# Apical Endpoint Benchmark Dose Modeling Results; Toxicology Benchmark Dose Results

* 1. BMD Results for: SD4

BMDS version: BMDS v2.7.0

* + 1. Input dataset

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 55 | 110 | 220 | 441 | 881 |
| N | 5 | 5 | 5 | 5 | 5 | 5 |
| Mean ± SD | 276.3 ± 10.286 | 271.3 ± 11.404 | 271.9 ± 8.273 | 278.8 ± 10.51 | 262.4 ± 18.112 | 232.5 ± 21.019 |

* + 1. Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear | 0.261 | 193.134 | 283.489 | 209.164 | Polynomial-2 recommended as best-fitting model on the basis of the lowest AIC. |
| Polynomial 2°b | 0.735 | 189.873 | 486.413 | 278.1 |
| Polynomial 3° (equivalent models include Polynomial 4°, 5°) | 0.571 | 191.873 | 489.883 | 274.988 |
| Power | 0.574 | 191.861 | 500.092 | 285.353 |
| Hill | 0.753 | 191.069 | 442.808 | 322.87 |
| Exponential M2 (equivalent models include Exponential M4) | 0.22 | 193.606 | 274.199 | 197.845 |
| Exponential M3 | 0.58 | 191.83 | 497.585 | 289.961 |
| Exponential M5 | 0.548 | 193.069 | 442.523 | 321.919 |

a Constant variance case presented (BMDS Test 2 p-value = 0.233, BMDS Test 3 p-value = 0.233).

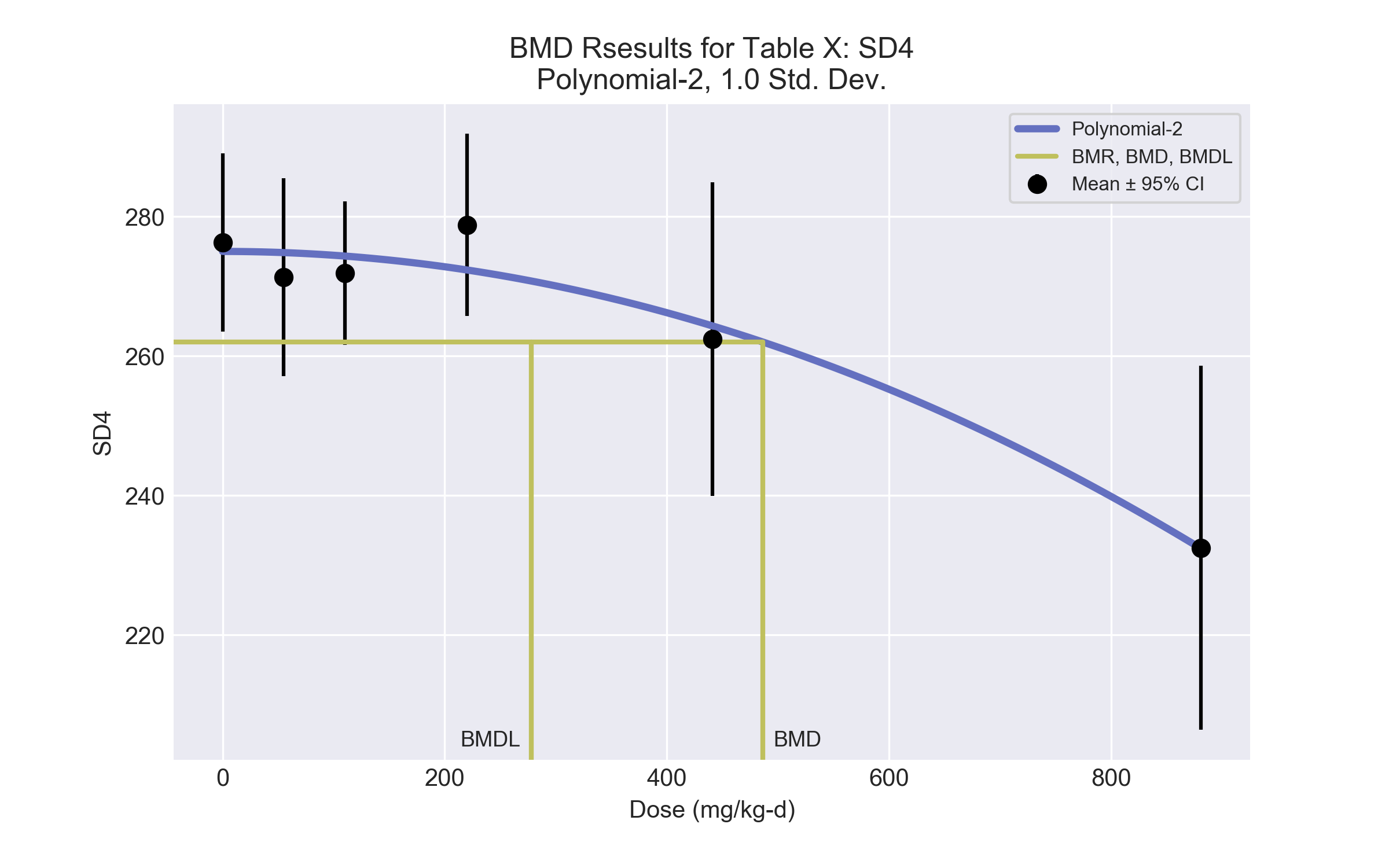
b Recommended model

* + 1. Model recommendation details

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

a Recommended model

* + 1. Recommended model



====================================================================   
 Polynomial Model. (Version: 2.21; Date: 03/14/2017)   
 Input Data File: C:\Users\USERNAME\AppData\Local\Temp\2\bmds-ghxikak\_.(d)   
 Gnuplot Plotting File: C:\Users\USERNAME\AppData\Local\Temp\2\bmds-ghxikak\_.plt  
 Mon Dec 18 12:02:51 2017  
 ====================================================================   
  
 BMDS\_Model\_Run   
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~  
   
 The form of the response function is:   
  
 Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ...  
  
  
 Dependent variable = Response  
 Independent variable = Dose  
 rho is set to 0  
 The polynomial coefficients are restricted to be negative  
 A constant variance model is fit  
  
 Total number of dose groups = 6  
 Total number of records with missing values = 0  
 Maximum number of iterations = 500  
 Relative Function Convergence has been set to: 1e-008  
 Parameter Convergence has been set to: 1e-008  
  
  
  
 Default Initial Parameter Values   
 alpha = 197.433  
 rho = 0 Specified  
 beta\_0 = 274.363  
 beta\_1 = 0  
 beta\_2 = -6.13731e-005  
  
  
 Asymptotic Correlation Matrix of Parameter Estimates  
  
 ( \*\*\* The model parameter(s) -rho -beta\_1   
 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\_2  
  
 alpha 1 1.4e-007 -1.4e-008  
  
 beta\_0 1.4e-007 1 -0.53  
  
 beta\_2 -1.4e-008 -0.53 1  
  
  
  
 Parameter Estimates  
  
 95.0% Wald Confidence Interval  
 Variable Estimate Std. Err. Lower Conf. Limit Upper Conf. Limit  
 alpha 168.866 43.601 83.4096 254.322  
 beta\_0 275 2.79087 269.53 280.47  
 beta\_1 -0 NA  
 beta\_2 -5.49239e-005 8.52697e-006 -7.16365e-005 -3.82114e-005  
  
NA - Indicates that this parameter has hit a bound  
 implied by some inequality constraint and thus  
 has no standard error.  
  
  
  
 Table of Data and Estimated Values of Interest  
  
 Dose N Obs Mean Est Mean Obs Std Dev Est Std Dev Scaled Res.  
------ --- -------- -------- ----------- ----------- ----------  
  
 0 5 276 275 10.3 13 0.224  
 55 5 271 275 11.4 13 -0.608  
 110 5 272 274 8.27 13 -0.419  
 220 5 279 272 10.5 13 1.11  
 441 5 262 264 18.1 13 -0.33  
 881 5 233 232 21 13 0.0223  
  
  
  
 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 -90.933862 7 195.867723  
 A2 -87.513245 12 199.026491  
 A3 -90.933862 7 195.867723  
 fitted -91.936585 3 189.873170  
 R -104.961782 2 213.923564  
  
  
 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 34.8971 10 0.00013  
 Test 2 6.84123 5 0.2327  
 Test 3 6.84123 5 0.2327  
 Test 4 2.00545 4 0.7348  
  
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 = 486.413  
  
  
 BMDL = 278.1  
  
  
 BMDU = 593.803

* 1. BMD Results for: Globulin (g/dL)

BMDS version: BMDS v2.7.0

* + 1. Input dataset

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 55 | 110 | 220 | 441 | 881 |
| N | 5 | 5 | 5 | 5 | 5 | 5 |
| Mean ± SD | 2.5 ± 0.157 | 2.56 ± 0.157 | 2.52 ± 0.112 | 2.66 ± 0.112 | 2.76 ± 0.134 | 2.72 ± 0.335 |

* + 1. Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linearb (equivalent models include Power, Polynomial 2°, 3°, 4°, 5°) | 0.801 | -73.456 | 328.341 | 174.01 | Linear recommended as best-fitting model on the basis of the lowest AIC. |
| Hill | 0.544 | -69.882 | 295.513 | -999 |
| Exponential M2 (equivalent models include Exponential M3) | 0.79 | -73.393 | 341.287 | 184.628 |
| Exponential M4 | 0.692 | -71.642 | 264.571 | 89.233 |
| Exponential M5 | 0.532 | -69.839 | 298.123 | 92.828 |

a Modeled variance case presented (BMDS Test 2 p-value = 0.061, BMDS Test 3 p-value = 0.238).

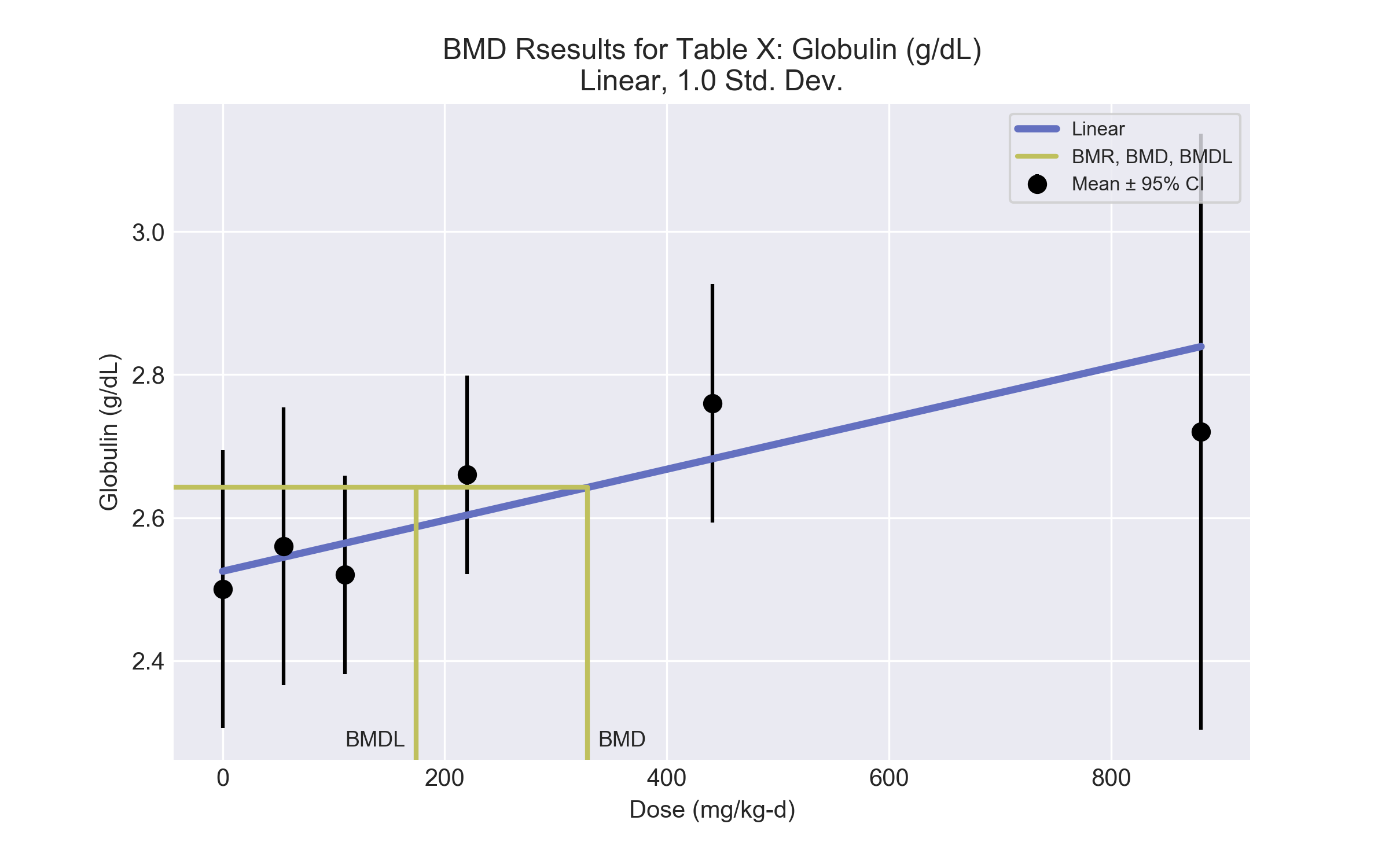
b Recommended model

* + 1. Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Lineara (equivalent models include Power, Polynomial 2°, 3°, 4°, 5°) | Valid | - |
| Hill | Failure | **Failures**  • BMDL does not exist  **Cautions**  • Warning(s): BMDL computation failed. |
| Exponential M2 (equivalent models include Exponential M3) | Valid | - |
| Exponential M4 | Valid | - |
| Exponential M5 | Valid | - |

a Recommended model

* + 1. Recommended model



====================================================================   
 Polynomial Model. (Version: 2.21; Date: 03/14/2017)   
 Input Data File: C:\Users\USERNAME\AppData\Local\Temp\2\bmds-o1vuem1o.(d)   
 Gnuplot Plotting File: C:\Users\USERNAME\AppData\Local\Temp\2\bmds-o1vuem1o.plt  
 Mon Dec 18 12:02:51 2017  
 ====================================================================   
  
 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 = 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   
 lalpha = -3.37895  
 rho = 0  
 beta\_0 = 2.54514  
 beta\_1 = 0  
  
  
 Asymptotic Correlation Matrix of Parameter Estimates  
  
 lalpha rho beta\_0 beta\_1  
  
 lalpha 1 -1 0.4 -0.55  
  
 rho -1 1 -0.4 0.55  
  
 beta\_0 0.4 -0.4 1 -0.71  
  
 beta\_1 -0.55 0.55 -0.71 1  
  
  
  
 Parameter Estimates  
  
 95.0% Wald Confidence Interval  
 Variable Estimate Std. Err. Lower Conf. Limit Upper Conf. Limit  
 lalpha -18.0817 6.56888 -30.9565 -5.20694  
 rho 14.89 6.80127 1.55975 28.2202  
 beta\_0 2.52507 0.0378055 2.45097 2.59917  
 beta\_1 0.000356622 0.000169673 2.40692e-005 0.000689175  
  
  
  
 Table of Data and Estimated Values of Interest  
  
 Dose N Obs Mean Est Mean Obs Std Dev Est Std Dev Scaled Res.  
------ --- -------- -------- ----------- ----------- ----------  
  
 0 5 2.5 2.53 0.157 0.117 -0.479  
 55 5 2.56 2.54 0.157 0.124 0.276  
 110 5 2.52 2.56 0.112 0.131 -0.754  
 220 5 2.66 2.6 0.112 0.147 0.859  
 441 5 2.76 2.68 0.134 0.184 0.946  
 881 5 2.72 2.84 0.335 0.28 -0.951  
  
  
  
 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 39.031368 7 -64.062736  
 A2 44.308187 12 -64.616375  
 A3 41.549606 8 -67.099212  
 fitted 40.727847 4 -73.455694  
 R 34.398613 2 -64.797227  
  
  
 Explanation of Tests   
  
 Test 1: Do responses and/or variances differ among Dose levels?   
 (A2 vs. R)  
 Test 2: Are Variances Homogeneous? (A1 vs A2)  
 Test 3: Are variances adequately modeled? (A2 vs. A3)  
 Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)  
 (Note: When rho=0 the results of Test 3 and Test 2 will be the same.)  
  
 Tests of Interest   
  
 Test -2\*log(Likelihood Ratio) Test df p-value   
  
 Test 1 19.8191 10 0.03101  
 Test 2 10.5536 5 0.06098  
 Test 3 5.51716 4 0.2382  
 Test 4 1.64352 4 0.801  
  
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 = 328.341  
  
  
 BMDL = 174.01  
  
  
 BMDU = 836.468

* 1. BMD Results for: A/G Ratio

BMDS version: BMDS v2.7.0

* + 1. Input dataset

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 55 | 110 | 220 | 441 | 881 |
| N | 5 | 5 | 5 | 5 | 5 | 5 |
| Mean ± SD | 1.38 ± 0.067 | 1.31 ± 0.022 | 1.34 ± 0.045 | 1.28 ± 0.045 | 1.22 ± 0.067 | 1.16 ± 0.157 |

* + 1. Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear (equivalent models include Power, Polynomial 2°, 3°, 4°, 5°) | 0.579 | -128.729 | 162.514 | 104.092 | No model was recommended as a best-fitting model. |
| Hill | 0.464 | -127.042 | 128.658 | 55.684 |
| Exponential M2 (equivalent models include Exponential M3) | 0.606 | -128.888 | 151.177 | 95.514 |
| Exponential M4 (equivalent models include Exponential M5) | 0.463 | -127.036 | 130.281 | 61.506 |

a Modeled variance case presented (BMDS Test 2 p-value = 8.6E-04, BMDS Test 3 p-value = 0.044).

* + 1. Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear (equivalent models include Power, Polynomial 2°, 3°, 4°, 5°) | Warning | **Warnings**  • Variance model fit p-value is less than threshold (0.0435 < 0.1)  • Ratio of modeled to actual stdev. at control is greater than threshold (1.51 > 1.5) |
| Hill | Warning | **Warnings**  • Variance model fit p-value is less than threshold (0.0435 < 0.1)  • Ratio of modeled to actual stdev. at control is greater than threshold (1.54 > 1.5) |
| Exponential M2 (equivalent models include Exponential M3) | Warning | **Warnings**  • Variance model fit p-value is less than threshold (0.0435 < 0.1) |
| Exponential M4 (equivalent models include Exponential M5) | Warning | **Warnings**  • Variance model fit p-value is less than threshold (0.0435 < 0.1) |

* + 1. Recommended model

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

* 1. BMD Results for: Albumin (g/dL)

BMDS version: BMDS v2.7.0

* + 1. Input dataset

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 55 | 110 | 220 | 441 | 881 |
| N | 5 | 5 | 5 | 5 | 5 | 5 |
| Mean ± SD | 3.44 ± 0.157 | 3.36 ± 0.157 | 3.38 ± 0.089 | 3.4 ± 0.089 | 3.36 ± 0.134 | 3.12 ± 0.134 |

* + 1. Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear | 0.458 | -89.592 | 393.215 | 271.887 | Polynomial-2 recommended as best-fitting model on the basis of the lowest AIC. |
| Polynomial 2°b | 0.811 | -91.639 | 575.928 | 322.39 |
| Polynomial 3° | 0.739 | -89.967 | 644.104 | 337.35 |
| Polynomial 4° | 0.752 | -90.021 | 666.397 | 338.843 |
| Polynomial 5° | 0.755 | -90.033 | 686.724 | 338.672 |
| Power | 0.733 | -89.941 | 663.984 | 338.51 |
| Hill | 0.529 | -87.954 | 484.721 | -999 |
| Exponential M2 (equivalent models include Exponential M4) | 0.438 | -89.453 | 388.098 | 263.966 |
| Exponential M3 | 0.733 | -89.941 | 662.072 | 342.222 |
| Exponential M5 | 0.529 | -87.954 | 481.377 | 343.203 |

a Constant variance case presented (BMDS Test 2 p-value = 0.698, BMDS Test 3 p-value = 0.698).

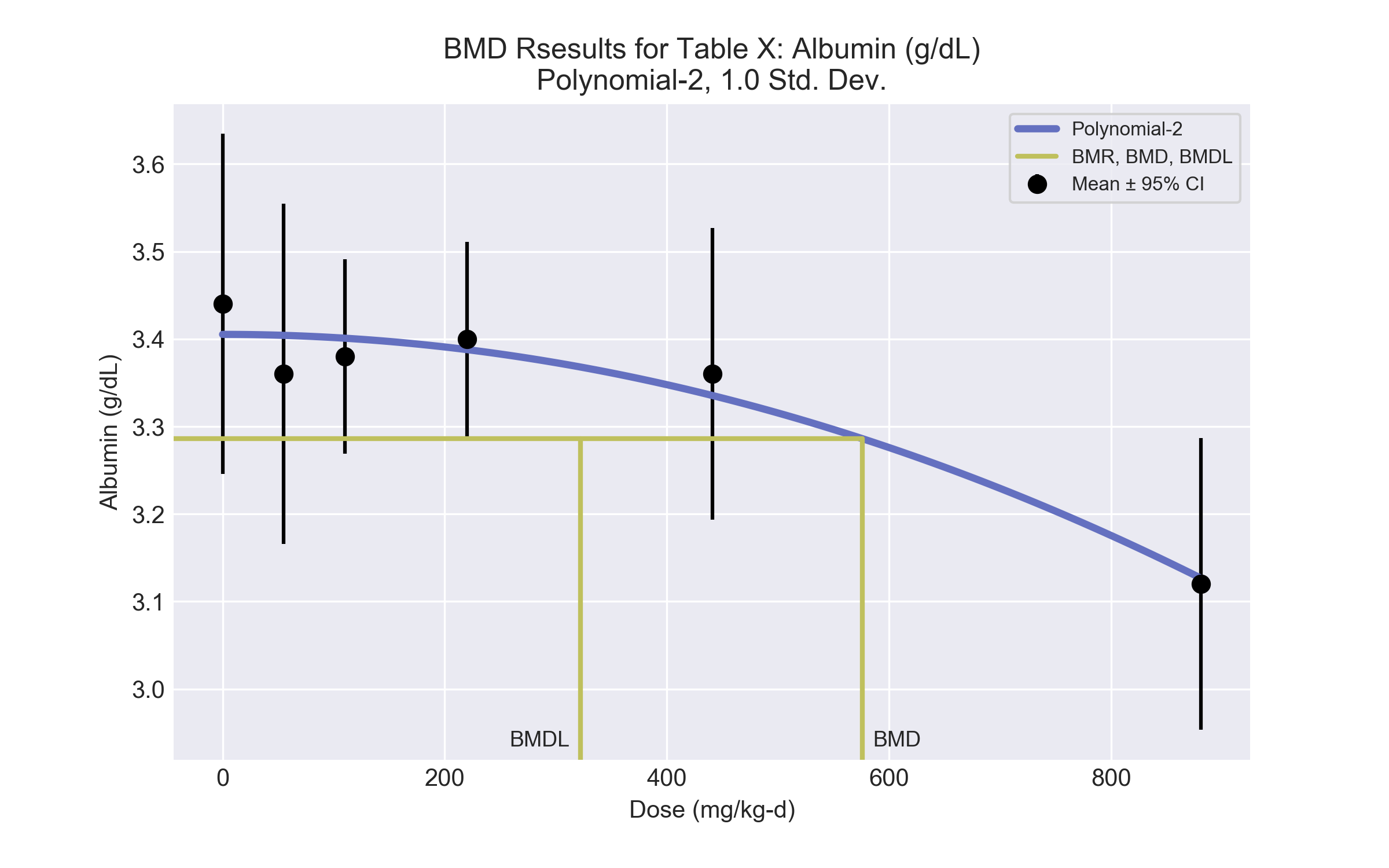
b Recommended model

* + 1. Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear | Valid | - |
| Polynomial 2°a | Valid | - |
| Polynomial 3° | Valid | - |
| Polynomial 4° | Valid | - |
| Polynomial 5° | Valid | - |
| Power | Valid | - |
| Hill | Failure | **Failures**  • BMDL does not exist  **Cautions**  • Warning(s): BMDL computation failed. |
| Exponential M2 (equivalent models include Exponential M4) | Valid | - |
| Exponential M3 | Valid | - |
| Exponential M5 | Valid | - |

a Recommended model

* + 1. Recommended model



====================================================================   
 Polynomial Model. (Version: 2.21; Date: 03/14/2017)   
 Input Data File: C:\Users\USERNAME\AppData\Local\Temp\2\bmds-5aoqc6m7.(d)   
 Gnuplot Plotting File: C:\Users\USERNAME\AppData\Local\Temp\2\bmds-5aoqc6m7.plt  
 Mon Dec 18 12:02:54 2017  
 ====================================================================   
  
 BMDS\_Model\_Run   
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~  
   
 The form of the response function is:   
  
 Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ...  
  
  
 Dependent variable = Response  
 Independent variable = Dose  
 rho is set to 0  
 The polynomial coefficients are restricted to be negative  
 A constant variance model is fit  
  
 Total number of dose groups = 6  
 Total number of records with missing values = 0  
 Maximum number of iterations = 500  
 Relative Function Convergence has been set to: 1e-008  
 Parameter Convergence has been set to: 1e-008  
  
  
  
 Default Initial Parameter Values   
 alpha = 0.0168334  
 rho = 0 Specified  
 beta\_0 = 3.39645  
 beta\_1 = 0  
 beta\_2 = -4.48363e-007  
  
  
 Asymptotic Correlation Matrix of Parameter Estimates  
  
 ( \*\*\* The model parameter(s) -rho -beta\_1   
 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\_2  
  
 alpha 1 -2.3e-013 9.5e-014  
  
 beta\_0 -2.3e-013 1 -0.53  
  
 beta\_2 9.5e-014 -0.53 1  
  
  
  
 Parameter Estimates  
  
 95.0% Wald Confidence Interval  
 Variable Estimate Std. Err. Lower Conf. Limit Upper Conf. Limit  
 alpha 0.0141983 0.00366597 0.00701308 0.0213834  
 beta\_0 3.40525 0.0255909 3.35509 3.45541  
 beta\_1 -0 NA  
 beta\_2 -3.59237e-007 7.81882e-008 -5.12483e-007 -2.05991e-007  
  
NA - Indicates that this parameter has hit a bound  
 implied by some inequality constraint and thus  
 has no standard error.  
  
  
  
 Table of Data and Estimated Values of Interest  
  
 Dose N Obs Mean Est Mean Obs Std Dev Est Std Dev Scaled Res.  
------ --- -------- -------- ----------- ----------- ----------  
  
 0 5 3.44 3.41 0.157 0.119 0.652  
 55 5 3.36 3.4 0.157 0.119 -0.829  
 110 5 3.38 3.4 0.0894 0.119 -0.392  
 220 5 3.4 3.39 0.0894 0.119 0.228  
 441 5 3.36 3.34 0.134 0.119 0.462  
 881 5 3.12 3.13 0.134 0.119 -0.121  
  
  
  
 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 49.613036 7 -85.226071  
 A2 51.121009 12 -78.242019  
 A3 49.613036 7 -85.226071  
 fitted 48.819541 3 -91.639083  
 R 40.827911 2 -77.655822  
  
  
 Explanation of Tests   
  
 Test 1: Do responses and/or variances differ among Dose levels?   
 (A2 vs. R)  
 Test 2: Are Variances Homogeneous? (A1 vs A2)  
 Test 3: Are variances adequately modeled? (A2 vs. A3)  
 Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)  
 (Note: When rho=0 the results of Test 3 and Test 2 will be the same.)  
  
 Tests of Interest   
  
 Test -2\*log(Likelihood Ratio) Test df p-value   
  
 Test 1 20.5862 10 0.02417  
 Test 2 3.01595 5 0.6975  
 Test 3 3.01595 5 0.6975  
 Test 4 1.58699 4 0.8111  
  
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 = 575.928  
  
  
 BMDL = 322.39  
  
  
 BMDU = 752.524

* 1. BMD Results for: Cholesterol (mg/dL)

BMDS version: BMDS v2.7.0

* + 1. Input dataset

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 55 | 110 | 220 | 441 | 881 |
| N | 5 | 5 | 5 | 5 | 5 | 5 |
| Mean ± SD | 101 ± 12.969 | 115 ± 14.534 | 122.4 ± 13.864 | 127.8 ± 14.087 | 145.4 ± 16.323 | 170 ± 43.38 |

* + 1. Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linearb (equivalent models include Power, Polynomial 2°, 3°, 4°, 5°) | 0.621 | 207.282 | 141.641 | 90.374 | Linear recommended as best-fitting model on the basis of the lowest AIC. |
| Hill | 0.604 | 208.5 | 86.758 | -999 |
| Exponential M2 (equivalent models include Exponential M3) | 0.474 | 208.175 | 181.264 | 121.434 |
| Exponential M4 (equivalent models include Exponential M5) | 0.583 | 208.599 | 94.577 | 41.241 |

a Modeled variance case presented (BMDS Test 2 p-value = 0.011, BMDS Test 3 p-value = 0.63).

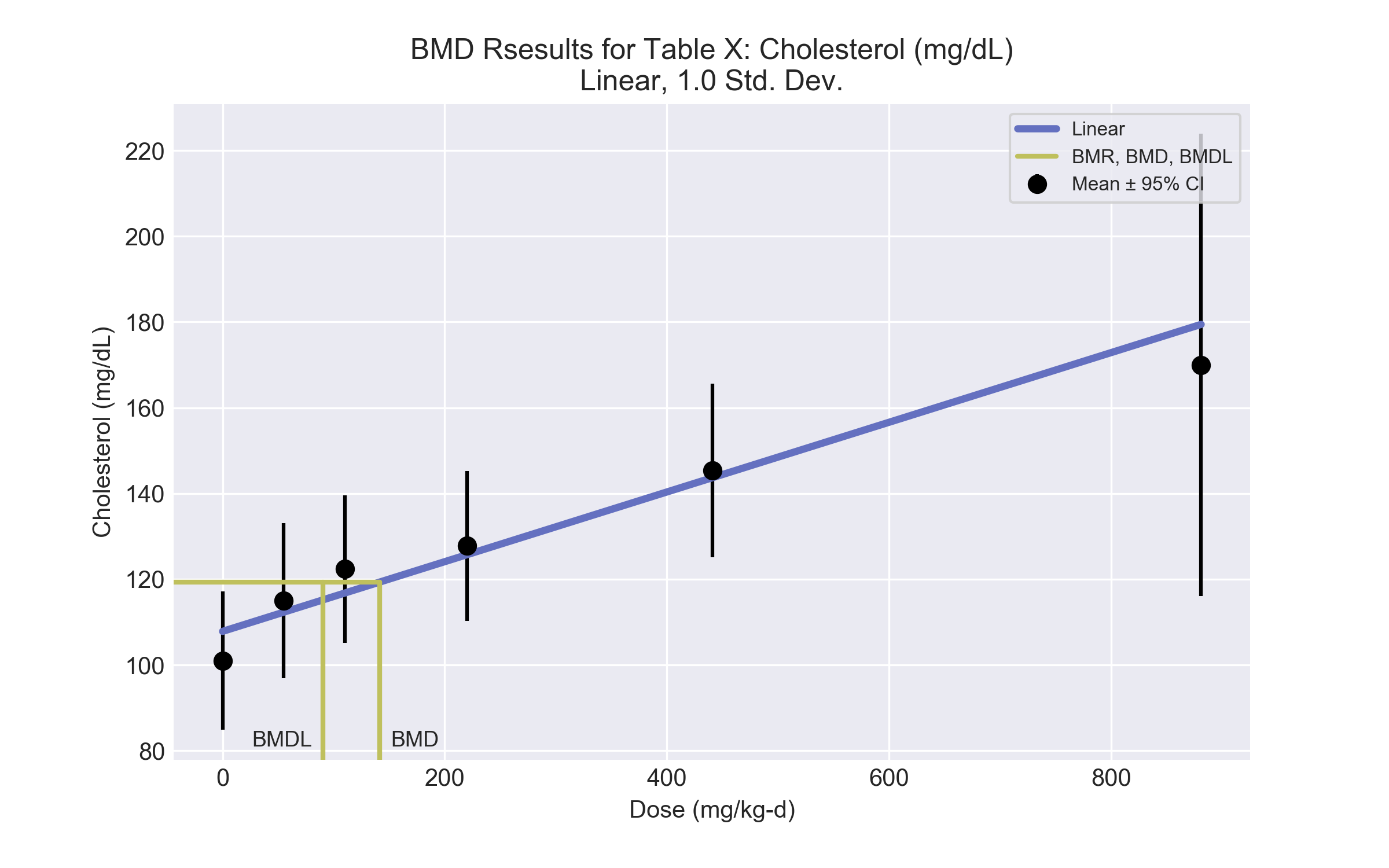
b Recommended model

* + 1. Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Lineara (equivalent models include Power, Polynomial 2°, 3°, 4°, 5°) | Valid | - |
| Hill | Failure | **Failures**  • BMDL does not exist  **Cautions**  • Warning(s): BMDL computation failed. |
| Exponential M2 (equivalent models include Exponential M3) | Valid | - |
| Exponential M4 (equivalent models include Exponential M5) | Valid | - |

a Recommended model

* + 1. Recommended model



====================================================================   
 Polynomial Model. (Version: 2.21; Date: 03/14/2017)   
 Input Data File: C:\Users\USERNAME\AppData\Local\Temp\2\bmds-pveozi1h.(d)   
 Gnuplot Plotting File: C:\Users\USERNAME\AppData\Local\Temp\2\bmds-pveozi1h.plt  
 Mon Dec 18 12:02:56 2017  
 ====================================================================   
  
 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 = 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   
 lalpha = 6.18701  
 rho = 0  
 beta\_0 = 109.815  
 beta\_1 = 0.0718858  
  
  
 Asymptotic Correlation Matrix of Parameter Estimates  
  
 lalpha rho beta\_0 beta\_1  
  
 lalpha 1 -1 0.27 -0.38  
  
 rho -1 1 -0.27 0.38  
  
 beta\_0 0.27 -0.27 1 -0.64  
  
 beta\_1 -0.38 0.38 -0.64 1  
  
  
  
 Parameter Estimates  
  
 95.0% Wald Confidence Interval  
 Variable Estimate Std. Err. Lower Conf. Limit Upper Conf. Limit  
 lalpha -14.9482 6.91119 -28.4939 -1.40256  
 rho 4.23775 1.42088 1.45289 7.02262  
 beta\_0 107.835 3.58466 100.81 114.861  
 beta\_1 0.0812855 0.0164193 0.0491043 0.113467  
  
  
  
 Table of Data and Estimated Values of Interest  
  
 Dose N Obs Mean Est Mean Obs Std Dev Est Std Dev Scaled Res.  
------ --- -------- -------- ----------- ----------- ----------  
  
 0 5 101 108 13 11.5 -1.33  
 55 5 115 112 14.5 12.5 0.48  
 110 5 122 117 13.9 13.6 0.923  
 220 5 128 126 14.1 15.9 0.292  
 441 5 145 144 16.3 21.1 0.182  
 881 5 170 179 43.4 33.9 -0.624  
  
  
  
 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 -104.458060 7 222.916119  
 A2 -97.033947 12 218.067894  
 A3 -98.324126 8 212.648251  
 fitted -99.641128 4 207.282256  
 R -116.755577 2 237.511154  
  
  
 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 39.4433 10 <.0001  
 Test 2 14.8482 5 0.01103  
 Test 3 2.58036 4 0.6303  
 Test 4 2.634 4 0.6208  
  
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 = 141.641  
  
  
 BMDL = 90.3744  
  
  
 BMDU = 238.643

* 1. BMD Results for: Triglyceride (mg/dL)

BMDS version: BMDS v2.7.0

* + 1. Input dataset

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 55 | 110 | 220 | 441 | 881 |
| N | 5 | 5 | 5 | 5 | 5 | 5 |
| Mean ± SD | 54 ± 13.416 | 53.8 ± 3.13 | 61.6 ± 15.205 | 74 ± 13.64 | 53 ± 11.851 | 140.6 ± 132.152 |

* + 1. Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear | 0.005 | 219.404 | 187.888 | 86.465 | No model was recommended as a best-fitting model. |
| Polynomial 2° | 0.004 | 219.699 | 288.455 | 107.505 |
| Polynomial 3° | 0.005 | 219.061 | 329.975 | 113.749 |
| Polynomial 4° | 0.007 | 218.469 | 373.155 | 119.889 |
| Polynomial 5° | 0.009 | 218.03 | 414.794 | 125.005 |
| Power | 0.02 | 216.027 | 797.502 | 161.184 |
| Hill | 0.009 | 218.027 | 795.352 | -999 |
| Exponential M2 | 0.008 | 218.079 | 199.274 | 116.768 |
| Exponential M3 | 0.004 | 219.593 | 284.268 | 121.676 |
| Exponential M4 | 0.002 | 221.404 | 187.89 | 86.464 |
| Exponential M5 | 0.001 | 221.98 | 276.407 | 105.057 |

a Modeled variance case presented (BMDS Test 2 p-value = <0.0001, BMDS Test 3 p-value = 0.067).

* + 1. Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear | Warning | **Warnings**  • Variance model fit p-value is less than threshold (0.0672 < 0.1)  • Goodness of fit p-value is less than threshold (0.00461 < 0.1)  • Ratio of modeled to actual stdev. at control is greater than threshold (1.59 > 1.5)  **Cautions**  • Warning(s): THE MODEL HAS PROBABLY NOT CONVERGED!!!; THIS USUALLY MEANS THE MODEL HAS NOT CONVERGED! |
| Polynomial 2° | Warning | **Warnings**  • Variance model fit p-value is less than threshold (0.0672 < 0.1)  • Goodness of fit p-value is less than threshold (0.00396 < 0.1)  **Cautions**  • Warning(s): THE MODEL HAS PROBABLY NOT CONVERGED!!!; THIS USUALLY MEANS THE MODEL HAS NOT CONVERGED! |
| Polynomial 3° | Warning | **Warnings**  • Variance model fit p-value is less than threshold (0.0672 < 0.1)  • Goodness of fit p-value is less than threshold (0.00533 < 0.1)  **Cautions**  • Warning(s): THE MODEL HAS PROBABLY NOT CONVERGED!!!; THIS USUALLY MEANS THE MODEL HAS NOT CONVERGED! |
| Polynomial 4° | Warning | **Warnings**  • Variance model fit p-value is less than threshold (0.0672 < 0.1)  • Goodness of fit p-value is less than threshold (0.00702 < 0.1) |
| Polynomial 5° | Warning | **Warnings**  • Variance model fit p-value is less than threshold (0.0672 < 0.1)  • Goodness of fit p-value is less than threshold (0.0086 < 0.1) |
| Power | Warning | **Warnings**  • Variance model fit p-value is less than threshold (0.0672 < 0.1)  • Goodness of fit p-value is less than threshold (0.02 < 0.1) |
| Hill | Failure | **Failures**  • BMDL does not exist  **Warnings**  • Variance model fit p-value is less than threshold (0.0672 < 0.1)  • Goodness of fit p-value is less than threshold (0.00861 < 0.1)  **Cautions**  • Warning(s): BMDL computation failed. |
| Exponential M2 | Warning | **Warnings**  • Variance model fit p-value is less than threshold (0.0672 < 0.1)  • Goodness of fit p-value is less than threshold (0.00825 < 0.1) |
| Exponential M3 | Warning | **Warnings**  • Variance model fit p-value is less than threshold (0.0672 < 0.1)  • Goodness of fit p-value is less than threshold (0.00416 < 0.1) |
| Exponential M4 | Warning | **Warnings**  • Variance model fit p-value is less than threshold (0.0672 < 0.1)  • Goodness of fit p-value is less than threshold (0.00178 < 0.1) |
| Exponential M5 | Warning | **Warnings**  • Variance model fit p-value is less than threshold (0.0672 < 0.1)  • Goodness of fit p-value is less than threshold (0.0011 < 0.1) |

* + 1. Recommended model

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

* 1. BMD Results for: LDL Cholesterol (mg/dL)

BMDS version: BMDS v2.7.0

* + 1. Input dataset

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 55 | 110 | 220 | 441 | 881 |
| N | 5 | 5 | 5 | 5 | 5 | 5 |
| Mean ± SD | 21.8 ± 1.565 | 21.8 ± 2.46 | 23.2 ± 2.012 | 23.8 ± 3.354 | 23.4 ± 2.46 | 32.8 ± 14.311 |

* + 1. Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear | 0.273 | 106.015 | 197.86 | 104.536 | Exponential-M2 recommended as best-fitting model on the basis of the lowest AIC. |
| Polynomial 2° | 0.218 | 107.306 | 299.379 | 112.801 |
| Polynomial 3° | 0.287 | 106.648 | 346.581 | 123.133 |
| Polynomial 4° | 0.35 | 106.156 | 375.742 | 132.71 |
| Polynomial 5° | 0.393 | 105.863 | 390.392 | 137.804 |
| Power | 0.186 | 107.689 | 582.268 | 108.07 |
| Hill | 0.09 | 109.69 | 582.718 | -999 |
| Exponential M2b | 0.308 | 105.68 | 212.502 | 123.028 |
| Exponential M3 | 0.198 | 107.544 | 288.549 | 124.467 |
| Exponential M4 | 0.162 | 108.017 | 197.799 | 92.074 |
| Exponential M5 | 0.086 | 109.777 | 290.279 | 95.73 |

a Modeled variance case presented (BMDS Test 2 p-value = <0.0001, BMDS Test 3 p-value = 0.848).

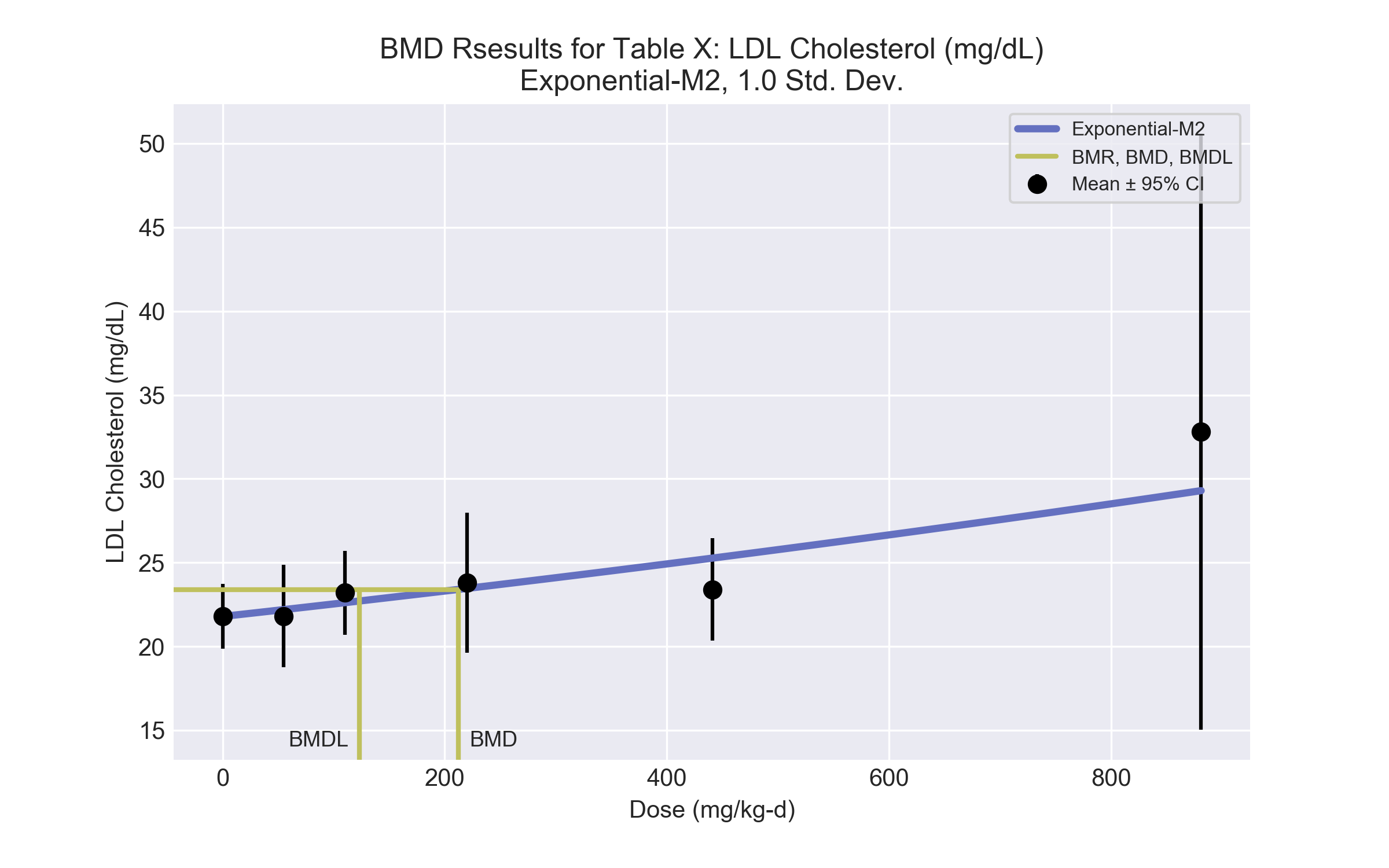
b Recommended model

* + 1. Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear | Valid | - |
| Polynomial 2° | Valid | **Cautions**  • Warning(s): THE MODEL HAS PROBABLY NOT CONVERGED!!!; THIS USUALLY MEANS THE MODEL HAS NOT CONVERGED! |
| Polynomial 3° | Valid | - |
| Polynomial 4° | Valid | - |
| Polynomial 5° | Valid | - |
| Power | Valid | **Cautions**  • BMD/BMDL ratio is greater than threshold (5.39 > 5.0) |
| Hill | Failure | **Failures**  • BMDL does not exist  **Warnings**  • Goodness of fit p-value is less than threshold (0.0899 < 0.1)  **Cautions**  • Warning(s): BMDL computation failed. |
| Exponential M2a | Valid | - |
| Exponential M3 | Valid | - |
| Exponential M4 | Valid | - |
| Exponential M5 | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0861 < 0.1) |

a Recommended model

* + 1. Recommended model



====================================================================   
 Exponential Model. (Version: 1.11; Date: 03/14/2017)   
 Input Data File: C:\Users\USERNAME\AppData\Local\Temp\2\bmds-fv1sx\_c7.(d)   
 Gnuplot Plotting File:   
 Mon Dec 18 12:03:02 2017  
 ====================================================================   
  
 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 2  
 -------- --------  
 lnalpha -29.4871   
 rho 9.96609   
 a 21.3967   
 b 0.000434333   
 c 0 Specified  
 d 1 Specified  
  
  
  
 Parameter Estimates  
  
 Variable Model 2 Std. Err.  
 -------- ------- ---------  
 lnalpha -40.9993 19.7613  
 rho 13.6154 6.31919  
 a 21.7884 0.51354  
 b 0.000335881 0.000138741  
  
 NC = No Convergence  
  
  
 Table of Stats From Input Data  
  
 Dose N Obs Mean Obs Std Dev  
 ----- --- ---------- -------------  
 0 5 21.8 1.565  
 55 5 21.8 2.46  
 110 5 23.2 2.012  
 220 5 23.8 3.354  
 441 5 23.4 2.46  
 881 5 32.8 14.31  
  
  
 Estimated Values of Interest  
  
 Dose Est Mean Est Std Scaled Residual  
 ------ ---------- --------- ----------------  
 0 21.79 1.612 0.01608  
 55 22.19 1.828 -0.4827  
 110 22.61 2.073 0.6381  
 220 23.46 2.666 0.2857  
 441 25.27 4.419 -0.9448  
 881 29.29 12.08 0.6492  
  
  
  
 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 -66.64788 7 147.2958  
 A2 -45.74616 12 115.4923  
 A3 -46.43633 8 108.8727  
 R -72.35188 2 148.7038  
 2 -48.84015 4 105.6803  
  
  
 Additive constant for all log-likelihoods = -27.57. This constant added to the  
 above values gives the log-likelihood including the term that does not  
 depend on the model parameters.  
  
  
 Explanation of Tests  
  
 Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)  
 Test 2: Are Variances Homogeneous? (A2 vs. A1)  
 Test 3: Are variances adequately modeled? (A2 vs. A3)  
 Test 4: Does Model 2 fit the data? (A3 vs. 2)  
  
  
 Tests of Interest  
  
 Test -2\*log(Likelihood Ratio) D. F. p-value  
 -------- ------------------------ ------ --------------  
 Test 1 53.21 10 < 0.0001  
 Test 2 41.8 5 < 0.0001  
 Test 3 1.38 4 0.8476  
 Test 4 4.808 4 0.3076  
  
  
 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. 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 = 212.502  
  
 BMDL = 123.028  
  
 BMDU = 426.784

* 1. BMD Results for: HDL Cholesterol (mg/dL)

BMDS version: BMDS v2.7.0

* + 1. Input dataset

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 55 | 110 | 220 | 441 | 881 |
| N | 5 | 5 | 5 | 5 | 5 | 5 |
| Mean ± SD | 46 ± 6.485 | 54.6 ± 6.037 | 56.8 ± 6.261 | 60.6 ± 6.485 | 70.6 ± 7.155 | 78.2 ± 11.404 |

* + 1. Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear (equivalent models include Power, Polynomial 2°, 3°, 4°, 5°) | 0.176 | 156.83 | 225.091 | 171.588 | Hill recommended as best-fitting model on the basis of the lowest BMDL. |
| Hillb | 0.762 | 153.671 | 79.236 | 38.558 |
| Exponential M2 (equivalent models include Exponential M3) | 0.085 | 158.696 | 281.293 | 221.34 |
| Exponential M4 (equivalent models include Exponential M5) | 0.722 | 153.84 | 90.238 | 51.481 |

a Constant variance case presented (BMDS Test 2 p-value = 0.627, BMDS Test 3 p-value = 0.627).

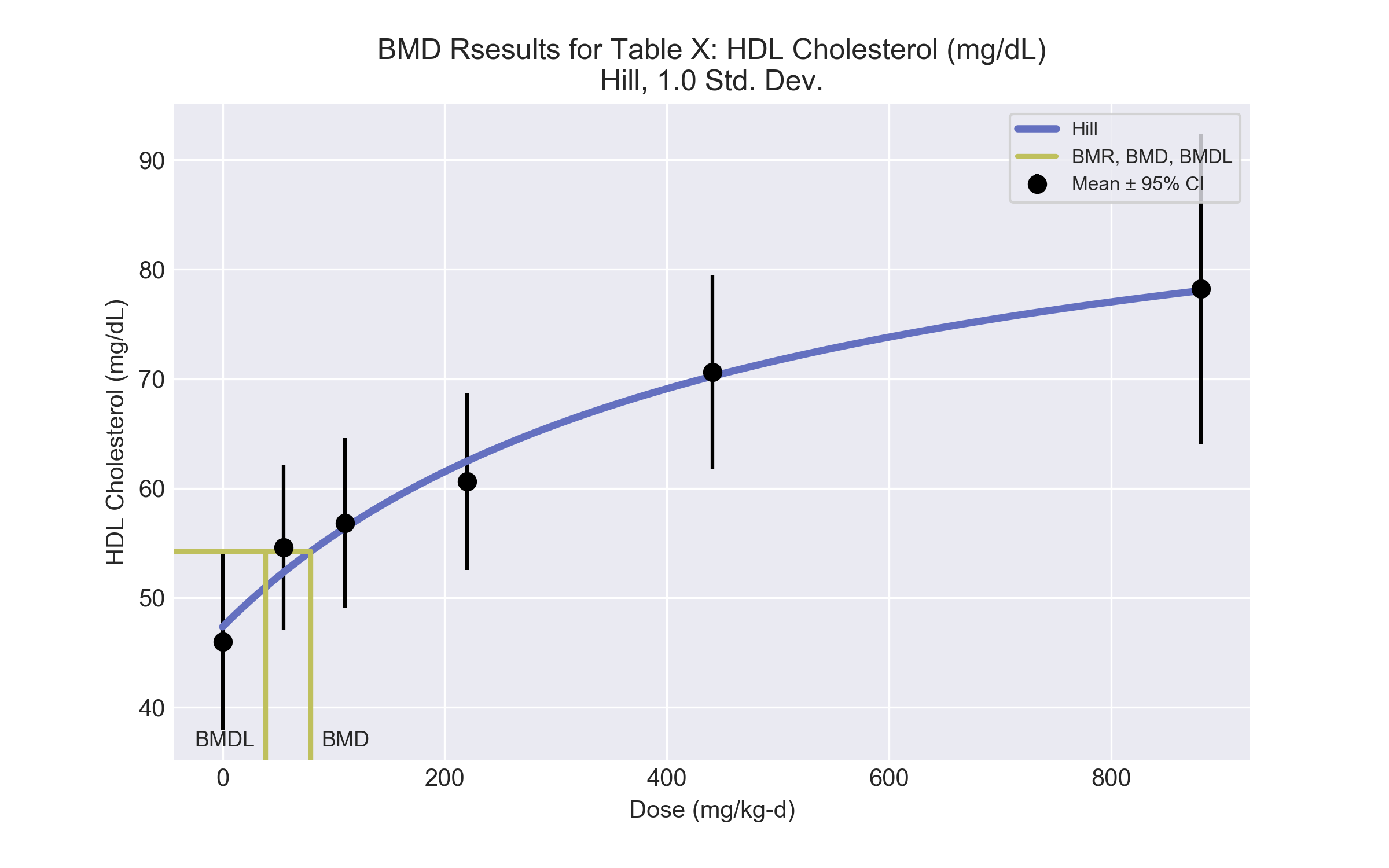
b Recommended model

* + 1. Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear (equivalent models include Power, Polynomial 2°, 3°, 4°, 5°) | Valid | - |
| Hilla | Valid | - |
| Exponential M2 (equivalent models include Exponential M3) | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.085 < 0.1) |
| Exponential M4 (equivalent models include Exponential M5) | Valid | - |

a Recommended model

* + 1. Recommended model



====================================================================   
 Hill Model. (Version: 2.18; Date: 03/14/2017)   
 Input Data File: C:\Users\USERNAME\AppData\Local\Temp\2\bmds-rsm6s3g8.(d)   
 Gnuplot Plotting File: C:\Users\USERNAME\AppData\Local\Temp\2\bmds-rsm6s3g8.plt  
 Mon Dec 18 12:03:04 2017  
 ====================================================================   
  
 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 = 56.8333  
 rho = 0 Specified  
 intercept = 46  
 v = 32.2  
 n = 0.246121  
 k = 628.85  
  
  
 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 -1.2e-006 -2.4e-006 -2.9e-006  
  
 intercept -1.2e-006 1 0.3 0.66  
  
 v -2.4e-006 0.3 1 0.89  
  
 k -2.9e-006 0.66 0.89 1  
  
  
  
 Parameter Estimates  
  
 95.0% Wald Confidence Interval  
 Variable Estimate Std. Err. Lower Conf. Limit Upper Conf. Limit  
 alpha 47.2616 12.2029 23.3444 71.1788  
 intercept 47.3418 2.75195 41.9481 52.7356  
 v 46.7113 12.0284 23.1362 70.2865  
 n 1 NA  
 k 459.144 309.077 -146.636 1064.92  
  
NA - Indicates that this parameter has hit a bound  
 implied by some inequality constraint and thus  
 has no standard error.  
  
  
  
 Table of Data and Estimated Values of Interest  
  
 Dose N Obs Mean Est Mean Obs Std Dev Est Std Dev Scaled Res.  
------ --- -------- -------- ----------- ----------- ----------  
  
 0 5 46 47.3 6.48 6.87 -0.436  
 55 5 54.6 52.3 6.04 6.87 0.735  
 110 5 56.8 56.4 6.26 6.87 0.14  
 220 5 60.6 62.5 6.48 6.87 -0.609  
 441 5 70.6 70.2 7.16 6.87 0.121  
 881 5 78.2 78 11.4 6.87 0.049  
  
  
  
 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 -72.254692 7 158.509385  
 A2 -70.517836 12 165.035672  
 A3 -72.254692 7 158.509385  
 fitted -72.835514 4 153.671029  
 R -90.882702 2 185.765405  
  
  
 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 40.7297 10 <.0001  
 Test 2 3.47371 5 0.6274  
 Test 3 3.47371 5 0.6274  
 Test 4 1.16164 3 0.7622  
  
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 = 79.2356  
  
 BMDL = 38.5579  
  
 BMDU = 186.702

* 1. BMD Results for: Manual Hematocrit (%)

BMDS version: BMDS v2.7.0

* + 1. Input dataset

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 55 | 110 | 220 | 441 | 881 |
| N | 5 | 5 | 5 | 5 | 5 | 5 |
| Mean ± SD | 40 ± 2.236 | 42 ± 0 | 41 ± 2.236 | 41 ± 2.236 | 42 ± 2.236 | 44 ± 2.236 |

* + 1. Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linearb | <0.0001 | 76.939 | 509.521 | 298.479 | Linear recommended as best-fitting model on the basis of the lowest AIC. |
| Polynomial 2° | <0.0001 | 78.814 | 593.958 | 301.95 |
| Polynomial 3° | <0.0001 | 78.779 | 610.688 | 302.927 |
| Polynomial 4° (equivalent models include Polynomial 5°) | <0.0001 | 78.775 | 620.644 | 303.051 |
| Power | <0.0001 | 78.904 | 593.051 | 299.438 |
| Hill | <0.0001 | 80.904 | 593.405 | -999 |
| Exponential M2 | <0.0001 | 85.609 | 1 | -999 |
| Exponential M3 | <0.0001 | 69128 | 1 | -999 |
| Exponential M4 | <0.0001 | 87.609 | -999 | 0 |
| Exponential M5 | <0.0001 | 89.609 | 93622 | 308.133 |

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

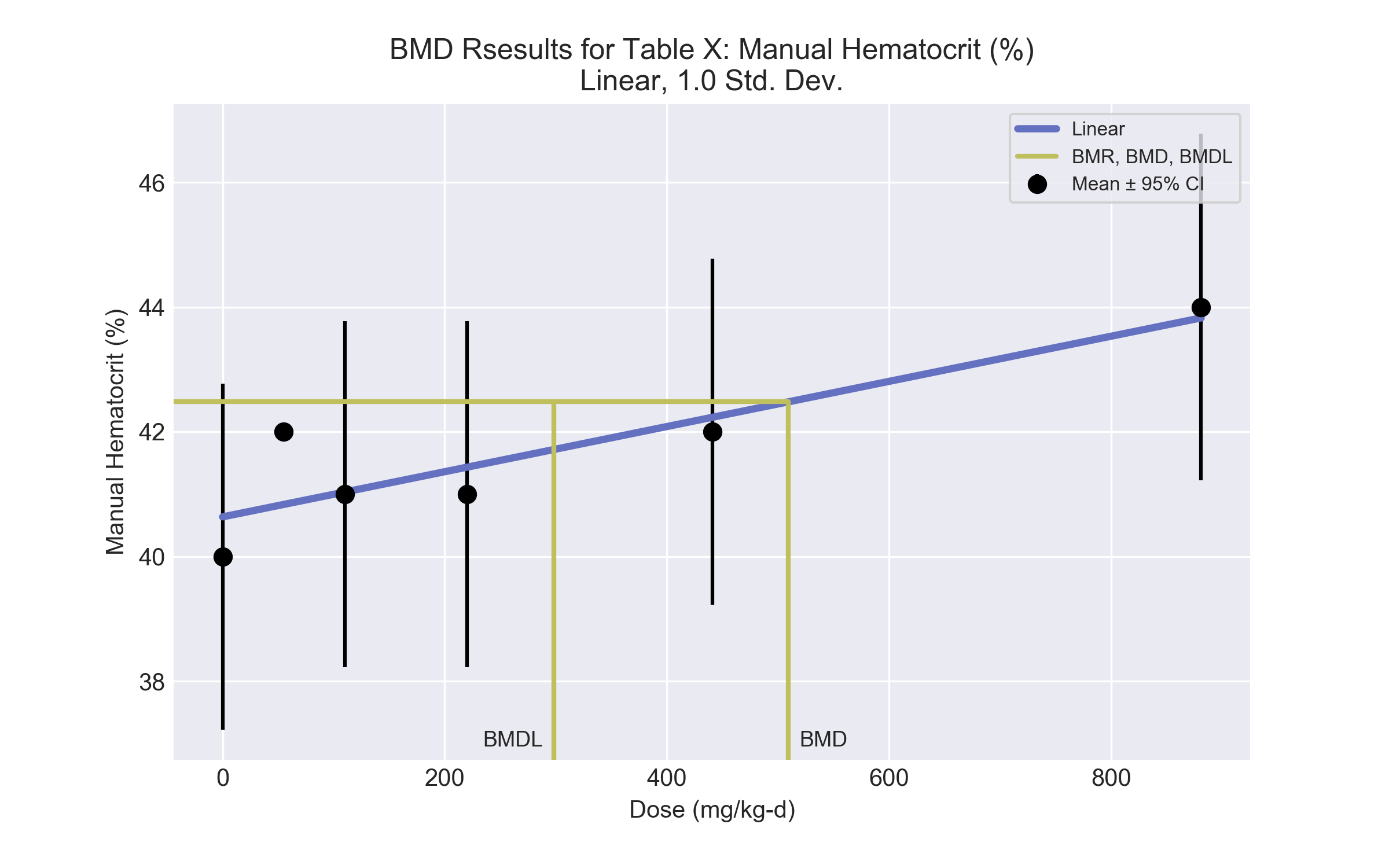
b Recommended model

* + 1. Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Lineara | Valid | **Cautions**  • Warning(s): Warning: Likelihood for fitted model larger than the Likelihood for model A3. |
| Polynomial 2° | Valid | **Cautions**  • Warning(s): Warning: Likelihood for fitted model larger than the Likelihood for model A3. |
| Polynomial 3° | Valid | **Cautions**  • Warning(s): Warning: Likelihood for fitted model larger than the Likelihood for model A3. |
| Polynomial 4° (equivalent models include Polynomial 5°) | Valid | **Cautions**  • Warning(s): Warning: Likelihood for fitted model larger than the Likelihood for model A3. |
| Power | Valid | **Cautions**  • Warning(s): Warning: Likelihood for fitted model larger than the Likelihood for model A3. |
| Hill | Failure | **Failures**  • BMDL does not exist  **Cautions**  • Warning(s): BMDL computation failed. |
| Exponential M2 | Failure | **Failures**  • BMDL does not exist  **Warnings**  • BMD/minimum dose ratio is greater than threshold (55.0 > 10.0)  **Cautions**  • BMD/minimum dose ratio is greater than threshold (55.0 > 3.0) |
| Exponential M3 | Failure | **Failures**  • BMDL does not exist  **Warnings**  • BMD/minimum dose ratio is greater than threshold (55.0 > 10.0)  **Cautions**  • BMD/minimum dose ratio is greater than threshold (55.0 > 3.0) |
| Exponential M4 | Failure | **Failures**  • BMD does not exist  **Warnings**  • Residual of Interest does not exist |
| Exponential M5 | Warning | **Warnings**  • BMD/BMDL ratio is greater than threshold (3.04e+02 > 20.0)  **Cautions**  • BMD/BMDL ratio is greater than threshold (3.04e+02 > 5.0)  • Residual of interest is greater than threshold (2.36 > 2.0)  • BMD/high dose ratio is greater than threshold (1.06e+02 > 1.0) |

a Recommended model

* + 1. Recommended model



====================================================================   
 Polynomial Model. (Version: 2.21; Date: 03/14/2017)   
 Input Data File: C:\Users\USERNAME\AppData\Local\Temp\2\bmds-6lmxm28l.(d)   
 Gnuplot Plotting File: C:\Users\USERNAME\AppData\Local\Temp\2\bmds-6lmxm28l.plt  
 Mon Dec 18 12:03:04 2017  
 ====================================================================   
  
 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 = 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   
 lalpha = 1.42712  
 rho = 0  
 beta\_0 = 40.6288  
 beta\_1 = 0  
  
  
 Asymptotic Correlation Matrix of Parameter Estimates  
  
 lalpha rho beta\_0 beta\_1  
  
 lalpha 1 -1 -0.054 0.08  
  
 rho -1 1 0.054 -0.08  
  
 beta\_0 -0.054 0.054 1 -0.67  
  
 beta\_1 0.08 -0.08 -0.67 1  
  
  
  
 Parameter Estimates  
  
 95.0% Wald Confidence Interval  
 Variable Estimate Std. Err. Lower Conf. Limit Upper Conf. Limit  
 lalpha -9.68576 37.9496 -84.0656 64.6941  
 rho 2.9452 10.1757 -16.9987 22.8892  
 beta\_0 40.6362 0.47116 39.7127 41.5596  
 beta\_1 0.0036215 0.00120702 0.00125578 0.00598722  
  
  
  
 Table of Data and Estimated Values of Interest  
  
 Dose N Obs Mean Est Mean Obs Std Dev Est Std Dev Scaled Res.  
------ --- -------- -------- ----------- ----------- ----------  
  
 0 5 40 40.6 2.24 1.85 -0.771  
 55 5 42 40.8 0 1.86 1.4  
 110 5 41 41 2.24 1.87 -0.0412  
 220 5 41 41.4 2.24 1.9 -0.51  
 441 5 42 42.2 2.24 1.95 -0.267  
 881 5 44 43.8 2.24 2.06 0.188  
   
 Warning: Likelihood for fitted model larger than the Likelihood for model A3.  
  
  
  
 Model Descriptions for likelihoods calculated  
  
  
 Model A1: Yij = Mu(i) + e(ij)  
 Var{e(ij)} = Sigma^2  
  
 Model A2: Yij = Mu(i) + e(ij)  
 Var{e(ij)} = Sigma(i)^2  
  
 Model A3: Yij = Mu(i) + e(ij)  
 Var{e(ij)} = exp(lalpha + rho\*ln(Mu(i)))  
 Model A3 uses any fixed variance parameters that  
 were specified by the user  
  
 Model R: Yi = Mu + e(i)  
 Var{e(i)} = Sigma^2  
  
  
 Likelihoods of Interest  
  
 Model Log(likelihood) # Param's AIC  
 A1 -33.059592 7 80.119185  
 A2 1.#INF00 12 -1.#INF00  
 A3 -368262177617.213380 8 736524355250.426760  
 fitted -34.469285 4 76.938570  
 R -38.804476 2 81.608952  
  
  
 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 1.#INF 10 <.0001  
 Test 2 1.#INF 5 <.0001  
 Test 3 1.#INF 4 <.0001  
 Test 4 -7.36524e+011 4 <.0001  
  
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. Consider running a   
homogeneous model  
  
The p-value for Test 3 is greater than .1. The modeled variance appears   
 to be appropriate here  
  
The p-value for Test 4 is less than .1. You may want to try a different   
model  
   
  
 Benchmark Dose Computation  
  
Specified effect = 1  
  
Risk Type = Estimated standard deviations from the control mean  
  
Confidence level = 0.95  
  
 BMD = 509.521  
  
  
 BMDL = 298.479  
  
  
 BMDU = 1248.27

* 1. BMD Results for: Reticulocytes (10^3/uL)

BMDS version: BMDS v2.7.0

* + 1. Input dataset

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 55 | 110 | 220 | 441 | 881 |
| N | 5 | 5 | 5 | 5 | 5 | 5 |
| Mean ± SD | 0.3 ± 0 | 0.3 ± 0 | 0.3 ± 0 | 0.2 ± 0 | 0.2 ± 0 | 0.1 ± 0 |

* + 1. Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear | <0.0001 | 1614634 | -9999 | 0.225 | No model was recommended as a best-fitting model. |
| Polynomial 2° | <0.0001 | 1614634 | -9999 | -999 |
| Polynomial 3° | <0.0001 | 1614634 | -9999 | 0.152 |
| Polynomial 4° | <0.0001 | 1614634 | -9999 | 0.646 |
| Polynomial 5° | <0.0001 | 1614634 | -9999 | 82031 |
| Power | <0.0001 | -266.442 | 375.386 | -999 |
| Hill | <0.0001 | -235.572 | 0 | 0 |
| Exponential M2 | <0.0001 | -196.901 | 95.042 | 59.866 |
| Exponential M3 | <0.0001 | -266.869 | 354.669 | -999 |
| Exponential M4 | <0.0001 | -260.24 | 1.0E-04 | 1.0E-04 |
| Exponential M5 | <0.0001 | -285.266 | 403.68 | -999 |

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

* + 1. Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear | Warning | **Warnings**  • Residual of Interest does not exist  • BMDL/minimum dose ratio is greater than threshold (2.44e+02 > 10.0)  • Residual at lowest dose is greater than threshold (nan > 2.0)  • Ratio of modeled to actual stdev. at control is greater than threshold (nan > 1.5)  **Cautions**  • Warning(s): THE MODEL HAS PROBABLY NOT CONVERGED!!!; THIS USUALLY MEANS THE MODEL HAS NOT CONVERGED!; BMD = 100\*(maximum dose)  • BMDL/minimum dose ratio is greater than threshold (2.44e+02 > 3.0) |
| Polynomial 2° | Failure | **Failures**  • BMDL does not exist  **Warnings**  • Residual of Interest does not exist  • Residual at lowest dose is greater than threshold (nan > 2.0)  • Ratio of modeled to actual stdev. at control is greater than threshold (nan > 1.5)  **Cautions**  • Warning(s): THE MODEL HAS PROBABLY NOT CONVERGED!!!; THIS USUALLY MEANS THE MODEL HAS NOT CONVERGED!; BMD = 100\*(maximum dose); BMDL computation failed. |
| Polynomial 3° | Warning | **Warnings**  • Residual of Interest does not exist  • BMDL/minimum dose ratio is greater than threshold (3.61e+02 > 10.0)  • Residual at lowest dose is greater than threshold (nan > 2.0)  • Ratio of modeled to actual stdev. at control is greater than threshold (nan > 1.5)  **Cautions**  • Warning(s): THE MODEL HAS PROBABLY NOT CONVERGED!!!; THIS USUALLY MEANS THE MODEL HAS NOT CONVERGED!; BMD = 100\*(maximum dose)  • BMDL/minimum dose ratio is greater than threshold (3.61e+02 > 3.0) |
| Polynomial 4° | Warning | **Warnings**  • Residual of Interest does not exist  • BMDL/minimum dose ratio is greater than threshold (85.2 > 10.0)  • Residual at lowest dose is greater than threshold (nan > 2.0)  • Ratio of modeled to actual stdev. at control is greater than threshold (nan > 1.5)  **Cautions**  • Warning(s): THE MODEL HAS PROBABLY NOT CONVERGED!!!; THIS USUALLY MEANS THE MODEL HAS NOT CONVERGED!; BMD = 100\*(maximum dose)  • BMDL/minimum dose ratio is greater than threshold (85.2 > 3.0) |
| Polynomial 5° | Warning | **Warnings**  • Residual of Interest does not exist  • BMDL/high dose ratio is greater than threshold (93.1 > 1.0)  • Residual at lowest dose is greater than threshold (nan > 2.0)  • Ratio of modeled to actual stdev. at control is greater than threshold (nan > 1.5)  **Cautions**  • Warning(s): THE MODEL HAS PROBABLY NOT CONVERGED!!!; THIS USUALLY MEANS THE MODEL HAS NOT CONVERGED!; BMD = 100\*(maximum dose) |
| Power | Failure | **Failures**  • BMDL does not exist  **Cautions**  • Warning(s): BMDL computation failed. |
| Hill | Warning | **Warnings**  • BMD/minimum dose ratio is greater than threshold (1.45e+14 > 10.0)  • BMDL/minimum dose ratio is greater than threshold (1.45e+14 > 10.0)  **Cautions**  • Warning(s): THE MODEL HAS PROBABLY NOT CONVERGED!!!; THIS USUALLY MEANS THE MODEL HAS NOT CONVERGED!  • BMD/minimum dose ratio is greater than threshold (1.45e+14 > 3.0)  • BMDL/minimum dose ratio is greater than threshold (1.45e+14 > 3.0) |
| Exponential M2 | Warning | **Warnings**  • Correct variance model cannot be determined (p-value 2 = -999) |
| Exponential M3 | Failure | **Failures**  • BMDL does not exist  **Warnings**  • Correct variance model cannot be determined (p-value 2 = -999) |
| Exponential M4 | Warning | **Warnings**  • Correct variance model cannot be determined (p-value 2 = -999)  • BMD/minimum dose ratio is greater than threshold (5.52e+05 > 10.0)  • BMDL/minimum dose ratio is greater than threshold (5.52e+05 > 10.0)  **Cautions**  • BMD/minimum dose ratio is greater than threshold (5.52e+05 > 3.0)  • BMDL/minimum dose ratio is greater than threshold (5.52e+05 > 3.0) |
| Exponential M5 | Failure | **Failures**  • BMDL does not exist  **Warnings**  • Correct variance model cannot be determined (p-value 2 = -999) |

* + 1. Recommended model

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

* 1. BMD Results for: Reticulocyte Percentage

BMDS version: BMDS v2.7.0

* + 1. Input dataset

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 55 | 110 | 220 | 441 | 881 |
| N | 5 | 5 | 5 | 5 | 5 | 5 |
| Mean ± SD | 3.9 ± 0.671 | 3.5 ± 0.447 | 3.6 ± 0.447 | 3.1 ± 0.447 | 3.2 ± 0.894 | 0.9 ± 0.447 |

* + 1. Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear | 0.058 | 6.229 | 196.072 | 151.749 | Polynomial-5 recommended as best-fitting model on the basis of the lowest AIC. |
| Polynomial 2° | 0.198 | 3.755 | 377.077 | 210.906 |
| Polynomial 3° | 0.3 | 2.756 | 385.68 | 213.713 |
| Polynomial 4° | 0.363 | 2.279 | 386.374 | 211.462 |
| Polynomial 5°b | 0.398 | 2.047 | 384.409 | 209.417 |
| Power | 0.202 | 3.706 | 445.629 | 240.526 |
| Hill | 0.099 | 5.711 | 445.994 | 241.152 |
| Exponential M2 (equivalent models include Exponential M4) | 0.006 | 11.45 | 165.095 | 115.404 |
| Exponential M3 | 0.169 | 4.128 | 476.424 | 307.449 |
| Exponential M5 | 0.08 | 6.128 | 476.424 | 307.449 |

a Constant variance case presented (BMDS Test 2 p-value = 0.406, BMDS Test 3 p-value = 0.406).

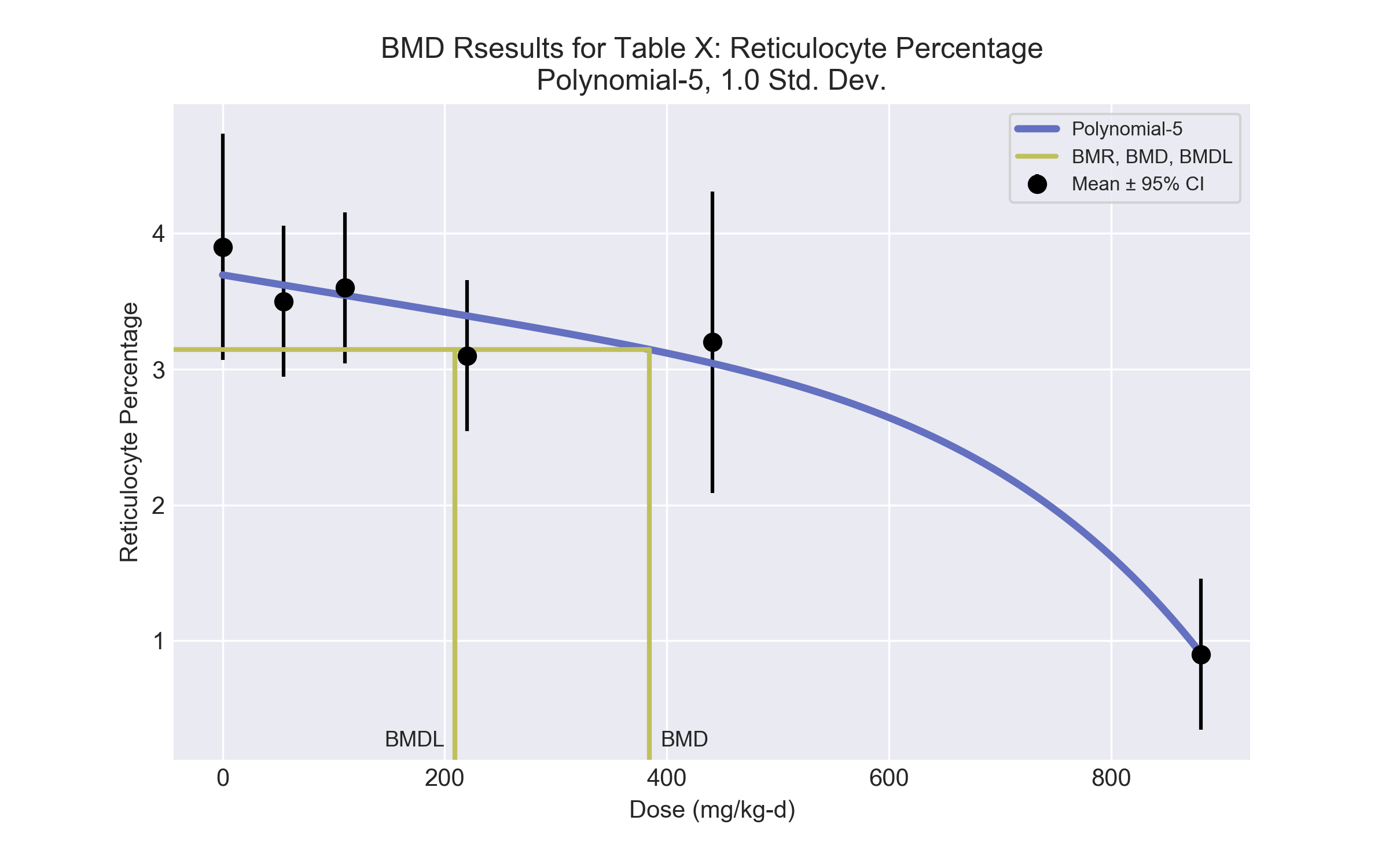
b Recommended model

* + 1. Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0577 < 0.1) |
| Polynomial 2° | Valid | - |
| Polynomial 3° | Valid | - |
| Polynomial 4° | Valid | - |
| Polynomial 5°a | Valid | - |
| Power | Valid | - |
| Hill | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0991 < 0.1) |
| Exponential M2 (equivalent models include Exponential M4) | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.00622 < 0.1) |
| Exponential M3 | Valid | - |
| Exponential M5 | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0805 < 0.1) |

a Recommended model

* + 1. Recommended model



====================================================================   
 Polynomial Model. (Version: 2.21; Date: 03/14/2017)   
 Input Data File: C:\Users\USERNAME\AppData\Local\Temp\2\bmds-i9xvenm6.(d)   
 Gnuplot Plotting File: C:\Users\USERNAME\AppData\Local\Temp\2\bmds-i9xvenm6.plt  
 Mon Dec 18 12:03:11 2017  
 ====================================================================   
  
 BMDS\_Model\_Run   
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~  
   
 The form of the response function is:   
  
 Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ...  
  
  
 Dependent variable = Response  
 Independent variable = Dose  
 rho is set to 0  
 The polynomial coefficients are restricted to be negative  
 A constant variance model is fit  
  
 Total number of dose groups = 6  
 Total number of records with missing values = 0  
 Maximum number of iterations = 500  
 Relative Function Convergence has been set to: 1e-008  
 Parameter Convergence has been set to: 1e-008  
  
  
  
 Default Initial Parameter Values   
 alpha = 0.341667  
 rho = 0 Specified  
 beta\_0 = 3.9  
 beta\_1 = -0.0184134  
 beta\_2 = 0  
 beta\_3 = -1.57957e-006  
 beta\_4 = 0  
 beta\_5 = -2.00925e-012  
  
  
 Asymptotic Correlation Matrix of Parameter Estimates  
  
 ( \*\*\* The model parameter(s) -rho -beta\_2 -beta\_3 -beta\_4   
 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 beta\_5  
  
 alpha 1 -3.3e-008 5.4e-008 -7.3e-008  
  
 beta\_0 -2.9e-008 1 -0.73 0.52  
  
 beta\_1 5.3e-008 -0.73 1 -0.89  
  
 beta\_5 -6.6e-008 0.52 -0.89 1  
  
  
  
 Parameter Estimates  
  
 95.0% Wald Confidence Interval  
 Variable Estimate Std. Err. Lower Conf. Limit Upper Conf. Limit  
 alpha 0.301671 0.077891 0.149007 0.454334  
 beta\_0 3.69462 0.161704 3.37768 4.01155  
 beta\_1 -0.00136344 0.000742936 -0.00281957 9.26894e-005  
 beta\_2 -1.58452e-028 NA  
 beta\_3 0 NA  
 beta\_4 -3.78114e-034 NA  
 beta\_5 -2.99355e-015 1.14257e-015 -5.23294e-015 -7.54163e-016  
  
NA - Indicates that this parameter has hit a bound  
 implied by some inequality constraint and thus  
 has no standard error.  
  
  
  
 Table of Data and Estimated Values of Interest  
  
 Dose N Obs Mean Est Mean Obs Std Dev Est Std Dev Scaled Res.  
------ --- -------- -------- ----------- ----------- ----------  
  
 0 5 3.9 3.69 0.671 0.549 0.836  
 55 5 3.5 3.62 0.447 0.549 -0.487  
 110 5 3.6 3.54 0.447 0.549 0.226  
 220 5 3.1 3.39 0.447 0.549 -1.19  
 441 5 3.2 3.04 0.894 0.549 0.638  
 881 5 0.9 0.905 0.447 0.549 -0.0189  
  
  
  
 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 4.455944 7 5.088112  
 A2 6.995646 12 10.008707  
 A3 4.455944 7 5.088112  
 fitted 2.976293 4 2.047415  
 R -18.373797 2 40.747594  
  
  
 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 50.7389 10 <.0001  
 Test 2 5.0794 5 0.4063  
 Test 3 5.0794 5 0.4063  
 Test 4 2.9593 3 0.3979  
  
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 = 384.409  
  
  
 BMDL = 209.417  
  
  
 BMDU = 643.489

* 1. BMD Results for: Mean Cell Hemoglobin (pg)

BMDS version: BMDS v2.7.0

* + 1. Input dataset

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 55 | 110 | 220 | 441 | 881 |
| N | 2 | 5 | 5 | 5 | 5 | 5 |
| Mean ± SD | 20.2 ± 0 | 19.9 ± 0.671 | 20.1 ± 0.671 | 19.5 ± 0.224 | 19.4 ± 0.671 | 19.5 ± 0.224 |

* + 1. Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linearb (equivalent models include Power, Polynomial 2°, 3°, 4°, 5°) | <0.0001 | -4.36 | 847.462 | 465.287 | Linear recommended as best-fitting model on the basis of the lowest AIC. |
| Hill | <0.0001 | -7.308 | 181.062 | -999 |
| Exponential M2 | <0.0001 | 2.628 | 1 | -999 |
| Exponential M3 | <0.0001 | 4.628 | 321205 | 1952.36 |
| Exponential M4 (equivalent models include Exponential M5) | 1.#QO | 1.#QNAN | 1 | -999 |

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

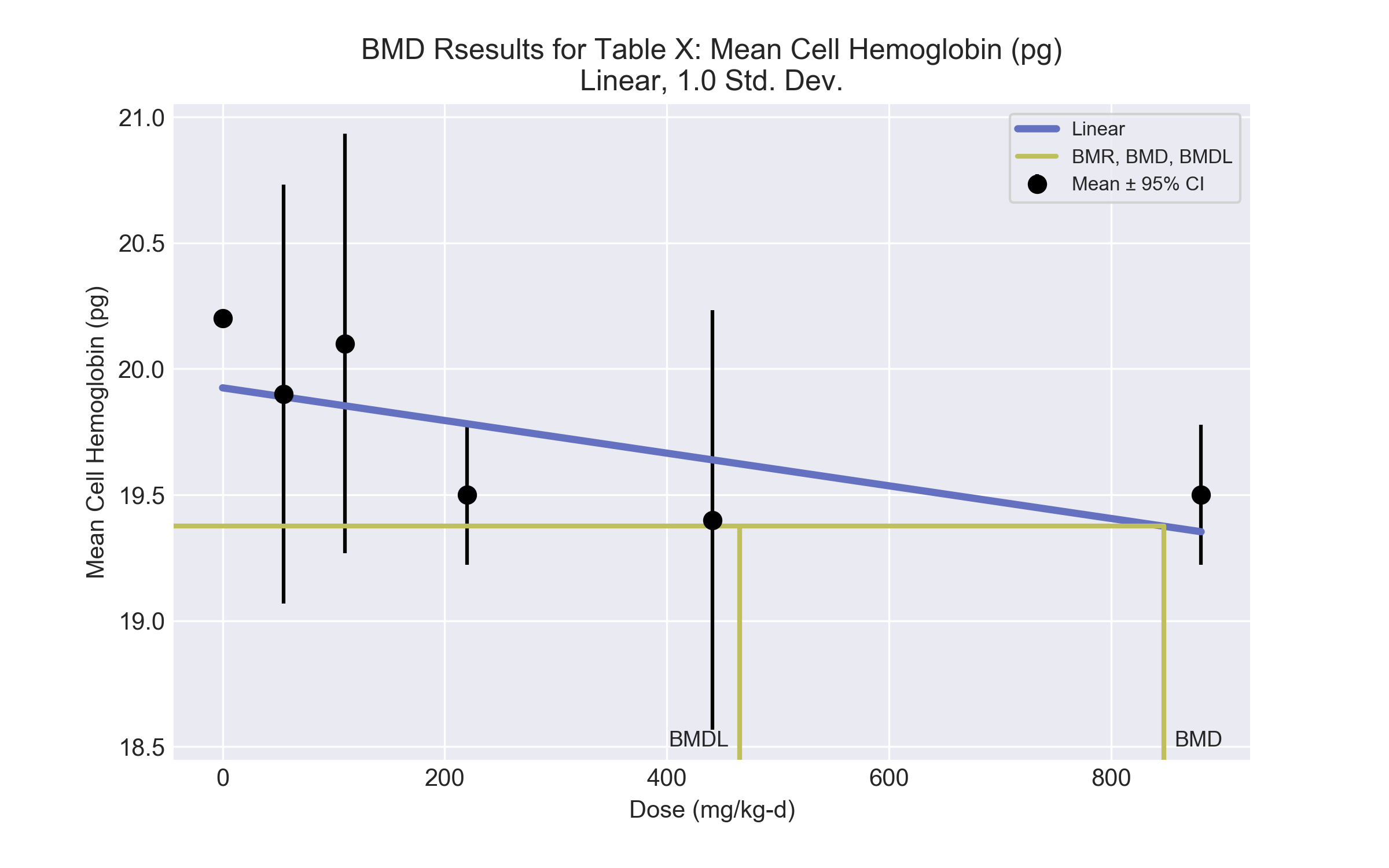
b Recommended model

* + 1. Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Lineara (equivalent models include Power, Polynomial 2°, 3°, 4°, 5°) | Valid | - |
| Hill | Failure | **Failures**  • BMDL does not exist  **Cautions**  • Warning(s): BMDL computation failed. |
| Exponential M2 | Failure | **Failures**  • BMDL does not exist  **Warnings**  • BMD/minimum dose ratio is greater than threshold (55.0 > 10.0)  **Cautions**  • BMD/minimum dose ratio is greater than threshold (55.0 > 3.0) |
| Exponential M3 | Warning | **Warnings**  • BMD/BMDL ratio is greater than threshold (1.65e+02 > 20.0)  • BMDL/high dose ratio is greater than threshold (2.22 > 1.0)  **Cautions**  • BMD/BMDL ratio is greater than threshold (1.65e+02 > 5.0)  • BMD/high dose ratio is greater than threshold (3.65e+02 > 1.0) |
| Exponential M4 (equivalent models include Exponential M5) | Failure | **Failures**  • BMDL does not exist  • AIC does not exist  **Warnings**  • BMD/minimum dose ratio is greater than threshold (55.0 > 10.0)  • Residual at lowest dose is greater than threshold (3.89e+22 > 2.0)  **Cautions**  • Residual of interest is greater than threshold (3.89e+22 > 2.0)  • BMD/minimum dose ratio is greater than threshold (55.0 > 3.0) |

a Recommended model

* + 1. Recommended model



====================================================================   
 Polynomial Model. (Version: 2.21; Date: 03/14/2017)   
 Input Data File: C:\Users\USERNAME\AppData\Local\Temp\2\bmds-334zlfwx.(d)   
 Gnuplot Plotting File: C:\Users\USERNAME\AppData\Local\Temp\2\bmds-334zlfwx.plt  
 Mon Dec 18 12:03:11 2017  
 ====================================================================   
  
 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 negative  
 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  
  
  
  
 Default Initial Parameter Values   
 lalpha = -1.28667  
 rho = 0  
 beta\_0 = 19.98  
 beta\_1 = -0.000749828  
  
  
 Asymptotic Correlation Matrix of Parameter Estimates  
  
 ( \*\*\* The model parameter(s) -rho   
 have been estimated at a boundary point, or have been specified by the user,  
 and do not appear in the correlation matrix )  
  
 lalpha beta\_0 beta\_1  
  
 lalpha 1 0.078 -0.1  
  
 beta\_0 0.078 1 -0.76  
  
 beta\_1 -0.1 -0.76 1  
  
  
  
 Parameter Estimates  
  
 95.0% Wald Confidence Interval  
 Variable Estimate Std. Err. Lower Conf. Limit Upper Conf. Limit  
 lalpha -55.0519 0.273663 -55.5883 -54.5156  
 rho 18 NA  
 beta\_0 19.9248 0.146173 19.6383 20.2113  
 beta\_1 -0.000648704 0.000290918 -0.00121889 -7.85156e-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 2 20.2 19.9 0 0.55 0.708  
 55 5 19.9 19.9 0.671 0.541 0.045  
 110 5 20.1 19.9 0.671 0.532 1.04  
 220 5 19.5 19.8 0.224 0.515 -1.22  
 441 5 19.4 19.6 0.671 0.483 -1.11  
 881 5 19.5 19.4 0.224 0.423 0.775  
  
  
  
 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 7.262729 7 -0.525458  
 A2 1.#INF00 12 -1.#INF00  
 A3 29.555549 8 -43.111098  
 fitted 5.179767 3 -4.359535  
 R 2.685911 2 -1.371822  
  
  
 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 1.#INF 10 <.0001  
 Test 2 1.#INF 5 <.0001  
 Test 3 1.#INF 4 <.0001  
 Test 4 48.7516 5 <.0001  
  
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. Consider running a   
homogeneous model  
  
The p-value for Test 3 is greater than .1. The modeled variance appears   
 to be appropriate here  
  
The p-value for Test 4 is less than .1. You may want to try a different   
model  
   
  
 Benchmark Dose Computation  
  
Specified effect = 1  
  
Risk Type = Estimated standard deviations from the control mean  
  
Confidence level = 0.95  
  
 BMD = 847.462  
  
  
 BMDL = 465.287  
  
  
 BMDU = 2856.88

* 1. BMD Results for: Mean Cell Hemoglobin Concentration (g/dL)

BMDS version: BMDS v2.7.0

* + 1. Input dataset

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 55 | 110 | 220 | 441 | 881 |
| N | 2 | 5 | 5 | 5 | 5 | 5 |
| Mean ± SD | 35.4 ± 0.141 | 34.5 ± 0.447 | 34.3 ± 0.447 | 34 ± 0.447 | 33.8 ± 0.671 | 34.3 ± 1.565 |

* + 1. Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear (equivalent models include Power, Polynomial 2°, 4°, 5°) | 0.009 | 13.729 | 276.247 | 110.652 | No model was recommended as a best-fitting model. |
| Polynomial 3° | 0.009 | 13.729 | 276.248 | 110.652 |
| Hill | 0.331 | 5.616 | 3.275 | -999 |
| Exponential M2 (equivalent models include Exponential M3) | 0.009 | 13.69 | 268.705 | 105.9 |
| Exponential M4 (equivalent models include Exponential M5) | 0.091 | 8.647 | 5.135 | 2.007 |

a Modeled variance case presented (BMDS Test 2 p-value = 9.0E-04, BMDS Test 3 p-value = 0.458).

* + 1. Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear (equivalent models include Power, Polynomial 2°, 4°, 5°) | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.00893 < 0.1)  • Residual at lowest dose is greater than threshold (2.48 > 2.0)  • Ratio of modeled to actual stdev. at control is greater than threshold (3.05 > 1.5)  **Cautions**  • Warning(s): THE MODEL HAS PROBABLY NOT CONVERGED!!!; THIS USUALLY MEANS THE MODEL HAS NOT CONVERGED! |
| Polynomial 3° | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.00893 < 0.1)  • Residual at lowest dose is greater than threshold (2.48 > 2.0)  • Ratio of modeled to actual stdev. at control is greater than threshold (3.05 > 1.5)  **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**  • BMD/minimum dose ratio is greater than threshold (16.8 > 10.0)  **Cautions**  • Warning(s): BMDL computation failed.  • BMD/minimum dose ratio is greater than threshold (16.8 > 3.0) |
| Exponential M2 (equivalent models include Exponential M3) | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.00908 < 0.1)  • Residual at lowest dose is greater than threshold (2.48 > 2.0) |
| Exponential M4 (equivalent models include Exponential M5) | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0914 < 0.1)  • BMD/minimum dose ratio is greater than threshold (10.7 > 10.0)  • BMDL/minimum dose ratio is greater than threshold (27.4 > 10.0)  **Cautions**  • BMD/minimum dose ratio is greater than threshold (10.7 > 3.0)  • BMDL/minimum dose ratio is greater than threshold (27.4 > 3.0) |

* + 1. Recommended model

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

* 1. BMD Results for: White Blood Cells (10^3/uL)

BMDS version: BMDS v2.7.0

* + 1. Input dataset

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 55 | 110 | 220 | 441 | 881 |
| N | 5 | 5 | 5 | 5 | 5 | 5 |
| Mean ± SD | 11.5 ± 0.894 | 14.25 ± 1.364 | 12.07 ± 1.789 | 13.4 ± 0.984 | 14.37 ± 2.437 | 16.25 ± 2.236 |

* + 1. Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear (equivalent models include Power, Polynomial 2°, 4°, 5°) | 0.11 | 69.413 | 394.049 | 272.328 | Exponential-M2 recommended as best-fitting model on the basis of the lowest AIC. |
| Polynomial 3° | 0.11 | 69.413 | 394.048 | 272.328 |
| Hill | 0.057 | 71.389 | 362.716 | 97.985 |
| Exponential M2b (equivalent models include Exponential M3) | 0.107 | 69.479 | 426.561 | 308.468 |
| Exponential M4 (equivalent models include Exponential M5) | 0.057 | 71.39 | 364.08 | 131.164 |

a Constant variance case presented (BMDS Test 2 p-value = 0.158, BMDS Test 3 p-value = 0.158).

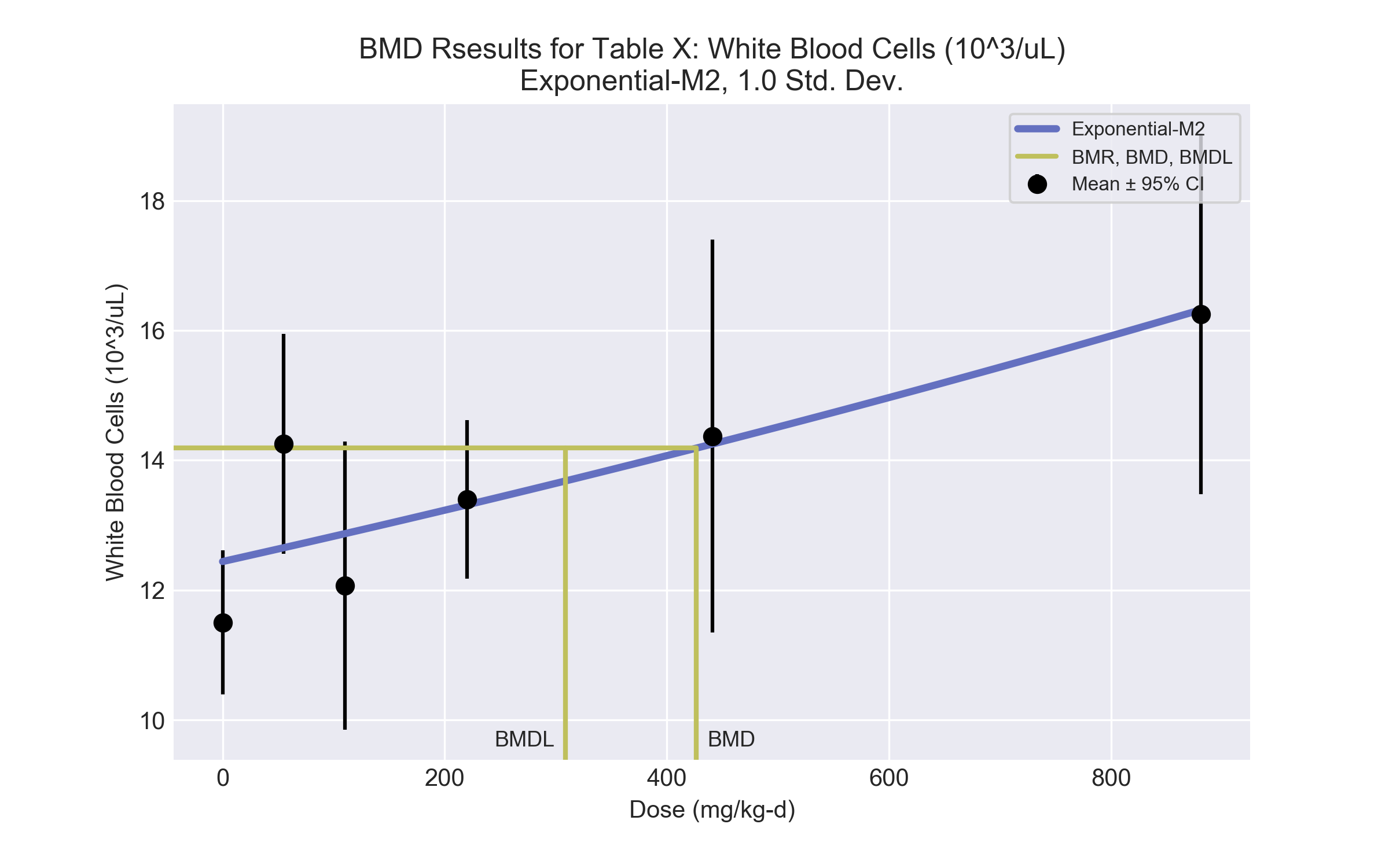
b Recommended model

* + 1. Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear (equivalent models include Power, Polynomial 2°, 4°, 5°) | Warning | **Warnings**  • Ratio of modeled to actual stdev. at control is greater than threshold (1.96 > 1.5) |
| Polynomial 3° | Warning | **Warnings**  • Ratio of modeled to actual stdev. at control is greater than threshold (1.96 > 1.5) |
| Hill | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0572 < 0.1)  • Ratio of modeled to actual stdev. at control is greater than threshold (1.95 > 1.5) |
| Exponential M2a (equivalent models include Exponential M3) | Valid | - |
| Exponential M4 (equivalent models include Exponential M5) | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0572 < 0.1) |

a Recommended model

* + 1. Recommended model



====================================================================   
 Exponential Model. (Version: 1.11; Date: 03/14/2017)   
 Input Data File: C:\Users\USERNAME\AppData\Local\Temp\2\bmds-801nvws5.(d)   
 Gnuplot Plotting File:   
 Mon Dec 18 12:03:15 2017  
 ====================================================================   
  
 BMDS\_Model\_Run   
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~  
   
 The form of the response function by Model:   
 Model 2: Y[dose] = a \* exp{sign \* b \* dose}  
 Model 3: Y[dose] = a \* exp{sign \* (b \* dose)^d}  
 Model 4: Y[dose] = a \* [c-(c-1) \* exp{-b \* dose}]  
 Model 5: Y[dose] = a \* [c-(c-1) \* exp{-(b \* dose)^d}]  
  
 Note: Y[dose] is the median response for exposure = dose;  
 sign = +1 for increasing trend in data;  
 sign = -1 for decreasing trend.  
  
 Model 2 is nested within Models 3 and 4.  
 Model 3 is nested within Model 5.  
 Model 4 is nested within Model 5.  
  
  
 Dependent variable = Response  
 Independent variable = Dose  
 Data are assumed to be distributed: normally  
 Variance Model: exp(lnalpha +rho \*ln(Y[dose]))  
 rho is set to 0.  
 A constant variance model is fit.  
  
 Total number of dose groups = 6  
 Total number of records with missing values = 0  
 Maximum number of iterations = 500  
 Relative Function Convergence has been set to: 1e-008  
 Parameter Convergence has been set to: 1e-008  
  
 MLE solution provided: Exact  
  
  
 Initial Parameter Values  
  
 Variable Model 2  
 -------- --------  
 lnalpha 0.862552   
 rho 0 Specified  
 a 12.3833   
 b 0.000316473   
 c 0 Specified  
 d 1 Specified  
  
  
  
 Parameter Estimates  
  
 Variable Model 2 Std. Err.  
 -------- ------- ---------  
 lnalpha 1.11598 0.788169  
 a 12.4397 0.419638  
 b 0.000308099 7.05315e-005  
  
 NC = No Convergence  
  
  
 Table of Stats From Input Data  
  
 Dose N Obs Mean Obs Std Dev  
 ----- --- ---------- -------------  
 0 5 11.5 0.8944  
 55 5 14.25 1.364  
 110 5 12.07 1.789  
 220 5 13.4 0.9839  
 441 5 14.37 2.437  
 881 5 16.25 2.236  
  
  
 Estimated Values of Interest  
  
 Dose Est Mean Est Std Scaled Residual  
 ------ ---------- --------- ----------------  
 0 12.44 1.747 -1.203  
 55 12.65 1.747 2.045  
 110 12.87 1.747 -1.022  
 220 13.31 1.747 0.1124  
 441 14.25 1.747 0.1534  
 881 16.32 1.747 -0.0883  
  
  
  
 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 -27.93828 7 69.87657  
 A2 -23.95174 12 71.90349  
 A3 -27.93828 7 69.87657  
 R -38.65083 2 81.30165  
 2 -31.73973 3 69.47946  
  
  
 Additive constant for all log-likelihoods = -27.57. This constant added to the  
 above values gives the log-likelihood including the term that does not  
 depend on the model parameters.  
  
  
 Explanation of Tests  
  
 Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)  
 Test 2: Are Variances Homogeneous? (A2 vs. A1)  
 Test 3: Are variances adequately modeled? (A2 vs. A3)  
 Test 4: Does Model 2 fit the data? (A3 vs. 2)  
  
  
 Tests of Interest  
  
 Test -2\*log(Likelihood Ratio) D. F. p-value  
 -------- ------------------------ ------ --------------  
 Test 1 29.4 10 0.001074  
 Test 2 7.973 5 0.1577  
 Test 3 7.973 5 0.1577  
 Test 4 7.603 4 0.1073  
  
  
 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 = 426.561  
  
 BMDL = 308.468  
  
 BMDU = 724.926

* 1. BMD Results for: Monocytes (10^3/uL)

BMDS version: BMDS v2.7.0

* + 1. Input dataset

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 55 | 110 | 220 | 441 | 881 |
| N | 5 | 5 | 5 | 5 | 5 | 5 |
| Mean ± SD | 0.2 ± 0.134 | 0.39 ± 0.134 | 0.35 ± 0.179 | 0.32 ± 0.134 | 0.31 ± 0.134 | 0.65 ± 0.089 |

* + 1. Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear | 0.041 | -80.176 | 380.169 | 264.927 | Power recommended as best-fitting model on the basis of the lowest AIC. |
| Polynomial 2° | 0.112 | -82.628 | 562.8 | 474.887 |
| Polynomial 3° | 0.164 | -83.608 | 649.251 | 489.349 |
| Polynomial 4° | 0.102 | -81.931 | 685.395 | 382.128 |
| Polynomial 5° | 0.109 | -82.064 | 708.898 | 385.61 |
| Powerb | 0.193 | -84.048 | 837.561 | 454 |
| Hill | 0.048 | -80.048 | 837.508 | 454.223 |
| Exponential M2 | 0.074 | -81.583 | 442.793 | 350.29 |
| Exponential M3 | 0.108 | -82.048 | 846.977 | -999 |
| Exponential M4 | 0.019 | -78.175 | 380.143 | 240.496 |
| Exponential M5 | 0.048 | -80.048 | 837.556 | 454.007 |

a Constant variance case presented (BMDS Test 2 p-value = 0.811, BMDS Test 3 p-value = 0.811).

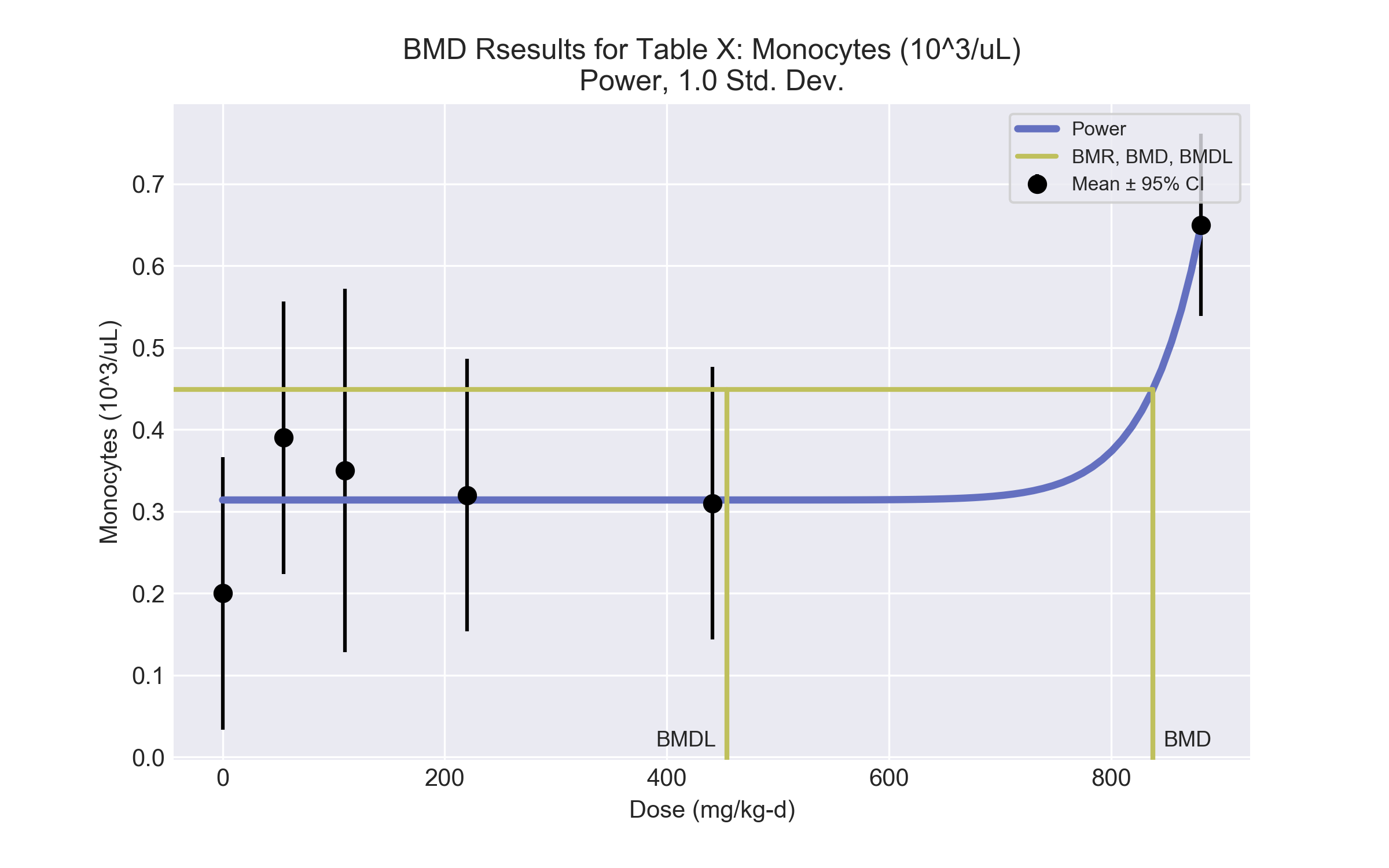
b Recommended model

* + 1. Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0413 < 0.1) |
| Polynomial 2° | Valid | - |
| Polynomial 3° | Valid | - |
| Polynomial 4° | Valid | - |
| Polynomial 5° | Valid | - |
| Powera | Valid | - |
| Hill | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0479 < 0.1)  **Cautions**  • Warning(s): THE MODEL HAS PROBABLY NOT CONVERGED!!!; THIS USUALLY MEANS THE MODEL HAS NOT CONVERGED! |
| Exponential M2 | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0736 < 0.1) |
| Exponential M3 | Failure | **Failures**  • BMDL does not exist |
| Exponential M4 | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.019 < 0.1) |
| Exponential M5 | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0479 < 0.1) |

a Recommended model

* + 1. Recommended model



====================================================================   
 Power Model. (Version: 2.19; Date: 03/14/2017)   
 Input Data File: C:\Users\USERNAME\AppData\Local\Temp\2\bmds-qfdv4o34.(d)   
 Gnuplot Plotting File: C:\Users\USERNAME\AppData\Local\Temp\2\bmds-qfdv4o34.plt  
 Mon Dec 18 12:03:15 2017  
 ====================================================================   
  
 BMDS\_Model\_Run   
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~  
   
 The form of the response function is:   
  
 Y[dose] = control + slope \* dose^power  
  
  
 Dependent variable = Response  
 Independent variable = Dose  
 rho is set to 0  
 The power is restricted to be greater than or equal to 1  
 A constant variance model is fit  
  
 Total number of dose groups = 6  
 Total number of records with missing values = 0  
 Maximum number of iterations = 500  
 Relative Function Convergence has been set to: 1e-008  
 Parameter Convergence has been set to: 1e-008  
  
  
  
 Default Initial Parameter Values   
 alpha = 0.0186666  
 rho = 0 Specified  
 control = 0.2  
 slope = 0.0586607  
 power = -9999  
  
  
 Asymptotic Correlation Matrix of Parameter Estimates  
  
 ( \*\*\* The model parameter(s) -rho -power   
 have been estimated at a boundary point, or have been specified by the user,  
 and do not appear in the correlation matrix )  
  
 alpha control slope  
  
 alpha 1 -8e-009 2.9e-008  
  
 control -7.4e-009 1 -0.41  
  
 slope 2.4e-008 -0.41 1  
  
  
  
 Parameter Estimates  
  
 95.0% Wald Confidence Interval  
 Variable Estimate Std. Err. Lower Conf. Limit Upper Conf. Limit  
 alpha 0.0182866 0.00472159 0.00903249 0.0275408  
 control 0.314 0.0270456 0.260991 0.367008  
 slope 3.2868e-054 6.48047e-055 2.01665e-054 4.55695e-054  
 power 18 NA  
  
NA - Indicates that this parameter has hit a bound  
 implied by some inequality constraint and thus  
 has no standard error.  
  
  
  
 Table of Data and Estimated Values of Interest  
  
 Dose N Obs Mean Est Mean Obs Std Dev Est Std Dev Scaled Res.  
------ --- -------- -------- ----------- ----------- ----------  
  
 0 5 0.2 0.314 0.134 0.135 -1.89  
 55 5 0.39 0.314 0.134 0.135 1.26  
 110 5 0.35 0.314 0.179 0.135 0.595  
 220 5 0.32 0.314 0.134 0.135 0.0992  
 441 5 0.31 0.314 0.134 0.135 -0.0662  
 881 5 0.65 0.65 0.0894 0.135 1.67e-007  
  
  
  
 Model Descriptions for likelihoods calculated  
  
  
 Model A1: Yij = Mu(i) + e(ij)  
 Var{e(ij)} = Sigma^2  
  
 Model A2: Yij = Mu(i) + e(ij)  
 Var{e(ij)} = Sigma(i)^2  
  
 Model A3: Yij = Mu(i) + e(ij)  
 Var{e(ij)} = 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 48.062417 7 -82.124834  
 A2 49.196830 12 -74.393659  
 A3 48.062417 7 -82.124834  
 fitted 45.023766 3 -84.047531  
 R 35.735646 2 -67.471291  
  
  
 Explanation of Tests   
  
 Test 1: Do responses and/or variances differ among Dose levels?   
 (A2 vs. R)  
 Test 2: Are Variances Homogeneous? (A1 vs A2)  
 Test 3: Are variances adequately modeled? (A2 vs. A3)  
 Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)  
 (Note: When rho=0 the results of Test 3 and Test 2 will be the same.)  
  
 Tests of Interest   
  
 Test -2\*log(Likelihood Ratio) Test df p-value   
  
 Test 1 26.9224 10 0.002679  
 Test 2 2.26883 5 0.8108  
 Test 3 2.26883 5 0.8108  
 Test 4 6.0773 4 0.1934  
  
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 = 837.561   
  
  
 BMDL = 454.003   
  
  
 BMDU = 860.518

* 1. BMD Results for: Monocyte percentage

BMDS version: BMDS v2.7.0

* + 1. Input dataset

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 55 | 110 | 220 | 441 | 881 |
| N | 5 | 5 | 5 | 5 | 5 | 5 |
| Mean ± SD | 1.8 ± 1.297 | 2.8 ± 1.096 | 2.8 ± 1.297 | 2.4 ± 0.894 | 2.2 ± 0.827 | 4 ± 0 |

* + 1. Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linearb | <0.0001 | 31.455 | 702.71 | 483.824 | Linear recommended as best-fitting model on the basis of the lowest AIC. |
| Polynomial 2° | <0.0001 | 6.707 | 892.816 | 733.587 |
| Polynomial 3° | <0.0001 | -58.631 | 1120.5 | -999 |
| Polynomial 4° | <0.0001 | -88.09 | 816.356 | -999 |
| Polynomial 5° | <0.0001 | -93.305 | 802.06 | -999 |
| Power | <0.0001 | -100.093 | 805.999 | -999 |
| Hill | <0.0001 | 104.052 | 1 | -999 |
| Exponential M2 | -999 | 45.455 | 1 | -999 |
| Exponential M3 | -999 | 47.455 | 499116 | 9652.65 |
| Exponential M4 | -999 | 47.455 | -999 | 0 |
| Exponential M5 | -999 | 49.455 | -999 | 0 |

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

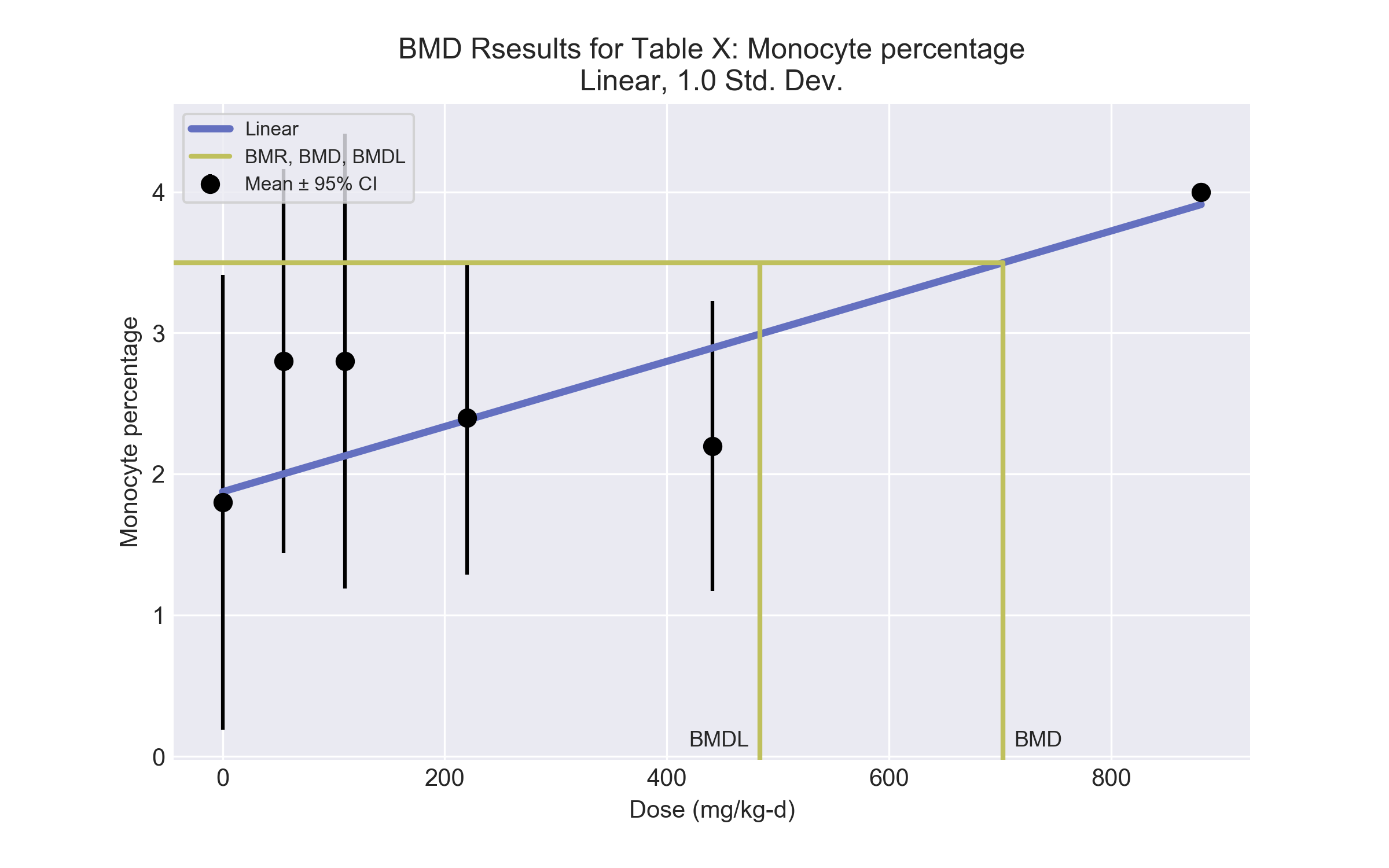
b Recommended model

* + 1. Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Lineara | Valid | **Cautions**  • Warning(s): Warning: Likelihood for fitted model larger than the Likelihood for model A3. |
| Polynomial 2° | Warning | **Warnings**  • Ratio of modeled to actual stdev. at control is greater than threshold (1.6 > 1.5)  **Cautions**  • Warning(s): THE MODEL HAS PROBABLY NOT CONVERGED!!!; THIS USUALLY MEANS THE MODEL HAS NOT CONVERGED!; Warning: Likelihood for fitted model larger than the Likelihood for model A3.  • BMD/high dose ratio is greater than threshold (1.01 > 1.0) |
| Polynomial 3° | Failure | **Failures**  • BMDL does not exist  **Warnings**  • Ratio of modeled to actual stdev. at control is greater than threshold (3.12 > 1.5)  **Cautions**  • Warning(s): THE MODEL HAS PROBABLY NOT CONVERGED!!!; THIS USUALLY MEANS THE MODEL HAS NOT CONVERGED!; BMDL computation failed.; Warning: Likelihood for fitted model larger than the Likelihood for model A3.  • BMD/high dose ratio is greater than threshold (1.27 > 1.0) |
| Polynomial 4° | Failure | **Failures**  • BMDL does not exist  **Cautions**  • Warning(s): THE MODEL HAS PROBABLY NOT CONVERGED!!!; THIS USUALLY MEANS THE MODEL HAS NOT CONVERGED!; BMDL computation failed.; Warning: Likelihood for fitted model larger than the Likelihood for model A3. |
| Polynomial 5° | Failure | **Failures**  • BMDL does not exist  **Cautions**  • Warning(s): BMDL computation failed.; Warning: Likelihood for fitted model larger than the Likelihood for model A3. |
| Power | Failure | **Failures**  • BMDL does not exist  **Cautions**  • Warning(s): THE MODEL HAS PROBABLY NOT CONVERGED!!!; THIS USUALLY MEANS THE MODEL HAS NOT CONVERGED!; BMDL computation failed.; Warning: Likelihood for fitted model larger than the Likelihood for model A3. |
| Hill | Failure | **Failures**  • BMDL does not exist  **Warnings**  • BMD/minimum dose ratio is greater than threshold (55.0 > 10.0)  • Ratio of modeled to actual stdev. at control is greater than threshold (2.02 > 1.5)  **Cautions**  • Warning(s): THIS USUALLY MEANS THE MODEL HAS NOT CONVERGED!; BMDL computation failed.  • BMD/minimum dose ratio is greater than threshold (55.0 > 3.0) |
| Exponential M2 | Failure | **Failures**  • BMDL does not exist  **Warnings**  • BMD/minimum dose ratio is greater than threshold (55.0 > 10.0)  **Cautions**  • BMD/minimum dose ratio is greater than threshold (55.0 > 3.0) |
| Exponential M3 | Warning | **Warnings**  • BMD/BMDL ratio is greater than threshold (51.7 > 20.0)  • BMDL/high dose ratio is greater than threshold (11.0 > 1.0)  **Cautions**  • BMD/BMDL ratio is greater than threshold (51.7 > 5.0)  • Residual of interest is greater than threshold (2.63 > 2.0)  • BMD/high dose ratio is greater than threshold (5.67e+02 > 1.0) |
| Exponential M4 | Failure | **Failures**  • BMD does not exist  **Warnings**  • Residual of Interest does not exist |
| Exponential M5 | Failure | **Failures**  • BMD does not exist  **Warnings**  • Residual of Interest does not exist |

a Recommended model

* + 1. Recommended model



====================================================================   
 Polynomial Model. (Version: 2.21; Date: 03/14/2017)   
 Input Data File: C:\Users\USERNAME\AppData\Local\Temp\2\bmds-hpklbqy1.(d)   
 Gnuplot Plotting File: C:\Users\USERNAME\AppData\Local\Temp\2\bmds-hpklbqy1.plt  
 Mon Dec 18 12:03:15 2017  
 ====================================================================   
  
 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 = 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   
 lalpha = 0.00813292  
 rho = 0  
 beta\_0 = 2.18317  
 beta\_1 = 0  
  
  
 Asymptotic Correlation Matrix of Parameter Estimates  
  
 lalpha rho beta\_0 beta\_1  
  
 lalpha 1 -0.98 0.075 -0.016  
  
 rho -0.98 1 -0.059 -0.00099  
  
 beta\_0 0.075 -0.059 1 -0.86  
  
 beta\_1 -0.016 -0.00099 -0.86 1  
  
  
  
 Parameter Estimates  
  
 95.0% Wald Confidence Interval  
 Variable Estimate Std. Err. Lower Conf. Limit Upper Conf. Limit  
 lalpha 3.76568 1.34871 1.12225 6.40911  
 rho -4.44799 1.47702 -7.3429 -1.55309  
 beta\_0 1.87538 0.221881 1.44051 2.31026  
 beta\_1 0.00230982 0.000303993 0.00171401 0.00290564  
  
  
  
 Table of Data and Estimated Values of Interest  
  
 Dose N Obs Mean Est Mean Obs Std Dev Est Std Dev Scaled Res.  
------ --- -------- -------- ----------- ----------- ----------  
  
 0 5 1.8 1.88 1.3 1.62 -0.104  
 55 5 2.8 2 1.1 1.4 1.27  
 110 5 2.8 2.13 1.3 1.22 1.23  
 220 5 2.4 2.38 0.894 0.952 0.0386  
 441 5 2.2 2.89 0.827 0.618 -2.51  
 881 5 4 3.91 0 0.317 0.633  
   
 Warning: Likelihood for fitted model larger than the Likelihood for model A3.  
  
  
  
 Model Descriptions for likelihoods calculated  
  
  
 Model A1: Yij = Mu(i) + e(ij)  
 Var{e(ij)} = Sigma^2  
  
 Model A2: Yij = Mu(i) + e(ij)  
 Var{e(ij)} = Sigma(i)^2  
  
 Model A3: Yij = Mu(i) + e(ij)  
 Var{e(ij)} = exp(lalpha + rho\*ln(Mu(i)))  
 Model A3 uses any fixed variance parameters that  
 were specified by the user  
  
 Model R: Yi = Mu + e(i)  
 Var{e(i)} = Sigma^2  
  
  
 Likelihoods of Interest  
  
 Model Log(likelihood) # Param's AIC  
 A1 -11.774841 7 37.549681  
 A2 1.#INF00 12 -1.#INF00  
 A3 -4766885752703518.000000 8 9533771505407052.000000  
 fitted -11.727505 4 31.455009  
 R -18.727355 2 41.454710  
  
  
 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 1.#INF 10 <.0001  
 Test 2 1.#INF 5 <.0001  
 Test 3 1.#INF 4 <.0001  
 Test 4 -9.53377e+015 4 <.0001  
  
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. Consider running a   
homogeneous model  
  
The p-value for Test 3 is greater than .1. The modeled variance appears   
 to be appropriate here  
  
The p-value for Test 4 is less than .1. You may want to try a different   
model  
   
  
 Benchmark Dose Computation  
  
Specified effect = 1  
  
Risk Type = Estimated standard deviations from the control mean  
  
Confidence level = 0.95  
  
 BMD = 702.71  
  
  
 BMDL = 483.824  
  
  
 BMDU = 1084.56

* 1. BMD Results for: Free Thyroxine (ng/dL)

BMDS version: BMDS v2.7.0

* + 1. Input dataset

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 55 | 110 | 220 | 441 | 881 |
| N | 5 | 5 | 5 | 5 | 5 | 5 |
| Mean ± SD | 5.122 ± 0.508 | 5.114 ± 0.438 | 4.678 ± 0.68 | 4.274 ± 0.588 | 4.066 ± 0.74 | 1.87 ± 0.959 |

* + 1. Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linearb | 0.455 | 9.289 | 178.3 | 139.212 | Linear recommended as best-fitting model on the basis of the lowest AIC. |
| Polynomial 2° | 0.506 | 9.97 | 257.756 | 148.564 |
| Polynomial 3° | 0.578 | 9.609 | 253.687 | 152.149 |
| Polynomial 4° | 0.619 | 9.418 | 248.575 | 154.114 |
| Polynomial 5° | 0.64 | 9.322 | 245.081 | 154.784 |
| Power | 0.438 | 10.351 | 267.976 | 145.398 |
| Hill | 0.257 | 12.353 | 268.082 | 145.266 |
| Exponential M2 (equivalent models include Exponential M4) | 0.14 | 12.554 | 143.395 | 104.632 |
| Exponential M3 | 0.315 | 11.18 | 302.746 | 148.225 |
| Exponential M5 | 0.17 | 13.18 | 302.746 | 148.225 |

a Constant variance case presented (BMDS Test 2 p-value = 0.556, BMDS Test 3 p-value = 0.556).

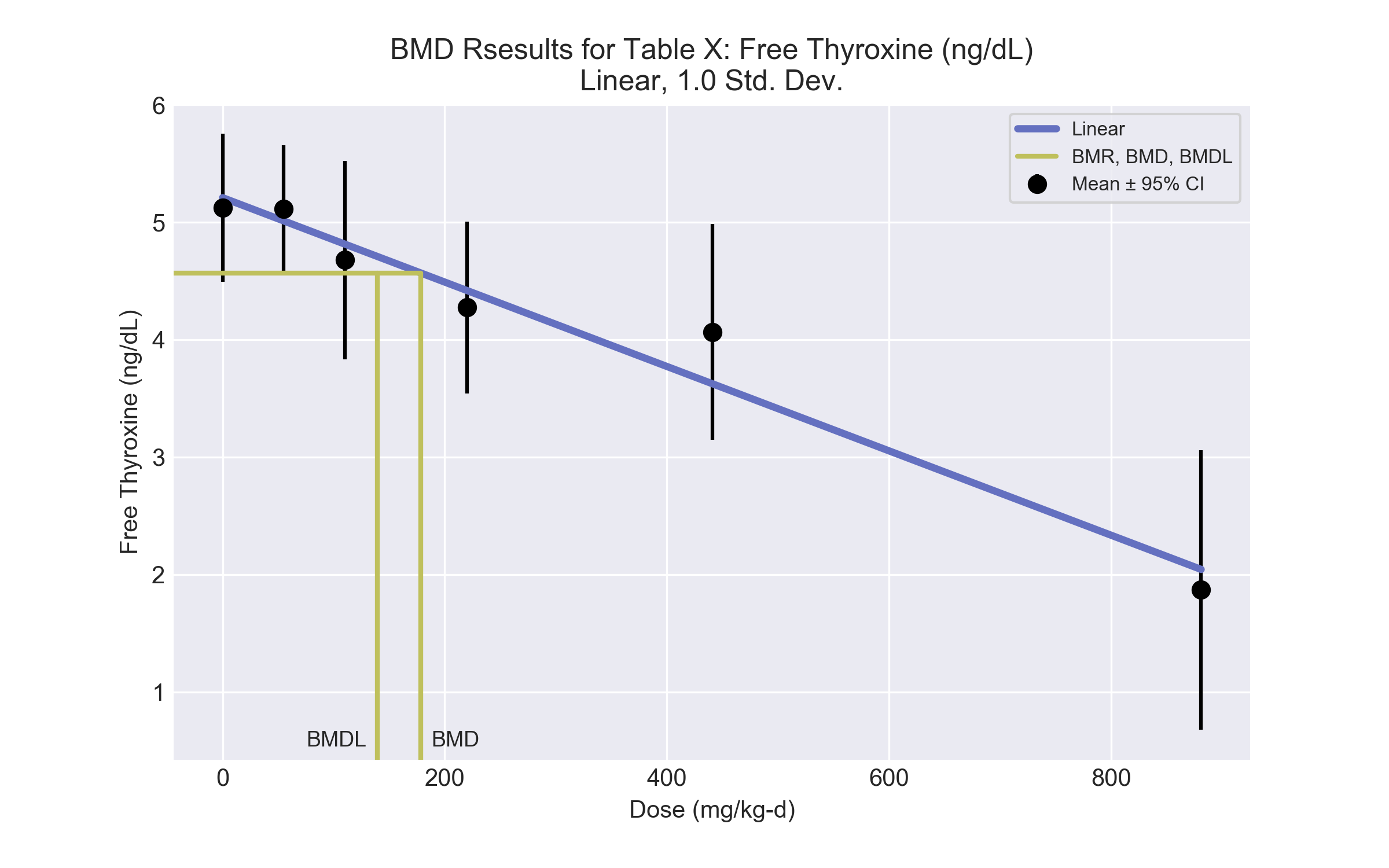
b Recommended model

* + 1. Model recommendation details

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

a Recommended model

* + 1. Recommended model



====================================================================   
 Polynomial Model. (Version: 2.21; Date: 03/14/2017)   
 Input Data File: C:\Users\USERNAME\AppData\Local\Temp\2\bmds-lc88i5yf.(d)   
 Gnuplot Plotting File: C:\Users\USERNAME\AppData\Local\Temp\2\bmds-lc88i5yf.plt  
 Mon Dec 18 12:03:18 2017  
 ====================================================================   
  
 BMDS\_Model\_Run   
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~  
   
 The form of the response function is:   
  
 Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ...  
  
  
 Dependent variable = Response  
 Independent variable = Dose  
 rho is set to 0  
 The polynomial coefficients are restricted to be negative  
 A constant variance model is fit  
  
 Total number of dose groups = 6  
 Total number of records with missing values = 0  
 Maximum number of iterations = 500  
 Relative Function Convergence has been set to: 1e-008  
 Parameter Convergence has been set to: 1e-008  
  
  
  
 Default Initial Parameter Values   
 alpha = 0.454277  
 rho = 0 Specified  
 beta\_0 = 5.20966  
 beta\_1 = -0.0035934  
  
  
 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 7.9e-008 -1.1e-007  
  
 beta\_0 7.9e-008 1 -0.69  
  
 beta\_1 -1.1e-007 -0.69 1  
  
  
  
 Parameter Estimates  
  
 95.0% Wald Confidence Interval  
 Variable Estimate Std. Err. Lower Conf. Limit Upper Conf. Limit  
 alpha 0.410502 0.105991 0.202763 0.61824  
 beta\_0 5.20966 0.160618 4.89485 5.52446  
 beta\_1 -0.0035934 0.000386878 -0.00435167 -0.00283513  
  
  
  
 Table of Data and Estimated Values of Interest  
  
 Dose N Obs Mean Est Mean Obs Std Dev Est Std Dev Scaled Res.  
------ --- -------- -------- ----------- ----------- ----------  
  
 0 5 5.12 5.21 0.508 0.641 -0.306  
 55 5 5.11 5.01 0.438 0.641 0.356  
 110 5 4.68 4.81 0.68 0.641 -0.476  
 220 5 4.27 4.42 0.588 0.641 -0.506  
 441 5 4.07 3.62 0.74 0.641 1.54  
 881 5 1.87 2.04 0.959 0.641 -0.607  
  
  
  
 Model Descriptions for likelihoods calculated  
  
  
 Model A1: Yij = Mu(i) + e(ij)  
 Var{e(ij)} = Sigma^2  
  
 Model A2: Yij = Mu(i) + e(ij)  
 Var{e(ij)} = Sigma(i)^2  
  
 Model A3: Yij = Mu(i) + e(ij)  
 Var{e(ij)} = Sigma^2  
 Model A3 uses any fixed variance parameters that  
 were specified by the user  
  
 Model R: Yi = Mu + e(i)  
 Var{e(i)} = Sigma^2  
  
  
 Likelihoods of Interest  
  
 Model Log(likelihood) # Param's AIC  
 A1 0.182885 7 13.634231  
 A2 2.159136 12 19.681727  
 A3 0.182885 7 13.634231  
 fitted -1.644369 3 9.288738  
 R -21.965224 2 47.930447  
  
  
 Explanation of Tests   
  
 Test 1: Do responses and/or variances differ among Dose levels?   
 (A2 vs. R)  
 Test 2: Are Variances Homogeneous? (A1 vs A2)  
 Test 3: Are variances adequately modeled? (A2 vs. A3)  
 Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)  
 (Note: When rho=0 the results of Test 3 and Test 2 will be the same.)  
  
 Tests of Interest   
  
 Test -2\*log(Likelihood Ratio) Test df p-value   
  
 Test 1 48.2487 10 <.0001  
 Test 2 3.9525 5 0.5563  
 Test 3 3.9525 5 0.5563  
 Test 4 3.65451 4 0.4548  
  
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 = 178.3  
  
  
 BMDL = 139.212  
  
  
 BMDU = 244.897

* 1. BMD Results for: Cholinesterase (IU/L)

BMDS version: BMDS v2.7.0

* + 1. Input dataset

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 55 | 110 | 220 | 441 | 881 |
| N | 5 | 5 | 5 | 5 | 5 | 5 |
| Mean ± SD | 277.4 ± 37.119 | 178.4 ± 17.889 | 162.6 ± 16.994 | 116.6 ± 12.969 | 108.8 ± 18.559 | 82.8 ± 4.696 |

* + 1. Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear (equivalent models include Power, Polynomial 2°) | <0.0001 | 242.029 | 742.57 | 499.78 | No model was recommended as a best-fitting model. |
| Polynomial 3° | <0.0001 | 289.538 | 3560.28 | -999 |
| Polynomial 4° | <0.0001 | 242.029 | 742.571 | 499.78 |
| Polynomial 5° | <0.0001 | 344.267 | -9999 | -999 |
| Hill | 0.035 | 211 | 13.778 | -999 |
| Exponential M2 | <0.0001 | 289.708 | 1 | -999 |
| Exponential M3 | <0.0001 | 237.016 | 585.701 | 340.5 |
| Exponential M4 (equivalent models include Exponential M5) | 0.001 | 218.657 | 20.872 | 12.054 |

a Modeled variance case presented (BMDS Test 2 p-value = 0.003, BMDS Test 3 p-value = 0.24).

* + 1. Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear (equivalent models include Power, Polynomial 2°) | Warning | **Warnings**  • Residual at lowest dose is greater than threshold (3.65 > 2.0)  • Ratio of modeled to actual stdev. at control is greater than threshold (1.87 > 1.5) |
| Polynomial 3° | Failure | **Failures**  • BMDL does not exist  **Warnings**  • Residual at lowest dose is greater than threshold (4.14 > 2.0)  • Ratio of modeled to actual stdev. at control is greater than threshold (1.73 > 1.5)  **Cautions**  • Warning(s): THE MODEL HAS PROBABLY NOT CONVERGED!!!; THIS USUALLY MEANS THE MODEL HAS NOT CONVERGED!; BMDL computation failed.  • BMD/high dose ratio is greater than threshold (4.04 > 1.0) |
| Polynomial 4° | Warning | **Warnings**  • Residual at lowest dose is greater than threshold (3.65 > 2.0)  • Ratio of modeled to actual stdev. at control is greater than threshold (1.87 > 1.5) |
| Polynomial 5° | Failure | **Failures**  • BMDL does not exist  **Warnings**  • Residual of Interest does not exist  • Ratio of modeled to actual stdev. at control is greater than threshold (9.25 > 1.5)  **Cautions**  • Warning(s): BMD = 100\*(maximum dose); BMDL computation failed. |
| Hill | Failure | **Failures**  • BMDL does not exist  **Warnings**  • Goodness of fit p-value is less than threshold (0.0353 < 0.1)  **Cautions**  • Warning(s): BMDL computation failed.  • BMD/minimum dose ratio is greater than threshold (3.99 > 3.0) |
| Exponential M2 | Failure | **Failures**  • BMDL does not exist  **Warnings**  • BMD/minimum dose ratio is greater than threshold (55.0 > 10.0)  • Residual at lowest dose is greater than threshold (4.14 > 2.0)  **Cautions**  • Residual of interest is greater than threshold (4.14 > 2.0)  • BMD/minimum dose ratio is greater than threshold (55.0 > 3.0) |
| Exponential M3 | Warning | **Warnings**  • Residual at lowest dose is greater than threshold (3.42 > 2.0) |
| Exponential M4 (equivalent models include Exponential M5) | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.00101 < 0.1)  **Cautions**  • BMDL/minimum dose ratio is greater than threshold (4.56 > 3.0) |

* + 1. Recommended model

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

* 1. BMD Results for: Terminal Body Weight (g)

BMDS version: BMDS v2.7.0

* + 1. Input dataset

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 55 | 110 | 220 | 441 | 881 |
| N | 5 | 5 | 5 | 5 | 5 | 5 |
| Mean ± SD | 276.3 ± 10.286 | 271.3 ± 11.404 | 271.9 ± 8.273 | 278.8 ± 10.51 | 262.4 ± 18.112 | 232.5 ± 21.019 |

* + 1. Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear | 0.261 | 193.134 | 283.489 | 209.164 | Polynomial-2 recommended as best-fitting model on the basis of the lowest AIC. |
| Polynomial 2°b | 0.735 | 189.873 | 486.413 | 278.1 |
| Polynomial 3° (equivalent models include Polynomial 4°, 5°) | 0.571 | 191.873 | 489.883 | 274.988 |
| Power | 0.574 | 191.861 | 500.092 | 285.353 |
| Hill | 0.753 | 191.069 | 442.808 | 322.87 |
| Exponential M2 (equivalent models include Exponential M4) | 0.22 | 193.606 | 274.199 | 197.845 |
| Exponential M3 | 0.58 | 191.83 | 497.585 | 289.961 |
| Exponential M5 | 0.548 | 193.069 | 442.523 | 321.919 |

a Constant variance case presented (BMDS Test 2 p-value = 0.233, BMDS Test 3 p-value = 0.233).

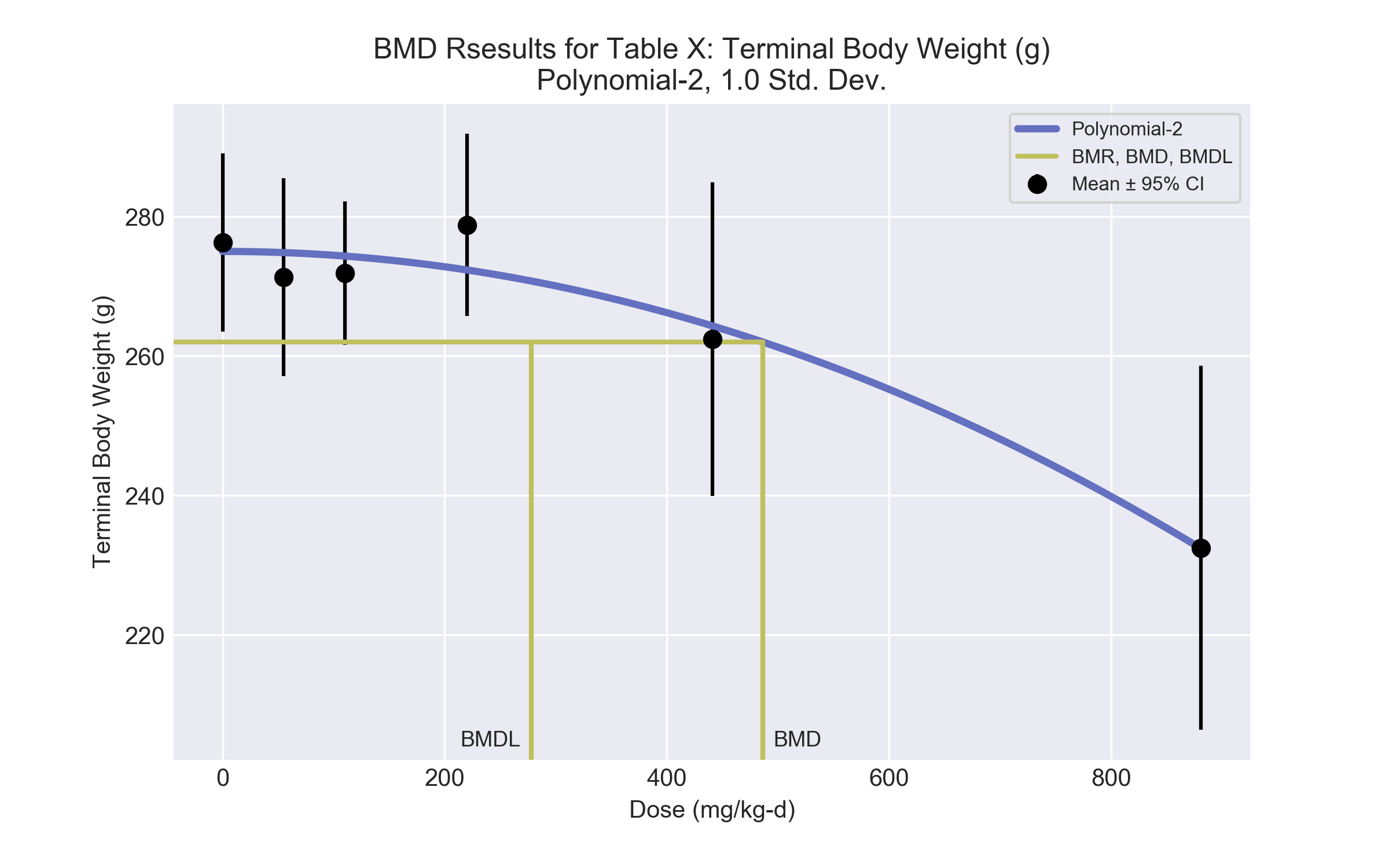
b Recommended model

* + 1. Model recommendation details

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

a Recommended model

* + 1. Recommended model



====================================================================   
 Polynomial Model. (Version: 2.21; Date: 03/14/2017)   
 Input Data File: C:\Users\USERNAME\AppData\Local\Temp\2\bmds-g238jbg9.(d)   
 Gnuplot Plotting File: C:\Users\USERNAME\AppData\Local\Temp\2\bmds-g238jbg9.plt  
 Mon Dec 18 12:03:18 2017  
 ====================================================================   
  
 BMDS\_Model\_Run   
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~  
   
 The form of the response function is:   
  
 Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ...  
  
  
 Dependent variable = Response  
 Independent variable = Dose  
 rho is set to 0  
 The polynomial coefficients are restricted to be negative  
 A constant variance model is fit  
  
 Total number of dose groups = 6  
 Total number of records with missing values = 0  
 Maximum number of iterations = 500  
 Relative Function Convergence has been set to: 1e-008  
 Parameter Convergence has been set to: 1e-008  
  
  
  
 Default Initial Parameter Values   
 alpha = 197.433  
 rho = 0 Specified  
 beta\_0 = 274.363  
 beta\_1 = 0  
 beta\_2 = -6.13731e-005  
  
  
 Asymptotic Correlation Matrix of Parameter Estimates  
  
 ( \*\*\* The model parameter(s) -rho -beta\_1   
 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\_2  
  
 alpha 1 1.4e-007 -1.4e-008  
  
 beta\_0 1.4e-007 1 -0.53  
  
 beta\_2 -1.4e-008 -0.53 1  
  
  
  
 Parameter Estimates  
  
 95.0% Wald Confidence Interval  
 Variable Estimate Std. Err. Lower Conf. Limit Upper Conf. Limit  
 alpha 168.866 43.601 83.4096 254.322  
 beta\_0 275 2.79087 269.53 280.47  
 beta\_1 -0 NA  
 beta\_2 -5.49239e-005 8.52697e-006 -7.16365e-005 -3.82114e-005  
  
NA - Indicates that this parameter has hit a bound  
 implied by some inequality constraint and thus  
 has no standard error.  
  
  
  
 Table of Data and Estimated Values of Interest  
  
 Dose N Obs Mean Est Mean Obs Std Dev Est Std Dev Scaled Res.  
------ --- -------- -------- ----------- ----------- ----------  
  
 0 5 276 275 10.3 13 0.224  
 55 5 271 275 11.4 13 -0.608  
 110 5 272 274 8.27 13 -0.419  
 220 5 279 272 10.5 13 1.11  
 441 5 262 264 18.1 13 -0.33  
 881 5 233 232 21 13 0.0223  
  
  
  
 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 -90.933862 7 195.867723  
 A2 -87.513245 12 199.026491  
 A3 -90.933862 7 195.867723  
 fitted -91.936585 3 189.873170  
 R -104.961782 2 213.923564  
  
  
 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 34.8971 10 0.00013  
 Test 2 6.84123 5 0.2327  
 Test 3 6.84123 5 0.2327  
 Test 4 2.00545 4 0.7348  
  
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 = 486.413  
  
  
 BMDL = 278.1  
  
  
 BMDU = 593.803

* 1. BMD Results for: Brain Weight Relative (mg/g)

BMDS version: BMDS v2.7.0

* + 1. Input dataset

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 55 | 110 | 220 | 441 | 881 |
| N | 5 | 5 | 5 | 5 | 4 | 5 |
| Mean ± SD | 6.28 ± 0.514 | 6.43 ± 0.134 | 6.52 ± 0.291 | 6.48 ± 0.067 | 7.03 ± 0.28 | 7.73 ± 0.827 |

* + 1. Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear | 0.544 | -23.015 | 176.18 | 122.545 | No model was recommended as a best-fitting model. |
| Polynomial 2° (equivalent models include Polynomial 3°, 4°, 5°) | 0.657 | -22.489 | 288.96 | 137.018 |
| Power | 0.682 | -22.6 | 298.105 | 138.523 |
| Hill | 0.884 | -23.446 | 418.997 | -999 |
| Exponential M2 | 0.611 | -23.407 | 186.914 | 132.369 |
| Exponential M3 | 0.671 | -22.552 | 294.221 | 143.142 |
| Exponential M4 | 0.378 | -21.01 | 176.068 | 113.837 |
| Exponential M5 | 0.721 | -21.446 | 422.297 | 156.103 |

a Modeled variance case presented (BMDS Test 2 p-value = <0.0001, BMDS Test 3 p-value = 2.2E-04).

* + 1. Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear | Warning | **Warnings**  • Variance model fit p-value is less than threshold (0.000218 < 0.1)  • Ratio of modeled to actual stdev. at control is greater than threshold (1.86 > 1.5) |
| Polynomial 2° (equivalent models include Polynomial 3°, 4°, 5°) | Warning | **Warnings**  • Variance model fit p-value is less than threshold (0.000218 < 0.1)  • Ratio of modeled to actual stdev. at control is greater than threshold (1.87 > 1.5) |
| Power | Warning | **Warnings**  • Variance model fit p-value is less than threshold (0.000218 < 0.1)  • Ratio of modeled to actual stdev. at control is greater than threshold (1.86 > 1.5) |
| Hill | Failure | **Failures**  • BMDL does not exist  **Warnings**  • Variance model fit p-value is less than threshold (0.000218 < 0.1)  • Ratio of modeled to actual stdev. at control is greater than threshold (1.85 > 1.5)  **Cautions**  • Warning(s): BMDL computation failed. |
| Exponential M2 | Warning | **Warnings**  • Variance model fit p-value is less than threshold (0.000218 < 0.1) |
| Exponential M3 | Warning | **Warnings**  • Variance model fit p-value is less than threshold (0.000218 < 0.1) |
| Exponential M4 | Warning | **Warnings**  • Variance model fit p-value is less than threshold (0.000218 < 0.1) |
| Exponential M5 | Warning | **Warnings**  • Variance model fit p-value is less than threshold (0.000218 < 0.1) |

* + 1. Recommended model

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

* 1. BMD Results for: Liver Weight Absolute (g)

BMDS version: BMDS v2.7.0

* + 1. Input dataset

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 55 | 110 | 220 | 441 | 881 |
| N | 5 | 5 | 5 | 5 | 5 | 5 |
| Mean ± SD | 11.46 ± 0.425 | 11.83 ± 1.252 | 11.84 ± 0.648 | 12.95 ± 1.073 | 12.92 ± 1.431 | 13.09 ± 0.85 |

* + 1. Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear (equivalent models include Power, Polynomial 3°, 4°, 5°) | 0.28 | 34.83 | 564.197 | 352.58 | Exponential-M4 recommended as best-fitting model on the basis of the lowest BMDL. |
| Polynomial 2° | 0.28 | 34.83 | 564.196 | 352.58 |
| Hill | 0.778 | 34.259 | 157.258 | 52.497 |
| Exponential M2 (equivalent models include Exponential M3) | 0.263 | 35.001 | 589.208 | 378.316 |
| Exponential M4b | 0.698 | 33.192 | 135.736 | 47.984 |
| Exponential M5 | 0.788 | 34.233 | 169.784 | 57.903 |

a Constant variance case presented (BMDS Test 2 p-value = 0.134, BMDS Test 3 p-value = 0.134).

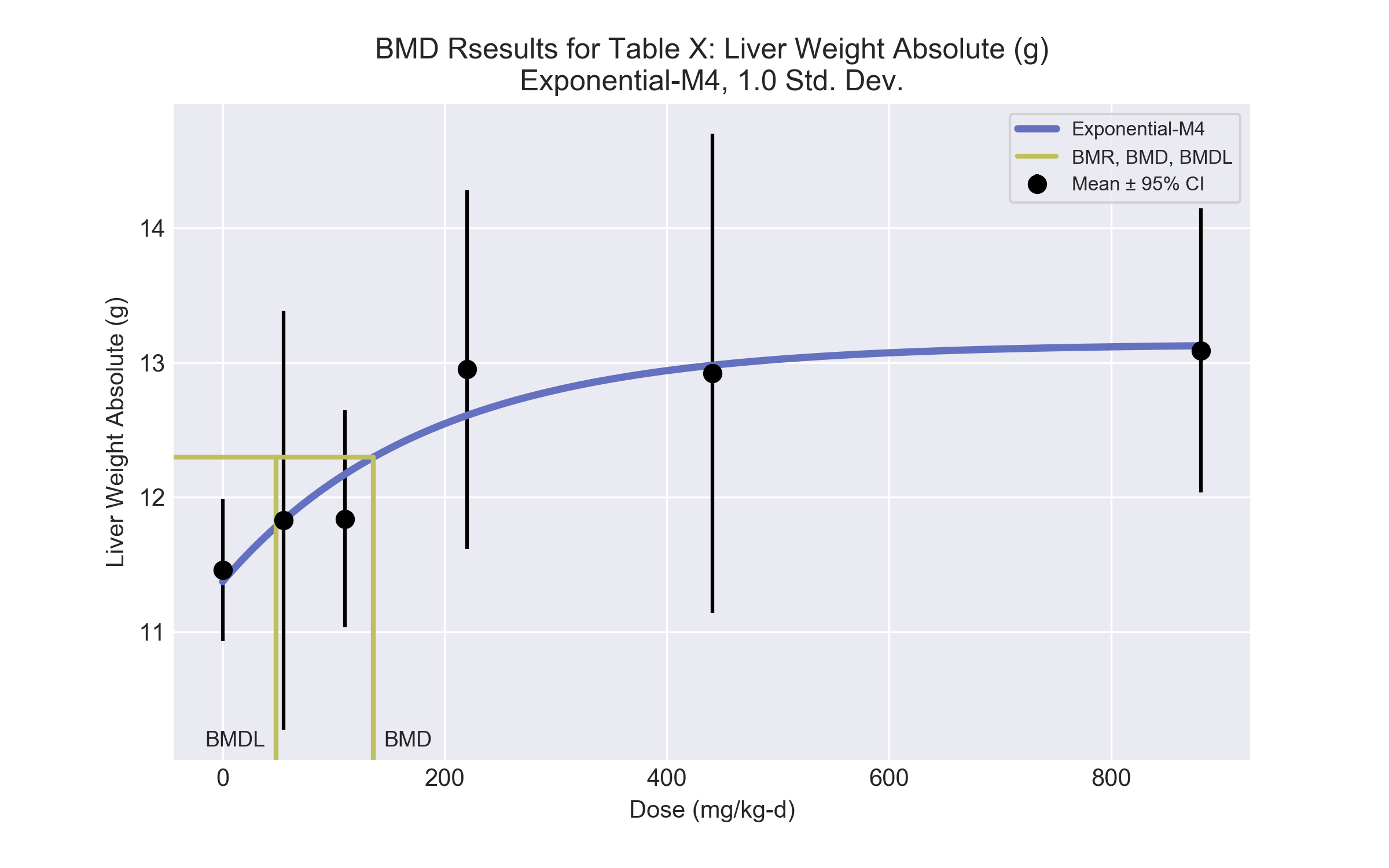
b Recommended model

* + 1. Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear (equivalent models include Power, Polynomial 3°, 4°, 5°) | Warning | **Warnings**  • Ratio of modeled to actual stdev. at control is greater than threshold (2.31 > 1.5) |
| Polynomial 2° | Warning | **Warnings**  • Ratio of modeled to actual stdev. at control is greater than threshold (2.31 > 1.5) |
| Hill | Warning | **Warnings**  • Ratio of modeled to actual stdev. at control is greater than threshold (2.14 > 1.5) |
| Exponential M2 (equivalent models include Exponential M3) | Valid | - |
| Exponential M4a | Valid | - |
| Exponential M5 | Valid | - |

a Recommended model

* + 1. Recommended model



====================================================================   
 Exponential Model. (Version: 1.11; Date: 03/14/2017)   
 Input Data File: C:\Users\USERNAME\AppData\Local\Temp\2\bmds-3dnbbsd\_.(d)   
 Gnuplot Plotting File:   
 Mon Dec 18 12:03:21 2017  
 ====================================================================   
  
 BMDS\_Model\_Run   
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~  
   
 The form of the response function by Model:   
 Model 2: Y[dose] = a \* exp{sign \* b \* dose}  
 Model 3: Y[dose] = a \* exp{sign \* (b \* dose)^d}  
 Model 4: Y[dose] = a \* [c-(c-1) \* exp{-b \* dose}]  
 Model 5: Y[dose] = a \* [c-(c-1) \* exp{-(b \* dose)^d}]  
  
 Note: Y[dose] is the median response for exposure = dose;  
 sign = +1 for increasing trend in data;  
 sign = -1 for decreasing trend.  
  
 Model 2 is nested within Models 3 and 4.  
 Model 3 is nested within Model 5.  
 Model 4 is nested within Model 5.  
  
  
 Dependent variable = Response  
 Independent variable = Dose  
 Data are assumed to be distributed: normally  
 Variance Model: exp(lnalpha +rho \*ln(Y[dose]))  
 rho is set to 0.  
 A constant variance model is fit.  
  
 Total number of dose groups = 6  
 Total number of records with missing values = 0  
 Maximum number of iterations = 500  
 Relative Function Convergence has been set to: 1e-008  
 Parameter Convergence has been set to: 1e-008  
  
 MLE solution provided: Exact  
  
  
 Initial Parameter Values  
  
 Variable Model 4  
 -------- --------  
 lnalpha -0.20809   
 rho 0 Specified  
 a 10.887   
 b 0.00212232   
 c 1.26247   
 d 1 Specified  
  
  
  
 Parameter Estimates  
  
 Variable Model 4 Std. Err.  
 -------- ------- ---------  
 lnalpha -0.160272 0.219963  
 a 11.3745 0.361185  
 b 0.00545253 0.00351911  
 c 1.15517 0.0459453  
  
 NC = No Convergence  
  
  
 Table of Stats From Input Data  
  
 Dose N Obs Mean Obs Std Dev  
 ----- --- ---------- -------------  
 0 5 11.46 0.4249  
 55 5 11.83 1.252  
 110 5 11.84 0.6485  
 220 5 12.95 1.073  
 441 5 12.92 1.431  
 881 5 13.09 0.8497  
  
  
 Estimated Values of Interest  
  
 Dose Est Mean Est Std Scaled Residual  
 ------ ---------- --------- ----------------  
 0 11.37 0.923 0.2071  
 55 11.83 0.923 -0.004481  
 110 12.17 0.923 -0.8011  
 220 12.61 0.923 0.8293  
 441 12.98 0.923 -0.1457  
 881 13.13 0.923 -0.08498  
  
  
  
 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 -11.87865 7 37.75729  
 A2 -7.663101 12 39.3262  
 A3 -11.87865 7 37.75729  
 R -18.20223 2 40.40445  
 4 -12.59592 4 33.19185  
  
  
 Additive constant for all log-likelihoods = -27.57. This constant added to the  
 above values gives the log-likelihood including the term that does not  
 depend on the model parameters.  
  
  
 Explanation of Tests  
  
 Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)  
 Test 2: Are Variances Homogeneous? (A2 vs. A1)  
 Test 3: Are variances adequately modeled? (A2 vs. A3)  
  
 Test 6a: Does Model 4 fit the data? (A3 vs 4)  
  
  
 Tests of Interest  
  
 Test -2\*log(Likelihood Ratio) D. F. p-value  
 -------- ------------------------ ------ --------------  
 Test 1 21.08 10 0.02055  
 Test 2 8.431 5 0.134  
 Test 3 8.431 5 0.134  
 Test 6a 1.435 3 0.6975  
  
  
 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 = 135.736  
  
 BMDL = 47.9838  
  
 BMDU = 8.81e+006

* 1. BMD Results for: Liver Weight Relative (mg/g)

BMDS version: BMDS v2.7.0

* + 1. Input dataset

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 55 | 110 | 220 | 441 | 881 |
| N | 5 | 5 | 5 | 5 | 5 | 5 |
| Mean ± SD | 41.5 ± 1.297 | 43.52 ± 3.153 | 43.51 ± 1.409 | 46.42 ± 2.862 | 49.14 ± 2.236 | 56.74 ± 7.2 |

* + 1. Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linearb (equivalent models include Power, Polynomial 2°) | 0.49 | 95.805 | 102.779 | 71.319 | Linear recommended as best-fitting model on the basis of the lowest AIC. |
| Polynomial 3° | 0.332 | 97.805 | 102.982 | 71.319 |
| Polynomial 4° | 0.332 | 97.798 | 104.625 | 71.351 |
| Polynomial 5° | 0.334 | 97.79 | 105.275 | 71.388 |
| Hill | 0.335 | 97.779 | 96.959 | -999 |
| Exponential M2 (equivalent models include Exponential M3) | 0.452 | 96.061 | 118.202 | 83.366 |
| Exponential M4 | 0.335 | 97.781 | 97.354 | 50.208 |
| Exponential M5 | 0.335 | 97.781 | 97.354 | 50.208 |

a Modeled variance case presented (BMDS Test 2 p-value = 6.9E-04, BMDS Test 3 p-value = 0.261).

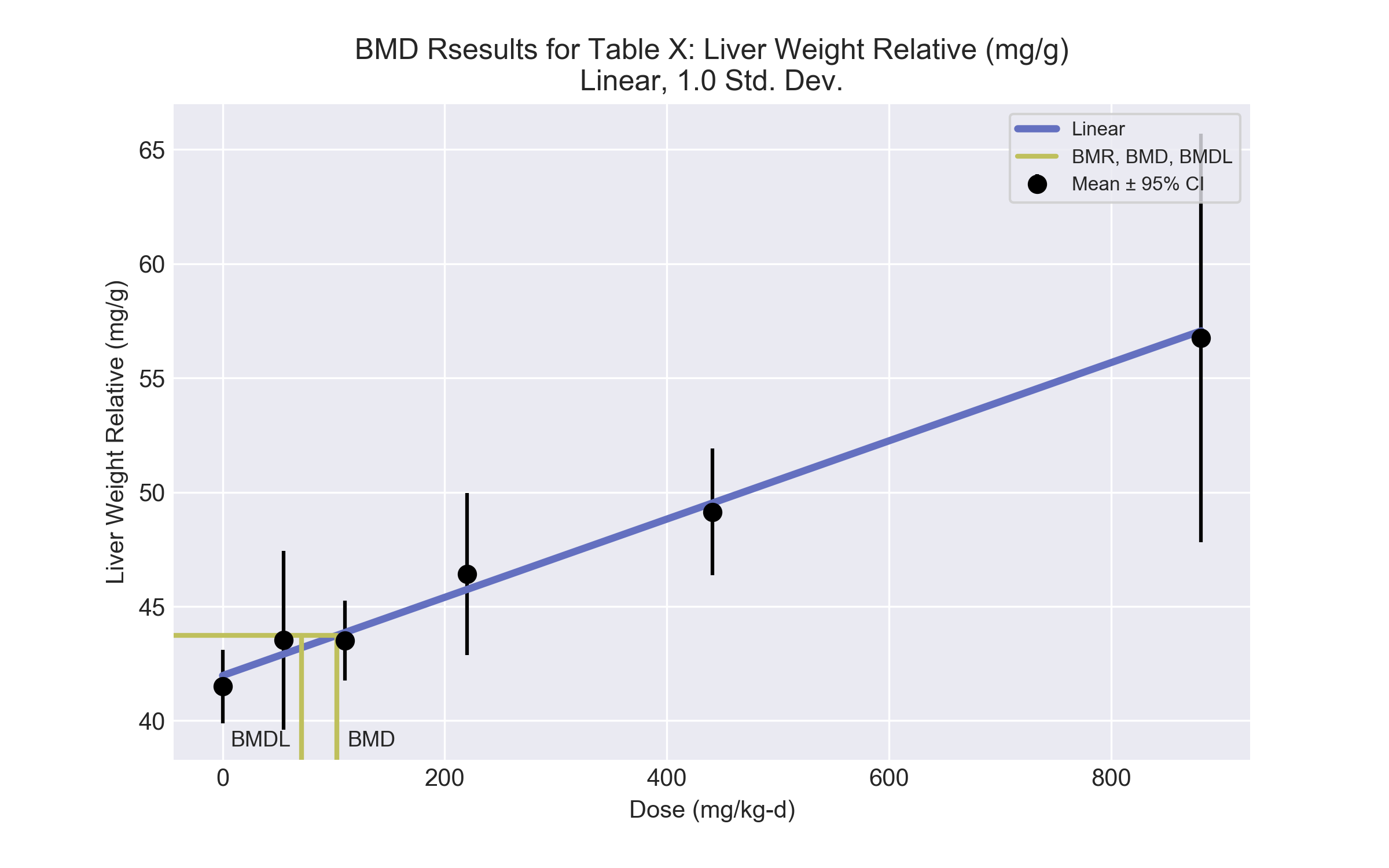
b Recommended model

* + 1. Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Lineara (equivalent models include Power, Polynomial 2°) | Valid | - |
| Polynomial 3° | Valid | - |
| Polynomial 4° | Valid | - |
| Polynomial 5° | Valid | - |
| Hill | Failure | **Failures**  • BMDL does not exist  **Cautions**  • Warning(s): BMDL computation failed. |
| Exponential M2 (equivalent models include Exponential M3) | Valid | - |
| Exponential M4 | Valid | - |
| Exponential M5 | Valid | - |

a Recommended model

* + 1. Recommended model



====================================================================   
 Polynomial Model. (Version: 2.21; Date: 03/14/2017)   
 Input Data File: C:\Users\USERNAME\AppData\Local\Temp\2\bmds-sn84zvo5.(d)   
 Gnuplot Plotting File: C:\Users\USERNAME\AppData\Local\Temp\2\bmds-sn84zvo5.plt  
 Mon Dec 18 12:03:22 2017  
 ====================================================================   
  
 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 = 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   
 lalpha = 2.57313  
 rho = 0  
 beta\_0 = 42.0568  
 beta\_1 = 0  
  
  
 Asymptotic Correlation Matrix of Parameter Estimates  
  
 lalpha rho beta\_0 beta\_1  
  
 lalpha 1 -1 0.096 -0.15  
  
 rho -1 1 -0.096 0.15  
  
 beta\_0 0.096 -0.096 1 -0.6  
  
 beta\_1 -0.15 0.15 -0.6 1  
  
  
  
 Parameter Estimates  
  
 95.0% Wald Confidence Interval  
 Variable Estimate Std. Err. Lower Conf. Limit Upper Conf. Limit  
 lalpha -27.4524 8.87189 -44.8409 -10.0638  
 rho 7.64854 2.30865 3.12366 12.1734  
 beta\_0 41.9742 0.53027 40.9349 43.0135  
 beta\_1 0.0171245 0.0024516 0.0123194 0.0219295  
  
  
  
 Table of Data and Estimated Values of Interest  
  
 Dose N Obs Mean Est Mean Obs Std Dev Est Std Dev Scaled Res.  
------ --- -------- -------- ----------- ----------- ----------  
  
 0 5 41.5 42 1.3 1.76 -0.602  
 55 5 43.5 42.9 3.15 1.92 0.705  
 110 5 43.5 43.9 1.41 2.08 -0.374  
 220 5 46.4 45.7 2.86 2.44 0.62  
 441 5 49.1 49.5 2.24 3.31 -0.261  
 881 5 56.7 57.1 7.2 5.7 -0.126  
  
  
  
 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 -50.249853 7 114.499706  
 A2 -39.559757 12 103.119515  
 A3 -42.192973 8 100.385946  
 fitted -43.902300 4 95.804601  
 R -68.822673 2 141.645346  
  
  
 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 58.5258 10 <.0001  
 Test 2 21.3802 5 0.0006864  
 Test 3 5.26643 4 0.261  
 Test 4 3.41865 4 0.4904  
  
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 = 102.779  
  
  
 BMDL = 71.319  
  
  
 BMDU = 156.112