# BMD Results for Table: Body Weight SD4

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 61 | 123 | 245 | 489 | 979 |
| N | 4 | 3 | 4 | 5 | 4 | 3 |
| Mean ± SD | 272.225 ± 0.806 | 275.5 ± 11.964 | 274.05 ± 15.57 | 270.22 ± 13.723 | 247.125 ± 13.411 | 258 ± 9.042 |

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear (equivalent models include Power, Polynomial 2°, 3°, 4°, 5°) | 0.099 | 146.364 | 336.228 | 160.857 | No model was recommended as a best-fitting model. Doses were dropped until there were only 3 remaining dose-groups. |
| Hill | 0.599 | 142.445 | 265.544 | -999 |
| Exponential M2 | 0.106 | 146.193 | 320.936 | 152.931 |
| Exponential M3 | 0.106 | 146.193 | 320.937 | 152.931 |
| Exponential M4 | 0.115 | 146.504 | 167.838 | 0.255 |
| Exponential M5 | 0.392 | 144.445 | 299.221 | 180.129 |

a Modeled variance case presented (BMDS Test 2 p-value = 0.002, BMDS Test 3 p-value = 6.9E-04).

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear (equivalent models include Power, Polynomial 2°, 3°, 4°, 5°) | Warning | **Warnings**  • Variance model poorly fits dataset (p-value 3 = 0.000694)  • Goodness of fit p-value is less than threshold (0.0994 < 0.1)  • Ratio of modeled to actual stdev. at control is greater than threshold (12.3 > 1.5) |
| Hill | Failure | **Failures**  • BMDL does not exist  **Warnings**  • Variance model poorly fits dataset (p-value 3 = 0.000694)  • Ratio of modeled to actual stdev. at control is greater than threshold (12.9 > 1.5)  **Cautions**  • Warning(s): BMDL computation failed. |
| Exponential M2 | Warning | **Warnings**  • Variance model poorly fits dataset (p-value 3 = 0.000694) |
| Exponential M3 | Warning | **Warnings**  • Variance model poorly fits dataset (p-value 3 = 0.000694) |
| Exponential M4 | Warning | **Warnings**  • Variance model poorly fits dataset (p-value 3 = 0.000694)  • BMD/BMDL ratio is greater than threshold (6.58e+02 > 20.0)  **Cautions**  • BMD/BMDL ratio is greater than threshold (6.58e+02 > 5.0) |
| Exponential M5 | Warning | **Warnings**  • Variance model poorly fits dataset (p-value 3 = 0.000694) |

## Recommended model

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

# BMD Results for Table: Brain Weight Relative

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 61 | 123 | 245 | 489 | 979 |
| N | 4 | 3 | 4 | 5 | 4 | 3 |
| Mean ± SD | 6.144 ± 0.525 | 6.529 ± 0.19 | 6.436 ± 0.4 | 6.637 ± 0.363 | 7.186 ± 0.458 | 6.763 ± 0.288 |

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear (equivalent models include Power, Polynomial 2°, 5°) | 0.046 | -10.578 | 627.657 | 361.024 | Exponential-M4 recommended as best-fitting model on the basis of the lowest AIC. |
| Polynomial 3° | 0.046 | -10.578 | 627.656 | 361.024 |
| Polynomial 4° | 0.046 | -10.578 | 627.655 | 361.024 |
| Hill | 0.08 | -11.212 | 143.406 | 20.625 |
| Exponential M2 (equivalent models include Exponential M3) | 0.043 | -10.409 | 659.486 | 388.258 |
| Exponential M4b | 0.199 | -13.613 | 123.685 | 43.317 |
| Exponential M5 | 0.111 | -11.864 | 231.716 | 45.976 |

a Constant variance case presented (BMDS Test 2 p-value = 0.542, BMDS Test 3 p-value = 0.542).

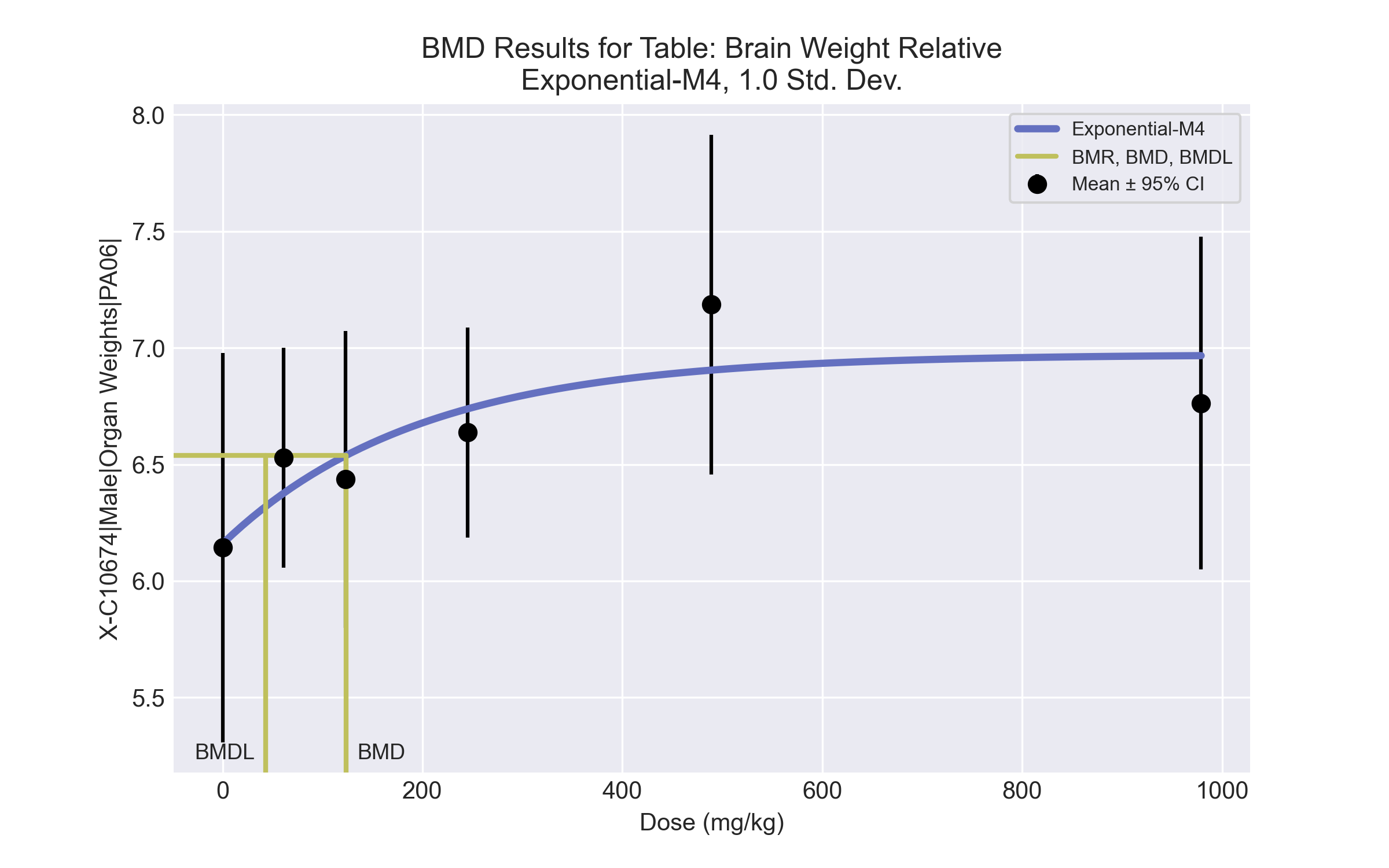
b Recommended model

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear (equivalent models include Power, Polynomial 2°, 5°) | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.046 < 0.1)  • Residual of interest is greater than threshold (2.09 > 2.0) |
| Polynomial 3° | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.046 < 0.1)  • Residual of interest is greater than threshold (2.09 > 2.0) |
| Polynomial 4° | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.046 < 0.1)  • Residual of interest is greater than threshold (2.09 > 2.0) |
| Hill | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0798 < 0.1)  **Cautions**  • BMD/BMDL ratio is greater than threshold (6.95 > 5.0) |
| Exponential M2 (equivalent models include Exponential M3) | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0429 < 0.1)  • Residual of interest is greater than threshold (2.12 > 2.0) |
| Exponential M4a | Valid | - |
| Exponential M5 | Valid | **Cautions**  • BMD/BMDL ratio is greater than threshold (5.04 > 5.0) |

a Recommended model

## Recommended model



====================================================================   
 Exponential Model. (Version: 1.11; Date: 03/14/2017)   
 Input Data File: C:\Windows\TEMP\bmds-rk\_y4odd.(d)   
 Gnuplot Plotting File:   
 Thu Jul 15 23:22:12 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 -2.14206   
 rho 0 Specified  
 a 5.8365   
 b 0.00138397   
 c 1.29286   
 d 1 Specified  
  
  
  
 Parameter Estimates  
  
 Variable Model 4 Std. Err.  
 -------- ------- ---------  
 lnalpha -1.9397 0.0423889  
 a 6.15963 0.165691  
 b 0.00508023 0.00292978  
 c 1.13194 0.0405247  
  
 NC = No Convergence  
  
  
 Table of Stats From Input Data  
  
 Dose N Obs Mean Obs Std Dev  
 ----- --- ---------- -------------  
 0 4 6.144 0.5249  
 61 3 6.529 0.1896  
 123 4 6.436 0.4  
 245 5 6.637 0.363  
 489 4 7.186 0.4581  
 979 3 6.763 0.2875  
  
  
 Estimated Values of Interest  
  
 Dose Est Mean Est Std Scaled Residual  
 ------ ---------- --------- ----------------  
 0 6.16 0.3791 -0.08408  
 61 6.376 0.3791 0.6976  
 123 6.537 0.3791 -0.5324  
 245 6.738 0.3791 -0.5977  
 489 6.905 0.3791 1.487  
 979 6.967 0.3791 -0.9314  
  
  
  
 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 13.13369 7 -12.26737  
 A2 15.16039 12 -6.320783  
 A3 13.13369 7 -12.26737  
 R 5.79212 2 -7.584241  
 4 10.8065 4 -13.61301  
  
  
 Additive constant for all log-likelihoods = -21.14. 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 18.74 10 0.04374  
 Test 2 4.053 5 0.5418  
 Test 3 4.053 5 0.5418  
 Test 6a 4.654 3 0.1989  
  
  
 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 = 123.685  
  
 BMDL = 43.3168  
  
 BMDU = 724.836

# BMD Results for Table: Liver Weight Absolute

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 61 | 123 | 245a | 489a | 979a |
| N | 4 | 3 | 4 | 5 | 4 | 3 |
| Mean ± SD | 10.4 ± 0.613 | 11.693 ± 1.619 | 12.395 ± 0.972 | 12.312 ± 0.548 | 11.907 ± 0.64 | 12.293 ± 1.682 |

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 2°, 3°, 4°, 5°) | 0.625 | 15.279 | 57.054 | 34.591 | Exponential-M2 recommended as best-fitting model on the basis of the lowest AIC. |
| Hill | 0.878 | 17.141 | 57.619 | 2.5E-13 |
| Exponential M2b (equivalent models include Exponential M3) | 0.578 | 15.35 | 60.364 | 37.973 |
| Exponential M4 | -999 | 17.041 | 38.913 | 0.147 |
| Exponential M5 | -999 | 19.141 | 51.506 | 0.22 |

a Constant variance case presented (BMDS Test 2 p-value = 0.246, BMDS Test 3 p-value = 0.246).

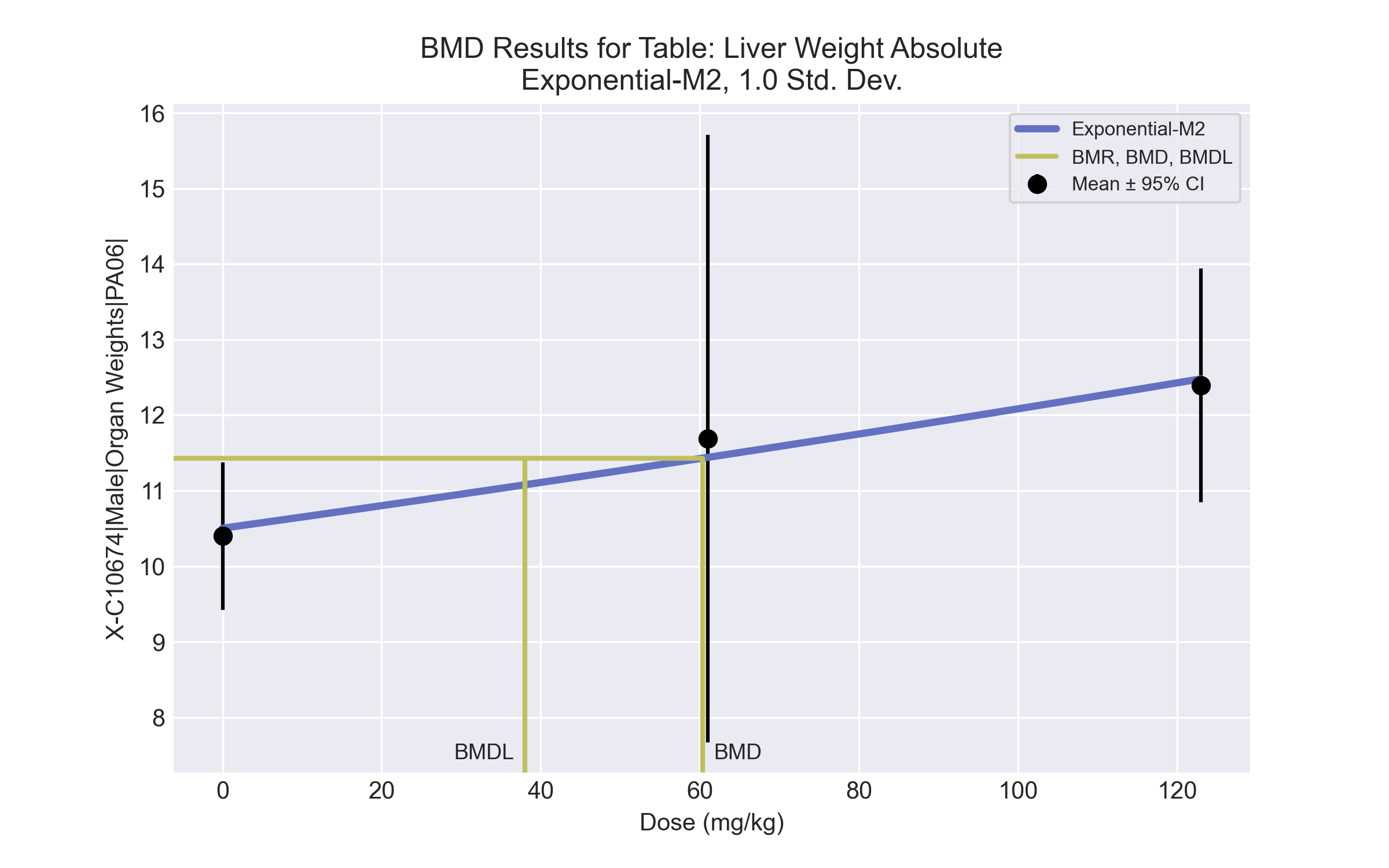
b Recommended model

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear (equivalent models include Power, Polynomial 2°, 3°, 4°, 5°) | Warning | **Warnings**  • Ratio of modeled to actual stdev. at control is greater than threshold (1.51 > 1.5) |
| Hill | Warning | **Warnings**  • BMD/BMDL ratio is greater than threshold (2.35e+14 > 20.0)  **Cautions**  • BMD/BMDL ratio is greater than threshold (2.35e+14 > 5.0) |
| Exponential M2a (equivalent models include Exponential M3) | Valid | - |
| Exponential M4 | Warning | **Warnings**  • BMD/BMDL ratio is greater than threshold (2.64e+02 > 20.0)  • Zero degrees of freedom; saturated model  **Cautions**  • BMD/BMDL ratio is greater than threshold (2.64e+02 > 5.0) |
| Exponential M5 | Warning | **Warnings**  • BMD/BMDL ratio is greater than threshold (2.34e+02 > 20.0)  • Zero degrees of freedom; saturated model  **Cautions**  • BMD/BMDL ratio is greater than threshold (2.34e+02 > 5.0) |

a Recommended model

## Recommended model



====================================================================   
 Exponential Model. (Version: 1.11; Date: 03/14/2017)   
 Input Data File: C:\Windows\TEMP\bmds-dh9n1n97.(d)   
 Gnuplot Plotting File:   
 Thu Jul 15 23:22:27 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 = 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  
  
 MLE solution provided: Exact  
  
  
 Initial Parameter Values  
  
 Variable Model 2  
 -------- --------  
 lnalpha -0.178087   
 rho 0 Specified  
 a 10.4867   
 b 0.00142564   
 c 0 Specified  
 d 1 Specified  
  
  
  
 Parameter Estimates  
  
 Variable Model 2 Std. Err.  
 -------- ------- ---------  
 lnalpha -0.149968 0.367019  
 a 10.5037 0.423097  
 b 0.0014022 0.00046529  
  
 NC = No Convergence  
  
  
 Table of Stats From Input Data  
  
 Dose N Obs Mean Obs Std Dev  
 ----- --- ---------- -------------  
 0 4 10.4 0.6131  
 61 3 11.69 1.619  
 123 4 12.4 0.9724  
  
  
 Estimated Values of Interest  
  
 Dose Est Mean Est Std Scaled Residual  
 ------ ---------- --------- ----------------  
 0 10.5 0.9278 -0.2235  
 61 11.44 0.9278 0.4699  
 123 12.48 0.9278 -0.185  
  
  
  
 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 -4.520522 4 17.04104  
 A2 -3.117596 6 18.23519  
 A3 -4.520522 4 17.04104  
 R -8.008415 2 20.01683  
 2 -4.675176 3 15.35035  
  
  
 Additive constant for all log-likelihoods = -10.11. 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 9.782 4 0.04427  
 Test 2 2.806 2 0.2459  
 Test 3 2.806 2 0.2459  
 Test 4 0.3093 1 0.5781  
  
  
 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 = 60.3637  
  
 BMDL = 37.9732  
  
 BMDU = 158.744

# BMD Results for Table: Liver Weight Relative

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 61 | 123 | 245 | 489 | 979 |
| N | 4 | 3 | 4 | 5 | 4 | 3 |
| Mean ± SD | 38.206 ± 2.298 | 42.338 ± 4.267 | 45.199 ± 1.524 | 45.699 ± 3.763 | 48.2 ± 1.499 | 47.539 ± 4.954 |

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear (equivalent models include Power, Polynomial 2°, 3°, 4°) | 0.012 | 88.068 | 459.426 | 293.312 | Exponential-M4 recommended as best-fitting model on the basis of the lowest AIC. |
| Polynomial 5° | 0.012 | 88.068 | 459.427 | 293.312 |
| Hill | 0.654 | 80.081 | 35.235 | 9.595 |
| Exponential M2 (equivalent models include Exponential M3) | 0.01 | 88.484 | 502.12 | 329.542 |
| Exponential M4b (equivalent models include Exponential M5) | 0.798 | 78.245 | 39.401 | 17.23 |

a Constant variance case presented (BMDS Test 2 p-value = 0.135, BMDS Test 3 p-value = 0.135).

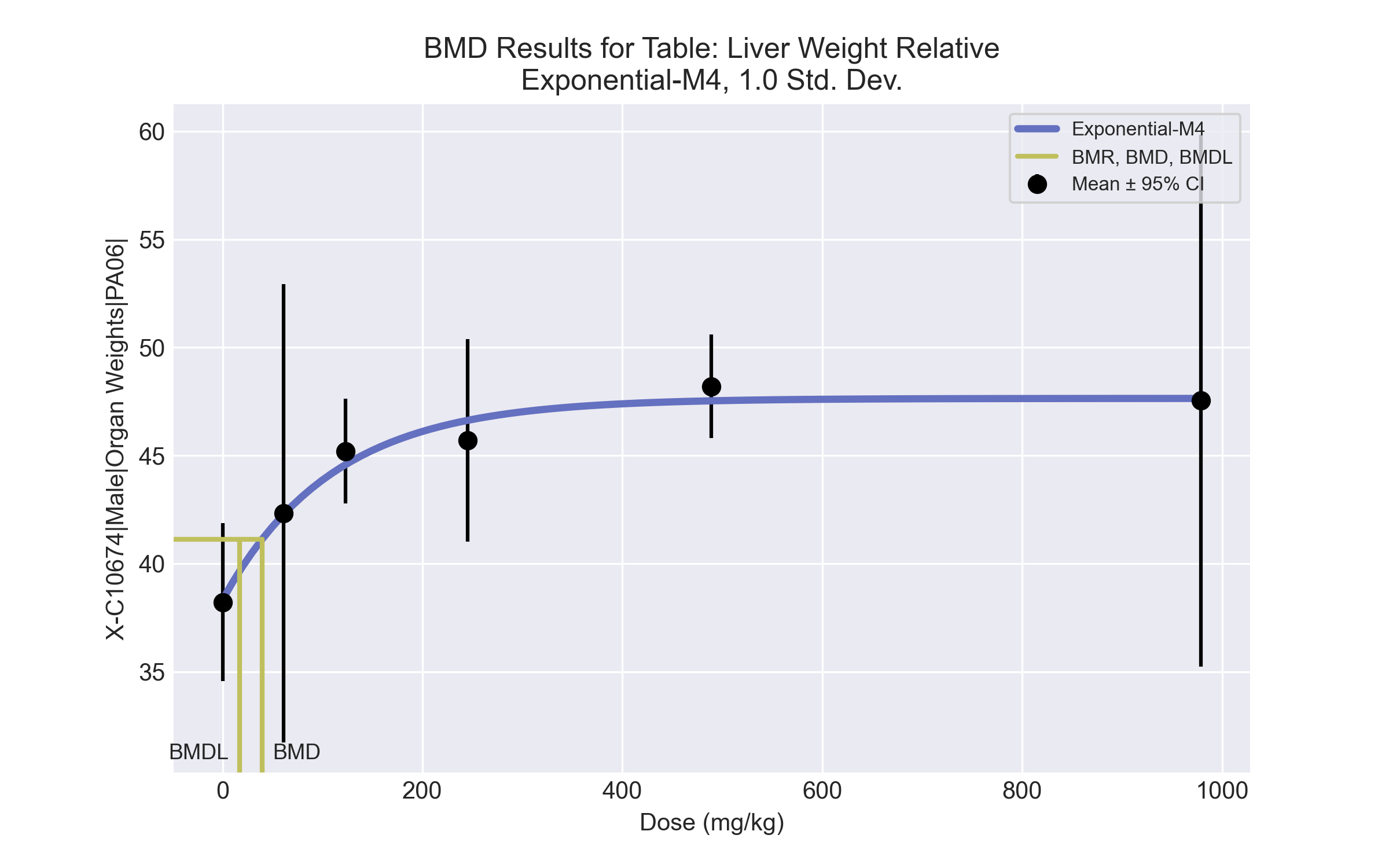
b Recommended model

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear (equivalent models include Power, Polynomial 2°, 3°, 4°) | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0121 < 0.1)  • Residual at lowest dose is greater than threshold (2.23 > 2.0)  • Ratio of modeled to actual stdev. at control is greater than threshold (1.57 > 1.5) |
| Polynomial 5° | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0121 < 0.1)  • Residual at lowest dose is greater than threshold (2.23 > 2.0)  • Ratio of modeled to actual stdev. at control is greater than threshold (1.57 > 1.5) |
| Hill | Valid | - |
| Exponential M2 (equivalent models include Exponential M3) | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0101 < 0.1)  • Residual at lowest dose is greater than threshold (2.29 > 2.0) |
| Exponential M4a (equivalent models include Exponential M5) | Valid | - |

a Recommended model

## Recommended model



====================================================================   
 Exponential Model. (Version: 1.11; Date: 03/14/2017)   
 Input Data File: C:\Windows\TEMP\bmds-62h2s0sl.(d)   
 Gnuplot Plotting File:   
 Thu Jul 15 23:22:31 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 2.01008   
 rho 0 Specified  
 a 36.2958   
 b 0.00218837   
 c 1.39439   
 d 1 Specified  
  
  
  
 Parameter Estimates  
  
 Variable Model 4 Std. Err.  
 -------- ------- ---------  
 lnalpha 2.05415 2.30015  
 a 38.3214 1.37876  
 b 0.00904205 0.00423166  
 c 1.24317 0.0494477  
  
 NC = No Convergence  
  
  
 Table of Stats From Input Data  
  
 Dose N Obs Mean Obs Std Dev  
 ----- --- ---------- -------------  
 0 4 38.21 2.298  
 61 3 42.34 4.267  
 123 4 45.2 1.524  
 245 5 45.7 3.763  
 489 4 48.2 1.499  
 979 3 47.54 4.954  
  
  
 Estimated Values of Interest  
  
 Dose Est Mean Est Std Scaled Residual  
 ------ ---------- --------- ----------------  
 0 38.32 2.793 -0.08261  
 61 42.27 2.793 0.04063  
 123 44.58 2.793 0.4466  
 245 46.62 2.793 -0.7401  
 489 47.53 2.793 0.4816  
 979 47.64 2.793 -0.06153  
  
  
  
 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 -34.61596 7 83.23192  
 A2 -30.41069 12 84.82139  
 A3 -34.61596 7 83.23192  
 R -45.32767 2 94.65535  
 4 -35.12269 4 78.24538  
  
  
 Additive constant for all log-likelihoods = -21.14. 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 29.83 10 0.0009119  
 Test 2 8.411 5 0.135  
 Test 3 8.411 5 0.135  
 Test 6a 1.013 3 0.798  
  
  
 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 = 39.401  
  
 BMDL = 17.2295  
  
 BMDU = 106.79

# BMD Results for Table: Terminal Body Weight

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 61 | 123 | 245 | 489 | 979 |
| N | 4 | 3 | 4 | 5 | 4 | 3 |
| Mean ± SD | 272.225 ± 0.806 | 275.5 ± 11.964 | 274.05 ± 15.57 | 270.22 ± 13.723 | 247.125 ± 13.411 | 258 ± 9.042 |

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear (equivalent models include Power, Polynomial 2°, 3°, 4°, 5°) | 0.099 | 146.364 | 336.228 | 160.857 | No model was recommended as a best-fitting model. Doses were dropped until there were only 3 remaining dose-groups. |
| Hill | 0.599 | 142.445 | 265.544 | -999 |
| Exponential M2 | 0.106 | 146.193 | 320.936 | 152.931 |
| Exponential M3 | 0.106 | 146.193 | 320.937 | 152.931 |
| Exponential M4 | 0.115 | 146.504 | 167.838 | 0.255 |
| Exponential M5 | 0.392 | 144.445 | 299.221 | 180.129 |

a Modeled variance case presented (BMDS Test 2 p-value = 0.002, BMDS Test 3 p-value = 6.9E-04).

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear (equivalent models include Power, Polynomial 2°, 3°, 4°, 5°) | Warning | **Warnings**  • Variance model poorly fits dataset (p-value 3 = 0.000694)  • Goodness of fit p-value is less than threshold (0.0994 < 0.1)  • Ratio of modeled to actual stdev. at control is greater than threshold (12.3 > 1.5) |
| Hill | Failure | **Failures**  • BMDL does not exist  **Warnings**  • Variance model poorly fits dataset (p-value 3 = 0.000694)  • Ratio of modeled to actual stdev. at control is greater than threshold (12.9 > 1.5)  **Cautions**  • Warning(s): BMDL computation failed. |
| Exponential M2 | Warning | **Warnings**  • Variance model poorly fits dataset (p-value 3 = 0.000694) |
| Exponential M3 | Warning | **Warnings**  • Variance model poorly fits dataset (p-value 3 = 0.000694) |
| Exponential M4 | Warning | **Warnings**  • Variance model poorly fits dataset (p-value 3 = 0.000694)  • BMD/BMDL ratio is greater than threshold (6.58e+02 > 20.0)  **Cautions**  • BMD/BMDL ratio is greater than threshold (6.58e+02 > 5.0) |
| Exponential M5 | Warning | **Warnings**  • Variance model poorly fits dataset (p-value 3 = 0.000694) |

## Recommended model

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

# BMD Results for Table: A/G Ratio

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 61 | 123 | 245 | 489 | 979 |
| N | 4 | 3 | 4 | 5 | 4 | 3 |
| Mean ± SD | 1.226 ± 0.116 | 1.195 ± 0.045 | 1.213 ± 0.085 | 1.162 ± 0.052 | 1.111 ± 0.087 | 1.138 ± 0.072 |

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear (equivalent models include Power, Polynomial 2°, 3°, 4°, 5°) | 0.53 | -90.771 | 732.334 | 396.104 | Exponential-M4 recommended as best-fitting model on the basis of the lowest BMDL. |
| Hill | 0.9 | -91.354 | 258.436 | 66.405 |
| Exponential M2 (equivalent models include Exponential M3) | 0.543 | -90.851 | 708.925 | 372.433 |
| Exponential M4b | 0.733 | -90.657 | 256.65 | 65.511 |
| Exponential M5 | 0.746 | -89.354 | 253.926 | 125.254 |

a Constant variance case presented (BMDS Test 2 p-value = 0.469, BMDS Test 3 p-value = 0.469).

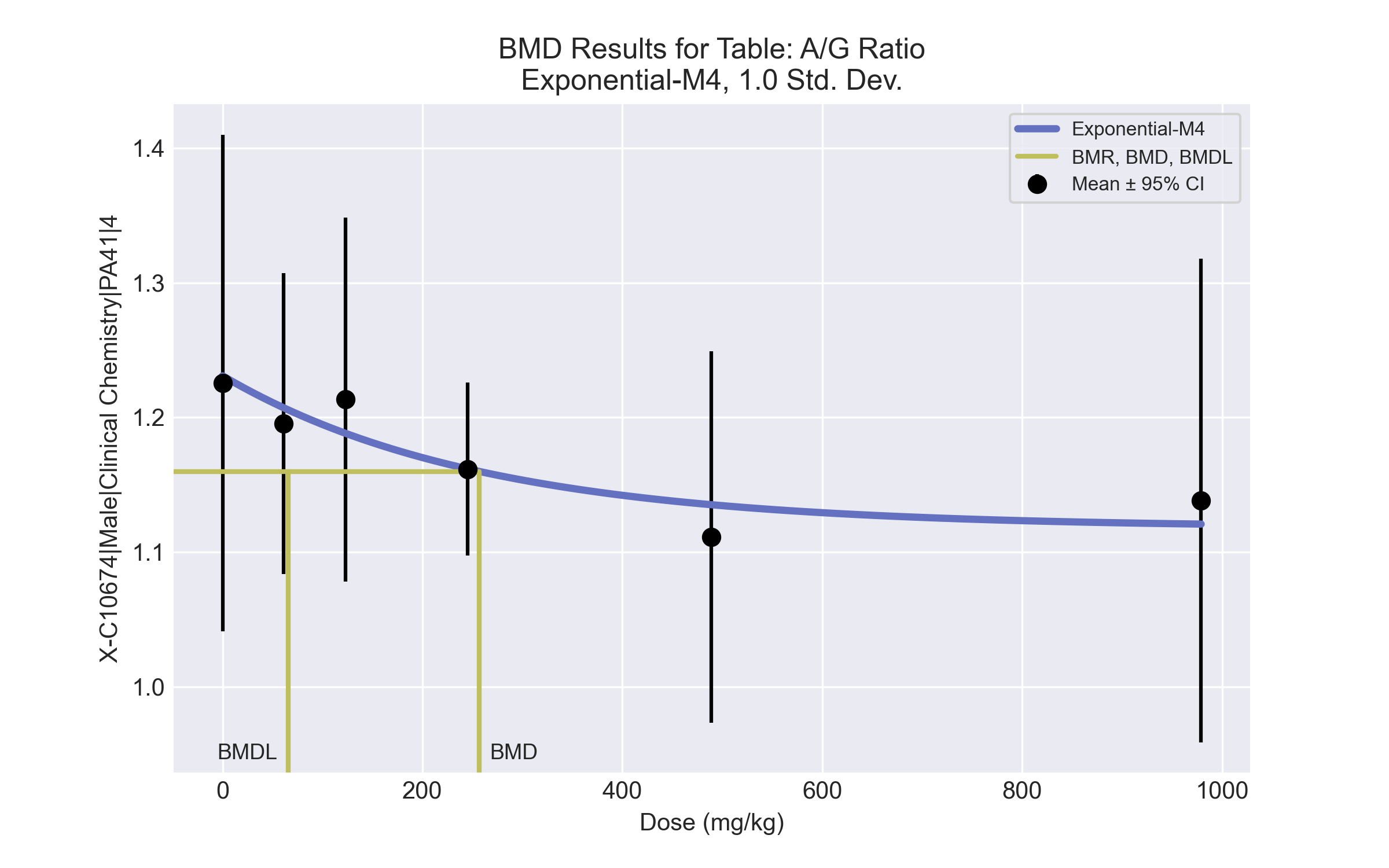
b Recommended model

## 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-anlrfp78.(d)   
 Gnuplot Plotting File:   
 Thu Jul 15 23:23:30 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 -5.34522   
 rho 0 Specified  
 a 1.287   
 b 0.00158017   
 c 0.822307   
 d 1 Specified  
  
  
  
 Parameter Estimates  
  
 Variable Model 4 Std. Err.  
 -------- ------- ---------  
 lnalpha -5.28942 0.00148759  
 a 1.23098 0.0298478  
 b 0.00387623 0.00334931  
 c 0.908447 0.0371745  
  
 NC = No Convergence  
  
  
 Table of Stats From Input Data  
  
 Dose N Obs Mean Obs Std Dev  
 ----- --- ---------- -------------  
 0 4 1.226 0.1159  
 61 3 1.195 0.04496  
 123 4 1.213 0.08494  
 245 5 1.162 0.0517  
 489 4 1.111 0.08677  
 979 3 1.138 0.07227  
  
  
 Estimated Values of Interest  
  
 Dose Est Mean Est Std Scaled Residual  
 ------ ---------- --------- ----------------  
 0 1.231 0.07103 -0.1483  
 61 1.207 0.07103 -0.2871  
 123 1.188 0.07103 0.7103  
 245 1.162 0.07103 -0.007456  
 489 1.135 0.07103 -0.6755  
 979 1.121 0.07103 0.4277  
  
  
  
 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 49.97007 7 -85.94015  
 A2 52.26005 12 -80.5201  
 A3 49.97007 7 -85.94015  
 R 46.50018 2 -89.00035  
 4 49.32839 4 -90.65677  
  
  
 Additive constant for all log-likelihoods = -21.14. 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 11.52 10 0.3185  
 Test 2 4.58 5 0.4693  
 Test 3 4.58 5 0.4693  
 Test 6a 1.283 3 0.7331  
  
  
 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 = 256.65  
  
 BMDL = 65.5111  
  
 BMDU = 9.79e+006

# BMD Results for Table: Aspartate Aminotransferase

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 61 | 123 | 245 | 489 | 979 |
| N | 4 | 3 | 4 | 5 | 4 | 3 |
| Mean ± SD | 169.75 ± 92.349 | 123 ± 47.508 | 115.75 ± 44.969 | 92.2 ± 33.7 | 69.5 ± 12.793 | 92.333 ± 28.537 |

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear | 0.003 | 206.266 | 2248.26 | 736.099 | Exponential-M4 recommended as best-fitting model on the basis of the lowest AIC. |
| Polynomial 2° | 0.003 | 206.266 | 2248.24 | 736.099 |
| Power (equivalent models include Polynomial 3°, 5°) | 0.003 | 206.266 | 2248.25 | 736.099 |
| Polynomial 4° | 0.003 | 206.266 | 2248.28 | 736.099 |
| Hill | 0.066 | 199.485 | 217.136 | -999 |
| Exponential M2 | 0.004 | 205.666 | 2069.82 | 433.801 |
| Exponential M3 | 0.004 | 205.666 | 2069.81 | 433.801 |
| Exponential M4b | 0.181 | 196.911 | 223.528 | 51.946 |
| Exponential M5 | 0.181 | 196.911 | 223.53 | 51.946 |

a Modeled variance case presented (BMDS Test 2 p-value = 0.012, BMDS Test 3 p-value = 0.969).

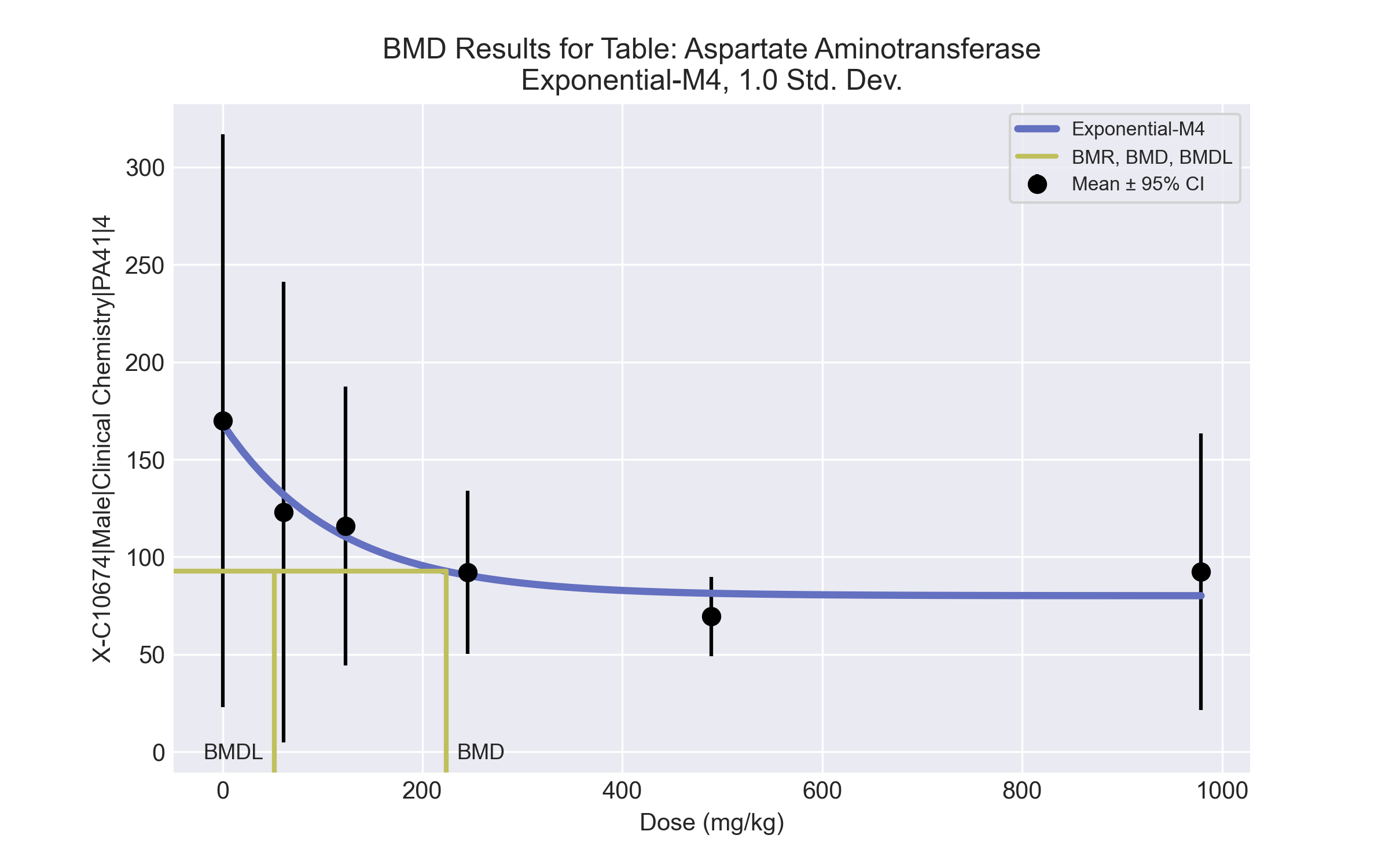
b Recommended model

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.00273 < 0.1)  • BMD/high dose ratio is greater than threshold (2.3 > 1.0)  **Cautions**  • Warning(s): THE MODEL HAS PROBABLY NOT CONVERGED!!!; THIS USUALLY MEANS THE MODEL HAS NOT CONVERGED! |
| Polynomial 2° | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.00273 < 0.1)  • BMD/high dose ratio is greater than threshold (2.3 > 1.0)  **Cautions**  • Warning(s): THE MODEL HAS PROBABLY NOT CONVERGED!!!; THIS USUALLY MEANS THE MODEL HAS NOT CONVERGED! |
| Power (equivalent models include Polynomial 3°, 5°) | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.00273 < 0.1)  • BMD/high dose ratio is greater than threshold (2.3 > 1.0) |
| Polynomial 4° | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.00273 < 0.1)  • BMD/high dose ratio is greater than threshold (2.3 > 1.0)  **Cautions**  • Warning(s): THE MODEL HAS PROBABLY NOT CONVERGED!!!; THIS USUALLY MEANS THE MODEL HAS NOT CONVERGED! |
| Hill | Failure | **Failures**  • BMDL does not exist  **Warnings**  • Goodness of fit p-value is less than threshold (0.0656 < 0.1)  **Cautions**  • Warning(s): BMDL computation failed. |
| Exponential M2 | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.00356 < 0.1)  • BMD/high dose ratio is greater than threshold (2.11 > 1.0) |
| Exponential M3 | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.00356 < 0.1)  • BMD/high dose ratio is greater than threshold (2.11 > 1.0) |
| 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-c4h5zof3.(d)   
 Gnuplot Plotting File:   
 Thu Jul 15 23:23:35 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 = 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 -12.3668   
 rho 4.1953   
 a 178.238   
 b 0.00285692   
 c 0.371361   
 d 1 Specified  
  
  
  
 Parameter Estimates  
  
 Variable Model 4 Std. Err.  
 -------- ------- ---------  
 lnalpha -8.21921 6.69937  
 rho 3.29125 1.44539  
 a 168.302 30.8638  
 b 0.00870592 0.00346191  
 c 0.475936 0.101602  
  
 NC = No Convergence  
  
  
 Table of Stats From Input Data  
  
 Dose N Obs Mean Obs Std Dev  
 ----- --- ---------- -------------  
 0 4 169.8 92.35  
 61 3 123 47.51  
 123 4 115.8 44.97  
 245 5 92.2 33.7  
 489 4 69.5 12.79  
 979 3 92.33 28.54  
  
  
 Estimated Values of Interest  
  
 Dose Est Mean Est Std Scaled Residual  
 ------ ---------- --------- ----------------  
 0 168.3 75.6 0.0383  
 61 132 50.66 -0.3064  
 123 110.3 37.73 0.2873  
 245 90.55 27.26 0.1352  
 489 81.35 22.85 -1.037  
 979 80.12 22.29 0.9493  
  
  
  
 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 -98.0887 7 210.1774  
 A2 -90.74528 12 205.4906  
 A3 -91.01879 8 198.0376  
 R -103.2055 2 210.411  
 4 -93.45561 5 196.9112  
  
  
 Additive constant for all log-likelihoods = -21.14. 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 24.92 10 0.005498  
 Test 2 14.69 5 0.01179  
 Test 3 0.547 4 0.9688  
 Test 6a 4.874 3 0.1813  
  
  
 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 = 223.528  
  
 BMDL = 51.9458  
  
 BMDU = 9.79e+006

# BMD Results for Table: Bile salts/acids

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 61 | 123 | 245 | 489 | 979 |
| N | 4 | 3 | 4 | 5 | 4 | 3 |
| Mean ± SD | 52.15 ± 10.314 | 34.867 ± 7.206 | 22.15 ± 9.499 | 27.62 ± 5.828 | 16.475 ± 9.049 | 20.033 ± 8.62 |

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear (equivalent models include Power, Polynomial 4°, 5°) | 2.0E-04 | 142.406 | 474.478 | 300.042 | Exponential-M4 recommended as best-fitting model on the basis of the lowest AIC. |
| Polynomial 2° (equivalent models include Polynomial 3°) | 2.0E-04 | 142.406 | 474.479 | 300.042 |
| Hill | 0.092 | 129.17 | 20.137 | 4.376 |
| Exponential M2 (equivalent models include Exponential M3) | 0.001 | 138.452 | 179.729 | 84.313 |
| Exponential M4b (equivalent models include Exponential M5) | 0.151 | 127.713 | 20.348 | 9.305 |

a Constant variance case presented (BMDS Test 2 p-value = 0.888, BMDS Test 3 p-value = 0.888).

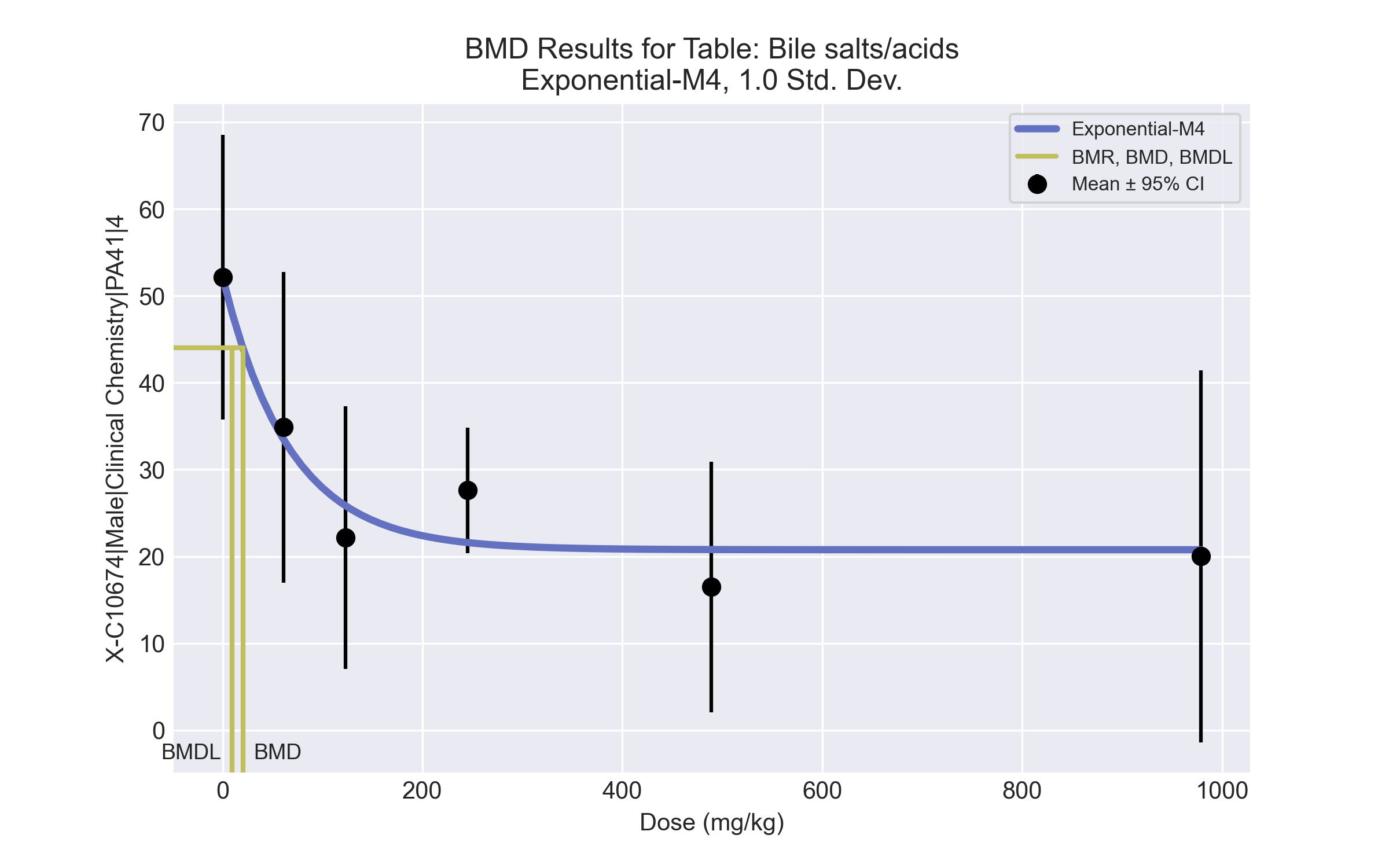
b Recommended model

## 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 (0.0002 < 0.1)  • Residual at lowest dose is greater than threshold (2.7 > 2.0) |
| Polynomial 2° (equivalent models include Polynomial 3°) | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0002 < 0.1)  • Residual at lowest dose is greater than threshold (2.7 > 2.0) |
| Hill | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0924 < 0.1)  **Cautions**  • Minimum dose/BMD ratio is greater than threshold (3.03 > 3.0) |
| Exponential M2 (equivalent models include Exponential M3) | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.00121 < 0.1) |
| Exponential M4a (equivalent models include Exponential M5) | Valid | - |

a Recommended model

## Recommended model



====================================================================   
 Exponential Model. (Version: 1.11; Date: 03/14/2017)   
 Input Data File: C:\Windows\TEMP\bmds-xj4294eq.(d)   
 Gnuplot Plotting File:   
 Thu Jul 15 23:23:39 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 3.9742   
 rho 0 Specified  
 a 54.7575   
 b 0.00361711   
 c 0.286545   
 d 1 Specified  
  
  
  
 Parameter Estimates  
  
 Variable Model 4 Std. Err.  
 -------- ------- ---------  
 lnalpha 4.20491 19.7614  
 a 52.1757 4.11884  
 b 0.0148412 0.00652523  
 c 0.398072 0.0583859  
  
 NC = No Convergence  
  
  
 Table of Stats From Input Data  
  
 Dose N Obs Mean Obs Std Dev  
 ----- --- ---------- -------------  
 0 4 52.15 10.31  
 61 3 34.87 7.206  
 123 4 22.15 9.499  
 245 5 27.62 5.828  
 489 4 16.48 9.049  
 979 3 20.03 8.62  
  
  
 Estimated Values of Interest  
  
 Dose Est Mean Est Std Scaled Residual  
 ------ ---------- --------- ----------------  
 0 52.18 8.186 -0.006276  
 61 33.47 8.186 0.2954  
 123 25.83 8.186 -0.8992  
 245 21.6 8.186 1.645  
 489 20.79 8.186 -1.055  
 979 20.77 8.186 -0.1558  
  
  
  
 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 -57.20326 7 128.4065  
 A2 -56.34909 12 136.6982  
 A3 -57.20326 7 128.4065  
 R -72.27099 2 148.542  
 4 -59.85641 4 127.7128  
  
  
 Additive constant for all log-likelihoods = -21.14. 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 31.84 10 0.0004252  
 Test 2 1.708 5 0.8878  
 Test 3 1.708 5 0.8878  
 Test 6a 5.306 3 0.1507  
  
  
 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 = 20.3484  
  
 BMDL = 9.30458  
  
 BMDU = 52.6453

# BMD Results for Table: Cholesterol

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 61 | 123 | 245 | 489 | 979 |
| N | 4 | 3 | 4 | 5 | 4 | 3 |
| Mean ± SD | 115 ± 18.111 | 113 ± 1.732 | 133.5 ± 4.123 | 128.6 ± 23.522 | 142.5 ± 22.279 | 150.333 ± 28.989 |

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear (equivalent models include Power, Polynomial 2°, 3°, 4°, 5°) | 0.12 | 161.422 | 328.551 | 159.337 | No model was recommended as a best-fitting model. Doses were dropped until there were only 3 remaining dose-groups. |
| Hill | 0.054 | 163.931 | 151.104 | -999 |
| Exponential M2 (equivalent models include Exponential M3) | 0.105 | 161.76 | 376.114 | 193.041 |
| Exponential M4 | 0.107 | 162.2 | 158.814 | 54.697 |
| Exponential M5 | 0.05 | 164.105 | 166.99 | 55.665 |

a Modeled variance case presented (BMDS Test 2 p-value = 4.9E-04, BMDS Test 3 p-value = 0.003).

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear (equivalent models include Power, Polynomial 2°, 3°, 4°, 5°) | Warning | **Warnings**  • Variance model poorly fits dataset (p-value 3 = 0.00345) |
| Hill | Failure | **Failures**  • BMDL does not exist  **Warnings**  • Variance model poorly fits dataset (p-value 3 = 0.00345)  • Goodness of fit p-value is less than threshold (0.0544 < 0.1)  **Cautions**  • Warning(s): BMDL computation failed. |
| Exponential M2 (equivalent models include Exponential M3) | Warning | **Warnings**  • Variance model poorly fits dataset (p-value 3 = 0.00345) |
| Exponential M4 | Warning | **Warnings**  • Variance model poorly fits dataset (p-value 3 = 0.00345) |
| Exponential M5 | Warning | **Warnings**  • Variance model poorly fits dataset (p-value 3 = 0.00345)  • Goodness of fit p-value is less than threshold (0.0499 < 0.1) |

## Recommended model

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

# BMD Results for Table: Globulin

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 61 | 123 | 245 | 489 | 979 |
| N | 4 | 3 | 4 | 5 | 4 | 3 |
| Mean ± SD | 2.9 ± 0.082 | 3.1 ± 0.2 | 2.925 ± 0.126 | 3.02 ± 0.259 | 3.2 ± 0.141 | 3.2 ± 0.2 |

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear (equivalent models include Power, Polynomial 2°, 3°, 4°, 5°) | 0.327 | -52.008 | 572.522 | 340.534 | Exponential-M4 recommended as best-fitting model on the basis of the lowest BMDL. |
| Hill | 0.389 | -51.617 | 274.074 | 93.751 |
| Exponential M2 (equivalent models include Exponential M3) | 0.32 | -51.939 | 590.042 | 359.696 |
| Exponential M4b | 0.27 | -50.718 | 336.018 | 95.21 |
| Exponential M5 | 0.221 | -49.617 | 266.172 | 121.341 |

a Constant variance case presented (BMDS Test 2 p-value = 0.264, BMDS Test 3 p-value = 0.264).

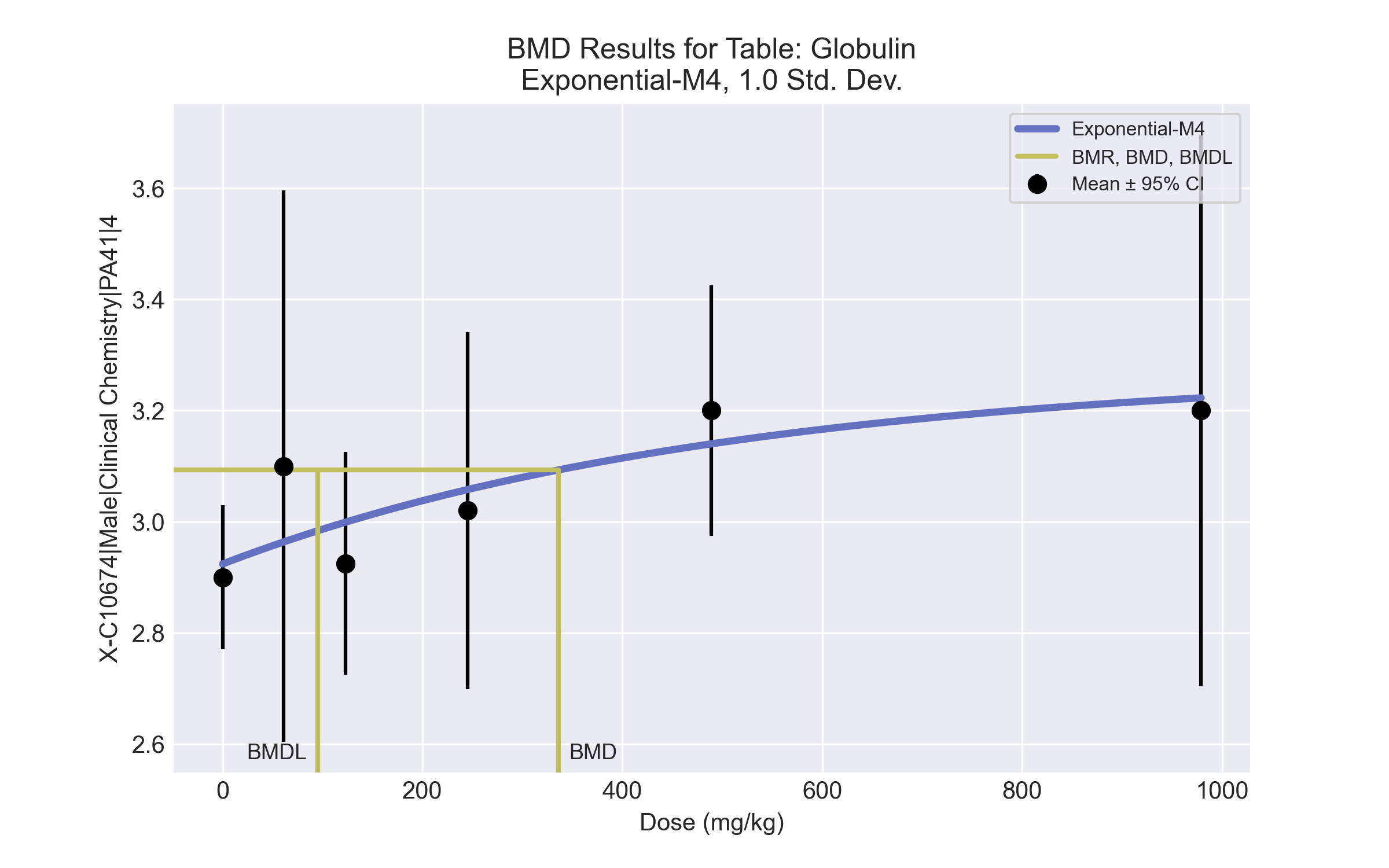
b Recommended model

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear (equivalent models include Power, Polynomial 2°, 3°, 4°, 5°) | Warning | **Warnings**  • Ratio of modeled to actual stdev. at control is greater than threshold (2.11 > 1.5) |
| Hill | Warning | **Warnings**  • Ratio of modeled to actual stdev. at control is greater than threshold (2.03 > 1.5) |
| 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-hq\_mulq7.(d)   
 Gnuplot Plotting File:   
 Thu Jul 15 23:23:59 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 -3.72338   
 rho 0 Specified  
 a 2.755   
 b 0.00171242   
 c 1.2196   
 d 1 Specified  
  
  
  
 Parameter Estimates  
  
 Variable Model 4 Std. Err.  
 -------- ------- ---------  
 lnalpha -3.55298 0.00844524  
 a 2.92391 0.066976  
 b 0.00196668 0.00247449  
 c 1.11969 0.0711117  
  
 NC = No Convergence  
  
  
 Table of Stats From Input Data  
  
 Dose N Obs Mean Obs Std Dev  
 ----- --- ---------- -------------  
 0 4 2.9 0.08165  
 61 3 3.1 0.2  
 123 4 2.925 0.1258  
 245 5 3.02 0.2588  
 489 4 3.2 0.1414  
 979 3 3.2 0.2  
  
  
 Estimated Values of Interest  
  
 Dose Est Mean Est Std Scaled Residual  
 ------ ---------- --------- ----------------  
 0 2.924 0.1692 -0.2826  
 61 2.963 0.1692 1.397  
 123 2.999 0.1692 -0.8758  
 245 3.058 0.1692 -0.4984  
 489 3.14 0.1692 0.7079  
 979 3.223 0.1692 -0.2337  
  
  
  
 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 31.31886 7 -48.63772  
 A2 34.55119 12 -45.10239  
 A3 31.31886 7 -48.63772  
 R 26.0624 2 -48.12479  
 4 29.35925 4 -50.7185  
  
  
 Additive constant for all log-likelihoods = -21.14. 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 16.98 10 0.07486  
 Test 2 6.465 5 0.2636  
 Test 3 6.465 5 0.2636  
 Test 6a 3.919 3 0.2703  
  
  
 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 = 336.018  
  
 BMDL = 95.2096  
  
 BMDU = 9.79e+006

# BMD Results for Table: HDL Cholesterol

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 61 | 123 | 245 | 489 | 979 |
| N | 4 | 3 | 4 | 5 | 4 | 3 |
| Mean ± SD | 50 ± 5.477 | 54.667 ± 6.658 | 68 ± 4.546 | 68 ± 9.899 | 74.75 ± 19.772 | 87.667 ± 16.653 |

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear (equivalent models include Polynomial 2°, 3°, 4°, 5°) | 0.083 | 137.591 | 141.175 | 61.805 | Exponential-M4 recommended as best-fitting model on the basis of the lowest AIC. |
| Power | 0.083 | 137.591 | 141.176 | 61.805 |
| Hill | 0.398 | 135.182 | 38.095 | -999 |
| Exponential M2 (equivalent models include Exponential M3) | 0.037 | 139.565 | 224.961 | 109.57 |
| Exponential M4b (equivalent models include Exponential M5) | 0.57 | 133.351 | 36.78 | 18.336 |

a Modeled variance case presented (BMDS Test 2 p-value = 0.026, BMDS Test 3 p-value = 0.334).

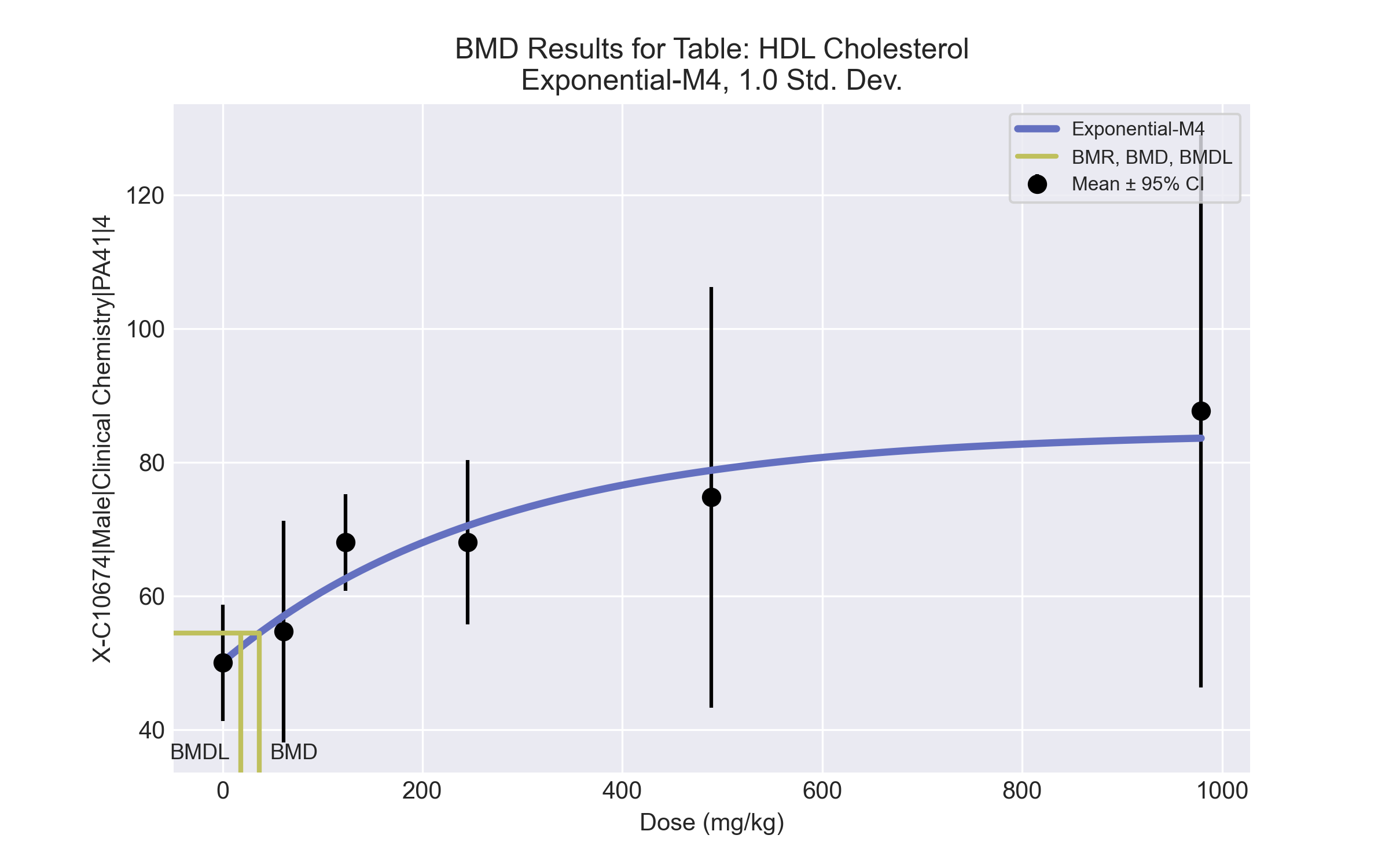
b Recommended model

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear (equivalent models include Polynomial 2°, 3°, 4°, 5°) | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0828 < 0.1) |
| Power | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0828 < 0.1) |
| Hill | Failure | **Failures**  • BMDL does not exist  **Cautions**  • Warning(s): BMDL computation failed. |
| Exponential M2 (equivalent models include Exponential M3) | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0368 < 0.1) |
| Exponential M4a (equivalent models include Exponential M5) | Valid | - |

a Recommended model

## Recommended model



====================================================================   
 Exponential Model. (Version: 1.11; Date: 03/14/2017)   
 Input Data File: C:\Windows\TEMP\bmds-zz490uzw.(d)   
 Gnuplot Plotting File:   
 Thu Jul 15 23:24:03 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 = 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 -13.5104   
 rho 4.27457   
 a 47.5   
 b 0.00232696   
 c 1.93789   
 d 1 Specified  
  
  
  
 Parameter Estimates  
  
 Variable Model 4 Std. Err.  
 -------- ------- ---------  
 lnalpha -17.4224 7.40795  
 rho 5.20012 1.77407  
 a 50.1146 2.0693  
 b 0.00365406 0.00165887  
 c 1.68755 0.17488  
  
 NC = No Convergence  
  
  
 Table of Stats From Input Data  
  
 Dose N Obs Mean Obs Std Dev  
 ----- --- ---------- -------------  
 0 4 50 5.477  
 61 3 54.67 6.658  
 123 4 68 4.546  
 245 5 68 9.899  
 489 4 74.75 19.77  
 979 3 87.67 16.65  
  
  
 Estimated Values of Interest  
  
 Dose Est Mean Est Std Scaled Residual  
 ------ ---------- --------- ----------------  
 0 50.11 4.333 -0.05288  
 61 57 6.055 -0.6671  
 123 62.59 7.723 1.401  
 245 70.5 10.52 -0.5302  
 489 78.8 14.06 -0.5762  
 979 83.61 16.4 0.4288  
  
  
  
 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 -64.75602 7 143.512  
 A2 -58.38394 12 140.7679  
 A3 -60.66957 8 137.3391  
 R -74.49106 2 152.9821  
 4 -61.67533 5 133.3507  
  
  
 Additive constant for all log-likelihoods = -21.14. 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 32.21 10 0.0003688  
 Test 2 12.74 5 0.0259  
 Test 3 4.571 4 0.3342  
 Test 6a 2.012 3 0.57  
  
  
 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 = 36.7796  
  
 BMDL = 18.3359  
  
 BMDU = 98.29

# BMD Results for Table: Cholinesterase

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 61 | 123 | 245 | 489 | 979 |
| N | 4 | 3 | 4 | 5 | 4 | 3 |
| Mean ± SD | 291.25 ± 18.768 | 200.333 ± 27.062 | 196 ± 20.928 | 164.8 ± 44.201 | 149 ± 22.39 | 133.667 ± 14.012 |

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear (equivalent models include Power, Polynomial 2°, 3°, 4°, 5°) | <0.0001 | 201.047 | 340.174 | 234.363 | Hill recommended as best-fitting model on the basis of the lowest AIC. |
| Hillb | 0.64 | 179.391 | 12.475 | 6.079 |
| Exponential M2 (equivalent models include Exponential M3) | 2.1E-04 | 197.586 | 195.139 | 121.455 |
| Exponential M4 (equivalent models include Exponential M5) | 0.265 | 181.675 | 20.665 | 11.486 |

a Constant variance case presented (BMDS Test 2 p-value = 0.184, BMDS Test 3 p-value = 0.184).

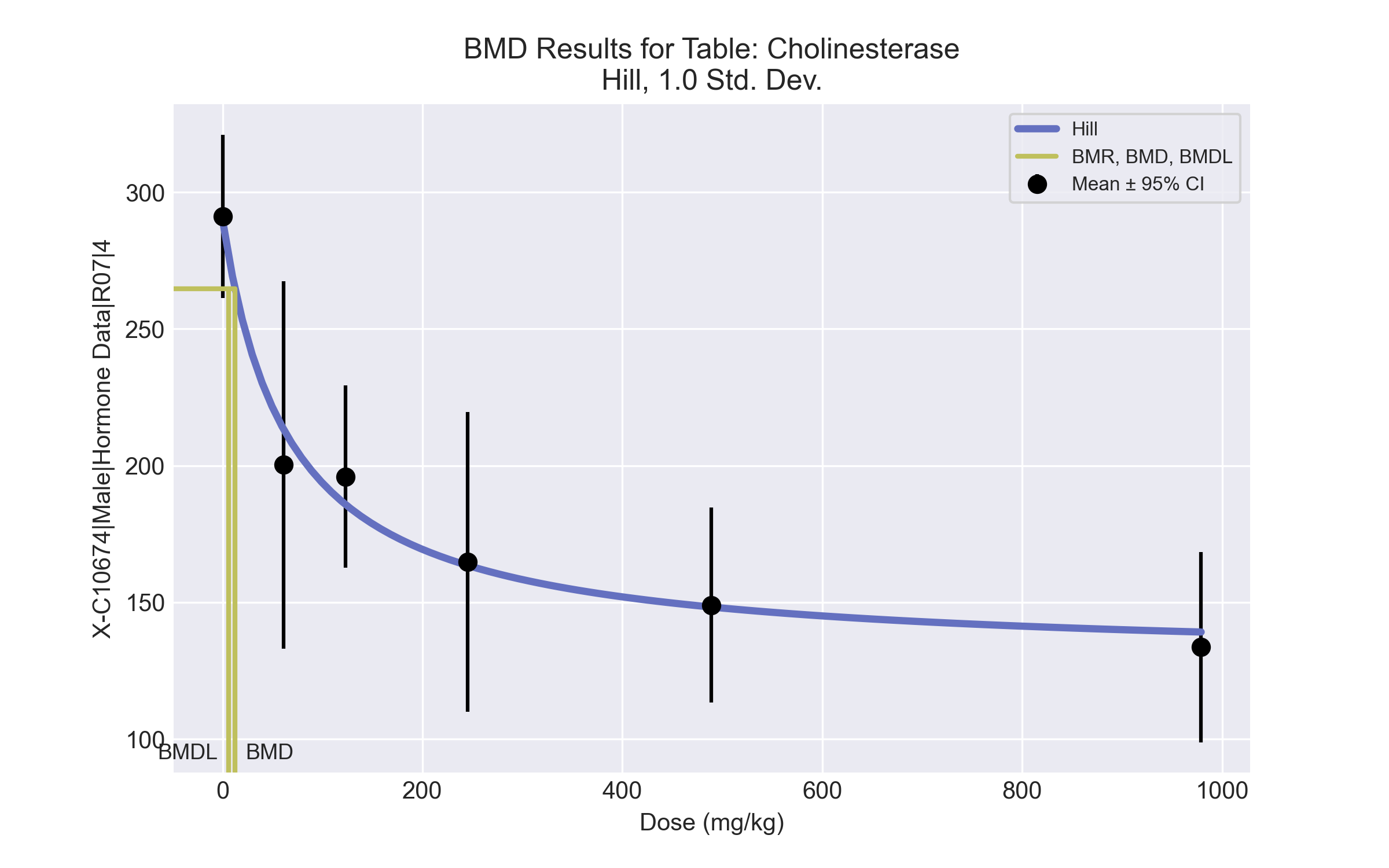
b Recommended model

## 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 (3.07 > 2.0)  • Ratio of modeled to actual stdev. at control is greater than threshold (2.24 > 1.5) |
| Hilla | Valid | **Cautions**  • Minimum dose/BMD ratio is greater than threshold (4.89 > 3.0) |
| Exponential M2 (equivalent models include Exponential M3) | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.000212 < 0.1)  • Residual at lowest dose is greater than threshold (2.67 > 2.0) |
| Exponential M4 (equivalent models include Exponential M5) | Valid | - |

a Recommended model

## Recommended model



====================================================================   
 Hill Model. (Version: 2.18; Date: 03/14/2017)   
 Input Data File: C:\Windows\TEMP\bmds-3akihw1i.(d)   
 Gnuplot Plotting File: C:\Windows\TEMP\bmds-3akihw1i.plt  
 Thu Jul 15 23:47:02 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 = 796.875  
 rho = 0 Specified  
 intercept = 291.25  
 v = -157.583  
 n = 1.14621  
 k = 52.8648  
  
  
 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 -3.1e-010 6.2e-008 4.8e-008  
  
 intercept -3.1e-010 1 -0.6 -0.41  
  
 v 6.2e-008 -0.6 1 -0.37  
  
 k 4.8e-008 -0.41 -0.37 1  
  
  
  
 Parameter Estimates  
  
 95.0% Wald Confidence Interval  
 Variable Estimate Std. Err. Lower Conf. Limit Upper Conf. Limit  
 alpha 633.834 186.907 267.502 1000.17  
 intercept 289.909 12.6747 265.067 314.751  
 v -161.142 17.8829 -196.192 -126.092  
 n 1 NA  
 k 67.374 28.996 10.5428 124.205  
  
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 4 291 290 18.8 25.2 0.107  
 61 3 200 213 27.1 25.2 -0.895  
 123 4 196 186 20.9 25.2 0.811  
 245 5 165 164 44.2 25.2 0.113  
 489 4 149 148 22.4 25.2 0.0572  
 979 3 134 139 14 25.2 -0.377  
  
  
  
 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 -84.851802 7 183.703604  
 A2 -81.085091 12 186.170182  
 A3 -84.851802 7 183.703604  
 fitted -85.695547 4 179.391095  
 R -104.445456 2 212.890913  
  
  
 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 46.7207 10 <.0001  
 Test 2 7.53342 5 0.1839  
 Test 3 7.53342 5 0.1839  
 Test 4 1.68749 3 0.6397  
  
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 = 12.4753  
  
 BMDL = 6.07923  
  
 BMDU = 32.3833