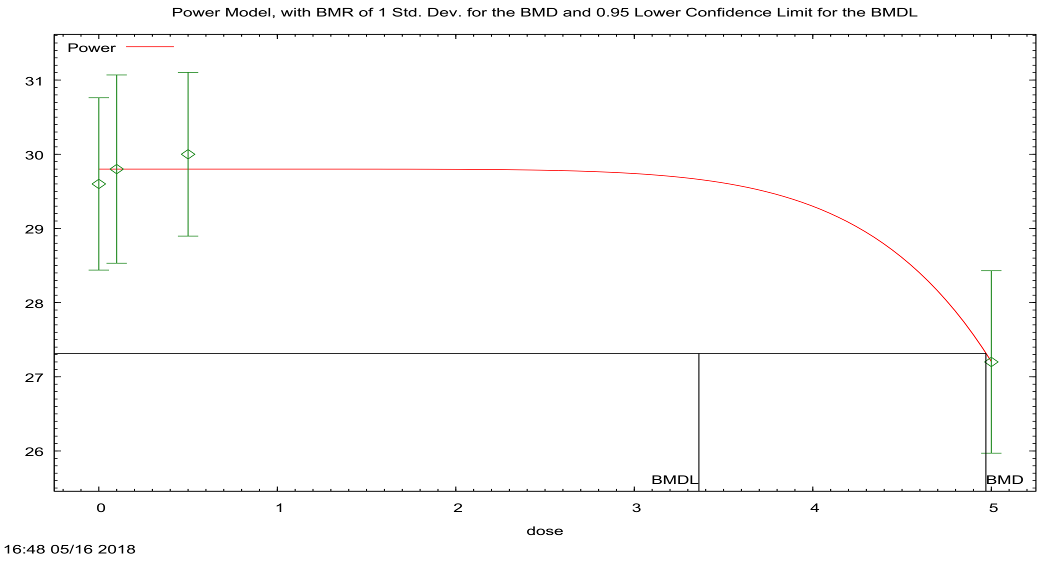

Figure 159. Plot of mean response by dose with fitted curve for Power model with constant variance for Offspring Body weight at PND40 in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

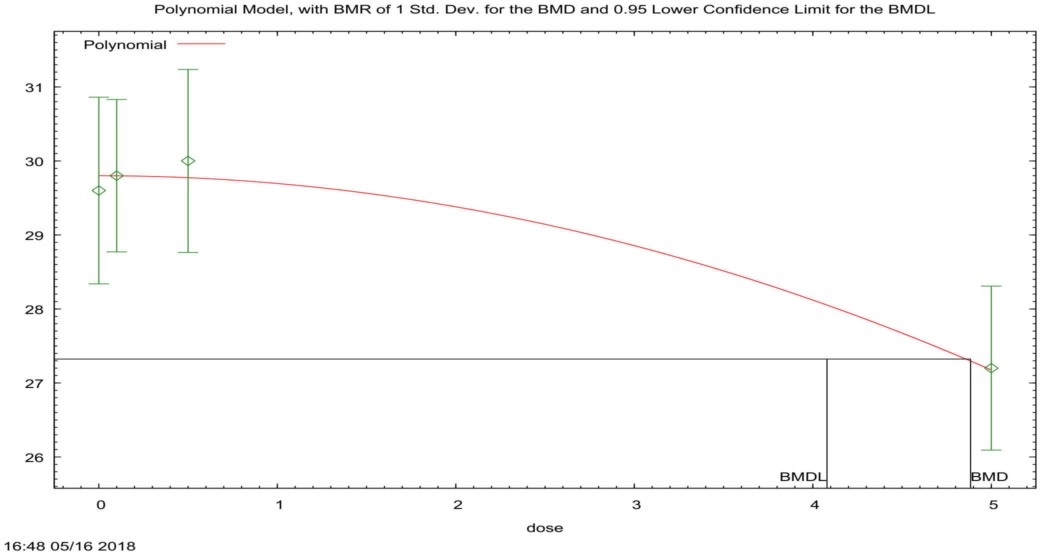

Figure 160. Plot of mean response by dose with fitted curve for Polynomial 2° model with constant variance for Offspring Body weight at PND40 in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

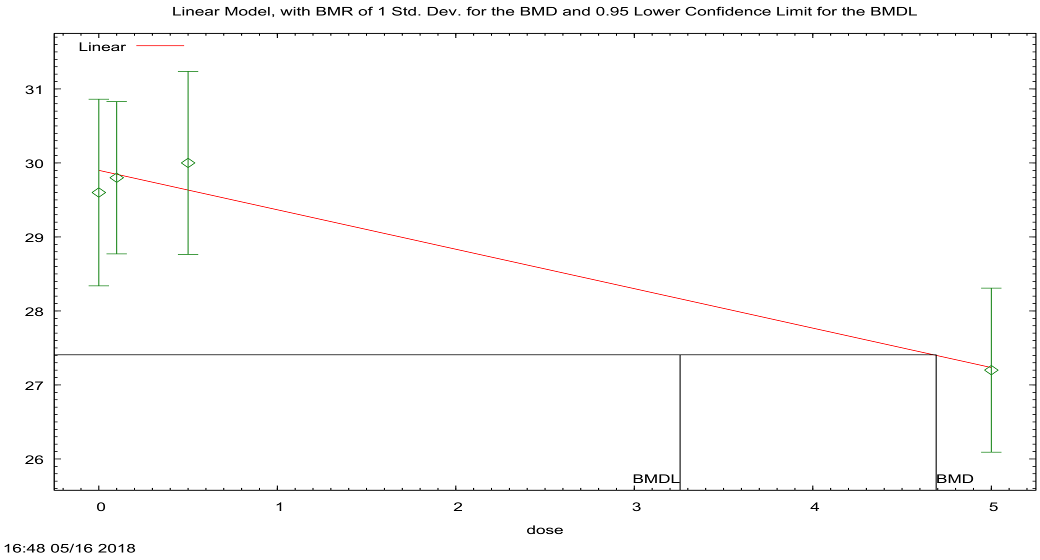

Figure 161. Plot of mean response by dose with fitted curve for Linear model with constant variance for Offspring Body weight at PND40 in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

BMDS WIZARD OUTPUT REPORT

BMDS Summary of Oral (Gavage) Prenatal Developmental Toxicity Study of H-28548 in Rats – Percent per Litter with Skeletal Variations

1.33. BMDS Summary of Percent per Litter with Skeletal Variations (Prenatal and Developmental Rats)

Table 33. 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	Models that met inclusion criteria are presented (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). 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	
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.

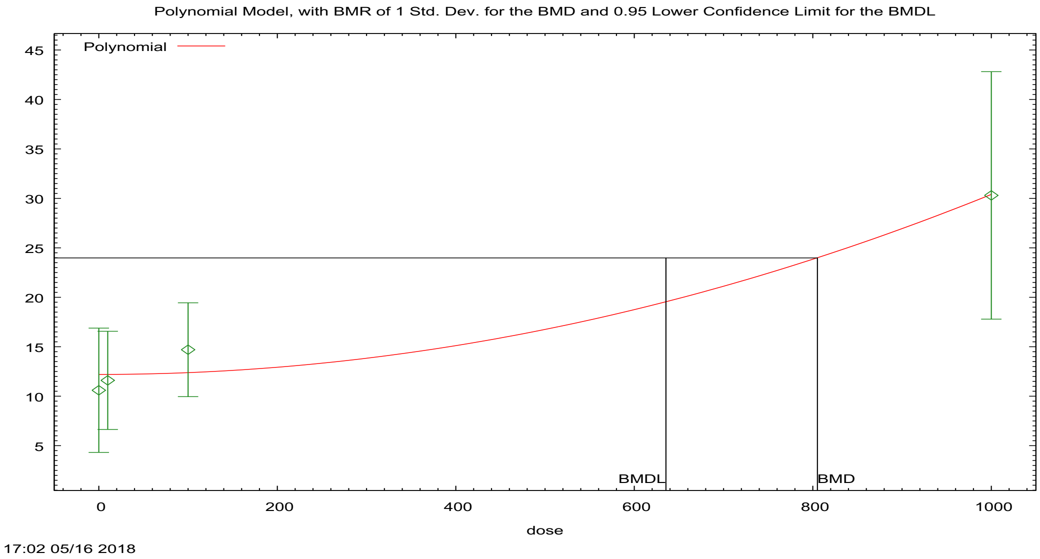

Figure 162. Plot of mean response by dose with fitted curve for Polynomial 2° model with modeled variance for Percent per Litter with Skeletal Variations (Prenatal and Developmental Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

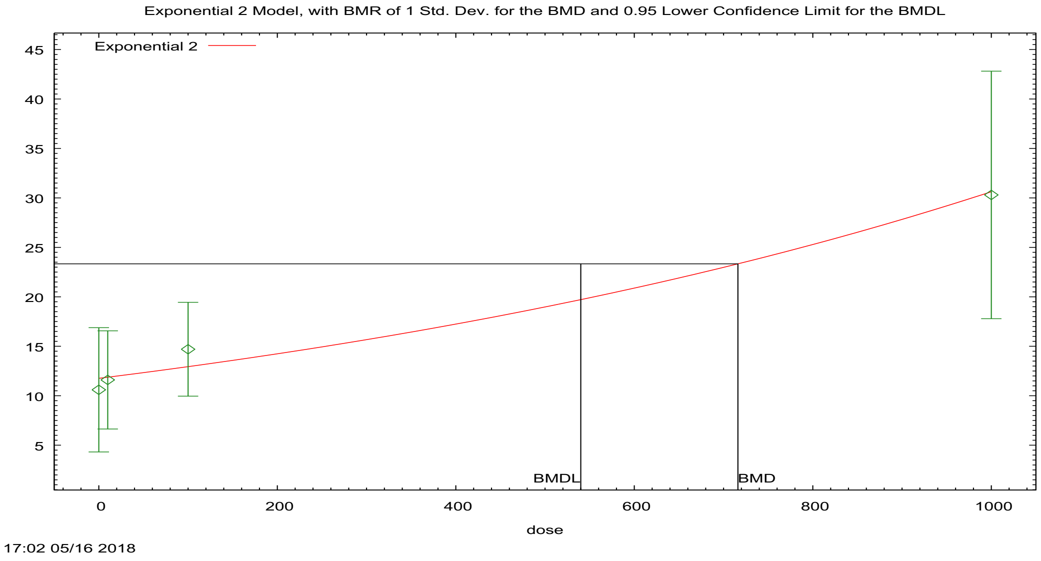

Figure 163. Plot of mean response by dose with fitted curve for Exponential (M2) model with modeled variance for Percent per Litter with Skeletal Variations (Prenatal and Developmental Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

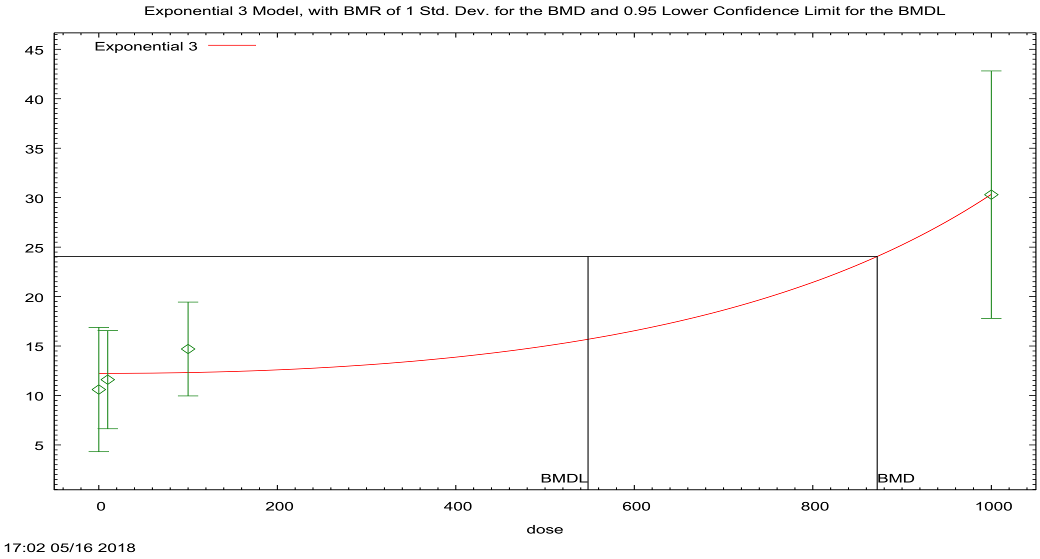

Figure 164. Plot of mean response by dose with fitted curve for Exponential (M3) model with modeled variance for Percent per Litter with Skeletal Variations (Prenatal and Developmental Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

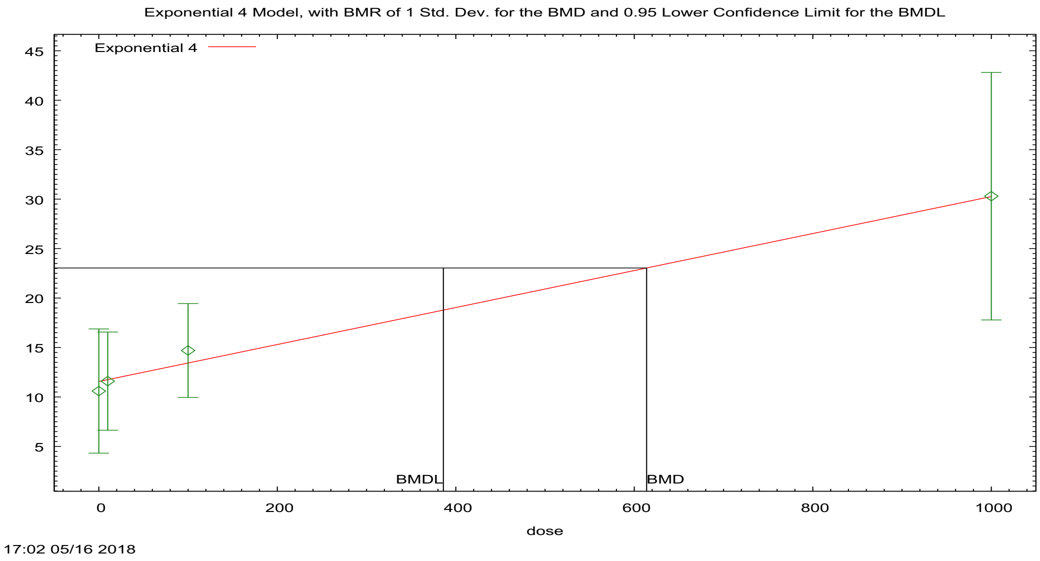

Figure 165. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Percent per Litter with Skeletal Variations (Prenatal and Developmental Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

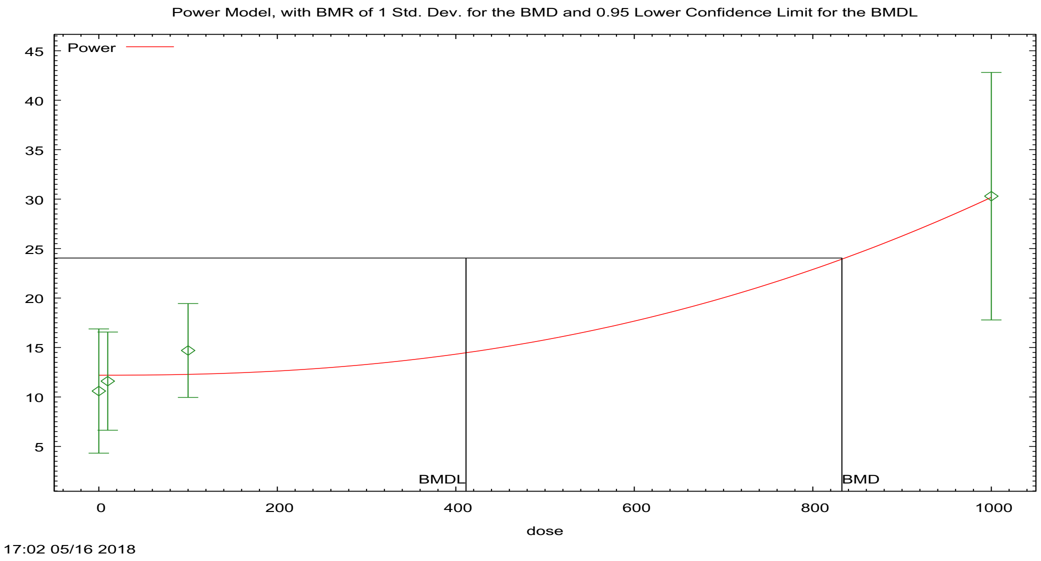

Figure 166. Plot of mean response by dose with fitted curve for Power model with modeled variance for Percent per Litter with Skeletal Variations (Prenatal and Developmental Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

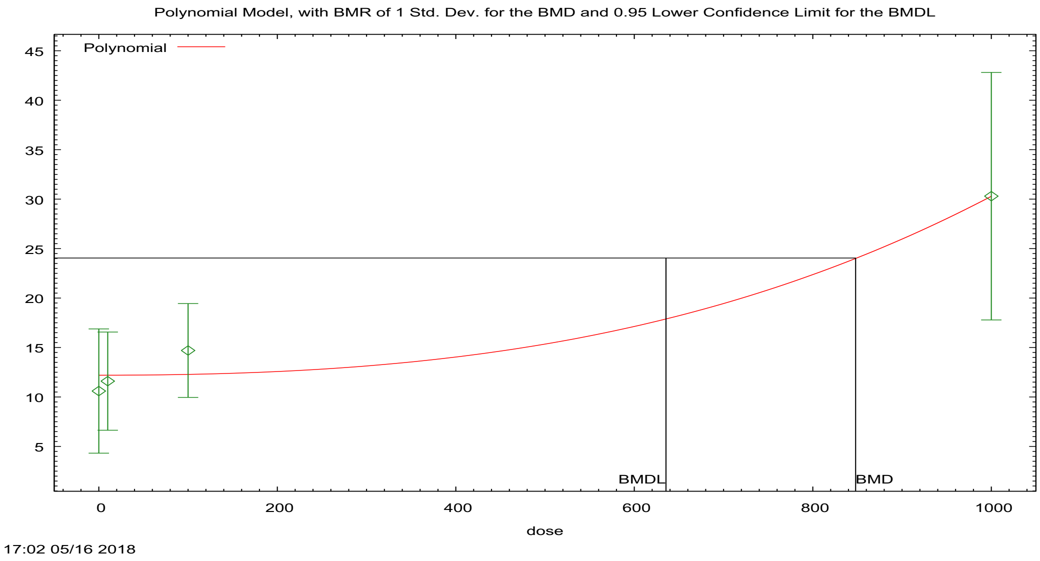

Figure 167. Plot of mean response by dose with fitted curve for Polynomial 3° model with modeled variance for Percent per Litter with Skeletal Variations (Prenatal and Developmental Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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

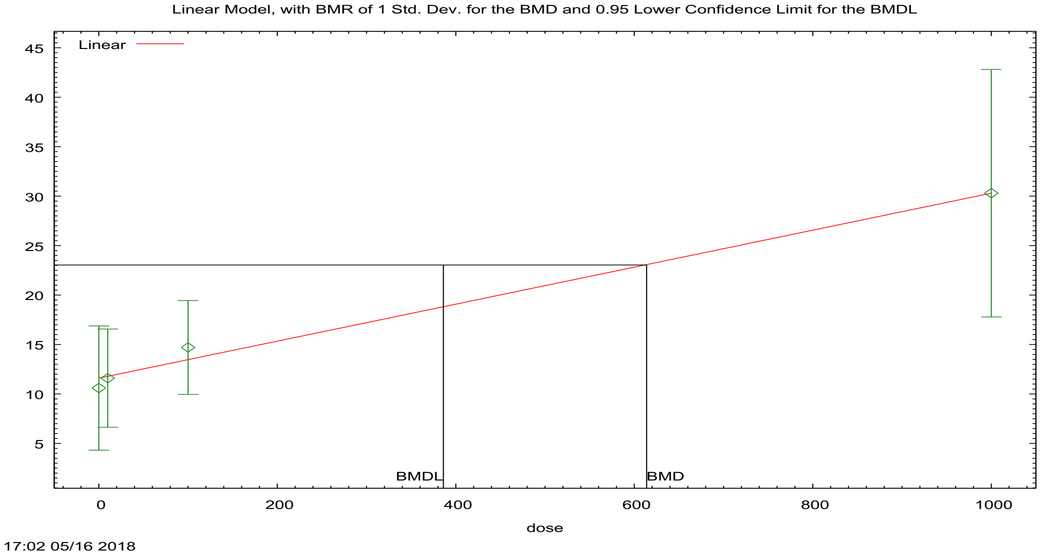

Figure 168. Plot of mean response by dose with fitted curve for Linear model with modeled variance for Percent per Litter with Skeletal Variations (Prenatal and Developmental Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

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