# BMD Results for Table: Body Weight SD4

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Dose | 0 | 77 | 153 | 306 | 611 |
| N | 5 | 5 | 5 | 5 | 5 |
| Mean ± SD | 247.16 ± 8.483 | 251.16 ± 7.732 | 245.78 ± 11.885 | 239.42 ± 9.316 | 230.58 ± 10.15 |

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linearb | 0.693 | 140.072 | 278.244 | 187.298 | Linear recommended as best-fitting model on the basis of the lowest AIC. |
| Polynomial 2° (equivalent models include Polynomial 3°, 4°) | 0.502 | 141.995 | 319.027 | 188.177 |
| Power | 0.536 | 141.864 | 329.161 | 189.734 |
| Hill | 0.399 | 143.329 | 285.94 | 141.473 |
| Exponential M2 (equivalent models include Exponential M4) | 0.687 | 140.098 | 272.458 | 180.45 |
| Exponential M3 | 0.542 | 141.844 | 327.538 | 183.472 |
| Exponential M5 | 0.392 | 143.35 | 289.255 | 142.229 |

a Constant variance case presented (BMDS Test 2 p-value = 0.891, BMDS Test 3 p-value = 0.891).

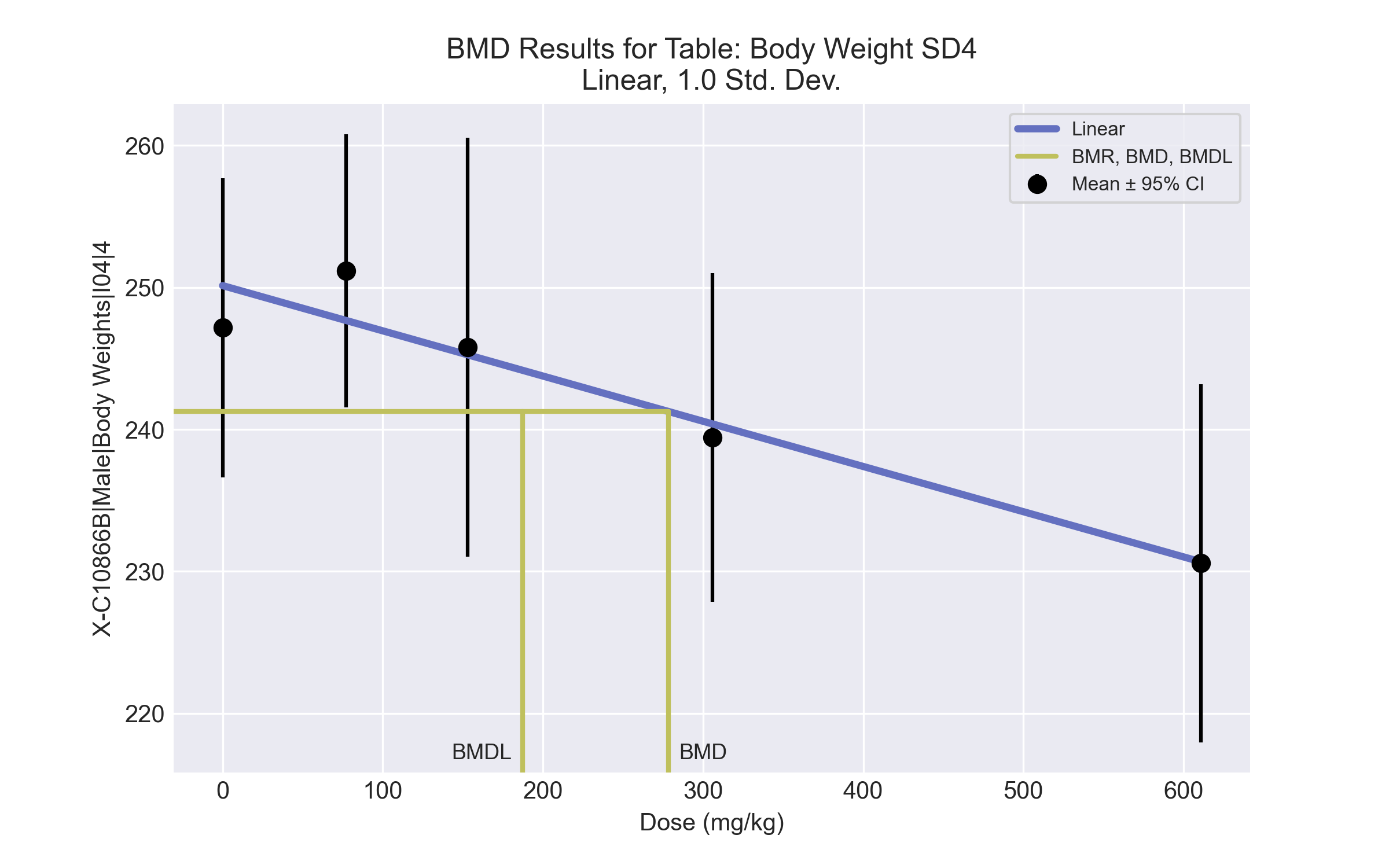
b Recommended model

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Lineara | Valid | - |
| Polynomial 2° (equivalent models include Polynomial 3°, 4°) | Valid | - |
| Power | Valid | - |
| Hill | Valid | - |
| Exponential M2 (equivalent models include Exponential M4) | Valid | - |
| Exponential M3 | Valid | - |
| Exponential M5 | Valid | - |

a Recommended model

## Recommended model



====================================================================   
 Polynomial Model. (Version: 2.21; Date: 03/14/2017)   
 Input Data File: C:\Windows\TEMP\bmds-h8cp7464.(d)   
 Gnuplot Plotting File: C:\Windows\TEMP\bmds-h8cp7464.plt  
 Tue Jul 06 12:34:52 2021  
 ====================================================================   
  
 BMDS\_Model\_Run   
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~  
   
 The form of the response function is:   
  
 Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ...  
  
  
 Dependent variable = Response  
 Independent variable = Dose  
 rho is set to 0  
 The polynomial coefficients are restricted to be negative  
 A constant variance model is fit  
  
 Total number of dose groups = 5  
 Total number of records with missing values = 0  
 Maximum number of iterations = 500  
 Relative Function Convergence has been set to: 1e-008  
 Parameter Convergence has been set to: 1e-008  
  
  
  
 Default Initial Parameter Values   
 alpha = 92.5624  
 rho = 0 Specified  
 beta\_0 = 250.124  
 beta\_1 = -0.0318389  
  
  
 Asymptotic Correlation Matrix of Parameter Estimates  
  
 ( \*\*\* The model parameter(s) -rho   
 have been estimated at a boundary point, or have been specified by the user,  
 and do not appear in the correlation matrix )  
  
 alpha beta\_0 beta\_1  
  
 alpha 1 -5.6e-011 -3e-010  
  
 beta\_0 -5.6e-011 1 -0.73  
  
 beta\_1 -3e-010 -0.73 1  
  
  
  
 Parameter Estimates  
  
 95.0% Wald Confidence Interval  
 Variable Estimate Std. Err. Lower Conf. Limit Upper Conf. Limit  
 alpha 78.4817 22.198 34.9745 121.989  
 beta\_0 250.124 2.58491 245.058 255.19  
 beta\_1 -0.0318389 0.00820465 -0.0479197 -0.0157581  
  
  
  
 Table of Data and Estimated Values of Interest  
  
 Dose N Obs Mean Est Mean Obs Std Dev Est Std Dev Scaled Res.  
------ --- -------- -------- ----------- ----------- ----------  
  
 0 5 247 250 8.48 8.86 -0.748  
 77 5 251 248 7.73 8.86 0.88  
 153 5 246 245 11.9 8.86 0.133  
 306 5 239 240 9.32 8.86 -0.243  
 611 5 231 231 10.1 8.86 -0.0228  
  
  
  
 Model Descriptions for likelihoods calculated  
  
  
 Model A1: Yij = Mu(i) + e(ij)  
 Var{e(ij)} = Sigma^2  
  
 Model A2: Yij = Mu(i) + e(ij)  
 Var{e(ij)} = Sigma(i)^2  
  
 Model A3: Yij = Mu(i) + e(ij)  
 Var{e(ij)} = Sigma^2  
 Model A3 uses any fixed variance parameters that  
 were specified by the user  
  
 Model R: Yi = Mu + e(i)  
 Var{e(i)} = Sigma^2  
  
  
 Likelihoods of Interest  
  
 Model Log(likelihood) # Param's AIC  
 A1 -66.309243 6 144.618487  
 A2 -65.750363 10 151.500726  
 A3 -66.309243 6 144.618487  
 fitted -67.035821 3 140.071643  
 R -72.929294 2 149.858588  
  
  
 Explanation of Tests   
  
 Test 1: Do responses and/or variances differ among Dose levels?   
 (A2 vs. R)  
 Test 2: Are Variances Homogeneous? (A1 vs A2)  
 Test 3: Are variances adequately modeled? (A2 vs. A3)  
 Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)  
 (Note: When rho=0 the results of Test 3 and Test 2 will be the same.)  
  
 Tests of Interest   
  
 Test -2\*log(Likelihood Ratio) Test df p-value   
  
 Test 1 14.3579 8 0.0729  
 Test 2 1.11776 4 0.8914  
 Test 3 1.11776 4 0.8914  
 Test 4 1.45316 3 0.6931  
  
The p-value for Test 1 is greater than .05. There may not be a  
diffence between responses and/or variances among the dose levels  
Modelling the data with a dose/response curve may not be appropriate  
  
The p-value for Test 2 is greater than .1. A homogeneous variance   
model appears to be appropriate here  
  
  
The p-value for Test 3 is greater than .1. The modeled variance appears   
 to be appropriate here  
  
The p-value for Test 4 is greater than .1. The model chosen seems   
to adequately describe the data  
   
  
 Benchmark Dose Computation  
  
Specified effect = 1  
  
Risk Type = Estimated standard deviations from the control mean  
  
Confidence level = 0.95  
  
 BMD = 278.244  
  
  
 BMDL = 187.298  
  
  
 BMDU = 536.529

# BMD Results for Table: Brain Weight Relative

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Dose | 0 | 77 | 153 | 306 | 611a |
| N | 5 | 5 | 5 | 5 | 5 |
| Mean ± SD | 6.824 ± 0.502 | 6.914 ± 0.157 | 6.959 ± 0.292 | 7.191 ± 0.264 | 6.947 ± 1.37 |

a Dose group removed in BMD modeling session

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linearb (equivalent models include Power, Polynomial 2°, 3°, 4°) | 0.625 | -22.645 | 287.243 | 153.671 | Linear recommended as best-fitting model on the basis of the lowest AIC. |
| Hill | 0.381 | -20.819 | 283.317 | -999 |
| Exponential M2 (equivalent models include Exponential M3) | 0.621 | -22.631 | 288.092 | 156.917 |
| Exponential M4 (equivalent models include Exponential M5) | 0.372 | -20.789 | 281.606 | 2.417 |

a Modeled variance case presented (BMDS Test 2 p-value = 0.089, BMDS Test 3 p-value = 0.139).

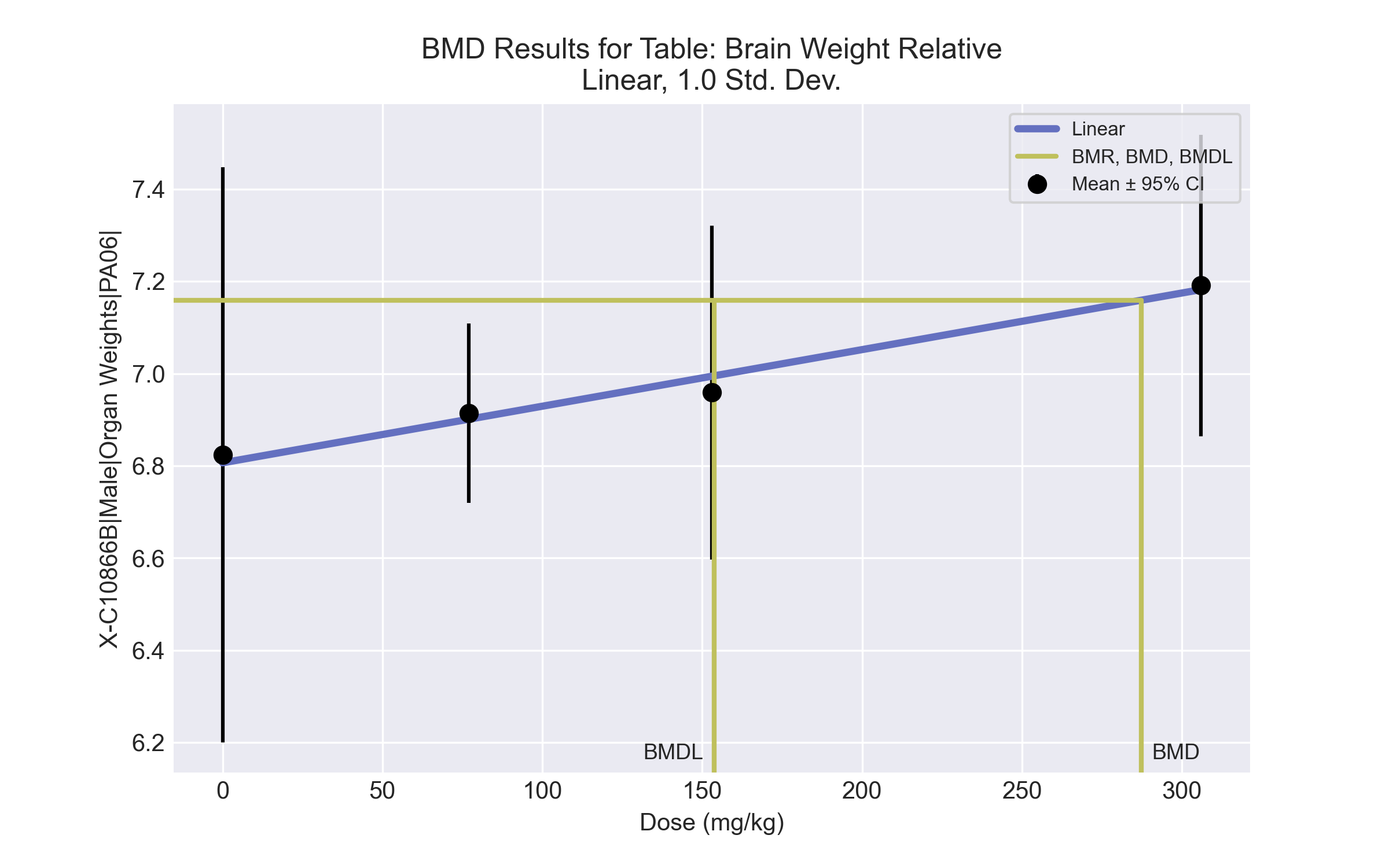
b Recommended model

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Lineara (equivalent models include Power, Polynomial 2°, 3°, 4°) | Valid | - |
| Hill | Failure | **Failures**  • BMDL does not exist  **Cautions**  • Warning(s): BMDL computation failed. |
| Exponential M2 (equivalent models include Exponential M3) | Valid | - |
| Exponential M4 (equivalent models include Exponential M5) | Warning | **Warnings**  • BMD/BMDL ratio is greater than threshold (1.17e+02 > 20.0)  **Cautions**  • BMD/BMDL ratio is greater than threshold (1.17e+02 > 5.0) |

a Recommended model

## Recommended model



====================================================================   
 Polynomial Model. (Version: 2.21; Date: 03/14/2017)   
 Input Data File: C:\Windows\TEMP\bmds-snoahh3x.(d)   
 Gnuplot Plotting File: C:\Windows\TEMP\bmds-snoahh3x.plt  
 Tue Jul 06 12:38:42 2021  
 ====================================================================   
  
 BMDS\_Model\_Run   
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~  
   
 The form of the response function is:   
  
 Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ...  
  
  
 Dependent variable = Response  
 Independent variable = Dose  
 The polynomial coefficients are restricted to be positive  
 The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) \* rho)  
  
 Total number of dose groups = 4  
 Total number of records with missing values = 0  
 Maximum number of iterations = 500  
 Relative Function Convergence has been set to: 1e-008  
 Parameter Convergence has been set to: 1e-008  
  
  
  
 Default Initial Parameter Values   
 lalpha = -2.22742  
 rho = 0  
 beta\_0 = 6.81332  
 beta\_1 = 0.00118416  
  
  
 Asymptotic Correlation Matrix of Parameter Estimates  
  
 lalpha rho beta\_0 beta\_1  
  
 lalpha 1 -1 -0.18 0.21  
  
 rho -1 1 0.18 -0.21  
  
 beta\_0 -0.18 0.18 1 -0.85  
  
 beta\_1 0.21 -0.21 -0.85 1  
  
  
  
 Parameter Estimates  
  
 95.0% Wald Confidence Interval  
 Variable Estimate Std. Err. Lower Conf. Limit Upper Conf. Limit  
 lalpha 34.1988 27.6451 -19.9847 88.3823  
 rho -18.9184 14.2376 -46.8237 8.98687  
 beta\_0 6.80638 0.116818 6.57742 7.03534  
 beta\_1 0.00122803 0.000557847 0.000134668 0.00232139  
  
  
  
 Table of Data and Estimated Values of Interest  
  
 Dose N Obs Mean Est Mean Obs Std Dev Est Std Dev Scaled Res.  
------ --- -------- -------- ----------- ----------- ----------  
  
 0 5 6.82 6.81 0.502 0.353 0.111  
 77 5 6.91 6.9 0.157 0.31 0.0961  
 153 5 6.96 6.99 0.292 0.273 -0.29  
 306 5 7.19 7.18 0.264 0.212 0.0934  
  
  
  
 Model Descriptions for likelihoods calculated  
  
  
 Model A1: Yij = Mu(i) + e(ij)  
 Var{e(ij)} = Sigma^2  
  
 Model A2: Yij = Mu(i) + e(ij)  
 Var{e(ij)} = Sigma(i)^2  
  
 Model A3: Yij = Mu(i) + e(ij)  
 Var{e(ij)} = exp(lalpha + rho\*ln(Mu(i)))  
 Model A3 uses any fixed variance parameters that  
 were specified by the user  
  
 Model R: Yi = Mu + e(i)  
 Var{e(i)} = Sigma^2  
  
  
 Likelihoods of Interest  
  
 Model Log(likelihood) # Param's AIC  
 A1 14.505680 5 -19.011359  
 A2 17.768339 8 -19.536679  
 A3 15.792373 6 -19.584746  
 fitted 15.322421 4 -22.644841  
 R 12.575874 2 -21.151749  
  
  
 Explanation of Tests   
  
 Test 1: Do responses and/or variances differ among Dose levels?   
 (A2 vs. R)  
 Test 2: Are Variances Homogeneous? (A1 vs A2)  
 Test 3: Are variances adequately modeled? (A2 vs. A3)  
 Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)  
 (Note: When rho=0 the results of Test 3 and Test 2 will be the same.)  
  
 Tests of Interest   
  
 Test -2\*log(Likelihood Ratio) Test df p-value   
  
 Test 1 10.3849 6 0.1093  
 Test 2 6.52532 3 0.08867  
 Test 3 3.95193 2 0.1386  
 Test 4 0.939905 2 0.625  
  
The p-value for Test 1 is greater than .05. There may not be a  
diffence between responses and/or variances among the dose levels  
Modelling the data with a dose/response curve may not be appropriate  
  
The p-value for Test 2 is less than .1. A non-homogeneous variance   
model appears to be appropriate  
  
The p-value for Test 3 is greater than .1. The modeled variance appears   
 to be appropriate here  
  
The p-value for Test 4 is greater than .1. The model chosen seems   
to adequately describe the data  
   
  
 Benchmark Dose Computation  
  
Specified effect = 1  
  
Risk Type = Estimated standard deviations from the control mean  
  
Confidence level = 0.95  
  
 BMD = 287.243  
  
  
 BMDL = 153.671  
  
  
 BMDU = 1122.71

# BMD Results for Table: Liver Weight Absolute

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Dose | 0 | 77 | 153 | 306 | 611 |
| N | 5 | 5 | 5 | 5 | 4 |
| Mean ± SD | 10.354 ± 0.504 | 11.23 ± 0.61 | 11.288 ± 0.831 | 11.95 ± 0.95 | 11.75 ± 0.926 |

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear (equivalent models include Power, Polynomial 2°, 3°, 4°) | 0.119 | 18.11 | 381.08 | 228.554 | Exponential-M2 recommended as best-fitting model on the basis of the lowest AIC. |
| Hill | 0.302 | 17.319 | 63.079 | 1.2E-04 |
| Exponential M2b (equivalent models include Exponential M3) | 0.11 | 18.286 | 399.984 | 246.025 |
| Exponential M4 | 0.615 | 15.224 | 70.786 | 0.343 |
| Exponential M5 | 0.615 | 15.224 | 70.786 | 0.294 |

a Constant variance case presented (BMDS Test 2 p-value = 0.622, BMDS Test 3 p-value = 0.622).

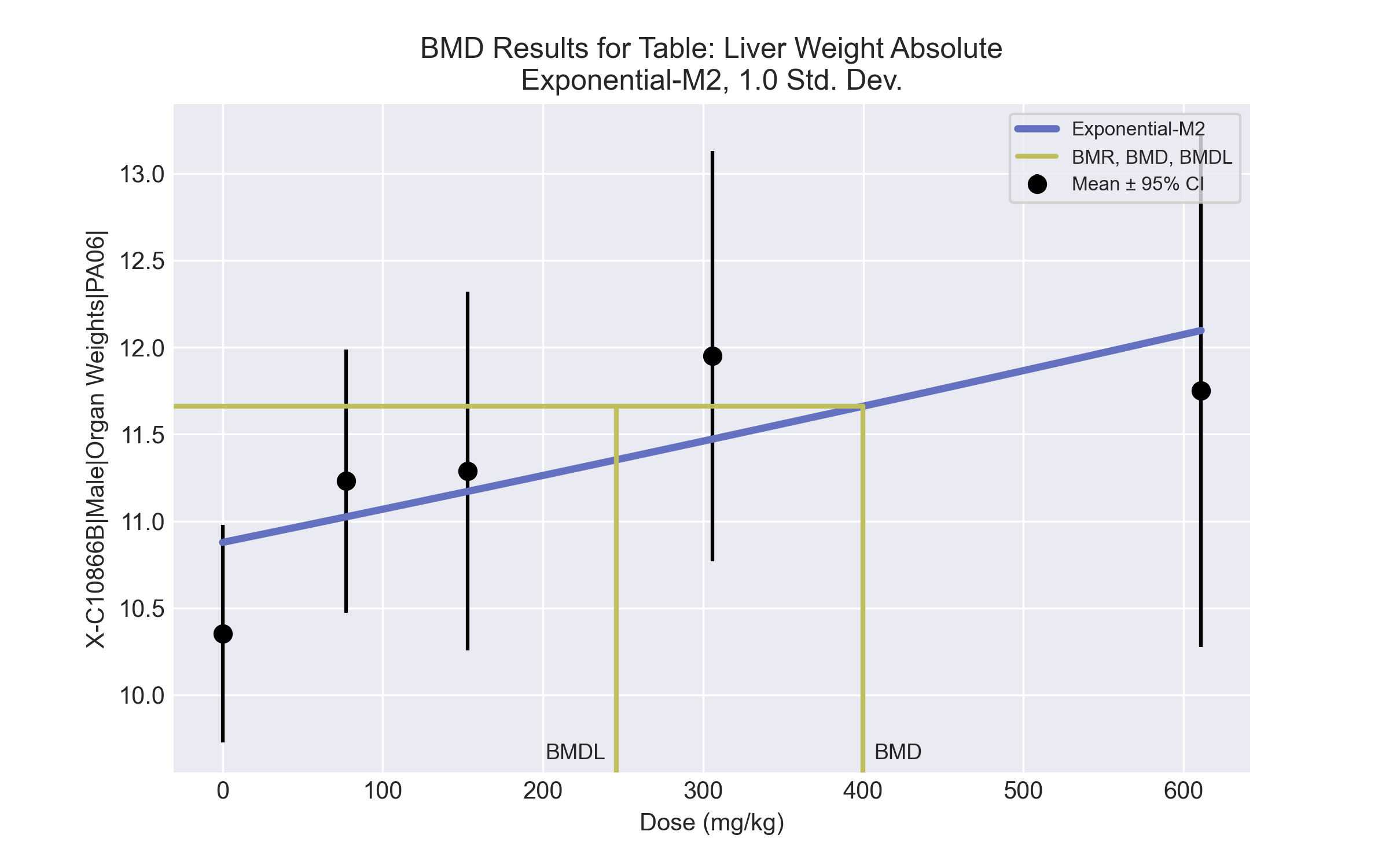
b Recommended model

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear (equivalent models include Power, Polynomial 2°, 3°, 4°) | Warning | **Warnings**  • Ratio of modeled to actual stdev. at control is greater than threshold (1.55 > 1.5) |
| Hill | Warning | **Warnings**  • BMD/BMDL ratio is greater than threshold (5.31e+05 > 20.0)  **Cautions**  • BMD/BMDL ratio is greater than threshold (5.31e+05 > 5.0) |
| Exponential M2a (equivalent models include Exponential M3) | Valid | - |
| Exponential M4 | Warning | **Warnings**  • BMD/BMDL ratio is greater than threshold (2.07e+02 > 20.0)  **Cautions**  • BMD/BMDL ratio is greater than threshold (2.07e+02 > 5.0) |
| Exponential M5 | Warning | **Warnings**  • BMD/BMDL ratio is greater than threshold (2.41e+02 > 20.0)  **Cautions**  • BMD/BMDL ratio is greater than threshold (2.41e+02 > 5.0) |

a Recommended model

## Recommended model



====================================================================   
 Exponential Model. (Version: 1.11; Date: 03/14/2017)   
 Input Data File: C:\Windows\TEMP\bmds-sy3yg\_g3.(d)   
 Gnuplot Plotting File:   
 Tue Jul 06 12:38:47 2021  
 ====================================================================   
  
 BMDS\_Model\_Run   
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~  
   
 The form of the response function by Model:   
 Model 2: Y[dose] = a \* exp{sign \* b \* dose}  
 Model 3: Y[dose] = a \* exp{sign \* (b \* dose)^d}  
 Model 4: Y[dose] = a \* [c-(c-1) \* exp{-b \* dose}]  
 Model 5: Y[dose] = a \* [c-(c-1) \* exp{-(b \* dose)^d}]  
  
 Note: Y[dose] is the median response for exposure = dose;  
 sign = +1 for increasing trend in data;  
 sign = -1 for decreasing trend.  
  
 Model 2 is nested within Models 3 and 4.  
 Model 3 is nested within Model 5.  
 Model 4 is nested within Model 5.  
  
  
 Dependent variable = Response  
 Independent variable = Dose  
 Data are assumed to be distributed: normally  
 Variance Model: exp(lnalpha +rho \*ln(Y[dose]))  
 rho is set to 0.  
 A constant variance model is fit.  
  
 Total number of dose groups = 5  
 Total number of records with missing values = 0  
 Maximum number of iterations = 500  
 Relative Function Convergence has been set to: 1e-008  
 Parameter Convergence has been set to: 1e-008  
  
 MLE solution provided: Exact  
  
  
 Initial Parameter Values  
  
 Variable Model 2  
 -------- --------  
 lnalpha -0.739488   
 rho 0 Specified  
 a 10.8494   
 b 0.000183253   
 c 0 Specified  
 d 1 Specified  
  
  
  
 Parameter Estimates  
  
 Variable Model 2 Std. Err.  
 -------- ------- ---------  
 lnalpha -0.488086 0.177189  
 a 10.8777 0.224787  
 b 0.000173877 6.58692e-005  
  
 NC = No Convergence  
  
  
 Table of Stats From Input Data  
  
 Dose N Obs Mean Obs Std Dev  
 ----- --- ---------- -------------  
 0 5 10.35 0.5038  
 77 5 11.23 0.6105  
 153 5 11.29 0.8314  
 306 5 11.95 0.9502  
 611 4 11.75 0.9263  
  
  
 Estimated Values of Interest  
  
 Dose Est Mean Est Std Scaled Residual  
 ------ ---------- --------- ----------------  
 0 10.88 0.7835 -1.495  
 77 11.02 0.7835 0.5869  
 153 11.17 0.7835 0.3339  
 306 11.47 0.7835 1.364  
 611 12.1 0.7835 -0.8858  
  
  
  
 Other models for which likelihoods are calculated:  
  
 Model A1: Yij = Mu(i) + e(ij)  
 Var{e(ij)} = Sigma^2  
  
 Model A2: Yij = Mu(i) + e(ij)  
 Var{e(ij)} = Sigma(i)^2  
  
 Model A3: Yij = Mu(i) + e(ij)  
 Var{e(ij)} = exp(lalpha + log(mean(i)) \* rho)  
  
 Model R: Yij = Mu + e(i)  
 Var{e(ij)} = Sigma^2  
  
  
 Likelihoods of Interest  
  
 Model Log(likelihood) DF AIC  
 ------- ----------------- ---- ------------  
 A1 -3.12615 6 18.2523  
 A2 -1.81263 10 23.62526  
 A3 -3.12615 6 18.2523  
 R -9.119681 2 22.23936  
 2 -6.142969 3 18.28594  
  
  
 Additive constant for all log-likelihoods = -22.05. This constant added to the  
 above values gives the log-likelihood including the term that does not  
 depend on the model parameters.  
  
  
 Explanation of Tests  
  
 Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)  
 Test 2: Are Variances Homogeneous? (A2 vs. A1)  
 Test 3: Are variances adequately modeled? (A2 vs. A3)  
 Test 4: Does Model 2 fit the data? (A3 vs. 2)  
  
  
 Tests of Interest  
  
 Test -2\*log(Likelihood Ratio) D. F. p-value  
 -------- ------------------------ ------ --------------  
 Test 1 14.61 8 0.0671  
 Test 2 2.627 4 0.622  
 Test 3 2.627 4 0.622  
 Test 4 6.034 3 0.11  
  
  
 The p-value for Test 1 is greater than .05. There may not be a  
 diffence between responses and/or variances among the dose levels  
 Modelling the data with a dose/response curve may not be appropriate.  
  
 The p-value for Test 2 is greater than .1. A homogeneous  
 variance model appears to be appropriate here.  
  
 The p-value for Test 3 is greater than .1. The modeled  
 variance appears to be appropriate here.  
  
 The p-value for Test 4 is greater than .1. Model 2 seems  
 to adequately describe the data.  
  
  
 Benchmark Dose Computations:  
  
 Specified Effect = 1.000000  
  
 Risk Type = Estimated standard deviations from control  
  
 Confidence Level = 0.950000  
  
 BMD = 399.984  
  
 BMDL = 246.025  
  
 BMDU = 1184.99

# BMD Results for Table: Liver Weight Relative

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Dose | 0 | 77 | 153 | 306 | 611 |
| N | 5 | 5 | 5 | 5 | 4 |
| Mean ± SD | 41.901 ± 1.714 | 44.7 ± 1.604 | 45.914 ± 2.128 | 49.87 ± 2.614 | 51.3 ± 3.188 |

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear (equivalent models include Power, Polynomial 2°, 3°, 4°) | 0.06 | 71.18 | 154.242 | 114.214 | Exponential-M4 recommended as best-fitting model on the basis of the lowest AIC. |
| Hill | 0.295 | 68.853 | 70.585 | 29.566 |
| Exponential M2 (equivalent models include Exponential M3) | 0.04 | 72.086 | 172.486 | 129.612 |
| Exponential M4b | 0.577 | 66.857 | 55.84 | 33.684 |
| Exponential M5 | 0.359 | 68.6 | 72.032 | 34.438 |

a Constant variance case presented (BMDS Test 2 p-value = 0.588, BMDS Test 3 p-value = 0.588).

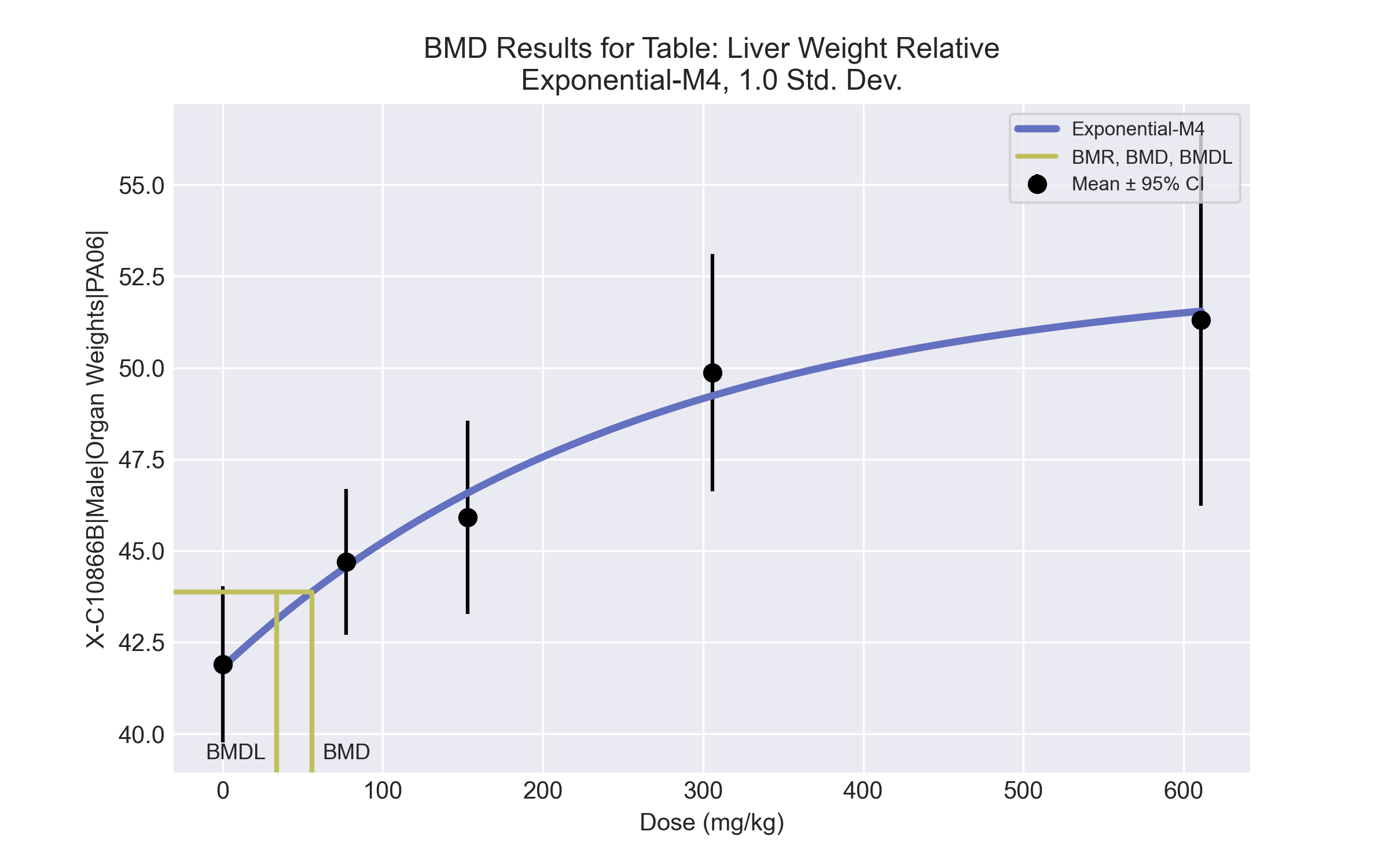
b Recommended model

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear (equivalent models include Power, Polynomial 2°, 3°, 4°) | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0596 < 0.1) |
| Hill | Valid | - |
| Exponential M2 (equivalent models include Exponential M3) | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0397 < 0.1) |
| Exponential M4a | Valid | - |
| Exponential M5 | Valid | - |

a Recommended model

## Recommended model



====================================================================   
 Exponential Model. (Version: 1.11; Date: 03/14/2017)   
 Input Data File: C:\Windows\TEMP\bmds-hcmdpqtz.(d)   
 Gnuplot Plotting File:   
 Tue Jul 06 12:38:50 2021  
 ====================================================================   
  
 BMDS\_Model\_Run   
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~  
   
 The form of the response function by Model:   
 Model 2: Y[dose] = a \* exp{sign \* b \* dose}  
 Model 3: Y[dose] = a \* exp{sign \* (b \* dose)^d}  
 Model 4: Y[dose] = a \* [c-(c-1) \* exp{-b \* dose}]  
 Model 5: Y[dose] = a \* [c-(c-1) \* exp{-(b \* dose)^d}]  
  
 Note: Y[dose] is the median response for exposure = dose;  
 sign = +1 for increasing trend in data;  
 sign = -1 for decreasing trend.  
  
 Model 2 is nested within Models 3 and 4.  
 Model 3 is nested within Model 5.  
 Model 4 is nested within Model 5.  
  
  
 Dependent variable = Response  
 Independent variable = Dose  
 Data are assumed to be distributed: normally  
 Variance Model: exp(lnalpha +rho \*ln(Y[dose]))  
 rho is set to 0.  
 A constant variance model is fit.  
  
 Total number of dose groups = 5  
 Total number of records with missing values = 0  
 Maximum number of iterations = 500  
 Relative Function Convergence has been set to: 1e-008  
 Parameter Convergence has been set to: 1e-008  
  
 MLE solution provided: Exact  
  
  
 Initial Parameter Values  
  
 Variable Model 4  
 -------- --------  
 lnalpha 1.40659   
 rho 0 Specified  
 a 39.8056   
 b 0.00311249   
 c 1.3532   
 d 1 Specified  
  
  
  
 Parameter Estimates  
  
 Variable Model 4 Std. Err.  
 -------- ------- ---------  
 lnalpha 1.45236 1.23356  
 a 41.8144 0.848432  
 b 0.00381167 0.00155013  
 c 1.25786 0.0459667  
  
 NC = No Convergence  
  
  
 Table of Stats From Input Data  
  
 Dose N Obs Mean Obs Std Dev  
 ----- --- ---------- -------------  
 0 5 41.9 1.714  
 77 5 44.7 1.604  
 153 5 45.91 2.128  
 306 5 49.87 2.614  
 611 4 51.3 3.188  
  
  
 Estimated Values of Interest  
  
 Dose Est Mean Est Std Scaled Residual  
 ------ ---------- --------- ----------------  
 0 41.81 2.067 0.09325  
 77 44.56 2.067 0.1553  
 153 46.58 2.067 -0.7188  
 306 49.24 2.067 0.6836  
 611 51.55 2.067 -0.2385  
  
  
  
 Other models for which likelihoods are calculated:  
  
 Model A1: Yij = Mu(i) + e(ij)  
 Var{e(ij)} = Sigma^2  
  
 Model A2: Yij = Mu(i) + e(ij)  
 Var{e(ij)} = Sigma(i)^2  
  
 Model A3: Yij = Mu(i) + e(ij)  
 Var{e(ij)} = exp(lalpha + log(mean(i)) \* rho)  
  
 Model R: Yij = Mu + e(i)  
 Var{e(ij)} = Sigma^2  
  
  
 Likelihoods of Interest  
  
 Model Log(likelihood) DF AIC  
 ------- ----------------- ---- ------------  
 A1 -28.87906 6 69.75811  
 A2 -27.46692 10 74.93384  
 A3 -28.87906 6 69.75811  
 R -44.84305 2 93.6861  
 4 -29.42827 4 66.85654  
  
  
 Additive constant for all log-likelihoods = -22.05. This constant added to the  
 above values gives the log-likelihood including the term that does not  
 depend on the model parameters.  
  
  
 Explanation of Tests  
  
 Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)  
 Test 2: Are Variances Homogeneous? (A2 vs. A1)  
 Test 3: Are variances adequately modeled? (A2 vs. A3)  
  
 Test 6a: Does Model 4 fit the data? (A3 vs 4)  
  
  
 Tests of Interest  
  
 Test -2\*log(Likelihood Ratio) D. F. p-value  
 -------- ------------------------ ------ --------------  
 Test 1 34.75 8 < 0.0001  
 Test 2 2.824 4 0.5877  
 Test 3 2.824 4 0.5877  
 Test 6a 1.098 2 0.5774  
  
  
 The p-value for Test 1 is less than .05. There appears to be a  
 difference between response and/or variances among the dose  
 levels, it seems appropriate to model the data.  
  
 The p-value for Test 2 is greater than .1. A homogeneous  
 variance model appears to be appropriate here.  
  
 The p-value for Test 3 is greater than .1. The modeled  
 variance appears to be appropriate here.  
  
 The p-value for Test 6a is greater than .1. Model 4 seems  
 to adequately describe the data.  
  
  
 Benchmark Dose Computations:  
  
 Specified Effect = 1.000000  
  
 Risk Type = Estimated standard deviations from control  
  
 Confidence Level = 0.950000  
  
 BMD = 55.8399  
  
 BMDL = 33.6836  
  
 BMDU = 109.52

# BMD Results for Table: Terminal Body Weight

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Dose | 0 | 77 | 153 | 306 | 611 |
| N | 5 | 5 | 5 | 5 | 5 |
| Mean ± SD | 247.16 ± 8.483 | 251.16 ± 7.732 | 245.78 ± 11.885 | 239.42 ± 9.316 | 230.58 ± 10.15 |

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linearb | 0.693 | 140.072 | 278.244 | 187.298 | Linear recommended as best-fitting model on the basis of the lowest AIC. |
| Polynomial 2° (equivalent models include Polynomial 3°, 4°) | 0.502 | 141.995 | 319.027 | 188.177 |
| Power | 0.536 | 141.864 | 329.161 | 189.734 |
| Hill | 0.399 | 143.329 | 285.94 | 141.473 |
| Exponential M2 (equivalent models include Exponential M4) | 0.687 | 140.098 | 272.458 | 180.45 |
| Exponential M3 | 0.542 | 141.844 | 327.538 | 183.472 |
| Exponential M5 | 0.392 | 143.35 | 289.255 | 142.229 |

a Constant variance case presented (BMDS Test 2 p-value = 0.891, BMDS Test 3 p-value = 0.891).

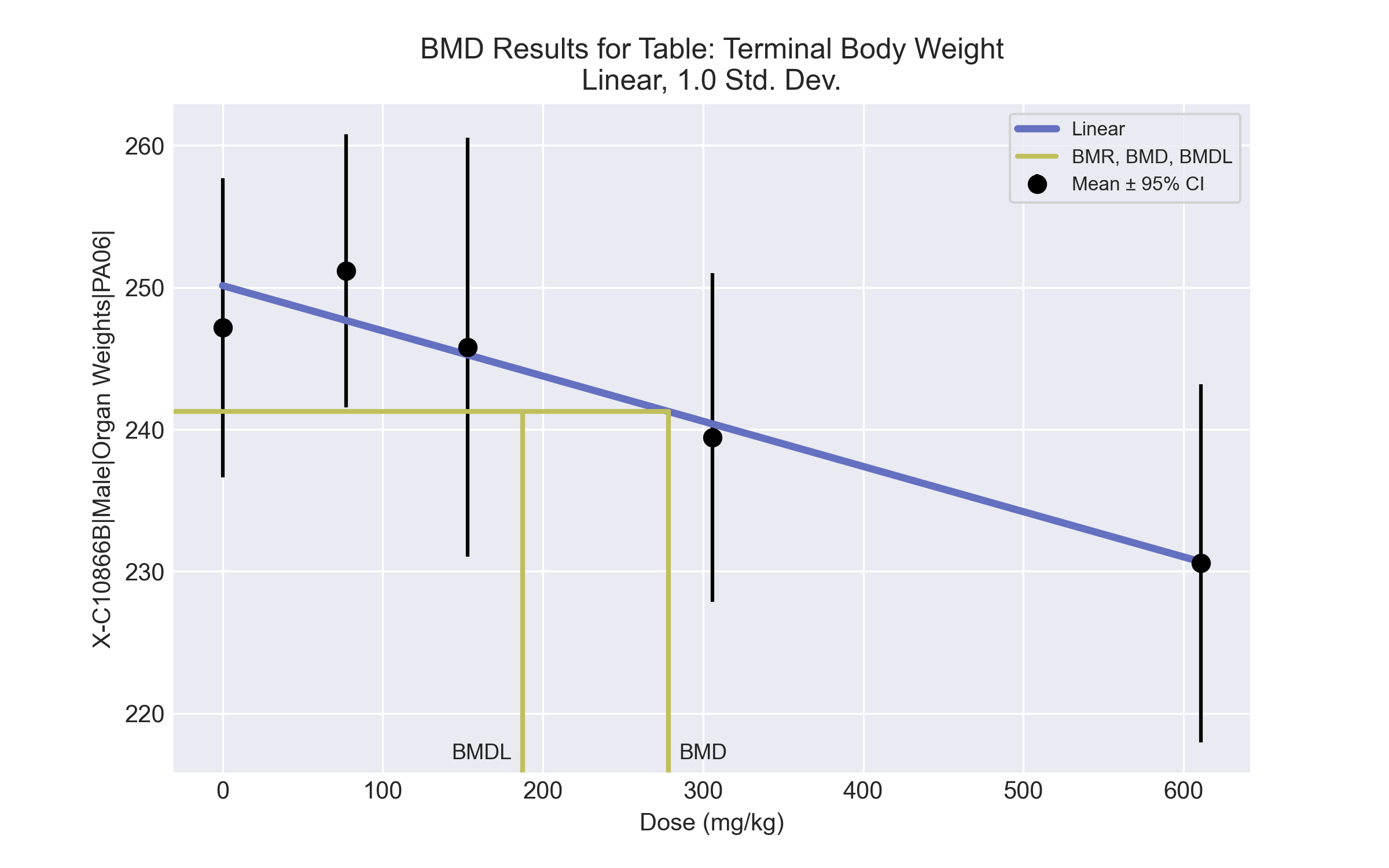
b Recommended model

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Lineara | Valid | - |
| Polynomial 2° (equivalent models include Polynomial 3°, 4°) | Valid | - |
| Power | Valid | - |
| Hill | Valid | - |
| Exponential M2 (equivalent models include Exponential M4) | Valid | - |
| Exponential M3 | Valid | - |
| Exponential M5 | Valid | - |

a Recommended model

## Recommended model



====================================================================   
 Polynomial Model. (Version: 2.21; Date: 03/14/2017)   
 Input Data File: C:\Windows\TEMP\bmds-7ln\_0m\_u.(d)   
 Gnuplot Plotting File: C:\Windows\TEMP\bmds-7ln\_0m\_u.plt  
 Tue Jul 06 12:38:52 2021  
 ====================================================================   
  
 BMDS\_Model\_Run   
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~  
   
 The form of the response function is:   
  
 Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ...  
  
  
 Dependent variable = Response  
 Independent variable = Dose  
 rho is set to 0  
 The polynomial coefficients are restricted to be negative  
 A constant variance model is fit  
  
 Total number of dose groups = 5  
 Total number of records with missing values = 0  
 Maximum number of iterations = 500  
 Relative Function Convergence has been set to: 1e-008  
 Parameter Convergence has been set to: 1e-008  
  
  
  
 Default Initial Parameter Values   
 alpha = 92.5624  
 rho = 0 Specified  
 beta\_0 = 250.124  
 beta\_1 = -0.0318389  
  
  
 Asymptotic Correlation Matrix of Parameter Estimates  
  
 ( \*\*\* The model parameter(s) -rho   
 have been estimated at a boundary point, or have been specified by the user,  
 and do not appear in the correlation matrix )  
  
 alpha beta\_0 beta\_1  
  
 alpha 1 -5.6e-011 -3e-010  
  
 beta\_0 -5.6e-011 1 -0.73  
  
 beta\_1 -3e-010 -0.73 1  
  
  
  
 Parameter Estimates  
  
 95.0% Wald Confidence Interval  
 Variable Estimate Std. Err. Lower Conf. Limit Upper Conf. Limit  
 alpha 78.4817 22.198 34.9745 121.989  
 beta\_0 250.124 2.58491 245.058 255.19  
 beta\_1 -0.0318389 0.00820465 -0.0479197 -0.0157581  
  
  
  
 Table of Data and Estimated Values of Interest  
  
 Dose N Obs Mean Est Mean Obs Std Dev Est Std Dev Scaled Res.  
------ --- -------- -------- ----------- ----------- ----------  
  
 0 5 247 250 8.48 8.86 -0.748  
 77 5 251 248 7.73 8.86 0.88  
 153 5 246 245 11.9 8.86 0.133  
 306 5 239 240 9.32 8.86 -0.243  
 611 5 231 231 10.1 8.86 -0.0228  
  
  
  
 Model Descriptions for likelihoods calculated  
  
  
 Model A1: Yij = Mu(i) + e(ij)  
 Var{e(ij)} = Sigma^2  
  
 Model A2: Yij = Mu(i) + e(ij)  
 Var{e(ij)} = Sigma(i)^2  
  
 Model A3: Yij = Mu(i) + e(ij)  
 Var{e(ij)} = Sigma^2  
 Model A3 uses any fixed variance parameters that  
 were specified by the user  
  
 Model R: Yi = Mu + e(i)  
 Var{e(i)} = Sigma^2  
  
  
 Likelihoods of Interest  
  
 Model Log(likelihood) # Param's AIC  
 A1 -66.309243 6 144.618487  
 A2 -65.750363 10 151.500726  
 A3 -66.309243 6 144.618487  
 fitted -67.035821 3 140.071643  
 R -72.929294 2 149.858588  
  
  
 Explanation of Tests   
  
 Test 1: Do responses and/or variances differ among Dose levels?   
 (A2 vs. R)  
 Test 2: Are Variances Homogeneous? (A1 vs A2)  
 Test 3: Are variances adequately modeled? (A2 vs. A3)  
 Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)  
 (Note: When rho=0 the results of Test 3 and Test 2 will be the same.)  
  
 Tests of Interest   
  
 Test -2\*log(Likelihood Ratio) Test df p-value   
  
 Test 1 14.3579 8 0.0729  
 Test 2 1.11776 4 0.8914  
 Test 3 1.11776 4 0.8914  
 Test 4 1.45316 3 0.6931  
  
The p-value for Test 1 is greater than .05. There may not be a  
diffence between responses and/or variances among the dose levels  
Modelling the data with a dose/response curve may not be appropriate  
  
The p-value for Test 2 is greater than .1. A homogeneous variance   
model appears to be appropriate here  
  
  
The p-value for Test 3 is greater than .1. The modeled variance appears   
 to be appropriate here  
  
The p-value for Test 4 is greater than .1. The model chosen seems   
to adequately describe the data  
   
  
 Benchmark Dose Computation  
  
Specified effect = 1  
  
Risk Type = Estimated standard deviations from the control mean  
  
Confidence level = 0.95  
  
 BMD = 278.244  
  
  
 BMDL = 187.298  
  
  
 BMDU = 536.529

# BMD Results for Table: A/G Ratio

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Dose | 0 | 77 | 153 | 306 | 611 |
| N | 5 | 5 | 5 | 5 | 5 |
| Mean ± SD | 1.348 ± 0.034 | 1.278 ± 0.073 | 1.232 ± 0.046 | 1.176 ± 0.066 | 1.171 ± 0.076 |

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear (equivalent models include Power, Polynomial 2°, 3°, 4°) | 0.038 | -105.806 | 247.441 | 171.193 | Exponential-M4 recommended as best-fitting model on the basis of the lowest AIC. |
| Hill | 0.609 | -109.954 | 65.806 | 20.656 |
| Exponential M2 (equivalent models include Exponential M3) | 0.047 | -106.242 | 229.65 | 156.035 |
| Exponential M4b | 0.865 | -111.925 | 51.337 | 26.983 |
| Exponential M5 | 0.74 | -110.106 | 64.049 | 27.542 |

a Constant variance case presented (BMDS Test 2 p-value = 0.384, BMDS Test 3 p-value = 0.384).

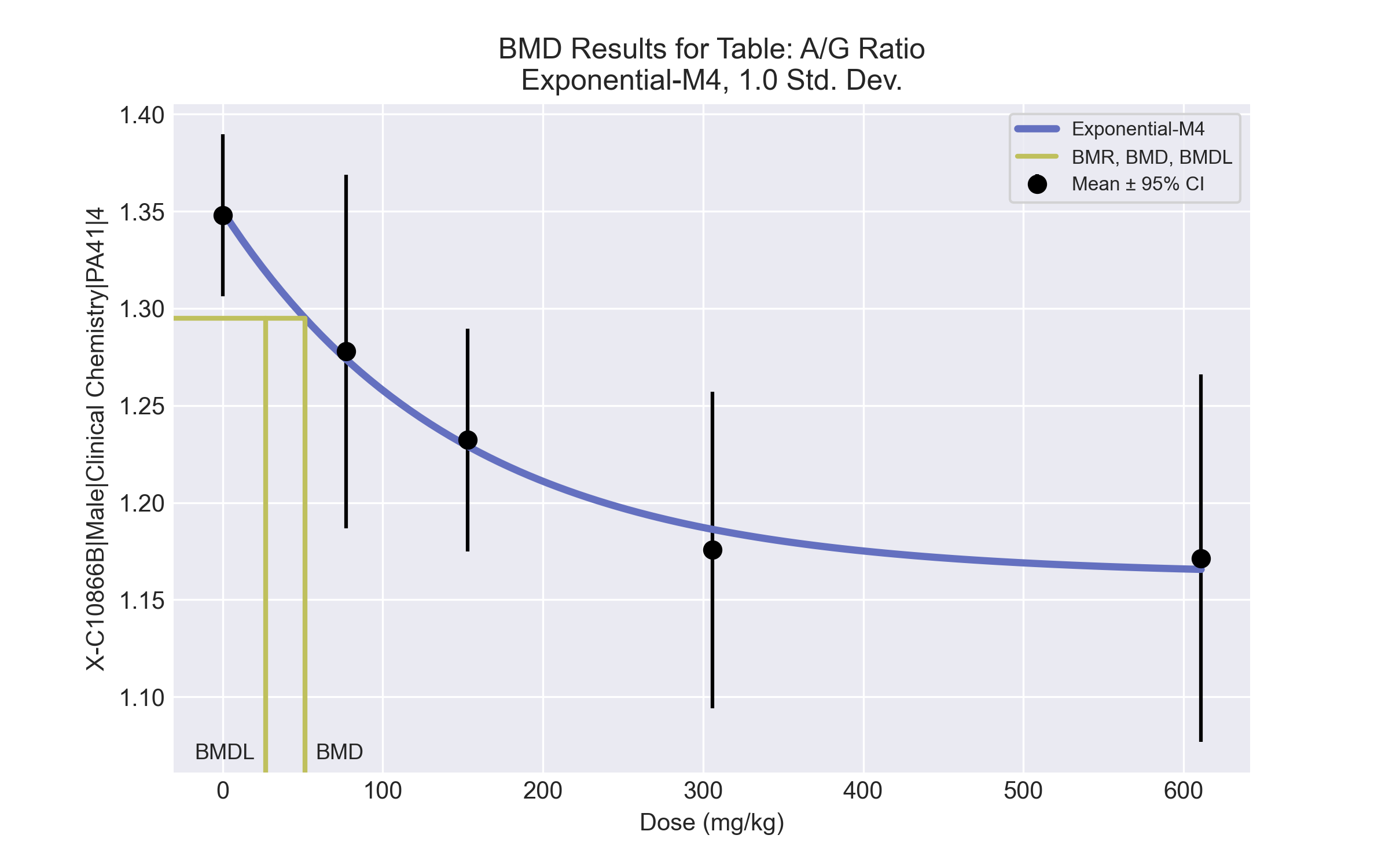
b Recommended model

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear (equivalent models include Power, Polynomial 2°, 3°, 4°) | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0382 < 0.1)  • Ratio of modeled to actual stdev. at control is greater than threshold (1.93 > 1.5) |
| Hill | Warning | **Warnings**  • Ratio of modeled to actual stdev. at control is greater than threshold (1.64 > 1.5) |
| Exponential M2 (equivalent models include Exponential M3) | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0466 < 0.1) |
| Exponential M4a | Valid | - |
| Exponential M5 | Valid | - |

a Recommended model

## Recommended model



====================================================================   
 Exponential Model. (Version: 1.11; Date: 03/14/2017)   
 Input Data File: C:\Windows\TEMP\bmds-v6s\_7qot.(d)   
 Gnuplot Plotting File:   
 Tue Jul 06 12:39:15 2021  
 ====================================================================   
  
 BMDS\_Model\_Run   
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~  
   
 The form of the response function by Model:   
 Model 2: Y[dose] = a \* exp{sign \* b \* dose}  
 Model 3: Y[dose] = a \* exp{sign \* (b \* dose)^d}  
 Model 4: Y[dose] = a \* [c-(c-1) \* exp{-b \* dose}]  
 Model 5: Y[dose] = a \* [c-(c-1) \* exp{-(b \* dose)^d}]  
  
 Note: Y[dose] is the median response for exposure = dose;  
 sign = +1 for increasing trend in data;  
 sign = -1 for decreasing trend.  
  
 Model 2 is nested within Models 3 and 4.  
 Model 3 is nested within Model 5.  
 Model 4 is nested within Model 5.  
  
  
 Dependent variable = Response  
 Independent variable = Dose  
 Data are assumed to be distributed: normally  
 Variance Model: exp(lnalpha +rho \*ln(Y[dose]))  
 rho is set to 0.  
 A constant variance model is fit.  
  
 Total number of dose groups = 5  
 Total number of records with missing values = 0  
 Maximum number of iterations = 500  
 Relative Function Convergence has been set to: 1e-008  
 Parameter Convergence has been set to: 1e-008  
  
 MLE solution provided: Exact  
  
  
 Initial Parameter Values  
  
 Variable Model 4  
 -------- --------  
 lnalpha -5.80866   
 rho 0 Specified  
 a 1.41532   
 b 0.00344767   
 c 0.788188   
 d 1 Specified  
  
  
  
 Parameter Estimates  
  
 Variable Model 4 Std. Err.  
 -------- ------- ---------  
 lnalpha -5.79702 0.00085888  
 a 1.35016 0.0235655  
 b 0.00677691 0.00273569  
 c 0.861099 0.0226097  
  
 NC = No Convergence  
  
  
 Table of Stats From Input Data  
  
 Dose N Obs Mean Obs Std Dev  
 ----- --- ---------- -------------  
 0 5 1.348 0.03351  
 77 5 1.278 0.07334  
 153 5 1.232 0.04624  
 306 5 1.176 0.06561  
 611 5 1.171 0.07625  
  
  
 Estimated Values of Interest  
  
 Dose Est Mean Est Std Scaled Residual  
 ------ ---------- --------- ----------------  
 0 1.35 0.05511 -0.09056  
 77 1.274 0.05511 0.1612  
 153 1.229 0.05511 0.1278  
 306 1.186 0.05511 -0.4303  
 611 1.166 0.05511 0.2319  
  
  
  
 Other models for which likelihoods are calculated:  
  
 Model A1: Yij = Mu(i) + e(ij)  
 Var{e(ij)} = Sigma^2  
  
 Model A2: Yij = Mu(i) + e(ij)  
 Var{e(ij)} = Sigma(i)^2  
  
 Model A3: Yij = Mu(i) + e(ij)  
 Var{e(ij)} = exp(lalpha + log(mean(i)) \* rho)  
  
 Model R: Yij = Mu + e(i)  
 Var{e(ij)} = Sigma^2  
  
  
 Likelihoods of Interest  
  
 Model Log(likelihood) DF AIC  
 ------- ----------------- ---- ------------  
 A1 60.10826 6 -108.2165  
 A2 62.1906 10 -104.3812  
 A3 60.10826 6 -108.2165  
 R 48.82469 2 -93.64939  
 4 59.96271 4 -111.9254  
  
  
 Additive constant for all log-likelihoods = -22.97. This constant added to the  
 above values gives the log-likelihood including the term that does not  
 depend on the model parameters.  
  
  
 Explanation of Tests  
  
 Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)  
 Test 2: Are Variances Homogeneous? (A2 vs. A1)  
 Test 3: Are variances adequately modeled? (A2 vs. A3)  
  
 Test 6a: Does Model 4 fit the data? (A3 vs 4)  
  
  
 Tests of Interest  
  
 Test -2\*log(Likelihood Ratio) D. F. p-value  
 -------- ------------------------ ------ --------------  
 Test 1 26.73 8 0.0007864  
 Test 2 4.165 4 0.3842  
 Test 3 4.165 4 0.3842  
 Test 6a 0.2911 2 0.8645  
  
  
 The p-value for Test 1 is less than .05. There appears to be a  
 difference between response and/or variances among the dose  
 levels, it seems appropriate to model the data.  
  
 The p-value for Test 2 is greater than .1. A homogeneous  
 variance model appears to be appropriate here.  
  
 The p-value for Test 3 is greater than .1. The modeled  
 variance appears to be appropriate here.  
  
 The p-value for Test 6a is greater than .1. Model 4 seems  
 to adequately describe the data.  
  
  
 Benchmark Dose Computations:  
  
 Specified Effect = 1.000000  
  
 Risk Type = Estimated standard deviations from control  
  
 Confidence Level = 0.950000  
  
 BMD = 51.3369  
  
 BMDL = 26.9832  
  
 BMDU = 121.485

# BMD Results for Table: Albumin

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Dose | 0 | 77 | 153 | 306 | 611 |
| N | 5 | 5 | 5 | 5 | 5 |
| Mean ± SD | 3.42 ± 0.13 | 3.42 ± 0.13 | 3.3 ± 0.141 | 3.24 ± 0.114 | 3.18 ± 0.164 |

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear (equivalent models include Power, Polynomial 2°, 3°, 4°) | 0.565 | -71.888 | 309.608 | 202.671 | Exponential-M4 recommended as best-fitting model on the basis of the lowest BMDL. |
| Hill | 0.531 | -69.533 | 161.757 | 66.186 |
| Exponential M2 (equivalent models include Exponential M3) | 0.581 | -71.966 | 300.878 | 193.856 |
| Exponential M4b | 0.6 | -70.906 | 167.591 | 63.215 |
| Exponential M5 | 0.438 | -69.323 | 175.482 | 67.894 |

a Constant variance case presented (BMDS Test 2 p-value = 0.947, BMDS Test 3 p-value = 0.947).

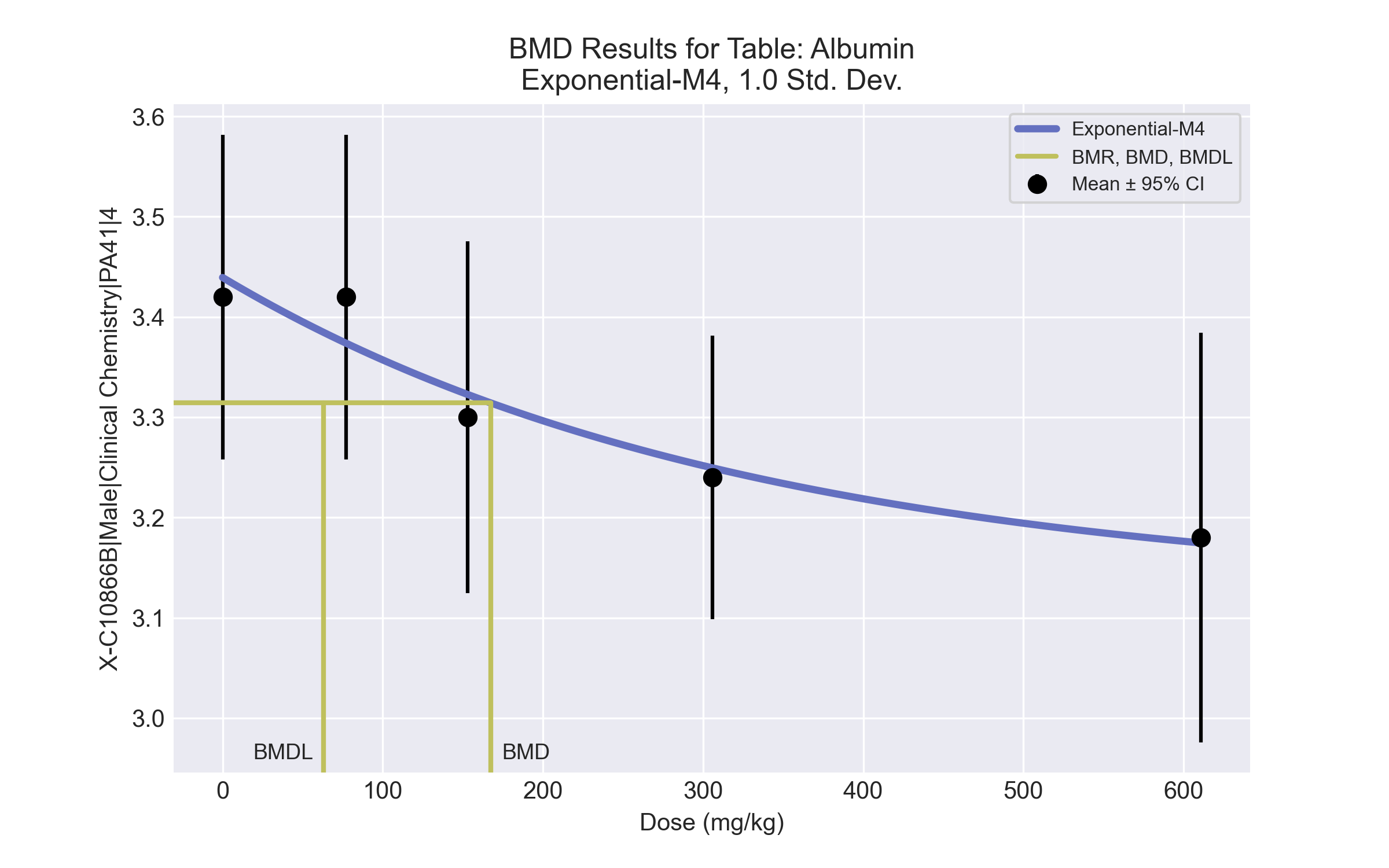
b Recommended model

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear (equivalent models include Power, Polynomial 2°, 3°, 4°) | Valid | - |
| Hill | Valid | - |
| Exponential M2 (equivalent models include Exponential M3) | Valid | - |
| Exponential M4a | Valid | - |
| Exponential M5 | Valid | - |

a Recommended model

## Recommended model



====================================================================   
 Exponential Model. (Version: 1.11; Date: 03/14/2017)   
 Input Data File: C:\Windows\TEMP\bmds-3l\_twgvj.(d)   
 Gnuplot Plotting File:   
 Tue Jul 06 12:39:19 2021  
 ====================================================================   
  
 BMDS\_Model\_Run   
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~  
   
 The form of the response function by Model:   
 Model 2: Y[dose] = a \* exp{sign \* b \* dose}  
 Model 3: Y[dose] = a \* exp{sign \* (b \* dose)^d}  
 Model 4: Y[dose] = a \* [c-(c-1) \* exp{-b \* dose}]  
 Model 5: Y[dose] = a \* [c-(c-1) \* exp{-(b \* dose)^d}]  
  
 Note: Y[dose] is the median response for exposure = dose;  
 sign = +1 for increasing trend in data;  
 sign = -1 for decreasing trend.  
  
 Model 2 is nested within Models 3 and 4.  
 Model 3 is nested within Model 5.  
 Model 4 is nested within Model 5.  
  
  
 Dependent variable = Response  
 Independent variable = Dose  
 Data are assumed to be distributed: normally  
 Variance Model: exp(lnalpha +rho \*ln(Y[dose]))  
 rho is set to 0.  
 A constant variance model is fit.  
  
 Total number of dose groups = 5  
 Total number of records with missing values = 0  
 Maximum number of iterations = 500  
 Relative Function Convergence has been set to: 1e-008  
 Parameter Convergence has been set to: 1e-008  
  
 MLE solution provided: Exact  
  
  
 Initial Parameter Values  
  
 Variable Model 4  
 -------- --------  
 lnalpha -4.19704   
 rho 0 Specified  
 a 3.591   
 b 0.0024995   
 c 0.843378   
 d 1 Specified  
  
  
  
 Parameter Estimates  
  
 Variable Model 4 Std. Err.  
 -------- ------- ---------  
 lnalpha -4.15623 0.00443117  
 a 3.43933 0.0501098  
 b 0.00303733 0.00305791  
 c 0.908772 0.0407013  
  
 NC = No Convergence  
  
  
 Table of Stats From Input Data  
  
 Dose N Obs Mean Obs Std Dev  
 ----- --- ---------- -------------  
 0 5 3.42 0.1304  
 77 5 3.42 0.1304  
 153 5 3.3 0.1414  
 306 5 3.24 0.114  
 611 5 3.18 0.1643  
  
  
 Estimated Values of Interest  
  
 Dose Est Mean Est Std Scaled Residual  
 ------ ---------- --------- ----------------  
 0 3.439 0.1252 -0.3454  
 77 3.374 0.1252 0.8236  
 153 3.323 0.1252 -0.4057  
 306 3.249 0.1252 -0.1686  
 611 3.175 0.1252 0.09613  
  
  
  
 Other models for which likelihoods are calculated:  
  
 Model A1: Yij = Mu(i) + e(ij)  
 Var{e(ij)} = Sigma^2  
  
 Model A2: Yij = Mu(i) + e(ij)  
 Var{e(ij)} = Sigma(i)^2  
  
 Model A3: Yij = Mu(i) + e(ij)  
 Var{e(ij)} = exp(lalpha + log(mean(i)) \* rho)  
  
 Model R: Yij = Mu + e(i)  
 Var{e(ij)} = Sigma^2  
  
  
 Likelihoods of Interest  
  
 Model Log(likelihood) DF AIC  
 ------- ----------------- ---- ------------  
 A1 39.96302 6 -67.92603  
 A2 40.32886 10 -60.65772  
 A3 39.96302 6 -67.92603  
 R 33.98864 2 -63.97727  
 4 39.45284 4 -70.90568  
  
  
 Additive constant for all log-likelihoods = -22.97. This constant added to the  
 above values gives the log-likelihood including the term that does not  
 depend on the model parameters.  
  
  
 Explanation of Tests  
  
 Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)  
 Test 2: Are Variances Homogeneous? (A2 vs. A1)  
 Test 3: Are variances adequately modeled? (A2 vs. A3)  
  
 Test 6a: Does Model 4 fit the data? (A3 vs 4)  
  
  
 Tests of Interest  
  
 Test -2\*log(Likelihood Ratio) D. F. p-value  
 -------- ------------------------ ------ --------------  
 Test 1 12.68 8 0.1233  
 Test 2 0.7317 4 0.9474  
 Test 3 0.7317 4 0.9474  
 Test 6a 1.02 2 0.6004  
  
  
 The p-value for Test 1 is greater than .05. There may not be a  
 diffence between responses and/or variances among the dose levels  
 Modelling the data with a dose/response curve may not be appropriate.  
  
 The p-value for Test 2 is greater than .1. A homogeneous  
 variance model appears to be appropriate here.  
  
 The p-value for Test 3 is greater than .1. The modeled  
 variance appears to be appropriate here.  
  
 The p-value for Test 6a is greater than .1. Model 4 seems  
 to adequately describe the data.  
  
  
 Benchmark Dose Computations:  
  
 Specified Effect = 1.000000  
  
 Risk Type = Estimated standard deviations from control  
  
 Confidence Level = 0.950000  
  
 BMD = 167.591  
  
 BMDL = 63.2153  
  
 BMDU = 538.632

# BMD Results for Table: Bile salts/acids

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Dose | 0 | 77 | 153 | 306 | 611 |
| N | 5 | 5 | 5 | 5 | 5 |
| Mean ± SD | 34.94 ± 9.852 | 33.46 ± 24.831 | 23.16 ± 4.993 | 26.36 ± 13.155 | 18.88 ± 9.13 |

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear | 0.056 | 159.007 | 684.223 | 352.992 | No model was recommended as a best-fitting model. Doses were dropped until there were only 3 remaining dose-groups. |
| Polynomial 2° (equivalent models include Power, Polynomial 3°) | 0.056 | 159.007 | 684.224 | 352.992 |
| Polynomial 4° | 0.056 | 159.007 | 684.226 | 352.992 |
| Hill | 0.097 | 158.113 | -999 | -999 |
| Exponential M2 | 0.058 | 158.931 | 685.433 | 262.33 |
| Exponential M3 | 0.024 | 160.929 | 687.829 | 262.422 |
| Exponential M4 | 0.024 | 160.922 | 691.565 | 111.413 |
| Exponential M5 | 0.007 | 162.861 | 828.948 | 78.334 |

a Modeled variance case presented (BMDS Test 2 p-value = 0.01, BMDS Test 3 p-value = 0.167).

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0563 < 0.1)  • BMD/high dose ratio is greater than threshold (1.12 > 1.0)  • Ratio of modeled to actual stdev. at control is greater than threshold (1.58 > 1.5) |
| Polynomial 2° (equivalent models include Power, Polynomial 3°) | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0563 < 0.1)  • BMD/high dose ratio is greater than threshold (1.12 > 1.0)  • Ratio of modeled to actual stdev. at control is greater than threshold (1.58 > 1.5) |
| Polynomial 4° | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0563 < 0.1)  • BMD/high dose ratio is greater than threshold (1.12 > 1.0)  • Ratio of modeled to actual stdev. at control is greater than threshold (1.58 > 1.5) |
| Hill | Failure | **Failures**  • BMD does not exist  • BMDL does not exist  **Warnings**  • Residual of Interest does not exist  • Goodness of fit p-value is less than threshold (0.0974 < 0.1)  • Ratio of modeled to actual stdev. at control is greater than threshold (1.72 > 1.5)  **Cautions**  • Warning(s): BMR value is not in the range of the mean function |
| Exponential M2 | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0582 < 0.1)  • BMD/high dose ratio is greater than threshold (1.12 > 1.0) |
| Exponential M3 | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0238 < 0.1)  • BMD/high dose ratio is greater than threshold (1.13 > 1.0) |
| Exponential M4 | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0239 < 0.1)  • BMD/high dose ratio is greater than threshold (1.13 > 1.0)  **Cautions**  • BMD/BMDL ratio is greater than threshold (6.21 > 5.0) |
| Exponential M5 | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0065 < 0.1)  • BMD/high dose ratio is greater than threshold (1.36 > 1.0)  **Cautions**  • BMD/BMDL ratio is greater than threshold (10.6 > 5.0) |

## Recommended model

*No model was recommended as a best-fitting model.*

# BMD Results for Table: Cholesterol

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Dose | 0 | 77 | 153 | 306 | 611a |
| N | 5 | 5 | 5 | 5 | 5 |
| Mean ± SD | 113.2 ± 11.345 | 140.6 ± 16.979 | 131.6 ± 11.546 | 134 ± 11.314 | 149 ± 8.66 |

a Dose group removed in BMD modeling session

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear (equivalent models include Polynomial 2°, 3°, 4°) | 0.012 | 133.092 | 314.543 | 152.967 | Hill recommended as best-fitting model on the basis of the lowest AIC. |
| Power | 0.012 | 133.092 | 314.542 | 152.967 |
| Hillb | 0.215 | 127.743 | 3.7E-13 | 3.7E-13 |
| Exponential M2 (equivalent models include Exponential M3) | 0.011 | 133.187 | 326.716 | 165.772 |
| Exponential M4 | 0.215 | 127.743 | 3.881 | 0.006 |
| Exponential M5 | -999 | 129.743 | 20.175 | 0.037 |

a Constant variance case presented (BMDS Test 2 p-value = 0.721, BMDS Test 3 p-value = 0.721).

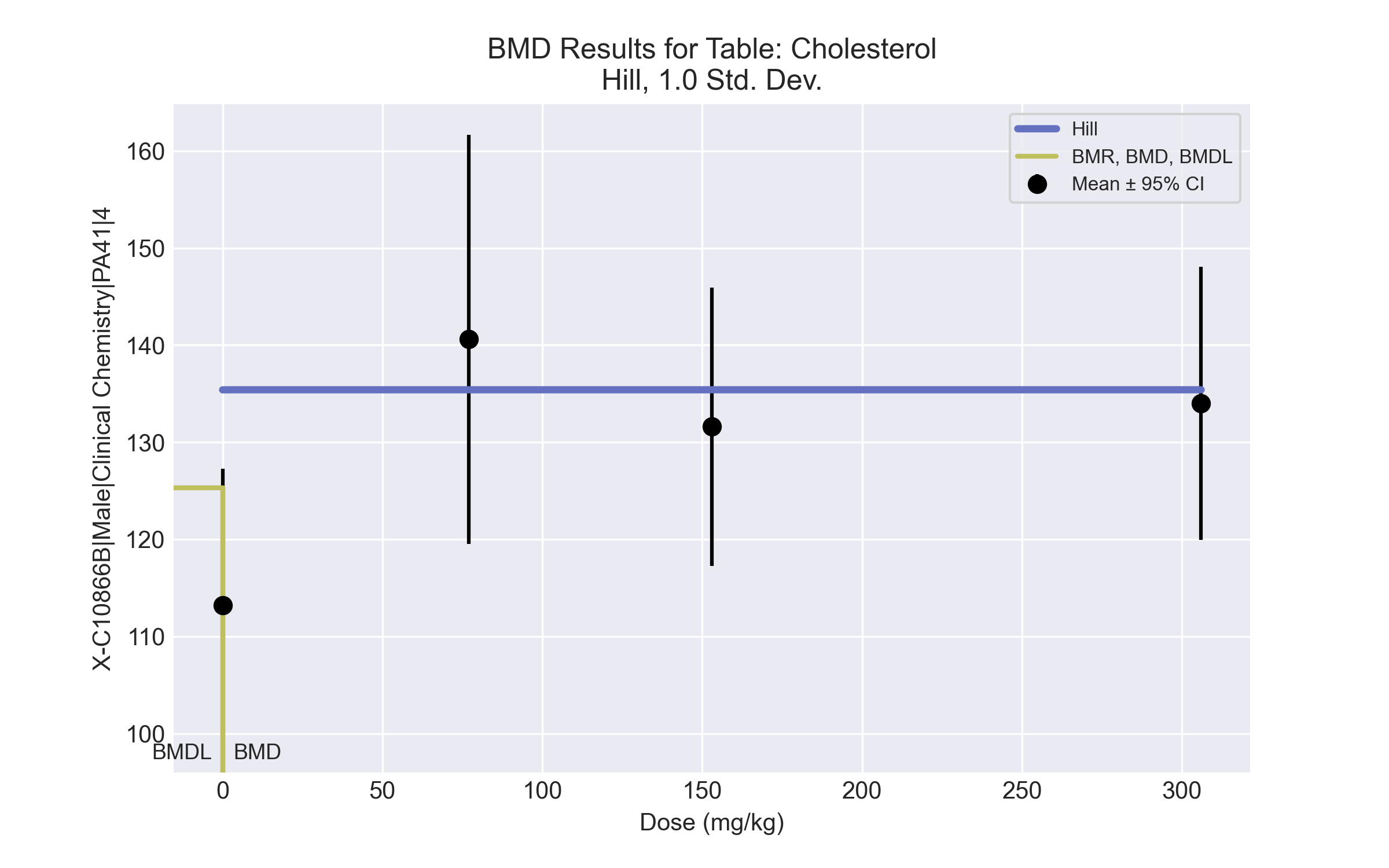
b Recommended model

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear (equivalent models include Polynomial 2°, 3°, 4°) | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0117 < 0.1)  • BMD/high dose ratio is greater than threshold (1.03 > 1.0) |
| Power | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0117 < 0.1)  • BMD/high dose ratio is greater than threshold (1.03 > 1.0) |
| Hilla | Valid | **Cautions**  • Minimum dose/BMD ratio is greater than threshold (2.1e+14 > 3.0) |
| Exponential M2 (equivalent models include Exponential M3) | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0112 < 0.1)  • BMD/high dose ratio is greater than threshold (1.07 > 1.0) |
| Exponential M4 | Warning | **Warnings**  • BMD/BMDL ratio is greater than threshold (6.57e+02 > 20.0)  **Cautions**  • BMD/BMDL ratio is greater than threshold (6.57e+02 > 5.0)  • Minimum dose/BMD ratio is greater than threshold (19.8 > 3.0) |
| Exponential M5 | Warning | **Warnings**  • BMD/BMDL ratio is greater than threshold (5.48e+02 > 20.0)  • Zero degrees of freedom; saturated model  **Cautions**  • BMD/BMDL ratio is greater than threshold (5.48e+02 > 5.0)  • Minimum dose/BMD ratio is greater than threshold (3.82 > 3.0) |

a Recommended model

## Recommended model



====================================================================   
 Hill Model. (Version: 2.18; Date: 03/14/2017)   
 Input Data File: C:\Windows\TEMP\bmds-012wqt80.(d)   
 Gnuplot Plotting File: C:\Windows\TEMP\bmds-012wqt80.plt  
 Tue Jul 06 12:39:37 2021  
 ====================================================================   
  
 BMDS\_Model\_Run   
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~  
   
 The form of the response function is:   
  
 Y[dose] = intercept + v\*dose^n/(k^n + dose^n)  
  
  
 Dependent variable = Response  
 Independent variable = Dose  
 rho is set to 0  
 Power parameter restricted to be greater than 1  
 A constant variance model is fit  
  
 Total number of dose groups = 4  
 Total number of records with missing values = 0  
 Maximum number of iterations = 500  
 Relative Function Convergence has been set to: 1e-008  
 Parameter Convergence has been set to: 1e-008  
  
  
  
 Default Initial Parameter Values   
 alpha = 169.575  
 rho = 0 Specified  
 intercept = 113.2  
 v = 27.4  
 n = 1.86078  
 k = 115.5  
  
  
 Asymptotic Correlation Matrix of Parameter Estimates  
  
 ( \*\*\* The model parameter(s) -rho -k   
 have been estimated at a boundary point, or have been specified by the user,  
 and do not appear in the correlation matrix )  
  
 alpha intercept v n  
  
 alpha 1 5e-009 -2e-008 -5.4e-006  
  
 intercept 5e-009 1 -0.87 -4.1e-006  
  
 v -2e-008 -0.87 1 -1.2e-005  
  
 n -5.4e-006 -4.1e-006 -1.2e-005 1  
  
  
  
 Parameter Estimates  
  
 95.0% Wald Confidence Interval  
 Variable Estimate Std. Err. Lower Conf. Limit Upper Conf. Limit  
 alpha 146.52 46.3338 55.7076 237.333  
 intercept 113.2 5.41332 102.59 123.81  
 v 22.2 6.25076 9.94873 34.4513  
 n 1.00006 2660.6 -5213.69 5215.69  
 k 3.06e-013 NA  
  
NA - Indicates that this parameter has hit a bound  
 implied by some inequality constraint and thus  
 has no standard error.  
  
  
  
 Table of Data and Estimated Values of Interest  
  
 Dose N Obs Mean Est Mean Obs Std Dev Est Std Dev Scaled Res.  
------ --- -------- -------- ----------- ----------- ----------  
  
 0 5 113 113 11.3 12.1 -1.59e-008  
 77 5 141 135 17 12.1 0.961  
 153 5 132 135 11.5 12.1 -0.702  
 306 5 134 135 11.3 12.1 -0.259  
  
  
  
 Model Descriptions for likelihoods calculated  
  
  
 Model A1: Yij = Mu(i) + e(ij)  
 Var{e(ij)} = Sigma^2  
  
 Model A2: Yij = Mu(i) + e(ij)  
 Var{e(ij)} = Sigma(i)^2  
  
 Model A3: Yij = Mu(i) + e(ij)  
 Var{e(ij)} = Sigma^2  
 Model A3 uses any fixed variance parameters that  
 were specified by the user  
  
 Model R: Yi = Mu + e(i)  
 Var{e(i)} = Sigma^2  
  
  
 Likelihoods of Interest  
  
 Model Log(likelihood) # Param's AIC  
 A1 -59.101517 5 128.203034  
 A2 -58.433860 8 132.867719  
 A3 -59.101517 5 128.203034  
 fitted -59.871619 4 127.743238  
 R -64.761601 2 133.523203  
  
  
 Explanation of Tests   
  
 Test 1: Do responses and/or variances differ among Dose levels?   
 (A2 vs. R)  
 Test 2: Are Variances Homogeneous? (A1 vs A2)  
 Test 3: Are variances adequately modeled? (A2 vs. A3)  
 Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)  
 (Note: When rho=0 the results of Test 3 and Test 2 will be the same.)  
  
 Tests of Interest   
  
 Test -2\*log(Likelihood Ratio) Test df p-value   
  
 Test 1 12.6555 6 0.04885  
 Test 2 1.33532 3 0.7208  
 Test 3 1.33532 3 0.7208  
 Test 4 1.5402 1 0.2146  
  
The p-value for Test 1 is less than .05. There appears to be a  
difference between response and/or variances among the dose levels  
It seems appropriate to model the data  
  
The p-value for Test 2 is greater than .1. A homogeneous variance   
model appears to be appropriate here  
  
  
The p-value for Test 3 is greater than .1. The modeled variance appears   
 to be appropriate here  
  
The p-value for Test 4 is greater than .1. The model chosen seems   
to adequately describe the data  
   
  
 Benchmark Dose Computation  
  
Specified effect = 1  
  
Risk Type = Estimated standard deviations from the control mean   
  
Confidence level = 0.95  
  
 BMD = 3.66893e-013  
  
 BMDL = 3.66893e-013  
  
 BMDU = 3.66895e-013

# BMD Results for Table: Creatinine

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Dose | 0 | 77 | 153 | 306 | 611 |
| N | 5 | 5 | 5 | 5 | 5 |
| Mean ± SD | 0.274 ± 0.017 | 0.278 ± 0.008 | 0.28 ± 0.023 | 0.25 ± 0.016 | 0.252 ± 0.008 |

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear (equivalent models include Power, Polynomial 2°, 3°, 4°) | 0.079 | -175.738 | 330.241 | 212.26 | Hill recommended as best-fitting model on the basis of the lowest AIC. |
| Hillb | 0.766 | -180.005 | 223.913 | 158.866 |
| Exponential M2 | 0.081 | -175.804 | 318.629 | 199.539 |
| Exponential M3 | 0.035 | -173.804 | 318.939 | 199.539 |
| Exponential M4 | 0.038 | -174.019 | 255.658 | 101.254 |
| Exponential M5 | 0.469 | -178.013 | 263.293 | 157.626 |

a Constant variance case presented (BMDS Test 2 p-value = 0.107, BMDS Test 3 p-value = 0.107).

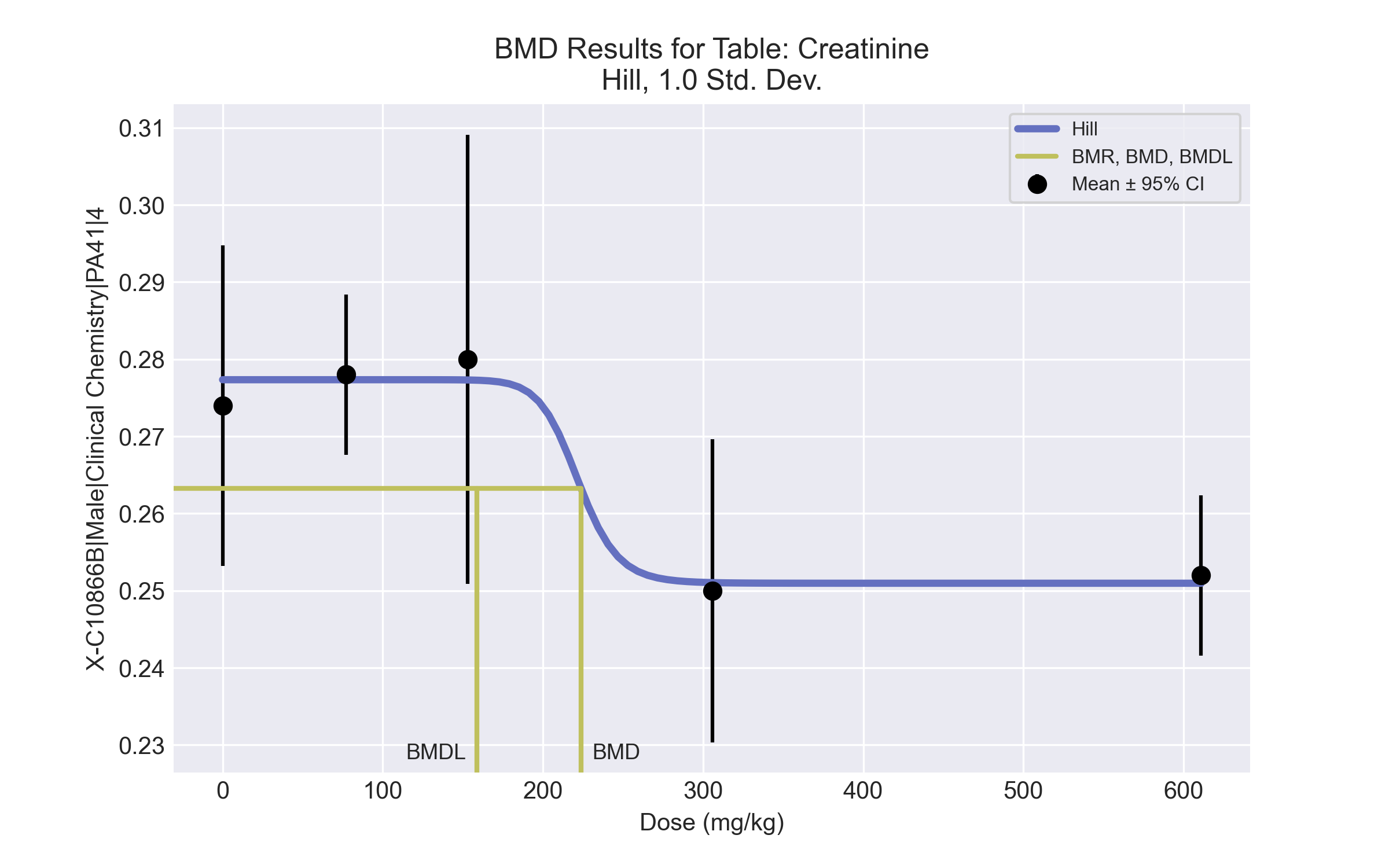
b Recommended model

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear (equivalent models include Power, Polynomial 2°, 3°, 4°) | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0786 < 0.1) |
| Hilla | Valid | - |
| Exponential M2 | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0809 < 0.1) |
| Exponential M3 | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0345 < 0.1) |
| Exponential M4 | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0384 < 0.1) |
| Exponential M5 | Valid | - |

a Recommended model

## Recommended model



====================================================================   
 Hill Model. (Version: 2.18; Date: 03/14/2017)   
 Input Data File: C:\Windows\TEMP\bmds-0asi5ygi.(d)   
 Gnuplot Plotting File: C:\Windows\TEMP\bmds-0asi5ygi.plt  
 Tue Jul 06 12:39:42 2021  
 ====================================================================   
  
 BMDS\_Model\_Run   
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~  
   
 The form of the response function is:   
  
 Y[dose] = intercept + v\*dose^n/(k^n + dose^n)  
  
  
 Dependent variable = Response  
 Independent variable = Dose  
 rho is set to 0  
 Power parameter restricted to be greater than 1  
 A constant variance model is fit  
  
 Total number of dose groups = 5  
 Total number of records with missing values = 0  
 Maximum number of iterations = 500  
 Relative Function Convergence has been set to: 1e-008  
 Parameter Convergence has been set to: 1e-008  
  
  
  
 Default Initial Parameter Values   
 alpha = 0.000243998  
 rho = 0 Specified  
 intercept = 0.274  
 v = -0.024  
 n = 2.62164  
 k = 244.8  
  
  
 Asymptotic Correlation Matrix of Parameter Estimates  
  
 ( \*\*\* The model parameter(s) -rho -n   
 have been estimated at a boundary point, or have been specified by the user,  
 and do not appear in the correlation matrix )  
  
 alpha intercept v k  
  
 alpha 1 -1e-006 4.1e-007 1.8e-006  
  
 intercept -1e-006 1 -0.63 -0.044  
  
 v 4.1e-007 -0.63 1 -0.079  
  
 k 1.8e-006 -0.044 -0.079 1  
  
  
  
 Parameter Estimates  
  
 95.0% Wald Confidence Interval  
 Variable Estimate Std. Err. Lower Conf. Limit Upper Conf. Limit  
 alpha 0.0001994 5.63988e-005 8.88602e-005 0.00030994  
 intercept 0.277342 0.00365103 0.270186 0.284498  
 v -0.0263798 0.00579447 -0.0377368 -0.0150229  
 n 18 NA  
 k 222.161 186.148 -142.683 587.005  
  
NA - Indicates that this parameter has hit a bound  
 implied by some inequality constraint and thus  
 has no standard error.  
  
  
  
 Table of Data and Estimated Values of Interest  
  
 Dose N Obs Mean Est Mean Obs Std Dev Est Std Dev Scaled Res.  
------ --- -------- -------- ----------- ----------- ----------  
  
 0 5 0.274 0.277 0.0167 0.0141 -0.529  
 77 5 0.278 0.277 0.00837 0.0141 0.104  
 153 5 0.28 0.277 0.0235 0.0141 0.426  
 306 5 0.25 0.251 0.0158 0.0141 -0.165  
 611 5 0.252 0.251 0.00837 0.0141 0.164  
  
  
  
 Model Descriptions for likelihoods calculated  
  
  
 Model A1: Yij = Mu(i) + e(ij)  
 Var{e(ij)} = Sigma^2  
  
 Model A2: Yij = Mu(i) + e(ij)  
 Var{e(ij)} = Sigma(i)^2  
  
 Model A3: Yij = Mu(i) + e(ij)  
 Var{e(ij)} = Sigma^2  
 Model A3 uses any fixed variance parameters that  
 were specified by the user  
  
 Model R: Yi = Mu + e(i)  
 Var{e(i)} = Sigma^2  
  
  
 Likelihoods of Interest  
  
 Model Log(likelihood) # Param's AIC  
 A1 94.268669 6 -176.537338  
 A2 98.075000 10 -176.150000  
 A3 94.268669 6 -176.537338  
 fitted 94.002481 4 -180.004962  
 R 86.419216 2 -168.838431  
  
  
 Explanation of Tests   
  
 Test 1: Do responses and/or variances differ among Dose levels?   
 (A2 vs. R)  
 Test 2: Are Variances Homogeneous? (A1 vs A2)  
 Test 3: Are variances adequately modeled? (A2 vs. A3)  
 Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)  
 (Note: When rho=0 the results of Test 3 and Test 2 will be the same.)  
  
 Tests of Interest   
  
 Test -2\*log(Likelihood Ratio) Test df p-value   
  
 Test 1 23.3116 8 0.002986  
 Test 2 7.61266 4 0.1068  
 Test 3 7.61266 4 0.1068  
 Test 4 0.532375 2 0.7663  
  
The p-value for Test 1 is less than .05. There appears to be a  
difference between response and/or variances among the dose levels  
It seems appropriate to model the data  
  
The p-value for Test 2 is greater than .1. A homogeneous variance   
model appears to be appropriate here  
  
  
The p-value for Test 3 is greater than .1. The modeled variance appears   
 to be appropriate here  
  
The p-value for Test 4 is greater than .1. The model chosen seems   
to adequately describe the data  
   
  
 Benchmark Dose Computation  
  
Specified effect = 1  
  
Risk Type = Estimated standard deviations from the control mean   
  
Confidence level = 0.95  
  
 BMD = 223.913  
  
 BMDL = 158.866  
  
 BMDU = 308.084

# BMD Results for Table: Globulin

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Dose | 0 | 77 | 153 | 306 | 611 |
| N | 5 | 5 | 5 | 5 | 5 |
| Mean ± SD | 2.54 ± 0.152 | 2.68 ± 0.11 | 2.68 ± 0.13 | 2.76 ± 0.114 | 2.72 ± 0.148 |

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linearb (equivalent models include Power, Polynomial 2°, 3°, 4°) | 0.175 | -70.91 | 567.648 | 299.379 | Linear recommended as best-fitting model on the basis of the lowest AIC. |
| Hill | 0.385 | -71.104 | 61.456 | 5.0E-05 |
| Exponential M2 (equivalent models include Exponential M3) | 0.172 | -70.857 | 577.927 | 310.406 |
| Exponential M4 (equivalent models include Exponential M5) | 0.688 | -73.112 | 74.039 | 0.209 |

a Constant variance case presented (BMDS Test 2 p-value = 0.93, BMDS Test 3 p-value = 0.93).

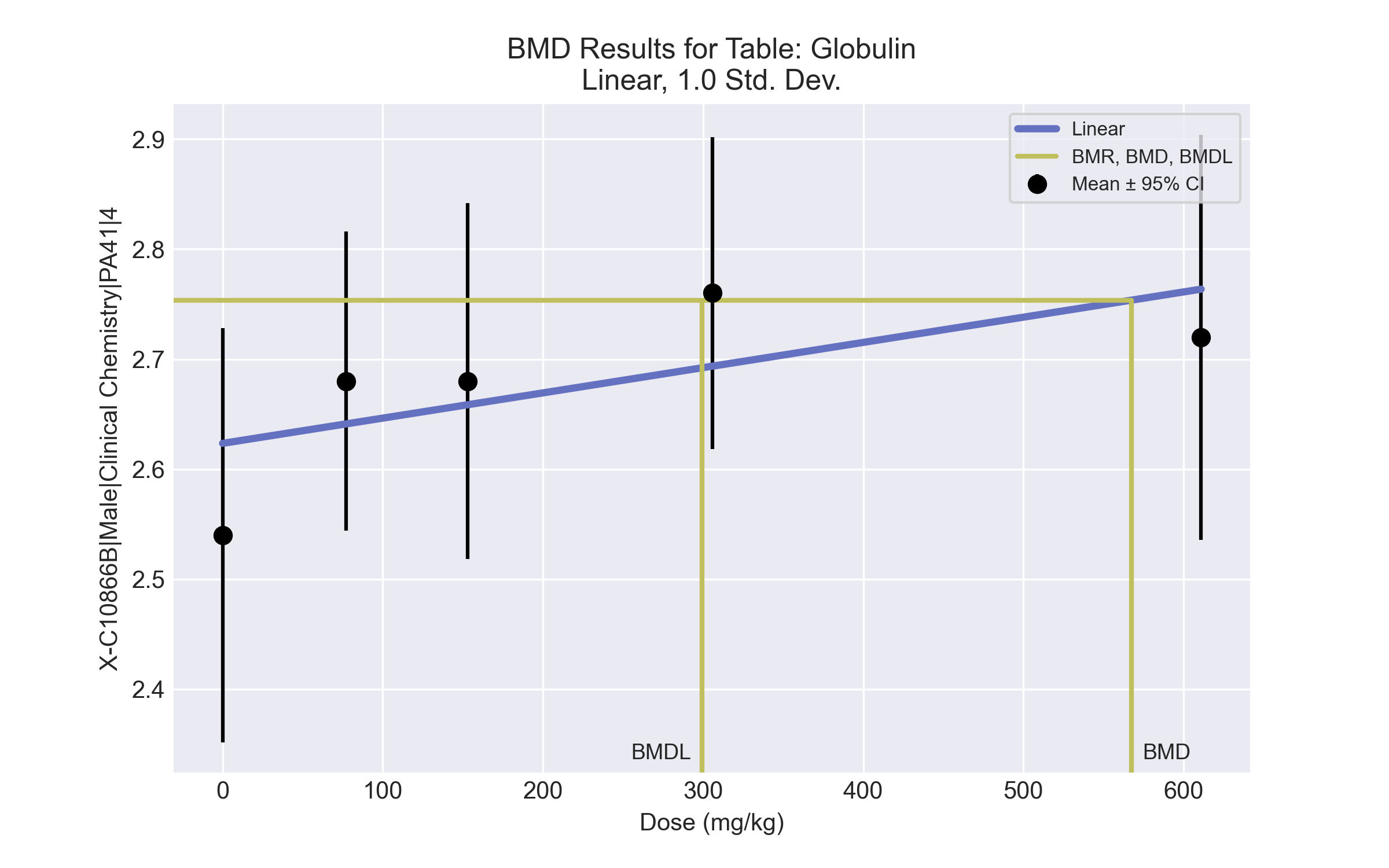
b Recommended model

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Lineara (equivalent models include Power, Polynomial 2°, 3°, 4°) | Valid | - |
| Hill | Warning | **Warnings**  • BMD/BMDL ratio is greater than threshold (1.23e+06 > 20.0)  **Cautions**  • BMD/BMDL ratio is greater than threshold (1.23e+06 > 5.0) |
| Exponential M2 (equivalent models include Exponential M3) | Valid | - |
| Exponential M4 (equivalent models include Exponential M5) | Warning | **Warnings**  • BMD/BMDL ratio is greater than threshold (3.55e+02 > 20.0)  **Cautions**  • BMD/BMDL ratio is greater than threshold (3.55e+02 > 5.0) |

a Recommended model

## Recommended model



====================================================================   
 Polynomial Model. (Version: 2.21; Date: 03/14/2017)   
 Input Data File: C:\Windows\TEMP\bmds-trty3tz9.(d)   
 Gnuplot Plotting File: C:\Windows\TEMP\bmds-trty3tz9.plt  
 Tue Jul 06 12:39:45 2021  
 ====================================================================   
  
 BMDS\_Model\_Run   
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~  
   
 The form of the response function is:   
  
 Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ...  
  
  
 Dependent variable = Response  
 Independent variable = Dose  
 rho is set to 0  
 The polynomial coefficients are restricted to be positive  
 A constant variance model is fit  
  
 Total number of dose groups = 5  
 Total number of records with missing values = 0  
 Maximum number of iterations = 500  
 Relative Function Convergence has been set to: 1e-008  
 Parameter Convergence has been set to: 1e-008  
  
  
  
 Default Initial Parameter Values   
 alpha = 0.0174001  
 rho = 0 Specified  
 beta\_0 = 2.62336  
 beta\_1 = 0  
  
  
 Asymptotic Correlation Matrix of Parameter Estimates  
  
 ( \*\*\* The model parameter(s) -rho   
 have been estimated at a boundary point, or have been specified by the user,  
 and do not appear in the correlation matrix )  
  
 alpha beta\_0 beta\_1  
  
 alpha 1 -9.1e-008 1e-007  
  
 beta\_0 -9.1e-008 1 -0.73  
  
 beta\_1 1e-007 -0.73 1  
  
  
  
 Parameter Estimates  
  
 95.0% Wald Confidence Interval  
 Variable Estimate Std. Err. Lower Conf. Limit Upper Conf. Limit  
 alpha 0.0169683 0.00479935 0.00756172 0.0263748  
 beta\_0 2.62336 0.0380084 2.54886 2.69785  
 beta\_1 0.000229478 0.000120641 -6.97431e-006 0.000465929  
  
  
  
 Table of Data and Estimated Values of Interest  
  
 Dose N Obs Mean Est Mean Obs Std Dev Est Std Dev Scaled Res.  
------ --- -------- -------- ----------- ----------- ----------  
  
 0 5 2.54 2.62 0.152 0.13 -1.43  
 77 5 2.68 2.64 0.11 0.13 0.669  
 153 5 2.68 2.66 0.13 0.13 0.37  
 306 5 2.76 2.69 0.114 0.13 1.14  
 611 5 2.72 2.76 0.148 0.13 -0.748  
  
  
  
 Model Descriptions for likelihoods calculated  
  
  
 Model A1: Yij = Mu(i) + e(ij)  
 Var{e(ij)} = Sigma^2  
  
 Model A2: Yij = Mu(i) + e(ij)  
 Var{e(ij)} = Sigma(i)^2  
  
 Model A3: Yij = Mu(i) + e(ij)  
 Var{e(ij)} = Sigma^2  
 Model A3 uses any fixed variance parameters that  
 were specified by the user  
  
 Model R: Yi = Mu + e(i)  
 Var{e(i)} = Sigma^2  
  
  
 Likelihoods of Interest  
  
 Model Log(likelihood) # Param's AIC  
 A1 40.930307 6 -69.860613  
 A2 41.362163 10 -62.724325  
 A3 40.930307 6 -69.860613  
 fitted 38.455119 3 -70.910238  
 R 36.765537 2 -69.531073  
  
  
 Explanation of Tests   
  
 Test 1: Do responses and/or variances differ among Dose levels?   
 (A2 vs. R)  
 Test 2: Are Variances Homogeneous? (A1 vs A2)  
 Test 3: Are variances adequately modeled? (A2 vs. A3)  
 Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)  
 (Note: When rho=0 the results of Test 3 and Test 2 will be the same.)  
  
 Tests of Interest   
  
 Test -2\*log(Likelihood Ratio) Test df p-value   
  
 Test 1 9.19325 8 0.3263  
 Test 2 0.863712 4 0.9297  
 Test 3 0.863712 4 0.9297  
 Test 4 4.95038 3 0.1755  
  
The p-value for Test 1 is greater than .05. There may not be a  
diffence between responses and/or variances among the dose levels  
Modelling the data with a dose/response curve may not be appropriate  
  
The p-value for Test 2 is greater than .1. A homogeneous variance   
model appears to be appropriate here  
  
  
The p-value for Test 3 is greater than .1. The modeled variance appears   
 to be appropriate here  
  
The p-value for Test 4 is greater than .1. The model chosen seems   
to adequately describe the data  
   
  
 Benchmark Dose Computation  
  
Specified effect = 1  
  
Risk Type = Estimated standard deviations from the control mean  
  
Confidence level = 0.95  
  
 BMD = 567.648  
  
  
 BMDL = 299.379  
  
   
BMDU computation failed.

# BMD Results for Table: HDL Cholesterol

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Dose | 0 | 77 | 153 | 306 | 611 |
| N | 5 | 5 | 5 | 5 | 5 |
| Mean ± SD | 52 ± 5 | 66.8 ± 7.563 | 59 ± 4.848 | 66 ± 3 | 71.2 ± 5.675 |

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear (equivalent models include Power, Polynomial 2°, 3°, 4°) | 0.002 | 124.476 | 269.605 | 182.885 | No model was recommended as a best-fitting model. Doses were dropped until there were only 3 remaining dose-groups. |
| Hill | 0.004 | 123.06 | 31.39 | 8.0E-05 |
| Exponential M2 (equivalent models include Exponential M3) | 0.002 | 124.757 | 293.929 | 206.963 |
| Exponential M4 (equivalent models include Exponential M5) | 0.002 | 124.552 | 89.056 | 0.403 |

a Constant variance case presented (BMDS Test 2 p-value = 0.399, BMDS Test 3 p-value = 0.399).

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear (equivalent models include Power, Polynomial 2°, 3°, 4°) | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.00225 < 0.1) |
| Hill | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.00383 < 0.1)  • BMD/BMDL ratio is greater than threshold (3.93e+05 > 20.0)  **Cautions**  • BMD/BMDL ratio is greater than threshold (3.93e+05 > 5.0) |
| Exponential M2 (equivalent models include Exponential M3) | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.00197 < 0.1) |
| Exponential M4 (equivalent models include Exponential M5) | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.00182 < 0.1)  • Residual of interest is greater than threshold (2.47 > 2.0)  • BMD/BMDL ratio is greater than threshold (2.21e+02 > 20.0)  **Cautions**  • BMD/BMDL ratio is greater than threshold (2.21e+02 > 5.0) |

## Recommended model

*No model was recommended as a best-fitting model.*

# BMD Results for Table: Sorbitol dehydrogenase

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Dose | 0 | 77 | 153 | 306 | 611 |
| N | 5 | 5 | 5 | 5 | 5 |
| Mean ± SD | 14.96 ± 3.365 | 10.04 ± 1.26 | 13.44 ± 4.45 | 11.34 ± 1.815 | 10.04 ± 2.763 |

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear | 0.011 | 87.75 | 665.59 | 330.332 | No model was recommended as a best-fitting model. Doses were dropped until there were only 3 remaining dose-groups. |
| Polynomial 2° (equivalent models include Polynomial 3°) | 0.011 | 87.75 | 665.588 | 330.332 |
| Polynomial 4° | 0.001 | 92.423 | 3700.2 | 223.577 |
| Power | 0.011 | 87.75 | 665.589 | 330.332 |
| Hill | 0.007 | 88.572 | 2.0E-12 | 2.0E-12 |
| Exponential M2 (equivalent models include Exponential M3) | 0.012 | 87.655 | 658.989 | 284.634 |
| Exponential M4 | 0.005 | 89.43 | 691.914 | 1.235 |
| Exponential M5 | 0.005 | 89.43 | 691.915 | 1.923 |

a Modeled variance case presented (BMDS Test 2 p-value = 0.07, BMDS Test 3 p-value = 0.289).

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0113 < 0.1)  • BMD/high dose ratio is greater than threshold (1.09 > 1.0) |
| Polynomial 2° (equivalent models include Polynomial 3°) | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0113 < 0.1)  • BMD/high dose ratio is greater than threshold (1.09 > 1.0) |
| Polynomial 4° | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.00128 < 0.1)  • BMD/high dose ratio is greater than threshold (6.06 > 1.0)  • Residual at lowest dose is greater than threshold (2.04 > 2.0)  **Cautions**  • BMD/BMDL ratio is greater than threshold (16.6 > 5.0)  • Warning(s): THE MODEL HAS PROBABLY NOT CONVERGED!!!; THIS USUALLY MEANS THE MODEL HAS NOT CONVERGED! |
| Power | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0113 < 0.1)  • BMD/high dose ratio is greater than threshold (1.09 > 1.0) |
| Hill | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.00709 < 0.1)  **Cautions**  • Minimum dose/BMD ratio is greater than threshold (3.9e+13 > 3.0) |
| Exponential M2 (equivalent models include Exponential M3) | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0118 < 0.1)  • BMD/high dose ratio is greater than threshold (1.08 > 1.0) |
| Exponential M4 | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.00462 < 0.1)  • BMD/BMDL ratio is greater than threshold (5.6e+02 > 20.0)  • BMD/high dose ratio is greater than threshold (1.13 > 1.0)  **Cautions**  • BMD/BMDL ratio is greater than threshold (5.6e+02 > 5.0) |
| Exponential M5 | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.00462 < 0.1)  • BMD/BMDL ratio is greater than threshold (3.6e+02 > 20.0)  • BMD/high dose ratio is greater than threshold (1.13 > 1.0)  **Cautions**  • BMD/BMDL ratio is greater than threshold (3.6e+02 > 5.0) |

## Recommended model

*No model was recommended as a best-fitting model.*

# BMD Results for Table: Urea Nitrogen

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Dose | 0 | 77 | 153 | 306a | 611a |
| N | 5 | 5 | 5 | 5 | 5 |
| Mean ± SD | 9.6 ± 0.548 | 10.8 ± 2.775 | 11.8 ± 4.764 | 12.6 ± 1.517 | 11.2 ± 1.643 |

a Dose group removed in BMD modeling session

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linearb (equivalent models include Power, Polynomial 2°, 3°, 4°) | <0.0001 | 39.068 | 35.114 | 14.754 | Linear recommended as best-fitting model on the basis of the lowest AIC. |
| Hill | 0.292 | 53.637 | 66.123 | -999 |
| Exponential M2 (equivalent models include Exponential M3) | -999 | 41.525 | 41.226 | 18.291 |
| Exponential M4 | -999 | 41.789 | 17.006 | 0.092 |
| Exponential M5 | -999 | 57.637 | 46.156 | 0.043 |

a Modeled variance case presented (BMDS Test 2 p-value = 5.3E-04, BMDS Test 3 p-value = 0.136).

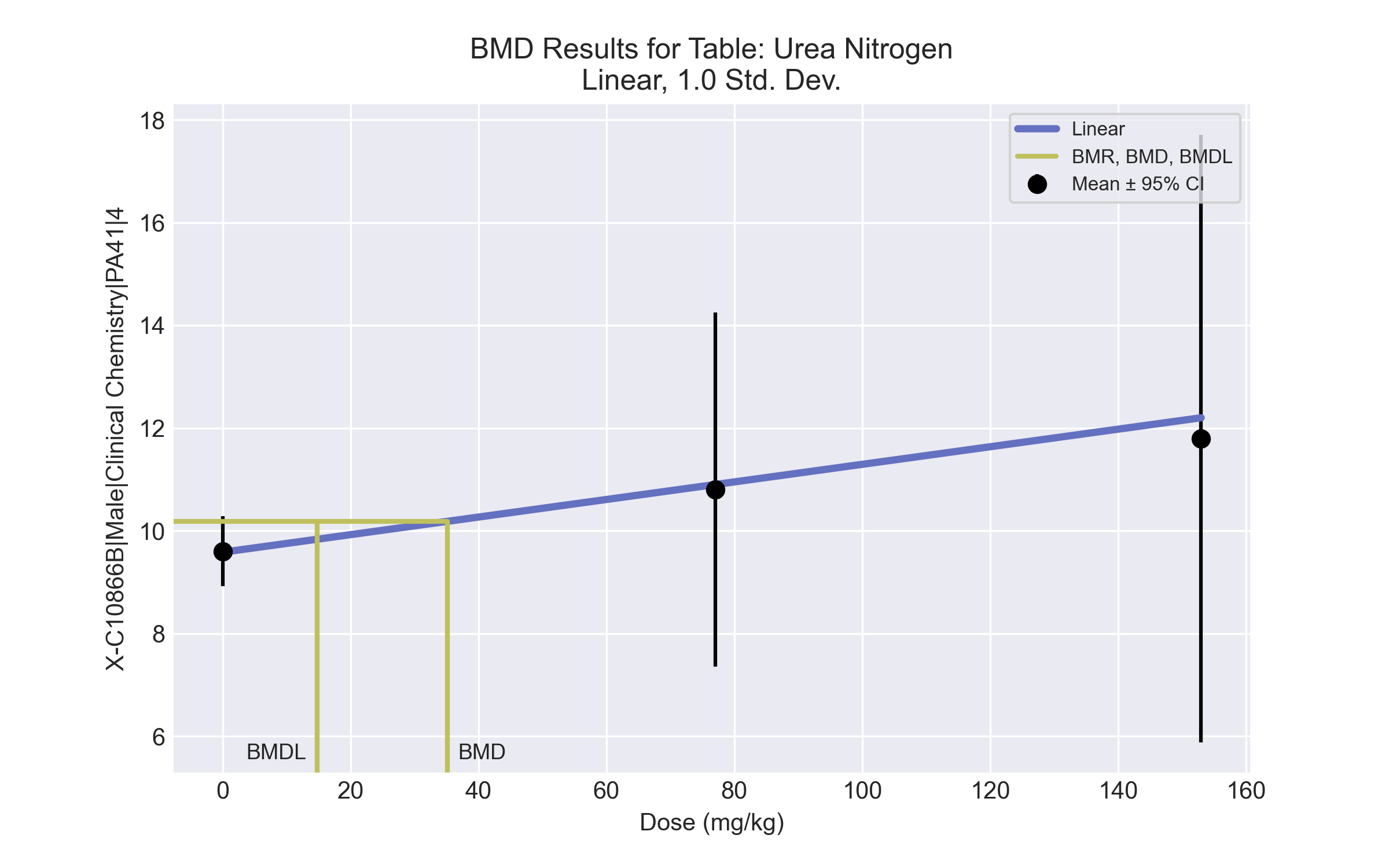
b Recommended model

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Lineara (equivalent models include Power, Polynomial 2°, 3°, 4°) | Valid | **Cautions**  • Warning(s): Warning: Likelihood for fitted model larger than the Likelihood for model A3. |
| Hill | Failure | **Failures**  • BMDL does not exist  **Cautions**  • Warning(s): BMDL computation failed. |
| Exponential M2 (equivalent models include Exponential M3) | Valid | - |
| Exponential M4 | Warning | **Warnings**  • BMD/BMDL ratio is greater than threshold (1.85e+02 > 20.0)  • Zero degrees of freedom; saturated model  **Cautions**  • BMD/BMDL ratio is greater than threshold (1.85e+02 > 5.0)  • Minimum dose/BMD ratio is greater than threshold (4.53 > 3.0) |
| Exponential M5 | Warning | **Warnings**  • BMD/BMDL ratio is greater than threshold (1.08e+03 > 20.0)  • Zero degrees of freedom; saturated model  **Cautions**  • BMD/BMDL ratio is greater than threshold (1.08e+03 > 5.0) |

a Recommended model

## Recommended model



====================================================================   
 Polynomial Model. (Version: 2.21; Date: 03/14/2017)   
 Input Data File: C:\Windows\TEMP\bmds-i0rxus4c.(d)   
 Gnuplot Plotting File: C:\Windows\TEMP\bmds-i0rxus4c.plt  
 Tue Jul 06 12:40:24 2021  
 ====================================================================   
  
 BMDS\_Model\_Run   
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~  
   
 The form of the response function is:   
  
 Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ...  
  
  
 Dependent variable = Response  
 Independent variable = Dose  
 The polynomial coefficients are restricted to be positive  
 The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) \* rho)  
  
 Total number of dose groups = 3  
 Total number of records with missing values = 0  
 Maximum number of iterations = 500  
 Relative Function Convergence has been set to: 1e-008  
 Parameter Convergence has been set to: 1e-008  
  
  
  
 Default Initial Parameter Values   
 lalpha = 2.32565  
 rho = 0  
 beta\_0 = 9.63073  
 beta\_1 = 0.0143817  
  
  
 Asymptotic Correlation Matrix of Parameter Estimates  
  
 ( \*\*\* The model parameter(s) -rho   
 have been estimated at a boundary point, or have been specified by the user,  
 and do not appear in the correlation matrix )  
  
 lalpha beta\_0 beta\_1  
  
 lalpha 1 -0.017 0.095  
  
 beta\_0 -0.017 1 -0.1  
  
 beta\_1 0.095 -0.1 1  
  
  
  
 Parameter Estimates  
  
 95.0% Wald Confidence Interval  
 Variable Estimate Std. Err. Lower Conf. Limit Upper Conf. Limit  
 lalpha -41.6966 0.366826 -42.4156 -40.9777  
 rho 18 NA  
 beta\_0 9.5822 0.254781 9.08284 10.0816  
 beta\_1 0.017116 0.00605784 0.00524287 0.0289892  
  
NA - Indicates that this parameter has hit a bound  
 implied by some inequality constraint and thus  
 has no standard error.  
  
  
  
 Table of Data and Estimated Values of Interest  
  
 Dose N Obs Mean Est Mean Obs Std Dev Est Std Dev Scaled Res.  
------ --- -------- -------- ----------- ----------- ----------  
  
 0 5 9.6 9.58 0.548 0.601 0.0662  
 77 5 10.8 10.9 2.77 1.92 -0.117  
 153 5 11.8 12.2 4.76 5.29 -0.17  
   
 Warning: Likelihood for fitted model larger than the Likelihood for model A3.  
  
  
  
 Model Descriptions for likelihoods calculated  
  
  
 Model A1: Yij = Mu(i) + e(ij)  
 Var{e(ij)} = Sigma^2  
  
 Model A2: Yij = Mu(i) + e(ij)  
 Var{e(ij)} = Sigma(i)^2  
  
 Model A3: Yij = Mu(i) + e(ij)  
 Var{e(ij)} = exp(lalpha + rho\*ln(Mu(i)))  
 Model A3 uses any fixed variance parameters that  
 were specified by the user  
  
 Model R: Yi = Mu + e(i)  
 Var{e(i)} = Sigma^2  
  
  
 Likelihoods of Interest  
  
 Model Log(likelihood) # Param's AIC  
 A1 -23.268801 4 54.537603  
 A2 -15.725458 6 43.450916  
 A3 -16.836426 5 43.672851  
 fitted -16.534036 3 39.068072  
 R -23.975480 2 51.950960  
  
  
 Explanation of Tests   
  
 Test 1: Do responses and/or variances differ among Dose levels?   
 (A2 vs. R)  
 Test 2: Are Variances Homogeneous? (A1 vs A2)  
 Test 3: Are variances adequately modeled? (A2 vs. A3)  
 Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)  
 (Note: When rho=0 the results of Test 3 and Test 2 will be the same.)  
  
 Tests of Interest   
  
 Test -2\*log(Likelihood Ratio) Test df p-value   
  
 Test 1 16.5 4 0.002417  
 Test 2 15.0867 2 0.0005296  
 Test 3 2.22194 1 0.1361  
 Test 4 -0.604779 2 <.0001  
  
The p-value for Test 1 is less than .05. There appears to be a  
difference between response and/or variances among the dose levels  
It seems appropriate to model the data  
  
The p-value for Test 2 is less than .1. A non-homogeneous variance   
model appears to be appropriate  
  
The p-value for Test 3 is greater than .1. The modeled variance appears   
 to be appropriate here  
  
The p-value for Test 4 is less than .1. You may want to try a different   
model  
   
  
 Benchmark Dose Computation  
  
Specified effect = 1  
  
Risk Type = Estimated standard deviations from the control mean  
  
Confidence level = 0.95  
  
 BMD = 35.1135  
  
  
 BMDL = 14.7537  
  
  
 BMDU = 104.848

# BMD Results for Table: Cholinesterase

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Dose | 0 | 77 | 153 | 306 | 611a |
| N | 5 | 5 | 5 | 5 | 5 |
| Mean ± SD | 285.4 ± 35.956 | 166.4 ± 17.785 | 146.4 ± 30.884 | 116.4 ± 13.813 | 104 ± 8.631 |

a Dose group removed in BMD modeling session

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear | <0.0001 | 173.917 | 82.83 | 60.034 | Hill recommended as best-fitting model on the basis of the lowest AIC. |
| Polynomial 2° (equivalent models include Power, Polynomial 3°, 4°) | <0.0001 | 173.917 | 82.83 | 60.034 |
| Hillb | 0.487 | 154.708 | 7.276 | 3.429 |
| Exponential M2 | 5.8E-04 | 167.125 | 39.616 | 27.343 |
| Exponential M3 | 5.8E-04 | 167.125 | 39.616 | 27.343 |
| Exponential M4 (equivalent models include Exponential M5) | 0.244 | 155.581 | 10.689 | 6.726 |

a Constant variance case presented (BMDS Test 2 p-value = 0.137, BMDS Test 3 p-value = 0.137).

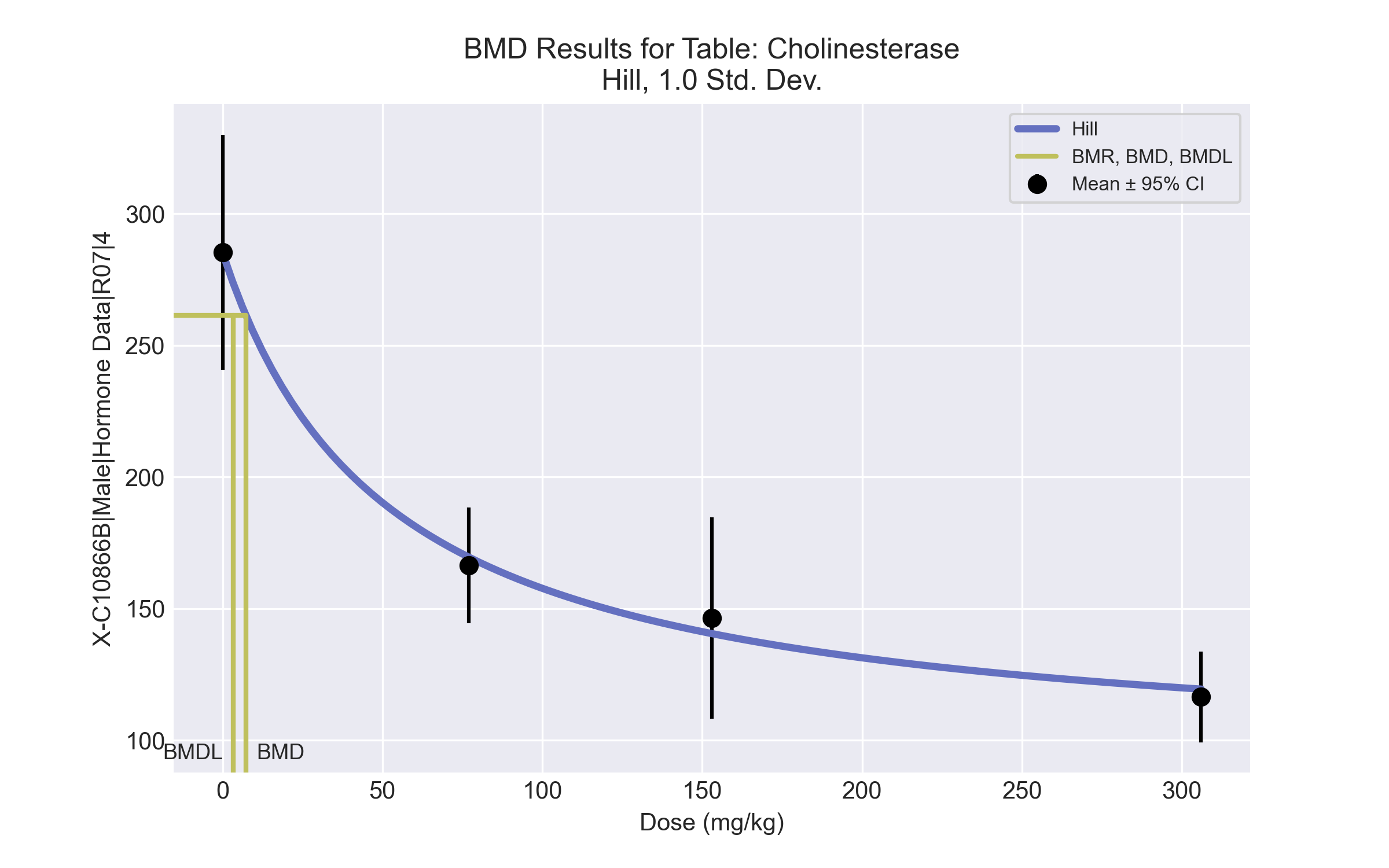
b Recommended model

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear | Warning | **Warnings**  • Residual at lowest dose is greater than threshold (2.3 > 2.0) |
| Polynomial 2° (equivalent models include Power, Polynomial 3°, 4°) | Warning | **Warnings**  • Residual at lowest dose is greater than threshold (2.3 > 2.0) |
| Hilla | Valid | **Cautions**  • Minimum dose/BMD ratio is greater than threshold (10.6 > 3.0) |
| Exponential M2 | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.000582 < 0.1) |
| Exponential M3 | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.000582 < 0.1) |
| Exponential M4 (equivalent models include Exponential M5) | Valid | **Cautions**  • Minimum dose/BMD ratio is greater than threshold (7.2 > 3.0) |

a Recommended model

## Recommended model



====================================================================   
 Hill Model. (Version: 2.18; Date: 03/14/2017)   
 Input Data File: C:\Windows\TEMP\bmds-2x4x97oc.(d)   
 Gnuplot Plotting File: C:\Windows\TEMP\bmds-2x4x97oc.plt  
 Tue Jul 06 12:41:45 2021  
 ====================================================================   
  
 BMDS\_Model\_Run   
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~  
   
 The form of the response function is:   
  
 Y[dose] = intercept + v\*dose^n/(k^n + dose^n)  
  
  
 Dependent variable = Response  
 Independent variable = Dose  
 rho is set to 0  
 Power parameter restricted to be greater than 1  
 A constant variance model is fit  
  
 Total number of dose groups = 4  
 Total number of records with missing values = 0  
 Maximum number of iterations = 500  
 Relative Function Convergence has been set to: 1e-008  
 Parameter Convergence has been set to: 1e-008  
  
  
  
 Default Initial Parameter Values   
 alpha = 688.425  
 rho = 0 Specified  
 intercept = 285.4  
 v = -169  
 n = 2.01134  
 k = 54.6765  
  
  
 Asymptotic Correlation Matrix of Parameter Estimates  
  
 ( \*\*\* The model parameter(s) -rho -n   
 have been estimated at a boundary point, or have been specified by the user,  
 and do not appear in the correlation matrix )  
  
 alpha intercept v k  
  
 alpha 1 -8.6e-007 8.8e-007 -3.6e-007  
  
 intercept -8.6e-007 1 -0.38 -0.24  
  
 v 8.8e-007 -0.38 1 -0.74  
  
 k -3.6e-007 -0.24 -0.74 1  
  
  
  
 Parameter Estimates  
  
 95.0% Wald Confidence Interval  
 Variable Estimate Std. Err. Lower Conf. Limit Upper Conf. Limit  
 alpha 564.187 178.412 214.507 913.867  
 intercept 285.211 10.6345 264.368 306.054  
 v -194.089 23.8154 -240.766 -147.411  
 n 1 NA  
 k 52.1748 23.7256 5.67351 98.6761  
  
NA - Indicates that this parameter has hit a bound  
 implied by some inequality constraint and thus  
 has no standard error.  
  
  
  
 Table of Data and Estimated Values of Interest  
  
 Dose N Obs Mean Est Mean Obs Std Dev Est Std Dev Scaled Res.  
------ --- -------- -------- ----------- ----------- ----------  
  
 0 5 285 285 36 23.8 0.0178  
 77 5 166 170 17.8 23.8 -0.293  
 153 5 146 140 30.9 23.8 0.558  
 306 5 116 119 13.8 23.8 -0.282  
  
  
  
 Model Descriptions for likelihoods calculated  
  
  
 Model A1: Yij = Mu(i) + e(ij)  
 Var{e(ij)} = Sigma^2  
  
 Model A2: Yij = Mu(i) + e(ij)  
 Var{e(ij)} = Sigma(i)^2  
  
 Model A3: Yij = Mu(i) + e(ij)  
 Var{e(ij)} = Sigma^2  
 Model A3 uses any fixed variance parameters that  
 were specified by the user  
  
 Model R: Yi = Mu + e(i)  
 Var{e(i)} = Sigma^2  
  
  
 Likelihoods of Interest  
  
 Model Log(likelihood) # Param's AIC  
 A1 -73.112628 5 156.225257  
 A2 -70.350906 8 156.701812  
 A3 -73.112628 5 156.225257  
 fitted -73.353855 4 154.707710  
 R -94.480419 2 192.960838  
  
  
 Explanation of Tests   
  
 Test 1: Do responses and/or variances differ among Dose levels?   
 (A2 vs. R)  
 Test 2: Are Variances Homogeneous? (A1 vs A2)  
 Test 3: Are variances adequately modeled? (A2 vs. A3)  
 Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)  
 (Note: When rho=0 the results of Test 3 and Test 2 will be the same.)  
  
 Tests of Interest   
  
 Test -2\*log(Likelihood Ratio) Test df p-value   
  
 Test 1 48.259 6 <.0001  
 Test 2 5.52344 3 0.1372  
 Test 3 5.52344 3 0.1372  
 Test 4 0.482454 1 0.4873  
  
The p-value for Test 1 is less than .05. There appears to be a  
difference between response and/or variances among the dose levels  
It seems appropriate to model the data  
  
The p-value for Test 2 is greater than .1. A homogeneous variance   
model appears to be appropriate here  
  
  
The p-value for Test 3 is greater than .1. The modeled variance appears   
 to be appropriate here  
  
The p-value for Test 4 is greater than .1. The model chosen seems   
to adequately describe the data  
   
  
 Benchmark Dose Computation  
  
Specified effect = 1  
  
Risk Type = Estimated standard deviations from the control mean   
  
Confidence level = 0.95  
  
 BMD = 7.27554  
  
 BMDL = 3.42945  
  
 BMDU = 40.7938