# Female BMD Results for Table: Liver Weight Absolute

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 0.15 | 0.5 | 1.4 | 4 | 12 | 37 | 111 | 333 | 1000 |
| N | 10 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Mean ± SD | 7.92 ± 1.3 | 8.474 ± 1.353 | 8.214 ± 0.482 | 7.8 ± 0.847 | 7.868 ± 1.026 | 8.15 ± 0.475 | 8.16 ± 0.534 | 7.868 ± 0.281 | 9.224 ± 0.397 | 12.018 ± 0.377 |

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear | 0.775 | 33.084 | 220.283 | 184.809 | No model was recommended as a best-fitting model. Doses were dropped until there were only 3 remaining dose-groups. |
| Polynomial 2° (equivalent models include Polynomial 3°, 4°, 5°, 6°, 7°, 8°) | 0.698 | 34.938 | 240.665 | 185.656 |
| Power | 0.705 | 34.88 | 246.095 | 186.002 |
| Hill | 0.658 | 36.387 | 282.368 | -999 |
| Exponential M2 (equivalent models include Exponential M3) | 0.782 | 33.017 | 256.915 | 218.11 |
| Exponential M4 | 0.68 | 35.091 | 219.881 | 162.44 |
| Exponential M5 | 0.659 | 36.386 | 284.698 | 170.216 |

a Modeled variance case presented (BMDS Test 2 p-value = 3.4E-04, BMDS Test 3 p-value = 0.005).

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear | Warning | **Warnings**  • Variance model poorly fits dataset (p-value 3 = 0.004616) |
| Polynomial 2° (equivalent models include Polynomial 3°, 4°, 5°, 6°, 7°, 8°) | Warning | **Warnings**  • Variance model poorly fits dataset (p-value 3 = 0.004616) |
| Power | Warning | **Warnings**  • Variance model poorly fits dataset (p-value 3 = 0.004616) |
| Hill | Failure | **Failures**  • BMDL does not exist  **Warnings**  • Variance model poorly fits dataset (p-value 3 = 0.004616)  **Cautions**  • Warning(s): BMDL computation failed. |
| Exponential M2 (equivalent models include Exponential M3) | Warning | **Warnings**  • Variance model poorly fits dataset (p-value 3 = 0.004616) |
| Exponential M4 | Warning | **Warnings**  • Variance model poorly fits dataset (p-value 3 = 0.004616) |
| Exponential M5 | Warning | **Warnings**  • Variance model poorly fits dataset (p-value 3 = 0.004616) |

## Recommended model

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

# Female BMD Results for Table: Liver Weight Relative

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 0.15 | 0.5 | 1.4 | 4 | 12 | 37 | 111 | 333 | 1000 |
| N | 10 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Mean ± SD | 36.004 ± 2.271 | 37.504 ± 2.883 | 37.543 ± 0.863 | 35.52 ± 1.434 | 36.674 ± 2.523 | 37.148 ± 1.614 | 36.755 ± 1.025 | 36.404 ± 0.763 | 42.013 ± 1.109 | 53.976 ± 2.062 |

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear | 0.152 | 132.052 | 109.581 | 91.979 | No model was recommended as a best-fitting model. Doses were dropped until there were only 3 remaining dose-groups. |
| Polynomial 2° (equivalent models include Polynomial 5°, 6°, 7°, 8°) | 0.147 | 132.882 | 134.341 | 95.897 |
| Polynomial 3° (equivalent models include Polynomial 4°) | 0.147 | 132.882 | 134.342 | 95.897 |
| Power | 0.179 | 132.24 | 148.196 | 98.895 |
| Hill | 0.369 | 130.574 | 302.32 | 143.094 |
| Exponential M2 | 0.208 | 130.962 | 128.406 | 108.411 |
| Exponential M3 | 0.152 | 132.765 | 143.12 | 109.068 |
| Exponential M4 | 0.101 | 134.062 | 109.5 | 89.216 |
| Exponential M5 | 0.369 | 130.574 | 304.527 | 143.251 |

a Modeled variance case presented (BMDS Test 2 p-value = 0.024, BMDS Test 3 p-value = 0.014).

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear | Warning | **Warnings**  • Variance model poorly fits dataset (p-value 3 = 0.01397) |
| Polynomial 2° (equivalent models include Polynomial 5°, 6°, 7°, 8°) | Warning | **Warnings**  • Variance model poorly fits dataset (p-value 3 = 0.01397) |
| Polynomial 3° (equivalent models include Polynomial 4°) | Warning | **Warnings**  • Variance model poorly fits dataset (p-value 3 = 0.01397) |
| Power | Warning | **Warnings**  • Variance model poorly fits dataset (p-value 3 = 0.01397) |
| Hill | Warning | **Warnings**  • Variance model poorly fits dataset (p-value 3 = 0.01397) |
| Exponential M2 | Warning | **Warnings**  • Variance model poorly fits dataset (p-value 3 = 0.01397) |
| Exponential M3 | Warning | **Warnings**  • Variance model poorly fits dataset (p-value 3 = 0.01397) |
| Exponential M4 | Warning | **Warnings**  • Variance model poorly fits dataset (p-value 3 = 0.01397) |
| Exponential M5 | Warning | **Warnings**  • Variance model poorly fits dataset (p-value 3 = 0.01397) |

## Recommended model

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

# Female BMD Results for Table: Aspartate Aminotransferase

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 0.15 | 0.5 | 1.4 | 4 | 12 | 37 | 111 | 333 | 1000 |
| N | 10 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Mean ± SD | 72.8 ± 5.613 | 73.6 ± 5.459 | 71.8 ± 4.55 | 76.4 ± 7.893 | 77 ± 5.788 | 75.6 ± 5.55 | 79.2 ± 6.648 | 74 ± 8.276 | 76 ± 6.124 | 103.6 ± 44.253 |

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear | 0.295 | 281.094 | 328.341 | 166.328 | Polynomial-2 recommended as best-fitting model on the basis of the lowest AIC. |
| Polynomial 2°b | 0.413 | 280.572 | 497.046 | 340.458 |
| Polynomial 3° | 0.382 | 281.829 | 581.505 | 276.527 |
| Polynomial 4° | 0.398 | 281.671 | 633.117 | 280.386 |
| Polynomial 5° | 0.402 | 281.625 | 678.281 | 281.014 |
| Polynomial 6° | 0.404 | 281.61 | 715.667 | 281.061 |
| Polynomial 7° | 0.404 | 281.605 | 746.075 | 281.034 |
| Polynomial 8° | 0.404 | 281.604 | 770.868 | 281.014 |
| Power | 0.386 | 281.789 | 653.695 | 319.255 |
| Hill | 0.283 | 283.789 | 645.285 | -999 |
| Exponential M2 | 0.239 | 282.752 | 349.77 | 181.833 |
| Exponential M3 | 0.386 | 281.788 | 665.246 | 310.922 |
| Exponential M4 | 0.151 | 285.098 | 328.082 | 158.902 |
| Exponential M5 | 0.283 | 283.789 | 652.659 | 319.256 |

a Modeled variance case presented (BMDS Test 2 p-value = <0.0001, BMDS Test 3 p-value = 0.967).

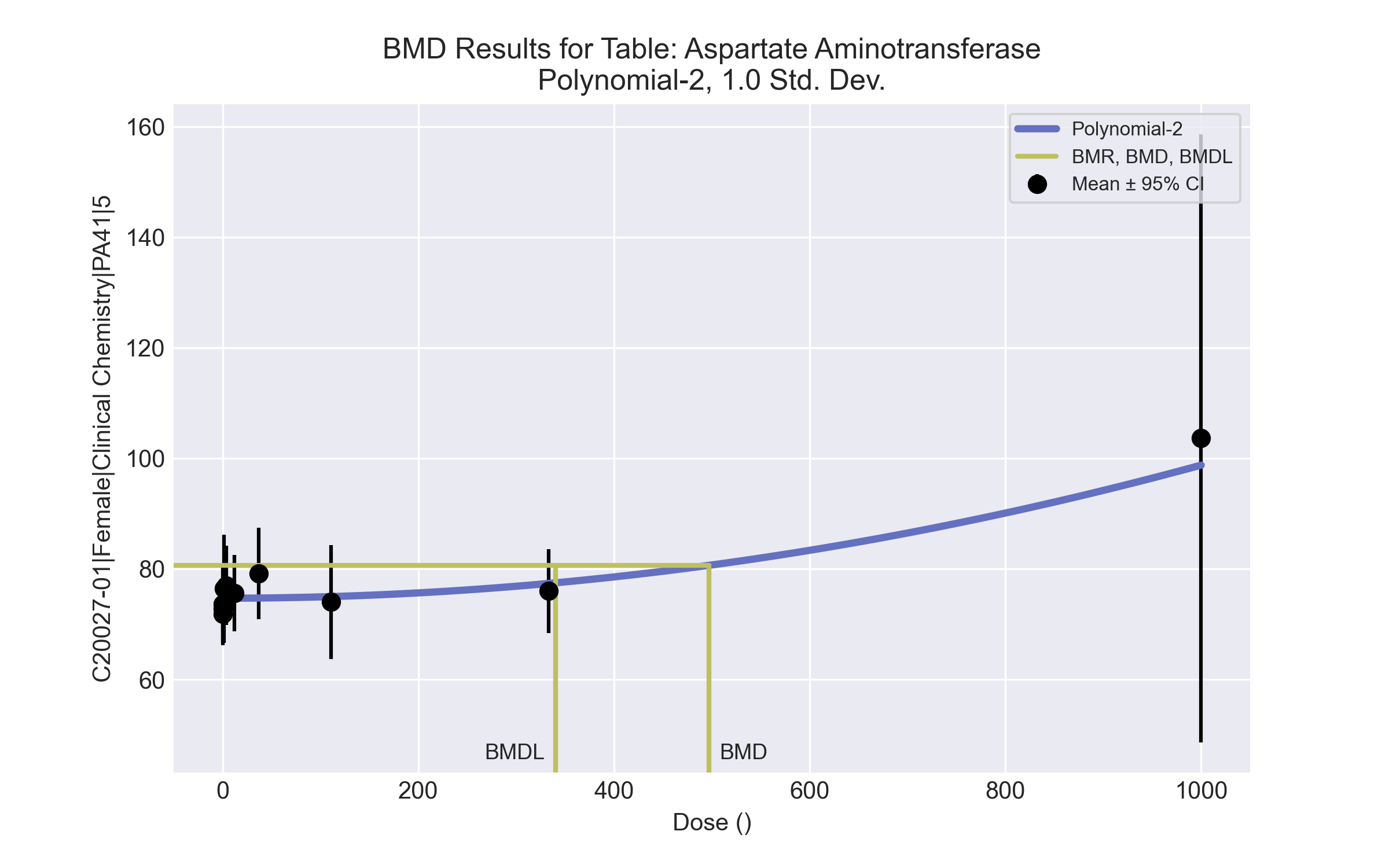
b Recommended model

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear | Valid | **Cautions**  • Warning(s): THE MODEL HAS PROBABLY NOT CONVERGED!!!; THIS USUALLY MEANS THE MODEL HAS NOT CONVERGED! |
| Polynomial 2°a | Valid | - |
| Polynomial 3° | Valid | - |
| Polynomial 4° | Valid | - |
| Polynomial 5° | Valid | - |
| Polynomial 6° | Valid | - |
| Polynomial 7° | Valid | - |
| Polynomial 8° | Valid | - |
| Power | Valid | - |
| Hill | Failure | **Failures**  • BMDL does not exist  **Cautions**  • Warning(s): BMDL computation failed. |
| Exponential M2 | Valid | - |
| Exponential M3 | Valid | - |
| Exponential M4 | Valid | - |
| Exponential M5 | Valid | - |

a Recommended model

## Recommended model



====================================================================   
 Polynomial Model. (Version: 2.21; Date: 03/14/2017)   
 Input Data File: C:\Windows\TEMP\bmds-06a6bhmm.(d)   
 Gnuplot Plotting File: C:\Windows\TEMP\bmds-06a6bhmm.plt  
 Thu Apr 15 13:45:31 2021  
 ====================================================================   
  
 BMDS\_Model\_Run   
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~  
   
 The form of the response function is:   
  
 Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ...  
  
  
 Dependent variable = Response  
 Independent variable = Dose  
 The polynomial coefficients are restricted to be positive  
 The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) \* rho)  
  
 Total number of dose groups = 10  
 Total number of records with missing values = 0  
 Maximum number of iterations = 500  
 Relative Function Convergence has been set to: 1e-008  
 Parameter Convergence has been set to: 1e-008  
  
  
  
 Default Initial Parameter Values   
 lalpha = 5.34456  
 rho = 0  
 beta\_0 = 75.1017  
 beta\_1 = 0  
 beta\_2 = 0  
  
  
 Asymptotic Correlation Matrix of Parameter Estimates  
  
 ( \*\*\* The model parameter(s) -beta\_1   
 have been estimated at a boundary point, or have been specified by the user,  
 and do not appear in the correlation matrix )  
  
 lalpha rho beta\_0 beta\_2  
  
 lalpha 1 -1 -0.00035 0.011  
  
 rho -1 1 0.00043 -0.011  
  
 beta\_0 -0.00035 0.00043 1 -0.26  
  
 beta\_2 0.011 -0.011 -0.26 1  
  
  
  
 Parameter Estimates  
  
 95.0% Wald Confidence Interval  
 Variable Estimate Std. Err. Lower Conf. Limit Upper Conf. Limit  
 lalpha -54.4827 10.1527 -74.3816 -34.5838  
 rho 13.4581 2.3377 8.87625 18.0399  
 beta\_0 74.6848 0.889435 72.9416 76.4281  
 beta\_1 2.58494e-029 NA  
 beta\_2 2.40701e-005 1.97954e-005 -1.47281e-005 6.28683e-005  
  
NA - Indicates that this parameter has hit a bound  
 implied by some inequality constraint and thus  
 has no standard error.  
  
  
  
 Table of Data and Estimated Values of Interest  
  
 Dose N Obs Mean Est Mean Obs Std Dev Est Std Dev Scaled Res.  
------ --- -------- -------- ----------- ----------- ----------  
  
 0 10 72.8 74.7 5.61 5.95 -1  
 0.15 5 73.6 74.7 5.46 5.95 -0.408  
 0.5 5 71.8 74.7 4.55 5.95 -1.08  
 1.4 5 76.4 74.7 7.89 5.95 0.645  
 4 5 77 74.7 5.79 5.95 0.87  
 12 5 75.6 74.7 5.55 5.95 0.343  
 37 5 79.2 74.7 6.65 5.96 1.68  
 111 5 74 75 8.28 6.11 -0.359  
 333 5 76 77.4 6.12 7.53 -0.402  
 1000 5 104 98.8 44.3 39 0.278  
  
  
  
 Model Descriptions for likelihoods calculated  
  
  
 Model A1: Yij = Mu(i) + e(ij)  
 Var{e(ij)} = Sigma^2  
  
 Model A2: Yij = Mu(i) + e(ij)  
 Var{e(ij)} = Sigma(i)^2  
  
 Model A3: Yij = Mu(i) + e(ij)  
 Var{e(ij)} = exp(lalpha + rho\*ln(Mu(i)))  
 Model A3 uses any fixed variance parameters that  
 were specified by the user  
  
 Model R: Yi = Mu + e(i)  
 Var{e(i)} = Sigma^2  
  
  
 Likelihoods of Interest  
  
 Model Log(likelihood) # Param's AIC  
 A1 -168.957083 11 359.914167  
 A2 -130.992657 20 301.985313  
 A3 -132.181824 12 288.363648  
 fitted -136.285898 4 280.571797  
 R -178.638723 2 361.277447  
  
  
 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 95.2921 18 <.0001  
 Test 2 75.9289 9 <.0001  
 Test 3 2.37834 8 0.9672  
 Test 4 8.20815 8 0.4134  
  
The p-value for Test 1 is less than .05. There appears to be a  
difference between response and/or variances among the dose levels  
It seems appropriate to model the data  
  
The p-value for Test 2 is less than .1. A non-homogeneous variance   
model appears to be appropriate  
  
The p-value for Test 3 is greater than .1. The modeled variance appears   
 to be appropriate here  
  
The p-value for Test 4 is greater than .1. The model chosen seems   
to adequately describe the data  
   
  
 Benchmark Dose Computation  
  
Specified effect = 1  
  
Risk Type = Estimated standard deviations from the control mean  
  
Confidence level = 0.95  
  
 BMD = 497.046  
  
  
 BMDL = 340.458  
  
  
 BMDU = 694.186

# Female BMD Results for Table: Bile salts/acids

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 0.15 | 0.5 | 1.4 | 4 | 12 | 37 | 111 | 333 | 1000a |
| N | 10 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Mean ± SD | 15.7 ± 5.143 | 26.2 ± 7.791 | 16.4 ± 5.273 | 21.2 ± 10.964 | 19.8 ± 8.044 | 17.6 ± 8.562 | 27 ± 14.23 | 21.8 ± 10.895 | 30 ± 12.39 | 24.8 ± 16.3 |

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°, 6°, 7°, 8°) | 0.28 | 277.398 | 286.331 | 169.743 | Exponential-M4 recommended as best-fitting model on the basis of the lowest BMDL. |
| Hill | 0.208 | 279.203 | 253.883 | 26.123 |
| Exponential M2 (equivalent models include Exponential M3) | 0.274 | 277.476 | 295.921 | 196.52 |
| Exponential M4b (equivalent models include Exponential M5) | 0.203 | 279.27 | 257.017 | 21.486 |

a Constant variance case presented (BMDS Test 2 p-value = 0.204, BMDS Test 3 p-value = 0.204).

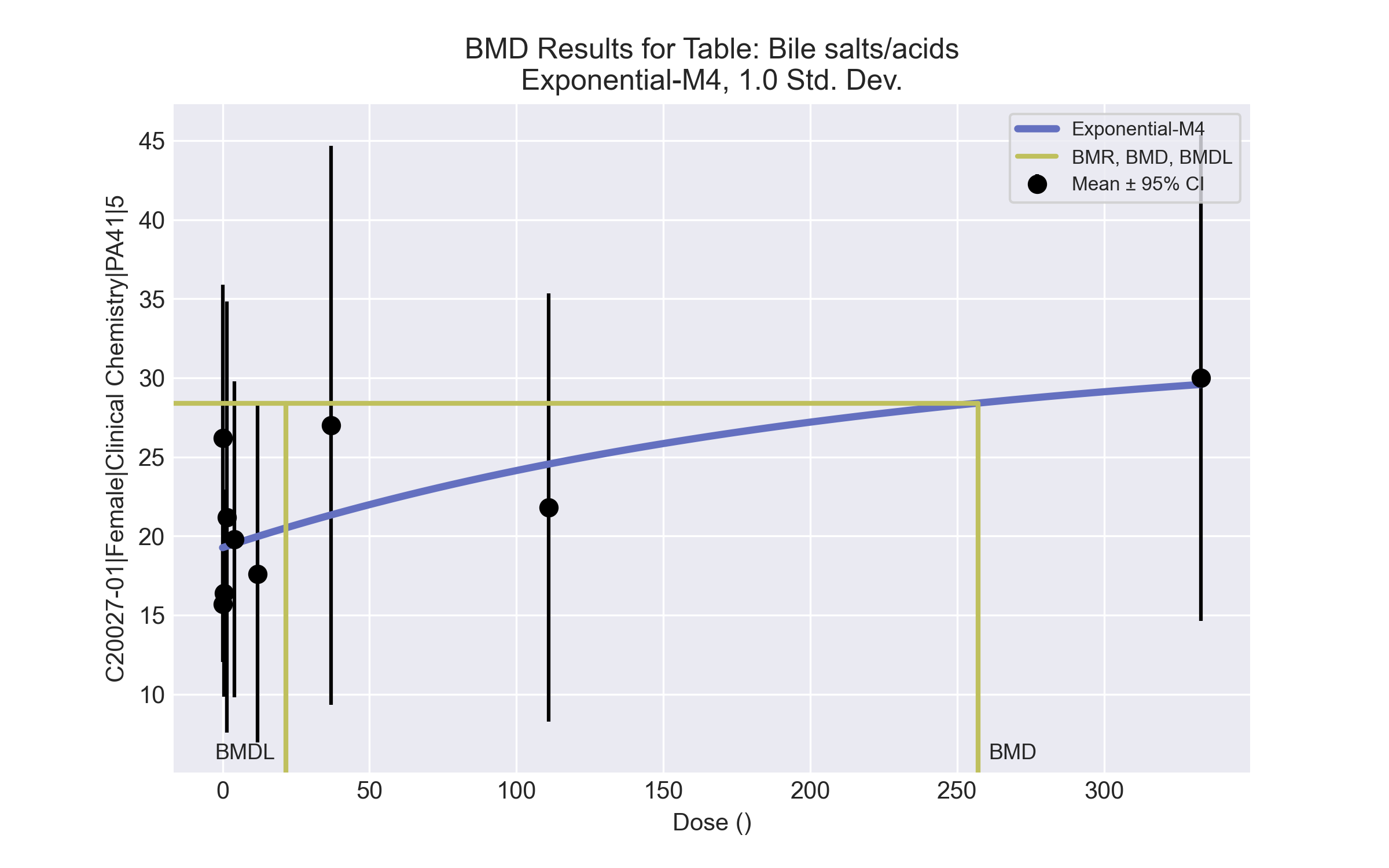
b Recommended model

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear (equivalent models include Power, Polynomial 2°, 3°, 4°, 5°, 6°, 7°, 8°) | Warning | **Warnings**  • Ratio of modeled to actual stdev. at control is greater than threshold (1.78 > 1.5) |
| Hill | Warning | **Warnings**  • Ratio of modeled to actual stdev. at control is greater than threshold (1.78 > 1.5)  **Cautions**  • BMD/BMDL ratio is greater than threshold (9.72 > 5.0) |
| Exponential M2 (equivalent models include Exponential M3) | Valid | - |
| Exponential M4a (equivalent models include Exponential M5) | Valid | **Cautions**  • BMD/BMDL ratio is greater than threshold (12.0 > 5.0) |

a Recommended model

## Recommended model



====================================================================   
 Exponential Model. (Version: 1.11; Date: 03/14/2017)   
 Input Data File: C:\Windows\TEMP\bmds-nyiku0fr.(d)   
 Gnuplot Plotting File:   
 Thu Apr 15 13:45:55 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 = 9  
 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 4.25524   
 rho 0 Specified  
 a 14.915   
 b 0.00731443   
 c 2.11197   
 d 1 Specified  
  
  
  
 Parameter Estimates  
  
 Variable Model 4 Std. Err.  
 -------- ------- ---------  
 lnalpha 4.42541 16.7094  
 a 19.2643 1.664  
 b 0.0046553 0.0138447  
 c 1.68001 0.976015  
  
 NC = No Convergence  
  
  
 Table of Stats From Input Data  
  
 Dose N Obs Mean Obs Std Dev  
 ----- --- ---------- -------------  
 0 10 15.7 5.143  
 0.15 5 26.2 7.791  
 0.5 5 16.4 5.273  
 1.4 5 21.2 10.96  
 4 5 19.8 8.044  
 12 5 17.6 8.562  
 37 5 27 14.23  
 111 5 21.8 10.89  
 333 5 30 12.39  
  
  
 Estimated Values of Interest  
  
 Dose Est Mean Est Std Scaled Residual  
 ------ ---------- --------- ----------------  
 0 19.26 9.14 -1.233  
 0.15 19.27 9.14 1.694  
 0.5 19.29 9.14 -0.7082  
 1.4 19.35 9.14 0.4527  
 4 19.51 9.14 0.07193  
 12 19.98 9.14 -0.5813  
 37 21.34 9.14 1.385  
 111 24.55 9.14 -0.6729  
 333 29.58 9.14 0.1017  
  
  
  
 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 -131.3811 10 282.7622  
 A2 -125.9014 18 287.8028  
 A3 -131.3811 10 282.7622  
 R -138.5718 2 281.1437  
 4 -135.6352 4 279.2704  
  
  
 Additive constant for all log-likelihoods = -45.95. 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 25.34 16 0.06404  
 Test 2 10.96 8 0.204  
 Test 3 10.96 8 0.204  
 Test 6a 8.508 6 0.2032  
  
  
 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 = 257.017  
  
 BMDL = 21.4864  
  
 BMDU = 3.33e+006

# Female BMD Results for Table: Cholesterol

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 0.15 | 0.5 | 1.4 | 4 | 12a | 37a | 111a | 333a | 1000a |
| N | 10 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Mean ± SD | 95.6 ± 15.543 | 100.6 ± 17.242 | 104.8 ± 17.992 | 93.6 ± 26.623 | 82.2 ± 8.585 | 84.8 ± 4.97 | 90.4 ± 6.107 | 92.8 ± 7.014 | 38 ± 10.124 | 54 ± 15.166 |

a Dose group removed in BMD modeling session

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear | 0.647 | 204.428 | 4.032 | 2.147 | Exponential-M5 recommended as best-fitting model on the basis of the lowest BMDL. |
| Polynomial 2° (equivalent models include Polynomial 4°, 5°, 8°) | 0.713 | 204.143 | 3.985 | 2.203 |
| Polynomial 3° (equivalent models include Polynomial 6°) | 0.713 | 204.143 | 3.985 | 2.934 |
| Polynomial 7° | 0.713 | 204.143 | 3.985 | 2.934 |
| Power | 0.509 | 206.127 | 3.963 | 2.206 |
| Hill | 0.29 | 207.895 | 1.763 | 0.639 |
| Exponential M2 (equivalent models include Exponential M4) | 0.637 | 204.475 | 4.098 | 2.008 |
| Exponential M3 | 0.511 | 206.119 | 3.955 | 2.085 |
| Exponential M5b | 0.29 | 207.895 | 1.591 | 0.58 |

a Constant variance case presented (BMDS Test 2 p-value = 0.22, BMDS Test 3 p-value = 0.22).

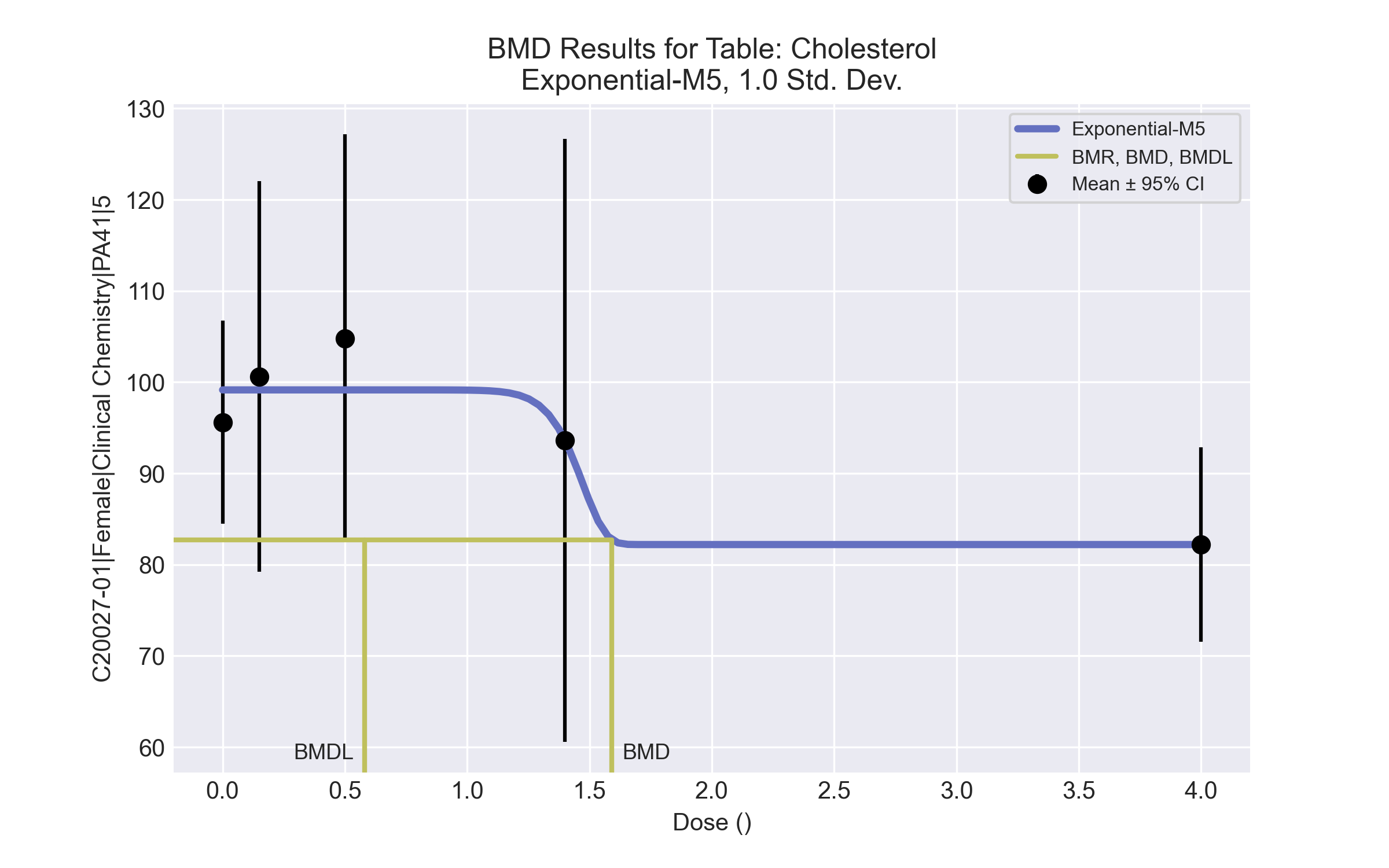
b Recommended model

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear | Warning | **Warnings**  • BMD/high dose ratio is greater than threshold (1.01 > 1.0) |
| Polynomial 2° (equivalent models include Polynomial 4°, 5°, 8°) | Valid | - |
| Polynomial 3° (equivalent models include Polynomial 6°) | Valid | - |
| Polynomial 7° | Valid | - |
| Power | Valid | - |
| Hill | Valid | - |
| Exponential M2 (equivalent models include Exponential M4) | Warning | **Warnings**  • BMD/high dose ratio is greater than threshold (1.02 > 1.0) |
| Exponential M3 | Valid | - |
| Exponential M5a | Valid | - |

a Recommended model

## Recommended model



====================================================================   
 Exponential Model. (Version: 1.11; Date: 03/14/2017)   
 Input Data File: C:\Windows\TEMP\bmds-\_g\_hf\_x9.(d)   
 Gnuplot Plotting File:   
 Thu Apr 15 13:46:49 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 = 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 5  
 -------- --------  
 lnalpha 5.55919   
 rho 0 Specified  
 a 110.04   
 b 0.52311   
 c 0.71143   
 d 1   
  
  
  
 Parameter Estimates  
  
 Variable Model 5 Std. Err.  
 -------- ------- ---------  
 lnalpha 5.59651 69.5807  
 a 99.15 3.67073  
 b 0.676323 15.4063  
 c 0.829047 0.0801534  
 d 16.932 7062.48  
  
 NC = No Convergence  
  
  
 Table of Stats From Input Data  
  
 Dose N Obs Mean Obs Std Dev  
 ----- --- ---------- -------------  
 0 10 95.6 15.54  
 0.15 5 100.6 17.24  
 0.5 5 104.8 17.99  
 1.4 5 93.6 26.62  
 4 5 82.2 8.585  
  
  
 Estimated Values of Interest  
  
 Dose Est Mean Est Std Scaled Residual  
 ------ ---------- --------- ----------------  
 0 99.15 16.42 -0.6839  
 0.15 99.15 16.42 0.1975  
 0.5 99.15 16.42 0.7696  
 1.4 93.6 16.42 -3.158e-008  
 4 82.2 16.42 1.523e-009  
  
  
  
 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 -98.3879 6 208.7758  
 A2 -95.52352 10 211.047  
 A3 -98.3879 6 208.7758  
 R -100.9729 2 205.9458  
 5 -98.94769 5 207.8954  
  
  
 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 7a: Does Model 5 fit the data? (A3 vs 5)  
  
  
 Tests of Interest  
  
 Test -2\*log(Likelihood Ratio) D. F. p-value  
 -------- ------------------------ ------ --------------  
 Test 1 10.9 8 0.2075  
 Test 2 5.729 4 0.2203  
 Test 3 5.729 4 0.2203  
 Test 7a 1.12 1 0.29  
  
  
 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 7a is greater than .1. Model 5 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 = 1.59098  
  
 BMDL = 0.579739  
  
 BMDU = 40000

# Female BMD Results for Table: Creatinine

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 0.15 | 0.5 | 1.4 | 4 | 12 | 37 | 111 | 333 | 1000 |
| N | 10 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Mean ± SD | 0.41 ± 0.057 | 0.4 ± 0 | 0.44 ± 0.055 | 0.42 ± 0.045 | 0.44 ± 0.055 | 0.42 ± 0.045 | 0.48 ± 0.045 | 0.4 ± 0 | 0.46 ± 0.055 | 0.46 ± 0.055 |

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear (equivalent models include Power, Polynomial 2°, 3°, 4°, 5°, 6°, 7°) | <0.0001 | -269.626 | 1195.15 | 555.747 | No model was recommended as a best-fitting model. Doses were dropped until there were only 3 remaining dose-groups. |
| Polynomial 8° | <0.0001 | -268.549 | -9999 | -999 |
| Hill | <0.0001 | -269.644 | -999 | -999 |
| Exponential M2 | -999 | 1495.624 | 611883 | 341.628 |
| Exponential M3 | -999 | -224.8 | 896911 | -999 |
| Exponential M4 | -999 | -26.965 | -999 | 0 |
| Exponential M5 | -999 | -24.95 | -999 | 0 |

a Modeled variance case presented (BMDS Test 2 p-value = <0.0001, BMDS Test 3 p-value = <0.0001).

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear (equivalent models include Power, Polynomial 2°, 3°, 4°, 5°, 6°, 7°) | Warning | **Warnings**  • Variance model poorly fits dataset (p-value 3 = 0.0001)  • BMD/high dose ratio is greater than threshold (1.2 > 1.0)  **Cautions**  • Warning(s): Warning: Likelihood for fitted model larger than the Likelihood for model A3. |
| Polynomial 8° | Failure | **Failures**  • BMDL does not exist  **Warnings**  • Residual of Interest does not exist  • Variance model poorly fits dataset (p-value 3 = 0.0001)  **Cautions**  • Warning(s): THIS USUALLY MEANS THE MODEL HAS NOT CONVERGED!; BMD = 100\*(maximum dose); BMDL computation failed.; Warning: Likelihood for fitted model larger than the Likelihood for model A3. |
| Hill | Failure | **Failures**  • BMD does not exist  • BMDL does not exist  **Warnings**  • Residual of Interest does not exist  • Variance model poorly fits dataset (p-value 3 = 0.0001)  **Cautions**  • Warning(s): BMR value is not in the range of the mean function |
| Exponential M2 | Warning | **Warnings**  • BMD/BMDL ratio is greater than threshold (1.79e+03 > 20.0)  • BMD/high dose ratio is greater than threshold (6.12e+02 > 1.0)  **Cautions**  • BMD/BMDL ratio is greater than threshold (1.79e+03 > 5.0) |
| Exponential M3 | Failure | **Failures**  • BMDL does not exist  **Warnings**  • BMD/high dose ratio is greater than threshold (8.97e+02 > 1.0)  • Residual at lowest dose is greater than threshold (2.83 > 2.0) |
| Exponential M4 | Failure | **Failures**  • BMD does not exist  **Warnings**  • Residual of Interest does not exist  • Residual at lowest dose is greater than threshold (3.04 > 2.0) |
| Exponential M5 | Failure | **Failures**  • BMD does not exist  **Warnings**  • Residual of Interest does not exist  • Residual at lowest dose is greater than threshold (3.02 > 2.0) |

## Recommended model

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

# Female BMD Results for Table: Triglycerides

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 0.15 | 0.5 | 1.4 | 4 | 12 | 37a | 111a | 333a | 1000a |
| N | 10 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Mean ± SD | 70.9 ± 32.882 | 68.6 ± 42.01 | 45.4 ± 14.153 | 40.6 ± 17.184 | 34.6 ± 20.756 | 39.4 ± 11.739 | 47 ± 23.558 | 53 ± 17.321 | 111 ± 15.859 | 143.2 ± 56.331 |

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°, 4°, 5°, 6°) | 0.015 | 268.534 | 21.641 | 11.162 | Exponential-M4 recommended as best-fitting model on the basis of the lowest AIC. |
| Polynomial 2° (equivalent models include Polynomial 7°) | 0.015 | 268.534 | 21.641 | 11.162 |
| Polynomial 8° | 5.0E-04 | 276.361 | -9999 | -999 |
| Hill | 0.836 | 260.603 | -999 | -999 |
| Exponential M2 (equivalent models include Exponential M3) | 0.018 | 268.148 | 24.51 | 9.52 |
| Exponential M4b | 0.493 | 260.648 | 1.518 | 0.255 |
| Exponential M5 | 0.836 | 260.603 | -999 | 0 |

a Modeled variance case presented (BMDS Test 2 p-value = 0.019, BMDS Test 3 p-value = 0.602).

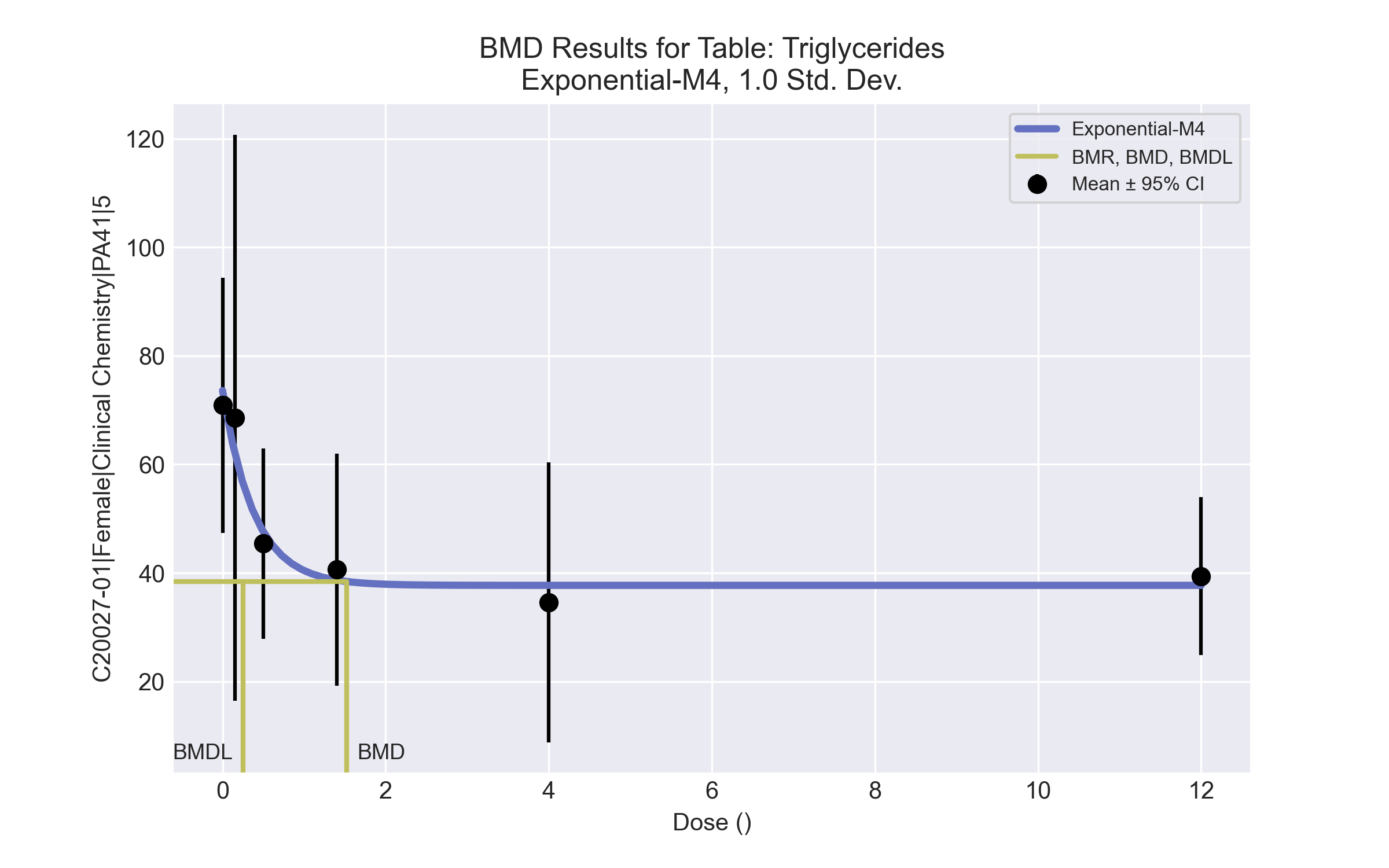
b Recommended model

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear (equivalent models include Power, Polynomial 3°, 4°, 5°, 6°) | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0153 < 0.1)  • BMD/high dose ratio is greater than threshold (1.8 > 1.0) |
| Polynomial 2° (equivalent models include Polynomial 7°) | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0153 < 0.1)  • BMD/high dose ratio is greater than threshold (1.8 > 1.0) |
| Polynomial 8° | Failure | **Failures**  • BMDL does not exist  **Warnings**  • Residual of Interest does not exist  • Goodness of fit p-value is less than threshold (0.000498 < 0.1)  **Cautions**  • Warning(s): THIS USUALLY MEANS THE MODEL HAS NOT CONVERGED!; BMD = 100\*(maximum dose); BMDL computation failed. |
| Hill | Failure | **Failures**  • BMD does not exist  • BMDL does not exist  **Warnings**  • Residual of Interest does not exist  **Cautions**  • Warning(s): BMR value is not in the range of the mean function |
| Exponential M2 (equivalent models include Exponential M3) | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0181 < 0.1)  • BMD/high dose ratio is greater than threshold (2.04 > 1.0) |
| Exponential M4a | Valid | **Cautions**  • BMD/BMDL ratio is greater than threshold (5.95 > 5.0) |
| Exponential M5 | Failure | **Failures**  • BMD does not exist  **Warnings**  • Residual of Interest does not exist |

a Recommended model

## Recommended model



====================================================================   
 Exponential Model. (Version: 1.11; Date: 03/14/2017)   
 Input Data File: C:\Windows\TEMP\bmds-tw0\_3cmf.(d)   
 Gnuplot Plotting File:   
 Thu Apr 15 13:48:19 2021  
 ====================================================================   
  
 BMDS\_Model\_Run   
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~  
   
 The form of the response function by Model:   
 Model 2: Y[dose] = a \* exp{sign \* b \* dose}  
 Model 3: Y[dose] = a \* exp{sign \* (b \* dose)^d}  
 Model 4: Y[dose] = a \* [c-(c-1) \* exp{-b \* dose}]  
 Model 5: Y[dose] = a \* [c-(c-1) \* exp{-(b \* dose)^d}]  
  
 Note: Y[dose] is the median response for exposure = dose;  
 sign = +1 for increasing trend in data;  
 sign = -1 for decreasing trend.  
  
 Model 2 is nested within Models 3 and 4.  
 Model 3 is nested within Model 5.  
 Model 4 is nested within Model 5.  
  
  
 Dependent variable = Response  
 Independent variable = Dose  
 Data are assumed to be distributed: normally  
 Variance Model: exp(lnalpha +rho \*ln(Y[dose]))  
 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 -4.03687   
 rho 2.61177   
 a 74.445   
 b 0.235703   
 c 0.442641   
 d 1 Specified  
  
  
  
 Parameter Estimates  
  
 Variable Model 4 Std. Err.  
 -------- ------- ---------  
 lnalpha -4.03693 4.19401  
 rho 2.59561 1.06922  
 a 73.5994 10.1082  
 b 2.58242 1.52944  
 c 0.51242 0.0877637  
  
 NC = No Convergence  
  
  
 Table of Stats From Input Data  
  
 Dose N Obs Mean Obs Std Dev  
 ----- --- ---------- -------------  
 0 10 70.9 32.88  
 0.15 5 68.6 42.01  
 0.5 5 45.4 14.15  
 1.4 5 40.6 17.18  
 4 5 34.6 20.76  
 12 5 39.4 11.74  
  
  
 Estimated Values of Interest  
  
 Dose Est Mean Est Std Scaled Residual  
 ------ ---------- --------- ----------------  
 0 73.6 35.17 -0.2427  
 0.15 62.07 28.2 0.5174  
 0.5 47.58 19.97 -0.2441  
 1.4 38.68 15.26 0.2814  
 4 37.72 14.77 -0.4716  
 12 37.71 14.77 0.2553  
  
  
  
 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 -129.4853 7 272.9706  
 A2 -122.7507 12 269.5014  
 A3 -124.1228 8 264.2456  
 R -135.1807 2 274.3615  
 4 -125.3239 5 260.6478  
  
  
 Additive constant for all log-likelihoods = -32.16. 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 24.86 10 0.005617  
 Test 2 13.47 5 0.01936  
 Test 3 2.744 4 0.6015  
 Test 6a 2.402 3 0.4932  
  
  
 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 = 1.51846  
  
 BMDL = 0.255109  
  
 BMDU = 120000

# Female BMD Results for Table: Large Unstained Cell count

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 0.15 | 0.5 | 1.4 | 4 | 12 | 37 | 111 | 333 | 1000a |
| N | 9 | 5 | 5 | 4 | 5 | 5 | 5 | 5 | 5 | 5 |
| Mean ± SD | 0.038 ± 0.019 | 0.06 ± 0.022 | 0.054 ± 0.011 | 0.05 ± 0.016 | 0.054 ± 0.017 | 0.044 ± 0.017 | 0.064 ± 0.005 | 0.072 ± 0.019 | 0.068 ± 0.018 | 0.07 ± 0.038 |

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°, 6°, 7°, 8°) | 0.041 | -332.839 | 265.641 | 161.565 | Exponential-M4 recommended as best-fitting model on the basis of the lowest AIC. |
| Hill | 0.134 | -335.018 | 38.173 | -999 |
| Exponential M2 (equivalent models include Exponential M3) | 0.035 | -332.386 | 289.862 | 190.393 |
| Exponential M4b | 0.143 | -335.86 | 54.339 | 15.759 |
| Exponential M5 | 0.134 | -335.018 | 37.347 | 12.803 |

a Constant variance case presented (BMDS Test 2 p-value = 0.292, BMDS Test 3 p-value = 0.292).

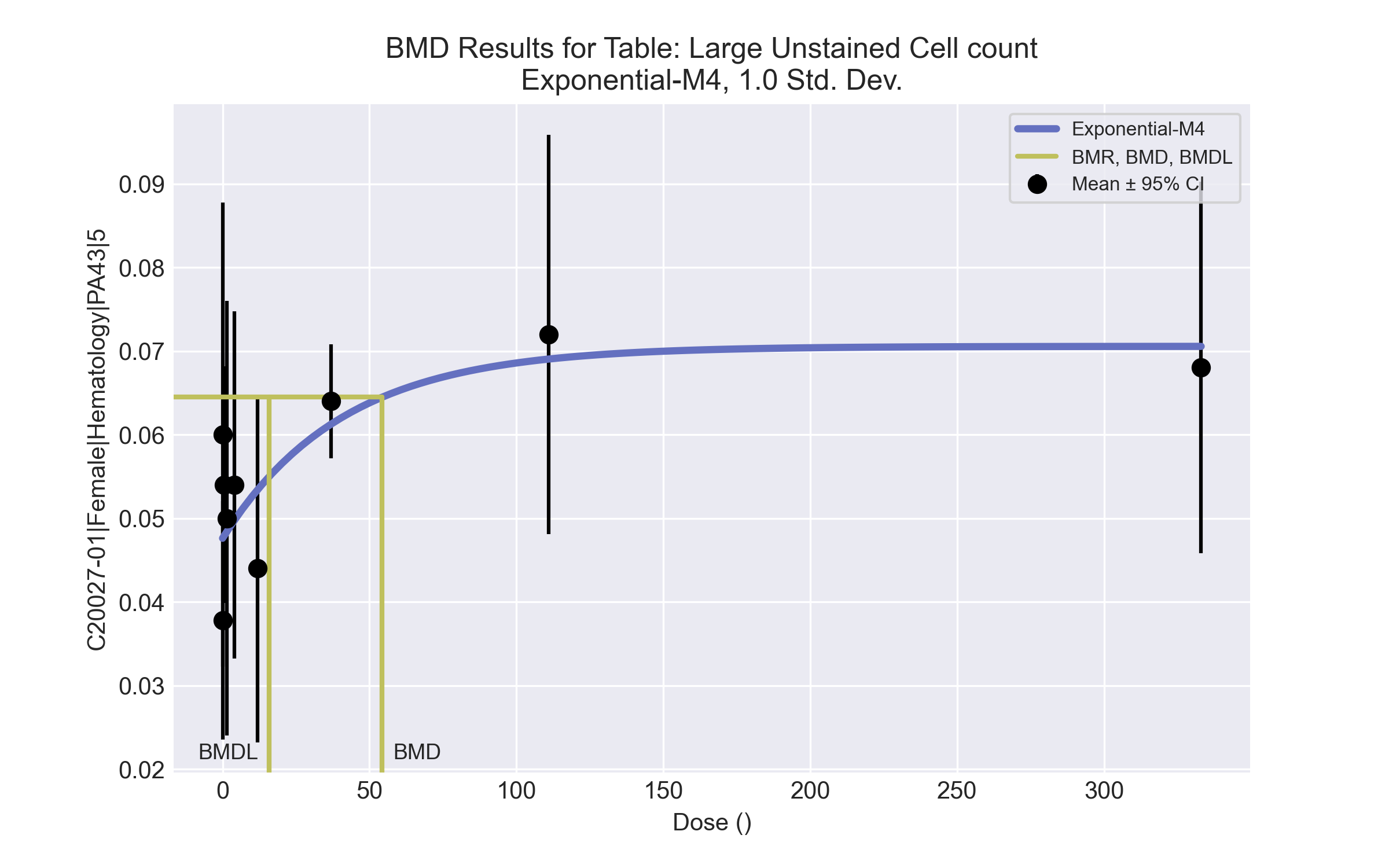
b Recommended model

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear (equivalent models include Power, Polynomial 2°, 3°, 4°, 5°, 6°, 7°, 8°) | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0414 < 0.1)  • Residual at lowest dose is greater than threshold (2.25 > 2.0) |
| 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 (0.0352 < 0.1)  • Residual at lowest dose is greater than threshold (2.3 > 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-y8k9w5r5.(d)   
 Gnuplot Plotting File:   
 Thu Apr 15 13:45:44 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 = 9  
 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 -8.36344   
 rho 0 Specified  
 a 0.0358891   
 b 0.00696525   
 c 2.10649   
 d 1 Specified  
  
  
  
 Parameter Estimates  
  
 Variable Model 4 Std. Err.  
 -------- ------- ---------  
 lnalpha -8.16375 5.8133e-005  
 a 0.0476037 0.00324839  
 b 0.0244522 0.0183599  
 c 1.4822 0.159195  
  
 NC = No Convergence  
  
  
 Table of Stats From Input Data  
  
 Dose N Obs Mean Obs Std Dev  
 ----- --- ---------- -------------  
 0 9 0.03778 0.01856  
 0.15 5 0.06 0.02236  
 0.5 5 0.054 0.0114  
 1.4 4 0.05 0.01633  
 4 5 0.054 0.01673  
 12 5 0.044 0.01673  
 37 5 0.064 0.005477  
 111 5 0.072 0.01923  
 333 5 0.068 0.01789  
  
  
 Estimated Values of Interest  
  
 Dose Est Mean Est Std Scaled Residual  
 ------ ---------- --------- ----------------  
 0 0.0476 0.01688 -1.747  
 0.15 0.04769 0.01688 1.631  
 0.5 0.04788 0.01688 0.8106  
 1.4 0.04838 0.01688 0.1924  
 4 0.04974 0.01688 0.5641  
 12 0.05344 0.01688 -1.251  
 37 0.06127 0.01688 0.3618  
 111 0.06904 0.01688 0.3926  
 333 0.07055 0.01688 -0.3381  
  
  
  
 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 176.7226 10 -333.4452  
 A2 181.5353 18 -327.0706  
 A3 176.7226 10 -333.4452  
 R 166.1513 2 -328.3026  
 4 171.93 4 -335.86  
  
  
 Additive constant for all log-likelihoods = -44.11. 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 6a: Does Model 4 fit the data? (A3 vs 4)  
  
  
 Tests of Interest  
  
 Test -2\*log(Likelihood Ratio) D. F. p-value  
 -------- ------------------------ ------ --------------  
 Test 1 30.77 16 0.0144  
 Test 2 9.625 8 0.2923  
 Test 3 9.625 8 0.2923  
 Test 6a 9.585 6 0.1432  
  
  
 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 = 54.3394  
  
 BMDL = 15.7594  
  
 BMDU = 3.33e+006

# Female BMD Results for Table: Monocyte count

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 0.15 | 0.5 | 1.4 | 4 | 12 | 37 | 111 | 333 | 1000 |
| N | 9 | 5 | 5 | 4 | 5 | 5 | 5 | 5 | 5 | 5 |
| Mean ± SD | 0.191 ± 0.125 | 0.31 ± 0.18 | 0.284 ± 0.068 | 0.29 ± 0.079 | 0.284 ± 0.109 | 0.22 ± 0.097 | 0.282 ± 0.071 | 0.368 ± 0.117 | 0.402 ± 0.141 | 0.656 ± 0.411 |

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linearb | 0.573 | -155.832 | 257.111 | 160.613 | Linear recommended as best-fitting model on the basis of the lowest AIC. |
| Polynomial 2° | 0.468 | -153.872 | 280.155 | 161.13 |
| Polynomial 3° | 0.47 | -153.892 | 285.634 | 161.389 |
| Polynomial 4° | 0.472 | -153.901 | 287.736 | 161.517 |
| Polynomial 5° | 0.472 | -153.905 | 288.39 | 161.565 |
| Polynomial 6° | 0.472 | -153.906 | 288.581 | 161.582 |
| Polynomial 7° | 0.472 | -153.907 | 288.635 | 161.587 |
| Polynomial 8° | 0.472 | -153.907 | 288.651 | 161.589 |
| Power | 0.467 | -153.864 | 275.45 | 161.02 |
| Hill | 0.355 | -151.863 | 275.404 | -999 |
| Exponential M2 (equivalent models include Exponential M3) | 0.553 | -155.653 | 353.037 | 251.765 |
| Exponential M4 | 0.464 | -153.831 | 256.625 | 115.12 |
| Exponential M5 | 0.355 | -151.863 | 275.19 | 115.704 |

a Modeled variance case presented (BMDS Test 2 p-value = <0.0001, BMDS Test 3 p-value = 0.191).

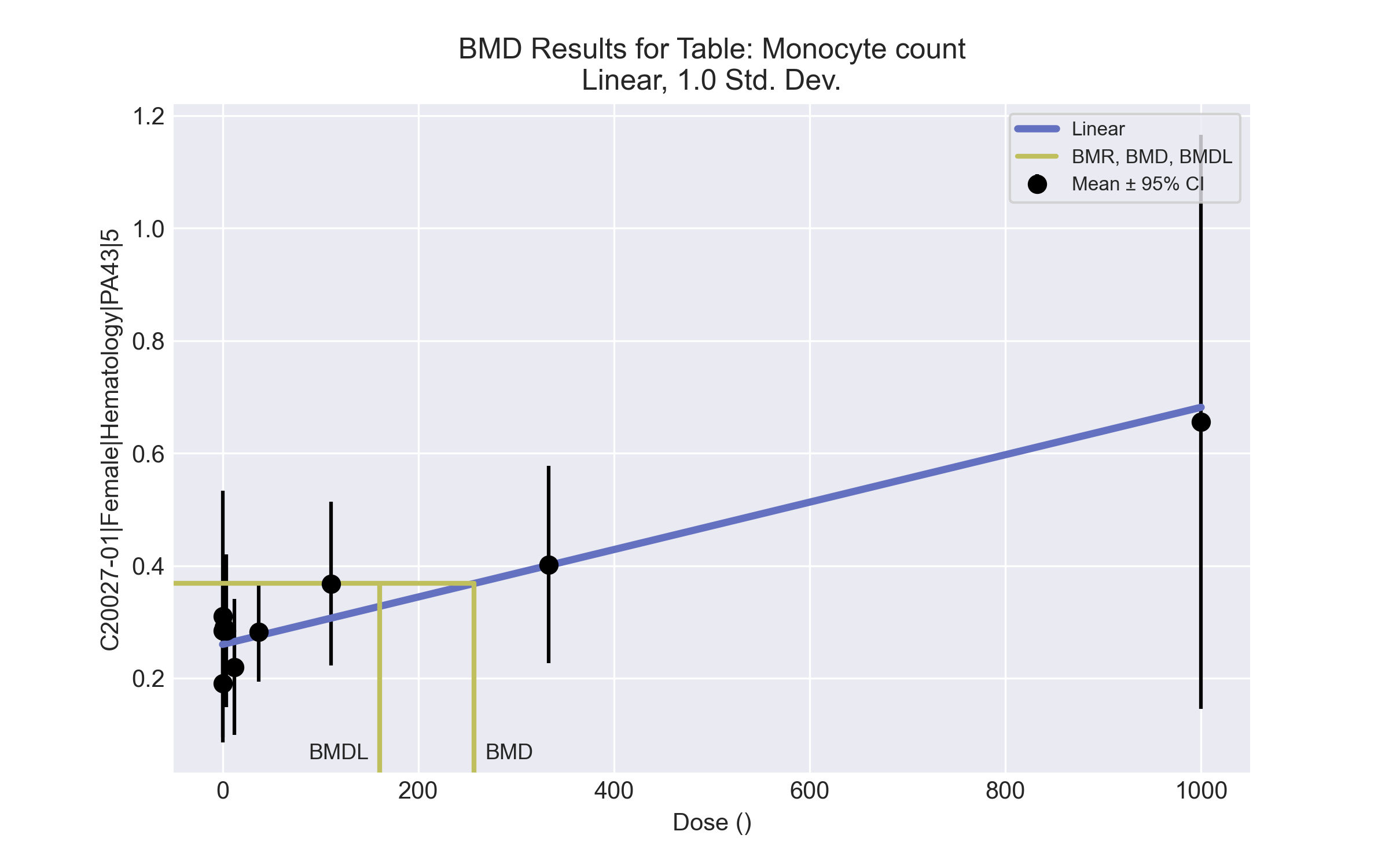
b Recommended model

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Lineara | Valid | - |
| Polynomial 2° | Valid | - |
| Polynomial 3° | Valid | - |
| Polynomial 4° | Valid | - |
| Polynomial 5° | Valid | - |
| Polynomial 6° | Valid | - |
| Polynomial 7° | Valid | - |
| Polynomial 8° | Valid | - |
| Power | Valid | - |
| Hill | Failure | **Failures**  • BMDL does not exist  **Cautions**  • Warning(s): BMDL computation failed. |
| Exponential M2 (equivalent models include Exponential M3) | Warning | **Warnings**  • Residual at lowest dose is greater than threshold (2.01 > 2.0) |
| Exponential M4 | Valid | - |
| Exponential M5 | Valid | - |

a Recommended model

## Recommended model



====================================================================   
 Polynomial Model. (Version: 2.21; Date: 03/14/2017)   
 Input Data File: C:\Windows\TEMP\bmds-nhr3za80.(d)   
 Gnuplot Plotting File: C:\Windows\TEMP\bmds-nhr3za80.plt  
 Thu Apr 15 13:45:55 2021  
 ====================================================================   
  
 BMDS\_Model\_Run   
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~  
   
 The form of the response function is:   
  
 Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ...  
  
  
 Dependent variable = Response  
 Independent variable = Dose  
 The polynomial coefficients are restricted to be positive  
 The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) \* rho)  
  
 Total number of dose groups = 10  
 Total number of records with missing values = 0  
 Maximum number of iterations = 500  
 Relative Function Convergence has been set to: 1e-008  
 Parameter Convergence has been set to: 1e-008  
  
  
  
 Default Initial Parameter Values   
 lalpha = -3.57282  
 rho = 0  
 beta\_0 = 0.269956  
 beta\_1 = 0  
  
  
 Asymptotic Correlation Matrix of Parameter Estimates  
  
 lalpha rho beta\_0 beta\_1  
  
 lalpha 1 0.97 -0.083 0.15  
  
 rho 0.97 1 -0.091 0.17  
  
 beta\_0 -0.083 -0.091 1 -0.33  
  
 beta\_1 0.15 0.17 -0.33 1  
  
  
  
 Parameter Estimates  
  
 95.0% Wald Confidence Interval  
 Variable Estimate Std. Err. Lower Conf. Limit Upper Conf. Limit  
 lalpha -1.38176 0.765495 -2.88211 0.118578  
 rho 2.27391 0.622603 1.05363 3.49419  
 beta\_0 0.260037 0.0176078 0.225526 0.294548  
 beta\_1 0.000421459 0.000130575 0.000165538 0.000677381  
  
  
  
 Table of Data and Estimated Values of Interest  
  
 Dose N Obs Mean Est Mean Obs Std Dev Est Std Dev Scaled Res.  
------ --- -------- -------- ----------- ----------- ----------  
  
 0 9 0.191 0.26 0.125 0.108 -1.91  
 0.15 5 0.31 0.26 0.18 0.108 1.03  
 0.5 5 0.284 0.26 0.0684 0.108 0.49  
 1.4 4 0.29 0.261 0.0787 0.109 0.541  
 4 5 0.284 0.262 0.109 0.109 0.456  
 12 5 0.22 0.265 0.097 0.111 -0.91  
 37 5 0.282 0.276 0.0712 0.116 0.123  
 111 5 0.368 0.307 0.117 0.131 1.05  
 333 5 0.402 0.4 0.141 0.177 0.0204  
 1000 5 0.656 0.681 0.411 0.324 -0.176  
  
  
  
 Model Descriptions for likelihoods calculated  
  
  
 Model A1: Yij = Mu(i) + e(ij)  
 Var{e(ij)} = Sigma^2  
  
 Model A2: Yij = Mu(i) + e(ij)  
 Var{e(ij)} = Sigma(i)^2  
  
 Model A3: Yij = Mu(i) + e(ij)  
 Var{e(ij)} = exp(lalpha + rho\*ln(Mu(i)))  
 Model A3 uses any fixed variance parameters that  
 were specified by the user  
  
 Model R: Yi = Mu + e(i)  
 Var{e(i)} = Sigma^2  
  
  
 Likelihoods of Interest  
  
 Model Log(likelihood) # Param's AIC  
 A1 73.720722 11 -125.441445  
 A2 90.852404 20 -141.704808  
 A3 85.251176 12 -146.502352  
 fitted 81.916175 4 -155.832350  
 R 59.811074 2 -115.622148  
  
  
 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 62.0827 18 <.0001  
 Test 2 34.2634 9 <.0001  
 Test 3 11.2025 8 0.1905  
 Test 4 6.67 8 0.5726  
  
The p-value for Test 1 is less than .05. There appears to be a  
difference between response and/or variances among the dose levels  
It seems appropriate to model the data  
  
The p-value for Test 2 is less than .1. A non-homogeneous variance   
model appears to be appropriate  
  
The p-value for Test 3 is greater than .1. The modeled variance appears   
 to be appropriate here  
  
The p-value for Test 4 is greater than .1. The model chosen seems   
to adequately describe the data  
   
  
 Benchmark Dose Computation  
  
Specified effect = 1  
  
Risk Type = Estimated standard deviations from the control mean  
  
Confidence level = 0.95  
  
 BMD = 257.111  
  
  
 BMDL = 160.613  
  
  
 BMDU = 544.663

# Female BMD Results for Table: Platelet count

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 0.15 | 0.5 | 1.4 | 4 | 12 | 37 | 111 | 333 | 1000 |
| N | 9 | 5 | 5 | 4 | 5 | 5 | 5 | 5 | 5 | 5 |
| Mean ± SD | 993.556 ± 259.673 | 781.8 ± 350.486 | 841.2 ± 311.888 | 864.5 ± 152.292 | 980.2 ± 19.627 | 1005.4 ± 159.702 | 1005.6 ± 202.638 | 1083.8 ± 144.835 | 1214.2 ± 218.572 | 1003.8 ± 228.639 |

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear | 0.036 | 637.71 | -9999 | 2465.23 | No model was recommended as a best-fitting model. Doses were dropped until there were only 3 remaining dose-groups. |
| Polynomial 2° | 0.036 | 637.71 | -9999 | 1301.18 |
| Polynomial 3° | 0.036 | 637.71 | -9999 | 1908.41 |
| Polynomial 4° | 0.036 | 637.71 | -9999 | -999 |
| Polynomial 5° | <0.0001 | 934.036 | -9999 | -999 |
| Polynomial 6° | 0.037 | 637.618 | -9999 | 1088.05 |
| Polynomial 7° | <0.0001 | 1030.282 | -9999 | -999 |
| Polynomial 8° | <0.0001 | 1036.091 | -9999 | -999 |
| Power | 0.034 | 638.423 | 1864.08 | 582.129 |
| Hill | 0.34 | 632.571 | -999 | -999 |
| Exponential M2 | 0.022 | 639.71 | 1 | -999 |
| Exponential M3 | 0.012 | 641.71 | 340037 | 1218.86 |
| Exponential M4 | 0.012 | 641.71 | -999 | 0 |
| Exponential M5 | 0.006 | 643.71 | -999 | 0 |

a Modeled variance case presented (BMDS Test 2 p-value = 0.001, BMDS Test 3 p-value = 0.002).

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear | Warning | **Warnings**  • Residual of Interest does not exist  • Variance model poorly fits dataset (p-value 3 = 0.002246)  • Goodness of fit p-value is less than threshold (0.036 < 0.1)  **Cautions**  • Warning(s): BMD = 100\*(maximum dose)  • BMDL/high dose ratio is greater than threshold (2.47 > 1.0) |
| Polynomial 2° | Warning | **Warnings**  • Residual of Interest does not exist  • Variance model poorly fits dataset (p-value 3 = 0.002246)  • Goodness of fit p-value is less than threshold (0.036 < 0.1)  **Cautions**  • Warning(s): THIS USUALLY MEANS THE MODEL HAS NOT CONVERGED!; BMD = 100\*(maximum dose)  • BMDL/high dose ratio is greater than threshold (1.3 > 1.0) |
| Polynomial 3° | Warning | **Warnings**  • Residual of Interest does not exist  • Variance model poorly fits dataset (p-value 3 = 0.002246)  • Goodness of fit p-value is less than threshold (0.036 < 0.1)  **Cautions**  • Warning(s): THIS USUALLY MEANS THE MODEL HAS NOT CONVERGED!; BMD = 100\*(maximum dose)  • BMDL/high dose ratio is greater than threshold (1.91 > 1.0) |
| Polynomial 4° | Failure | **Failures**  • BMDL does not exist  **Warnings**  • Residual of Interest does not exist  • Variance model poorly fits dataset (p-value 3 = 0.002246)  • Goodness of fit p-value is less than threshold (0.036 < 0.1)  **Cautions**  • Warning(s): THIS USUALLY MEANS THE MODEL HAS NOT CONVERGED!; BMD = 100\*(maximum dose); BMDL computation failed. |
| Polynomial 5° | Failure | **Failures**  • BMDL does not exist  **Warnings**  • Residual of Interest does not exist  • Variance model poorly fits dataset (p-value 3 = 0.002246)  • Ratio of modeled to actual stdev. at control is greater than threshold (2.94 > 1.5)  **Cautions**  • Warning(s): BMD = 100\*(maximum dose); BMDL computation failed. |
| Polynomial 6° | Warning | **Warnings**  • Residual of Interest does not exist  • Variance model poorly fits dataset (p-value 3 = 0.002246)  • Goodness of fit p-value is less than threshold (0.0371 < 0.1)  **Cautions**  • Warning(s): BMD = 100\*(maximum dose)  • BMDL/high dose ratio is greater than threshold (1.09 > 1.0) |
| Polynomial 7° | Failure | **Failures**  • BMDL does not exist  **Warnings**  • Residual of Interest does not exist  • Variance model poorly fits dataset (p-value 3 = 0.002246)  • Ratio of modeled to actual stdev. at control is greater than threshold (2.74 > 1.5)  **Cautions**  • Warning(s): THIS USUALLY MEANS THE MODEL HAS NOT CONVERGED!; BMD = 100\*(maximum dose); BMDL computation failed. |
| Polynomial 8° | Failure | **Failures**  • BMDL does not exist  **Warnings**  • Residual of Interest does not exist  • Variance model poorly fits dataset (p-value 3 = 0.002246)  • Ratio of modeled to actual stdev. at control is greater than threshold (2.12 > 1.5)  **Cautions**  • Warning(s): THIS USUALLY MEANS THE MODEL HAS NOT CONVERGED!; BMD = 100\*(maximum dose); BMDL computation failed. |
| Power | Warning | **Warnings**  • Variance model poorly fits dataset (p-value 3 = 0.002246)  • Goodness of fit p-value is less than threshold (0.034 < 0.1)  • BMD/high dose ratio is greater than threshold (1.86 > 1.0) |
| Hill | Failure | **Failures**  • BMD does not exist  • BMDL does not exist  **Warnings**  • Residual of Interest does not exist  • Variance model poorly fits dataset (p-value 3 = 0.002246)  **Cautions**  • Warning(s): BMR value is not in the range of the mean function |
| Exponential M2 | Failure | **Failures**  • BMDL does not exist  **Warnings**  • Variance model poorly fits dataset (p-value 3 = 0.002246)  • Goodness of fit p-value is less than threshold (0.0217 < 0.1) |
| Exponential M3 | Warning | **Warnings**  • Variance model poorly fits dataset (p-value 3 = 0.002246)  • Goodness of fit p-value is less than threshold (0.0123 < 0.1)  • BMD/BMDL ratio is greater than threshold (2.79e+02 > 20.0)  • BMD/high dose ratio is greater than threshold (3.4e+02 > 1.0)  **Cautions**  • BMD/BMDL ratio is greater than threshold (2.79e+02 > 5.0)  • BMDL/high dose ratio is greater than threshold (1.22 > 1.0) |
| Exponential M4 | Failure | **Failures**  • BMD does not exist  **Warnings**  • Residual of Interest does not exist  • Variance model poorly fits dataset (p-value 3 = 0.002246)  • Goodness of fit p-value is less than threshold (0.0123 < 0.1) |
| Exponential M5 | Failure | **Failures**  • BMD does not exist  **Warnings**  • Residual of Interest does not exist  • Variance model poorly fits dataset (p-value 3 = 0.002246)  • Goodness of fit p-value is less than threshold (0.0064 < 0.1) |

## Recommended model

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

# Female BMD Results for Table: Reticulocyte count

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 0.15 | 0.5 | 1.4 | 4 | 12 | 37 | 111a | 333a | 1000a |
| N | 9 | 5 | 5 | 4 | 5 | 5 | 5 | 5 | 5 | 5 |
| Mean ± SD | 224.633 ± 34.579 | 235.06 ± 39.379 | 205.26 ± 38.534 | 206.55 ± 15.202 | 210.7 ± 26.564 | 200.64 ± 31.256 | 161.88 ± 14.639 | 199.44 ± 45.236 | 126.44 ± 21.113 | 112.26 ± 28.319 |

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°, 6°, 7°, 8°) | 0.625 | 300.986 | 18.568 | 12.823 | Hill recommended as best-fitting model on the basis of the lowest BMDL. |
| Hillb | 0.493 | 302.902 | 15.578 | 3.622 |
| Exponential M2 (equivalent models include Exponential M3) | 0.634 | 300.929 | 17.123 | 11.118 |
| Exponential M4 (equivalent models include Exponential M5) | 0.492 | 302.907 | 15.736 | 5.229 |

a Constant variance case presented (BMDS Test 2 p-value = 0.208, BMDS Test 3 p-value = 0.208).

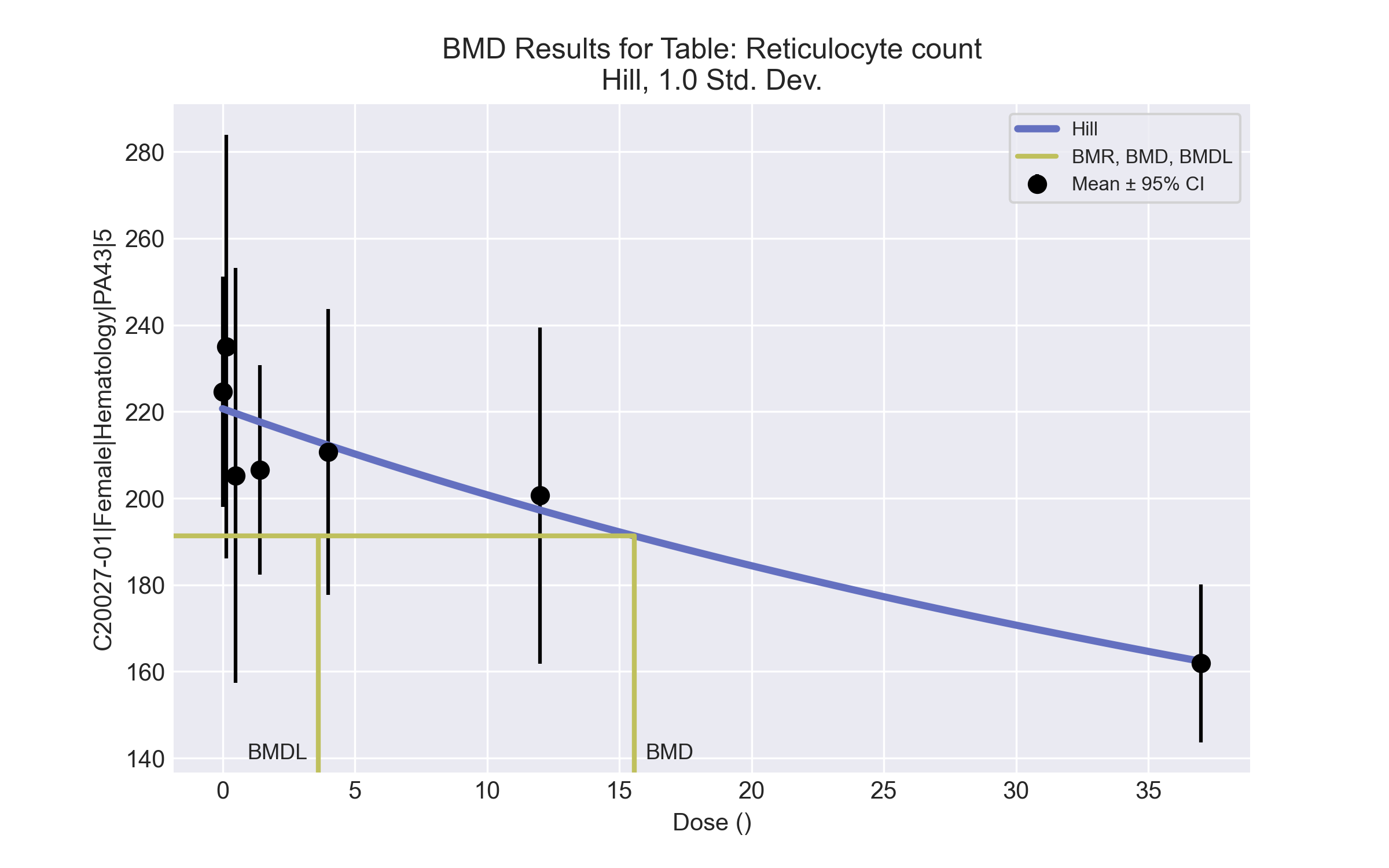
b Recommended model

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear (equivalent models include Power, Polynomial 2°, 3°, 4°, 5°, 6°, 7°, 8°) | Valid | - |
| Hilla | Valid | - |
| Exponential M2 (equivalent models include Exponential M3) | Valid | - |
| 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-onpbqya\_.(d)   
 Gnuplot Plotting File: C:\Windows\TEMP\bmds-onpbqya\_.plt  
 Thu Apr 15 13:47:43 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 = 7  
 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 = 967.385  
 rho = 0 Specified  
 intercept = 224.633  
 v = -62.7533  
 n = 0.725967  
 k = 16.7622  
  
  
 Asymptotic Correlation Matrix of Parameter Estimates  
  
 ( \*\*\* The model parameter(s) -rho -n   
 have been estimated at a boundary point, or have been specified by the user,  
 and do not appear in the correlation matrix )  
  
 alpha intercept v k  
  
 alpha 1 -1.7e-007 -2.8e-007 3e-007  
  
 intercept -1.7e-007 1 0.45 -0.49  
  
 v -2.8e-007 0.45 1 -1  
  
 k 3e-007 -0.49 -1 1  
  
  
  
 Parameter Estimates  
  
 95.0% Wald Confidence Interval  
 Variable Estimate Std. Err. Lower Conf. Limit Upper Conf. Limit  
 alpha 863.142 198.018 475.033 1251.25  
 intercept 220.675 6.50133 207.932 233.417  
 v -205.439 584.214 -1350.48 939.598  
 n 1 NA  
 k 93.3517 364.828 -621.698 808.401  
  
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 9 225 221 34.6 29.4 0.404  
 0.15 5 235 220 39.4 29.4 1.12  
 0.5 5 205 220 38.5 29.4 -1.09  
 1.4 4 207 218 15.2 29.4 -0.755  
 4 5 211 212 26.6 29.4 -0.117  
 12 5 201 197 31.3 29.4 0.256  
 37 5 162 162 14.6 29.4 -0.0366  
  
  
  
 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 -145.748953 8 307.497907  
 A2 -141.531344 14 311.062688  
 A3 -145.748953 8 307.497907  
 fitted -147.451003 4 302.902006  
 R -154.336538 2 312.673077  
  
  
 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 25.6104 12 0.01218  
 Test 2 8.43522 6 0.2079  
 Test 3 8.43522 6 0.2079  
 Test 4 3.4041 4 0.4926  
  
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 = 15.5777  
  
 BMDL = 3.62221  
  
 BMDU = 32.9829

# Female BMD Results for Table: Thyroid Stimulating Hormone

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 0.15 | 0.5 | 1.4 | 4 | 12 | 37 | 111 | 333 | 1000 |
| N | 9 | 4 | 3 | 4 | 5 | 4 | 5 | 5 | 4 | 5 |
| Mean ± SD | 3.122 ± 1.113 | 3.4 ± 2.026 | 2.8 ± 0.954 | 2.425 ± 0.75 | 3.02 ± 1.062 | 3.4 ± 1.651 | 2.54 ± 0.82 | 4.48 ± 0.867 | 3.775 ± 2.3 | 6.9 ± 2.087 |

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linearb (equivalent models include Power) | 0.601 | 83.361 | 356.61 | 268.917 | Linear recommended as best-fitting model on the basis of the lowest AIC. |
| Polynomial 2° | 0.494 | 85.345 | 380.134 | 269.122 |
| Polynomial 3° | 0.498 | 85.306 | 403.724 | 269.605 |
| Polynomial 4° | 0.501 | 85.286 | 414.764 | 269.854 |
| Polynomial 5° | 0.501 | 85.278 | 419.532 | 269.948 |
| Polynomial 6° | 0.502 | 85.276 | 421.518 | 269.981 |
| Polynomial 7° | 0.502 | 85.275 | 422.329 | 269.992 |
| Polynomial 8° | 0.502 | 85.275 | 422.661 | 269.996 |
| Hill | 0.492 | 85.362 | 356.205 | 268.497 |
| Exponential M2 (equivalent models include Exponential M3) | 0.593 | 83.428 | 452.862 | 370.185 |
| Exponential M4 | 0.492 | 85.363 | 355.503 | 157.934 |
| Exponential M5 | 0.492 | 85.363 | 355.546 | 157.936 |

a Constant variance case presented (BMDS Test 2 p-value = 0.12, BMDS Test 3 p-value = 0.12).

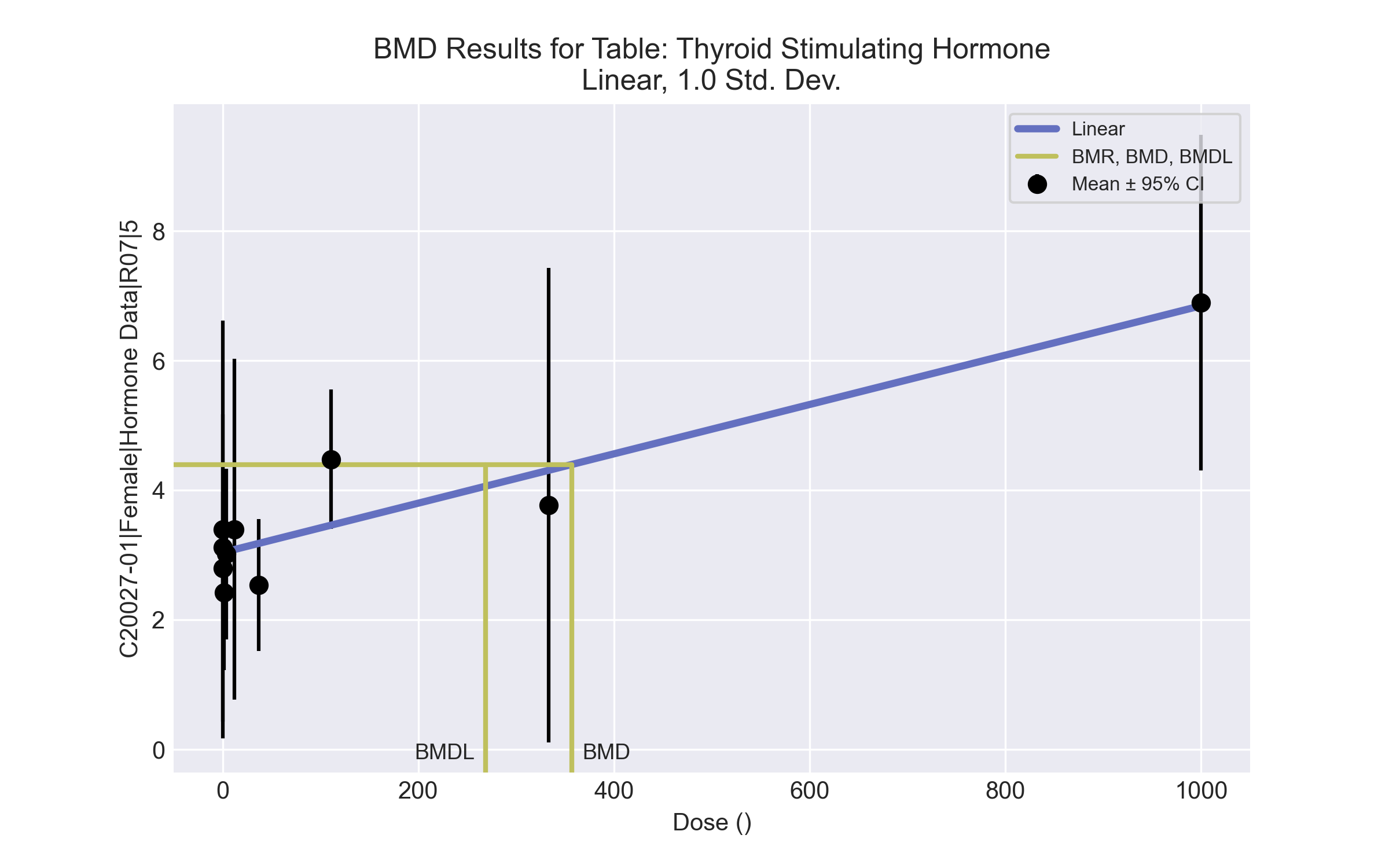
b Recommended model

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Lineara (equivalent models include Power) | Valid | - |
| Polynomial 2° | Valid | - |
| Polynomial 3° | Valid | - |
| Polynomial 4° | Valid | - |
| Polynomial 5° | Valid | - |
| Polynomial 6° | Valid | - |
| Polynomial 7° | Valid | - |
| Polynomial 8° | Valid | - |
| Hill | Valid | - |
| Exponential M2 (equivalent models include Exponential M3) | Valid | - |
| Exponential M4 | Valid | - |
| Exponential M5 | Valid | - |

a Recommended model

## Recommended model



====================================================================   
 Polynomial Model. (Version: 2.21; Date: 03/14/2017)   
 Input Data File: C:\Windows\TEMP\bmds-n7bi\_jou.(d)   
 Gnuplot Plotting File: C:\Windows\TEMP\bmds-n7bi\_jou.plt  
 Thu Apr 15 13:45:29 2021  
 ====================================================================   
  
 BMDS\_Model\_Run   
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~  
   
 The form of the response function is:   
  
 Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ...  
  
  
 Dependent variable = Response  
 Independent variable = Dose  
 rho is set to 0  
 The polynomial coefficients are restricted to be positive  
 A constant variance model is fit  
  
 Total number of dose groups = 10  
 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 = 2.03733  
 rho = 0 Specified  
 beta\_0 = 3.01484  
 beta\_1 = 0  
  
  
 Asymptotic Correlation Matrix of Parameter Estimates  
  
 ( \*\*\* The model parameter(s) -rho   
 have been estimated at a boundary point, or have been specified by the user,  
 and do not appear in the correlation matrix )  
  
 alpha beta\_0 beta\_1  
  
 alpha 1 5.1e-008 -2.8e-008  
  
 beta\_0 5.1e-008 1 -0.44  
  
 beta\_1 -2.8e-008 -0.44 1  
  
  
  
 Parameter Estimates  
  
 95.0% Wald Confidence Interval  
 Variable Estimate Std. Err. Lower Conf. Limit Upper Conf. Limit  
 alpha 1.84356 0.376314 1.10599 2.58112  
 beta\_0 3.04136 0.218168 2.61376 3.46896  
 beta\_1 0.00380746 0.00064377 0.00254569 0.00506923  
  
  
  
 Table of Data and Estimated Values of Interest  
  
 Dose N Obs Mean Est Mean Obs Std Dev Est Std Dev Scaled Res.  
------ --- -------- -------- ----------- ----------- ----------  
  
 0 9 3.12 3.04 1.11 1.36 0.179  
 0.15 4 3.4 3.04 2.03 1.36 0.527  
 0.5 3 2.8 3.04 0.954 1.36 -0.31  
 1.4 4 2.42 3.05 0.75 1.36 -0.916  
 4 5 3.02 3.06 1.06 1.36 -0.0603  
 12 4 3.4 3.09 1.65 1.36 0.461  
 37 5 2.54 3.18 0.82 1.36 -1.06  
 111 5 4.48 3.46 0.867 1.36 1.67  
 333 4 3.77 4.31 2.3 1.36 -0.787  
 1000 5 6.9 6.85 2.09 1.36 0.0843  
  
  
  
 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 -35.472611 11 92.945222  
 A2 -28.440017 20 96.880033  
 A3 -35.472611 11 92.945222  
 fitted -38.680723 3 83.361446  
 R -51.818026 2 107.636051  
  
  
 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 46.756 18 0.0002299  
 Test 2 14.0652 9 0.12  
 Test 3 14.0652 9 0.12  
 Test 4 6.41622 8 0.6007  
  
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 = 356.61  
  
  
 BMDL = 268.917  
  
  
 BMDU = 527.21

# Female BMD Results for Table: Total Thyroxine

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 0.15 | 0.5 | 1.4 | 4 | 12 | 37 | 111 | 333 | 1000 |
| N | 9 | 4 | 3 | 4 | 5 | 4 | 5 | 5 | 4 | 5 |
| Mean ± SD | 3.123 ± 0.871 | 2.833 ± 0.854 | 2.307 ± 0.136 | 2.64 ± 0.865 | 2.756 ± 0.24 | 2.785 ± 0.311 | 2.314 ± 0.484 | 2.642 ± 0.581 | 1.198 ± 0.36 | 0.86 ± 0.311 |

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear (equivalent models include Power, Polynomial 2°, 3°, 4°, 5°, 7°, 8°) | 0.005 | 11.025 | 362.43 | 274.092 | No model was recommended as a best-fitting model. Doses were dropped until there were only 3 remaining dose-groups. |
| Polynomial 6° | <0.0001 | 645.525 | 109.611 | -999 |
| Hill | 0.112 | 3.593 | 178.478 | 110.266 |
| Exponential M2 (equivalent models include Exponential M3) | 0.028 | 6.489 | 206.446 | 128.265 |
| Exponential M4 | 0.071 | 4.339 | 109.539 | 70.138 |
| Exponential M5 | 0.115 | 3.52 | 186.048 | 98.774 |

a Modeled variance case presented (BMDS Test 2 p-value = 0.002, BMDS Test 3 p-value = 0.024).

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear (equivalent models include Power, Polynomial 2°, 3°, 4°, 5°, 7°, 8°) | Warning | **Warnings**  • Variance model poorly fits dataset (p-value 3 = 0.02384)  • Goodness of fit p-value is less than threshold (0.00542 < 0.1) |
| Polynomial 6° | Failure | **Failures**  • BMDL does not exist  **Warnings**  • Variance model poorly fits dataset (p-value 3 = 0.02384)  • Residual at lowest dose is greater than threshold (3.17 > 2.0)  • Ratio of modeled to actual stdev. at control is greater than threshold (1.69e+02 > 1.5)  **Cautions**  • Warning(s): THE MODEL HAS PROBABLY NOT CONVERGED!!!; THIS USUALLY MEANS THE MODEL HAS NOT CONVERGED!; BMDL computation failed. |
| Hill | Warning | **Warnings**  • Variance model poorly fits dataset (p-value 3 = 0.02384) |
| Exponential M2 (equivalent models include Exponential M3) | Warning | **Warnings**  • Variance model poorly fits dataset (p-value 3 = 0.02384)  • Goodness of fit p-value is less than threshold (0.0281 < 0.1) |
| Exponential M4 | Warning | **Warnings**  • Variance model poorly fits dataset (p-value 3 = 0.02384)  • Goodness of fit p-value is less than threshold (0.0708 < 0.1) |
| Exponential M5 | Warning | **Warnings**  • Variance model poorly fits dataset (p-value 3 = 0.02384) |

## Recommended model

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

# Female BMD Results for Table: Triiodothyronine

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 0.15 | 0.5 | 1.4 | 4 | 12 | 37 | 111 | 333 | 1000 |
| N | 9 | 4 | 3 | 4 | 5 | 4 | 5 | 5 | 4 | 5 |
| Mean ± SD | 66 ± 10.365 | 58.825 ± 3.454 | 66.9 ± 8.472 | 59.825 ± 9.9 | 61.54 ± 9.648 | 62.7 ± 8.914 | 63.74 ± 6.175 | 59.04 ± 4.673 | 42.425 ± 4.124 | 31.06 ± 4.152 |

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear (equivalent models include Power, Polynomial 2°, 3°, 4°, 5°, 6°, 7°, 8°) | 0.174 | 251.312 | 230.195 | 184.46 | Exponential-M2 recommended as best-fitting model on the basis of the lowest AIC. |
| Hill | 0.544 | 248.8 | 153.425 | 84.443 |
| Exponential M2b (equivalent models include Exponential M3) | 0.369 | 248.492 | 161.48 | 122.215 |
| Exponential M4 | 0.435 | 248.745 | 108.24 | 67.644 |
| Exponential M5 | 0.541 | 248.825 | 159.836 | 83.086 |

a Constant variance case presented (BMDS Test 2 p-value = 0.102, BMDS Test 3 p-value = 0.102).

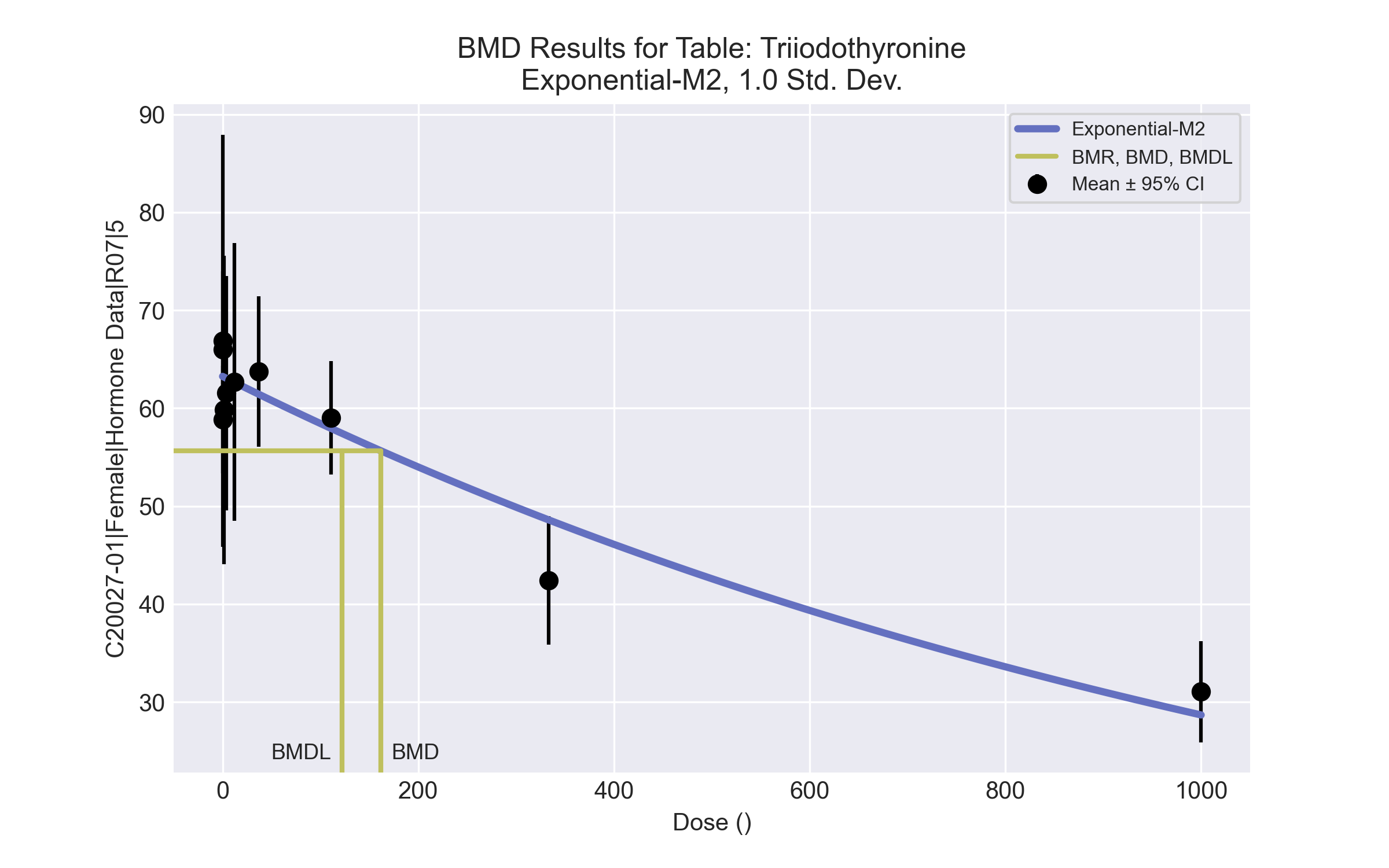
b Recommended model

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear (equivalent models include Power, Polynomial 2°, 3°, 4°, 5°, 6°, 7°, 8°) | Valid | - |
| Hill | Valid | - |
| Exponential M2a (equivalent models include Exponential M3) | Valid | - |
| Exponential M4 | Valid | - |
| Exponential M5 | Valid | - |

a Recommended model

## Recommended model



====================================================================   
 Exponential Model. (Version: 1.11; Date: 03/14/2017)   
 Input Data File: C:\Windows\TEMP\bmds-l0lnqngm.(d)   
 Gnuplot Plotting File:   
 Thu Apr 15 13:46:59 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 = 10  
 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 3.87091   
 rho 0 Specified  
 a 50.4179   
 b 0.000740297   
 c 0 Specified  
 d 1 Specified  
  
  
  
 Parameter Estimates  
  
 Variable Model 2 Std. Err.  
 -------- ------- ---------  
 lnalpha 4.05193 11.7388  
 a 63.2514 1.25318  
 b 0.000790886 0.000107381  
  
 NC = No Convergence  
  
  
 Table of Stats From Input Data  
  
 Dose N Obs Mean Obs Std Dev  
 ----- --- ---------- -------------  
 0 9 66 10.36  
 0.15 4 58.83 3.454  
 0.5 3 66.9 8.472  
 1.4 4 59.83 9.9  
 4 5 61.54 9.648  
 12 4 62.7 8.914  
 37 5 63.74 6.175  
 111 5 59.04 4.673  
 333 4 42.42 4.124  
 1000 5 31.06 4.152  
  
  
 Estimated Values of Interest  
  
 Dose Est Mean Est Std Scaled Residual  
 ------ ---------- --------- ----------------  
 0 63.25 7.583 1.087  
 0.15 63.24 7.583 -1.165  
 0.5 63.23 7.583 0.8391  
 1.4 63.18 7.583 -0.8852  
 4 63.05 7.583 -0.4457  
 12 62.65 7.583 0.01214  
 37 61.43 7.583 0.6819  
 111 57.94 7.583 0.3257  
 333 48.61 7.583 -1.63  
 1000 28.68 7.583 0.7015  
  
  
  
 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 -116.9018 11 255.8037  
 A2 -109.594 20 259.1881  
 A3 -116.9018 11 255.8037  
 R -146.9247 2 297.8494  
 2 -121.2462 3 248.4924  
  
  
 Additive constant for all log-likelihoods = -44.11. 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 74.66 18 < 0.0001  
 Test 2 14.62 9 0.1021  
 Test 3 14.62 9 0.1021  
 Test 4 8.689 8 0.3692  
  
  
 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 = 161.48  
  
 BMDL = 122.215  
  
 BMDU = 227.372