# BMD Results for Table: Liver Weight Absolute

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 66 | 132 | 264 | 527 | 1054 |
| N | 5 | 5 | 5 | 5 | 5 | 5 |
| Mean ± SD | 11.46 ± 0.434 | 12.02 ± 0.976 | 12.854 ± 0.671 | 12.942 ± 1.012 | 13.54 ± 1.347 | 13.21 ± 0.802 |

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear (equivalent models include Power, Polynomial 4°, 5°) | 0.045 | 34.026 | 703.636 | 433.635 | Exponential-M4 recommended as best-fitting model on the basis of the lowest AIC. |
| Polynomial 2° (equivalent models include Polynomial 3°) | 0.045 | 34.026 | 703.637 | 433.635 |
| Hill | 0.609 | 29.264 | 82.94 | 22.859 |
| Exponential M2 (equivalent models include Exponential M3) | 0.041 | 34.244 | 738.689 | 466.39 |
| Exponential M4b | 0.755 | 27.463 | 74.612 | 30.211 |
| Exponential M5 | 0.567 | 29.407 | 81.387 | 30.483 |

a Constant variance case presented (BMDS Test 2 p-value = 0.248, BMDS Test 3 p-value = 0.248).

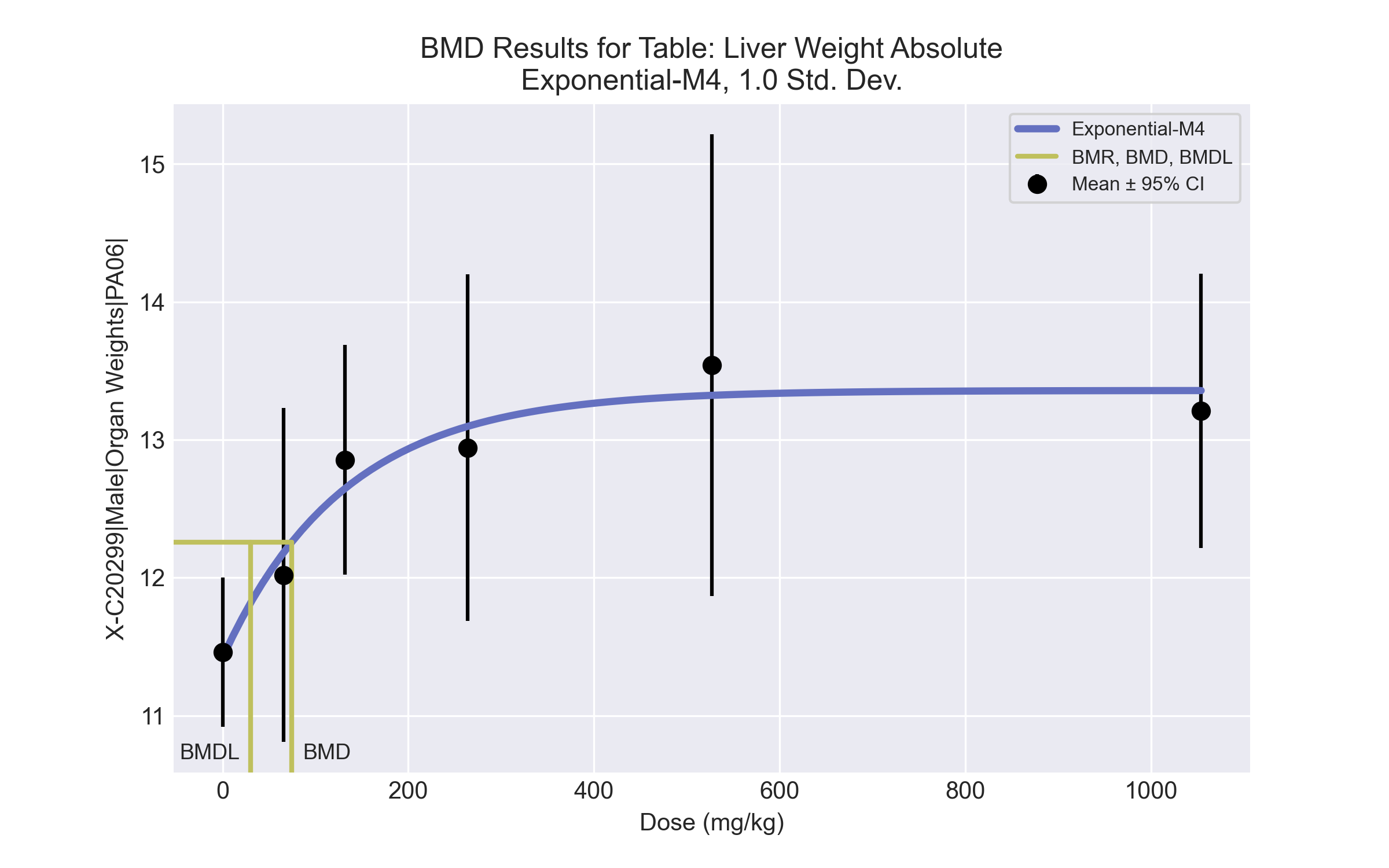
b Recommended model

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear (equivalent models include Power, Polynomial 4°, 5°) | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0448 < 0.1)  • Ratio of modeled to actual stdev. at control is greater than threshold (2.23 > 1.5) |
| Polynomial 2° (equivalent models include Polynomial 3°) | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0448 < 0.1)  • Ratio of modeled to actual stdev. at control is greater than threshold (2.23 > 1.5) |
| Hill | Warning | **Warnings**  • Ratio of modeled to actual stdev. at control is greater than threshold (1.93 > 1.5) |
| Exponential M2 (equivalent models include Exponential M3) | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0409 < 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-46rjeyg4.(d)   
 Gnuplot Plotting File:   
 Tue May 18 15:25:49 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 -0.390961   
 rho 0 Specified  
 a 10.887   
 b 0.00168833   
 c 1.30587   
 d 1 Specified  
  
  
  
 Parameter Estimates  
  
 Variable Model 4 Std. Err.  
 -------- ------- ---------  
 lnalpha -0.351244 0.181724  
 a 11.4196 0.355487  
 b 0.00760452 0.00382981  
 c 1.16967 0.0417406  
  
 NC = No Convergence  
  
  
 Table of Stats From Input Data  
  
 Dose N Obs Mean Obs Std Dev  
 ----- --- ---------- -------------  
 0 5 11.46 0.4343  
 66 5 12.02 0.9764  
 132 5 12.85 0.6709  
 264 5 12.94 1.012  
 527 5 13.54 1.347  
 1054 5 13.21 0.8018  
  
  
 Estimated Values of Interest  
  
 Dose Est Mean Est Std Scaled Residual  
 ------ ---------- --------- ----------------  
 0 11.42 0.8389 0.1077  
 66 12.18 0.8389 -0.4376  
 132 12.65 0.8389 0.5516  
 264 13.1 0.8389 -0.4128  
 527 13.32 0.8389 0.5814  
 1054 13.36 0.8389 -0.3904  
  
  
  
 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 -9.135592 7 32.27118  
 A2 -5.811431 12 35.62286  
 A3 -9.135592 7 32.27118  
 R -17.52793 2 39.05587  
 4 -9.731343 4 27.46269  
  
  
 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 23.43 10 0.009256  
 Test 2 6.648 5 0.2481  
 Test 3 6.648 5 0.2481  
 Test 6a 1.192 3 0.755  
  
  
 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 = 74.6117  
  
 BMDL = 30.2109  
  
 BMDU = 258.766

# BMD Results for Table: Liver Weight Relative

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 66 | 132 | 264 | 527 | 1054 |
| N | 5 | 5 | 5 | 5 | 5 | 5 |
| Mean ± SD | 41.498 ± 1.3 | 43.952 ± 3.128 | 46.822 ± 2.587 | 47.715 ± 1.597 | 48.752 ± 2.43 | 49.087 ± 1.597 |

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear (equivalent models include Power, Polynomial 3°, 4°, 5°) | 0.001 | 94.416 | 460.681 | 320.065 | Exponential-M4 recommended as best-fitting model on the basis of the lowest AIC. |
| Polynomial 2° | 0.001 | 94.416 | 460.682 | 320.065 |
| Hill | 0.819 | 81.149 | 53.114 | 17.614 |
| Exponential M2 (equivalent models include Exponential M3) | 0.001 | 94.864 | 492.294 | 347.858 |
| Exponential M4b | 0.839 | 79.593 | 39.811 | 22.359 |
| Exponential M5 | 0.671 | 81.546 | 44.93 | 22.463 |

a Constant variance case presented (BMDS Test 2 p-value = 0.34, BMDS Test 3 p-value = 0.34).

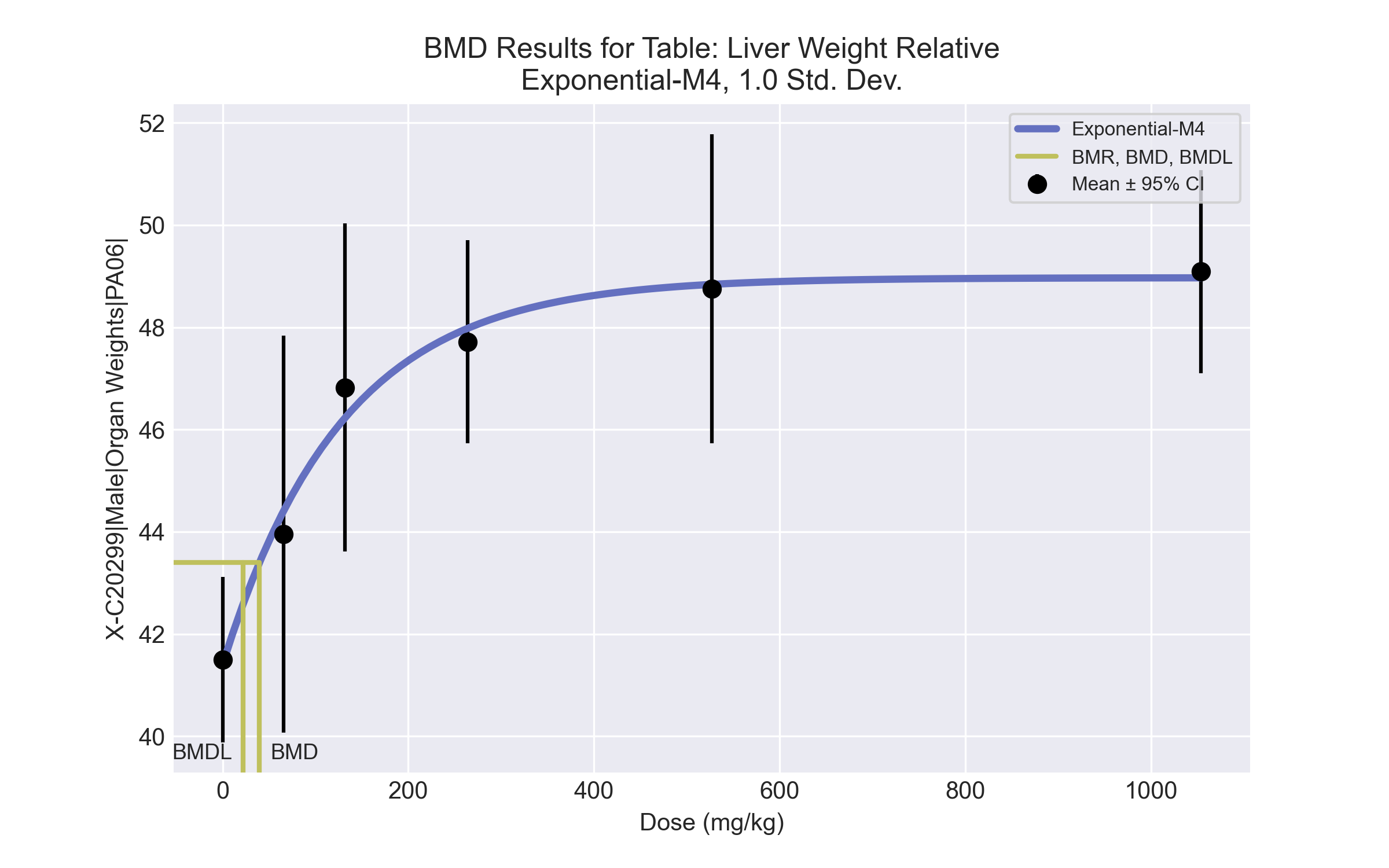
b Recommended model

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear (equivalent models include Power, Polynomial 3°, 4°, 5°) | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.00143 < 0.1)  • Residual at lowest dose is greater than threshold (2.41 > 2.0)  • Ratio of modeled to actual stdev. at control is greater than threshold (2.04 > 1.5) |
| Polynomial 2° | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.00143 < 0.1)  • Residual at lowest dose is greater than threshold (2.41 > 2.0)  • Ratio of modeled to actual stdev. at control is greater than threshold (2.04 > 1.5) |
| Hill | Warning | **Warnings**  • Ratio of modeled to actual stdev. at control is greater than threshold (1.53 > 1.5) |
| Exponential M2 (equivalent models include Exponential M3) | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.00117 < 0.1)  • Residual at lowest dose is greater than threshold (2.46 > 2.0) |
| 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-z8g8ms42.(d)   
 Gnuplot Plotting File:   
 Tue May 18 15:25:52 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 1.3583   
 rho 0 Specified  
 a 39.4234   
 b 0.0019707   
 c 1.30738   
 d 1 Specified  
  
  
  
 Parameter Estimates  
  
 Variable Model 4 Std. Err.  
 -------- ------- ---------  
 lnalpha 1.38643 1.03294  
 a 41.3975 0.859599  
 b 0.00770556 0.00250819  
 c 1.18289 0.0276895  
  
 NC = No Convergence  
  
  
 Table of Stats From Input Data  
  
 Dose N Obs Mean Obs Std Dev  
 ----- --- ---------- -------------  
 0 5 41.5 1.3  
 66 5 43.95 3.128  
 132 5 46.82 2.587  
 264 5 47.72 1.597  
 527 5 48.75 2.43  
 1054 5 49.09 1.597  
  
  
 Estimated Values of Interest  
  
 Dose Est Mean Est Std Scaled Residual  
 ------ ---------- --------- ----------------  
 0 41.4 2 0.1126  
 66 44.42 2 -0.5181  
 132 46.23 2 0.661  
 264 47.98 2 -0.2942  
 527 48.84 2 -0.09631  
 1054 48.97 2 0.135  
  
  
  
 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 -35.37453 7 84.74906  
 A2 -32.54082 12 89.08164  
 A3 -35.37453 7 84.74906  
 R -51.40794 2 106.8159  
 4 -35.79647 4 79.59294  
  
  
 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 37.73 10 < 0.0001  
 Test 2 5.667 5 0.3399  
 Test 3 5.667 5 0.3399  
 Test 6a 0.8439 3 0.8389  
  
  
 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 = 39.8113  
  
 BMDL = 22.359  
  
 BMDU = 84.6062

# BMD Results for Table: A/G Ratio

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 66 | 132 | 264 | 527 | 1054 |
| N | 5 | 5 | 5 | 5 | 5 | 5 |
| Mean ± SD | 1.379 ± 0.076 | 1.413 ± 0.075 | 1.334 ± 0.052 | 1.306 ± 0.039 | 1.243 ± 0.032 | 1.282 ± 0.068 |

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear (equivalent models include Power, Polynomial 2°, 4°) | 0.009 | -126.531 | 588.666 | 383.693 | Hill recommended as best-fitting model on the basis of the lowest AIC. |
| Polynomial 3° | 0.009 | -126.531 | 588.664 | 383.693 |
| Polynomial 5° | 0.009 | -126.531 | 588.667 | 383.693 |
| Hillb | 0.137 | -132.062 | 146.207 | 85.833 |
| Exponential M2 (equivalent models include Exponential M3) | 0.01 | -126.774 | 561.456 | 359.676 |
| Exponential M4 | 0.086 | -131.452 | 124.448 | 60.084 |
| Exponential M5 | 0.128 | -131.925 | 170.603 | 85.166 |

a Constant variance case presented (BMDS Test 2 p-value = 0.348, BMDS Test 3 p-value = 0.348).

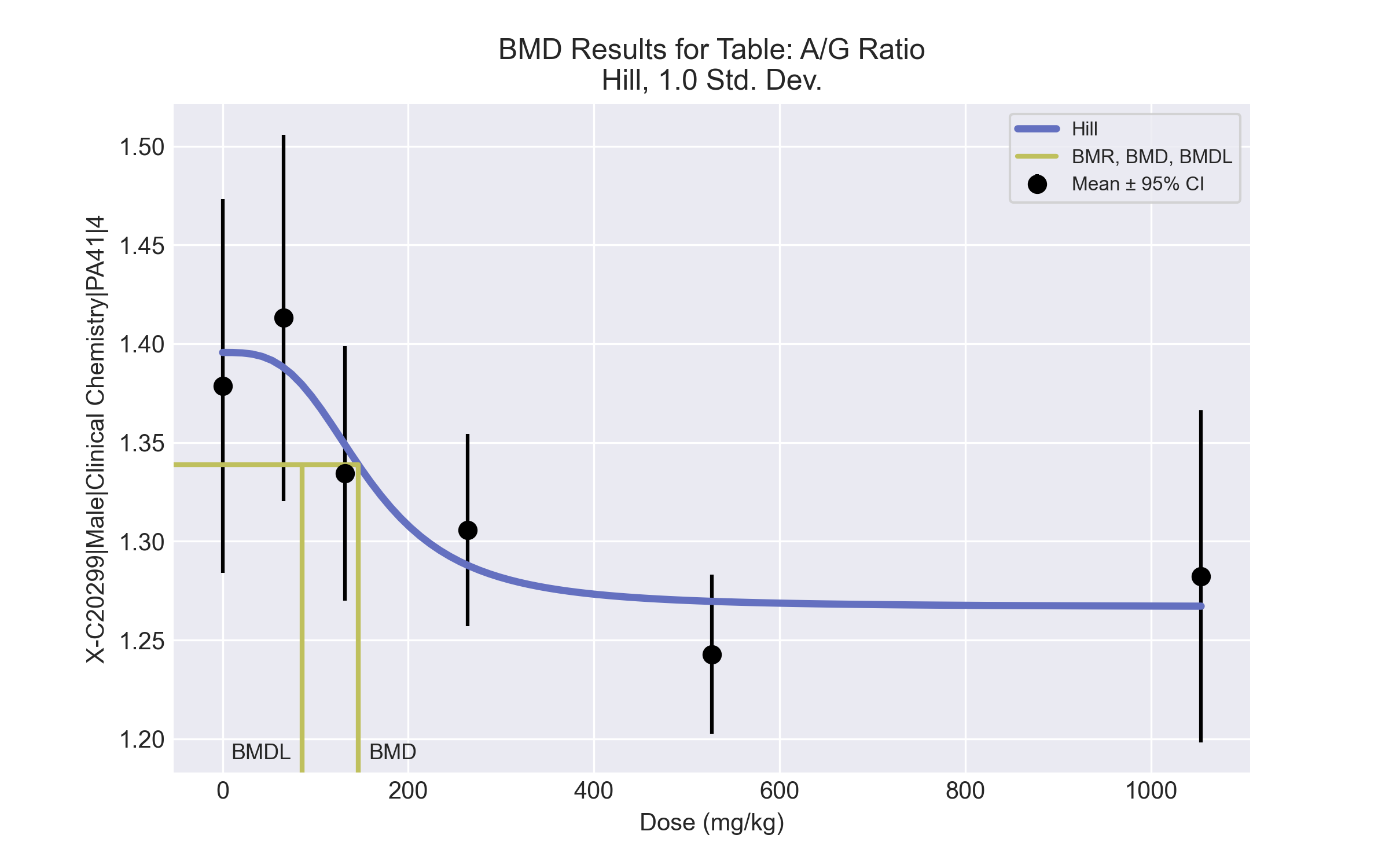
b Recommended model

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear (equivalent models include Power, Polynomial 2°, 4°) | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.00906 < 0.1) |
| Polynomial 3° | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.00906 < 0.1) |
| Polynomial 5° | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.00906 < 0.1) |
| Hilla | Valid | - |
| Exponential M2 (equivalent models include Exponential M3) | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0101 < 0.1) |
| Exponential M4 | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0865 < 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-e92k0nhl.(d)   
 Gnuplot Plotting File: C:\Windows\TEMP\bmds-e92k0nhl.plt  
 Tue May 18 15:27:32 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 = 0.00353629  
 rho = 0 Specified  
 intercept = 1.37858  
 v = -0.13584  
 n = 1.14358  
 k = 240.992  
  
  
 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 intercept v n k  
  
 alpha 1 1.8e-006 -4.4e-007 -6.3e-007 5.3e-007  
  
 intercept 1.8e-006 1 -0.65 -0.072 -0.44  
  
 v -4.4e-007 -0.65 1 0.48 -0.17  
  
 n -6.3e-007 -0.072 0.48 1 -0.49  
  
 k 5.3e-007 -0.44 -0.17 -0.49 1  
  
  
  
 Parameter Estimates  
  
 95.0% Wald Confidence Interval  
 Variable Estimate Std. Err. Lower Conf. Limit Upper Conf. Limit  
 alpha 0.00322957 0.000833871 0.00159521 0.00486393  
 intercept 1.39557 0.0203584 1.35567 1.43547  
 v -0.128748 0.0285522 -0.18471 -0.0727872  
 n 3.16678 1.87971 -0.517385 6.85095  
 k 157.494 59.261 41.345 273.644  
  
  
  
 Table of Data and Estimated Values of Interest  
  
 Dose N Obs Mean Est Mean Obs Std Dev Est Std Dev Scaled Res.  
------ --- -------- -------- ----------- ----------- ----------  
  
 0 5 1.38 1.4 0.0761 0.0568 -0.669  
 66 5 1.41 1.39 0.0747 0.0568 0.996  
 132 5 1.33 1.35 0.052 0.0568 -0.567  
 264 5 1.31 1.29 0.0391 0.0568 0.702  
 527 5 1.24 1.27 0.0324 0.0568 -1.06  
 1054 5 1.28 1.27 0.0676 0.0568 0.594  
  
  
  
 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 73.017307 7 -132.034614  
 A2 75.815103 12 -127.630206  
 A3 73.017307 7 -132.034614  
 fitted 71.031094 5 -132.062188  
 R 61.463529 2 -118.927058  
  
  
 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 28.7031 10 0.001392  
 Test 2 5.59559 5 0.3476  
 Test 3 5.59559 5 0.3476  
 Test 4 3.97243 2 0.1372  
  
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 = 146.207  
  
 BMDL = 85.8333  
  
 BMDU = 296.661

# BMD Results for Table: Bile salts/acids

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 66 | 132 | 264 | 527 | 1054 |
| N | 5 | 5 | 5 | 5 | 5 | 5 |
| Mean ± SD | 57.42 ± 19.77 | 53.86 ± 9.082 | 34.46 ± 9.546 | 40.76 ± 13.985 | 32.34 ± 12.625 | 32.14 ± 9.553 |

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear (equivalent models include Polynomial 2°, 4°) | 0.043 | 192.947 | 684.501 | 425.744 | Hill recommended as best-fitting model on the basis of the lowest AIC. |
| Power (equivalent models include Polynomial 3°, 5°) | 0.043 | 192.947 | 684.5 | 425.744 |
| Hillb | 0.625 | 186.86 | 72.929 | 49.692 |
| Exponential M2 (equivalent models include Exponential M3) | 0.065 | 191.968 | 517.109 | 272.333 |
| Exponential M4 | 0.269 | 189.036 | 86.639 | 31.433 |
| Exponential M5 | 0.416 | 188.86 | 81.985 | 52.948 |

a Constant variance case presented (BMDS Test 2 p-value = 0.413, BMDS Test 3 p-value = 0.413).

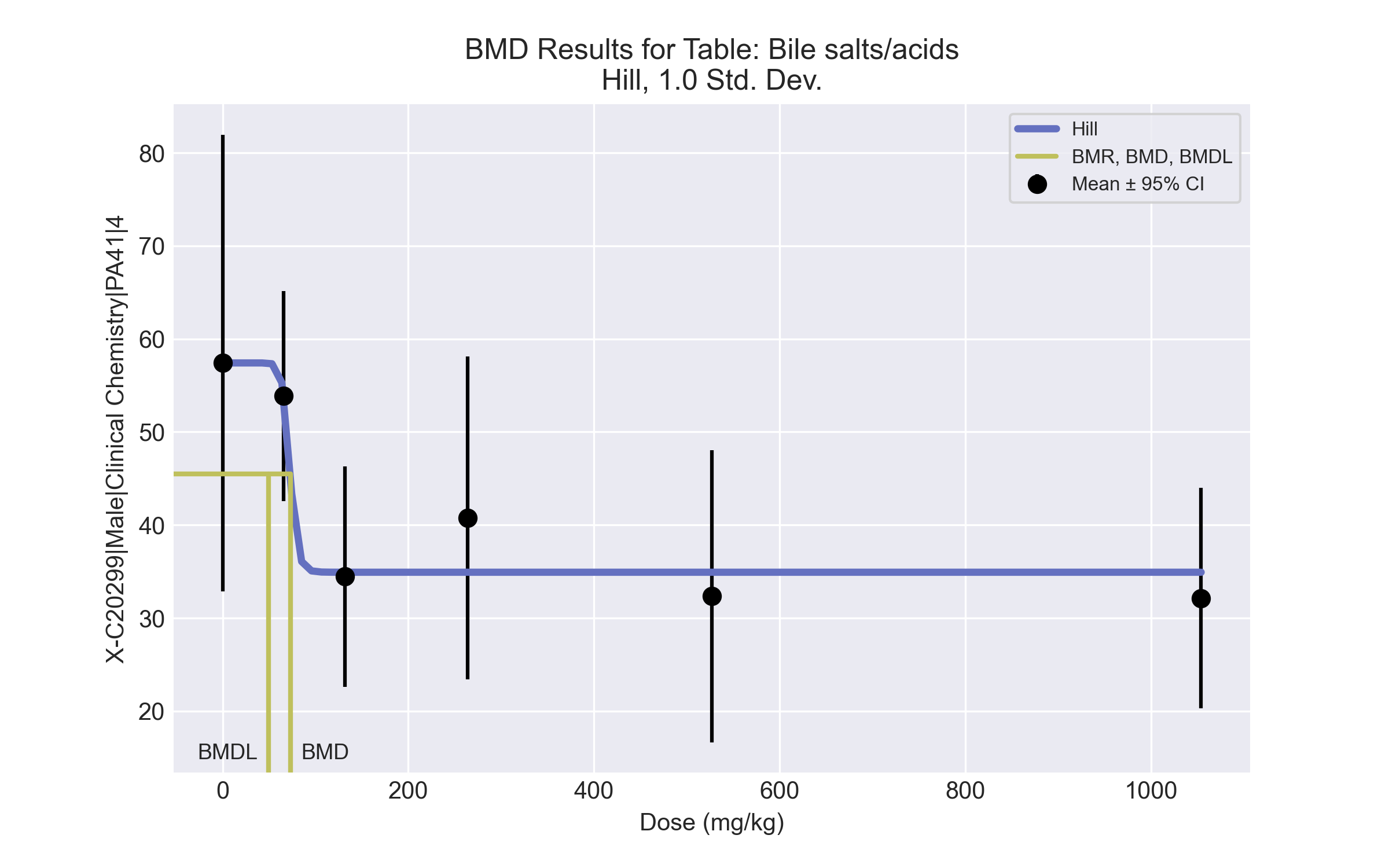
b Recommended model

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear (equivalent models include Polynomial 2°, 4°) | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0432 < 0.1) |
| Power (equivalent models include Polynomial 3°, 5°) | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0432 < 0.1) |
| Hilla | Valid | - |
| Exponential M2 (equivalent models include Exponential M3) | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0646 < 0.1) |
| Exponential M4 | Valid | - |
| Exponential M5 | Valid | - |

a Recommended model

## Recommended model



====================================================================   
 Hill Model. (Version: 2.18; Date: 03/14/2017)   
 Input Data File: C:\Windows\TEMP\bmds-eehn2o5v.(d)   
 Gnuplot Plotting File: C:\Windows\TEMP\bmds-eehn2o5v.plt  
 Tue May 18 15:27:36 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 = 168.454  
 rho = 0 Specified  
 intercept = 57.42  
 v = -25.28  
 n = 3.90836  
 k = 96.8907  
  
  
 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 -2e-006 1.7e-006 1.4e-006  
  
 intercept -2e-006 1 -0.89 -0.64  
  
 v 1.7e-006 -0.89 1 0.55  
  
 k 1.4e-006 -0.64 0.55 1  
  
  
  
 Parameter Estimates  
  
 95.0% Wald Confidence Interval  
 Variable Estimate Std. Err. Lower Conf. Limit Upper Conf. Limit  
 alpha 142.881 36.8917 70.5744 215.187  
 intercept 57.42 5.34559 46.9428 67.8972  
 v -22.4951 5.97646 -34.2088 -10.7815  
 n 18 NA  
 k 72.4213 9.39835 54.0009 90.8418  
  
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 57.4 57.4 19.8 12 -1.74e-006  
 66 5 53.9 53.9 9.08 12 1.25e-005  
 132 5 34.5 34.9 9.55 12 -0.0871  
 264 5 40.8 34.9 14 12 1.09  
 527 5 32.3 34.9 12.6 12 -0.484  
 1054 5 32.1 34.9 9.55 12 -0.521  
  
  
  
 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 -88.552832 7 191.105664  
 A2 -86.039153 12 196.078306  
 A3 -88.552832 7 191.105664  
 fitted -89.430145 4 186.860290  
 R -97.165442 2 198.330884  
  
  
 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 22.2526 10 0.01387  
 Test 2 5.02736 5 0.4126  
 Test 3 5.02736 5 0.4126  
 Test 4 1.75463 3 0.6249  
  
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 = 72.9287  
  
 BMDL = 49.692  
  
  
BMDU computation failed.

# BMD Results for Table: Cholesterol

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 66 | 132 | 264 | 527 | 1054 |
| N | 5 | 5 | 5 | 5 | 5 | 5 |
| Mean ± SD | 101 ± 12.865 | 105.6 ± 10.237 | 111.2 ± 13.918 | 122.2 ± 8.044 | 142.2 ± 5.675 | 146.4 ± 14.588 |

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear (equivalent models include Power, Polynomial 2°, 3°, 4°, 5°) | 0.032 | 185.634 | 270.887 | 206.34 | Exponential-M4 recommended as best-fitting model on the basis of the lowest AIC. |
| Hill | 0.703 | 179.794 | 156.037 | 63.905 |
| Exponential M2 (equivalent models include Exponential M3) | 0.013 | 187.683 | 331.261 | 258.661 |
| Exponential M4b | 0.59 | 179.006 | 89.302 | 55.89 |
| Exponential M5 | 0.881 | 179.343 | 150.58 | 66.028 |

a Constant variance case presented (BMDS Test 2 p-value = 0.343, BMDS Test 3 p-value = 0.343).

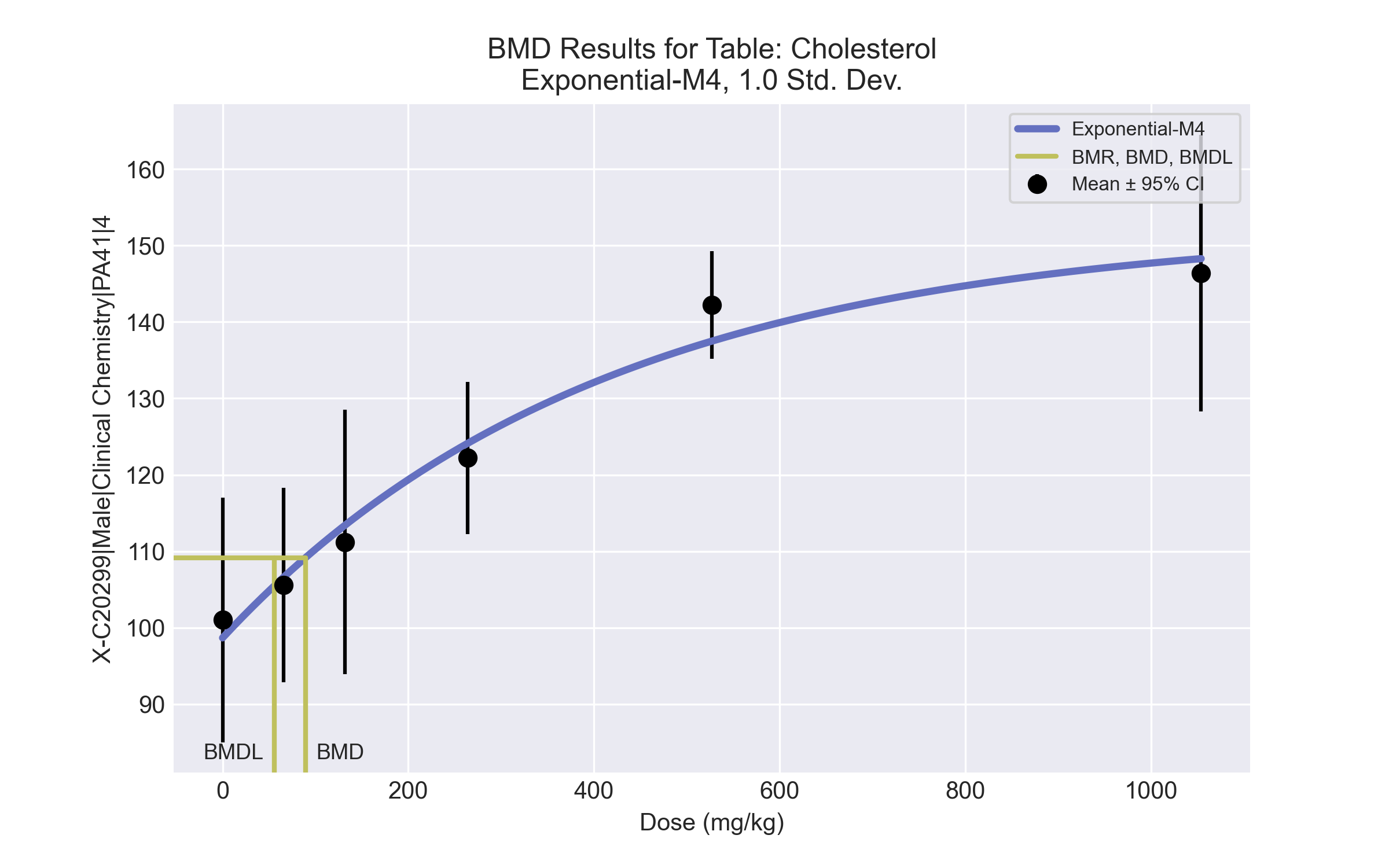
b Recommended model

## 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 (0.0322 < 0.1) |
| Hill | Valid | - |
| Exponential M2 (equivalent models include Exponential M3) | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0134 < 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-23av62sc.(d)   
 Gnuplot Plotting File:   
 Tue May 18 15:27:39 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 4.63628   
 rho 0 Specified  
 a 95.95   
 b 0.00218874   
 c 1.60208   
 d 1 Specified  
  
  
  
 Parameter Estimates  
  
 Variable Model 4 Std. Err.  
 -------- ------- ---------  
 lnalpha 4.70019 28.3935  
 a 98.6658 3.75754  
 b 0.00242966 0.000847307  
 c 1.54491 0.0828219  
  
 NC = No Convergence  
  
  
 Table of Stats From Input Data  
  
 Dose N Obs Mean Obs Std Dev  
 ----- --- ---------- -------------  
 0 5 101 12.86  
 66 5 105.6 10.24  
 132 5 111.2 13.92  
 264 5 122.2 8.044  
 527 5 142.2 5.675  
 1054 5 146.4 14.59  
  
  
 Estimated Values of Interest  
  
 Dose Est Mean Est Std Scaled Residual  
 ------ ---------- --------- ----------------  
 0 98.67 10.49 0.4977  
 66 106.6 10.49 -0.22  
 132 113.4 10.49 -0.4727  
 264 124.1 10.49 -0.4096  
 527 137.5 10.49 1.005  
 1054 148.3 10.49 -0.4002  
  
  
  
 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 -84.54422 7 183.0884  
 A2 -81.72639 12 187.4528  
 A3 -84.54422 7 183.0884  
 R -105.1633 2 214.3267  
 4 -85.5028 4 179.0056  
  
  
 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 46.87 10 < 0.0001  
 Test 2 5.636 5 0.3433  
 Test 3 5.636 5 0.3433  
 Test 6a 1.917 3 0.5898  
  
  
 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 = 89.3018  
  
 BMDL = 55.89  
  
 BMDU = 163.285

# BMD Results for Table: Globulin

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 66 | 132 | 264 | 527 | 1054 |
| N | 5 | 5 | 5 | 5 | 5 | 5 |
| Mean ± SD | 2.5 ± 0.158 | 2.44 ± 0.167 | 2.58 ± 0.084 | 2.56 ± 0.152 | 2.72 ± 0.084 | 2.66 ± 0.207 |

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear (equivalent models include Power, Polynomial 2°, 3°, 4°, 5°) | 0.2 | -78.982 | 767.531 | 458.874 | Exponential-M4 recommended as best-fitting model on the basis of the lowest BMDL. |
| Hill | 0.216 | -77.904 | 293.529 | -999 |
| Exponential M2 (equivalent models include Exponential M3) | 0.193 | -78.888 | 787.682 | 480.461 |
| Exponential M4b | 0.301 | -79.309 | 278.025 | 89.601 |
| Exponential M5 | 0.248 | -78.179 | 324.082 | 107.695 |

a Constant variance case presented (BMDS Test 2 p-value = 0.282, BMDS Test 3 p-value = 0.282).

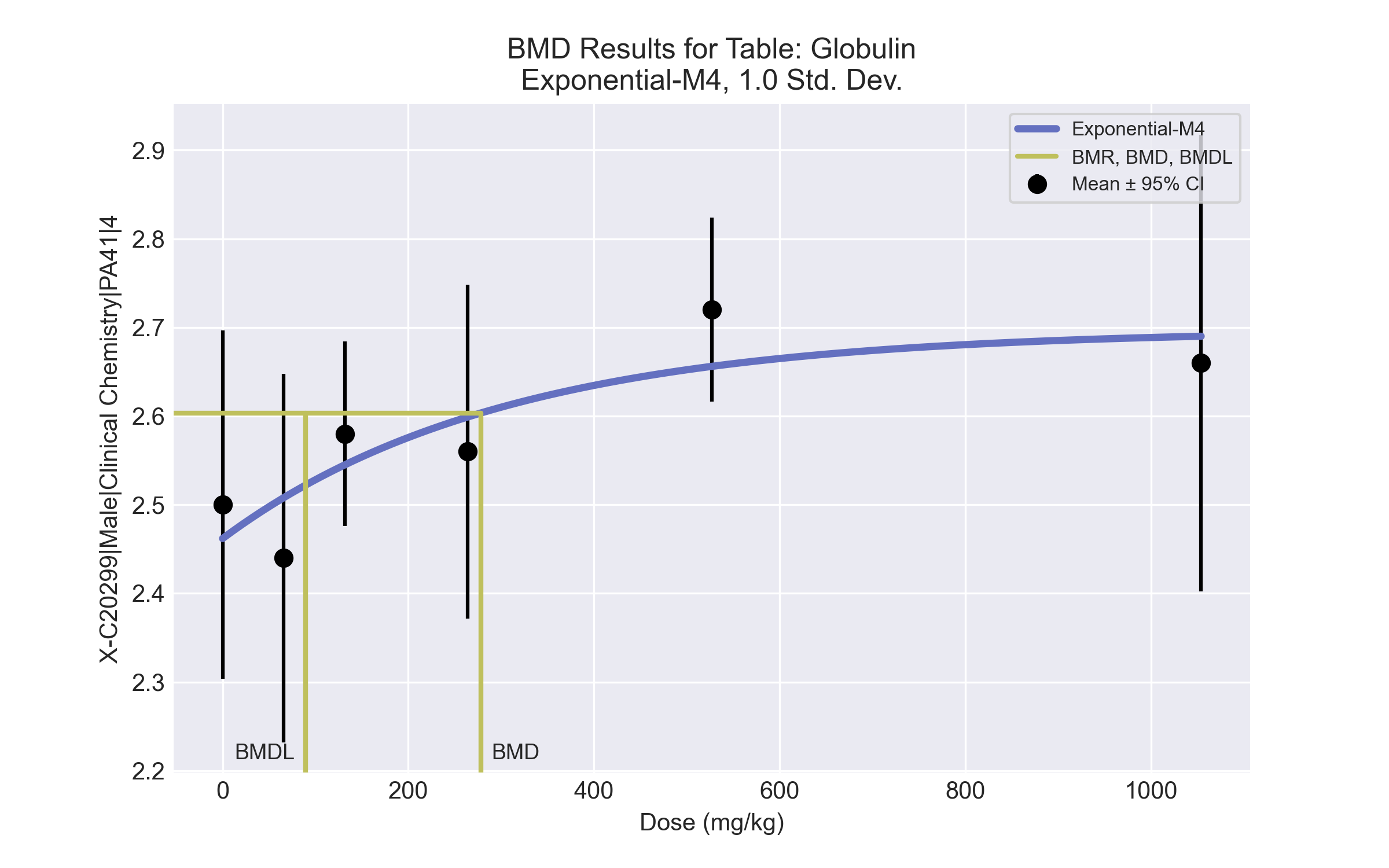
b Recommended model

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear (equivalent models include Power, Polynomial 2°, 3°, 4°, 5°) | Valid | - |
| Hill | Failure | **Failures**  • BMDL does not exist  **Cautions**  • Warning(s): BMDL computation failed. |
| 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-rkqlzbvy.(d)   
 Gnuplot Plotting File:   
 Tue May 18 15:27:41 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 -4.03231   
 rho 0 Specified  
 a 2.318   
 b 0.00138625   
 c 1.2321   
 d 1 Specified  
  
  
  
 Parameter Estimates  
  
 Variable Model 4 Std. Err.  
 -------- ------- ---------  
 lnalpha -3.91031 0.00517281  
 a 2.46186 0.051  
 b 0.00330866 0.00245628  
 c 1.09559 0.0335809  
  
 NC = No Convergence  
  
  
 Table of Stats From Input Data  
  
 Dose N Obs Mean Obs Std Dev  
 ----- --- ---------- -------------  
 0 5 2.5 0.1581  
 66 5 2.44 0.1673  
 132 5 2.58 0.08367  
 264 5 2.56 0.1517  
 527 5 2.72 0.08367  
 1054 5 2.66 0.2074  
  
  
 Estimated Values of Interest  
  
 Dose Est Mean Est Std Scaled Residual  
 ------ ---------- --------- ----------------  
 0 2.462 0.1415 0.6026  
 66 2.508 0.1415 -1.075  
 132 2.545 0.1415 0.5508  
 264 2.599 0.1415 -0.6152  
 527 2.656 0.1415 1.01  
 1054 2.69 0.1415 -0.4739  
  
  
  
 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 45.48464 7 -76.96927  
 A2 48.61449 12 -73.22897  
 A3 45.48464 7 -76.96927  
 R 39.48434 2 -74.96867  
 4 43.65472 4 -79.30945  
  
  
 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 18.26 10 0.05073  
 Test 2 6.26 5 0.2818  
 Test 3 6.26 5 0.2818  
 Test 6a 3.66 3 0.3006  
  
  
 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 = 278.025  
  
 BMDL = 89.6012  
  
 BMDU = 1.054e+007

# BMD Results for Table: HDL Cholesterol

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 66 | 132 | 264 | 527 | 1054 |
| N | 5 | 5 | 5 | 5 | 5 | 5 |
| Mean ± SD | 46 ± 6.442 | 50 ± 5.148 | 51.8 ± 5.675 | 54 ± 4.359 | 64.8 ± 3.701 | 69.8 ± 9.365 |

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear (equivalent models include Power, Polynomial 2°, 3°, 4°, 5°) | 0.286 | 142.451 | 263.252 | 201.211 | Hill recommended as best-fitting model on the basis of the lowest BMDL. |
| Hillb | 0.442 | 143.076 | 161.652 | 68.114 |
| Exponential M2 (equivalent models include Exponential M3) | 0.161 | 144.007 | 320.194 | 251.617 |
| Exponential M4 | 0.658 | 141.051 | 131.165 | 76.77 |
| Exponential M5 | 0.497 | 142.84 | 177.765 | 78.288 |

a Constant variance case presented (BMDS Test 2 p-value = 0.349, BMDS Test 3 p-value = 0.349).

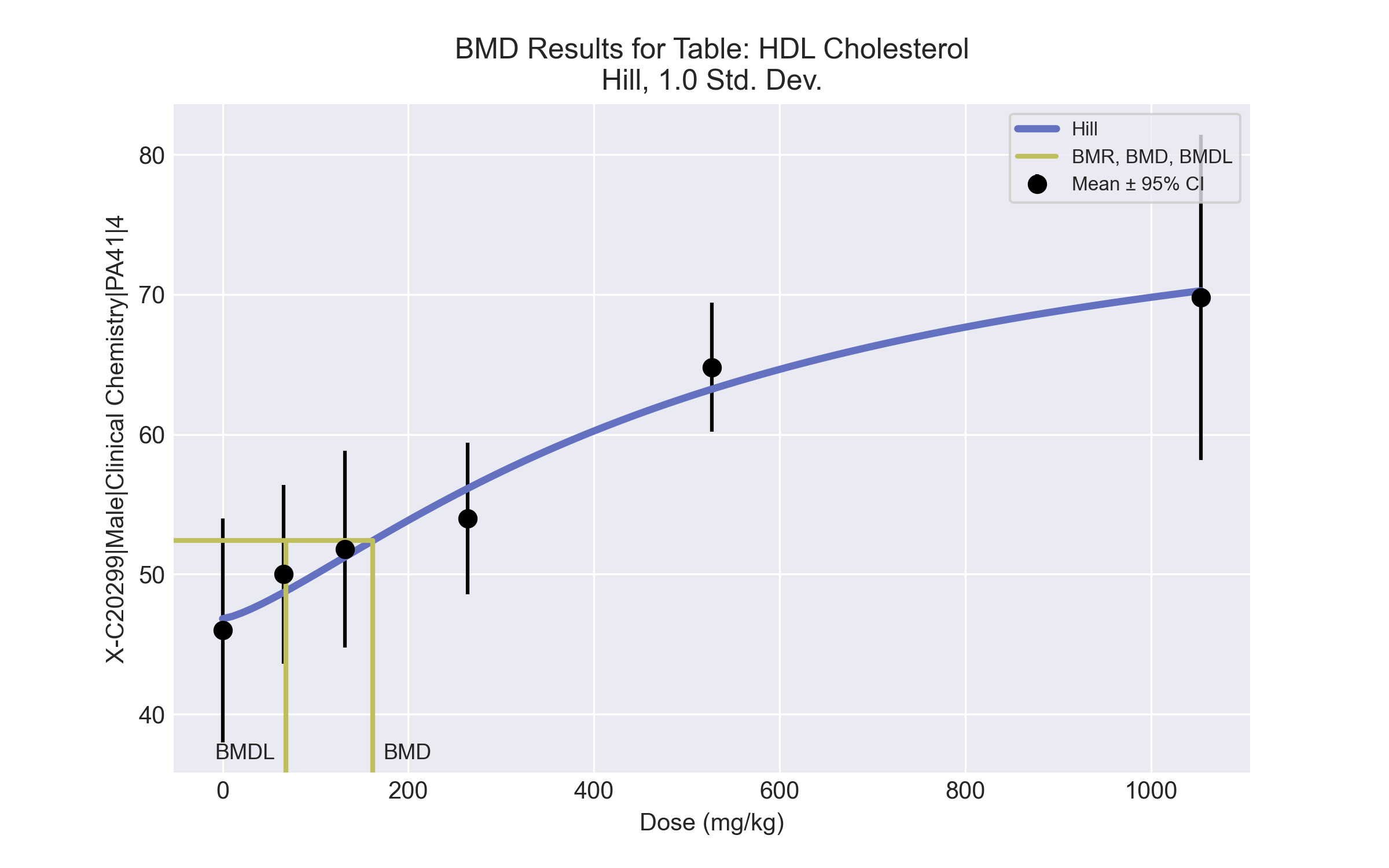
b Recommended model

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear (equivalent models include Power, Polynomial 2°, 3°, 4°, 5°) | Valid | - |
| Hilla | Valid | - |
| Exponential M2 (equivalent models include Exponential M3) | Valid | - |
| Exponential M4 | Valid | - |
| Exponential M5 | Valid | - |

a Recommended model

## Recommended model



====================================================================   
 Hill Model. (Version: 2.18; Date: 03/14/2017)   
 Input Data File: C:\Windows\TEMP\bmds-n9d6krck.(d)   
 Gnuplot Plotting File: C:\Windows\TEMP\bmds-n9d6krck.plt  
 Tue May 18 15:27:46 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 = 36.7667  
 rho = 0 Specified  
 intercept = 46  
 v = 23.8  
 n = 0.516044  
 k = 695.028  
  
  
 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 intercept v n k  
  
 alpha 1 -1.1e-006 1.8e-006 -1.5e-006 2e-006  
  
 intercept -1.1e-006 1 -0.72 0.78 -0.55  
  
 v 1.8e-006 -0.72 1 -0.96 0.97  
  
 n -1.5e-006 0.78 -0.96 1 -0.91  
  
 k 2e-006 -0.55 0.97 -0.91 1  
  
  
  
 Parameter Estimates  
  
 95.0% Wald Confidence Interval  
 Variable Estimate Std. Err. Lower Conf. Limit Upper Conf. Limit  
 alpha 31.0585 8.01926 15.341 46.7759  
 intercept 46.8229 2.98722 40.9681 52.6778  
 v 32.3741 24.1669 -14.9921 79.7402  
 n 1.35197 1.17244 -0.945976 3.64991  
 k 516.506 560.725 -582.495 1615.51  
  
  
  
 Table of Data and Estimated Values of Interest  
  
 Dose N Obs Mean Est Mean Obs Std Dev Est Std Dev Scaled Res.  
------ --- -------- -------- ----------- ----------- ----------  
  
 0 5 46 46.8 6.44 5.57 -0.33  
 66 5 50 48.7 5.15 5.57 0.517  
 132 5 51.8 51.2 5.67 5.57 0.224  
 264 5 54 56.1 4.36 5.57 -0.855  
 527 5 64.8 63.2 3.7 5.57 0.63  
 1054 5 69.8 70.3 9.36 5.57 -0.185  
  
  
  
 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 -65.721721 7 145.443442  
 A2 -62.929249 12 149.858499  
 A3 -65.721721 7 145.443442  
 fitted -66.538066 5 143.076133  
 R -84.126805 2 172.253610  
  
  
 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 42.3951 10 <.0001  
 Test 2 5.58494 5 0.3487  
 Test 3 5.58494 5 0.3487  
 Test 4 1.63269 2 0.442  
  
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 = 161.652  
  
 BMDL = 68.1144  
  
 BMDU = 380.332

# BMD Results for Table: Cholinesterase

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 66 | 132 | 264 | 527 | 1054a |
| N | 5 | 5 | 5 | 5 | 5 | 5 |
| Mean ± SD | 277.4 ± 37.092 | 201 ± 13.285 | 172.4 ± 17.799 | 148.4 ± 19.36 | 141.2 ± 9.365 | 110.2 ± 21.822 |

a Dose group removed in BMD modeling session

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear (equivalent models include Power, Polynomial 3°) | <0.0001 | 200.701 | 497.837 | 280.799 | Exponential-M4 recommended as best-fitting model on the basis of the lowest AIC. |
| Polynomial 2° (equivalent models include Polynomial 4°, 5°) | <0.0001 | 200.701 | 497.838 | 280.799 |
| Hill | 0.738 | 178.239 | 20.125 | -999 |
| Exponential M2 (equivalent models include Exponential M3) | <0.0001 | 198.952 | 427.482 | 200.187 |
| Exponential M4b (equivalent models include Exponential M5) | 0.761 | 176.673 | 21.291 | 12.337 |

a Modeled variance case presented (BMDS Test 2 p-value = 0.029, BMDS Test 3 p-value = 0.271).

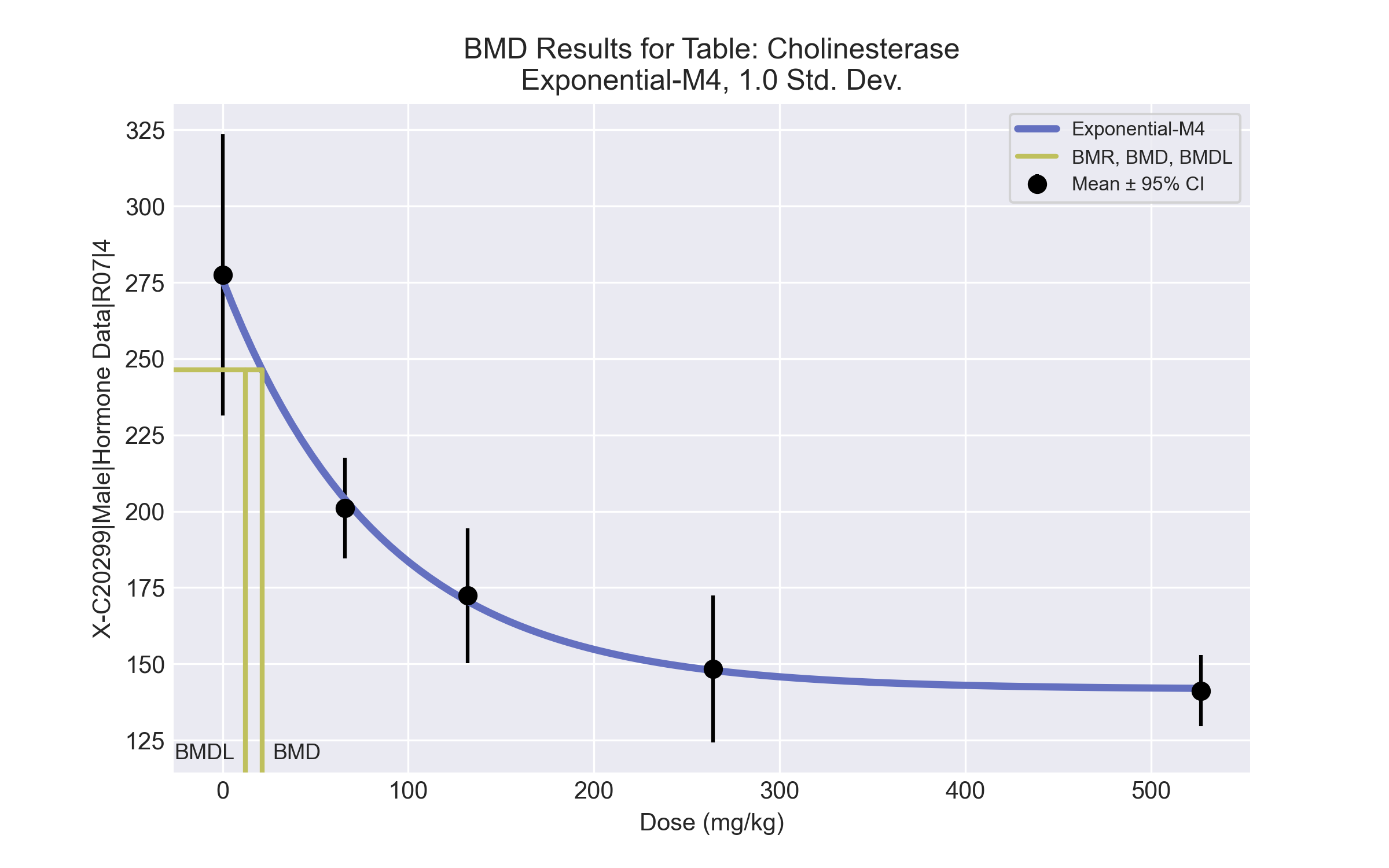
b Recommended model

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear (equivalent models include Power, Polynomial 3°) | Warning | **Warnings**  • Residual at lowest dose is greater than threshold (3.01 > 2.0)  • Ratio of modeled to actual stdev. at control is greater than threshold (1.54 > 1.5) |
| Polynomial 2° (equivalent models include Polynomial 4°, 5°) | Warning | **Warnings**  • Residual at lowest dose is greater than threshold (3.01 > 2.0)  • Ratio of modeled to actual stdev. at control is greater than threshold (1.54 > 1.5) |
| Hill | Failure | **Failures**  • BMDL does not exist  **Cautions**  • Warning(s): BMDL computation failed.  • Minimum dose/BMD ratio is greater than threshold (3.28 > 3.0) |
| Exponential M2 (equivalent models include Exponential M3) | Warning | **Warnings**  • Residual at lowest dose is greater than threshold (2.88 > 2.0) |
| Exponential M4a (equivalent models include Exponential M5) | Valid | **Cautions**  • Minimum dose/BMD ratio is greater than threshold (3.1 > 3.0) |

a Recommended model

## Recommended model



====================================================================   
 Exponential Model. (Version: 1.11; Date: 03/14/2017)   
 Input Data File: C:\Windows\TEMP\bmds-2m6nsg\_1.(d)   
 Gnuplot Plotting File:   
 Tue May 18 15:28:33 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]))  
 The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) \* rho)  
  
 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 -9.26382   
 rho 2.87674   
 a 291.27   
 b 0.00688734   
 c 0.461689   
 d 1 Specified  
  
  
  
 Parameter Estimates  
  
 Variable Model 4 Std. Err.  
 -------- ------- ---------  
 lnalpha -8.16635 5.86558  
 rho 2.65733 1.12578  
 a 275.873 12.7729  
 b 0.0116554 0.00213413  
 c 0.513672 0.027418  
  
 NC = No Convergence  
  
  
 Table of Stats From Input Data  
  
 Dose N Obs Mean Obs Std Dev  
 ----- --- ---------- -------------  
 0 5 277.4 37.09  
 66 5 201 13.29  
 132 5 172.4 17.8  
 264 5 148.4 19.36  
 527 5 141.2 9.365  
  
  
 Estimated Values of Interest  
  
 Dose Est Mean Est Std Scaled Residual  
 ------ ---------- --------- ----------------  
 0 275.9 29.48 0.1158  
 66 203.9 19.73 -0.3258  
 132 170.5 15.56 0.2711  
 264 147.9 12.88 0.08808  
 527 142 12.2 -0.146  
  
  
  
 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 -86.52161 6 185.0432  
 A2 -81.10745 10 182.2149  
 A3 -83.06319 7 180.1264  
 R -111.7425 2 227.485  
 4 -83.33651 5 176.673  
  
  
 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 61.27 8 < 0.0001  
 Test 2 10.83 4 0.02856  
 Test 3 3.911 3 0.2712  
 Test 6a 0.5466 2 0.7608  
  
  
 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 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 = 21.2905  
  
 BMDL = 12.3373  
  
 BMDU = 46.9321

# BMD Results for Table: Total Thyroxine

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 66 | 132 | 264 | 527 | 1054 |
| N | 5 | 5 | 5 | 5 | 5 | 5 |
| Mean ± SD | 5.122 ± 0.507 | 4.45 ± 0.465 | 4.228 ± 0.504 | 3.638 ± 0.978 | 4.21 ± 0.612 | 3.312 ± 0.801 |

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear (equivalent models include Power, Polynomial 2°, 3°, 4°, 5°) | 0.053 | 14.715 | 563.072 | 371.695 | Hill recommended as best-fitting model on the basis of the lowest AIC. |
| Hillb | 0.165 | 12.449 | 67.016 | 15.613 |
| Exponential M2 (equivalent models include Exponential M3) | 0.06 | 14.402 | 500.175 | 306.505 |
| Exponential M4 | 0.131 | 12.982 | 70.584 | 25.208 |
| Exponential M5 | 0.131 | 12.982 | 70.584 | 25.208 |

a Constant variance case presented (BMDS Test 2 p-value = 0.453, BMDS Test 3 p-value = 0.453).

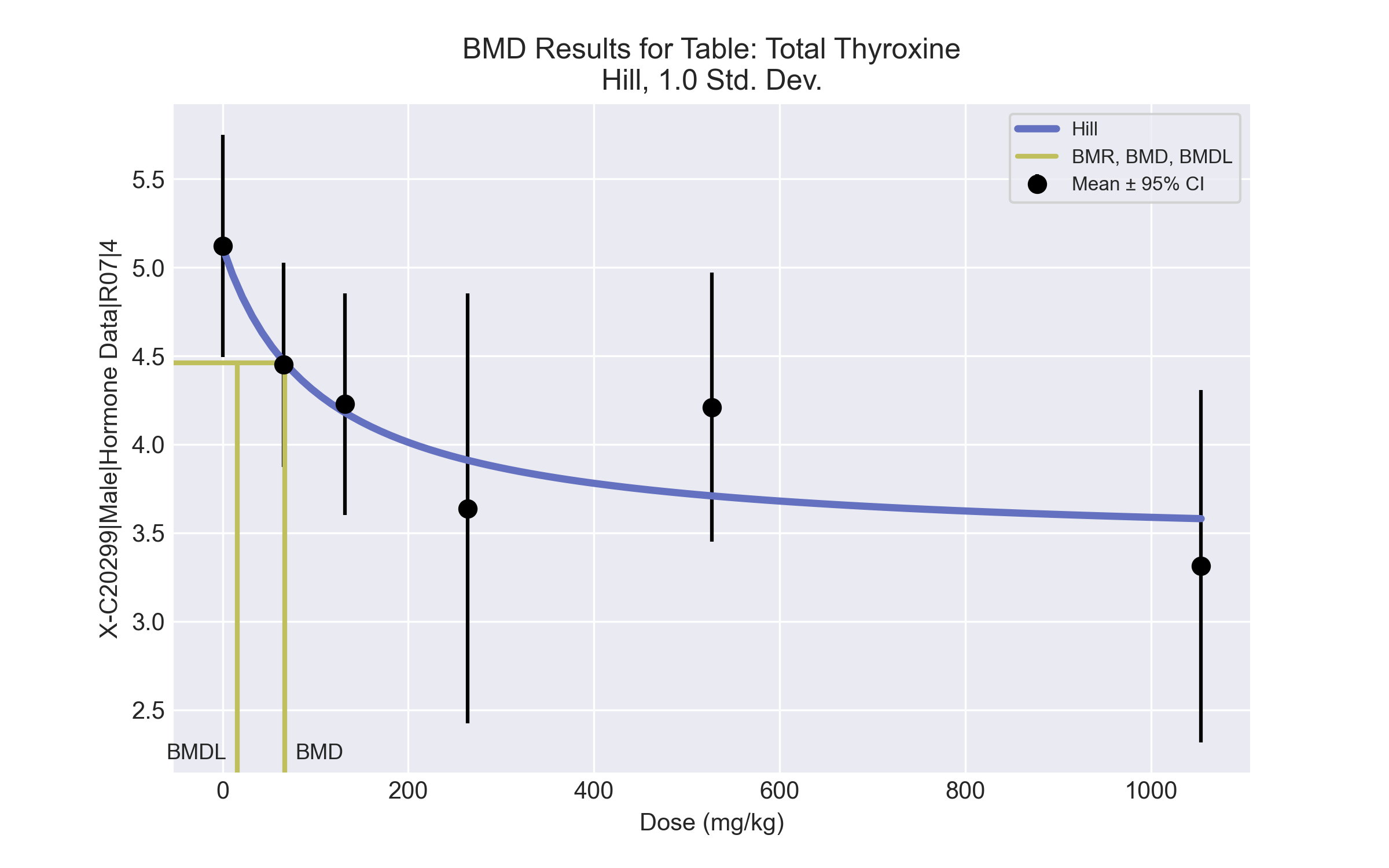
b Recommended model

## 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 (0.0527 < 0.1) |
| Hilla | Valid | - |
| Exponential M2 (equivalent models include Exponential M3) | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0599 < 0.1) |
| Exponential M4 | Valid | - |
| Exponential M5 | Valid | - |

a Recommended model

## Recommended model



====================================================================   
 Hill Model. (Version: 2.18; Date: 03/14/2017)   
 Input Data File: C:\Windows\TEMP\bmds-jhpl8sxy.(d)   
 Gnuplot Plotting File: C:\Windows\TEMP\bmds-jhpl8sxy.plt  
 Tue May 18 15:28:38 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 = 0.450046  
 rho = 0 Specified  
 intercept = 5.122  
 v = -1.81  
 n = 1.07851  
 k = 134.461  
  
  
 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 2.8e-006 -2.4e-006 -6.3e-007  
  
 intercept 2.8e-006 1 -0.54 -0.52  
  
 v -2.4e-006 -0.54 1 -0.32  
  
 k -6.3e-007 -0.52 -0.32 1  
  
  
  
 Parameter Estimates  
  
 95.0% Wald Confidence Interval  
 Variable Estimate Std. Err. Lower Conf. Limit Upper Conf. Limit  
 alpha 0.426686 0.11017 0.210758 0.642615  
 intercept 5.11457 0.292247 4.54178 5.68737  
 v -1.68926 0.411297 -2.49539 -0.883133  
 n 1 NA  
 k 106.293 93.8395 -77.6288 290.215  
  
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 5.12 5.11 0.507 0.653 0.0254  
 66 5 4.45 4.47 0.465 0.653 -0.0598  
 132 5 4.23 4.18 0.504 0.653 0.168  
 264 5 3.64 3.91 0.978 0.653 -0.932  
 527 5 4.21 3.71 0.612 0.653 1.72  
 1054 5 3.31 3.58 0.801 0.653 -0.918  
  
  
  
 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 0.323220 7 13.353561  
 A2 2.675191 12 18.649618  
 A3 0.323220 7 13.353561  
 fitted -2.224432 4 12.448863  
 R -9.536877 2 23.073753  
  
  
 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 24.4241 10 0.006551  
 Test 2 4.70394 5 0.4531  
 Test 3 4.70394 5 0.4531  
 Test 4 5.0953 3 0.165  
  
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 = 67.0162  
  
 BMDL = 15.6129  
  
 BMDU = 377.196