# BMD Results for Table: Body Weight SD4

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 62 | 125 | 249 | 497 | 995 |
| N | 5 | 6 | 5 | 5 | 5 | 5 |
| Mean ± SD | 247.16 ± 8.483 | 244.95 ± 3.814 | 239.46 ± 8.697 | 245.74 ± 10.843 | 240.42 ± 9.175 | 232.18 ± 14.339 |

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linearb | 0.675 | 172.738 | 687.041 | 420.179 | Linear recommended as best-fitting model on the basis of the lowest AIC. |
| Polynomial 2° | 0.532 | 174.608 | 771.942 | 424.188 |
| Polynomial 3° | 0.539 | 174.57 | 791.06 | 425.405 |
| Polynomial 4° | 0.541 | 174.563 | 804.821 | 425.634 |
| Polynomial 5° | 0.34 | 176.563 | 813.967 | 425.635 |
| Power | 0.518 | 174.676 | 778.372 | 422.071 |
| Hill | 0.526 | 174.635 | 547.553 | 309.205 |
| Exponential M2 (equivalent models include Exponential M4) | 0.672 | 172.753 | 682.716 | 410.835 |
| Exponential M3 | 0.518 | 174.68 | 780.511 | 413.101 |
| Exponential M5 | 0.321 | 176.68 | 780.511 | 413.101 |

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

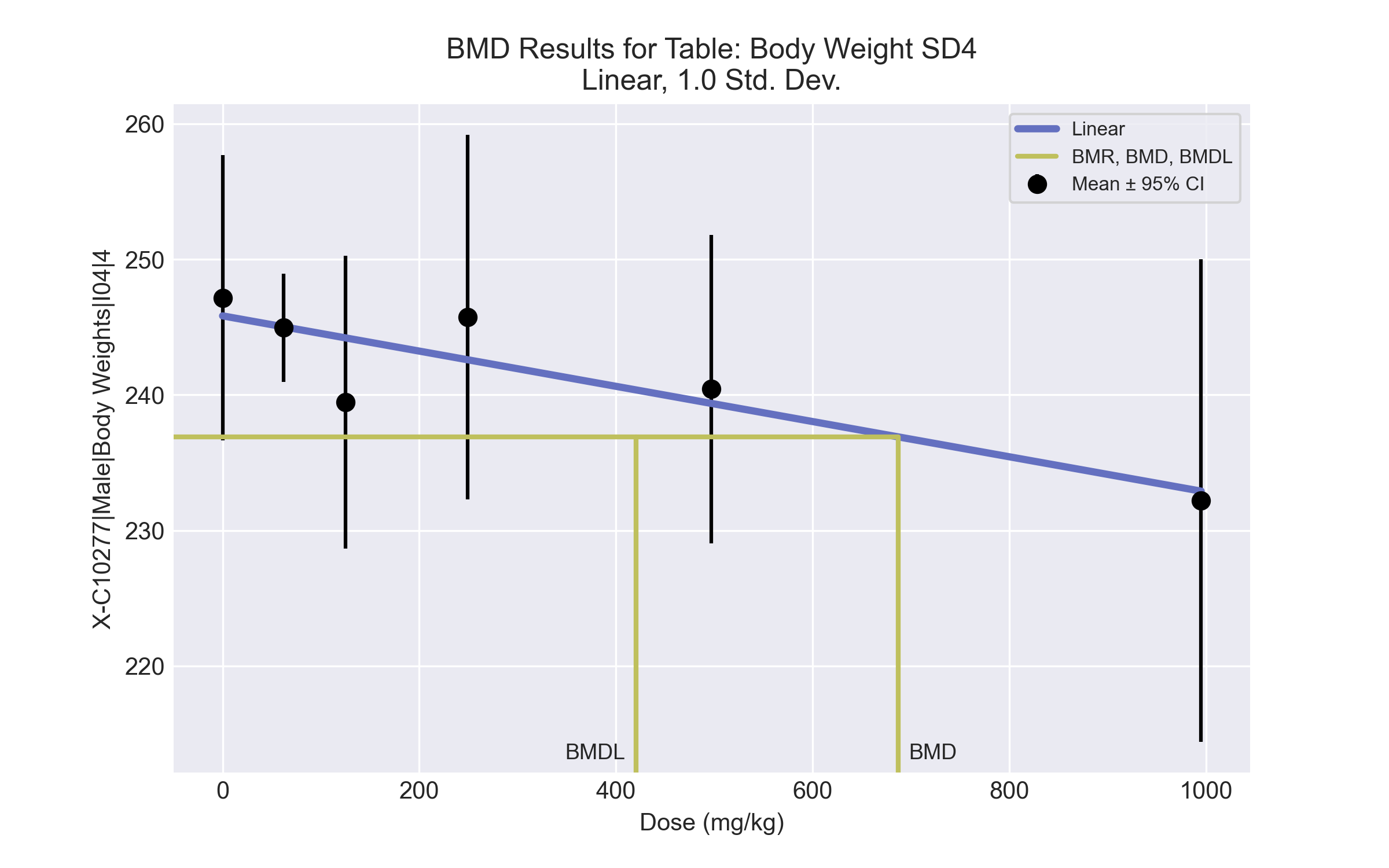
b Recommended model

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Lineara | Valid | - |
| Polynomial 2° | Valid | - |
| Polynomial 3° | Valid | - |
| Polynomial 4° | Valid | - |
| Polynomial 5° | 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-5q1kh7lv.(d)   
 Gnuplot Plotting File: C:\Windows\TEMP\bmds-5q1kh7lv.plt  
 Wed May 19 09:24:59 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 = 6  
 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 = 91.7043  
 rho = 0 Specified  
 beta\_0 = 245.83  
 beta\_1 = -0.0130018  
  
  
 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 -1.3e-006 4.3e-007  
  
 beta\_0 -1.3e-006 1 -0.68  
  
 beta\_1 4.3e-007 -0.68 1  
  
  
  
 Parameter Estimates  
  
 95.0% Wald Confidence Interval  
 Variable Estimate Std. Err. Lower Conf. Limit Upper Conf. Limit  
 alpha 79.7308 20.2516 40.0383 119.423  
 beta\_0 245.826 2.18304 241.547 250.104  
 beta\_1 -0.0129966 0.00473251 -0.0222722 -0.00372107  
  
  
  
 Table of Data and Estimated Values of Interest  
  
 Dose N Obs Mean Est Mean Obs Std Dev Est Std Dev Scaled Res.  
------ --- -------- -------- ----------- ----------- ----------  
  
 0 5 247 246 8.48 8.93 0.334  
 62 6 245 245 3.81 8.93 -0.0191  
 125 5 239 244 8.7 8.93 -1.19  
 249 5 246 243 10.8 8.93 0.789  
 497 5 240 239 9.17 8.93 0.264  
 995 5 232 233 14.3 8.93 -0.179  
  
  
  
 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 -82.203594 7 178.407187  
 A2 -78.016121 12 180.032243  
 A3 -82.203594 7 178.407187  
 fitted -83.369176 3 172.738353  
 R -86.744423 2 177.488845  
  
  
 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 17.4566 10 0.06485  
 Test 2 8.37494 5 0.1367  
 Test 3 8.37494 5 0.1367  
 Test 4 2.33117 4 0.6751  
  
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 = 687.041  
  
  
 BMDL = 420.179  
  
  
 BMDU = 1874.8

# BMD Results for Table: Liver Weight Absolute

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 62 | 125 | 249 | 497 | 995 |
| N | 5 | 4 | 5 | 5 | 5 | 4 |
| Mean ± SD | 10.354 ± 0.504 | 10.512 ± 0.709 | 10.02 ± 0.676 | 11.104 ± 0.482 | 11.426 ± 0.659 | 11.57 ± 0.883 |

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear (equivalent models include Polynomial 2°, 3°, 4°, 5°) | 0.107 | 10.896 | 456.635 | 306.488 | Exponential-M4 recommended as best-fitting model on the basis of the lowest BMDL. |
| Power | 0.107 | 10.896 | 456.634 | 306.488 |
| Hill | 0.611 | 7.113 | 238.378 | 139.073 |
| Exponential M2 (equivalent models include Exponential M3) | 0.099 | 11.105 | 480.897 | 329.91 |
| Exponential M4b | 0.122 | 11.094 | 223.801 | 97.057 |
| Exponential M5 | 0.403 | 9.113 | 241.925 | 136.502 |

a Constant variance case presented (BMDS Test 2 p-value = 0.841, BMDS Test 3 p-value = 0.841).

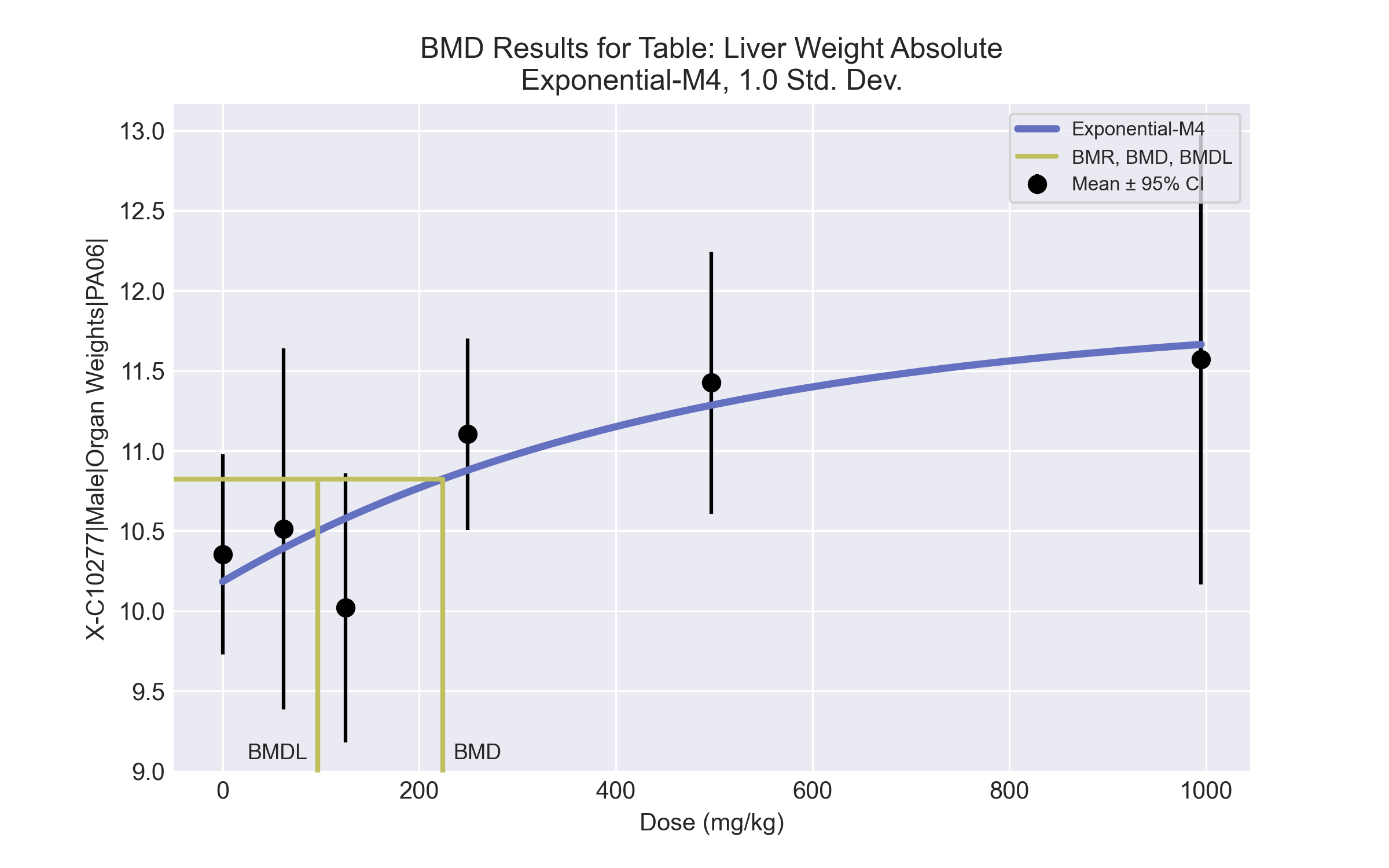
b Recommended model

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear (equivalent models include Polynomial 2°, 3°, 4°, 5°) | Valid | - |
| Power | Valid | - |
| Hill | Valid | - |
| Exponential M2 (equivalent models include Exponential M3) | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0988 < 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-yhfby1wz.(d)   
 Gnuplot Plotting File:   
 Wed May 19 08:49:47 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 = 6  
 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 -1.09663   
 rho 0 Specified  
 a 9.519   
 b 0.00184627   
 c 1.27624   
 d 1 Specified  
  
  
  
 Parameter Estimates  
  
 Variable Model 4 Std. Err.  
 -------- ------- ---------  
 lnalpha -0.889512 0.109806  
 a 10.1829 0.226073  
 b 0.00214804 0.00167576  
 c 1.16492 0.0587037  
  
 NC = No Convergence  
  
  
 Table of Stats From Input Data  
  
 Dose N Obs Mean Obs Std Dev  
 ----- --- ---------- -------------  
 0 5 10.35 0.5038  
 62 4 10.51 0.7088  
 125 5 10.02 0.6756  
 249 5 11.1 0.482  
 497 5 11.43 0.6588  
 995 4 11.57 0.8828  
  
  
 Estimated Values of Interest  
  
 Dose Est Mean Est Std Scaled Residual  
 ------ ---------- --------- ----------------  
 0 10.18 0.641 0.5968  
 62 10.39 0.641 0.375  
 125 10.58 0.641 -1.948  
 249 10.88 0.641 0.7863  
 497 11.28 0.641 0.4923  
 995 11.66 0.641 -0.2939  
  
  
  
 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 1.352842 7 11.29432  
 A2 2.381641 12 19.23672  
 A3 1.352842 7 11.29432  
 R -8.201613 2 20.40323  
 4 -1.546837 4 11.09367  
  
  
 Additive constant for all log-likelihoods = -25.73. 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 21.17 10 0.01996  
 Test 2 2.058 5 0.8411  
 Test 3 2.058 5 0.8411  
 Test 6a 5.799 3 0.1218  
  
  
 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 = 223.801  
  
 BMDL = 97.0572  
  
 BMDU = 642.486

# BMD Results for Table: Liver Weight Relative

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 62 | 125 | 249 | 497 | 995 |
| N | 5 | 4 | 5 | 5 | 5 | 4 |
| Mean ± SD | 41.901 ± 1.714 | 42.955 ± 2.467 | 41.832 ± 2.142 | 45.192 ± 0.792 | 47.534 ± 2.349 | 50.112 ± 1.502 |

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear (equivalent models include Power, Polynomial 2°, 3°, 4°, 5°) | 0.148 | 70.071 | 216.842 | 166.022 | Exponential-M4 recommended as best-fitting model on the basis of the lowest AIC. |
| Hill | 0.229 | 70.244 | 195.314 | 91.397 |
| Exponential M2 (equivalent models include Exponential M3) | 0.113 | 70.767 | 238.53 | 184.843 |
| Exponential M4b | 0.212 | 69.797 | 129.542 | 78.353 |
| Exponential M5 | 0.199 | 70.523 | 188.235 | 88.942 |

a Constant variance case presented (BMDS Test 2 p-value = 0.272, BMDS Test 3 p-value = 0.272).

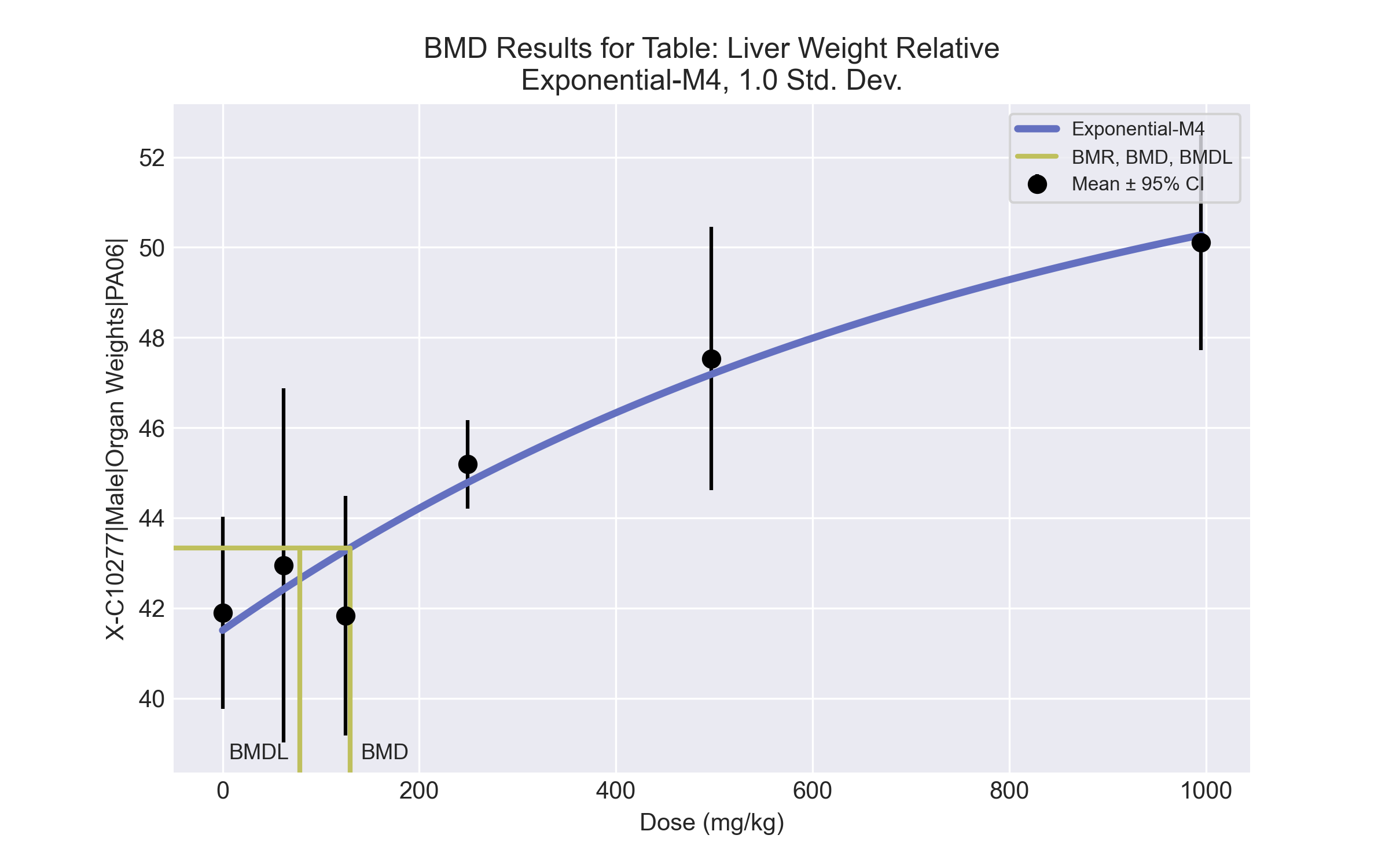
b Recommended model

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear (equivalent models include Power, Polynomial 2°, 3°, 4°, 5°) | 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-62tugs36.(d)   
 Gnuplot Plotting File:   
 Wed May 19 08:49:50 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 = 6  
 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 1.04621   
 rho 0 Specified  
 a 39.7402   
 b 0.00171991   
 c 1.32405   
 d 1 Specified  
  
  
  
 Parameter Estimates  
  
 Variable Model 4 Std. Err.  
 -------- ------- ---------  
 lnalpha 1.20702 0.89359  
 a 41.5083 0.634254  
 b 0.00122901 0.000815868  
 c 1.2993 0.109835  
  
 NC = No Convergence  
  
  
 Table of Stats From Input Data  
  
 Dose N Obs Mean Obs Std Dev  
 ----- --- ---------- -------------  
 0 5 41.9 1.714  
 62 4 42.96 2.467  
 125 5 41.83 2.142  
 249 5 45.19 0.7915  
 497 5 47.53 2.349  
 995 4 50.11 1.502  
  
  
 Estimated Values of Interest  
  
 Dose Est Mean Est Std Scaled Residual  
 ------ ---------- --------- ----------------  
 0 41.51 1.829 0.4797  
 62 42.42 1.829 0.5854  
 125 43.28 1.829 -1.768  
 249 44.78 1.829 0.4998  
 497 47.19 1.829 0.4237  
 995 50.27 1.829 -0.1776  
  
  
  
 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 -28.64692 7 71.29385  
 A2 -25.461 12 74.92199  
 A3 -28.64692 7 71.29385  
 R -48.55427 2 101.1085  
 4 -30.89829 4 69.79658  
  
  
 Additive constant for all log-likelihoods = -25.73. 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 46.19 10 < 0.0001  
 Test 2 6.372 5 0.2717  
 Test 3 6.372 5 0.2717  
 Test 6a 4.503 3 0.212  
  
  
 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 = 129.542  
  
 BMDL = 78.3535  
  
 BMDU = 246.865

# BMD Results for Table: Terminal Body Weight

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 62 | 125 | 249 | 497 | 995 |
| N | 5 | 6 | 5 | 5 | 5 | 5 |
| Mean ± SD | 247.16 ± 8.483 | 244.95 ± 3.814 | 239.46 ± 8.697 | 245.74 ± 10.843 | 240.42 ± 9.175 | 232.18 ± 14.339 |

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linearb | 0.675 | 172.738 | 687.041 | 420.179 | Linear recommended as best-fitting model on the basis of the lowest AIC. |
| Polynomial 2° | 0.532 | 174.608 | 771.942 | 424.188 |
| Polynomial 3° | 0.539 | 174.57 | 791.06 | 425.405 |
| Polynomial 4° | 0.541 | 174.563 | 804.821 | 425.634 |
| Polynomial 5° | 0.34 | 176.563 | 813.967 | 425.635 |
| Power | 0.518 | 174.676 | 778.372 | 422.071 |
| Hill | 0.526 | 174.635 | 547.553 | 309.205 |
| Exponential M2 (equivalent models include Exponential M4) | 0.672 | 172.753 | 682.716 | 410.835 |
| Exponential M3 | 0.518 | 174.68 | 780.511 | 413.101 |
| Exponential M5 | 0.321 | 176.68 | 780.511 | 413.101 |

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

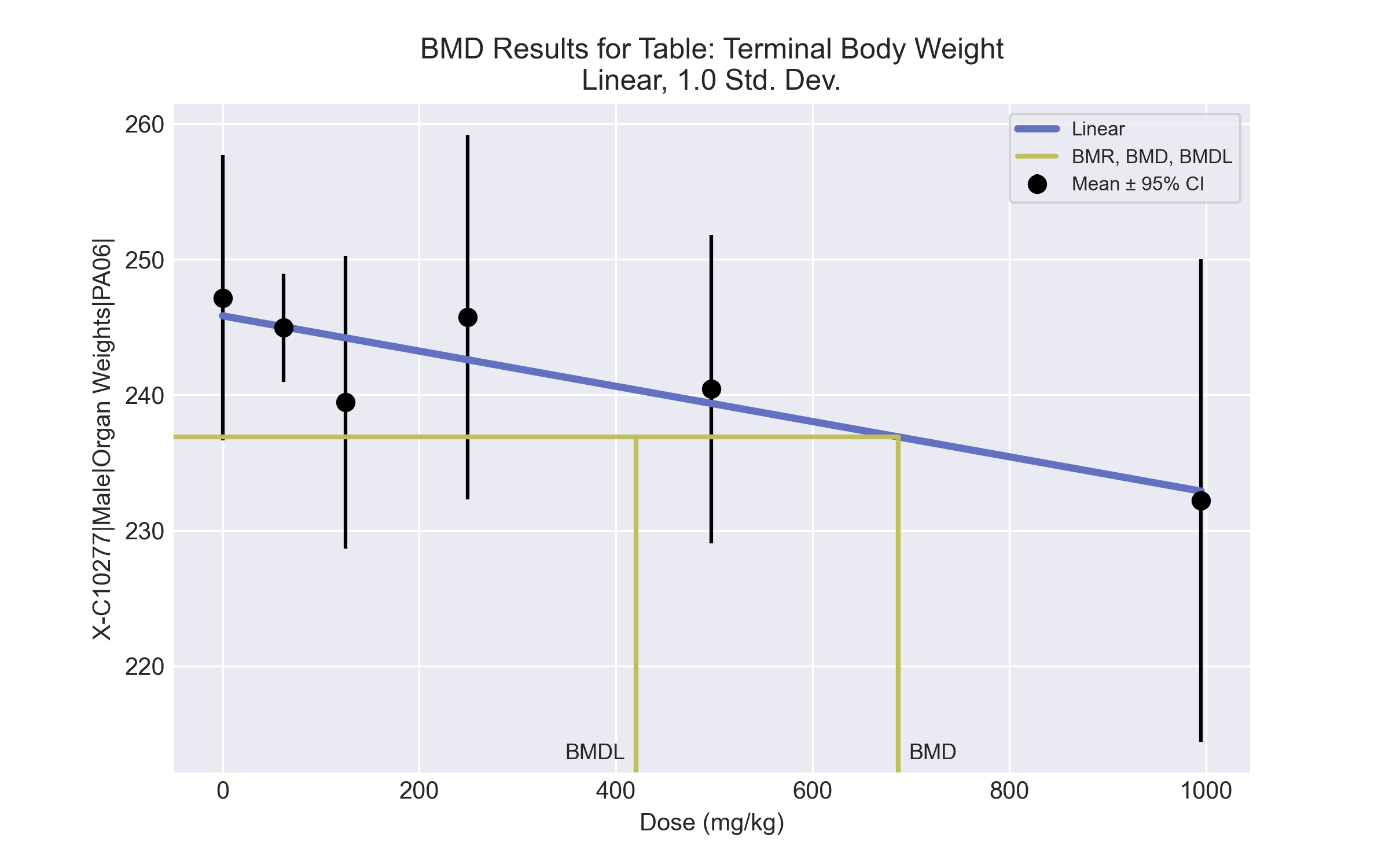
b Recommended model

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Lineara | Valid | - |
| Polynomial 2° | Valid | - |
| Polynomial 3° | Valid | - |
| Polynomial 4° | Valid | - |
| Polynomial 5° | 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-g04dmez1.(d)   
 Gnuplot Plotting File: C:\Windows\TEMP\bmds-g04dmez1.plt  
 Wed May 19 08:49:53 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 = 6  
 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 = 91.7043  
 rho = 0 Specified  
 beta\_0 = 245.83  
 beta\_1 = -0.0130018  
  
  
 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 -1.3e-006 4.3e-007  
  
 beta\_0 -1.3e-006 1 -0.68  
  
 beta\_1 4.3e-007 -0.68 1  
  
  
  
 Parameter Estimates  
  
 95.0% Wald Confidence Interval  
 Variable Estimate Std. Err. Lower Conf. Limit Upper Conf. Limit  
 alpha 79.7308 20.2516 40.0383 119.423  
 beta\_0 245.826 2.18304 241.547 250.104  
 beta\_1 -0.0129966 0.00473251 -0.0222722 -0.00372107  
  
  
  
 Table of Data and Estimated Values of Interest  
  
 Dose N Obs Mean Est Mean Obs Std Dev Est Std Dev Scaled Res.  
------ --- -------- -------- ----------- ----------- ----------  
  
 0 5 247 246 8.48 8.93 0.334  
 62 6 245 245 3.81 8.93 -0.0191  
 125 5 239 244 8.7 8.93 -1.19  
 249 5 246 243 10.8 8.93 0.789  
 497 5 240 239 9.17 8.93 0.264  
 995 5 232 233 14.3 8.93 -0.179  
  
  
  
 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 -82.203594 7 178.407187  
 A2 -78.016121 12 180.032243  
 A3 -82.203594 7 178.407187  
 fitted -83.369176 3 172.738353  
 R -86.744423 2 177.488845  
  
  
 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 17.4566 10 0.06485  
 Test 2 8.37494 5 0.1367  
 Test 3 8.37494 5 0.1367  
 Test 4 2.33117 4 0.6751  
  
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 = 687.041  
  
  
 BMDL = 420.179  
  
  
 BMDU = 1874.8

# BMD Results for Table: A/G Ratio

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 62 | 125 | 249 | 497 | 995 |
| N | 5 | 5 | 5 | 5 | 5 | 5 |
| Mean ± SD | 1.348 ± 0.034 | 1.303 ± 0.035 | 1.294 ± 0.03 | 1.241 ± 0.055 | 1.238 ± 0.05 | 1.114 ± 0.019 |

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear (equivalent models include Power, Polynomial 2°, 3°, 4°) | 0.133 | -158.387 | 186.27 | 146.35 | Exponential-M2 recommended as best-fitting model on the basis of the lowest AIC. |
| Polynomial 5° | 0.07 | -156.387 | 186.95 | 146.352 |
| Hill | 0.081 | -156.733 | 148.906 | 76.973 |
| Exponential M2b (equivalent models include Exponential M3) | 0.142 | -158.572 | 172.758 | 134.476 |
| Exponential M4 (equivalent models include Exponential M5) | 0.08 | -156.685 | 154.388 | 89.483 |

a Constant variance case presented (BMDS Test 2 p-value = 0.288, BMDS Test 3 p-value = 0.288).

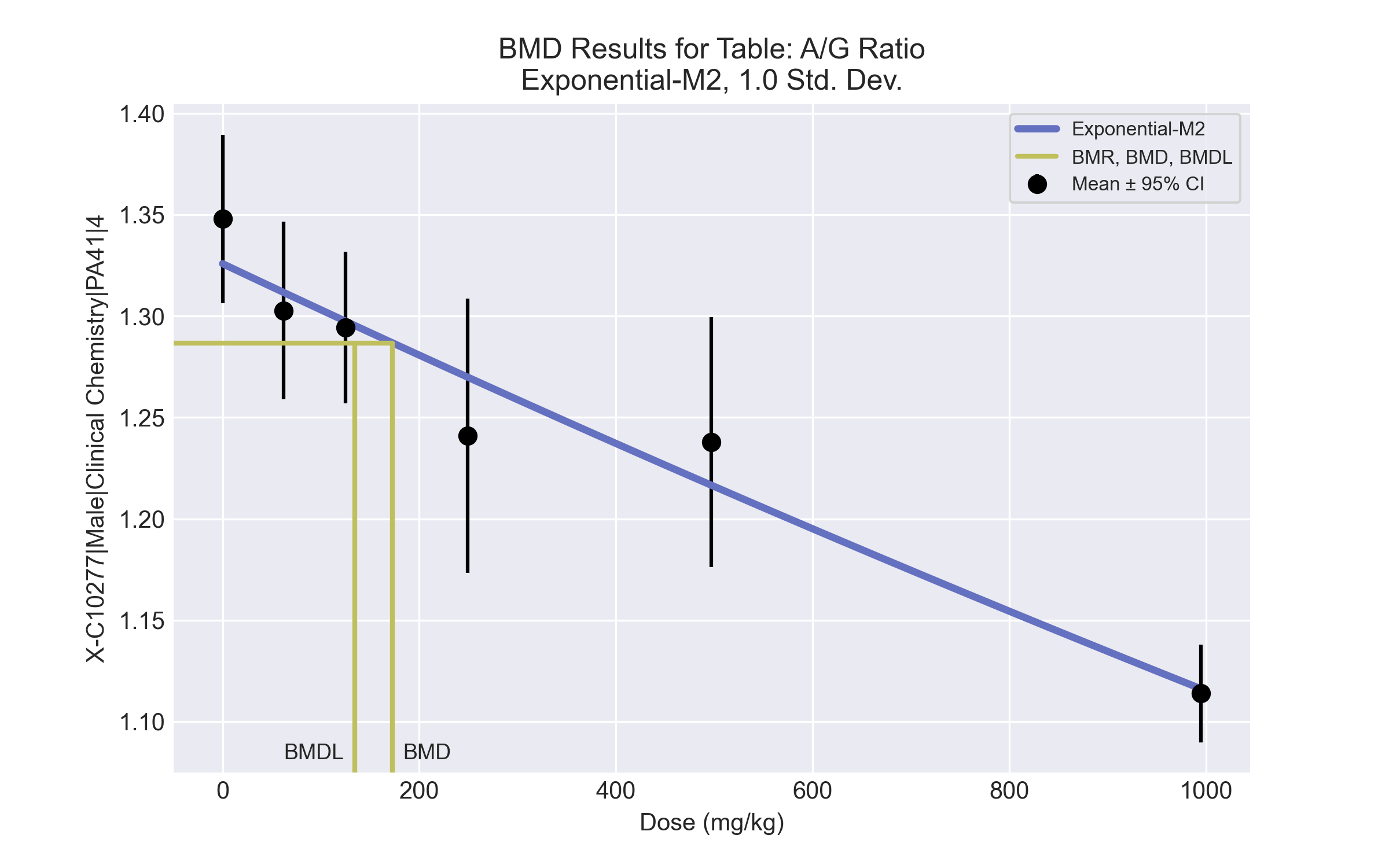
b Recommended model

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear (equivalent models include Power, Polynomial 2°, 3°, 4°) | Valid | - |
| Polynomial 5° | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0699 < 0.1) |
| Hill | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0814 < 0.1) |
| Exponential M2a (equivalent models include Exponential M3) | Valid | - |
| Exponential M4 (equivalent models include Exponential M5) | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0797 < 0.1) |

a Recommended model

## Recommended model



====================================================================   
 Exponential Model. (Version: 1.11; Date: 03/14/2017)   
 Input Data File: C:\Windows\TEMP\bmds-kz2554nk.(d)   
 Gnuplot Plotting File:   
 Wed May 19 08:52:32 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 = 6  
 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 -6.71507   
 rho 0 Specified  
 a 1.18635   
 b 0.000172577   
 c 0 Specified  
 d 1 Specified  
  
  
  
 Parameter Estimates  
  
 Variable Model 2 Std. Err.  
 -------- ------- ---------  
 lnalpha -6.48574 0.000393762  
 a 1.32583 0.0100446  
 b 0.000173057 1.77366e-005  
  
 NC = No Convergence  
  
  
 Table of Stats From Input Data  
  
 Dose N Obs Mean Obs Std Dev  
 ----- --- ---------- -------------  
 0 5 1.348 0.03351  
 62 5 1.303 0.0353  
 125 5 1.294 0.03019  
 249 5 1.241 0.05451  
 497 5 1.238 0.04967  
 995 5 1.114 0.01938  
  
  
 Estimated Values of Interest  
  
 Dose Est Mean Est Std Scaled Residual  
 ------ ---------- --------- ----------------  
 0 1.326 0.03905 1.265  
 62 1.312 0.03905 -0.5173  
 125 1.297 0.03905 -0.1773  
 249 1.27 0.03905 -1.66  
 497 1.217 0.03905 1.216  
 995 1.116 0.03905 -0.1254  
  
  
  
 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 85.72609 7 -157.4522  
 A2 88.82356 12 -153.6471  
 A3 85.72609 7 -157.4522  
 R 60.11491 2 -116.2298  
 2 82.28609 3 -158.5722  
  
  
 Additive constant for all log-likelihoods = -27.57. 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 57.42 10 < 0.0001  
 Test 2 6.195 5 0.2877  
 Test 3 6.195 5 0.2877  
 Test 4 6.88 4 0.1424  
  
  
 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. 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 = 172.758  
  
 BMDL = 134.476  
  
 BMDU = 237.635

# BMD Results for Table: Alanine aminotransferase

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 62 | 125 | 249a | 497a | 995a |
| N | 5 | 5 | 5 | 5 | 5 | 5 |
| Mean ± SD | 59.6 ± 8.933 | 89.8 ± 63.978 | 78 ± 16.956 | 83.8 ± 21.464 | 98 ± 26.524 | 104.6 ± 31.809 |

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 3°, 4°) | <0.0001 | 128.6 | 31.122 | 10.11 | Linear recommended as best-fitting model on the basis of the lowest AIC. |
| Polynomial 2° | <0.0001 | 128.252 | 1041.82 | -999 |
| Polynomial 5° | 1.9E-04 | 125.975 | 411.763 | -999 |
| Hill | 0.002 | 158.497 | 3.3E-10 | 3.3E-10 |
| Exponential M2 (equivalent models include Exponential M3) | <0.0001 | 130.305 | 119.381 | 21.291 |
| Exponential M4 | -999 | 120.665 | 1.233 | 0.002 |
| Exponential M5 | -999 | 160.497 | 26.849 | 0.03 |

a Modeled variance case presented (BMDS Test 2 p-value = 1.4E-04, BMDS Test 3 p-value = 0.431).

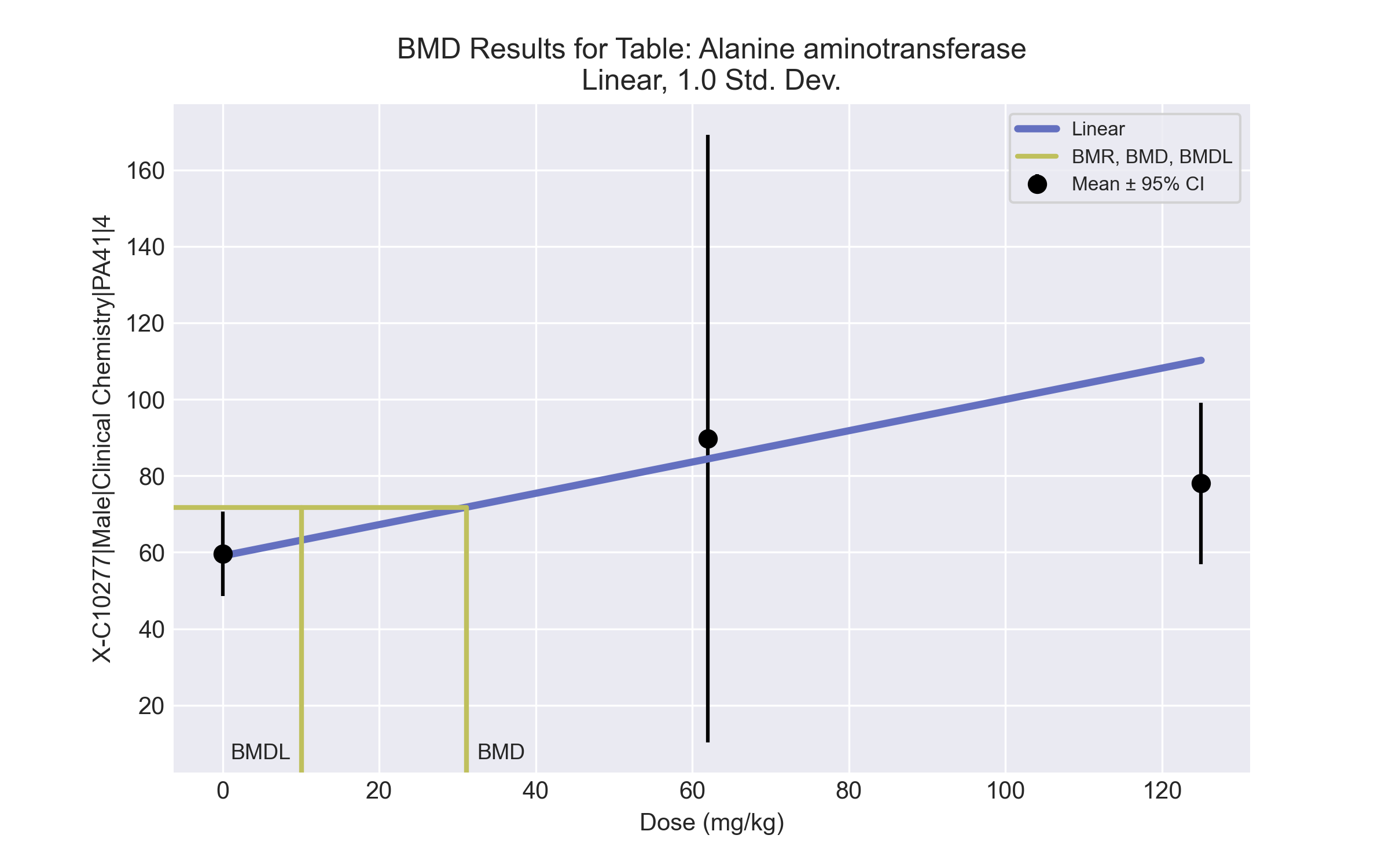
b Recommended model

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Lineara (equivalent models include Power, Polynomial 3°, 4°) | Valid | **Cautions**  • Warning(s): THE MODEL HAS PROBABLY NOT CONVERGED!!!; THIS USUALLY MEANS THE MODEL HAS NOT CONVERGED! |
| Polynomial 2° | Failure | **Failures**  • BMDL does not exist  **Warnings**  • BMD/high dose ratio is greater than threshold (8.33 > 1.0)  • Ratio of modeled to actual stdev. at control is greater than threshold (5.82 > 1.5)  **Cautions**  • Warning(s): BMDL computation failed. |
| Polynomial 5° | Failure | **Failures**  • BMDL does not exist  **Warnings**  • Goodness of fit p-value is less than threshold (0.000191 < 0.1)  • BMD/high dose ratio is greater than threshold (3.29 > 1.0)  • Ratio of modeled to actual stdev. at control is greater than threshold (4.99 > 1.5)  **Cautions**  • Warning(s): BMDL computation failed. |
| Hill | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.00194 < 0.1)  **Cautions**  • Minimum dose/BMD ratio is greater than threshold (1.88e+11 > 3.0) |
| Exponential M2 (equivalent models include Exponential M3) | Valid | **Cautions**  • BMD/BMDL ratio is greater than threshold (5.61 > 5.0) |
| Exponential M4 | Warning | **Warnings**  • BMD/BMDL ratio is greater than threshold (6.55e+02 > 20.0)  • Zero degrees of freedom; saturated model  **Cautions**  • BMD/BMDL ratio is greater than threshold (6.55e+02 > 5.0)  • Minimum dose/BMD ratio is greater than threshold (50.3 > 3.0) |
| Exponential M5 | Warning | **Warnings**  • BMD/BMDL ratio is greater than threshold (9.09e+02 > 20.0)  • Zero degrees of freedom; saturated model  **Cautions**  • BMD/BMDL ratio is greater than threshold (9.09e+02 > 5.0) |

a Recommended model

## Recommended model



====================================================================   
 Polynomial Model. (Version: 2.21; Date: 03/14/2017)   
 Input Data File: C:\Windows\TEMP\bmds-6py4gmcr.(d)   
 Gnuplot Plotting File: C:\Windows\TEMP\bmds-6py4gmcr.plt  
 Tue Jul 27 18:01:56 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 = 7.3044  
 rho = 0  
 beta\_0 = 66.6806  
 beta\_1 = 0  
  
  
 Asymptotic Correlation Matrix of Parameter Estimates  
  
 lalpha rho beta\_0 beta\_1  
  
 lalpha NA NA NA NA   
  
 rho NA NA NA NA   
  
 beta\_0 NA NA NA NA   
  
 beta\_1 NA NA NA NA   
  
  
NA - This parameter's variance has been estimated as zero or less.  
THE MODEL HAS PROBABLY NOT CONVERGED!!!  
  
  
  
 Parameter Estimates  
  
 95.0% Wald Confidence Interval  
 Variable Estimate Std. Err. Lower Conf. Limit Upper Conf. Limit  
 lalpha -19.2388 NA NA NA  
 rho 5.96486 NA NA NA  
 beta\_0 59.0562 NA NA NA  
 beta\_1 0.409232 NA NA NA  
  
At least some variance estimates are negative.  
THIS USUALLY MEANS THE MODEL HAS NOT CONVERGED!  
Try again from another starting point.  
  
  
  
 Table of Data and Estimated Values of Interest  
  
 Dose N Obs Mean Est Mean Obs Std Dev Est Std Dev Scaled Res.  
------ --- -------- -------- ----------- ----------- ----------  
  
 0 5 59.6 59.1 8.93 12.7 0.0955  
 62 5 89.8 84.4 64 37 0.325  
 125 5 78 110 17 81.9 -0.88  
  
  
  
 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 -60.609452 4 129.218905  
 A2 -51.720995 6 115.441991  
 A3 -52.031591 5 114.063182  
 fitted -60.299993 4 128.599986  
 R -61.524946 2 127.049892  
  
  
 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 19.6079 4 0.0005967  
 Test 2 17.7769 2 0.000138  
 Test 3 0.621192 1 0.4306  
 Test 4 16.5368 1 <.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 = 31.1217  
  
  
 BMDL = 10.1097  
  
  
 BMDU = 1.5625e+008

# BMD Results for Table: Albumin

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 62 | 125 | 249 | 497 | 995 |
| N | 5 | 5 | 5 | 5 | 5 | 5 |
| Mean ± SD | 3.42 ± 0.13 | 3.36 ± 0.114 | 3.26 ± 0.055 | 3.2 ± 0.1 | 3.24 ± 0.055 | 3.14 ± 0.089 |

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear (equivalent models include Power, Polynomial 2°, 3°, 4°, 5°) | 0.034 | -101.574 | 448.51 | 309.36 | Exponential-M4 recommended as best-fitting model on the basis of the lowest AIC. |
| Hill | 0.212 | -104.907 | 74.436 | 23.215 |
| Exponential M2 (equivalent models include Exponential M3) | 0.036 | -101.711 | 435.265 | 296.908 |
| Exponential M4b | 0.287 | -106.235 | 62.522 | 28.385 |
| Exponential M5 | 0.191 | -104.701 | 79.027 | 30.243 |

a Constant variance case presented (BMDS Test 2 p-value = 0.303, BMDS Test 3 p-value = 0.303).

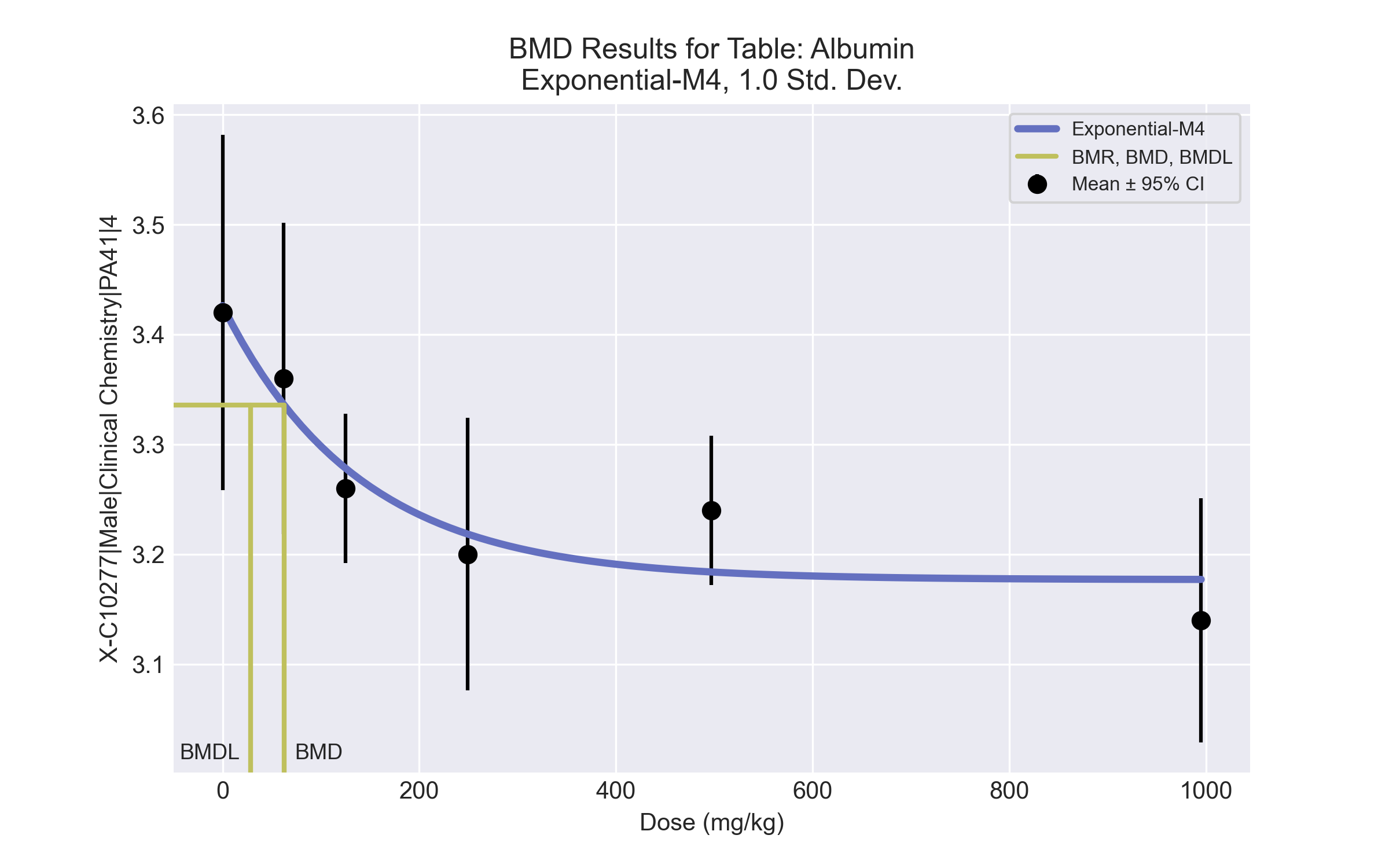
b Recommended model

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear (equivalent models include Power, Polynomial 2°, 3°, 4°, 5°) | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0337 < 0.1) |
| Hill | Valid | - |
| Exponential M2 (equivalent models include Exponential M3) | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0357 < 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-7g3yjtqh.(d)   
 Gnuplot Plotting File:   
 Wed May 19 08:52:57 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 = 6  
 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 -4.93367   
 rho 0 Specified  
 a 3.591   
 b 0.0016779   
 c 0.83277   
 d 1 Specified  
  
  
  
 Parameter Estimates  
  
 Variable Model 4 Std. Err.  
 -------- ------- ---------  
 lnalpha -4.80783 0.00210835  
 a 3.42617 0.0392838  
 b 0.00719866 0.00359235  
 c 0.927227 0.0129028  
  
 NC = No Convergence  
  
  
 Table of Stats From Input Data  
  
 Dose N Obs Mean Obs Std Dev  
 ----- --- ---------- -------------  
 0 5 3.42 0.1304  
 62 5 3.36 0.114  
 125 5 3.26 0.05477  
 249 5 3.2 0.1  
 497 5 3.24 0.05477  
 995 5 3.14 0.08944  
  
  
 Estimated Values of Interest  
  
 Dose Est Mean Est Std Scaled Residual  
 ------ ---------- --------- ----------------  
 0 3.426 0.09036 -0.1527  
 62 3.336 0.09036 0.5838  
 125 3.278 0.09036 -0.451  
 249 3.218 0.09036 -0.4544  
 497 3.184 0.09036 1.391  
 995 3.177 0.09036 -0.9163  
  
  
  
 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 59.00509 7 -104.0102  
 A2 62.01996 12 -100.0399  
 A3 59.00509 7 -104.0102  
 R 46.93403 2 -89.86806  
 4 57.1174 4 -106.2348  
  
  
 Additive constant for all log-likelihoods = -27.57. 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 30.17 10 0.0008029  
 Test 2 6.03 5 0.3033  
 Test 3 6.03 5 0.3033  
 Test 6a 3.775 3 0.2868  
  
  
 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 = 62.5221  
  
 BMDL = 28.3846  
  
 BMDU = 207.059

# BMD Results for Table: Cholesterol

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 62 | 125 | 249 | 497a | 995a |
| N | 5 | 5 | 5 | 5 | 5 | 5 |
| Mean ± SD | 113.2 ± 11.345 | 125.6 ± 12.759 | 114 ± 12.629 | 135.6 ± 3.507 | 140.6 ± 11.059 | 152.8 ± 7.328 |

a Dose group removed in BMD modeling session

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear | 0.013 | 122.862 | 192.184 | 110.72 | Power recommended as best-fitting model on the basis of the lowest AIC. |
| Polynomial 2° | 0.223 | 117.151 | 213.586 | 174.562 |
| Polynomial 3° | 0.489 | 115.576 | 221.577 | 186.417 |
| Polynomial 4° | 0.617 | 115.11 | 227.254 | 191.513 |
| Polynomial 5° | 0.67 | 114.947 | 231.156 | 192.569 |
| Powerb | 0.711 | 114.827 | 243.836 | 193.058 |
| Hill | -999 | 118.827 | 243.569 | -999 |
| Exponential M2 | 0.018 | 122.174 | 196.222 | 120.105 |
| Exponential M3 | 0.409 | 116.827 | 244.131 | 194.002 |
| Exponential M4 | 0.003 | 124.862 | 192.183 | 110.719 |
| Exponential M5 | -999 | 118.827 | 243.836 | 134.389 |

a Modeled variance case presented (BMDS Test 2 p-value = 0.061, BMDS Test 3 p-value = 0.229).

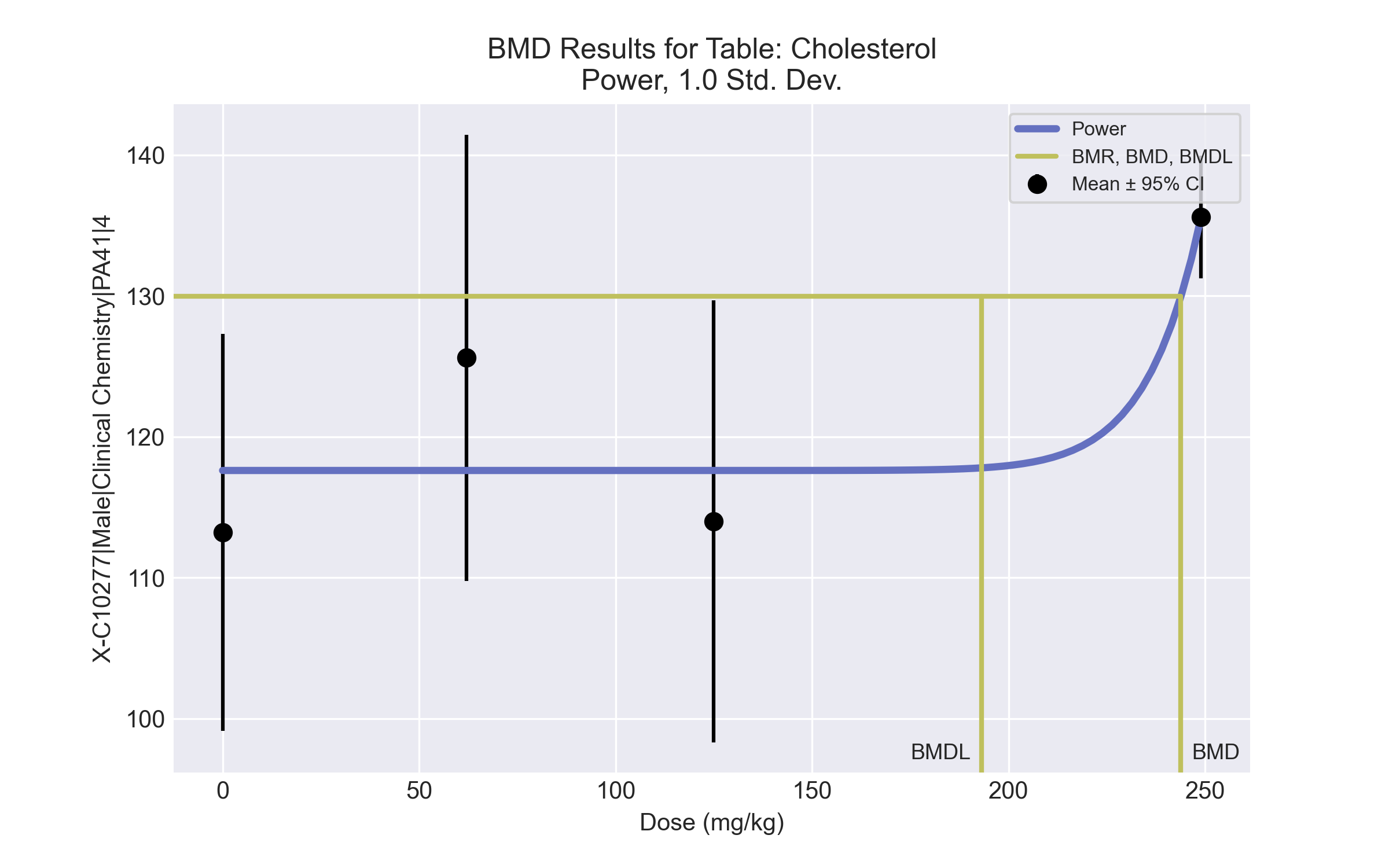
b Recommended model

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0128 < 0.1)  • Ratio of modeled to actual stdev. at control is greater than threshold (1.6 > 1.5) |
| Polynomial 2° | Valid | - |
| Polynomial 3° | Valid | - |
| Polynomial 4° | Valid | - |
| Polynomial 5° | Valid | - |
| Powera | Valid | - |
| Hill | Failure | **Failures**  • BMDL does not exist  **Warnings**  • Zero degrees of freedom; saturated model  **Cautions**  • Warning(s): BMDL computation failed. |
| Exponential M2 | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0181 < 0.1) |
| Exponential M3 | Valid | - |
| Exponential M4 | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.00315 < 0.1) |
| Exponential M5 | Warning | **Warnings**  • Zero degrees of freedom; saturated model |

a Recommended model

## Recommended model



====================================================================   
 Power Model. (Version: 2.19; Date: 03/14/2017)   
 Input Data File: C:\Windows\TEMP\bmds-vvgaraed.(d)   
 Gnuplot Plotting File: C:\Windows\TEMP\bmds-vvgaraed.plt  
 Wed May 19 08:53:07 2021  
 ====================================================================   
  
 BMDS\_Model\_Run   
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~  
   
 The form of the response function is:   
  
 Y[dose] = control + slope \* dose^power  
  
  
 Dependent variable = Response  
 Independent variable = Dose  
 The power is restricted to be greater than or equal to 1  
 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 = 4.75208  
 rho = 0  
 control = 113.2  
 slope = 0.827038  
 power = -9999  
  
  
 Asymptotic Correlation Matrix of Parameter Estimates  
  
 ( \*\*\* The model parameter(s) -power   
 have been estimated at a boundary point, or have been specified by the user,  
 and do not appear in the correlation matrix )  
  
 lalpha rho control slope  
  
 lalpha 1 -1 0.58 -0.61  
  
 rho -1 1 -0.57 0.61  
  
 control 0.58 -0.57 1 -0.92  
  
 slope -0.61 0.61 -0.92 1  
  
  
  
 Parameter Estimates  
  
 95.0% Wald Confidence Interval  
 Variable Estimate Std. Err. Lower Conf. Limit Upper Conf. Limit  
 lalpha 96.7393 31.2104 35.5681 157.91  
 rho -19.238 6.4536 -31.8868 -6.58915  
 control 117.6 3.1872 111.353 123.847  
 slope 1.32949e-042 2.57203e-043 8.25382e-043 1.8336e-042  
 power 18 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 5 113 118 11.3 12.3 -0.797  
 62 5 126 118 12.8 12.3 1.45  
 125 5 114 118 12.6 12.3 -0.652  
 249 5 136 136 3.51 3.14 6.67e-007  
  
  
  
 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 -55.289369 5 120.578737  
 A2 -51.597689 8 119.195379  
 A3 -53.072649 6 118.145298  
 fitted -53.413648 4 114.827297  
 R -61.789143 2 127.578285  
  
  
 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 20.3829 6 0.002366  
 Test 2 7.38336 3 0.06063  
 Test 3 2.94992 2 0.2288  
 Test 4 0.681999 2 0.7111  
  
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 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 = 243.836   
  
  
 BMDL = 193.058   
  
  
 BMDU = 258.682

# BMD Results for Table: Globulin

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 62 | 125 | 249 | 497 | 995 |
| N | 5 | 5 | 5 | 5 | 5 | 5 |
| Mean ± SD | 2.54 ± 0.152 | 2.58 ± 0.084 | 2.52 ± 0.084 | 2.58 ± 0.045 | 2.62 ± 0.084 | 2.82 ± 0.11 |

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear | 0.497 | -106.494 | 336.307 | 246.067 | Exponential-M2 recommended as best-fitting model on the basis of the lowest AIC. |
| Polynomial 2° (equivalent models include Polynomial 3°, 4°, 5°) | 0.699 | -106.437 | 553.583 | 281.647 |
| Power | 0.699 | -106.438 | 552.805 | 281.687 |
| Hill | 0.49 | -104.438 | 551.931 | 280.301 |
| Exponential M2b | 0.531 | -106.703 | 344.789 | 255.822 |
| Exponential M3 | 0.699 | -106.437 | 553.689 | 285.34 |
| Exponential M4 | 0.337 | -104.489 | 336.145 | 223.772 |
| Exponential M5 | 0.49 | -104.438 | 552.036 | 280.339 |

a Constant variance case presented (BMDS Test 2 p-value = 0.199, BMDS Test 3 p-value = 0.199).

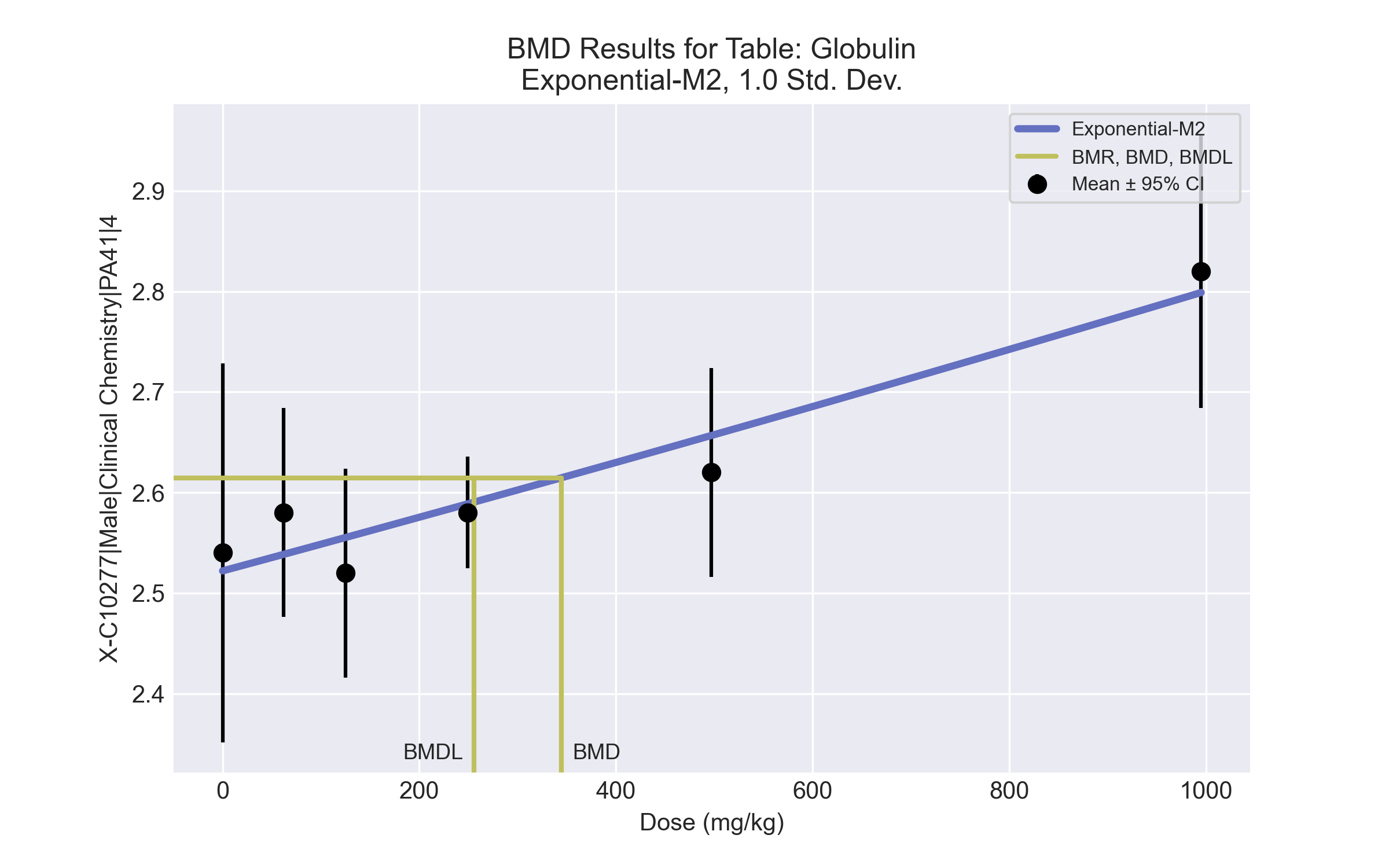
b Recommended model

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear | Valid | - |
| Polynomial 2° (equivalent models include Polynomial 3°, 4°, 5°) | Valid | - |
| Power | Valid | - |
| Hill | Valid | - |
| Exponential M2a | Valid | - |
| Exponential M3 | Valid | - |
| Exponential M4 | 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-g5e3w4jj.(d)   
 Gnuplot Plotting File:   
 Wed May 19 08:53:11 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 = 6  
 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 -4.86221   
 rho 0 Specified  
 a 2.52295   
 b 0.000103386   
 c 0 Specified  
 d 1 Specified  
  
  
  
 Parameter Estimates  
  
 Variable Model 2 Std. Err.  
 -------- ------- ---------  
 lnalpha -4.75677 0.00221879  
 a 2.52201 0.0229148  
 b 0.000104693 1.83724e-005  
  
 NC = No Convergence  
  
  
 Table of Stats From Input Data  
  
 Dose N Obs Mean Obs Std Dev  
 ----- --- ---------- -------------  
 0 5 2.54 0.1517  
 62 5 2.58 0.08367  
 125 5 2.52 0.08367  
 249 5 2.58 0.04472  
 497 5 2.62 0.08367  
 995 5 2.82 0.1095  
  
  
 Estimated Values of Interest  
  
 Dose Est Mean Est Std Scaled Residual  
 ------ ---------- --------- ----------------  
 0 2.522 0.0927 0.4338  
 62 2.538 0.0927 1.003  
 125 2.555 0.0927 -0.85  
 249 2.589 0.0927 -0.208  
 497 2.657 0.0927 -0.8856  
 995 2.799 0.0927 0.5089  
  
  
  
 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 57.93317 7 -101.8663  
 A2 61.58529 12 -99.17058  
 A3 57.93317 7 -101.8663  
 R 45.62626 2 -87.25251  
 2 56.3515 3 -106.703  
  
  
 Additive constant for all log-likelihoods = -27.57. 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 31.92 10 0.0004132  
 Test 2 7.304 5 0.199  
 Test 3 7.304 5 0.199  
 Test 4 3.163 4 0.5309  
  
  
 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. 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 = 344.789  
  
 BMDL = 255.822  
  
 BMDU = 529.789

# BMD Results for Table: HDL Cholesterol

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 62 | 125 | 249 | 497a | 995a |
| N | 5 | 5 | 5 | 5 | 5 | 5 |
| Mean ± SD | 52 ± 5 | 58.4 ± 5.771 | 54.2 ± 6.611 | 64.8 ± 1.924 | 63.6 ± 3.912 | 65.6 ± 5.857 |

a Dose group removed in BMD modeling session

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear | 0.017 | 93.011 | 150.265 | 85.899 | Power recommended as best-fitting model on the basis of the lowest AIC. |
| Polynomial 2° | 0.177 | 88.318 | 196.451 | 151.061 |
| Polynomial 3° | 0.339 | 87.023 | 210.395 | 167.5 |
| Polynomial 4° | 0.408 | 86.651 | 218.738 | 172.466 |
| Polynomial 5° | 0.198 | 88.52 | 223.706 | 176.19 |
| Powerb | 0.456 | 86.431 | 241.788 | 175.102 |
| Hill | 0.21 | 88.431 | 241.716 | -999 |
| Exponential M2 | 0.023 | 92.378 | 158.615 | 96.076 |
| Exponential M3 | 0.21 | 88.431 | 242.234 | 175.627 |
| Exponential M4 | 0.004 | 95.012 | 150.264 | 85.898 |
| Exponential M5 | -999 | 90.431 | 241.786 | 175.102 |

a Modeled variance case presented (BMDS Test 2 p-value = 0.092, BMDS Test 3 p-value = 0.321).

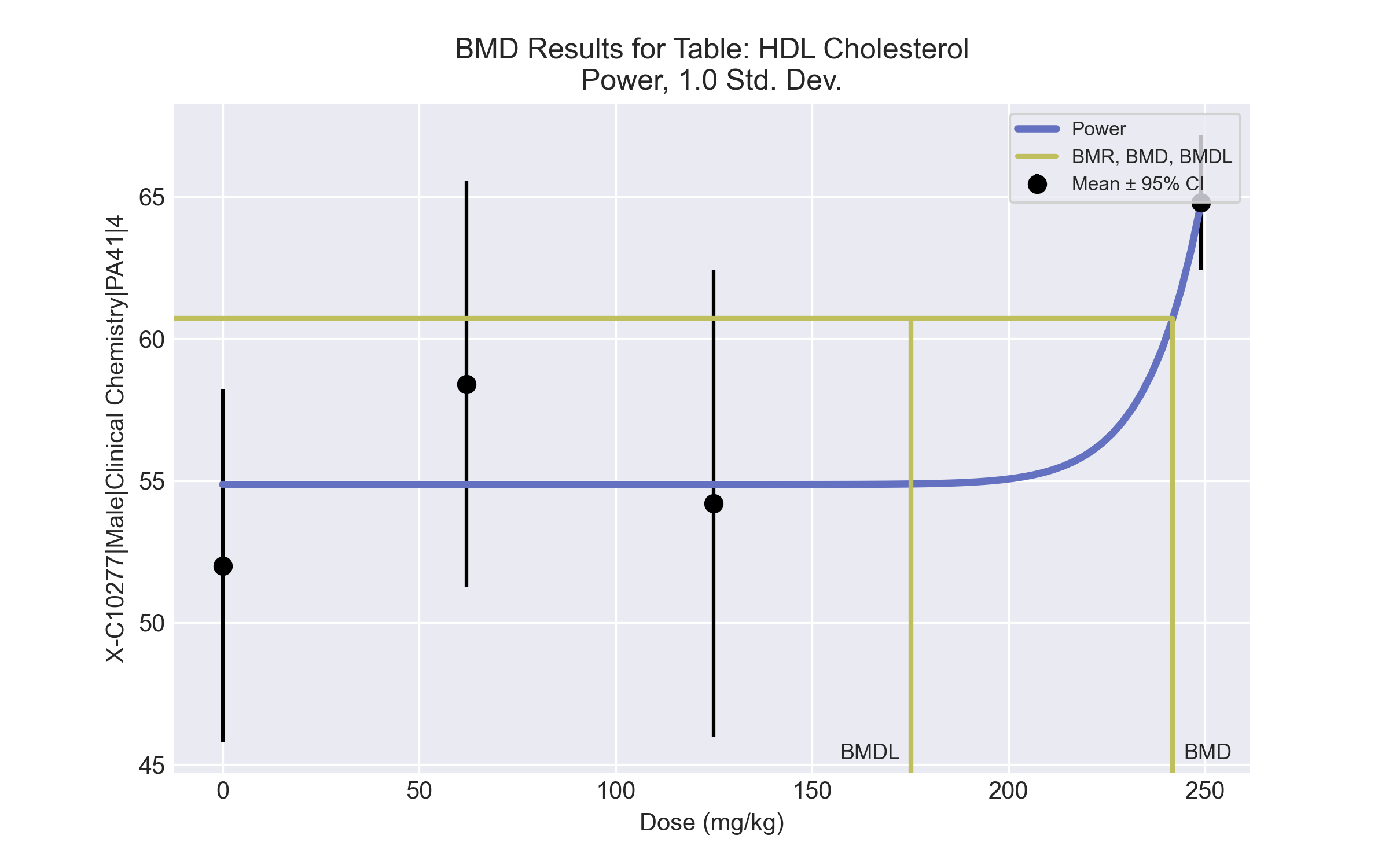
b Recommended model

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.017 < 0.1)  • Ratio of modeled to actual stdev. at control is greater than threshold (1.51 > 1.5) |
| Polynomial 2° | Valid | - |
| Polynomial 3° | Valid | - |
| Polynomial 4° | Valid | - |
| Polynomial 5° | Valid | - |
| Powera | Valid | - |
| Hill | Failure | **Failures**  • BMDL does not exist  **Cautions**  • Warning(s): BMDL computation failed. |
| Exponential M2 | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0233 < 0.1) |
| Exponential M3 | Valid | - |
| Exponential M4 | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0043 < 0.1) |
| Exponential M5 | Warning | **Warnings**  • Zero degrees of freedom; saturated model |

a Recommended model

## Recommended model



====================================================================   
 Power Model. (Version: 2.19; Date: 03/14/2017)   
 Input Data File: C:\Windows\TEMP\bmds-99f8bx\_s.(d)   
 Gnuplot Plotting File: C:\Windows\TEMP\bmds-99f8bx\_s.plt  
 Wed May 19 08:53:21 2021  
 ====================================================================   
  
 BMDS\_Model\_Run   
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~  
   
 The form of the response function is:   
  
 Y[dose] = control + slope \* dose^power  
  
  
 Dependent variable = Response  
 Independent variable = Dose  
 The power is restricted to be greater than or equal to 1  
 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 = 3.27431  
 rho = 0  
 control = 52  
 slope = 0.524466  
 power = -9999  
  
  
 Asymptotic Correlation Matrix of Parameter Estimates  
  
 ( \*\*\* The model parameter(s) -power   
 have been estimated at a boundary point, or have been specified by the user,  
 and do not appear in the correlation matrix )  
  
 lalpha rho control slope  
  
 lalpha 1 -1 0.49 -0.52  
  
 rho -1 1 -0.47 0.52  
  
 control 0.49 -0.47 1 -0.89  
  
 slope -0.52 0.52 -0.89 1  
  
  
  
 Parameter Estimates  
  
 95.0% Wald Confidence Interval  
 Variable Estimate Std. Err. Lower Conf. Limit Upper Conf. Limit  
 lalpha 62.4633 20.8895 21.5206 103.406  
 rho -14.7144 5.12786 -24.7648 -4.66395  
 control 54.8667 1.51105 51.9051 57.8283  
 slope 7.33681e-043 1.25242e-043 4.88211e-043 9.79152e-043  
 power 18 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 52 54.9 5 5.85 -1.1  
 62 5 58.4 54.9 5.77 5.85 1.35  
 125 5 54.2 54.9 6.61 5.85 -0.255  
 249 5 64.8 64.8 1.92 1.72 4.67e-007  
  
  
  
 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 -40.511670 5 91.023340  
 A2 -37.293849 8 90.587698  
 A3 -38.430002 6 88.860004  
 fitted -39.215383 4 86.430766  
 R -48.050501 2 100.101002  
  
  
 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 21.5133 6 0.001483  
 Test 2 6.43564 3 0.09224  
 Test 3 2.27231 2 0.3211  
 Test 4 1.57076 2 0.4559  
  
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 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 = 241.788   
  
  
 BMDL = 175.102   
  
  
 BMDU = 248.644

# BMD Results for Table: LDL Cholesterol

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 62 | 125 | 249 | 497 | 995 |
| N | 5 | 5 | 5 | 5 | 5 | 5 |
| Mean ± SD | 23.2 ± 2.95 | 22 ± 2.739 | 22.2 ± 2.28 | 23.8 ± 1.924 | 26.8 ± 2.168 | 28.6 ± 2.074 |

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linearb (equivalent models include Power, Polynomial 2°, 3°, 4°, 5°) | 0.428 | 85.273 | 335.623 | 245.654 | Linear recommended as best-fitting model on the basis of the lowest AIC. |
| Hill | 0.593 | 86.477 | 317.739 | 190.706 |
| Exponential M2 (equivalent models include Exponential M3) | 0.392 | 85.537 | 370.665 | 279.671 |
| Exponential M4 | 0.308 | 87.03 | 274.016 | 136.991 |
| Exponential M5 | 0.568 | 86.562 | 332.266 | 190.387 |

a Constant variance case presented (BMDS Test 2 p-value = 0.922, BMDS Test 3 p-value = 0.922).

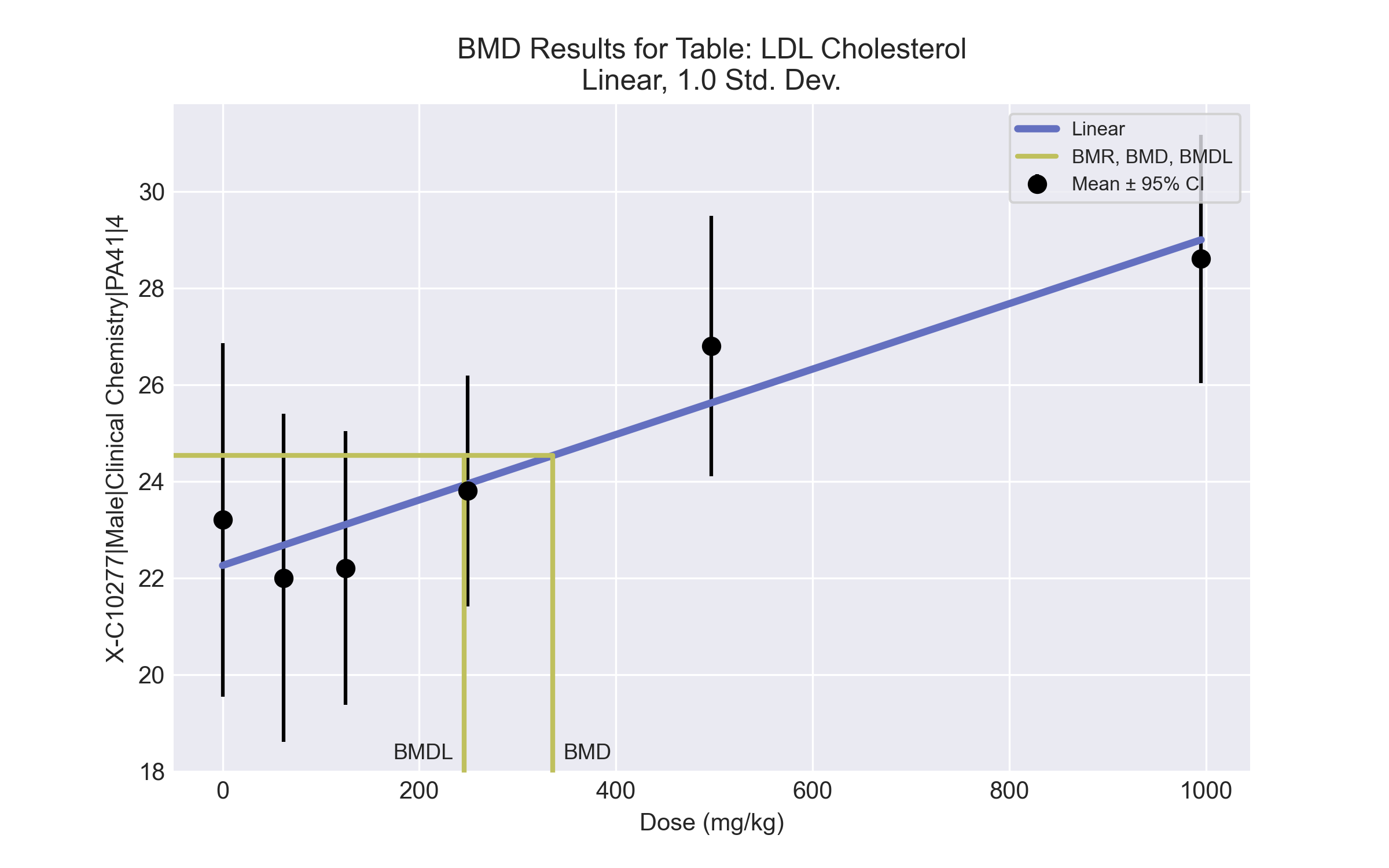
b Recommended model

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Lineara (equivalent models include Power, Polynomial 2°, 3°, 4°, 5°) | Valid | - |
| Hill | Valid | - |
| Exponential M2 (equivalent models include Exponential M3) | Valid | - |
| Exponential M4 | 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-yiqt1gz6.(d)   
 Gnuplot Plotting File: C:\Windows\TEMP\bmds-yiqt1gz6.plt  
 Wed May 19 08:53:24 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  
 rho is set to 0  
 The polynomial coefficients are restricted to be positive  
 A constant variance model is fit  
  
 Total number of dose groups = 6  
 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 = 5.68333  
 rho = 0 Specified  
 beta\_0 = 22.2569  
 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 -4.4e-009 5.1e-009  
  
 beta\_0 -4.4e-009 1 -0.69  
  
 beta\_1 5.1e-009 -0.69 1  
  
  
  
 Parameter Estimates  
  
 95.0% Wald Confidence Interval  
 Variable Estimate Std. Err. Lower Conf. Limit Upper Conf. Limit  
 alpha 5.16774 1.3343 2.55255 7.78293  
 beta\_0 22.2569 0.570033 21.1396 23.3741  
 beta\_1 0.00677327 0.001216 0.00438994 0.00915659  
  
  
  
 Table of Data and Estimated Values of Interest  
  
 Dose N Obs Mean Est Mean Obs Std Dev Est Std Dev Scaled Res.  
------ --- -------- -------- ----------- ----------- ----------  
  
 0 5 23.2 22.3 2.95 2.27 0.928  
 62 5 22 22.7 2.74 2.27 -0.666  
 125 5 22.2 23.1 2.28 2.27 -0.889  
 249 5 23.8 23.9 1.92 2.27 -0.141  
 497 5 26.8 25.6 2.17 2.27 1.16  
 995 5 28.6 29 2.07 2.27 -0.39  
  
  
  
 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 -37.715914 7 89.431828  
 A2 -37.006332 12 98.012665  
 A3 -37.715914 7 89.431828  
 fitted -39.636525 3 85.273049  
 R -50.288078 2 104.576157  
  
  
 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 26.5635 10 0.003052  
 Test 2 1.41916 5 0.9222  
 Test 3 1.41916 5 0.9222  
 Test 4 3.84122 4 0.4279  
  
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 = 335.623  
  
  
 BMDL = 245.654  
  
  
 BMDU = 525.34

# BMD Results for Table: Cholinesterase

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 62 | 125 | 249 | 497 | 995 |
| N | 5 | 5 | 5 | 5 | 5 | 5 |
| Mean ± SD | 285.4 ± 35.956 | 164 ± 24.042 | 138.6 ± 15.192 | 111 ± 12.826 | 80.4 ± 18.284 | 63.4 ± 17.615 |

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear (equivalent models include Power, Polynomial 2°, 3°, 4°, 5°) | <0.0001 | 272.943 | 321.957 | 237.311 | Hill recommended as best-fitting model on the basis of the lowest AIC. |
| Hillb | 0.473 | 219.352 | 6.447 | 4.494 |
| Exponential M2 | <0.0001 | 257.341 | 66.899 | 41.221 |
| Exponential M3 | <0.0001 | 257.341 | 66.899 | 41.221 |
| Exponential M4 (equivalent models include Exponential M5) | 0.014 | 227.421 | 11.585 | 8.254 |

a Constant variance case presented (BMDS Test 2 p-value = 0.19, BMDS Test 3 p-value = 0.19).

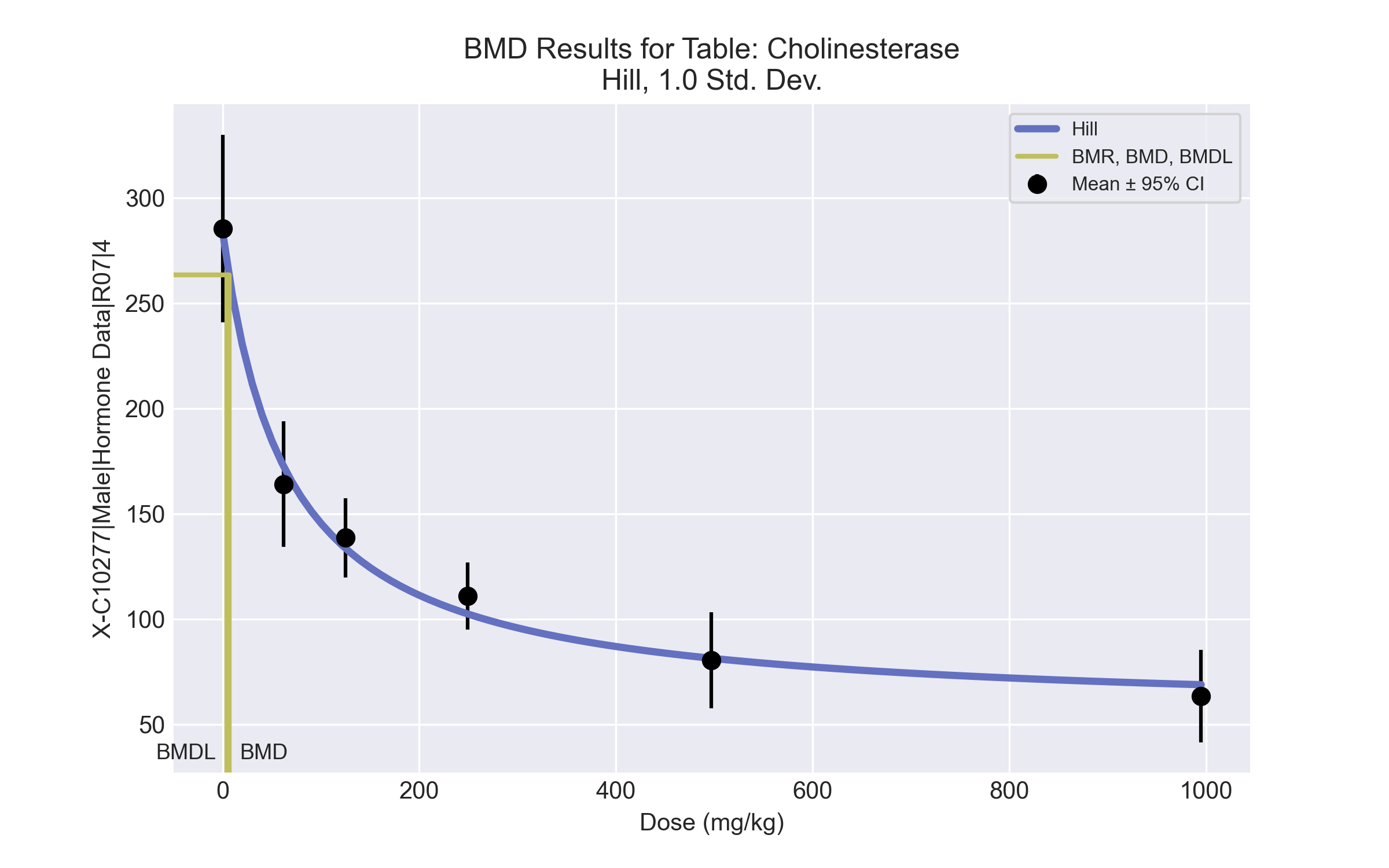
b Recommended model

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear (equivalent models include Power, Polynomial 2°, 3°, 4°, 5°) | Warning | **Warnings**  • Residual at lowest dose is greater than threshold (4.01 > 2.0) |
| Hilla | Valid | **Cautions**  • Minimum dose/BMD ratio is greater than threshold (9.62 > 3.0) |
| Exponential M2 | Warning | **Warnings**  • Residual at lowest dose is greater than threshold (2.67 > 2.0) |
| Exponential M3 | Warning | **Warnings**  • Residual at lowest dose is greater than threshold (2.67 > 2.0) |
| Exponential M4 (equivalent models include Exponential M5) | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0142 < 0.1)  **Cautions**  • Minimum dose/BMD ratio is greater than threshold (5.35 > 3.0) |

a Recommended model

## Recommended model



====================================================================   
 Hill Model. (Version: 2.18; Date: 03/14/2017)   
 Input Data File: C:\Windows\TEMP\bmds-8l6vmcwh.(d)   
 Gnuplot Plotting File: C:\Windows\TEMP\bmds-8l6vmcwh.plt  
 Wed May 19 08:54:06 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 = 6  
 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 = 485.117  
 rho = 0 Specified  
 intercept = 285.4  
 v = -222  
 n = 1.24217  
 k = 56.6886  
  
  
 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 1.3e-007 8.8e-007 -1.9e-006  
  
 intercept 1.3e-007 1 -0.65 -0.44  
  
 v 8.8e-007 -0.65 1 -0.27  
  
 k -1.9e-006 -0.44 -0.27 1  
  
  
  
 Parameter Estimates  
  
 95.0% Wald Confidence Interval  
 Variable Estimate Std. Err. Lower Conf. Limit Upper Conf. Limit  
 alpha 422.025 108.966 208.455 635.595  
 intercept 284.076 9.2229 265.999 302.152  
 v -229.454 12.2828 -253.528 -205.38  
 n 1 NA  
 k 65.5594 13.0561 39.97 91.1487  
  
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 5 285 284 36 20.5 0.144  
 62 5 164 173 24 20.5 -0.931  
 125 5 139 134 15.2 20.5 0.548  
 249 5 111 102 12.8 20.5 0.931  
 497 5 80.4 81.4 18.3 20.5 -0.105  
 995 5 63.4 68.8 17.6 20.5 -0.588  
  
  
  
 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 -104.418688 7 222.837376  
 A2 -100.698297 12 225.396593  
 A3 -104.418688 7 222.837376  
 fitted -105.675972 4 219.351944  
 R -144.770219 2 293.540438  
  
  
 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 88.1438 10 <.0001  
 Test 2 7.44078 5 0.1899  
 Test 3 7.44078 5 0.1899  
 Test 4 2.51457 3 0.4727  
  
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 = 6.44679  
  
 BMDL = 4.49367  
  
 BMDU = 11.7492