# Male BMD Results for Table: Liver Weight Absolute

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 0.07 | 0.2 | 0.7 | 2 | 6 | 18 | 55 | 160 | 475 |
| N | 10 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Mean ± SD | 12.517 ± 1.388 | 11.808 ± 1.671 | 12.574 ± 1.217 | 12.612 ± 1.23 | 12.054 ± 0.654 | 13.144 ± 1.171 | 13.484 ± 1.405 | 14.296 ± 0.883 | 15.69 ± 1.218 | 15.34 ± 1.186 |

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear (equivalent models include Power, Polynomial 2°, 3°, 4°, 5°, 6°, 7°, 8°) | 0.004 | 97.2 | 203.084 | 148.888 | Exponential-M4 recommended as best-fitting model on the basis of the lowest AIC. |
| Hill | 0.675 | 82.493 | 18.249 | 6.926 |
| Exponential M2 (equivalent models include Exponential M3) | 0.003 | 98.158 | 224.813 | 168.943 |
| Exponential M4b (equivalent models include Exponential M5) | 0.814 | 80.177 | 21.893 | 10.337 |

a Constant variance case presented (BMDS Test 2 p-value = 0.773, BMDS Test 3 p-value = 0.773).

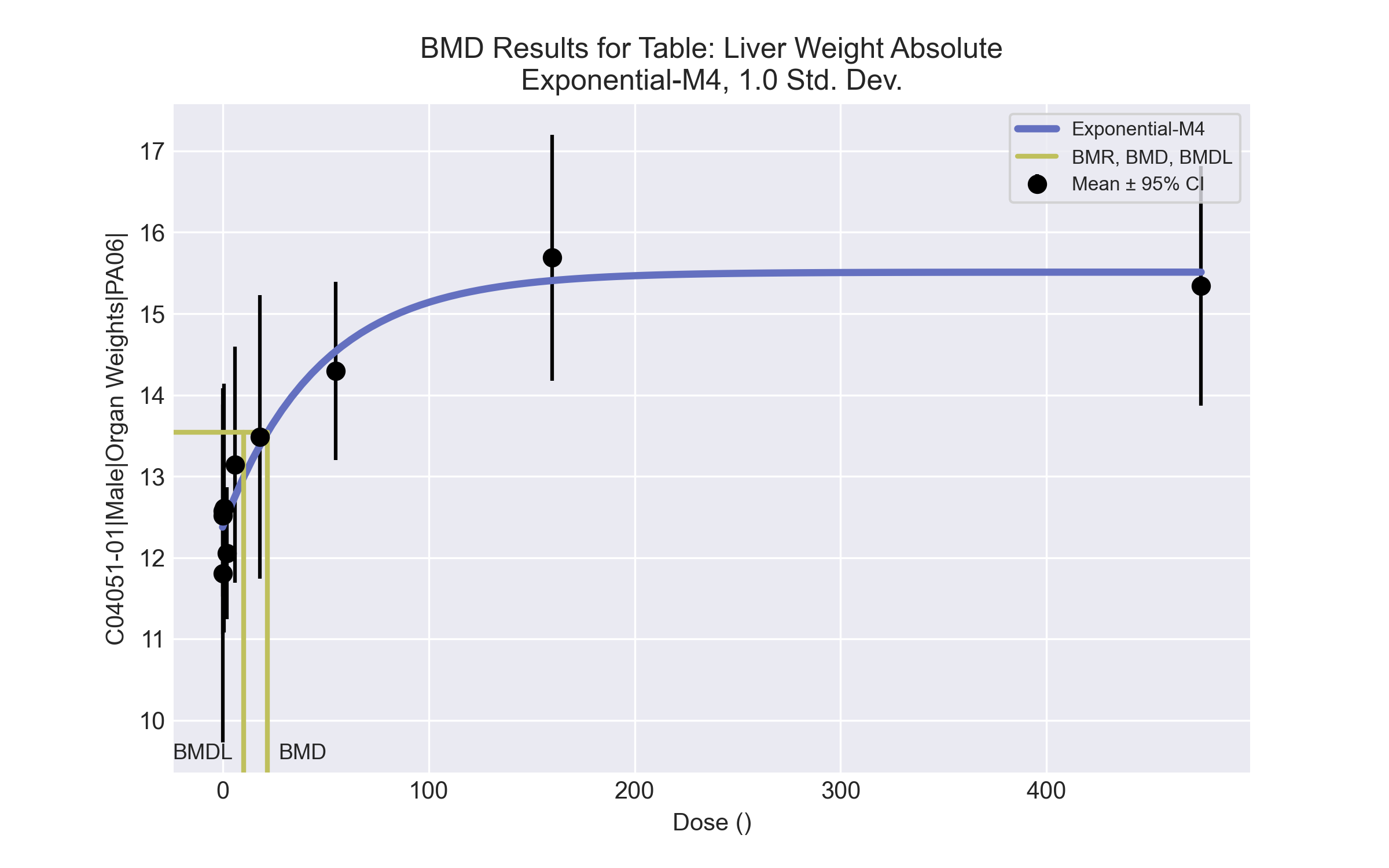
b Recommended model

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear (equivalent models include Power, Polynomial 2°, 3°, 4°, 5°, 6°, 7°, 8°) | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.00375 < 0.1)  • Residual of interest is greater than threshold (2.84 > 2.0) |
| Hill | Valid | - |
| Exponential M2 (equivalent models include Exponential M3) | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0026 < 0.1)  • Residual of interest is greater than threshold (2.95 > 2.0) |
| Exponential M4a (equivalent models include Exponential M5) | Valid | - |

a Recommended model

## Recommended model



====================================================================   
 Exponential Model. (Version: 1.11; Date: 03/14/2017)   
 Input Data File: C:\Windows\TEMP\bmds-yl9p0x3f.(d)   
 Gnuplot Plotting File:   
 Tue Apr 13 09:11:44 2021  
 ====================================================================   
  
 BMDS\_Model\_Run   
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~  
   
 The form of the response function by Model:   
 Model 2: Y[dose] = a \* exp{sign \* b \* dose}  
 Model 3: Y[dose] = a \* exp{sign \* (b \* dose)^d}  
 Model 4: Y[dose] = a \* [c-(c-1) \* exp{-b \* dose}]  
 Model 5: Y[dose] = a \* [c-(c-1) \* exp{-(b \* dose)^d}]  
  
 Note: Y[dose] is the median response for exposure = dose;  
 sign = +1 for increasing trend in data;  
 sign = -1 for decreasing trend.  
  
 Model 2 is nested within Models 3 and 4.  
 Model 3 is nested within Model 5.  
 Model 4 is nested within Model 5.  
  
  
 Dependent variable = Response  
 Independent variable = Dose  
 Data are assumed to be distributed: normally  
 Variance Model: exp(lnalpha +rho \*ln(Y[dose]))  
 rho is set to 0.  
 A constant variance model is fit.  
  
 Total number of dose groups = 10  
 Total number of records with missing values = 0  
 Maximum number of iterations = 500  
 Relative Function Convergence has been set to: 1e-008  
 Parameter Convergence has been set to: 1e-008  
  
 MLE solution provided: Exact  
  
  
 Initial Parameter Values  
  
 Variable Model 4  
 -------- --------  
 lnalpha 0.245131   
 rho 0 Specified  
 a 11.2176   
 b 0.00429934   
 c 1.46863   
 d 1 Specified  
  
  
  
 Parameter Estimates  
  
 Variable Model 4 Std. Err.  
 -------- ------- ---------  
 lnalpha 0.312317 0.260598  
 a 12.3759 0.20837  
 b 0.0213164 0.00970104  
 c 1.2533 0.037875  
  
 NC = No Convergence  
  
  
 Table of Stats From Input Data  
  
 Dose N Obs Mean Obs Std Dev  
 ----- --- ---------- -------------  
 0 10 12.52 1.388  
 0.07 5 11.81 1.671  
 0.2 5 12.57 1.217  
 0.7 5 12.61 1.23  
 2 5 12.05 0.6544  
 6 5 13.14 1.171  
 18 5 13.48 1.405  
 55 5 14.3 0.8832  
 160 5 15.69 1.218  
 475 5 15.34 1.186  
  
  
 Estimated Values of Interest  
  
 Dose Est Mean Est Std Scaled Residual  
 ------ ---------- --------- ----------------  
 0 12.38 1.169 0.3816  
 0.07 12.38 1.169 -1.095  
 0.2 12.39 1.169 0.3533  
 0.7 12.42 1.169 0.3627  
 2 12.51 1.169 -0.8661  
 6 12.75 1.169 0.7492  
 18 13.37 1.169 0.2087  
 55 14.54 1.169 -0.4669  
 160 15.41 1.169 0.5409  
 475 15.51 1.169 -0.3263  
  
  
  
 Other models for which likelihoods are calculated:  
  
 Model A1: Yij = Mu(i) + e(ij)  
 Var{e(ij)} = Sigma^2  
  
 Model A2: Yij = Mu(i) + e(ij)  
 Var{e(ij)} = Sigma(i)^2  
  
 Model A3: Yij = Mu(i) + e(ij)  
 Var{e(ij)} = exp(lalpha + log(mean(i)) \* rho)  
  
 Model R: Yij = Mu + e(i)  
 Var{e(ij)} = Sigma^2  
  
  
 Likelihoods of Interest  
  
 Model Log(likelihood) DF AIC  
 ------- ----------------- ---- ------------  
 A1 -34.24111 11 90.48222  
 A2 -31.40933 20 102.8187  
 A3 -34.24111 11 90.48222  
 R -55.97339 2 115.9468  
 4 -36.08871 4 80.17742  
  
  
 Additive constant for all log-likelihoods = -50.54. 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 49.13 18 0.0001021  
 Test 2 5.664 9 0.7731  
 Test 3 5.664 9 0.7731  
 Test 6a 3.695 7 0.8141  
  
  
 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 = 21.8929  
  
 BMDL = 10.3368  
  
 BMDU = 46.3444

# Male BMD Results for Table: Liver Weight Relative

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 0.07 | 0.2 | 0.7 | 2 | 6 | 18 | 55 | 160 | 475 |
| N | 10 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Mean ± SD | 37.411 ± 2.087 | 36.069 ± 2.902 | 37.695 ± 2.143 | 37.424 ± 2.103 | 36.768 ± 0.94 | 39.294 ± 1.968 | 41.443 ± 3.293 | 42.312 ± 1.855 | 46.853 ± 2.601 | 45.932 ± 2.044 |

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear (equivalent models include Power, Polynomial 2°, 3°, 4°, 5°, 6°, 7°, 8°) | <0.0001 | 184.721 | 154.464 | 119.222 | Hill recommended as best-fitting model on the basis of the lowest AIC. |
| Hillb | 0.366 | 149.057 | 8.087 | 4.336 |
| Exponential M2 (equivalent models include Exponential M3) | <0.0001 | 186.292 | 173.4 | 136.091 |
| Exponential M4 (equivalent models include Exponential M5) | 0.325 | 149.511 | 12.437 | 7.255 |

a Constant variance case presented (BMDS Test 2 p-value = 0.52, BMDS Test 3 p-value = 0.52).

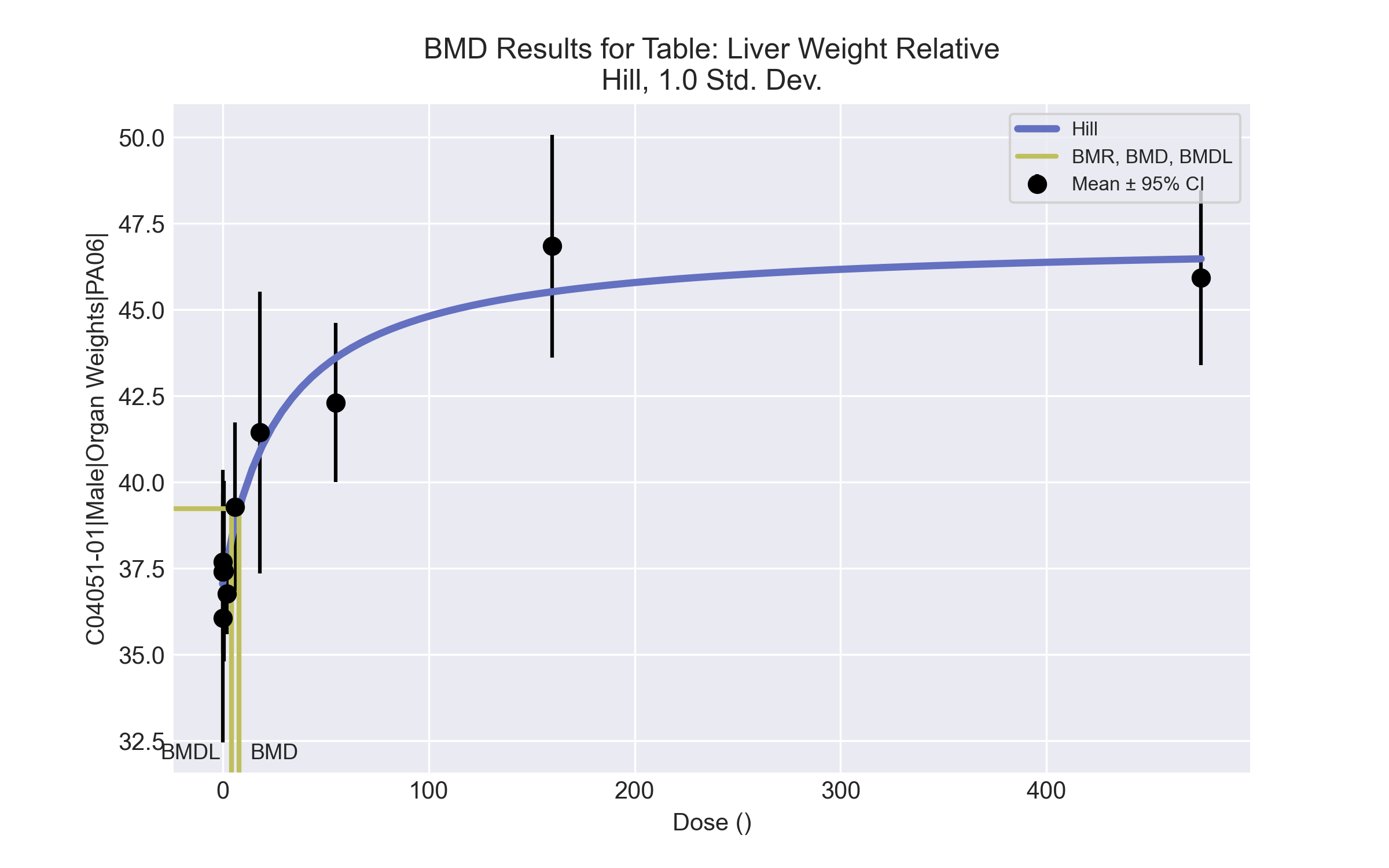
b Recommended model

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear (equivalent models include Power, Polynomial 2°, 3°, 4°, 5°, 6°, 7°, 8°) | Warning | **Warnings**  • Residual of interest is greater than threshold (3.7 > 2.0) |
| Hilla | Valid | - |
| Exponential M2 (equivalent models include Exponential M3) | Warning | **Warnings**  • Residual of interest is greater than threshold (3.81 > 2.0) |
| Exponential M4 (equivalent models include Exponential M5) | Valid | - |

a Recommended model

## Recommended model



====================================================================   
 Hill Model. (Version: 2.18; Date: 03/14/2017)   
 Input Data File: C:\Windows\TEMP\bmds-usaqyob6.(d)   
 Gnuplot Plotting File: C:\Windows\TEMP\bmds-usaqyob6.plt  
 Tue Apr 13 09:11:47 2021  
 ====================================================================   
  
 BMDS\_Model\_Run   
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~  
   
 The form of the response function is:   
  
 Y[dose] = intercept + v\*dose^n/(k^n + dose^n)  
  
  
 Dependent variable = Response  
 Independent variable = Dose  
 rho is set to 0  
 Power parameter restricted to be greater than 1  
 A constant variance model is fit  
  
 Total number of dose groups = 10  
 Total number of records with missing values = 0  
 Maximum number of iterations = 500  
 Relative Function Convergence has been set to: 1e-008  
 Parameter Convergence has been set to: 1e-008  
  
  
  
 Default Initial Parameter Values   
 alpha = 5.08645  
 rho = 0 Specified  
 intercept = 37.4106  
 v = 9.4426  
 n = 0.665024  
 k = 62.6735  
  
  
 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-007 3.4e-007 6.5e-007  
  
 intercept 1.2e-007 1 -0.23 0.43  
  
 v 3.4e-007 -0.23 1 0.56  
  
 k 6.5e-007 0.43 0.56 1  
  
  
  
 Parameter Estimates  
  
 95.0% Wald Confidence Interval  
 Variable Estimate Std. Err. Lower Conf. Limit Upper Conf. Limit  
 alpha 4.78111 0.911722 2.99417 6.56805  
 intercept 37.0578 0.418998 36.2366 37.879  
 v 9.99469 1.01661 8.00217 11.9872  
 n 1 NA  
 k 28.8785 12.2415 4.88559 52.8715  
  
NA - Indicates that this parameter has hit a bound  
 implied by some inequality constraint and thus  
 has no standard error.  
  
  
  
 Table of Data and Estimated Values of Interest  
  
 Dose N Obs Mean Est Mean Obs Std Dev Est Std Dev Scaled Res.  
------ --- -------- -------- ----------- ----------- ----------  
  
 0 10 37.4 37.1 2.09 2.19 0.51  
 0.07 5 36.1 37.1 2.9 2.19 -1.04  
 0.2 5 37.7 37.1 2.14 2.19 0.582  
 0.7 5 37.4 37.3 2.1 2.19 0.132  
 2 5 36.8 37.7 0.94 2.19 -0.958  
 6 5 39.3 38.8 1.97 2.19 0.528  
 18 5 41.4 40.9 3.29 2.19 0.56  
 55 5 42.3 43.6 1.86 2.19 -1.33  
 160 5 46.9 45.5 2.6 2.19 1.36  
 475 5 45.9 46.5 2.04 2.19 -0.561  
  
  
  
 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 -66.712529 11 155.425059  
 A2 -62.643595 20 165.287191  
 A3 -66.712529 11 155.425059  
 fitted -70.528494 4 149.056988  
 R -105.403485 2 214.806970  
  
  
 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 85.5198 18 <.0001  
 Test 2 8.13787 9 0.5203  
 Test 3 8.13787 9 0.5203  
 Test 4 7.63193 7 0.3662  
  
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 = 8.08711  
  
 BMDL = 4.33554  
  
 BMDU = 17.7394

# Male BMD Results for Table: A/G Ratio

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 0.07 | 0.2 | 0.7 | 2 | 6 | 18 | 55 | 160 | 475 |
| N | 9 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 4 |
| Mean ± SD | 2.654 ± 0.222 | 2.671 ± 0.462 | 2.751 ± 0.309 | 2.562 ± 0.102 | 2.536 ± 0.282 | 2.55 ± 0.367 | 2.681 ± 0.519 | 2.562 ± 0.119 | 2.354 ± 0.268 | 2.332 ± 0.19 |

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear (equivalent models include Power, Polynomial 2°, 3°, 5°, 6°) | 0.257 | -72.66 | 463 | 269.118 | No model was recommended as a best-fitting model. Doses were dropped until there were only 3 remaining dose-groups. |
| Polynomial 4° (equivalent models include Polynomial 7°) | 0.257 | -72.66 | 463.005 | 269.118 |
| Polynomial 8° | <0.0001 | 308.588 | 18.057 | -999 |
| Hill | 0.285 | -71.371 | -999 | -999 |
| Exponential M2 (equivalent models include Exponential M3) | 0.263 | -72.757 | 456.651 | 253.828 |
| Exponential M4 | 0.295 | -72.336 | 312.295 | 79.049 |
| Exponential M5 | 0.285 | -71.371 | -999 | 0 |

a Modeled variance case presented (BMDS Test 2 p-value = 0.011, BMDS Test 3 p-value = 0.09).

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear (equivalent models include Power, Polynomial 2°, 3°, 5°, 6°) | Warning | **Warnings**  • Variance model poorly fits dataset (p-value 3 = 0.09035) |
| Polynomial 4° (equivalent models include Polynomial 7°) | Warning | **Warnings**  • Variance model poorly fits dataset (p-value 3 = 0.09035) |
| Polynomial 8° | Failure | **Failures**  • BMDL does not exist  **Warnings**  • Variance model poorly fits dataset (p-value 3 = 0.09035)  • Residual of interest is greater than threshold (2.73 > 2.0)  • Ratio of modeled to actual stdev. at control is greater than threshold (2.43 > 1.5)  **Cautions**  • Warning(s): THE MODEL HAS PROBABLY NOT CONVERGED!!!; THIS USUALLY MEANS THE MODEL HAS NOT CONVERGED!; BMDL computation failed. |
| Hill | Failure | **Failures**  • BMD does not exist  • BMDL does not exist  **Warnings**  • Residual of Interest does not exist  • Variance model poorly fits dataset (p-value 3 = 0.09035)  **Cautions**  • Warning(s): BMR value is not in the range of the mean function |
| Exponential M2 (equivalent models include Exponential M3) | Warning | **Warnings**  • Variance model poorly fits dataset (p-value 3 = 0.09035) |
| Exponential M4 | Warning | **Warnings**  • Variance model poorly fits dataset (p-value 3 = 0.09035) |
| Exponential M5 | Failure | **Failures**  • BMD does not exist  **Warnings**  • Residual of Interest does not exist  • Variance model poorly fits dataset (p-value 3 = 0.09035) |

## Recommended model

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

# Male BMD Results for Table: Alanine aminotransferase

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 0.07 | 0.2 | 0.7 | 2 | 6 | 18 | 55 | 160 | 475 |
| N | 9 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 4 |
| Mean ± SD | 61.778 ± 9.189 | 54.4 ± 7.232 | 60.4 ± 7.893 | 64.2 ± 13.773 | 58.6 ± 6.066 | 55.8 ± 1.095 | 63.8 ± 6.261 | 64 ± 21.378 | 66.6 ± 7.403 | 96 ± 20.992 |

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear (equivalent models include Power) | 0.008 | 307.617 | 134.227 | 88.022 | No model was recommended as a best-fitting model. Doses were dropped until there were only 3 remaining dose-groups. |
| Polynomial 2° | 0.004 | 309.49 | 160 | 88.892 |
| Polynomial 3° | 0.004 | 309.34 | 174.489 | 89.962 |
| Polynomial 4° | 0.005 | 309.274 | 180.951 | 90.444 |
| Polynomial 5° | 0.005 | 309.25 | 183.764 | 90.621 |
| Polynomial 6° | <0.0001 | 340.555 | -9999 | -999 |
| Polynomial 7° | 0.005 | 309.239 | 185.424 | 90.704 |
| Polynomial 8° | 0.005 | 309.238 | 185.615 | 90.711 |
| Hill | 0.004 | 309.619 | 134.004 | -999 |
| Exponential M2 (equivalent models include Exponential M3) | 0.008 | 307.482 | 152.446 | 108.005 |
| Exponential M4 | <0.0001 | 342.555 | 1 | -999 |
| Exponential M5 | 0.004 | 309.619 | 134.037 | 46.088 |

a Modeled variance case presented (BMDS Test 2 p-value = <0.0001, BMDS Test 3 p-value = 0.021).

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear (equivalent models include Power) | Warning | **Warnings**  • Variance model poorly fits dataset (p-value 3 = 0.02115)  • Goodness of fit p-value is less than threshold (0.0075 < 0.1) |
| Polynomial 2° | Warning | **Warnings**  • Variance model poorly fits dataset (p-value 3 = 0.02115)  • Goodness of fit p-value is less than threshold (0.00417 < 0.1) |
| Polynomial 3° | Warning | **Warnings**  • Variance model poorly fits dataset (p-value 3 = 0.02115)  • Goodness of fit p-value is less than threshold (0.00442 < 0.1) |
| Polynomial 4° | Warning | **Warnings**  • Variance model poorly fits dataset (p-value 3 = 0.02115)  • Goodness of fit p-value is less than threshold (0.00454 < 0.1) |
| Polynomial 5° | Warning | **Warnings**  • Variance model poorly fits dataset (p-value 3 = 0.02115)  • Goodness of fit p-value is less than threshold (0.00458 < 0.1) |
| Polynomial 6° | Failure | **Failures**  • BMDL does not exist  **Warnings**  • Residual of Interest does not exist  • Variance model poorly fits dataset (p-value 3 = 0.02115)  • Ratio of modeled to actual stdev. at control is greater than threshold (1.55 > 1.5)  **Cautions**  • Warning(s): BMD = 100\*(maximum dose); BMDL computation failed. |
| Polynomial 7° | Warning | **Warnings**  • Variance model poorly fits dataset (p-value 3 = 0.02115)  • Goodness of fit p-value is less than threshold (0.0046 < 0.1) |
| Polynomial 8° | Warning | **Warnings**  • Variance model poorly fits dataset (p-value 3 = 0.02115)  • Goodness of fit p-value is less than threshold (0.0046 < 0.1) |
| Hill | Failure | **Failures**  • BMDL does not exist  **Warnings**  • Variance model poorly fits dataset (p-value 3 = 0.02115)  • Goodness of fit p-value is less than threshold (0.00396 < 0.1)  **Cautions**  • Warning(s): BMDL computation failed. |
| Exponential M2 (equivalent models include Exponential M3) | Warning | **Warnings**  • Variance model poorly fits dataset (p-value 3 = 0.02115)  • Goodness of fit p-value is less than threshold (0.00789 < 0.1) |
| Exponential M4 | Failure | **Failures**  • BMDL does not exist  **Warnings**  • Variance model poorly fits dataset (p-value 3 = 0.02115) |
| Exponential M5 | Warning | **Warnings**  • Variance model poorly fits dataset (p-value 3 = 0.02115)  • Goodness of fit p-value is less than threshold (0.00396 < 0.1) |

## Recommended model

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

# Male BMD Results for Table: Alkaline phosphatase

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 0.07 | 0.2 | 0.7 | 2 | 6 | 18 | 55 | 160 | 475 |
| N | 9 | 5 | 5 | 5 | 4 | 5 | 5 | 5 | 5 | 4 |
| Mean ± SD | 267.778 ± 23.926 | 253.4 ± 55.025 | 252.8 ± 19.344 | 277 ± 40.682 | 269.5 ± 16.34 | 263.8 ± 23.973 | 285 ± 9.975 | 284.8 ± 45.746 | 326 ± 53.094 | 351 ± 25.547 |

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear (equivalent models include Power, Polynomial 2°, 3°, 4°, 5°, 6°, 7°, 8°) | 0.459 | 424.127 | 149.957 | 87.451 | No model was recommended as a best-fitting model. Doses were dropped until there were only 3 remaining dose-groups. |
| Hill | 0.792 | 423.518 | 55.827 | -999 |
| Exponential M2 (equivalent models include Exponential M3) | 0.368 | 425.089 | 174.338 | 106.358 |
| Exponential M4 | 0.88 | 421.435 | 56.015 | 23.484 |
| Exponential M5 | 0.803 | 423.427 | 57.836 | 23.515 |

a Modeled variance case presented (BMDS Test 2 p-value = 0.005, BMDS Test 3 p-value = 0.004).

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear (equivalent models include Power, Polynomial 2°, 3°, 4°, 5°, 6°, 7°, 8°) | Warning | **Warnings**  • Variance model poorly fits dataset (p-value 3 = 0.003843) |
| Hill | Failure | **Failures**  • BMDL does not exist  **Warnings**  • Variance model poorly fits dataset (p-value 3 = 0.003843)  **Cautions**  • Warning(s): BMDL computation failed. |
| Exponential M2 (equivalent models include Exponential M3) | Warning | **Warnings**  • Variance model poorly fits dataset (p-value 3 = 0.003843) |
| Exponential M4 | Warning | **Warnings**  • Variance model poorly fits dataset (p-value 3 = 0.003843) |
| Exponential M5 | Warning | **Warnings**  • Variance model poorly fits dataset (p-value 3 = 0.003843) |

## Recommended model

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

# Male BMD Results for Table: Aspartate Aminotransferase

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 0.07 | 0.2 | 0.7 | 2 | 6 | 18 | 55 | 160 | 475 |
| N | 9 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 4 |
| Mean ± SD | 80.222 ± 10.592 | 77.8 ± 6.76 | 86 ± 16.386 | 83.2 ± 14.789 | 78.6 ± 6.656 | 76.6 ± 5.505 | 76.8 ± 5.215 | 87 ± 19.774 | 88.4 ± 8.961 | 122.25 ± 22.911 |

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear | 0.024 | 319.775 | 129.607 | 89.156 | No model was recommended as a best-fitting model. Doses were dropped until there were only 3 remaining dose-groups. |
| Polynomial 2° | 0.017 | 321.237 | 175.747 | 92.609 |
| Polynomial 3° | 0.017 | 321.134 | 184.671 | 93.329 |
| Polynomial 4° | 0.018 | 321.088 | 189.873 | 93.656 |
| Polynomial 5° | 0.018 | 321.071 | 192.598 | 93.777 |
| Polynomial 6° | 0.018 | 321.066 | 193.927 | 93.819 |
| Polynomial 7° | 0.018 | 321.064 | 194.541 | 93.834 |
| Polynomial 8° | 0.018 | 321.063 | 194.814 | 93.838 |
| Power | 0.016 | 321.313 | 168.965 | 92.084 |
| Hill | 0.009 | 323.338 | 168.18 | -999 |
| Exponential M2 | 0.027 | 319.437 | 144.888 | 105.443 |
| Exponential M3 | 0.017 | 321.243 | 172.549 | 106.647 |
| Exponential M4 | 0.014 | 321.78 | 129.461 | 71.556 |
| Exponential M5 | 0.009 | 323.315 | 168.931 | 76.86 |

a Modeled variance case presented (BMDS Test 2 p-value = 0.006, BMDS Test 3 p-value = 0.6).

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0241 < 0.1) |
| Polynomial 2° | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0168 < 0.1) |
| Polynomial 3° | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0174 < 0.1) |
| Polynomial 4° | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0177 < 0.1) |
| Polynomial 5° | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0178 < 0.1) |
| Polynomial 6° | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0179 < 0.1) |
| Polynomial 7° | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0179 < 0.1) |
| Polynomial 8° | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0179 < 0.1) |
| Power | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0163 < 0.1) |
| Hill | Failure | **Failures**  • BMDL does not exist  **Warnings**  • Goodness of fit p-value is less than threshold (0.00856 < 0.1)  **Cautions**  • Warning(s): BMDL computation failed. |
| Exponential M2 | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0271 < 0.1) |
| Exponential M3 | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0167 < 0.1) |
| Exponential M4 | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0137 < 0.1) |
| Exponential M5 | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.00864 < 0.1) |

## Recommended model

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

# Male BMD Results for Table: Cholesterol

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 0.07 | 0.2 | 0.7 | 2 | 6 | 18 | 55a | 160a | 475a |
| N | 9 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 4 |
| Mean ± SD | 118.111 ± 11.062 | 117 ± 11.446 | 110 ± 6.205 | 114.8 ± 5.586 | 113.8 ± 6.261 | 118.6 ± 8.204 | 104.6 ± 14.571 | 115.6 ± 12.402 | 107.6 ± 12.798 | 100.75 ± 2.872 |

a Dose group removed in BMD modeling session

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear | 0.424 | 220.037 | 17.099 | 9.572 | Polynomial-7 recommended as best-fitting model on the basis of the lowest AIC. |
| Polynomial 2° | 0.556 | 219.059 | 16.693 | 10.501 |
| Polynomial 3° | 0.601 | 218.749 | 16.989 | 12.919 |
| Polynomial 4° | 0.616 | 218.653 | 17.212 | 11.034 |
| Polynomial 5° | 0.62 | 218.622 | 17.36 | 12.99 |
| Polynomial 6° | 0.622 | 218.611 | 17.464 | 12.996 |
| Polynomial 7°b | 0.623 | 218.608 | 17.539 | 14.31 |
| Polynomial 8° | 0.173 | 224.609 | 17.543 | 14.31 |
| Power | 0.477 | 220.606 | 17.773 | 11.105 |
| Hill | 0.32 | 222.606 | 17.792 | 10.964 |
| Exponential M2 (equivalent models include Exponential M4) | 0.417 | 220.089 | 17.292 | 9.333 |
| Exponential M3 | 0.477 | 220.606 | 17.778 | 11.032 |
| Exponential M5 | 0.32 | 222.606 | 17.74 | 6.356 |

a Constant variance case presented (BMDS Test 2 p-value = 0.198, BMDS Test 3 p-value = 0.198).

b Recommended model

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear | Valid | - |
| Polynomial 2° | Valid | - |
| Polynomial 3° | Valid | - |
| Polynomial 4° | Valid | - |
| Polynomial 5° | Valid | - |
| Polynomial 6° | Valid | - |
| Polynomial 7°a | Valid | - |
| Polynomial 8° | Valid | **Cautions**  • Warning(s): THE MODEL HAS PROBABLY NOT CONVERGED!!!; THIS USUALLY MEANS THE MODEL HAS NOT CONVERGED! |
| Power | Valid | - |
| Hill | Valid | **Cautions**  • Warning(s): THIS USUALLY MEANS THE MODEL HAS NOT CONVERGED! |
| Exponential M2 (equivalent models include Exponential M4) | Valid | - |
| Exponential M3 | Valid | - |
| Exponential M5 | Valid | - |

a Recommended model

## Recommended model



====================================================================   
 Polynomial Model. (Version: 2.21; Date: 03/14/2017)   
 Input Data File: C:\Windows\TEMP\bmds-yddlnpcd.(d)   
 Gnuplot Plotting File: C:\Windows\TEMP\bmds-yddlnpcd.plt  
 Tue Apr 13 09:17:53 2021  
 ====================================================================   
  
 BMDS\_Model\_Run   
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~  
   
 The form of the response function is:   
  
 Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ...  
  
  
 Dependent variable = Response  
 Independent variable = Dose  
 rho is set to 0  
 The polynomial coefficients are restricted to be negative  
 A constant variance model is fit  
  
 Total number of dose groups = 7  
 Total number of records with missing values = 0  
 Maximum number of iterations = 500  
 Relative Function Convergence has been set to: 1e-008  
 Parameter Convergence has been set to: 1e-008  
  
  
  
 Default Initial Parameter Values   
 alpha = 95.5278  
 rho = 0 Specified  
 beta\_0 = 32.8116  
 beta\_1 = -15.3838  
 beta\_2 = -258.964  
 beta\_3 = 0  
 beta\_4 = -266.2  
 beta\_5 = 0  
 beta\_6 = 0  
 beta\_7 = -0.124249  
  
  
 Asymptotic Correlation Matrix of Parameter Estimates  
  
 ( \*\*\* The model parameter(s) -rho -beta\_1 -beta\_2 -beta\_3 -beta\_4 -beta\_5 -beta\_6   
 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\_7  
  
 alpha 1 8.4e-008 -8.8e-008  
  
 beta\_0 8.4e-008 1 -0.36  
  
 beta\_7 -8.9e-008 -0.36 1  
  
  
  
 Parameter Estimates  
  
 95.0% Wald Confidence Interval  
 Variable Estimate Std. Err. Lower Conf. Limit Upper Conf. Limit  
 alpha 85.754 19.4194 47.6926 123.815  
 beta\_0 115.706 1.58824 112.594 118.819  
 beta\_1 -4.71417e-022 NA  
 beta\_2 -1.70097e-023 NA  
 beta\_3 -0 NA  
 beta\_4 0 NA  
 beta\_5 -7.67619e-027 NA  
 beta\_6 -2.23902e-028 NA  
 beta\_7 -1.81391e-008 7.2453e-009 -3.23396e-008 -3.93855e-009  
  
NA - Indicates that this parameter has hit a bound  
 implied by some inequality constraint and thus  
 has no standard error.  
  
  
  
 Table of Data and Estimated Values of Interest  
  
 Dose N Obs Mean Est Mean Obs Std Dev Est Std Dev Scaled Res.  
------ --- -------- -------- ----------- ----------- ----------  
  
 0 9 118 116 11.1 9.26 0.779  
 0.07 5 117 116 11.4 9.26 0.312  
 0.2 5 110 116 6.2 9.26 -1.38  
 0.7 5 115 116 5.59 9.26 -0.219  
 2 5 114 116 6.26 9.26 -0.46  
 6 5 119 116 8.2 9.26 0.7  
 18 5 105 105 14.6 9.26 -0.00032  
  
  
  
 Model Descriptions for likelihoods calculated  
  
  
 Model A1: Yij = Mu(i) + e(ij)  
 Var{e(ij)} = Sigma^2  
  
 Model A2: Yij = Mu(i) + e(ij)  
 Var{e(ij)} = Sigma(i)^2  
  
 Model A3: Yij = Mu(i) + e(ij)  
 Var{e(ij)} = Sigma^2  
 Model A3 uses any fixed variance parameters that  
 were specified by the user  
  
 Model R: Yi = Mu + e(i)  
 Var{e(i)} = Sigma^2  
  
  
 Likelihoods of Interest  
  
 Model Log(likelihood) # Param's AIC  
 A1 -104.551031 8 225.102062  
 A2 -100.259495 14 228.518991  
 A3 -104.551031 8 225.102062  
 fitted -106.303913 3 218.607825  
 R -109.210095 2 222.420190  
  
  
 Explanation of Tests   
  
 Test 1: Do responses and/or variances differ among Dose levels?   
 (A2 vs. R)  
 Test 2: Are Variances Homogeneous? (A1 vs A2)  
 Test 3: Are variances adequately modeled? (A2 vs. A3)  
 Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)  
 (Note: When rho=0 the results of Test 3 and Test 2 will be the same.)  
  
 Tests of Interest   
  
 Test -2\*log(Likelihood Ratio) Test df p-value   
  
 Test 1 17.9012 12 0.1187  
 Test 2 8.58307 6 0.1984  
 Test 3 8.58307 6 0.1984  
 Test 4 3.50576 5 0.6225  
  
The p-value for Test 1 is greater than .05. There may not be a  
diffence between responses and/or variances among the dose levels  
Modelling the data with a dose/response curve may not be appropriate  
  
The p-value for Test 2 is greater than .1. A homogeneous variance   
model appears to be appropriate here  
  
  
The p-value for Test 3 is greater than .1. The modeled variance appears   
 to be appropriate here  
  
The p-value for Test 4 is greater than .1. The model chosen seems   
to adequately describe the data  
   
  
 Benchmark Dose Computation  
  
Specified effect = 1  
  
Risk Type = Estimated standard deviations from the control mean  
  
Confidence level = 0.95  
  
 BMD = 17.5389  
  
  
 BMDL = 14.3102  
  
  
 BMDU = 24.6502

# Male BMD Results for Table: Creatinine

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 0.07 | 0.2 | 0.7 | 2 | 6 | 18 | 55 | 160 | 475 |
| N | 9 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 4 |
| Mean ± SD | 0.478 ± 0.044 | 0.46 ± 0.055 | 0.46 ± 0.055 | 0.5 ± 0 | 0.42 ± 0.045 | 0.42 ± 0.045 | 0.42 ± 0.045 | 0.38 ± 0.11 | 0.44 ± 0.055 | 0.475 ± 0.05 |

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear | <0.0001 | -238.868 | -9999 | 454.687 | No model was recommended as a best-fitting model. Doses were dropped until there were only 3 remaining dose-groups. |
| Polynomial 2° | <0.0001 | -238.868 | -9999 | 655.211 |
| Polynomial 3° | <0.0001 | -238.868 | -9999 | 643.396 |
| Polynomial 4° | <0.0001 | -238.868 | -9999 | 597.384 |
| Polynomial 5° | <0.0001 | -200.154 | -9999 | -999 |
| Polynomial 6° | <0.0001 | -238.868 | -9999 | -999 |
| Polynomial 7° | <0.0001 | 672.235 | -9999 | -999 |
| Polynomial 8° | <0.0001 | -238.868 | -9999 | -999 |
| Power | <0.0001 | -236.518 | 582.081 | 436 |
| Hill | <0.0001 | -246.746 | 2.016 | -999 |
| Exponential M2 | -999 | -236.868 | 1 | -999 |
| Exponential M3 | -999 | -234.868 | 26102 | -999 |
| Exponential M4 | -999 | -239.607 | -999 | 0 |
| Exponential M5 | -999 | -238.605 | -999 | 0 |

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

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear | Warning | **Warnings**  • Residual of Interest does not exist  • Variance model poorly fits dataset (p-value 3 = 0.0001)  **Cautions**  • Warning(s): THIS USUALLY MEANS THE MODEL HAS NOT CONVERGED!; BMD = 100\*(maximum dose); Warning: Likelihood for fitted model larger than the Likelihood for model A3. |
| Polynomial 2° | Warning | **Warnings**  • Residual of Interest does not exist  • Variance model poorly fits dataset (p-value 3 = 0.0001)  **Cautions**  • Warning(s): BMD = 100\*(maximum dose); Warning: Likelihood for fitted model larger than the Likelihood for model A3.  • BMDL/high dose ratio is greater than threshold (1.38 > 1.0) |
| Polynomial 3° | Warning | **Warnings**  • Residual of Interest does not exist  • Variance model poorly fits dataset (p-value 3 = 0.0001)  **Cautions**  • Warning(s): THIS USUALLY MEANS THE MODEL HAS NOT CONVERGED!; BMD = 100\*(maximum dose); Warning: Likelihood for fitted model larger than the Likelihood for model A3.  • BMDL/high dose ratio is greater than threshold (1.35 > 1.0) |
| Polynomial 4° | Warning | **Warnings**  • Residual of Interest does not exist  • Variance model poorly fits dataset (p-value 3 = 0.0001)  **Cautions**  • Warning(s): THIS USUALLY MEANS THE MODEL HAS NOT CONVERGED!; BMD = 100\*(maximum dose); Warning: Likelihood for fitted model larger than the Likelihood for model A3.  • BMDL/high dose ratio is greater than threshold (1.26 > 1.0) |
| Polynomial 5° | Failure | **Failures**  • BMDL does not exist  **Warnings**  • Residual of Interest does not exist  • Variance model poorly fits dataset (p-value 3 = 0.0001)  • Ratio of modeled to actual stdev. at control is greater than threshold (1.56 > 1.5)  **Cautions**  • Warning(s): BMD = 100\*(maximum dose); BMDL computation failed.; Warning: Likelihood for fitted model larger than the Likelihood for model A3. |
| Polynomial 6° | Failure | **Failures**  • BMDL does not exist  **Warnings**  • Residual of Interest does not exist  • Variance model poorly fits dataset (p-value 3 = 0.0001)  **Cautions**  • Warning(s): THIS USUALLY MEANS THE MODEL HAS NOT CONVERGED!; BMD = 100\*(maximum dose); BMDL computation failed.; Warning: Likelihood for fitted model larger than the Likelihood for model A3. |
| Polynomial 7° | Failure | **Failures**  • BMDL does not exist  **Warnings**  • Residual of Interest does not exist  • Variance model poorly fits dataset (p-value 3 = 0.0001)  • Residual at lowest dose is greater than threshold (3.18 > 2.0)  • Ratio of modeled to actual stdev. at control is greater than threshold (3.2e+03 > 1.5)  **Cautions**  • Warning(s): THIS USUALLY MEANS THE MODEL HAS NOT CONVERGED!; BMD = 100\*(maximum dose); BMDL computation failed.; Warning: Likelihood for fitted model larger than the Likelihood for model A3. |
| Polynomial 8° | Failure | **Failures**  • BMDL does not exist  **Warnings**  • Residual of Interest does not exist  • Variance model poorly fits dataset (p-value 3 = 0.0001)  **Cautions**  • Warning(s): THE MODEL HAS PROBABLY NOT CONVERGED!!!; THIS USUALLY MEANS THE MODEL HAS NOT CONVERGED!; BMD = 100\*(maximum dose); BMDL computation failed.; Warning: Likelihood for fitted model larger than the Likelihood for model A3. |
| Power | Warning | **Warnings**  • Variance model poorly fits dataset (p-value 3 = 0.0001)  • BMD/high dose ratio is greater than threshold (1.23 > 1.0)  **Cautions**  • Warning(s): Warning: Likelihood for fitted model larger than the Likelihood for model A3. |
| Hill | Failure | **Failures**  • BMDL does not exist  **Warnings**  • Variance model poorly fits dataset (p-value 3 = 0.0001)  **Cautions**  • Warning(s): BMDL computation failed. |
| Exponential M2 | Failure | **Failures**  • BMDL does not exist  **Warnings**  • Variance model poorly fits dataset (p-value 3 = 0.0001) |
| Exponential M3 | Failure | **Failures**  • BMDL does not exist  **Warnings**  • Variance model poorly fits dataset (p-value 3 = 0.0001)  • BMD/high dose ratio is greater than threshold (55.0 > 1.0) |
| Exponential M4 | Failure | **Failures**  • BMD does not exist  **Warnings**  • Residual of Interest does not exist  • Variance model poorly fits dataset (p-value 3 = 0.0001) |
| Exponential M5 | Failure | **Failures**  • BMD does not exist  **Warnings**  • Residual of Interest does not exist  • Variance model poorly fits dataset (p-value 3 = 0.0001) |

## Recommended model

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

# Male BMD Results for Table: Globulin (measured)

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 0.07 | 0.2 | 0.7 | 2 | 6 | 18 | 55 | 160 | 475a |
| N | 9 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 4 |
| Mean ± SD | 1.678 ± 0.12 | 1.68 ± 0.192 | 1.6 ± 0.1 | 1.72 ± 0.084 | 1.78 ± 0.148 | 1.74 ± 0.27 | 1.66 ± 0.279 | 1.76 ± 0.114 | 1.9 ± 0.255 | 1.875 ± 0.171 |

a Dose group removed in BMD modeling session

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear (equivalent models include Power) | 0.148 | -116.789 | 124.821 | 65.1 | Exponential-M2 recommended as best-fitting model on the basis of the lowest AIC. |
| Polynomial 2° | 0.095 | -114.795 | 127.215 | 65.14 |
| Polynomial 3° | 0.096 | -114.815 | 131.477 | 65.279 |
| Polynomial 4° | 0.096 | -114.823 | 134.312 | 65.335 |
| Polynomial 5° | 0.096 | -114.826 | 136.452 | 65.355 |
| Polynomial 6° | 0.096 | -114.827 | 138.155 | 65.361 |
| Polynomial 7° | 0.096 | -114.827 | 139.555 | 65.364 |
| Polynomial 8° | 0.096 | -114.827 | 140.736 | 65.364 |
| Hill | 0.095 | -114.789 | 124.752 | -999 |
| Exponential M2b (equivalent models include Exponential M3) | 0.148 | -116.794 | 125.835 | 68.45 |
| Exponential M4 | 0.095 | -114.789 | 124.771 | 0.44 |
| Exponential M5 | 0.095 | -114.789 | 124.765 | 8.165 |

a Modeled variance case presented (BMDS Test 2 p-value = 0.039, BMDS Test 3 p-value = 0.318).

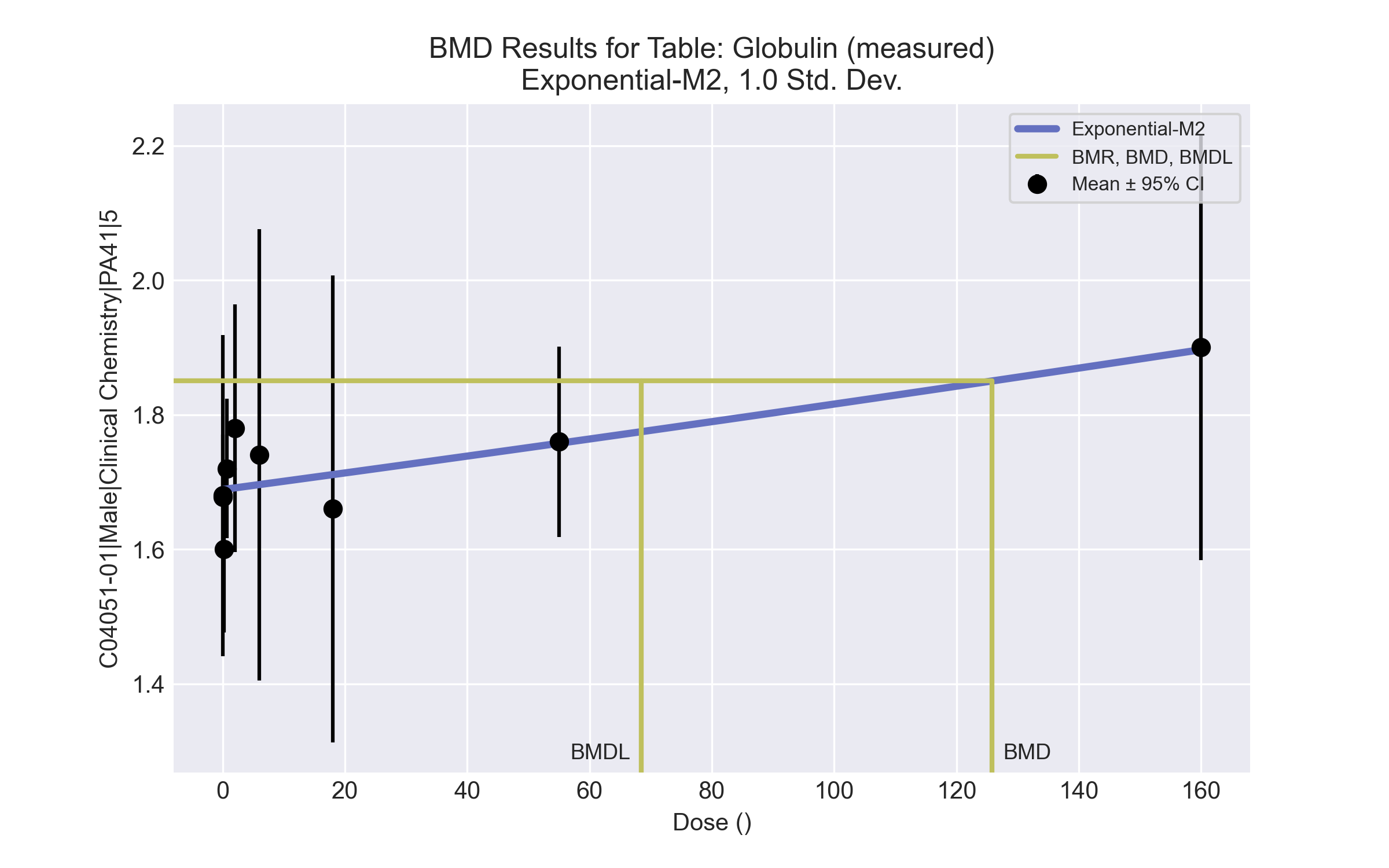
b Recommended model

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear (equivalent models include Power) | Valid | - |
| Polynomial 2° | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0954 < 0.1) |
| Polynomial 3° | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.096 < 0.1) |
| Polynomial 4° | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0963 < 0.1) |
| Polynomial 5° | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0964 < 0.1) |
| Polynomial 6° | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0964 < 0.1) |
| Polynomial 7° | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0964 < 0.1) |
| Polynomial 8° | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0964 < 0.1) |
| Hill | Failure | **Failures**  • BMDL does not exist  **Warnings**  • Goodness of fit p-value is less than threshold (0.0951 < 0.1)  **Cautions**  • Warning(s): BMDL computation failed. |
| Exponential M2a (equivalent models include Exponential M3) | Valid | - |
| Exponential M4 | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0951 < 0.1)  • BMD/BMDL ratio is greater than threshold (2.84e+02 > 20.0)  **Cautions**  • BMD/BMDL ratio is greater than threshold (2.84e+02 > 5.0) |
| Exponential M5 | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0951 < 0.1)  **Cautions**  • BMD/BMDL ratio is greater than threshold (15.3 > 5.0) |

a Recommended model

## Recommended model



====================================================================   
 Exponential Model. (Version: 1.11; Date: 03/14/2017)   
 Input Data File: C:\Windows\TEMP\bmds-6fn5mbu1.(d)   
 Gnuplot Plotting File:   
 Tue Apr 13 09:18:53 2021  
 ====================================================================   
  
 BMDS\_Model\_Run   
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~  
   
 The form of the response function by Model:   
 Model 2: Y[dose] = a \* exp{sign \* b \* dose}  
 Model 3: Y[dose] = a \* exp{sign \* (b \* dose)^d}  
 Model 4: Y[dose] = a \* [c-(c-1) \* exp{-b \* dose}]  
 Model 5: Y[dose] = a \* [c-(c-1) \* exp{-(b \* dose)^d}]  
  
 Note: Y[dose] is the median response for exposure = dose;  
 sign = +1 for increasing trend in data;  
 sign = -1 for decreasing trend.  
  
 Model 2 is nested within Models 3 and 4.  
 Model 3 is nested within Model 5.  
 Model 4 is nested within Model 5.  
  
  
 Dependent variable = Response  
 Independent variable = Dose  
 Data are assumed to be distributed: normally  
 Variance Model: exp(lnalpha +rho \*ln(Y[dose]))  
 The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) \* rho)  
  
 Total number of dose groups = 9  
 Total number of records with missing values = 0  
 Maximum number of iterations = 500  
 Relative Function Convergence has been set to: 1e-008  
 Parameter Convergence has been set to: 1e-008  
  
 MLE solution provided: Exact  
  
  
 Initial Parameter Values  
  
 Variable Model 2  
 -------- --------  
 lnalpha -7.00167   
 rho 6.10097   
 a 1.68783   
 b 0.000732677   
 c 0 Specified  
 d 1 Specified  
  
  
  
 Parameter Estimates  
  
 Variable Model 2 Std. Err.  
 -------- ------- ---------  
 lnalpha -6.57539 3.47089  
 rho 5.58872 6.40013  
 a 1.68876 0.0261302  
 b 0.000725655 0.000334428  
  
 NC = No Convergence  
  
  
 Table of Stats From Input Data  
  
 Dose N Obs Mean Obs Std Dev  
 ----- --- ---------- -------------  
 0 9 1.678 0.1202  
 0.07 5 1.68 0.1924  
 0.2 5 1.6 0.1  
 0.7 5 1.72 0.08367  
 2 5 1.78 0.1483  
 6 5 1.74 0.2702  
 18 5 1.66 0.2793  
 55 5 1.76 0.114  
 160 5 1.9 0.255  
  
  
 Estimated Values of Interest  
  
 Dose Est Mean Est Std Scaled Residual  
 ------ ---------- --------- ----------------  
 0 1.689 0.1615 -0.204  
 0.07 1.689 0.1615 -0.1224  
 0.2 1.689 0.1615 -1.232  
 0.7 1.69 0.1617 0.4202  
 2 1.691 0.1621 1.225  
 6 1.696 0.1634 0.6002  
 18 1.711 0.1675 -0.6804  
 55 1.758 0.1805 0.03072  
 160 1.897 0.2233 0.03338  
  
  
  
 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 63.76057 10 -107.5211  
 A2 71.87408 18 -107.7482  
 A3 67.78869 11 -113.5774  
 R 58.73563 2 -113.4713  
 2 62.39679 4 -116.7936  
  
  
 Additive constant for all log-likelihoods = -45.03. 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 26.28 16 0.05025  
 Test 2 16.23 8 0.03924  
 Test 3 8.171 7 0.3178  
 Test 4 10.78 7 0.1483  
  
  
 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 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 = 125.835  
  
 BMDL = 68.4501  
  
 BMDU = 523.332

# Male BMD Results for Table: Reticulocyte count

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 0.07 | 0.2 | 0.7 | 2 | 6 | 18 | 55 | 160a | 475a |
| N | 10 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 4 |
| Mean ± SD | 227.38 ± 30.772 | 226.36 ± 20.748 | 264.32 ± 36.085 | 258.4 ± 42.383 | 234.7 ± 33.706 | 241.22 ± 26.565 | 216.68 ± 39.678 | 210.62 ± 8.811 | 226.56 ± 54.38 | 174.5 ± 14.537 |

a Dose group removed in BMD modeling session

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear | 0.061 | 364.058 | -9999 | 195.613 | Power recommended as best-fitting model on the basis of the lowest AIC. |
| Polynomial 2° | 0.061 | 364.058 | -9999 | 99.776 |
| Polynomial 3° | 0.061 | 364.058 | -9999 | 80.906 |
| Polynomial 4° | 0.061 | 364.058 | -9999 | 73.256 |
| Polynomial 5° | 0.061 | 364.058 | -9999 | 70.604 |
| Polynomial 6° | 0.061 | 364.058 | -9999 | 75.058 |
| Polynomial 7° | 0.061 | 364.058 | -9999 | -999 |
| Polynomial 8° | 0.061 | 364.058 | -9999 | -999 |
| Powerb | 0.162 | 361.774 | 54.227 | 30.205 |
| Hill | 0.145 | 362.77 | -999 | -999 |
| Exponential M2 | 0.117 | 362.742 | -44.298 | -999 |
| Exponential M3 | 0.117 | 362.742 | -44.298 | -999 |
| Exponential M4 | 0.019 | 368.058 | -999 | 0 |
| Exponential M5 | 0.009 | 370.058 | -999 | 0 |

a Constant variance case presented (BMDS Test 2 p-value = 0.111, BMDS Test 3 p-value = 0.111).

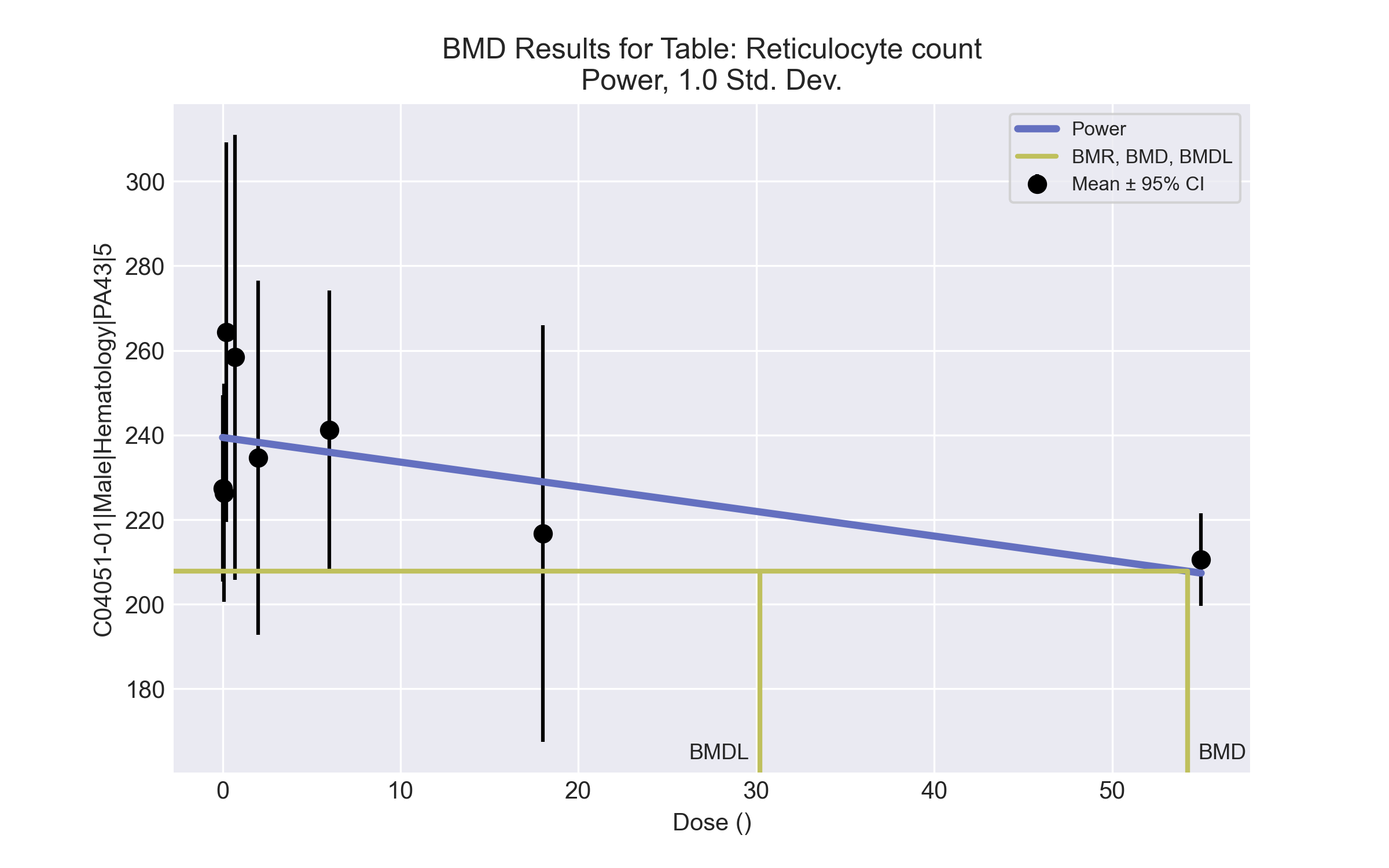
b Recommended model

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear | Warning | **Warnings**  • Residual of Interest does not exist  • Goodness of fit p-value is less than threshold (0.061 < 0.1)  **Cautions**  • Warning(s): BMD = 100\*(maximum dose)  • BMDL/high dose ratio is greater than threshold (3.56 > 1.0) |
| Polynomial 2° | Warning | **Warnings**  • Residual of Interest does not exist  • Goodness of fit p-value is less than threshold (0.061 < 0.1)  **Cautions**  • Warning(s): BMD = 100\*(maximum dose)  • BMDL/high dose ratio is greater than threshold (1.81 > 1.0) |
| Polynomial 3° | Warning | **Warnings**  • Residual of Interest does not exist  • Goodness of fit p-value is less than threshold (0.061 < 0.1)  **Cautions**  • Warning(s): BMD = 100\*(maximum dose)  • BMDL/high dose ratio is greater than threshold (1.47 > 1.0) |
| Polynomial 4° | Warning | **Warnings**  • Residual of Interest does not exist  • Goodness of fit p-value is less than threshold (0.061 < 0.1)  **Cautions**  • Warning(s): BMD = 100\*(maximum dose)  • BMDL/high dose ratio is greater than threshold (1.33 > 1.0) |
| Polynomial 5° | Warning | **Warnings**  • Residual of Interest does not exist  • Goodness of fit p-value is less than threshold (0.061 < 0.1)  **Cautions**  • Warning(s): BMD = 100\*(maximum dose)  • BMDL/high dose ratio is greater than threshold (1.28 > 1.0) |
| Polynomial 6° | Warning | **Warnings**  • Residual of Interest does not exist  • Goodness of fit p-value is less than threshold (0.061 < 0.1)  **Cautions**  • Warning(s): BMD = 100\*(maximum dose)  • BMDL/high dose ratio is greater than threshold (1.36 > 1.0) |
| Polynomial 7° | Failure | **Failures**  • BMDL does not exist  **Warnings**  • Residual of Interest does not exist  • Goodness of fit p-value is less than threshold (0.061 < 0.1)  **Cautions**  • Warning(s): BMD = 100\*(maximum dose); BMDL computation failed. |
| Polynomial 8° | Failure | **Failures**  • BMDL does not exist  **Warnings**  • Residual of Interest does not exist  • Goodness of fit p-value is less than threshold (0.061 < 0.1)  **Cautions**  • Warning(s): BMD = 100\*(maximum dose); BMDL computation failed. |
| Powera | Valid | - |
| Hill | Failure | **Failures**  • BMD does not exist  • BMDL does not exist  **Warnings**  • Residual of Interest does not exist  **Cautions**  • Warning(s): BMR value is not in the range of the mean function |
| Exponential M2 | Failure | **Failures**  • BMDL does not exist  **Warnings**  • Residual of Interest does not exist |
| Exponential M3 | Failure | **Failures**  • BMDL does not exist  **Warnings**  • Residual of Interest does not exist  • Residual at lowest dose is greater than threshold (25.2 > 2.0) |
| Exponential M4 | Failure | **Failures**  • BMD does not exist  **Warnings**  • Residual of Interest does not exist  • Goodness of fit p-value is less than threshold (0.0192 < 0.1) |
| Exponential M5 | Failure | **Failures**  • BMD does not exist  **Warnings**  • Residual of Interest does not exist  • Goodness of fit p-value is less than threshold (0.00911 < 0.1) |

a Recommended model

## Recommended model



====================================================================   
 Power Model. (Version: 2.19; Date: 03/14/2017)   
 Input Data File: C:\Windows\TEMP\bmds-3cwza94\_.(d)   
 Gnuplot Plotting File: C:\Windows\TEMP\bmds-3cwza94\_.plt  
 Tue Apr 13 09:19:34 2021  
 ====================================================================   
  
 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 = 8  
 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 = 989.533  
 rho = 0 Specified  
 control = 210.62  
 slope = 24.3155  
 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 -5.6e-010 -1.1e-010  
  
 control -5.6e-010 1 -0.47  
  
 slope -1.1e-010 -0.47 1  
  
  
  
 Parameter Estimates  
  
 95.0% Wald Confidence Interval  
 Variable Estimate Std. Err. Lower Conf. Limit Upper Conf. Limit  
 alpha 998.335 210.468 585.827 1410.84  
 control 239.425 5.33404 228.97 249.879  
 slope -0.582672 0.274857 -1.12138 -0.0439619  
 power 1 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 10 227 239 30.8 31.6 -1.21  
 0.07 5 226 239 20.7 31.6 -0.922  
 0.2 5 264 239 36.1 31.6 1.77  
 0.7 5 258 239 42.4 31.6 1.37  
 2 5 235 238 33.7 31.6 -0.252  
 6 5 241 236 26.6 31.6 0.374  
 18 5 217 229 39.7 31.6 -0.867  
 55 5 211 207 8.81 31.6 0.229  
  
  
  
 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 -173.283492 9 364.566983  
 A2 -167.429620 16 366.859239  
 A3 -173.283492 9 364.566983  
 fitted -177.887010 3 361.774020  
 R -180.028767 2 364.057534  
  
  
 Explanation of Tests   
  
 Test 1: Do responses and/or variances differ among Dose levels?   
 (A2 vs. R)  
 Test 2: Are Variances Homogeneous? (A1 vs A2)  
 Test 3: Are variances adequately modeled? (A2 vs. A3)  
 Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)  
 (Note: When rho=0 the results of Test 3 and Test 2 will be the same.)  
  
 Tests of Interest   
  
 Test -2\*log(Likelihood Ratio) Test df p-value   
  
 Test 1 25.1983 14 0.03266  
 Test 2 11.7077 7 0.1106  
 Test 3 11.7077 7 0.1106  
 Test 4 9.20704 6 0.1623  
  
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 = 54.2268   
  
  
 BMDL = 30.2052   
  
  
 BMDU = 264.27

# Male BMD Results for Table: Free Thyroxine

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 0.07 | 0.2 | 0.7 | 2 | 6 | 18 | 55 | 160 | 475 |
| N | 9 | 4 | 4 | 4 | 4 | 4 | 4 | 5 | 5 | 5 |
| Mean ± SD | 7.26 ± 0.875 | 7.205 ± 0.474 | 6.785 ± 0.398 | 5.98 ± 0.734 | 6.84 ± 1.37 | 6.485 ± 1.167 | 6.98 ± 0.945 | 7.042 ± 0.557 | 5.604 ± 0.792 | 6.232 ± 1.187 |

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear (equivalent models include Power, Polynomial 2°) | 0.067 | 47.108 | 515.172 | 276.926 | Exponential-M5 recommended as best-fitting model on the basis of the lowest AIC. |
| Polynomial 3° (equivalent models include Polynomial 4°, 6°, 7°, 8°) | 0.067 | 47.108 | 515.171 | 276.926 |
| Polynomial 5° | 0.067 | 47.108 | 515.173 | 276.926 |
| Hill | 0.213 | 44.102 | 104.854 | -999 |
| Exponential M2 (equivalent models include Exponential M3) | 0.07 | 46.99 | 502.014 | 256.124 |
| Exponential M4 | 0.092 | 46.796 | 401.957 | 59.72 |
| Exponential M5b | 0.143 | 46.102 | 142.469 | 57.746 |

a Constant variance case presented (BMDS Test 2 p-value = 0.263, BMDS Test 3 p-value = 0.263).

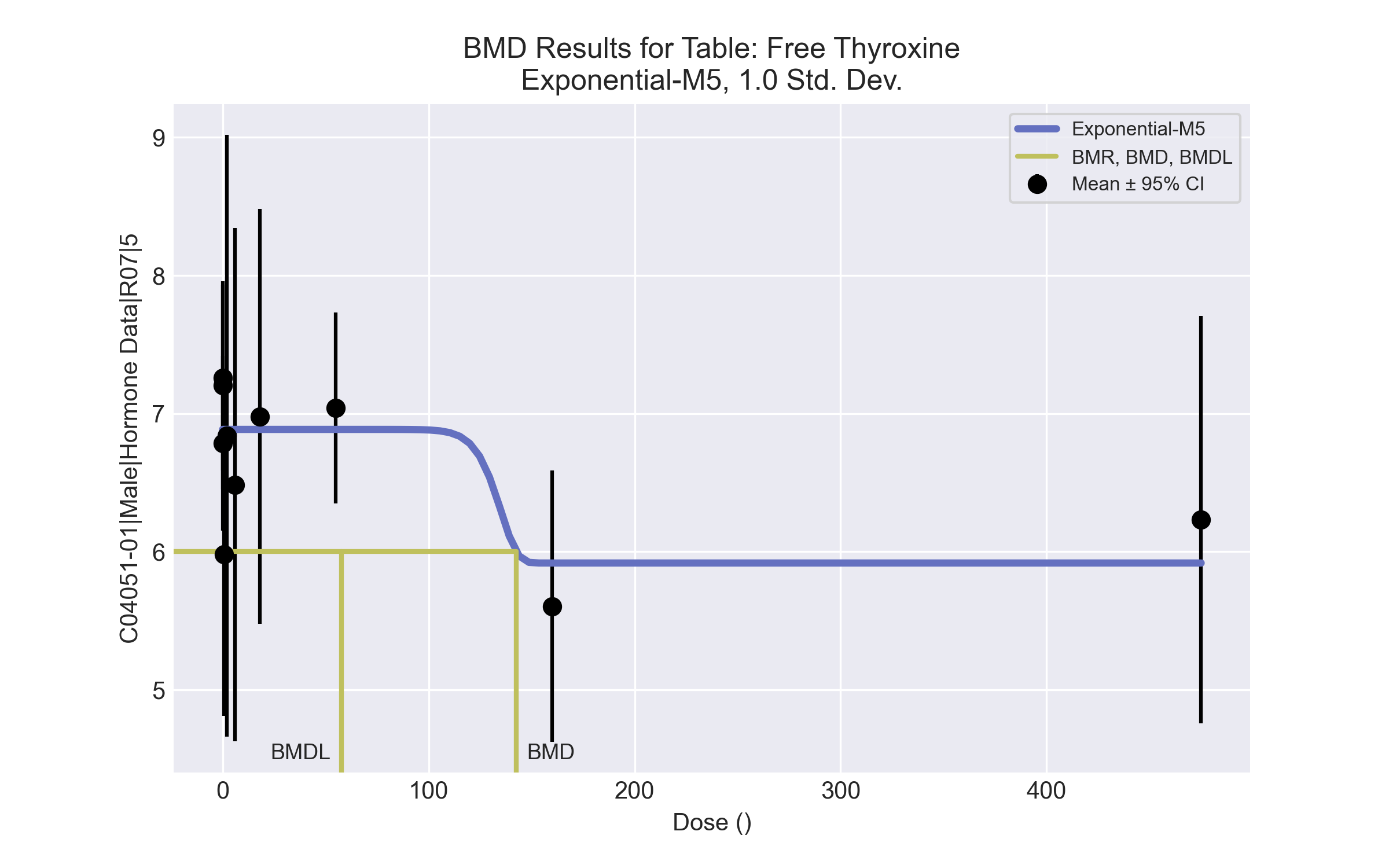
b Recommended model

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Linear (equivalent models include Power, Polynomial 2°) | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0675 < 0.1)  • BMD/high dose ratio is greater than threshold (1.08 > 1.0) |
| Polynomial 3° (equivalent models include Polynomial 4°, 6°, 7°, 8°) | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0675 < 0.1)  • BMD/high dose ratio is greater than threshold (1.08 > 1.0) |
| Polynomial 5° | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0675 < 0.1)  • BMD/high dose ratio is greater than threshold (1.08 > 1.0) |
| Hill | Failure | **Failures**  • BMDL does not exist  **Cautions**  • Warning(s): BMDL computation failed. |
| Exponential M2 (equivalent models include Exponential M3) | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0701 < 0.1)  • BMD/high dose ratio is greater than threshold (1.06 > 1.0) |
| Exponential M4 | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.0916 < 0.1)  **Cautions**  • BMD/BMDL ratio is greater than threshold (6.73 > 5.0) |
| Exponential M5a | Valid | - |

a Recommended model

## Recommended model



====================================================================   
 Exponential Model. (Version: 1.11; Date: 03/14/2017)   
 Input Data File: C:\Windows\TEMP\bmds-4o5xn1pi.(d)   
 Gnuplot Plotting File:   
 Tue Apr 13 09:27:33 2021  
 ====================================================================   
  
 BMDS\_Model\_Run   
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~  
   
 The form of the response function by Model:   
 Model 2: Y[dose] = a \* exp{sign \* b \* dose}  
 Model 3: Y[dose] = a \* exp{sign \* (b \* dose)^d}  
 Model 4: Y[dose] = a \* [c-(c-1) \* exp{-b \* dose}]  
 Model 5: Y[dose] = a \* [c-(c-1) \* exp{-(b \* dose)^d}]  
  
 Note: Y[dose] is the median response for exposure = dose;  
 sign = +1 for increasing trend in data;  
 sign = -1 for decreasing trend.  
  
 Model 2 is nested within Models 3 and 4.  
 Model 3 is nested within Model 5.  
 Model 4 is nested within Model 5.  
  
  
 Dependent variable = Response  
 Independent variable = Dose  
 Data are assumed to be distributed: normally  
 Variance Model: exp(lnalpha +rho \*ln(Y[dose]))  
 rho is set to 0.  
 A constant variance model is fit.  
  
 Total number of dose groups = 10  
 Total number of records with missing values = 0  
 Maximum number of iterations = 500  
 Relative Function Convergence has been set to: 1e-008  
 Parameter Convergence has been set to: 1e-008  
  
 MLE solution provided: Exact  
  
  
 Initial Parameter Values  
  
 Variable Model 5  
 -------- --------  
 lnalpha -0.447682   
 rho 0 Specified  
 a 7.623   
 b 0.00320938   
 c 0.700137   
 d 1   
  
  
  
 Parameter Estimates  
  
 Variable Model 5 Std. Err.  
 -------- ------- ---------  
 lnalpha -0.247876 0.15931  
 a 6.88553 0.143312  
 b 0.00737614 0.287471  
 c 0.859484 0.0443416  
 d 18 NA  
  
 NC = No Convergence  
  
  
 Table of Stats From Input Data  
  
 Dose N Obs Mean Obs Std Dev  
 ----- --- ---------- -------------  
 0 9 7.26 0.8753  
 0.07 4 7.205 0.4737  
 0.2 4 6.785 0.3985  
 0.7 4 5.98 0.7344  
 2 4 6.84 1.37  
 6 4 6.485 1.167  
 18 4 6.98 0.9446  
 55 5 7.042 0.5573  
 160 5 5.604 0.7917  
 475 5 6.232 1.187  
  
  
 Estimated Values of Interest  
  
 Dose Est Mean Est Std Scaled Residual  
 ------ ---------- --------- ----------------  
 0 6.886 0.8834 1.272  
 0.07 6.886 0.8834 0.7233  
 0.2 6.886 0.8834 -0.2276  
 0.7 6.886 0.8834 -2.05  
 2 6.886 0.8834 -0.1031  
 6 6.886 0.8834 -0.9067  
 18 6.886 0.8834 0.2139  
 55 6.886 0.8834 0.3961  
 160 5.918 0.8834 -0.7948  
 475 5.918 0.8834 0.7948  
  
  
  
 Other models for which likelihoods are calculated:  
  
 Model A1: Yij = Mu(i) + e(ij)  
 Var{e(ij)} = Sigma^2  
  
 Model A2: Yij = Mu(i) + e(ij)  
 Var{e(ij)} = Sigma(i)^2  
  
 Model A3: Yij = Mu(i) + e(ij)  
 Var{e(ij)} = exp(lalpha + log(mean(i)) \* rho)  
  
 Model R: Yij = Mu + e(i)  
 Var{e(ij)} = Sigma^2  
  
  
 Likelihoods of Interest  
  
 Model Log(likelihood) DF AIC  
 ------- ----------------- ---- ------------  
 A1 -13.25564 11 48.51129  
 A2 -7.657695 20 55.31539  
 A3 -13.25564 11 48.51129  
 R -22.38312 2 48.76624  
 5 -18.05097 5 46.10194  
  
  
 Additive constant for all log-likelihoods = -44.11. This constant added to the  
 above values gives the log-likelihood including the term that does not  
 depend on the model parameters.  
  
  
 Explanation of Tests  
  
 Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)  
 Test 2: Are Variances Homogeneous? (A2 vs. A1)  
 Test 3: Are variances adequately modeled? (A2 vs. A3)  
  
 Test 7a: Does Model 5 fit the data? (A3 vs 5)  
  
  
 Tests of Interest  
  
 Test -2\*log(Likelihood Ratio) D. F. p-value  
 -------- ------------------------ ------ --------------  
 Test 1 29.45 18 0.04314  
 Test 2 11.2 9 0.2625  
 Test 3 11.2 9 0.2625  
 Test 7a 9.591 6 0.143  
  
  
 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 7a is greater than .1. Model 5 seems  
 to adequately describe the data.  
  
  
 Benchmark Dose Computations:  
  
 Specified Effect = 1.000000  
  
 Risk Type = Estimated standard deviations from control  
  
 Confidence Level = 0.950000  
  
 BMD = 142.469  
  
 BMDL = 57.7463  
  
 BMDU = 4.75e+006

# Male BMD Results for Table: Thyroid Stimulating Hormone

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 0.07 | 0.2 | 0.7 | 2 | 6 | 18 | 55 | 160 | 475 |
| N | 9 | 4 | 4 | 4 | 4 | 4 | 4 | 5 | 5 | 5 |
| Mean ± SD | 4.5 ± 2.001 | 3.275 ± 1.735 | 2.725 ± 1.204 | 4.05 ± 2.011 | 3.425 ± 1.613 | 5.4 ± 2.317 | 6.8 ± 3.058 | 12.48 ± 4.847 | 5.76 ± 1.935 | 11.56 ± 5.11 |

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linearb (equivalent models include Power, Polynomial 2°, 3°, 4°, 5°, 6°, 7°, 8°) | <0.0001 | 175.161 | 138.723 | 20.376 | Linear recommended as best-fitting model on the basis of the lowest BMDL. |
| Hill | 0.005 | 150.239 | 9.382 | 4.195 |
| Exponential M2 (equivalent models include Exponential M3) | <0.0001 | 177.709 | 274.775 | 183.257 |
| Exponential M4 | 0.007 | 149.081 | 7.502 | 3.519 |
| Exponential M5 | 0.006 | 149.7 | 10.678 | 4.426 |

a Modeled variance case presented (BMDS Test 2 p-value = 0.014, BMDS Test 3 p-value = 0.999).

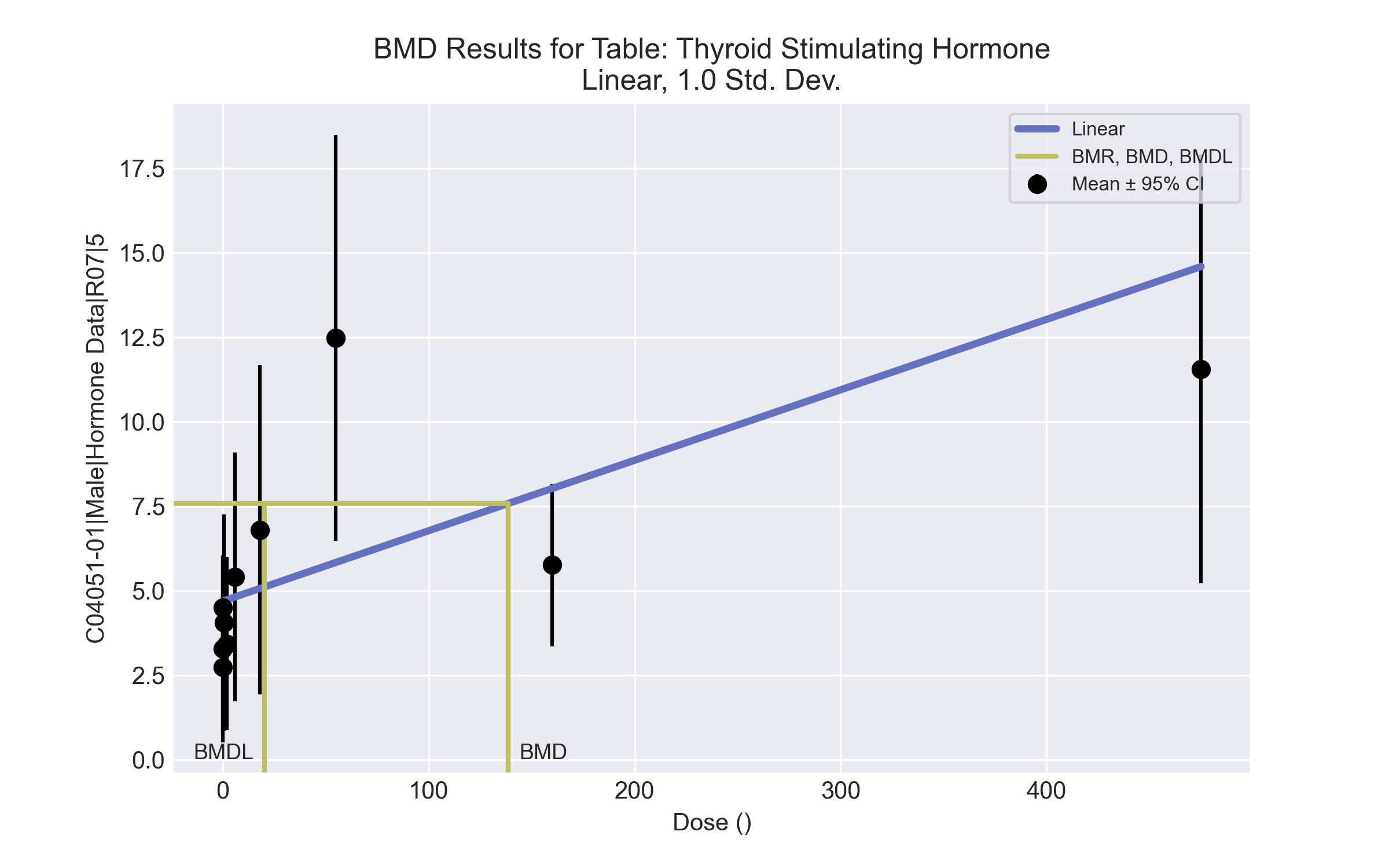
b Recommended model

## Model recommendation details

|  |  |  |
| --- | --- | --- |
| Model | Bin | Notes |
| Lineara (equivalent models include Power, Polynomial 2°, 3°, 4°, 5°, 6°, 7°, 8°) | Valid | **Cautions**  • BMD/BMDL ratio is greater than threshold (6.81 > 5.0) |
| Hill | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.00483 < 0.1) |
| Exponential M2 (equivalent models include Exponential M3) | Valid | - |
| Exponential M4 | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.00682 < 0.1) |
| Exponential M5 | Warning | **Warnings**  • Goodness of fit p-value is less than threshold (0.006 < 0.1) |

a Recommended model

## Recommended model



====================================================================   
 Polynomial Model. (Version: 2.21; Date: 03/14/2017)   
 Input Data File: C:\Windows\TEMP\bmds-wyu1dkx8.(d)   
 Gnuplot Plotting File: C:\Windows\TEMP\bmds-wyu1dkx8.plt  
 Tue Apr 13 09:27:37 2021  
 ====================================================================   
  
 BMDS\_Model\_Run   
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~  
   
 The form of the response function is:   
  
 Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ...  
  
  
 Dependent variable = Response  
 Independent variable = Dose  
 The polynomial coefficients are restricted to be positive  
 The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) \* rho)  
  
 Total number of dose groups = 10  
 Total number of records with missing values = 0  
 Maximum number of iterations = 500  
 Relative Function Convergence has been set to: 1e-008  
 Parameter Convergence has been set to: 1e-008  
  
  
  
 Default Initial Parameter Values   
 lalpha = 2.13971  
 rho = 0  
 beta\_0 = 4.95165  
 beta\_1 = 0  
  
  
 Asymptotic Correlation Matrix of Parameter Estimates  
  
 lalpha rho beta\_0 beta\_1  
  
 lalpha 1 -0.99 0.037 -0.4  
  
 rho -0.99 1 -0.046 0.42  
  
 beta\_0 0.037 -0.046 1 -0.28  
  
 beta\_1 -0.4 0.42 -0.28 1  
  
  
  
 Parameter Estimates  
  
 95.0% Wald Confidence Interval  
 Variable Estimate Std. Err. Lower Conf. Limit Upper Conf. Limit  
 lalpha -0.546647 1.57813 -3.63973 2.54643  
 rho 1.72954 0.89955 -0.0335498 3.49262  
 beta\_0 4.68593 0.483509 3.73827 5.63359  
 beta\_1 0.020856 0.00694542 0.00724324 0.0344688  
  
  
  
 Table of Data and Estimated Values of Interest  
  
 Dose N Obs Mean Est Mean Obs Std Dev Est Std Dev Scaled Res.  
------ --- -------- -------- ----------- ----------- ----------  
  
 0 9 4.5 4.69 2 2.89 -0.193  
 0.07 4 3.27 4.69 1.73 2.89 -0.976  
 0.2 4 2.73 4.69 1.2 2.9 -1.36  
 0.7 4 4.05 4.7 2.01 2.9 -0.448  
 2 4 3.42 4.73 1.61 2.92 -0.894  
 6 4 5.4 4.81 2.32 2.96 0.398  
 18 4 6.8 5.06 3.06 3.09 1.12  
 55 5 12.5 5.83 4.85 3.5 4.25  
 160 5 5.76 8.02 1.93 4.61 -1.1  
 475 5 11.6 14.6 5.11 7.73 -0.878  
  
  
  
 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 -69.746250 11 161.492500  
 A2 -59.419402 20 158.838804  
 A3 -59.801919 12 143.603837  
 fitted -83.580438 4 175.160876  
 R -92.286909 2 188.573817  
  
  
 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 65.735 18 <.0001  
 Test 2 20.6537 9 0.01428  
 Test 3 0.765033 8 0.9993  
 Test 4 47.557 8 <.0001  
  
The p-value for Test 1 is less than .05. There appears to be a  
difference between response and/or variances among the dose levels  
It seems appropriate to model the data  
  
The p-value for Test 2 is less than .1. A non-homogeneous variance   
model appears to be appropriate  
  
The p-value for Test 3 is greater than .1. The modeled variance appears   
 to be appropriate here  
  
The p-value for Test 4 is less than .1. You may want to try a different   
model  
   
  
 Benchmark Dose Computation  
  
Specified effect = 1  
  
Risk Type = Estimated standard deviations from the control mean  
  
Confidence level = 0.95  
  
 BMD = 138.723  
  
  
 BMDL = 20.3764  
  
  
 BMDU = 359.799

# Male BMD Results for Table: Triiodothyronine

BMDS version: BMDS v2.7.0

## Input dataset

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Dose | 0 | 0.07 | 0.2 | 0.7 | 2 | 6 | 18 | 55 | 160 | 475 |
| N | 9 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 5 | 5 |
| Mean ± SD | 47.989 ± 6.689 | 47.45 ± 7.953 | 51.25 ± 2.031 | 48.025 ± 5.934 | 42.975 ± 3.478 | 51.75 ± 4.605 | 50.825 ± 4.984 | 45.9 ± 6.139 | 40.6 ± 4.03 | 39.74 ± 2.967 |

## Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Modela | Goodness of fit | | BMD | BMDL | Comments |
| *p*-value | AIC |
| Linear (equivalent models include Power, Polynomial 2°, 3°, 4°, 5°, 6°, 8°) | 0.103 | 212.404 | 267.551 | 181.943 | Hill recommended as best-fitting model on the basis of the lowest BMDL. |
| Polynomial 7° | 0.103 | 212.404 | 267.55 | 181.943 |
| Hillb | 0.167 | 212.269 | 76.524 | 42.495 |
| Exponential M2 (equivalent models include Exponential M3) | 0.114 | 212.074 | 247.938 | 161.19 |
| Exponential M4 | 0.156 | 211.768 | 109.275 | 43.172 |
| Exponential M5 | 0.167 | 212.275 | 58.757 | 45.513 |

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

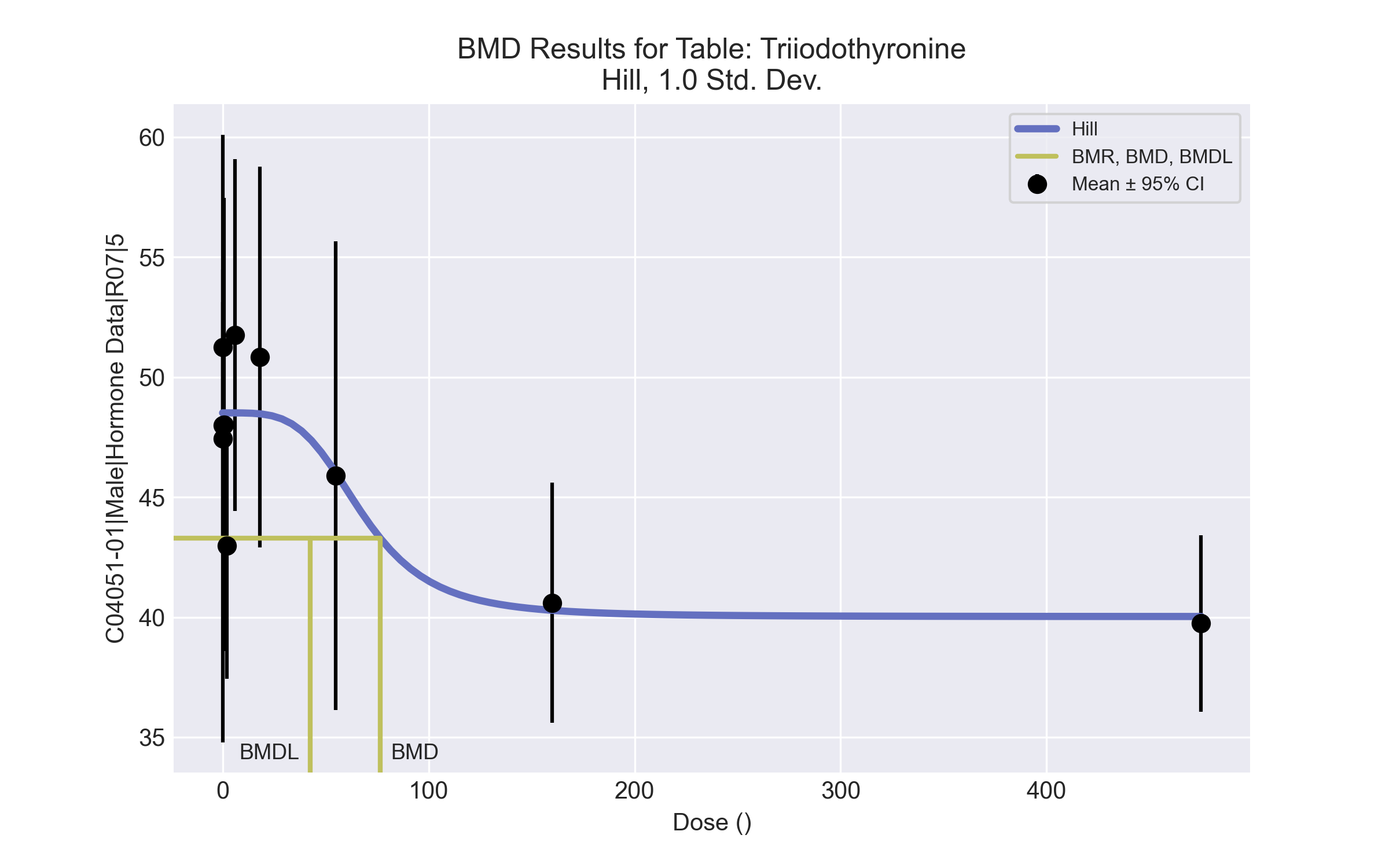
b Recommended model

## Model recommendation details

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

a Recommended model

## Recommended model



====================================================================   
 Hill Model. (Version: 2.18; Date: 03/14/2017)   
 Input Data File: C:\Windows\TEMP\bmds-szfx65yj.(d)   
 Gnuplot Plotting File: C:\Windows\TEMP\bmds-szfx65yj.plt  
 Tue Apr 13 09:27:40 2021  
 ====================================================================   
  
 BMDS\_Model\_Run   
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~  
   
 The form of the response function is:   
  
 Y[dose] = intercept + v\*dose^n/(k^n + dose^n)  
  
  
 Dependent variable = Response  
 Independent variable = Dose  
 rho is set to 0  
 Power parameter restricted to be greater than 1  
 A constant variance model is fit  
  
 Total number of dose groups = 10  
 Total number of records with missing values = 0  
 Maximum number of iterations = 500  
 Relative Function Convergence has been set to: 1e-008  
 Parameter Convergence has been set to: 1e-008  
  
  
  
 Default Initial Parameter Values   
 alpha = 28.4679  
 rho = 0 Specified  
 intercept = 47.9889  
 v = -8.24889  
 n = 1.22627  
 k = 1.77103  
  
  
 Asymptotic Correlation Matrix of Parameter Estimates  
  
 ( \*\*\* The model parameter(s) -rho   
 have been estimated at a boundary point, or have been specified by the user,  
 and do not appear in the correlation matrix )  
  
 alpha intercept v n k  
  
 alpha 1 -2.3e-008 2.9e-008 6.4e-008 -4.7e-008  
  
 intercept -2.3e-008 1 -0.29 0.049 -0.14  
  
 v 2.9e-008 -0.29 1 0.7 -0.68  
  
 n 6.4e-008 0.049 0.7 1 -0.91  
  
 k -4.7e-008 -0.14 -0.68 -0.91 1  
  
  
  
 Parameter Estimates  
  
 95.0% Wald Confidence Interval  
 Variable Estimate Std. Err. Lower Conf. Limit Upper Conf. Limit  
 alpha 27.2102 5.61304 16.2089 38.2115  
 intercept 48.5108 0.911925 46.7235 50.2982  
 v -8.48535 2.70003 -13.7773 -3.1934  
 n 4.05187 12.092 -19.648 27.7517  
 k 68.1879 65.9871 -61.1444 197.52  
  
  
  
 Table of Data and Estimated Values of Interest  
  
 Dose N Obs Mean Est Mean Obs Std Dev Est Std Dev Scaled Res.  
------ --- -------- -------- ----------- ----------- ----------  
  
 0 9 48 48.5 6.69 5.22 -0.3  
 0.07 4 47.5 48.5 7.95 5.22 -0.407  
 0.2 4 51.3 48.5 2.03 5.22 1.05  
 0.7 4 48 48.5 5.93 5.22 -0.186  
 2 4 43 48.5 3.48 5.22 -2.12  
 6 4 51.8 48.5 4.6 5.22 1.24  
 18 4 50.8 48.5 4.98 5.22 0.902  
 55 4 45.9 46 6.14 5.22 -0.041  
 160 5 40.6 40.3 4.03 5.22 0.135  
 475 5 39.7 40 2.97 5.22 -0.124  
  
  
  
 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 -96.574389 11 215.148778  
 A2 -90.364749 20 220.729498  
 A3 -96.574389 11 215.148778  
 fitted -101.134412 5 212.268823  
 R -109.363943 2 222.727886  
  
  
 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 37.9984 18 0.003875  
 Test 2 12.4193 9 0.1907  
 Test 3 12.4193 9 0.1907  
 Test 4 9.12005 6 0.1669  
  
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 = 76.5236  
  
 BMDL = 42.4946  
  
 BMDU = 241.026