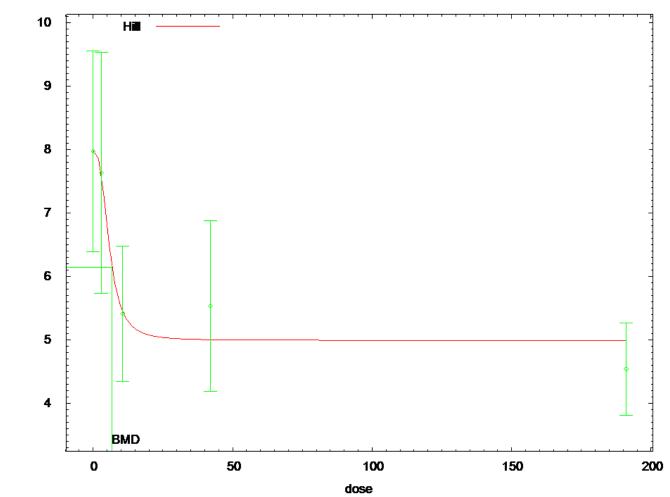
# **Appendix A**

**Benchmark Dose Modeling Output** 

BMDS Model Results for White Blood Cell Count (Untransformed Doses, Concurrent Controls)



12:14 06/21 2014

Mean Response

Hill Model

=== Hill Model. (Version: 2.17; Date: 01/28/2013) Input Data File: C:/Users/dmayfield/Desktop/Norm/WBC\_Concurrent-HLS 2001-White Blood Cell Count-HillCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Norm/WBC\_Concurrent-HLS 2001-White Blood Cell Count-HillCV-1SD-5d.plt Sat Jun 21 12:14:46 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = intercept + v\*dose^n/(k^n + dose^n) Dependent variable = MeanResponse 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 = 5Total 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 = 3.64969 Specified rho = 0 7.97 intercept = v = -3.43 n = 2.04485 k = 7.66914 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 )

and do not appear	in t	the	correlation	matrix	)
-------------------	------	-----	-------------	--------	---

k		alpha	intercept	v	n
al 1.5e-00	pha 06	1	-1.1e-006	-5.8e-007	-5e-008
interc -0.5	ept	-1.1e-006	1	-0.81	-0.48
0.17	v	-5.8e-007	-0.81	1	0.59
0.094	n	-5e-008	-0.48	0.59	1
1	k	1.5e-006	-0.5	0.17	0.094

# Parameter Estimates

			95.0%
Wald Confidence In	terval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Conf	. Limit		
alpha	3.36457	0.686789	
2.01848	4.71065		
intercept	7.98132	0.579373	
6.84577	9.11687		
v	-2.98857	0.748734	-
4.45606	-1.52107		
n	2.86103	2.49408	-
2.02726	7.74933		
k	5.76726	3.11705	_
0.342045	11.8766		

# Table of Data and Estimated Values of Interest

Dose Scaled R		Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 -0.0195	10	7.97	7.98	2.21	1.83

2.9	10	7.63	7.61	2.65	1.83
0.0266		E 44		1 00	1 0 0
10.6	9	5.41	5.44	1.39	1.83
-0.0465	0		-	1 86	1 0 0
42	9	5.53	5	1.76	1.83
0.862					
191.1	10	4.54	4.99	1.02	1.83
-0.781					

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
Al	-52.431420	6	116.862840
A2	-47.292184	10	114.584369
A3	-52.431420	б	116.862840
fitted	-53.119185	5	116.238371
R	-63.201706	2	130.403412

# Explanation of Tests

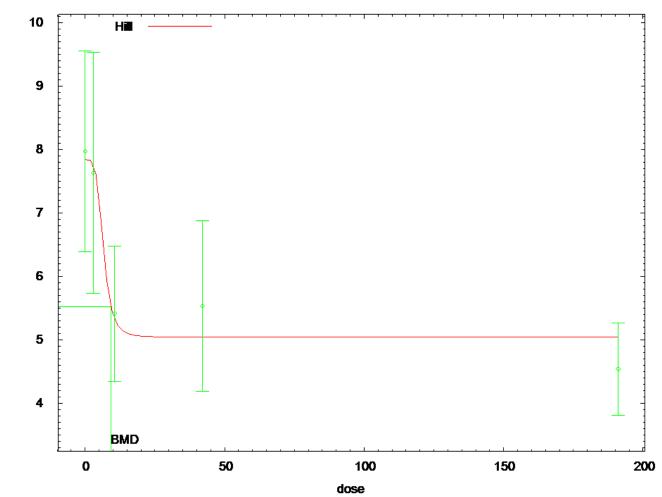
## Tests of Interest

Test	-2*log(Likelihood Ra	tio) Test df	p-value
TCDC	a rea(minerineed na	CIO, ICDC GI	p varac

3

31.819 8 4 Test 1 0.0001004 Test 2 10.2785 0.03599 Test 3 10.2785 4 0.03599 1 Test 4 1.37553 0.2409 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. Consider running a non-homogeneous variance model The p-value for Test 3 is less than .1. You may want to consider а different variance model 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 = Estimated standard deviations from the Risk Type control mean Confidence level = 0.95 BMD = 6.78072

BMDL computation failed.



12:14 06/21 2014

Mean Response

Hill Model

=== Hill Model. (Version: 2.17; Date: 01/28/2013) Input Data File: C:/Users/dmayfield/Desktop/Norm/WBC\_Concurrent-HLS 2001-White Blood Cell Count-HillNCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Norm/WBC\_Concurrent-HLS 2001-White Blood Cell Count-HillNCV-1SD-5d.plt Sat Jun 21 12:14:47 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = intercept + v\*dose^n/(k^n + dose^n) Dependent variable = MeanResponse Independent variable = Dose Power parameter restricted to be greater than 1 The variance is to be modeled as Var(i) = exp(lalpha + rho \* ln(mean(i))) Total number of dose groups = 5Total number of records with missing values = 0Maximum 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 = 1.29464 rho = 0 7.97 intercept = -3.43 v = n = 2.04485 k = 7.66914 Asymptotic Correlation Matrix of Parameter Estimates lalpha rho intercept v

n	k			
lalpha -0.13	1 -0.095	-0.99	0.3	-0.39
rho 0.13	-0.99 0.095	1	-0.32	0.4
intercept -0.67	0.3-0.67	-0.32	1	-0.92
v 0.66	-0.39 0.59	0.4	-0.92	1
n 1 0	-0.13	0.13	-0.67	0.66
k 0.93	-0.095 1	0.095	-0.67	0.59

Parameter Estimates

				95.0%
Wald Confider	nce Interv	al		
Variak	ole	Estimate	Std. Err.	Lower Conf.
Limit Upper	Conf. Li	mit		
lalp	oha	-3.20747	1.98544	_
7.09886	0.6	83917		
l	cho	2.3751	1.09133	
0.236133	4	.51407		
interce	ept	7.84141	0.710303	
6.44924	9.	23357		
	v	-2.7994	0.803986	_
4.37518	-1.	22362		
	n	4.58295	11.6557	-
18.2617	27	.4276		
	k	6.55959	7.97954	_
9.08003	22	.1992		

Table of Data and Estimated Values of Interest

Dose Scaled R	N es.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 0.175	10	7.97	7.84	2.21	2.32

2.9	10	7.63	7.78	2.65	2.3
-0.202 10.6	9	5.41	5.32	1.39	1.46
0.182	-	•••			
42 1.06	9	5.53	5.04	1.76	1.37
191.1 -1.16	10	4.54	5.04	1.02	1.37

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
Al	-52.431420	6	116.862840
A2	-47.292184	10	114.584369
A3	-47.758770	7	109.517540
fitted	-50.207108	6	112.414215
R	-63.201706	2	130.403412

# 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.)	

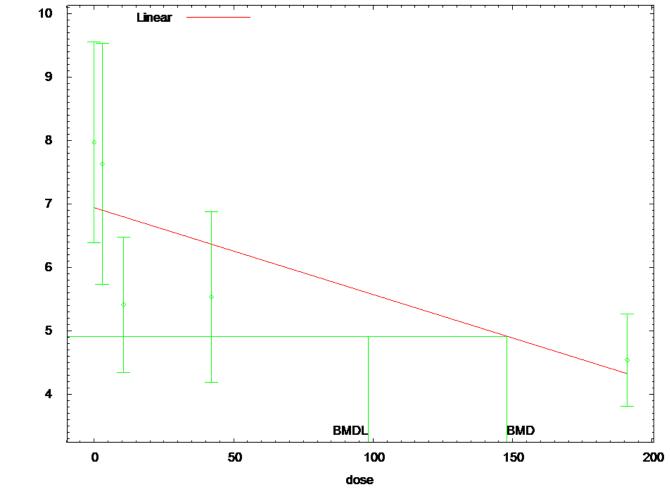
## Tests of Interest

Test	-2*log(Likelihood Rat	io) Test	df p-value
ICBC	z iog(hikerinood kac	IO, ICBC	ur p varue

Test 131.81980.0001004Test 210.278540.03599Test 30.93317130.8174Test 44.8966810.02691

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 = Estimated standard deviations from the Risk Type control mean Confidence level = 0.95 BMD = 9.25758

BMDL computation failed.



# Linear Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

12:51 07/09 2014

Mean Response

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_WBC\_Concurrent/WBC\_Concurrent-HLS 2001-White Blood Cell Count-LinearCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_WBC\_Concurrent/WBC\_Concurrent-HLS 2001-White Blood Cell Count-LinearCV-1SD-5d.plt Wed Jul 09 12:51:15 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse Independent variable = Dose rho is set to 0 Signs of the polynomial coefficients are not restricted A constant variance model is fit Total number of dose groups = 5Total number of records with missing values = 0Maximum 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 = 3.64969 rho = rho = 0 beta\_0 = 6.88046 beta\_1 = -0.0134724 0 Specified 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	6e-008	-3.1e-008
beta_0	6e-008	1	-0.56
beta_1	-3.1e-008	-0.56	1

# Parameter Estimates

			95.0%
Wald Confidence	Interval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Con	nf. Limit		
alpha	4.10153	0.83722	
2.4606	5.74245		
beta_0	6.93587	0.35384	
6.24236	7.62939		
beta_1	-0.0136993	0.00396554	-
0.0214716	-0.00592698		

Table of Data and Estimated Values of Interest

Dose Scaled	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0	10	7.97	6.94	2.21	2.03
1.61					
2.9 1.15	10	7.63	6.9	2.65	2.03
10.6 -2.05	9	5.41	6.79	1.39	2.03
-2.05 42	9	5.53	6.36	1.76	2.03
-1.23					
191.1 0.347	10	4.54	4.32	1.02	2.03

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
Al	-52.431420	6	116.862840
A2	-47.292184	10	114.584369
A3	-52.431420	6	116.862840
fitted	-57.872613	3	121.745227
R	-63.201706	2	130.403412

## 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	31.819	8	0.0001004
Test 2	10.2785	4	0.03599
Test 3	10.2785	4	0.03599
Test 4	10.8824	3	0.01238

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. Consider running a non-homogeneous variance model

The p-value for Test 3 is less than .1. You may want to consider a

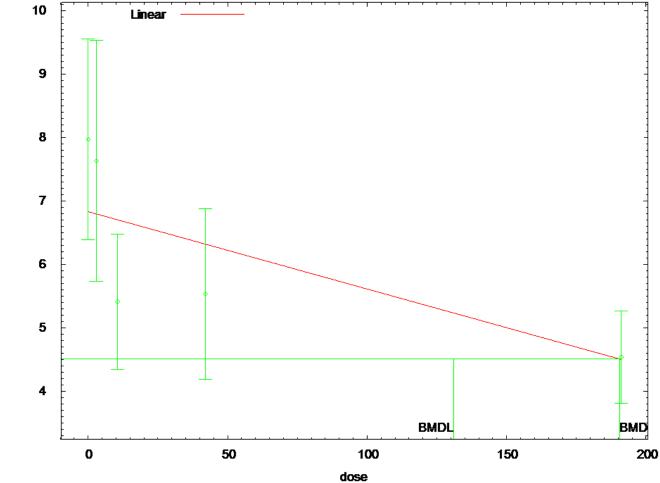
different variance model

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 = 147.834

BMDL = 98.2036



# Linear Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

12:51 07/09 2014

Mean Response

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_WBC\_Concurrent/WBC\_Concurrent-HLS 2001-White Blood Cell Count-LinearNCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_WBC\_Concurrent/WBC\_Concurrent-HLS 2001-White Blood Cell Count-LinearNCV-1SD-5d.plt Wed Jul 09 12:51:16 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse Independent variable = Dose Signs of the polynomial coefficients are not restricted The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) \* rho) Total number of dose groups = 5Total number of records with missing values = 0Maximum 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 = 1.29464 rho = 0 beta\_0 = 6.88046  $beta_1 = -0.0134724$ Asymptotic Correlation Matrix of Parameter Estimates beta\_0 lalpha beta 1 rho -1 0.059 -0.074lalpha 1

rho	-1	1	-0.059	0.075
beta_0	0.059	-0.059	1	-0.81
beta_1	-0.074	0.075	-0.81	1

Parameter Estimates

# 95.0%

Wald Confidence	Interval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Co	nf. Limit		
lalpha	-6.51621	2.25638	-
10.9386	-2.09378		
rho	4.27037	1.23797	
1.84399	6.69675		
beta_0	6.83277	0.388873	
6.07059	7.59495		
beta_1	-0.0122267	0.00266203	_
0.0174442	-0.00700924		

Table of Data and Estimated Values of Interest

Dose Scaled	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0	10	7.97	6.83	2.21	2.33
1.54 2.9 1.14	10	7.63	б.8	2.65	2.3
10.6 -1.74	9	5.41	6.7	1.39	2.24
42	9	5.53	6.32	1.76	1.97
191.1 0.145	10	4.54	4.5	1.02	0.953

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<sup>2</sup>

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
Al	-52.431420	б	116.862840
A2	-47.292184	10	114.584369
A3	-47.758770	7	109.517540
fitted	-53.651165	4	115.302330
R	-63.201706	2	130.403412

#### Explanation of Tests

#### Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.819	8	0.0001004
Test 2	10.2785	4	0.03599
Test 3	0.933171	3	0.8174
Test 4	11.7848	3	0.008158

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

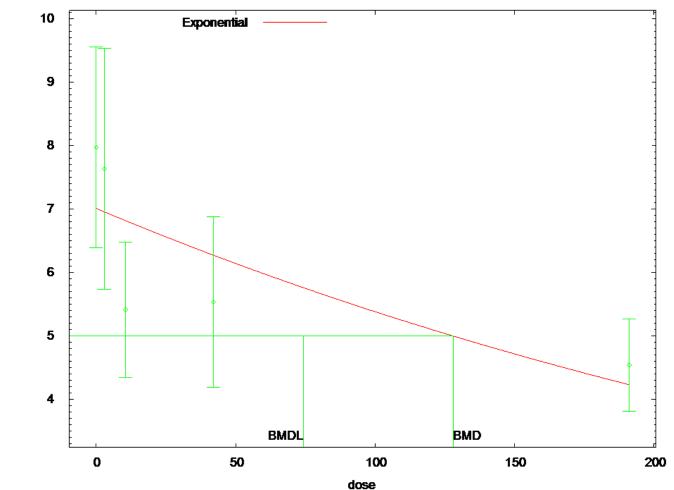
Benchmark Dose Computation

Specified effect = 1 Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 190.429

BMDL = 131.056



# Exponential Model 2, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Level for BMDL

12:14 06/21 2014

Mean Response

=== Exponential Model. (Version: 1.9; Date: 01/29/2013) Input Data File: C:/Users/dmayfield/Desktop/Norm/WBC\_Concurrent-HLS 2001-White Blood Cell Count-ExpCV-1SD-5d.(d) Gnuplot Plotting File: Sat Jun 21 12:14:45 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function by Model: Model 2:  $Y[dose] = a * exp{sign * b * dose}$  $Y[dose] = a * exp\{sign * (b * dose)^d\}$ Model 3:  $Y[dose] = a * [c-(c-1) * exp{-b * dose}]$ Model 4:  $Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]$ Model 5: 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 = MeanResponse 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 = 5Total 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	1.18464
rho(S)	0
a	5.42664
b	0.00232433
C	0
d	1

(S) = Specified

#### Parameter Estimates

Variable	Model 2
lnalpha	1.39884
rho	0
a	7.00671
b	0.00264475
C	0
d	1

# Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	10	7.97	2.213
2.9	10	7.63	2.653
10.6	9	5.41	1.392
42	9	5.53	1.756
191.1	10	4.54	1.019

# Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	7.007	2.013	1.514
2.9	6.953	2.013	1.063
10.6	6.813	2.013	-2.091
42	6.27	2.013	-1.103
191.1	4.227	2.013	0.492

Other models for which likelihoods are calculated:

Model Al: Yij = Mu(i) + e(ij) Var{e(ij)} = Sigma^2

Model A2:	Yij = Var{e(ij)} =	Mu(i) + e(ij) Sigma(i)^2
Model A3:		Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R:	Yij = Var{e(ij)} =	

Likelihoods of Interest

AIC	Model	Log(likelihood)	DF
ALC			
116 0600	A1	-52.43142	6
116.8628	A2	-47.29218	10
114.5844	A3	-52.43142	6
116.8628	R	-63.20171	2
130.4034	2	-57.57205	3
121.1441			

Additive constant for all log-likelihoods = -44.11. This constant added to the above values gives the log-likelihood including the term that does not

depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A2 vs. A1) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 4: Does Model 2 fit the data? (A3 vs. 2)

Tests of Interest

Test p-value	-2*log(Likelihood Ratio)	D. F.
Test 1	31.82	8

0.0001004			
Test	2	10.28	4
0.03599			
Test	3	10.28	4
0.03599			
Test	4	10.28	3
0.01632			

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. Consider running a non-homogeneous variance model.

The p-value for Test 3 is less than .1. You may want to consider a different variance model.

The p-value for Test 4 is less than .1. Model 2 may not adequately

describe the data; you may want to consider another model.

Benchmark Dose Computations:

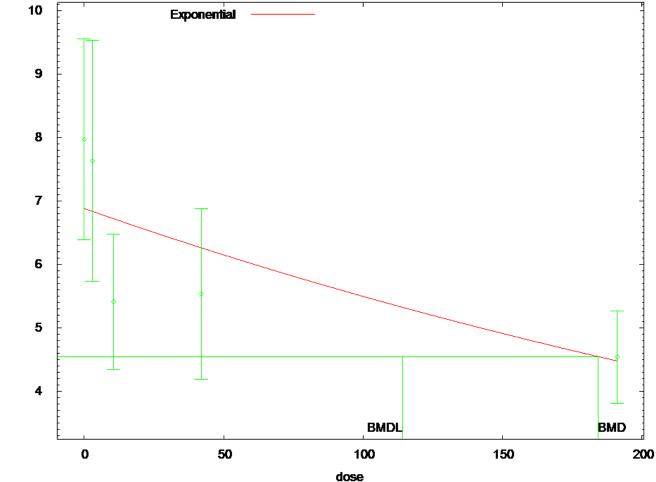
Specified Effect = 1.000000

Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

BMD = 128.029

BMDL = 74.2476



# Exponential Model 2, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Level for BMDL

12:14 06/21 2014

Mean Response

```
______
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Norm/WBC_Concurrent-HLS 2001-White
Blood Cell Count-ExpNCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sat Jun 21 12:14:46 2014
_____
===
BMDS Model Run
~~~~
  The form of the response function by Model:
     Model 2:
                Y[dose] = a * exp{sign * b * dose}
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
     Model 4:
                Y[dose] = a * [c-(c-1) * exp{-b * dose}]
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  The variance is to be modeled as Var(i) = exp(lalpha + log
(mean(i)) * rho)
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 2
lnalpha	-4.23146
rho	2.9407
a	5.42664
b	0.00232433
С	0
d	1

#### Parameter Estimates

Variable	Model 2
lnalpha	-6.33358
rho	4.16316
a	6.87983
b	0.00225038
С	0
d	1

# Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	10	7.97	2.213
2.9	10	7.63	2.653
10.6	9	5.41	1.392
42	9	5.53	1.756
191.1	10	4.54	1.019

# Estimated Values of Interest

Est Mean	Est Std	Scaled Residual
6.88	2.334	1.477
6.835	2.303	1.092
6.718	2.221	-1.766
6.259	1.917	-1.141
4.475	0.9537	0.2149
	6.88 6.835 6.718 6.259	6.882.3346.8352.3036.7182.2216.2591.917

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) <sup>2</sup>
Model A3:		Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R:	Yij = Var{e(ij)} =	

	Likelihoods of Int	erest
Model	Log(likelihood)	DF
Al	-52.43142	б
A2	-47.29218	10
۵З	-47 75877	7
		·
R	-63.20171	2
2	-53.3862	4
	A1 A2 A3 R	A1 -52.43142 A2 -47.29218 A3 -47.75877 R -63.20171

Additive constant for all log-likelihoods = -44.11. This constant added to the above values gives the log-likelihood including the term that

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 p-value	-2*log(Likelihood Ratio)	D. F.
Test 1	31.82	8
0.0001004		
Test 2	10.28	4

0.03599 Test 3 0.8174 Test 4 0.01042		0.9332 11.25	3 3	
be a	The p-value for Test 1 is	less than .05.	There appears to	
De 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 variance model appears to		non-homogeneous	
	The p-value for Test 3 is variance appears to be app	-	The modeled	
adeqı	The p-value for Test 4 is uately describe the data; you may		_	

Benchmark Dose Computations:

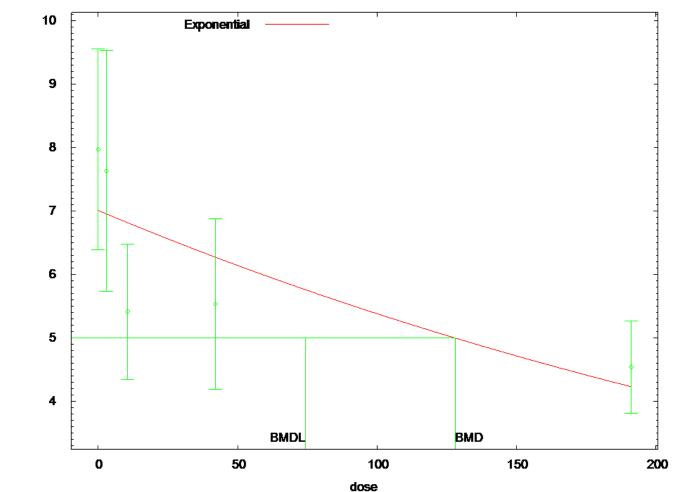
Specified Effect = 1.000000

Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

BMD = 184.175

BMDL = 114.201



Exponential Model 3, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Level for BMDL

Mean Response

12:14 06/21 2014

=== Exponential Model. (Version: 1.9; Date: 01/29/2013) Input Data File: C:/Users/dmayfield/Desktop/Norm/WBC\_Concurrent-HLS 2001-White Blood Cell Count-ExpCV-1SD-5d.(d) Gnuplot Plotting File: Sat Jun 21 12:14:45 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function by Model: Model 2:  $Y[dose] = a * exp{sign * b * dose}$  $Y[dose] = a * exp\{sign * (b * dose)^d\}$ Model 3:  $Y[dose] = a * [c-(c-1) * exp{-b * dose}]$ Model 4:  $Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]$ Model 5: 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 = MeanResponse 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 = 5Total 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 3
lnalpha	1.18464
rho(S)	0
a	5.42664
b	0.00232433
C	0
d	1

(S) = Specified

#### Parameter Estimates

Variable	Model 3
lnalpha	1.39884
rho	0
a	7.00671
b	0.00264475
С	0
d	1

# Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	10	7.97	2.213
2.9	10	7.63	2.653
10.6	9	5.41	1.392
42	9	5.53	1.756
191.1	10	4.54	1.019

# Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	7.007	2.013	1.514
2.9	6.953	2.013	1.063
10.6	6.813	2.013	-2.091
42	6.27	2.013	-1.103
191.1	4.227	2.013	0.492

Other models for which likelihoods are calculated:

Model Al: Yij = Mu(i) + e(ij) Var{e(ij)} = Sigma^2

Model A2:	Yij = Var{e(ij)} =	Mu(i) + e(ij) Sigma(i)^2
Model A3:		Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R:	Yij = Var{e(ij)} =	

Likelihoods of Interest

AIC	Model	Log(likelihood)	DF
ALC			
	Al	-52.43142	б
116.8628	A2	-47.29218	10
114.5844	A3	-52.43142	6
116.8628	R	-63.20171	2
130.4034	3	-57.57205	3
121.1441	5	57.57205	5

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

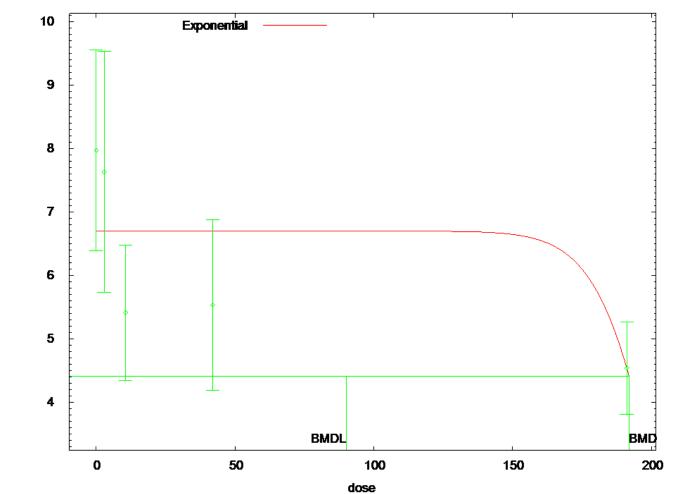
Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A2 vs. A1) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 5a: Does Model 3 fit the data? (A3 vs 3)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.
p-value		

Test 1 0.0001004	31.82	8
Test 2	10.28	4
0.03599 Test 3	10.28	4
0.03599 Test 5a	10.28	3
0.01632	10.10	5

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. Consider running a non-homogeneous variance model. The p-value for Test 3 is less than .1. You may want to consider a different variance model. The p-value for Test 5a is less than .1. Model 3 may not adequately describe the data; you may want to consider another model. Benchmark Dose Computations: Specified Effect = 1.000000 Risk Type = Estimated standard deviations from control Confidence Level = 0.950000BMD = 128.029 BMDL = 74.2476



Exponential Model 3, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Level for BMDL

12:14 06/21 2014

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______
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Norm/WBC_Concurrent-HLS 2001-White
Blood Cell Count-ExpNCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sat Jun 21 12:14:46 2014
_____
===
BMDS Model Run
~~~~
  The form of the response function by Model:
     Model 2:
                Y[dose] = a * exp{sign * b * dose}
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
     Model 4:
                Y[dose] = a * [c-(c-1) * exp{-b * dose}]
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  The variance is to be modeled as Var(i) = exp(lalpha + log
(mean(i)) * rho)
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 3
lnalpha	-4.23146
rho	2.9407
a	5.42664
b	0.00232433
С	0
d	1

## Parameter Estimates

Variable	Model 3
lnalpha	-6.79001
rho	4.44324
a	6.69632
b	0.00493533
С	0
d	16.145

# Table of Stats From Input Data

Dose	Ν	Obs Mean	Obs Std Dev
0	10	7.97	2.213
2.9	10	7.63	2.653
10.6	9	5.41	1.392
42	9	5.53	1.756
191.1	10	4.54	1.019

## Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	6.696	2.292	1.757
2.9	6.696	2.292	1.288
10.6	6.696	2.292	-1.683
42	6.696	2.292	-1.526
191.1	4.54	0.9667	-4.057e-007

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:			Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R:	Yij = Var{e(ij)} =		

		Likelihoods of Int	erest
	Model	Log(likelihood)	DF
AIC			
	Al	-52.43142	б
116.8628		45.00010	1.0
114.5844	A2	-47.29218	10
	A3	-47.75877	7
109.5175	R	-63.20171	2
130.4034	2		-
120.3671	3	-55.18356	5

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 5a: Does Model 3 fit the data? (A3 vs 3)

### Tests of Interest

Test p-value	-2*log(Likelihood Ratio)	D. F.
Test 1 0.0001004	31.82	8

Test 2 0.03599	10.28	4
Test 3	0.9332	3
0.8174		
Test 5a	14.85	2
0.0005963		

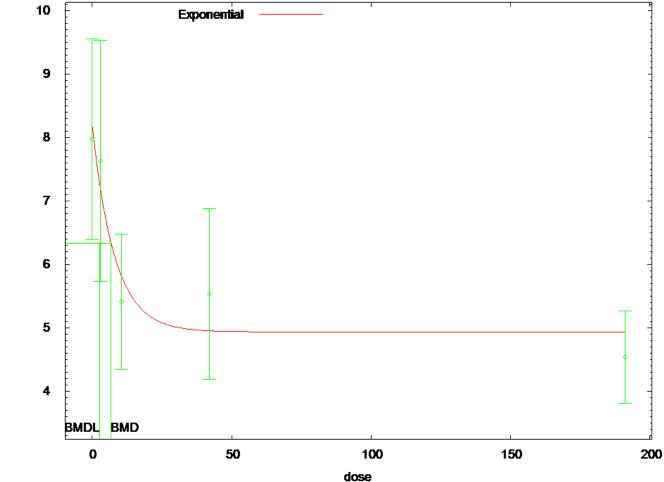
The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data. The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate. The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here. The p-value for Test 5a is less than .1. Model 3 may not adequately describe the data; you may want to consider another model. Benchmark Dose Computations: Specified Effect = 1.000000 Risk Type = Estimated standard deviations from

control

Confidence Level = 0.950000

BMD = 191.993

BMDL = 90.1184



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Mean Response

=== Exponential Model. (Version: 1.9; Date: 01/29/2013) Input Data File: C:/Users/dmayfield/Desktop/Norm/WBC\_Concurrent-HLS 2001-White Blood Cell Count-ExpCV-1SD-5d.(d) Gnuplot Plotting File: Sat Jun 21 12:14:45 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function by Model: Model 2:  $Y[dose] = a * exp{sign * b * dose}$  $Y[dose] = a * exp\{sign * (b * dose)^d\}$ Model 3:  $Y[dose] = a * [c-(c-1) * exp{-b * dose}]$ Model 4:  $Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]$ Model 5: 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 = MeanResponse 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 = 5Total number of records with missing values = 0 Maximum number of iterations = 500 Relative Function Convergence has been set to: 1e-008 Parameter Convergence has been set to: 1e-008 MLE solution provided: Exact Initial Parameter Values

Variable	Model 4
lnalpha	1.18464
rho(S)	0
a	8.3685
b	0.0162762
C	0.516677
d	1

(S) = Specified

### Parameter Estimates

Variable	Model 4
lnalpha	1.23597
rho	0
a	8.1813
b	0.124602
С	0.602967
d	1

# Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	10	7.97	2.213
2.9	10	7.63	2.653
10.6	9	5.41	1.392
42	9	5.53	1.756
191.1	10	4.54	1.019

# Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	8.181	1.855	-0.3602
2.9	7.196	1.855	0.7394
10.6	5.8	1.855	-0.6308
42	4.95	1.855	0.9373
191.1	4.933	1.855	-0.67

Other models for which likelihoods are calculated:

Model Al: Yij = Mu(i) + e(ij) Var{e(ij)} = Sigma^2

Model A2:	Yij = Var{e(ij)} =	Mu(i) + e(ij) Sigma(i)^2
Model A3:		Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R:	Yij = Var{e(ij)} =	

Likelihoods of Interest

AIC	Model	Log(likelihood)	DF
ALC			
	Al	-52.43142	6
116.8628	A2	-47.29218	10
114.5844	A3	-52.43142	6
116.8628	R	-63.20171	2
130.4034	4	-53.66337	4
115.3267			

Additive constant for all log-likelihoods = -44.11. This constant added to the above values gives the log-likelihood including the term that does not

depend on the model parameters.

## Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A2 vs. A1) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 6a: Does Model 4 fit the data? (A3 vs 4)

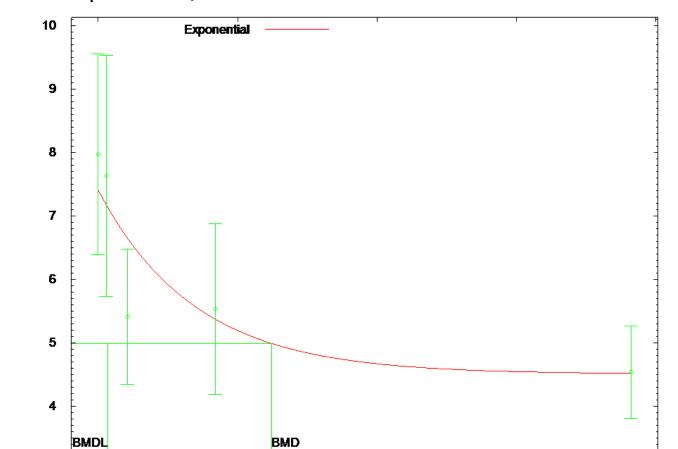
Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.
p-value		

31.82	8
10.28	4
10.28	4
2.464	2
	10.28

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. Consider running a non-homogeneous variance model. The p-value for Test 3 is less than .1. You may want to consider a different variance model. 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 = 0.950000BMD = 6.79455

BMDL = 2.70071



100

dose

1**50** 

200

# Exponential Model 4, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Level for BMDL

Mean Response

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0

50

```
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===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Norm/WBC_Concurrent-HLS 2001-White
Blood Cell Count-ExpNCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sat Jun 21 12:14:46 2014
_____
===
BMDS Model Run
~~~~
  The form of the response function by Model:
     Model 2:
                Y[dose] = a * exp{sign * b * dose}
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
     Model 4:
                Y[dose] = a * [c-(c-1) * exp{-b * dose}]
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  The variance is to be modeled as Var(i) = exp(lalpha + log
(mean(i)) * rho)
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 4
lnalpha	-4.23146
rho	2.9407
a	8.3685
b	0.0162762
С	0.516677
d	1

## Parameter Estimates

Variable	Model 4
lnalpha	-4.82434
rho	3.29183
a	7.40784
b	0.0288406
С	0.608181
d	1

# Table of Stats From Input Data

Dose	Ν	Obs Mean	Obs Std Dev
0	10	7.97	2.213
2.9	10	7.63	2.653
10.6	9	5.41	1.392
42	9	5.53	1.756
191.1	10	4.54	1.019

## Estimated Values of Interest

Est Mean	Est Std	Scaled Residual
7.408	2.42	0.7345
7.175	2.296	0.6267
6.643	2.023	-1.829
5.37	1.425	0.3374
4.517	1.072	0.06774
	7.408 7.175 6.643 5.37	7.4082.427.1752.2966.6432.0235.371.425

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) <sup>2</sup>
Model A3:			Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R:	Yij = Var{e(ij)} =		

		Likelihoods of Int	erest
210	Model	Log(likelihood)	DF
AIC			
	Al	-52.43142	6
116.8628	A2	-47.29218	10
114.5844			
109.5175	A3	-47.75877	7
130.4034	R	-63.20171	2
	4	-51.37641	5
112.7528			

Additive constant for all log-likelihoods = -44.11. This constant added to the above values gives the log-likelihood including the term that does not

depend on the model parameters.

### Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A2 vs. A1) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 6a: Does Model 4 fit the data? (A3 vs 4)

### Tests of Interest

Test p-value	-2*log(Likelihood Ratio)	D. F.
Test 1 0.0001004	31.82	8

Test 2 0.03599	10.28	4
Test 3	0.9332	3
0.8174		
Test ба	7.235	2
0.02685		

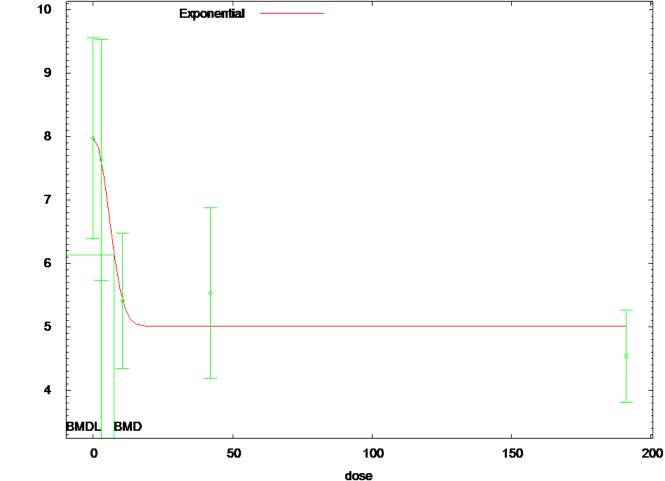
The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data. The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate. The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here. The p-value for Test 6a is less than .1. Model 4 may not adequately describe the data; you may want to consider another model. Benchmark Dose Computations: Specified Effect = 1.000000

Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

BMD = 62.2262

BMDL = 3.50341



Mean Response

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=== Exponential Model. (Version: 1.9; Date: 01/29/2013) Input Data File: C:/Users/dmayfield/Desktop/Norm/WBC\_Concurrent-HLS 2001-White Blood Cell Count-ExpCV-1SD-5d.(d) Gnuplot Plotting File: Sat Jun 21 12:14:45 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function by Model: Model 2:  $Y[dose] = a * exp{sign * b * dose}$  $Y[dose] = a * exp\{sign * (b * dose)^d\}$ Model 3:  $Y[dose] = a * [c-(c-1) * exp{-b * dose}]$ Model 4:  $Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]$ Model 5: 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 = MeanResponse 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 = 5Total 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	1.18464
rho(S)	0
a	8.3685
b	0.0162762
С	0.516677
d	1

(S) = Specified

### Parameter Estimates

Variable	Model 5
lnalpha	1.2138
rho	0
a	7.97
b	0.130055
С	0.628475
d	2.15774

# Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	10	7.97	2.213
2.9	10	7.63	2.653
10.6	9	5.41	1.392
42	9	5.53	1.756
191.1	10	4.54	1.019

## Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	7.97	1.835	-1.678e-008
2.9	7.63	1.835	-1.082e-008
10.6	5.41	1.835	-2.061e-008
42	5.009	1.835	0.852
191.1	5.009	1.835	-0.8083

Other models for which likelihoods are calculated:

Model Al: Yij = Mu(i) + e(ij) Var{e(ij)} = Sigma^2

Model A2:	Yij = Var{e(ij)} =	Mu(i) + e(ij) Sigma(i)^2
Model A3:		Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R:	Yij = Var{e(ij)} =	

Likelihoods of Interest

AIC	Model	Log(likelihood)	DF
ALC			
	A1	-52.43142	6
116.8628	A2	-47.29218	10
114.5844	A3	-52.43142	6
116.8628	R	-63.20171	2
130.4034	5	-53.1311	5
116.2622			

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)

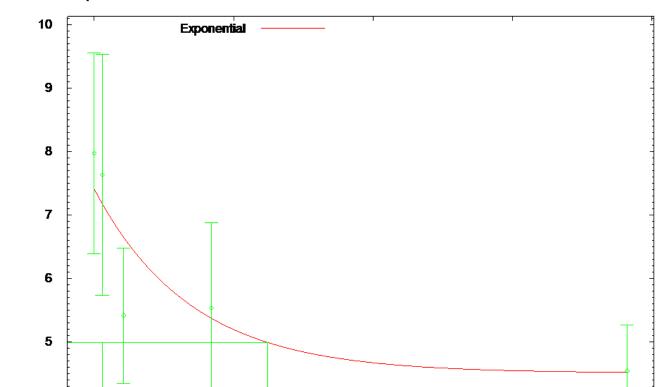
Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.
p-value		

Test 1 0.0001004	31.82	8
Test 2 0.03599	10.28	4
Test 3	10.28	4
0.03599 Test 7a 0.2368	1.399	1
0.2300		

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. Consider running a non-homogeneous variance model. The p-value for Test 3 is less than .1. You may want to consider a different variance model. 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 = 0.950000BMD = 7.56892

BMDL = 2.92959



100

dose

150

200

BMD

50

# Exponential Model 5, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Level for BMDL

12:14 06/21 2014

4

BMDL

0

```
______
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Norm/WBC_Concurrent-HLS 2001-White
Blood Cell Count-ExpNCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sat Jun 21 12:14:46 2014
_____
===
BMDS Model Run
~~~~
  The form of the response function by Model:
     Model 2:
                Y[dose] = a * exp{sign * b * dose}
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
     Model 4:
                Y[dose] = a * [c-(c-1) * exp{-b * dose}]
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  The variance is to be modeled as Var(i) = exp(lalpha + log
(mean(i)) * rho)
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 5
lnalpha	-4.23146
rho	2.9407
a	8.3685
b	0.0162762
С	0.516677
d	1

## Parameter Estimates

Variable	Model 5
lnalpha	-4.82434
rho	3.29183
a	7.40784
b	0.0288406
C	0.608181
d	1

# Table of Stats From Input Data

Dose	Ν	Obs Mean	Obs Std Dev
0	10	7.97	2.213
2.9	10	7.63	2.653
10.6	9	5.41	1.392
42	9	5.53	1.756
191.1	10	4.54	1.019

## Estimated Values of Interest

Est Mean	Est Std	Scaled Residual
7.408	2.42	0.7345
7.175	2.296	0.6267
6.643	2.023	-1.829
5.37	1.425	0.3374
4.517	1.072	0.06774
	7.408 7.175 6.643 5.37	7.4082.427.1752.2966.6432.0235.371.425

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)

	<pre>Var{e(ij)} =</pre>	Sigma(i) <sup>2</sup>
Model A3:	5	Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R:	Yij = Var{e(ij)} =	

		Likelihoods of Int	erest
210	Model	Log(likelihood)	DF
AIC			
	Al	-52.43142	6
116.8628	A2	-47.29218	10
114.5844			
109.5175	A3	-47.75877	7
130.4034	R	-63.20171	2
	5	-51.37641	5
112.7528			

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 p-value	-2*log(Likelihood Ratio)	D. F.
Test 1 0.0001004	31.82	8

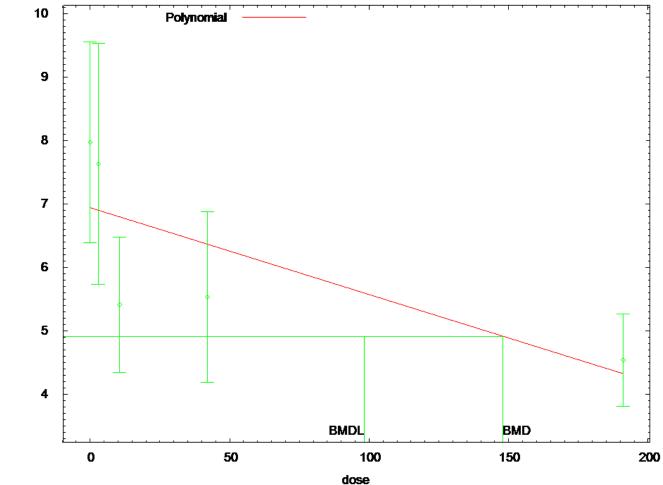
Test 2 0.03599	10.28	4
Test 3	0.9332	3
0.8174		
Test 7a	7.235	2
0.02685		

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 7a is less than .1. Model 5 may not adequately describe the data; you may want to consider another model. Benchmark Dose Computations: Specified Effect = 1.000000 Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

BMD = 62.2261

BMDL = 2.93936



# Polynomial Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

12:51 07/09 2014

Mean Response

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_WBC\_Concurrent/WBC\_Concurrent-HLS 2001-White Blood Cell Count-Poly2CV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_WBC\_Concurrent/WBC\_Concurrent-HLS 2001-White Blood Cell Count-Poly2CV-1SD-5d.plt Wed Jul 09 12:51:15 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse 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 = 5Total number of records with missing values = 0Maximum 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 = 3.64969 Specified rho = 0  $beta_0 = 7.40214$  $beta_1 = -0.0643244$ beta\_2 = 0 Asymptotic Correlation Matrix of Parameter Estimates ( \*\*\* The model parameter(s) -rho -beta 2 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	2.6e-007	-8.5e-007
beta_0	2.6e-007	1	-0.56
beta_1	-8.5e-007	-0.56	1

## Parameter Estimates

			95.0%
Wald Confidence In	terval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Conf	. Limit		
alpha	4.10152	0.83722	
2.4606	5.74244		
beta_0	6.93587	0.35384	
6.24236	7.62939		
beta_1	-0.0136993	0.00396554	-
0.0214716	-0.005927		
beta_2	0	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 Val	ues of Interest
---------------------------------	-----------------

Dose Scaled	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 1.61	10	7.97	6.94	2.21	2.03
2.9 1.15	10	7.63	6.9	2.65	2.03
10.6	9	5.41	6.79	1.39	2.03
42 -1.23	9	5.53	6.36	1.76	2.03
191.1 0.347	10	4.54	4.32	1.02	2.03

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<sup>2</sup>

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
Al	-52.431420	б	116.862840
A2	-47.292184	10	114.584369
A3	-52.431420	б	116.862840
fitted	-57.872613	3	121.745227
R	-63.201706	2	130.403412

### 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

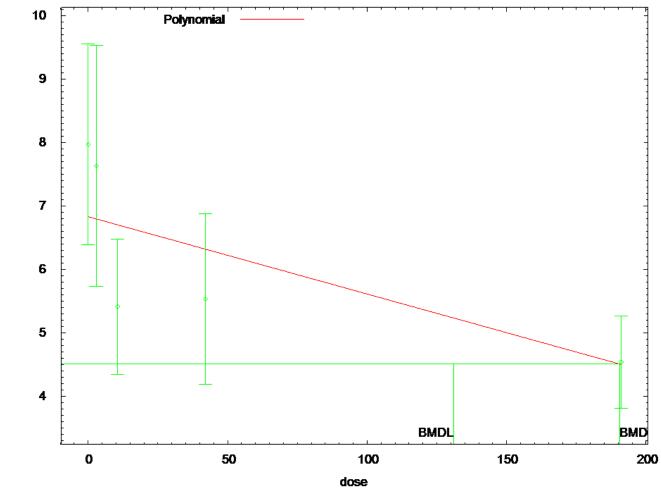
Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.819	8	0.0001004
Test 2	10.2785	4	0.03599
Test 3	10.2785	4	0.03599
Test 4	10.8824	3	0.01238

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. Consider running a non-homogeneous variance model The p-value for Test 3 is less than .1. You may want to consider a different variance model 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 = 147.834

BMDL = 98.2036



# Polynomial Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

12:51 07/09 2014

Mean Response

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_WBC\_Concurrent/WBC\_Concurrent-HLS 2001-White Blood Cell Count-Poly2NCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_WBC\_Concurrent/WBC\_Concurrent-HLS 2001-White Blood Cell Count-Poly2NCV-1SD-5d.plt Wed Jul 09 12:51:16 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse 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 = 5Total number of records with missing values = 0Maximum 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 = 1.29464 rho = 0  $beta_0 = 7.40214$  $beta_1 = -0.0643244$ 7.40214 beta\_2 = 0 Asymptotic Correlation Matrix of Parameter Estimates ( \*\*\* The model parameter(s) -beta\_2 have been estimated at a boundary point, or have been specified by the user,

and do not appear in the correlation matrix )

	lalpha	rho	beta_0	beta_1
lalpha	1	-1	0.059	-0.074
rho	-1	1	-0.059	0.075
beta_0	0.059	-0.059	1	-0.81
beta_1	-0.074	0.075	-0.81	1

Parameter Estimates

95	5.0	18

			95.0%
Wald Confidence	Interval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Con	nf. Limit		
lalpha	-6.5162	2.25638	-
10.9386	-2.09377		
rho	4.27037	1.23797	
1.84399	6.69675		
beta_0	6.83277	0.388873	
6.07059	7.59495		
beta_1	-0.0122267	0.00266203	-
0.0174442	-0.00700924		
beta_2	0	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 Scaled 1	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 1.54	10	7.97	6.83	2.21	2.33
2.9	10	7.63	6.8	2.65	2.3
10.6 -1.74	9	5.41	6.7	1.39	2.24
42 -1.2	9	5.53	6.32	1.76	1.97

191.1	10	4.54	4.5	1.02	0.953
0.145					

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
Al	-52.431420	б	116.862840
A2	-47.292184	10	114.584369
A3	-47.758770	7	109.517540
fitted	-53.651165	4	115.302330
R	-63.201706	2	130.403412

## 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.)

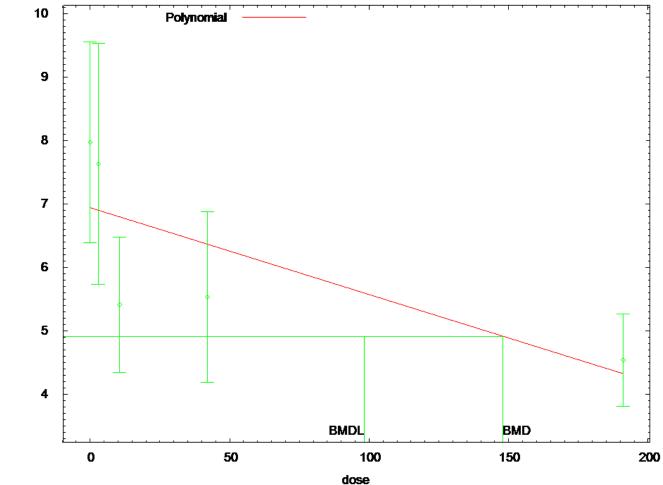
## Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.819	8	0.0001004
Test 2	10.2785	4	0.03599
Test 3	0.933171	3	0.8174
Test 4	11.7848	3	0.008158

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 = Estimated standard deviations from the Risk Type control mean Confidence level = 0.95 BMD = 190.429

131.056

BMDL =



# Polynomial Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

12:51 07/09 2014

Mean Response

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_WBC\_Concurrent/WBC\_Concurrent-HLS 2001-White Blood Cell Count-Poly3CV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_WBC\_Concurrent/WBC\_Concurrent-HLS 2001-White Blood Cell Count-Poly3CV-1SD-5d.plt Wed Jul 09 12:51:15 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse 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 = 5Total 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 = 3.64969 Specified rho = 0 beta\_0 = 8.18961 beta\_1 = -0.328545 beta\_2 = 0  $beta_3 = -3.14654e - 005$ Asymptotic Correlation Matrix of Parameter Estimates ( \*\*\* The model parameter(s) -rho -beta\_2 -

beta\_3 have been estimated at a boundary point, or have

been specified by the user, and do not appear in the correlation matrix )

beta_1	beta_0	alpha	
-7.5e-008	1.3e-008	1	alpha
-0.56	1	1.3e-008	beta_0
1	-0.56	-7.5e-008	beta_1

Parameter Estimates

95.0%

Wald Confidence Interval					
Estimate	Std. Err.	Lower Conf.			
f. Limit					
4.10152	0.83722				
5.74244					
6.93587	0.35384				
7.62939					
-0.0136993	0.00396554	-			
-0.00592698					
0	NA				
0	NA				
	Estimate f. Limit 4.10152 5.74244 6.93587 7.62939 -0.0136993	Estimate Std. Err. f. Limit 4.10152 0.83722 5.74244 6.93587 0.35384 7.62939 -0.0136993 0.00396554 -0.00592698 0 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	

Std Dev
2.03
2.03
2.03
2.03
2.03

Model Descriptions for likelihoods calculated

Var{e(i)} = Sigma^2

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)

#### Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
Al	-52.431420	6	116.862840
A2	-47.292184	10	114.584369
A3	-52.431420	6	116.862840
fitted	-57.872613	3	121.745227
R	-63.201706	2	130.403412

## Explanation of Tests

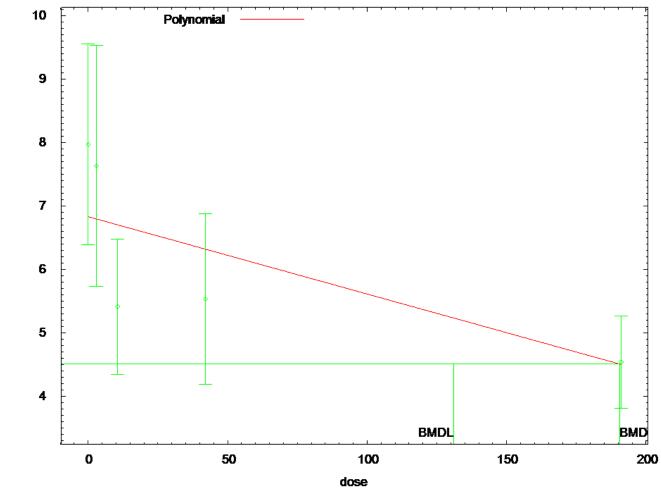
Test 1: Do responses and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A1 vs A2) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 4: Does the Model for the Mean Fit? (A3 vs. fitted) (Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

## Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1 Test 2 Test 3	31.819 10.2785 10.2785	8 4 4 2	$\begin{array}{c} 0.0001004 \\ 0.03599 \\ 0.03599 \\ 0.03599 \\ 0.01238 \end{array}$
Test 4	10.8824	3	0.01238

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. Consider running a non-homogeneous variance model The p-value for Test 3 is less than .1. You may want to consider а different variance model The p-value for Test 4 is less than .1. You may want to try a different model Benchmark Dose Computation Specified effect = 1 = Estimated standard deviations from the Risk Type control mean Confidence level = 0.95 147.834 BMD = BMDL = 98.2036



# Polynomial Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

12:51 07/09 2014

Mean Response

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_WBC\_Concurrent/WBC\_Concurrent-HLS 2001-White Blood Cell Count-Poly3NCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_WBC\_Concurrent/WBC\_Concurrent-HLS 2001-White Blood Cell Count-Poly3NCV-1SD-5d.plt Wed Jul 09 12:51:16 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse 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 = 5Total number of records with missing values = 0Maximum 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 = 1.29464 rho = 0 beta\_0 = 8.18961 beta\_1 = -0.328545 beta\_2 = 0  $beta_3 = -3.14654e - 005$ Asymptotic Correlation Matrix of Parameter Estimates ( \*\*\* The model parameter(s) -beta\_2 -beta\_3

have been estimated at a boundary point, or have been specified by the user, and do not appear in the correlation matrix )

	lalpha	rho	beta_0	beta_1
lalpha	1	-1	0.059	-0.074
rho	-1	1	-0.059	0.075
beta_0	0.059	-0.059	1	-0.81
beta_1	-0.074	0.075	-0.81	1

Parameter Estimates

			95.0%
Wald Confidence I	Interval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Con	ıf. Limit		
lalpha	-6.5162	2.25638	_
10.9386	-2.09378		
rho	4.27037	1.23797	
1.84399	6.69675		
beta O	6.83277	0.388873	
6.07059	7.59495		
beta 1	-0.0122267	0.00266203	_
0.0174442	-0.00700924		
beta_2	0	NA	
beta_3	0	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 Scaled 1	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 1.54	10	7.97	6.83	2.21	2.33
2.9	10	7.63	6.8	2.65	2.3
10.6 -1.74	9	5.41	6.7	1.39	2.24

9 5.53 6.32 1.76 1.97 42 -1.2 10 4.54 4.5 1.02 0.953 191.1 0.145 Model Descriptions for likelihoods calculated Model A1: Yij = Mu(i) + e(ij) Var{e(ij)} = Sigma^2 Yij = Mu(i) + e(ij)Model A2: 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

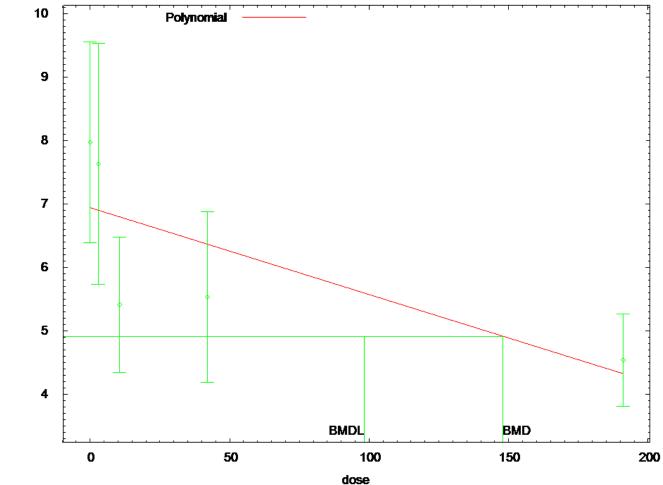
Model	Log(likelihood)	# Param's	AIC
Al	-52.431420	6	116.862840
A2	-47.292184	10	114.584369
A3	-47.758770	7	109.517540
fitted	-53.651165	4	115.302330
R	-63.201706	2	130.403412

#### Explanation of Tests

#### Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.819	8	0.0001004
Test 2	10.2785	4	0.03599
Test 3	0.933171	3	0.8174

11.7848 3 0.008158 Test 4 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 = Estimated standard deviations from the Risk Type control mean Confidence level = 0.95 BMD = 190.429 BMDL = 131.056



# Polynomial Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

12:51 07/09 2014

Mean Response

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_WBC\_Concurrent/WBC\_Concurrent-HLS 2001-White Blood Cell Count-Poly4CV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_WBC\_Concurrent/WBC\_Concurrent-HLS 2001-White Blood Cell Count-Poly4CV-1SD-5d.plt Wed Jul 09 12:51:15 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse 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 = 5Total 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 = 3.64969 rho = beta\_0 = Specified 0 7.97  $beta_1 = -0.0490906$  $beta_2 = -0.0256112$ beta 3 = 0  $beta_4 = -3.15099e-006$ 

Asymptotic Correlation Matrix of Parameter Estimates

	arpila	Deta_0	Deta_1
alpha	1	-1.2e-008	1.8e-008
beta_0	-1.2e-008	1	-0.56
beta_1	1.8e-008	-0.56	1

Parameter Estimates

9	5	0	è

Wald Confi	dence Inte	rval			
Var	iable	Estimate	e Std.	Err.	Lower Conf.
Limit Up	per Conf.	Limit			
	alpha	4.10153	β Ο.	83722	
2.4606	5	.74245			
b	eta_0	6.93587	0.	35384	
6.24236		7.62939			
b	eta_1	-0.0136993	0.003	96554	-
0.0214716	- 0	.00592698			
b	eta_2	C	)	NA	
b	eta_3	C	)	NA	
b	eta_4	C	)	NA	

NA - Indicates that this parameter has hit a bound implied by some inequality constraint and thus has no standard error.

Dose Scaled	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 1.61	10	7.97	6.94	2.21	2.03
2.9	10	7.63	6.9	2.65	2.03
10.6	9	5.41	6.79	1.39	2.03
42	9	5.53	6.36	1.76	2.03

Table of Data and Estimated Values of Interest

-1.23 191.1 0.347	10	4.54	4.32	1.02	2.03
Model	Description	ns for likelil	noods calcula	ted	
Model		Yij = Mu(i) ij)} = Sigma^2			
Model		Yij = Mu(i) ij)} = Sigma(:			
Мо	Var{e(: odel A3 uses	Yij = Mu(i) ij)} = Sigma^2 s any fixed va ed by the uses	2 ariance param	eters that	
Model		Yi = Mu + e (i)} = Sigma^2			

## Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
Al	-52.431420	6	116.862840
A2	-47.292184	10	114.584369
A3	-52.431420	б	116.862840
fitted	-57.872613	3	121.745227
R	-63.201706	2	130.403412

## 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

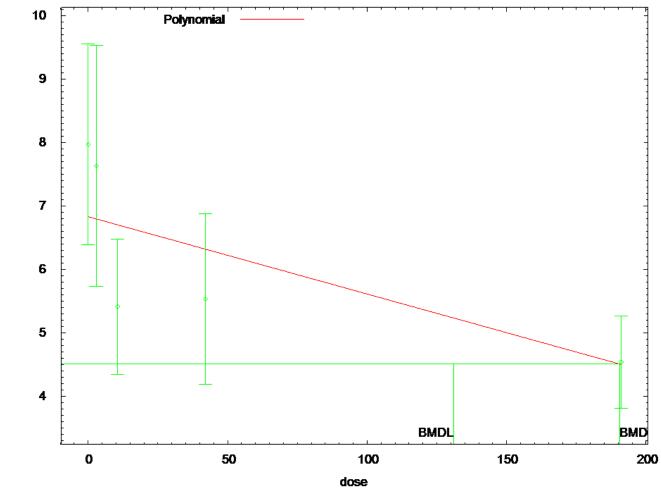
Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.819	8	0.0001004
Test 2	10.2785	4	0.03599
Test 3	10.2785	4	0.03599
Test 4	10.8824	3	0.01238

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. Consider running a non-homogeneous variance model The p-value for Test 3 is less than .1. You may want to consider а different variance model The p-value for Test 4 is less than .1. You may want to try a different model Benchmark Dose Computation Specified effect = 1 = Estimated standard deviations from the Risk Type control mean

Confidence level = 0.95

BMD = 147.834

BMDL = 98.2036



# Polynomial Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

12:51 07/09 2014

Mean Response

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_WBC\_Concurrent/WBC\_Concurrent-HLS 2001-White Blood Cell Count-Poly4NCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_WBC\_Concurrent/WBC\_Concurrent-HLS 2001-White Blood Cell Count-Poly4NCV-1SD-5d.plt Wed Jul 09 12:51:16 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse 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 = 5Total number of records with missing values = 0Maximum 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 = 1.29464 rho = 0 \_\_\_\_ --- -beta\_0 = 7.97  $beta_1 = -0.0490906$  $beta_2 = -0.0256112$ beta 3 = 0  $beta_4 = -3.15099e-006$ Asymptotic Correlation Matrix of Parameter Estimates

1

lalpha	1	-1	0.059	-0.074
rho	-1	1	-0.059	0.075
beta_0	0.059	-0.059	1	-0.81
beta_1	-0.074	0.075	-0.81	1

#### Parameter Estimates

### 95.0%

				95.08
Wald Conf	idence I	nterval		
Va	riable	Estimate	Std. Err.	Lower Conf.
Limit U	Ipper Con:	f. Limit		
	lalpha	-6.5162	2.25638	-
10.9386		-2.09377		
	rho	4.27037	1.23797	
1.84399		6.69675		
	beta_0	6.83277	0.388873	
6.07059		7.59495		
	beta_1	-0.0122267	0.00266204	-
0.0174442	)	-0.00700925		
	beta_2	0	NA	
	beta 3	-2.01002e-197	NA	
		0	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 Scaled F	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 1.54	10	7.97	6.83	2.21	2.33
2.9	10	7.63	6.8	2.65	2.3

1.14 10.6	9	5.41	6.7	1.39	2.24
-1.74	9	5.41	0.7	1.39	2.24
42	9	5.53	6.32	1.76	1.97
-1.2					
191.1	10	4.54	4.5	1.02	0.953
0.145					

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<sup>2</sup>

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
Al	-52.431420	б	116.862840
A2	-47.292184	10	114.584369
A3	-47.758770	7	109.517540
fitted	-53.651165	4	115.302330
R	-63.201706	2	130.403412

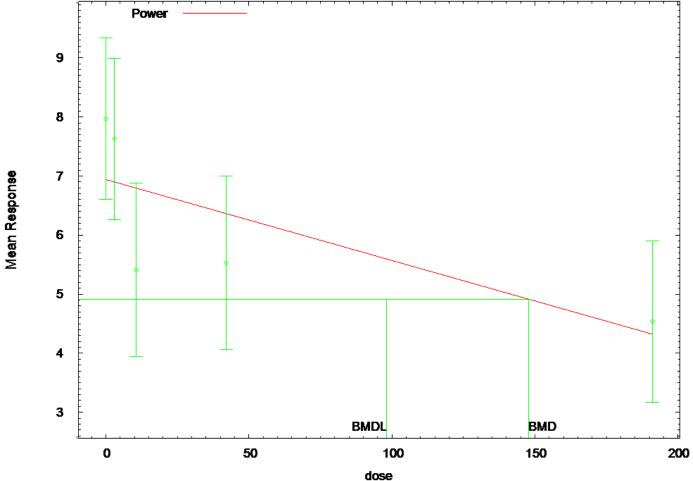
#### Explanation of Tests

#### Tests of Interest

Test	-2*log(I	ikelihood	Ratio)	Test df	p-value
------	----------	-----------	--------	---------	---------

3

31.819 8 4 Test 1 0.0001004 Test 2 10.2785 0.03599 Test 3 0.933171 3 0.8174 Test 4 11.7848 3 0.008158 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 = Estimated standard deviations from the Risk Type control mean Confidence level = 0.95 BMD = 190.429 BMDL = 131.056



12:14 06/21 2014

=== Power Model. (Version: 2.18; Date: 05/19/2014) Input Data File: C:/Users/dmayfield/Desktop/Norm/WBC\_Concurrent-HLS 2001-White Blood Cell Count-PowerCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Norm/WBC\_Concurrent-HLS 2001-White Blood Cell Count-PowerCV-1SD-5d.plt Sat Jun 21 12:14:46 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = control + slope \* dose^power Dependent variable = MeanResponse 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 = 5 Total number of records with missing values = 0 Maximum number of iterations = 500 Relative Function Convergence has been set to: 1e-008 Parameter Convergence has been set to: 1e-008 Default Initial Parameter Values alpha = 3.64969 rho = Specified 0 control = 4.54 slope = 3.7818 power = -0.420444Asymptotic 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	-2.7e-009	-1.7e-010
ontrol	-2.7e-009	1	-0.56
slope	-1.7e-010	-0.56	1

#### Parameter Estimates

			95.0%
Wald Confidence I	nterval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Con	f. Limit		
alpha	4.10153	0.83722	
2.4606	5.74245		
control	6.93587	0.35384	
6.24236	7.62939		
slope	-0.0136993	0.00396554	-
0.0214716	-0.00592698		
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 Scaled	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 1.61	10	7.97	6.94	2.21	2.03
2.9 1.15	10	7.63	6.9	2.65	2.03
10.6	9	5.41	6.79	1.39	2.03
42 -1.23	9	5.53	6.36	1.76	2.03
191.1 0.347	10	4.54	4.32	1.02	2.03

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<sup>2</sup>

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
Al	-52.431420	б	116.862840
A2	-47.292184	10	114.584369
A3	-52.431420	б	116.862840
fitted	-57.872613	3	121.745227
R	-63.201706	2	130.403412

#### 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	31.819	8	0.0001004
Test 2	10.2785	4	0.03599
Test 3	10.2785	4	0.03599
Test 4	10.8824	3	0.01238

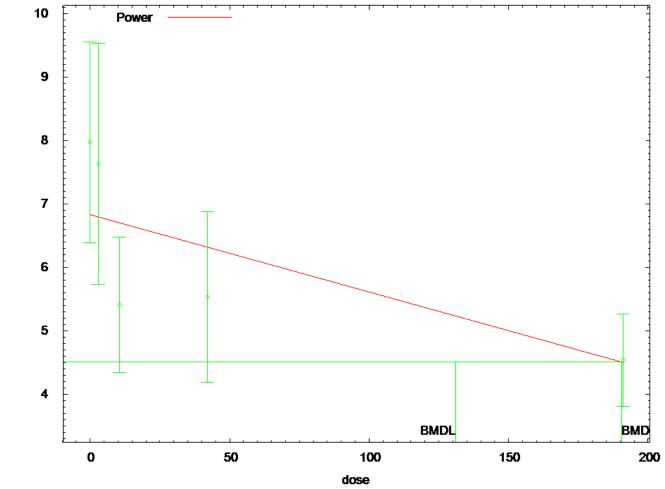
The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels It seems appropriate to model the data The p-value for Test 2 is less than .1. Consider running a non-homogeneous variance model The p-value for Test 3 is less than .1. You may want to consider a different variance model 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 = 147.834

BMDL = 98.2036



# Power Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

12:14 06/21 2014

Mean Response

=== Power Model. (Version: 2.18; Date: 05/19/2014) Input Data File: C:/Users/dmayfield/Desktop/Norm/WBC\_Concurrent-HLS 2001-White Blood Cell Count-PowerNCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Norm/WBC\_Concurrent-HLS 2001-White Blood Cell Count-PowerNCV-1SD-5d.plt Sat Jun 21 12:14:47 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = control + slope \* dose^power Dependent variable = MeanResponse Independent variable = Dose The power is restricted to be greater than or equal to 1 The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) \* rho) Total number of dose groups = 5Total number of records with missing values = 0Maximum 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 = 1.29464 rho = 0 control = 4.54 slope = 3.7818 power = -0.420444Asymptotic Correlation Matrix of Parameter Estimates ( \*\*\* The model parameter(s) -power have been estimated at a boundary point, or have been specified by the user,

		± ±		
	lalpha	rho	control	slope
lalpha	1	-1	0.39	-0.61
rho	-1	1	-0.45	0.64
control	0.39	-0.45	1	-0.81
slope	-0.61	0.64	-0.81	1

Parameter Estimates

and do not appear in the correlation matrix )

				95.08
Wald Confi	dence i	Interval		
Var	iable	Estimate	Std. Err.	Lower Conf.
Limit Up	per Com	nf. Limit		
1	alpha	-6.5162	2.91702	_
12.2334	-	-0.798956		
	rho	4.27037	1.62588	
1.0837		7.45704		
cc	ntrol	6.83277	0.390856	
6.06671		7.59883		
	slope	-0.0122267	0.00266832	_
0.0174565	-	-0.00699694		
	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 Scaled	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 1.54	10	7.97	6.83	2.21	2.33
2.9	10	7.63	6.8	2.65	2.3
1.14 10.6	9	5.41	6.7	1.39	2.24
-1.74 42 -1.2	9	5.53	6.32	1.76	1.97

191.1	10	4.54	4.5	1.02	0.953
0.145					

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
Al	-52.431420	6	116.862840
A2	-47.292184	10	114.584369
A3	-47.758770	7	109.517540
fitted	-53.651165	4	115.302330
R	-63.201706	2	130.403412

## Explanation of Tests

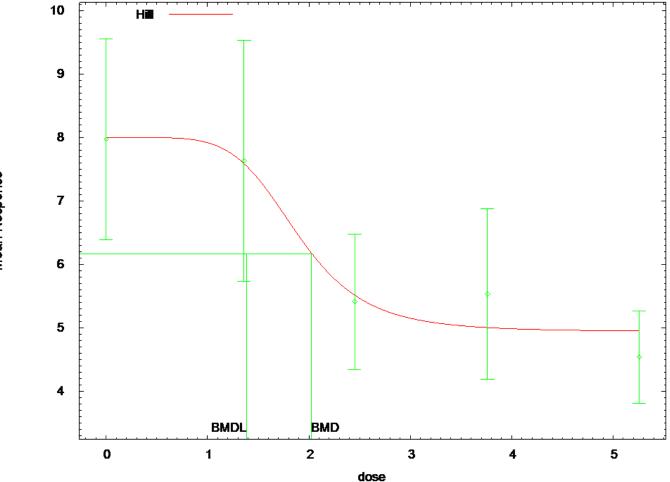
Test 1: Do responses and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A1 vs A2) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 4: Does the Model for the Mean Fit? (A3 vs. fitted) (Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

### Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.819	8	0.0001004
Test 2	10.2785	4	0.03599
Test 3	0.933171	3	0.8174
Test 4	11.7848	3	0.008158

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 = Estimated standard deviations from the Risk Type control mean Confidence level = 0.95 BMD = 190.429BMDL = 131.056

BMDS Model Results for White Blood Cell Count (Log-transformed Doses, Concurrent Controls)



Mean Response

11:32 06/21 2014

=== Hill Model. (Version: 2.17; Date: 01/28/2013) Input Data File: C:/Users/dmayfield/Desktop/Ln/WBC\_Concurrent\_Ln-HLS 2001-White Blood Cell Count-HillCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Ln/WBC\_Concurrent\_Ln-HLS 2001-White Blood Cell Count-HillCV-1SD-5d.plt Sat Jun 21 11:32:12 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = intercept + v\*dose^n/(k^n + dose^n) Dependent variable = MeanResponse 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 = 5Total 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 = 3.64969 Specified rho = 0 7.97 intercept = v = -3.43 n = 4.25613 k = 2.03611 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 co	orrelation matrix )
-----------------------------	---------------------

k		alpha	intercept	v	n
al 2.9e-00	pha 19	1	-1.2e-009	-7.3e-009	2.5e-009
interc -0.4	ept	-1.2e-009	1	-0.78	-0.46
-0.02	v	-7.3e-009	-0.78	1	0.68
-0.1	n	2.5e-009	-0.46	0.68	1
1	k	2.9e-009	-0.4	-0.02	-0.1

## Parameter Estimates

			95.0%
Wald Confidence In	nterval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Cont	E. Limit		
alpha	3.35938	0.68573	
2.01537	4.70338		
intercept	8.0005	0.570983	
6.88139	9.1196		
v	-3.06445	0.838523	-
4.70792	-1.42097		
n	5.65284	5.36582	_
4.86398	16.1697		
k	1.88908	0.444332	
1.0182	2.75995		

## Table of Data and Estimated Values of Interest

Dose Scaled R		Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 -0.0526	10	7.97	8	2.21	1.83

1.361 0.0771	10	7.63	7.59	2.65	1.83
2.451	9	5.41	5.51	1.39	1.83
-0.16 3.761	9	5.53	5	1.76	1.83
0.872 5.258	10	4.54	4.95	1.02	1.83
-0.699					

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
Al	-52.431420	б	116.862840
A2	-47.292184	10	114.584369
A3	-52.431420	б	116.862840
fitted	-53.082138	5	116.164276
R	-63.201706	2	130.403412

## Explanation of Tests

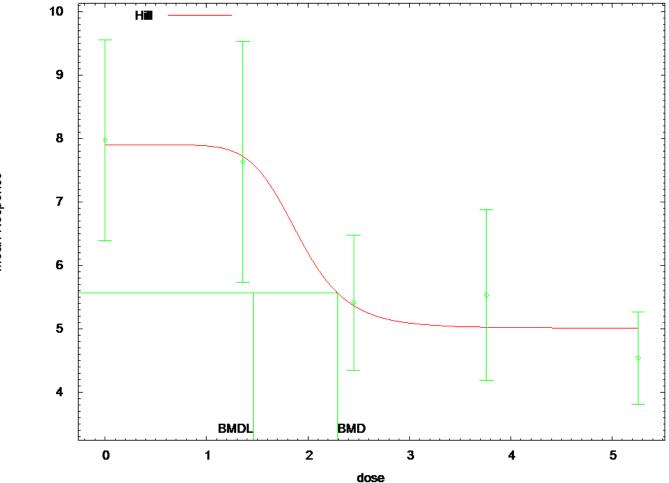
## Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
TCBC		ICSC UL	p varue

3

Test 131.81980.0001004Test 210.278540.03599Test 310.278540.03599Test 41.3014410.254

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. Consider running a non-homogeneous variance model The p-value for Test 3 is less than .1. You may want to consider а different variance model 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 = Estimated standard deviations from the Risk Type control mean Confidence level = 0.95 BMD = 2.02672 BMDL = 1.38253



Mean Response

11:32 06/21 2014

=== Hill Model. (Version: 2.17; Date: 01/28/2013) Input Data File: C:/Users/dmayfield/Desktop/Ln/WBC\_Concurrent\_Ln-HLS 2001-White Blood Cell Count-HillNCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Ln/WBC\_Concurrent\_Ln-HLS 2001-White Blood Cell Count-HillNCV-1SD-5d.plt Sat Jun 21 11:32:13 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = intercept + v\*dose^n/(k^n + dose^n) Dependent variable = MeanResponse Independent variable = Dose Power parameter restricted to be greater than 1 The variance is to be modeled as Var(i) = exp(lalpha + rho \* ln(mean(i))) Total number of dose groups = 5Total number of records with missing values = 0Maximum 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 = 1.29464 rho = 0 7.97 intercept = v = -3.43 n = 4.25613 k = 2.03611 Asymptotic Correlation Matrix of Parameter Estimates lalpha rho intercept v

n	k			
lalpha -0.12	1 -0.041	-0.99	0.29	-0.36
rho 0.12	-0.99 0.041	1	-0.32	0.37
intercept -0.61	0.29 -0.57	-0.32	1	-0.92
v 0.71	-0.36 0.47	0.37	-0.92	1
n 1 0	-0.12	0.12	-0.61	0.71
k 0.61	-0.041 1	0.041	-0.57	0.47

Parameter Estimates

				95.0%
Wald Conf	idence Ir	nterval		
Va	riable	Estimate	Std. Err.	Lower Conf.
Limit U	pper Conf	. Limit		
	lalpha	-3.17799	1.97663	-
7.05212		0.696131		
	rho	2.35847	1.08644	
0.229084		4.48786		
int	ercept	7.90015	0.704723	
6.51891		9.28138		
	v	-2.88616	0.877394	-
4.60582		-1.1665		
	n	7.90728	11.0414	-
13.7334		29.548		
	k	1.91117	0.488665	
0.953404		2.86894		

Table of Data and Estimated Values of Interest

Dose Scaled R	N les.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 0.0946	10	7.97	7.9	2.21	2.34

1.361 -0.119	10	7.63	7.72	2.65	2.27
2.451 0.0849	9	5.41	5.37	1.39	1.48
3.761 1.1	9	5.53	5.03	1.76	1.37
5.258 -1.1	10	4.54	5.01	1.02	1.37

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<sup>2</sup>

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-52.431420	6	116.862840
A2	-47.292184	10	114.584369
A3	-47.758770	7	109.517540
fitted	-50.185289	б	112.370578
R	-63.201706	2	130.403412

# Explanation of Tests

Test 1:	Do responses and/or variances differ among Dose levels? (A2 vs. R)
Test 2:	Are Variances Homogeneous? (Al vs A2)
	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	Patio)	Test df	
Iest	-z~iog(litkerinood	Ralio)	iest ai	p-value

3

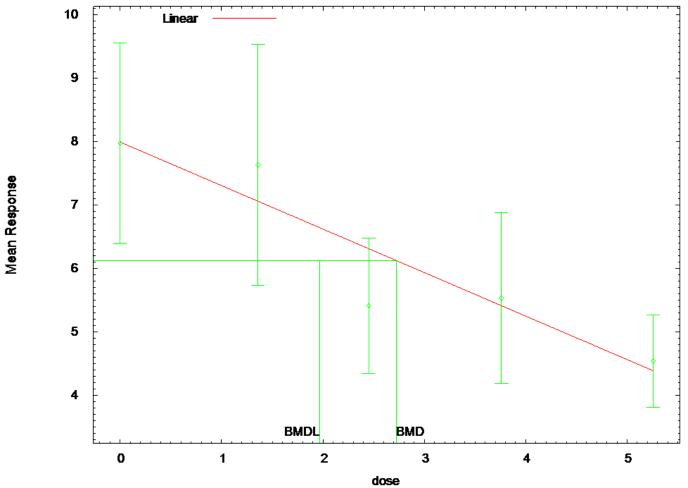
Test 1 Test 2 31.819 8 0.0001004 10.2785 4 0.03599 Test 3 0.933171 3 0.8174 1 Test 4 4.85304 0.0276

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

BMDL =

Specified effect = 1 Risk Type = Estimated standard deviations from the control mean Confidence level = 0.95 BMD = 2.29451 1.4635



12:43 07/09 2014

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_WBC\_Concurrent\_Ln/WBC\_Concurrent\_L n-HLS 2001-White Blood Cell Count-LinearCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_WBC\_Concurrent\_Ln/WBC\_Concurrent\_L n-HLS 2001-White Blood Cell Count-LinearCV-1SD-5d.plt Wed Jul 09 12:43:41 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse Independent variable = Dose rho is set to 0 Signs of the polynomial coefficients are not restricted A constant variance model is fit Total number of dose groups = 5Total number of records with missing values = 0Maximum 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 = 3.64969 rho = 0 beta\_0 = 7.97189 beta\_1 = -0.684236 0 Specified 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	-1.6e-007	-9.6e-008
beta_0	-1.6e-007	1	-0.81
beta_1	-9.6e-008	-0.81	1

## Parameter Estimates

			95.0%
Wald Confide	ence Interval		
Varia	ble Estir	nate Std. H	Err. Lower Conf.
Limit Uppe	er Conf. Limit		
al	pha 3.49	9739 0.713	3902
2.09817	4.89662		
bet	a_0 7.9	9913 0.45	7566
7.09448	8.88811		
bet	a_1 -0.685	5697 0.145	5247 –
0.970375	-0.401018		

Table of Data and Estimated Values of Interest

Dose Scaled 1	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0	10	7.97	7.99	2.21	1.87
-0.036	10	7.63	7.06	2.65	1.87
0.967	9	5.41	6.31	1.39	1.87
-1.44 3.761 0.189	9	5.53	5.41	1.76	1.87
5.258 0.261	10	4.54	4.39	1.02	1.87

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
Al	-52.431420	6	116.862840
A2	-47.292184	10	114.584369
A3	-52.431420	6	116.862840
fitted	-54.048454	3	114.096907
R	-63.201706	2	130.403412

## 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	31.819	8	0.0001004
Test 2	10.2785	4	0.03599
Test 3	10.2785	4	0.03599
Test 4	3.23407	3	0.3569

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. Consider running a non-homogeneous variance model

The p-value for Test 3 is less than .1. You may want to consider a

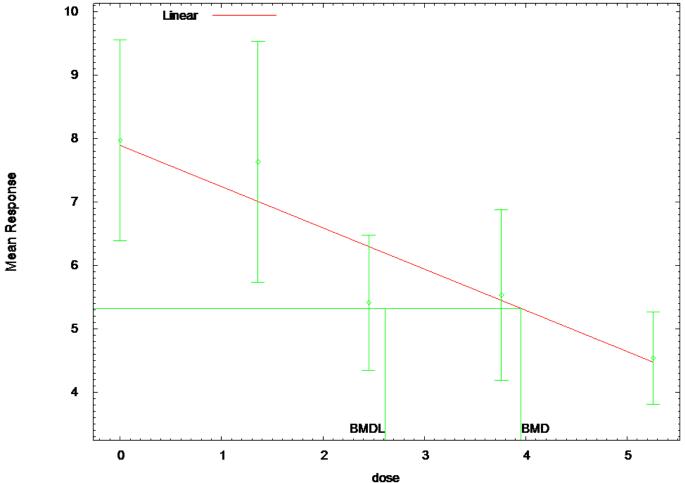
different variance model

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 = 2.72735

BMDL = 1.96547



12:43 07/09 2014

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_WBC\_Concurrent\_Ln/WBC\_Concurrent\_L n-HLS 2001-White Blood Cell Count-LinearNCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_WBC\_Concurrent\_Ln/WBC\_Concurrent\_L n-HLS 2001-White Blood Cell Count-LinearNCV-1SD-5d.plt Wed Jul 09 12:43:42 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse Independent variable = Dose Signs of the polynomial coefficients are not restricted The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) \* rho) Total number of dose groups = 5Total number of records with missing values = 0Maximum 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 = 1.29464 rho = 0 rno = 0 beta\_0 = 7.97189 beta\_1 = -0.684236 Asymptotic Correlation Matrix of Parameter Estimates rho lalpha beta\_0 beta 1 -0.99 0.15 -0.18 lalpha 1

rho	-0.99	1	-0.15	0.18
beta_0	0.15	-0.15	1	-0.91
beta_1	-0.18	0.18	-0.91	1

Parameter Estimates

## 95.0%

Wald Confidence	Interval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper C	onf. Limit		
lalpha	-4.45485	2.03072	-
8.43498	-0.474715		
rho	3.07104	1.1156	
0.884506	5.25758		
beta_0	7.88794	0.536104	
6.83719	8.93868		
beta_1	-0.649741	0.131724	_
0.907915	-0.391568		

Table of Data and Estimated Values of Interest

Dose Scaled	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 0.101	10	7.97	7.89	2.21	2.57
1.361 0.925	10	7.63	7	2.65	2.14
2.451 -1.46	9	5.41	6.3	1.39	1.82
3.761 0.177	9	5.53	5.44	1.76	1.45
5.258 0.201	10	4.54	4.47	1.02	1.08

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<sup>2</sup>

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
Al	-52.431420	б	116.862840
A2	-47.292184	10	114.584369
A3	-47.758770	7	109.517540
fitted	-50.527570	4	109.055140
R	-63.201706	2	130.403412

### Explanation of Tests

### Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.819	8	0.0001004
Test 2	10.2785	4	0.03599
Test 3	0.933171	3	0.8174
Test 4	5.5376	3	0.1364

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

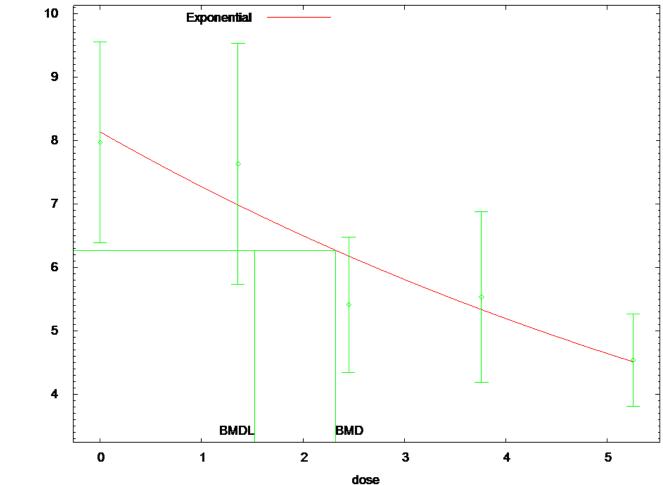
to be appropriate here

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 Confidence level = 0.95 BMD = 3.95557

BMDL = 2.61437



Mean Response

11:32 06/21 2014

=== Exponential Model. (Version: 1.9; Date: 01/29/2013) Input Data File: C:/Users/dmayfield/Desktop/Ln/WBC\_Concurrent\_Ln-HLS 2001-White Blood Cell Count-ExpCV-1SD-5d.(d) Gnuplot Plotting File: Sat Jun 21 11:32:11 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function by Model: Model 2:  $Y[dose] = a * exp{sign * b * dose}$  $Y[dose] = a * exp\{sign * (b * dose)^d\}$ Model 3:  $Y[dose] = a * [c-(c-1) * exp{-b * dose}]$ Model 4:  $Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]$ Model 5: 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 = MeanResponse 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 = 5Total 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	1.18464
rho(S)	0
a	4.59625
b	0.111233
C	0
d	1

(S) = Specified

### Parameter Estimates

Variable	Model 2
lnalpha	1.24723
rho	0
a	8.1349
b	0.112266
C	0
d	1

# Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	10	7.97	2.213
1.361	10	7.63	2.653
2.451	9	5.41	1.392
3.761	9	5.53	1.756
5.258	10	4.54	1.019

## Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	8.135	1.866	-0.2795
1.361	6.982	1.866	1.098
2.451	6.178	1.866	-1.235
3.761	5.333	1.866	0.3166
5.258	4.508	1.866	0.05411

Other models for which likelihoods are calculated:

Model Al: Yij = Mu(i) + e(ij) Var{e(ij)} = Sigma^2

Model A2:	Yij = Var{e(ij)} =	Mu(i) + e(ij) Sigma(i)^2
Model A3:		Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R:	Yij = Var{e(ij)} =	

Likelihoods of Interest

ATC.	Model	Log(likelihood)	DF
AIC			
	Al	-52.43142	6
116.8628	A2	-47.29218	10
114.5844	A3	-52.43142	6
116.8628	R	-63.20171	2
130.4034	2	-53.93348	3
113.867			-

Additive constant for all log-likelihoods = -44.11. This constant added to the above values gives the log-likelihood including the term that does not

depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A2 vs. A1) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 4: Does Model 2 fit the data? (A3 vs. 2)

Tests of Interest

Test p-value	-2*log(Likelihood Ratio)	D. F.
Test 1	31.82	8

0.0001004			
Test	2	10.28	4
0.03599			
Test	3	10.28	4
0.03599			
Test	4	3.004	3
0.391			

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. Consider running a non-homogeneous variance model.

The p-value for Test 3 is less than .1. You may want to consider a different variance model.

The p-value for Test 4 is greater than .1. Model 2 seems to adequately describe the data.

Benchmark Dose Computations:

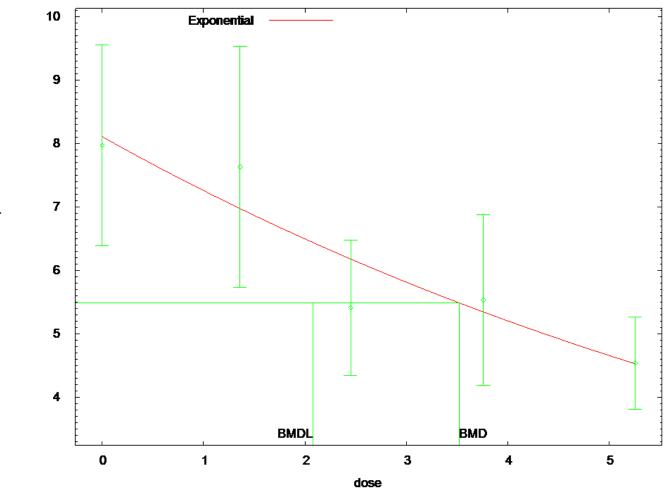
Specified Effect = 1.000000

Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

BMD = 2.32046

BMDL = 1.52174



Mean Response

11:32 06/21 2014

```
______
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Ln/WBC_Concurrent_Ln-HLS 2001-White
Blood Cell Count-ExpNCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sat Jun 21 11:32:13 2014
_____
===
BMDS Model Run
~~~~
  The form of the response function by Model:
     Model 2:
                Y[dose] = a * exp{sign * b * dose}
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
     Model 4:
                Y[dose] = a * [c-(c-1) * exp{-b * dose}]
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  The variance is to be modeled as Var(i) = exp(lalpha + log
(mean(i)) * rho)
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 2
lnalpha	-4.23146
rho	2.9407
a	4.59625
b	0.111233
C	0
d	1

## Parameter Estimates

Variable	Model 2
lnalpha	-4.1642
rho	2.91163
a	8.10768
b	0.110918
С	0
d	1

# Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	10	7.97	2.213
1.361	10	7.63	2.653
2.451	9	5.41	1.392
3.761	9	5.53	1.756
5.258	10	4.54	1.019

## Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	8.108	2.624	-0.1659
1.361	6.972	2.106	0.9884
2.451	6.178	1.766	-1.304
3.761	5.342	1.43	0.394
5.258	4.525	1.123	0.0424

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:		Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R:	Yij = Var{e(ij)} =	

		Likelihoods of Interest	
	Model	Log(likelihood)	DF
AIC			
	Al	-52.43142	6
116.8628	A2	-47.29218	10
114.5844	A3	-47.75877	7
109.5175	R	-63.20171	2
130.4034	2	-50.58738	4
109.1748	2	-30.30730	7

Additive constant for all log-likelihoods = -44.11. This constant added to the above values gives the log-likelihood including the term that does not

depend on the model parameters.

### Explanation of Tests

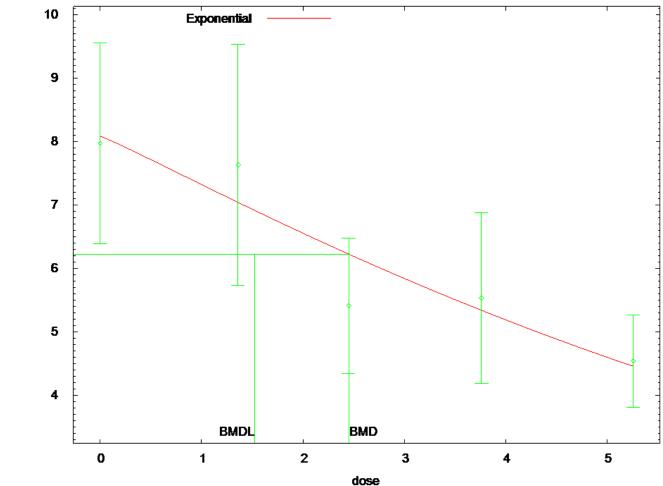
Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A2 vs. A1) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 4: Does Model 2 fit the data? (A3 vs. 2)

# Tests of Interest

Test p-value	-2*log(Likelihood Ratio)	D. F.
Test 1	31.82	8
0.0001004		
Test 2	10.28	4

0.03599 Test 3 0.8174 Test 4 0.1295 0.1295	
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 = 3.52524 BMDL = 2.07864



Mean Response

11:32 06/21 2014

=== Exponential Model. (Version: 1.9; Date: 01/29/2013) Input Data File: C:/Users/dmayfield/Desktop/Ln/WBC\_Concurrent\_Ln-HLS 2001-White Blood Cell Count-ExpCV-1SD-5d.(d) Gnuplot Plotting File: Sat Jun 21 11:32:11 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function by Model: Model 2:  $Y[dose] = a * exp{sign * b * dose}$  $Y[dose] = a * exp\{sign * (b * dose)^d\}$ Model 3:  $Y[dose] = a * [c-(c-1) * exp{-b * dose}]$ Model 4:  $Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]$ Model 5: 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 = MeanResponse 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 = 5Total 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 3
lnalpha	1.18464
rho(S)	0
a	4.59625
b	0.111233
C	0
d	1

(S) = Specified

### Parameter Estimates

Variable	Model 3
lnalpha	1.24644
rho	0
a	8.0841
b	0.117784
С	0
d	1.07945

# Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	10	7.97	2.213
1.361	10	7.63	2.653
2.451	9	5.41	1.392
3.761	9	5.53	1.756
5.258	10	4.54	1.019

## Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	8.084	1.865	-0.1935
1.361	7.038	1.865	1.004
2.451	6.224	1.865	-1.309
3.761	5.337	1.865	0.3105
5.258	4.454	1.865	0.1464

Other models for which likelihoods are calculated:

Model Al: Yij = Mu(i) + e(ij) Var{e(ij)} = Sigma^2

Model A2:	Yij = Var{e(ij)} =	Mu(i) + e(ij) Sigma(i)^2
Model A3:		Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R:	Yij = Var{e(ij)} =	

Likelihoods of Interest

	Model	Log(likelihood)	DF
AIC			
116 0600	Al	-52.43142	6
116.8628	A2	-47.29218	10
114.5844	A3	-52.43142	6
116.8628	R	-63.20171	2
130.4034	3	-53.91457	4
115.8291			

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 5a: Does Model 3 fit the data? (A3 vs 3)

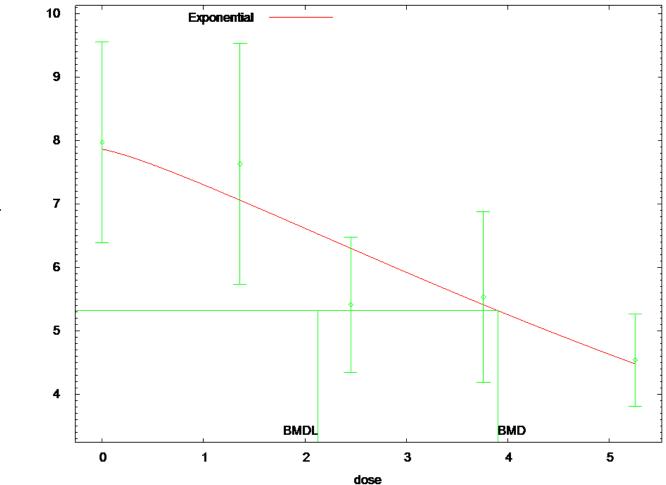
Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.
p-value		

Test 1 0.0001004	31.82	8
Test 2	10.28	4
0.03599 Test 3	10.28	4
0.03599 Test 5a	2.966	2
0.2269		

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. Consider running a non-homogeneous variance model. The p-value for Test 3 is less than .1. You may want to consider a different variance model. The p-value for Test 5a is greater than .1. Model 3 seems to adequately describe the data. Benchmark Dose Computations: Specified Effect = 1.000000 Risk Type = Estimated standard deviations from control Confidence Level = 0.950000BMD = 2.45714

BMDL = 1.52567



Mean Response

11:32 06/21 2014

```
______
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Ln/WBC_Concurrent_Ln-HLS 2001-White
Blood Cell Count-ExpNCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sat Jun 21 11:32:13 2014
_____
===
BMDS Model Run
~~~~
  The form of the response function by Model:
     Model 2:
                Y[dose] = a * exp{sign * b * dose}
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
     Model 4:
                Y[dose] = a * [c-(c-1) * exp{-b * dose}]
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  The variance is to be modeled as Var(i) = exp(lalpha + log
(mean(i)) * rho)
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 3
lnalpha	-4.23146
rho	2.9407
a	4.59625
b	0.111233
C	0
d	1

## Parameter Estimates

Variable	Model 3
lnalpha	-4.4078
rho	3.04324
a	7.86137
b	0.118958
С	0
d	1.22317

# Table of Stats From Input Data

Dose	Ν	Obs Mean	Obs Std Dev
0	10	7.97	2.213
1.361	10	7.63	2.653
2.451	9	5.41	1.392
3.761	9	5.53	1.756
5.258	10	4.54	1.019

## Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	7.861	2.544	0.135
1.361	7.058	2.159	0.8383
2.451	6.3	1.816	-1.47
3.761	5.409	1.44	0.252
5.258	4.476	1.079	0.1883

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:			Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R:	Yij = Var{e(ij)} =		

		Likelihoods of Int	erest
210	Model	Log(likelihood)	DF
AIC			
	Al	-52.43142	6
116.8628	A2	-47.29218	10
114.5844	7.2	-47 75977	
109.5175			
130.4034	R	-63.20171	2
110.8972	3	-50.44861	5
114.5844 109.5175	A2 A3 R	-47.29218 -47.75877 -63.20171	10 7 2

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 5a: Does Model 3 fit the data? (A3 vs 3)

### Tests of Interest

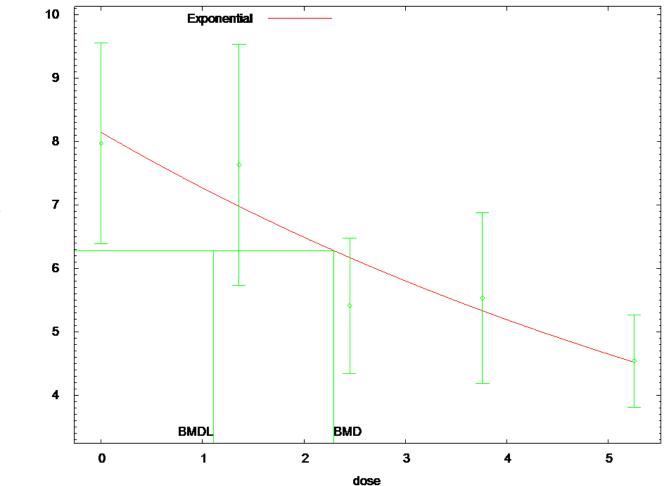
Test p-value	-2*log(Likelihood Ratio)	D. F.
Test 1 0.0001004	31.82	8

Test 2 0.03599	10.28	4
Test 3	0.9332	3
0.8174		
Test 5a	5.38	2
0.06789		

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 5a is less than .1. Model 3 may not adequately describe the data; you may want to consider another model. Benchmark Dose Computations: Specified Effect = 1.000000 Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

BMD = 3.90052 BMDL = 2.1309



Mean Response

11:32 06/21 2014

=== Exponential Model. (Version: 1.9; Date: 01/29/2013) Input Data File: C:/Users/dmayfield/Desktop/Ln/WBC\_Concurrent\_Ln-HLS 2001-White Blood Cell Count-ExpCV-1SD-5d.(d) Gnuplot Plotting File: Sat Jun 21 11:32:11 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function by Model: Model 2:  $Y[dose] = a * exp{sign * b * dose}$  $Y[dose] = a * exp\{sign * (b * dose)^d\}$ Model 3:  $Y[dose] = a * [c-(c-1) * exp{-b * dose}]$ Model 4:  $Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]$ Model 5: 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 = MeanResponse 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 = 5Total number of records with missing values = 0 Maximum number of iterations = 500 Relative Function Convergence has been set to: 1e-008 Parameter Convergence has been set to: 1e-008 MLE solution provided: Exact Initial Parameter Values

Variable	Model 4
lnalpha	1.18464
rho(S)	0
a	8.3685
b	0.188405
C	0.271255
d	1

(S) = Specified

#### Parameter Estimates

Variable	Model 4
lnalpha	1.24721
rho	0
a	8.14254
b	0.119801
С	0.0476533
d	1

# Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	10	7.97	2.213
1.361	10	7.63	2.653
2.451	9	5.41	1.392
3.761	9	5.53	1.756
5.258	10	4.54	1.019

## Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual	
0	8.143	1.866	-0.2925	
1.361	6.976	1.866	1.109	
2.451	6.169	1.866	-1.221	
3.761	5.33	1.866	0.3221	
5.258	4.518	1.866	0.03665	

Other models for which likelihoods are calculated:

Model Al: Yij = Mu(i) + e(ij) Var{e(ij)} = Sigma^2

Model A2:	Yij = Var{e(ij)} =	Mu(i) + e(ij) Sigma(i)^2
Model A3:		Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R:	Yij = Var{e(ij)} =	

Likelihoods of Interest

AIC	Model	Log(likelihood)	DF
ALC			
	Al	-52.43142	6
116.8628	A2	-47.29218	10
114.5844	A3	-52.43142	6
116.8628	R	-63.20171	2
130.4034	4	-53.93301	4
115.866	7	-33.330T	7

Additive constant for all log-likelihoods = -44.11. This constant added to the above values gives the log-likelihood including the term that does not

depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A2 vs. A1) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 6a: Does Model 4 fit the data? (A3 vs 4)

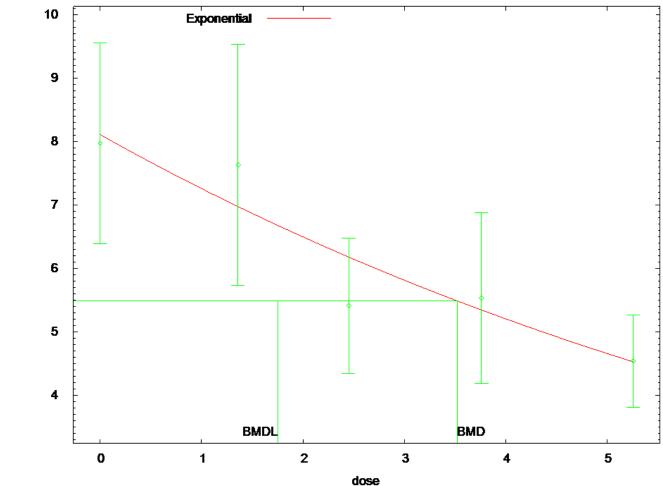
Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.
p-value		

Test 1 0.0001004	31.82	8
Test 2	10.28	4
0.03599 Test 3	10.28	4
0.03599 Test 6a	3.003	2
0.2228		

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. Consider running a non-homogeneous variance model. The p-value for Test 3 is less than .1. You may want to consider a different variance model. 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 = 0.950000BMD = 2.29723

BMDL = 1.10573



Mean Response

11:32 06/21 2014

```
______
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Ln/WBC_Concurrent_Ln-HLS 2001-White
Blood Cell Count-ExpNCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sat Jun 21 11:32:13 2014
_____
===
BMDS Model Run
~~~~
  The form of the response function by Model:
     Model 2:
                Y[dose] = a * exp{sign * b * dose}
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
     Model 4:
                Y[dose] = a * [c-(c-1) * exp{-b * dose}]
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  The variance is to be modeled as Var(i) = exp(lalpha + log
(mean(i)) * rho)
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 4	
lnalpha	-4.23146	
rho	2.9407	
a	8.3685	
b	0.12945	
C	0.0542511	
d	1	

### Parameter Estimates

Variable	Model 4
lnalpha	-4.1642
rho	2.91163
a	8.10768
b	0.110918
С	0
d	1

# Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	10	7.97	2.213
1.361	10	7.63	2.653
2.451	9	5.41	1.392
3.761	9	5.53	1.756
5.258	10	4.54	1.019

## Estimated Values of Interest

al	l Scaled Resi	Est Std	Est Mean	Dose
	·			
	-0.165	2.624	8.108	0
	0.988	2.106	6.972	1.361
	-1.30	1.766	6.178	2.451
	0.39	1.43	5.342	3.761
	0.0424	1.123	4.525	5.258

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)

	<pre>Var{e(ij)} =</pre>	Sigma(i) <sup>2</sup>
Model A3:		Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R:	Yij = Var{e(ij)} =	

		Likelihoods of Int	erest
	Model	Log(likelihood)	DF
AIC			
	Al	-52.43142	6
116.8628	A2	-47.29218	10
114.5844			
109.5175	A3	-47.75877	7
130.4034	R	-63.20171	2
	4	-50.58738	4
109.1748			

Additive constant for all log-likelihoods = -44.11. This constant added to the above values gives the log-likelihood including the term that does not

depend on the model parameters.

#### Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A2 vs. A1) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 6a: Does Model 4 fit the data? (A3 vs 4)

#### Tests of Interest

Test p-value	-2*log(Likelihood Ratio)	D. F.
Test 1 0.0001004	31.82	8

Test 2 0.03599	10.28	4
Test 3 0.8174	0.9332	3
Test 6a 0.1295	5.657	3
0.1295		

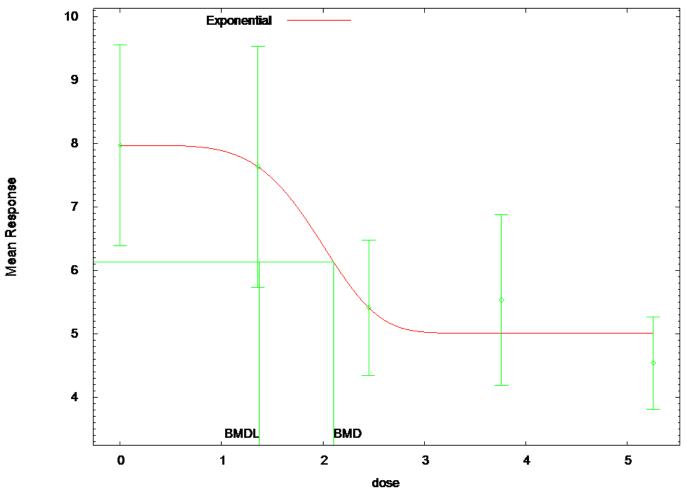
The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data. The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate. The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here. The p-value for Test 6a is greater than .1. Model 4 seems to adequately describe the data. Benchmark Dose Computations: Specified Effect = 1.000000

Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

BMD = 3.52524

BMDL = 1.74989



11:32 06/21 2014

=== Exponential Model. (Version: 1.9; Date: 01/29/2013) Input Data File: C:/Users/dmayfield/Desktop/Ln/WBC\_Concurrent\_Ln-HLS 2001-White Blood Cell Count-ExpCV-1SD-5d.(d) Gnuplot Plotting File: Sat Jun 21 11:32:11 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function by Model: Model 2:  $Y[dose] = a * exp{sign * b * dose}$  $Y[dose] = a * exp\{sign * (b * dose)^d\}$ Model 3:  $Y[dose] = a * [c-(c-1) * exp{-b * dose}]$ Model 4:  $Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]$ Model 5: 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 = MeanResponse 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 = 5Total 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	1.18464
rho(S)	0
a	8.3685
b	0.188405
C	0.271255
d	1

(S) = Specified

#### Parameter Estimates

Variable	Model 5
lnalpha	1.2138
rho	0
a	7.97001
b	0.471998
C	0.628474
d	4.754

# Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	10	7.97	2.213
1.361	10	7.63	2.653
2.451	9	5.41	1.392
3.761	9	5.53	1.756
5.258	10	4.54	1.019

## Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	7.97	1.835	-1.442e-005
1.361	7.63	1.835	1.875e-005
2.451	5.41	1.835	-1.872e-005
3.761	5.009	1.835	0.852
5.258	5.009	1.835	-0.8083

Other models for which likelihoods are calculated:

Model Al: Yij = Mu(i) + e(ij) Var{e(ij)} = Sigma^2

Model A2:	Yij = Var{e(ij)} =	Mu(i) + e(ij) Sigma(i)^2
Model A3:		Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R:	Yij = Var{e(ij)} =	

Likelihoods of Interest

AIC	Model	Log(likelihood)	DF
ALC			
	A1	-52.43142	6
116.8628	A2	-47.29218	10
114.5844	A3	-52.43142	6
116.8628	R	-63.20171	2
130.4034	5	-53.1311	5
116.2622			

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)

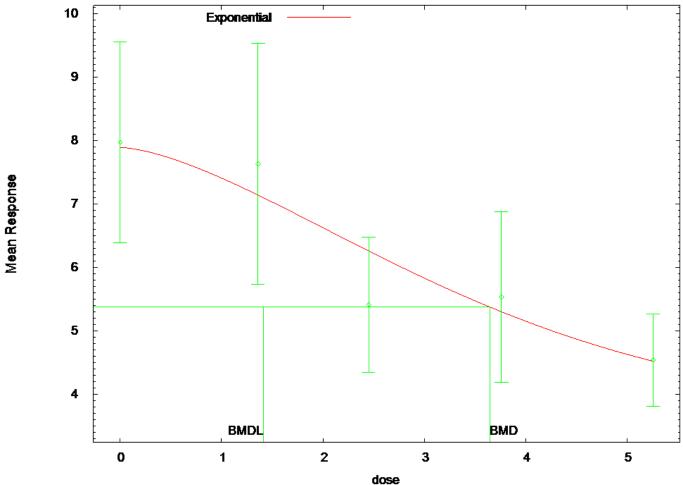
Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.
p-value		

Test 1 0.0001004	31.82	8
Test 2	10.28	4
0.03599 Test 3	10.28	4
0.03599 Test 7a	1.399	1
0.2368		

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. Consider running a non-homogeneous variance model. The p-value for Test 3 is less than .1. You may want to consider a different variance model. 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 = 0.950000BMD = 2.10356

BMDL = 1.37489



11:32 06/21 2014

```
______
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Ln/WBC_Concurrent_Ln-HLS 2001-White
Blood Cell Count-ExpNCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sat Jun 21 11:32:13 2014
_____
===
BMDS Model Run
~~~~
  The form of the response function by Model:
     Model 2:
                Y[dose] = a * exp{sign * b * dose}
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
     Model 4:
                Y[dose] = a * [c-(c-1) * exp{-b * dose}]
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  The variance is to be modeled as Var(i) = exp(lalpha + log
(mean(i)) * rho)
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 5
lnalpha	-4.23146
rho	2.9407
a	8.3685
b	0.12945
C	0.0542511
d	1

### Parameter Estimates

Variable	Model 5
lnalpha	-4.19069
rho	2.92196
a	7.88959
b	0.256919
С	0.46383
d	1.55237

# Table of Stats From Input Data

Dose	Ν	Obs Mean	Obs Std Dev
0	10	7.97	2.213
1.361	10	7.63	2.653
2.451	9	5.41	1.392
3.761	9	5.53	1.756
5.258	10	4.54	1.019

## Estimated Values of Interest

1
4
7
1
8

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) <sup>2</sup>
Model A3:			Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R:	Yij = Var{e(ij)} =		

		Likelihoods of Int	erest
	Model	Log(likelihood)	DF
AIC			
	Al	-52.43142	6
116.8628	A2	-47.29218	10
114.5844	A3	-47.75877	7
109.5175			
130.4034	R	-63.20171	2
112.763	5	-50.38152	6

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

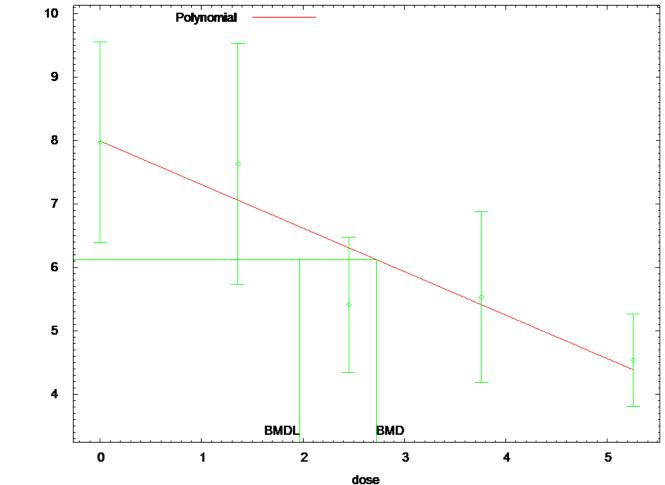
Test p-value	-2*log(Likelihood Ratio)	D. F.
Test 1 0.0001004	31.82	8

Test 2 0.03599	10.28	4
Test 3	0.9332	3
0.8174 Test 7a	5,245	1
0.022	5.215	Ŧ

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 7a is less than .1. Model 5 may not adequately describe the data; you may want to consider another model. Benchmark Dose Computations: Specified Effect = 1.000000 Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

BMD = 3.64435 BMDL = 1.41031



Mean Response

12:43 07/09 2014

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_WBC\_Concurrent\_Ln/WBC\_Concurrent\_L n-HLS 2001-White Blood Cell Count-Poly2CV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_WBC\_Concurrent\_Ln/WBC\_Concurrent\_L n-HLS 2001-White Blood Cell Count-Poly2CV-1SD-5d.plt Wed Jul 09 12:43:41 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse 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 = 5Total number of records with missing values = 0Maximum 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 = 3.64969 Specified rho = 0 beta\_0 = 8.15662 beta\_1 = -0.952983 beta\_2 = 0 Asymptotic Correlation Matrix of Parameter Estimates ( \*\*\* The model parameter(s) -rho -beta 2 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	-1.8e-008	6.2e-009
beta_0	-1.8e-008	1	-0.81
beta_1	6.2e-009	-0.81	1

## Parameter Estimates

			95.0%
Wald Confidence Ir	nterval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Conf	. Limit		
alpha	3.4974	0.713903	
2.09817	4.89662		
beta_0	7.9913	0.457567	
7.09448	8.88811		
beta_1	-0.685697	0.145247	_
0.970375	-0.401018		
beta_2	0	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 Scaled H	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 -0.036	10	7.97	7.99	2.21	1.87
1.361 0.967	10	7.63	7.06	2.65	1.87
$2.451 \\ -1.44$	9	5.41	6.31	1.39	1.87
3.761 0.189	9	5.53	5.41	1.76	1.87
5.258 0.261	10	4.54	4.39	1.02	1.87

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<sup>2</sup>

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
Al	-52.431420	б	116.862840
A2	-47.292184	10	114.584369
A3	-52.431420	б	116.862840
fitted	-54.048454	3	114.096907
R	-63.201706	2	130.403412

#### 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

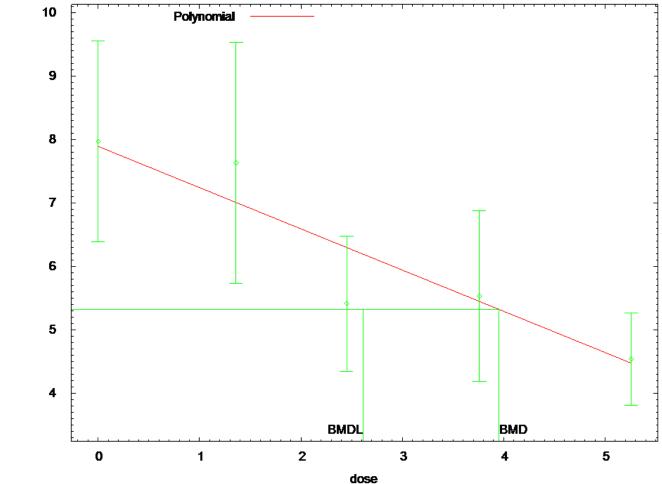
Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.819	8	0.0001004
Test 2	10.2785	4	0.03599
Test 3	10.2785	4	0.03599
Test 4	3.23407	3	0.3569

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. Consider running a non-homogeneous variance model The p-value for Test 3 is less than .1. You may want to consider a different variance model 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 = 2.72735

BMDL = 1.96547



Mean Response

12:43 07/09 2014

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_WBC\_Concurrent\_Ln/WBC\_Concurrent\_L n-HLS 2001-White Blood Cell Count-Poly2NCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_WBC\_Concurrent\_Ln/WBC\_Concurrent\_L n-HLS 2001-White Blood Cell Count-Poly2NCV-1SD-5d.plt Wed Jul 09 12:43:42 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse 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 = 5Total number of records with missing values = 0Maximum 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 = 1.29464 rho = 0 beta\_0 = 8.15662 beta\_1 = -0.952983 beta\_2 = 0 Asymptotic Correlation Matrix of Parameter Estimates ( \*\*\* The model parameter(s) -beta\_2 have been estimated at a boundary point, or have been specified by the user,

and do not appear in t	he correlation matrix )
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	lalpha	rho	beta_0	beta_1
lalpha	1	-0.99	0.15	-0.18
rho	-0.99	1	-0.15	0.18
beta_0	0.15	-0.15	1	-0.91
beta_1	-0.18	0.18	-0.91	1

Parameter Estimates

			95.0%
Wald Confidence 1	Interval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Cor	nf. Limit		
lalpha	-4.45485	2.03072	_
8.43498	-0.474714		
rho	3.07104	1.1156	
0.884506	5.25758		
beta_0	7.88794	0.536104	
6.83719	8.93868		
beta_1	-0.649741	0.131724	_
0.907915	-0.391568		
beta_2	0	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 Scaled	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 0.101	10	7.97	7.89	2.21	2.57
1.361 0.925	10	7.63	7	2.65	2.14
2.451 -1.46	9	5.41	6.3	1.39	1.82
3.761 0.177	9	5.53	5.44	1.76	1.45

5.258	10	4.54	4.47	1.02	1.08
0.201					

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
Al	-52.431420	6	116.862840
A2	-47.292184	10	114.584369
A3	-47.758770	7	109.517540
fitted	-50.527570	4	109.055140
R	-63.201706	2	130.403412

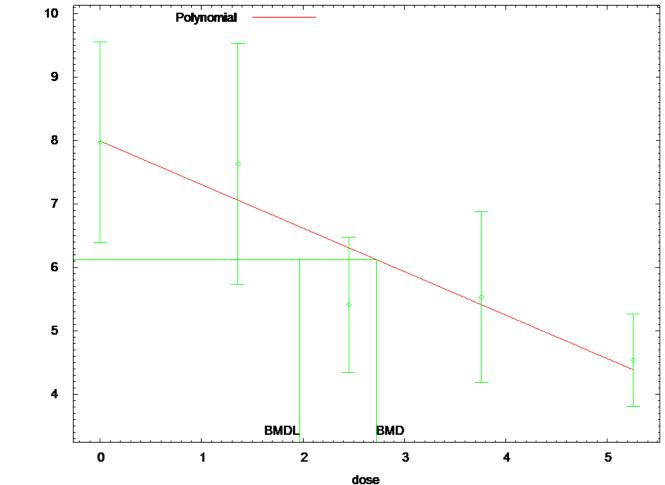
### Explanation of Tests

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	31.819	8	0.0001004
Test 2	10.2785	4	0.03599
Test 3	0.933171	3	0.8174
Test 4	5.5376	3	0.1364

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 = Estimated standard deviations from the Risk Type control mean Confidence level = 0.95 BMD = 3.95557 BMDL = 2.61437



Mean Response

12:43 07/09 2014

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beta\_3

have been estimated at a boundary point, or have been specified by the user,

and do not appear in the correlation matrix  $\ensuremath{)}$ 

beta_1	beta_0	alpha	
4.1e-009	-6.3e-008	1	alpha
-0.81	1	-6.3e-008	beta_0
1	-0.81	4.1e-009	beta_1

Parameter Estimates

95.0%

Wald Co	nfidence In	terval		
•	Variable	Estimate	Std. Err.	Lower Conf.
Limit	Upper Conf	. Limit		
	alpha	3.4974	0.713903	
2.09817		4.89662		
	beta_0	7.9913	0.457567	
7.09448		8.88811		
	beta_1	-0.685697	0.145247	-
0.97037	5	-0.401018		
	beta_2	0	NA	
	beta_3	0	NA	

NA - Indicates that this parameter has hit a bound implied by some inequality constraint and thus has no standard error.

Dose Scaled H	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev			
0 -0.036	10	7.97	7.99	2.21	1.87			
1.361 0.967	10	7.63	7.06	2.65	1.87			
2.451	9	5.41	6.31	1.39	1.87			
3.761	9	5.53	5.41	1.76	1.87			
5.258	10	4.54	4.39	1.02	1.87			

Table of Data and Estimated Values of Interest

Model Descriptions for likelihoods calculated

Var{e(i)} = Sigma^2

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)

#### Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
Al	-52.431420	6	116.862840
A2	-47.292184	10	114.584369
A3	-52.431420	6	116.862840
fitted	-54.048454	3	114.096907
R	-63.201706	2	130.403412

### Explanation of Tests

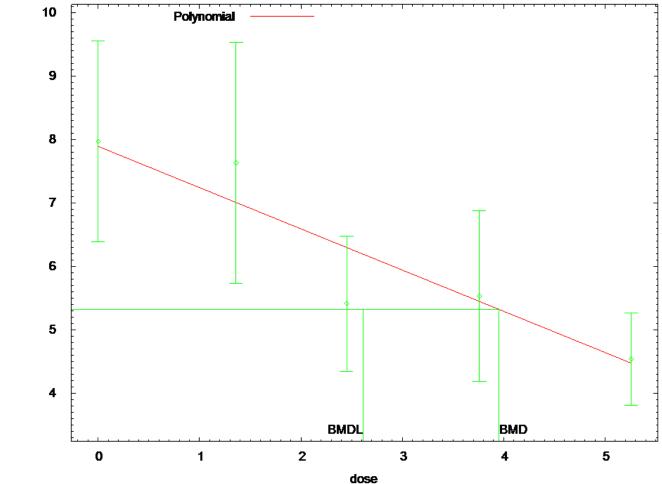
Test 1: Do responses and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A1 vs A2) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 4: Does the Model for the Mean Fit? (A3 vs. fitted) (Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

### Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.819	8	0.0001004
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Test 3	10.2785	4	0.03599
Test 4	3.23407	3	0.3569

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. Consider running a non-homogeneous variance model The p-value for Test 3 is less than .1. You may want to consider а different variance model 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 Estimated standard deviations from the Risk Type = control mean Confidence level = 0.95 2.72735 BMD = BMDL = 1.96547



Mean Response

12:43 07/09 2014

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have been estimated at a boundary point, or have been specified by the user, and do not appear in the correlation matrix )

	lalpha	rho	beta_0	beta_1
lalpha	1	-0.99	0.15	-0.18
rho	-0.99	1	-0.15	0.18
beta_0	0.15	-0.15	1	-0.91
beta_1	-0.18	0.18	-0.91	1

Parameter Estimates

			95.0%
Wald Confidence	Interval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Cor	nf. Limit		
lalpha	-4.45485	2.03072	-
8.43498	-0.474719		
rho	3.07105	1.1156	
0.884508	5.25759		
beta_0	7.88794	0.536104	
6.83719	8.93868		
beta_1	-0.649741	0.131724	-
0.907914	-0.391567		
beta_2	0	NA	
beta_3	- 0	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

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2

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Model Descriptions for likelihoods calculated

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Model R: Yi = Mu + e(i) $Var{e(i)} = Sigma^2$ 

## Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
Al	-52.431420	6	116.862840
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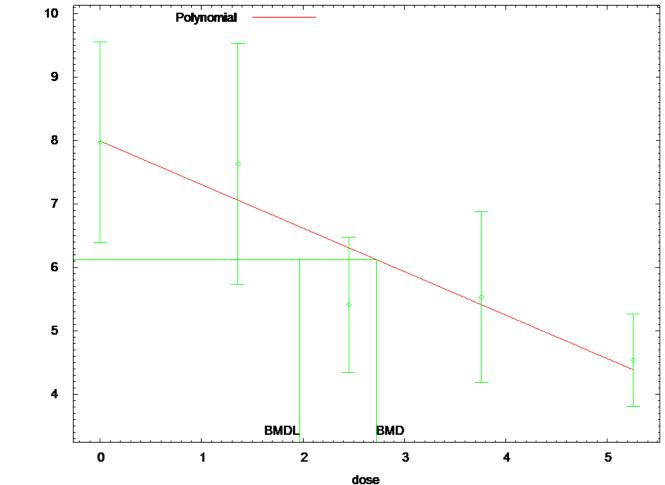
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#### Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.819	8	0.0001004
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Test 3	0.933171	3	0.8174

5.5376 3 0.1364 Test 4 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 = Estimated standard deviations from the Risk Type control mean Confidence level = 0.95 BMD = 3.95557 BMDL = 2.61437



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Asymptotic Correlation Matrix of Parameter Estimates

beta_1	beta_0	alpha	
-1.9e-007	4.7e-007	1	alpha
-0.81	1	4.7e-007	beta_0
1	-0.81	-1.9e-007	beta_1

Parameter Estimates

#### 95.0%

Wald Cor	nfidence Int	cerval		
I	/ariable	Estimate	Std. Err.	Lower Conf.
Limit	Upper Conf.	Limit		
	alpha	3.49739	0.713902	
2.09817		4.89662		
	beta_0	7.9913	0.457566	
7.09448		8.88811		
	beta_1	-0.685697	0.145247	_
0.970375	5	-0.401019		
	beta_2	0	NA	
	beta_3	0	NA	
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Dose Scaled :	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
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Table of Data and Estimated Values of Interest

0.189 5.258 0.261	10	4.54	4.39	1.02	1.87
Model	Descriptio	ns for likeli	hoods calcula	ted	
Model		Yij = Mu(i) ij)} = Sigma^			
Model		Yij = Mu(i) ij)} = Sigma(			
Мс	Var{e( odel A3 use	Yij = Mu(i) ij)} = Sigma^ s any fixed v ed by the use	2 ariance param	eters that	
Model		Yi = Mu + e (i)} = Sigma^			

# Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
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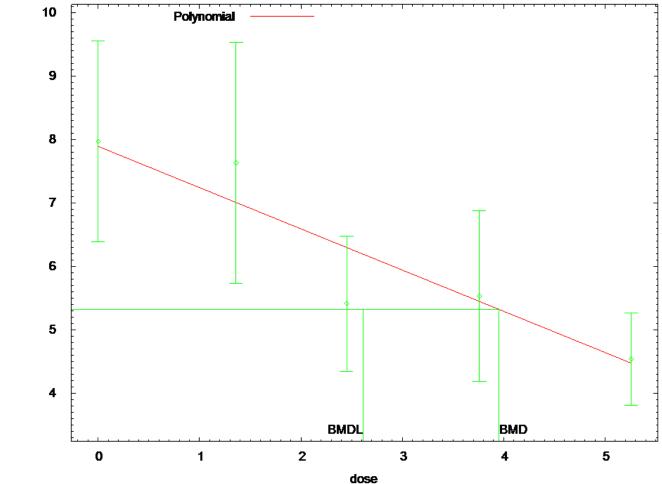
#### Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
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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. Consider running a non-homogeneous variance model The p-value for Test 3 is less than .1. You may want to consider а different variance model 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 = Estimated standard deviations from the Risk Type control mean Confidence level = 0.95

BMD = 2.72734

BMDL = 1.96547



Mean Response

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Asymptotic Correlation Matrix of Parameter Estimates

Deta_1	Deca_0	1110	Tatpila	
-0.18	0.15	-0.99	1	lalpha
0.18	-0.15	1	-0.99	rho
-0.91	1	-0.15	0.15	beta_0
1	-0.91	0.18	-0.18	beta_1

#### Parameter Estimates

## 95.0%

			95.08
Wald Confidence I	nterval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Con	f. Limit		
lalpha	-4.45484	2.03072	_
8.43497	-0.474713		
rho	3.07104	1.1156	
0.884505	5.25758		
beta_0	7.88794	0.536104	
6.83719	8.93868		
beta_1	-0.649741	0.131724	_
0.907915	-0.391568		
beta_2	0	NA	
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Table of Data and Estimated Values of Interest

Dose Scaled R	N es.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
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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

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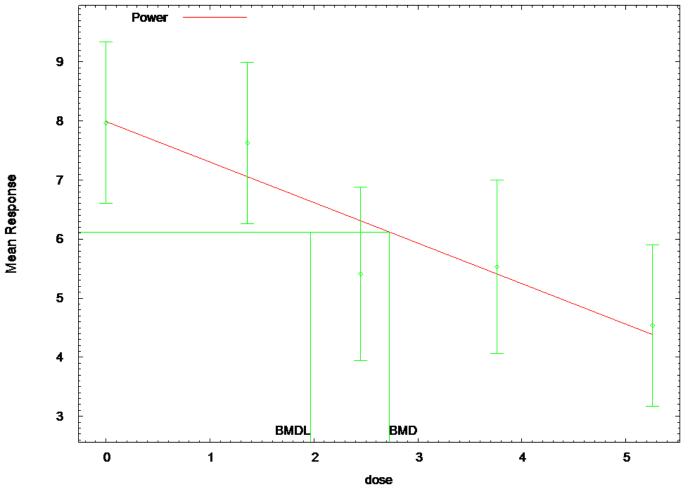
### Explanation of Tests

### Tests of Interest

Test	-2*log	(Likelihood	Ratio	) Test df	p-value
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3

31.819 8 4 Test 1 0.0001004 Test 2 10.2785 0.03599 Test 3 0.933171 3 0.8174 Test 4 5.5376 3 0.1364 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 = 3.95557 2.61437 BMDL =



Power Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

11:32 06/21 2014

=== Power Model. (Version: 2.18; Date: 05/19/2014) Input Data File: C:/Users/dmayfield/Desktop/Ln/WBC\_Concurrent\_Ln-HLS 2001-White Blood Cell Count-PowerCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Ln/WBC\_Concurrent\_Ln-HLS 2001-White Blood Cell Count-PowerCV-1SD-5d.plt Sat Jun 21 11:32:12 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = control + slope \* dose^power Dependent variable = MeanResponse 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 = 5Total 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 = 3.64969 rho = Specified 0 control = 4.54 slope = 3.75463 power = -1.18214 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	-4.1e-009	7.4e-009
control	-4.1e-009	1	-0.81
slope	7.4e-009	-0.81	1

## Parameter Estimates

			95.0%
Wald Confidence Int	zerval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Conf	. Limit		
alpha	3.4974	0.713903	
2.09817	4.89662		
control	7.9913	0.457567	
7.09448	8.88811		
slope	-0.685697	0.145247	-
0.970375	-0.401018		
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
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Dose Scaled 1	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
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1.361 0.967	10	7.63	7.06	2.65	1.87
2.451	9	5.41	6.31	1.39	1.87
3.761	9	5.53	5.41	1.76	1.87
5.258 0.261	10	4.54	4.39	1.02	1.87

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<sup>2</sup>

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
Al	-52.431420	б	116.862840
A2	-47.292184	10	114.584369
A3	-52.431420	б	116.862840
fitted	-54.048454	3	114.096907
R	-63.201706	2	130.403412

#### 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.)	

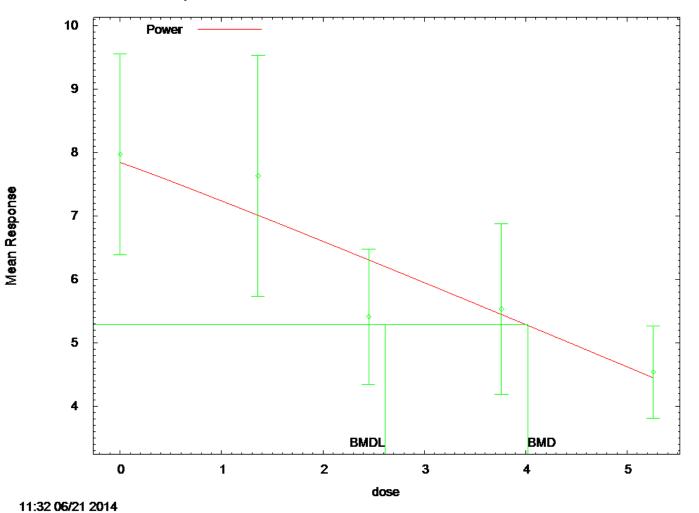
#### Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.819	8	0.0001004
Test 2	10.2785	4	0.03599
Test 3	10.2785	4	0.03599
Test 4	3.23407	3	0.3569

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. Consider running a non-homogeneous variance model The p-value for Test 3 is less than .1. You may want to consider а different variance model 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 = Estimated standard deviations from the Risk Type control mean Confidence level = 0.95 BMD = 2.72735

BMDL = 1.96547



=== Power Model. (Version: 2.18; Date: 05/19/2014) Input Data File: C:/Users/dmayfield/Desktop/Ln/WBC\_Concurrent\_Ln-HLS 2001-White Blood Cell Count-PowerNCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Ln/WBC\_Concurrent\_Ln-HLS 2001-White Blood Cell Count-PowerNCV-1SD-5d.plt Sat Jun 21 11:32:13 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = control + slope \* dose^power Dependent variable = MeanResponse Independent variable = Dose The power is restricted to be greater than or equal to 1 The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) \* rho) Total number of dose groups = 5Total number of records with missing values = 0Maximum 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 = 1.29464 rho = 0 control = 4.54 slope = 3.75463 power = -1.18214 Asymptotic Correlation Matrix of Parameter Estimates lalpha rho control slope power

lalpha -0.27	1	-1	0.47	-0.37
rho 0.27	-1	1	-0.49	0.38
control -0.7	0.47	-0.49	1	-0.82
slope 0.97	-0.37	0.38	-0.82	1
power 1	-0.27	0.27	-0.7	0.97

## Parameter Estimates

			95.0%
Wald Confidence In	terval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Conf	. Limit		
lalpha	-4.51069	2.46794	-
9.34776	0.326384		
rho	3.10193	1.36559	
0.425425	5.77844		
control	7.84366	0.738466	
6.3963	9.29103		
slope	-0.603526	0.542692	_
1.66718	0.460131		
power	1.03741	0.445048	
0.165135	1.90969		

## Table of Data and Estimated Values of Interest

Dose Scaled 1	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 0.156	10	7.97	7.84	2.21	2.56
1.361 0.908	10	7.63	7.01	2.65	2.15
2.451 -1.48	9	5.41	6.31	1.39	1.83
3.761 0.147	9	5.53	5.46	1.76	1.46

5.258	10	4.54	4.47	1.02	1.07
0.216					

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
Al	-52.431420	6	116.862840
A2	-47.292184	10	114.584369
A3	-47.758770	7	109.517540
fitted	-50.523874	5	111.047748
R	-63.201706	2	130.403412

## Explanation of Tests

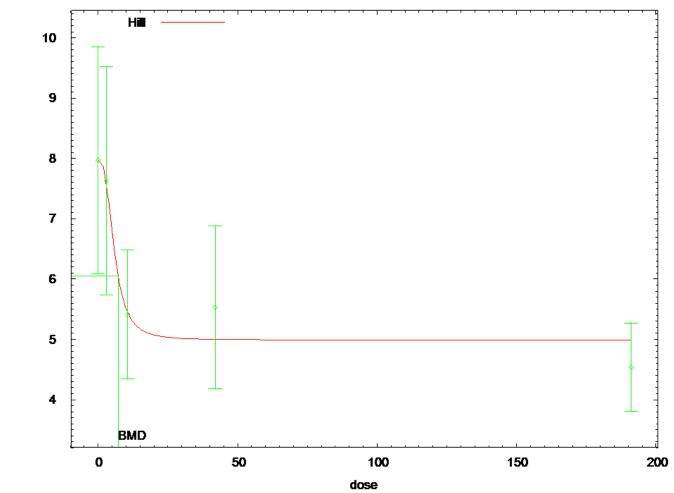
Test 1: Do responses and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A1 vs A2) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 4: Does the Model for the Mean Fit? (A3 vs. fitted) (Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

#### Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.819	8	0.0001004
Test 2	10.2785	4	0.03599
Test 3	0.933171	3	0.8174
Test 4	5.53021	2	0.06297

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 = Estimated standard deviations from the Risk Type control mean Confidence level = 0.95 BMD = 4.02318BMDL = 2.61571

BMDS Model Results for White Blood Cell Count (Untransformed Doses, Historical Controls)



09:34 06/22 2014

Mean Response

Hill Model

=== Hill Model. (Version: 2.17; Date: 01/28/2013) Input Data File: C:/Users/dmayfield/Desktop/Norm/WBC\_Historical-HLS 2001-White Blood Cell Count-HillCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Norm/WBC\_Historical-HLS 2001-White Blood Cell Count-HillCV-1SD-5d.plt Sun Jun 22 09:34:41 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = intercept + v\*dose^n/(k^n + dose^n) Dependent variable = MeanResponse 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 = 5Total 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 = 4.0681 Specified rho = 0 7.97 intercept = v = -3.43 n = 2.04485 k = 7.66914 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 )

and	do	not	appear	ın	the	corre.	Lation	matrıx	)

k		alpha	intercept	v	n
alpha -2.4e-007		1	-6.8e-008	1.6e-007	3e-007
interc -0.5	ept	-6.8e-008	1	-0.81	-0.48
0.17	v	1.6e-007	-0.81	1	0.59
0.094	n	3e-007	-0.48	0.59	1
1	k	-2.4e-007	-0.5	0.17	0.094

# Parameter Estimates

		95.0%
cerval		
Estimate	Std. Err.	Lower Conf.
. Limit		
3.73939	0.763299	
5.23543		
7.98132	0.610793	
9.17845		
-2.98856	0.789337	-
-1.44149		
2.86104	2.62932	-
8.01442		
5.76723	3.28608	-
12.2078		
	Estimate Limit 3.73939 5.23543 7.98132 9.17845 -2.98856 -1.44149 2.86104 8.01442 5.76723	Estimate Std. Err. Limit 3.73939 0.763299 5.23543 0.610793 9.17845 0.789337 -1.44149 2.86104 2.62932 8.01442 5.76723 3.28608

# Table of Data and Estimated Values of Interest

Dose Scaled R		Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 -0.0185	10	7.97	7.98	2.63	1.93

2.9	10	7.63	7.61	2.65	1.93
0.0253					
10.6	9	5.41	5.44	1.39	1.93
-0.0441	_		_		
42	9	5.53	5	1.76	1.93
0.818					
191.1	10	4.54	4.99	1.02	1.93
-0.741					

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
Al	-55.036182	6	122.072364
A2	-49.003692	10	118.007385
A3	-55.036182	6	122.072364
fitted	-55.654114	5	121.308228
R	-64.896924	2	133.793848

## Explanation of Tests

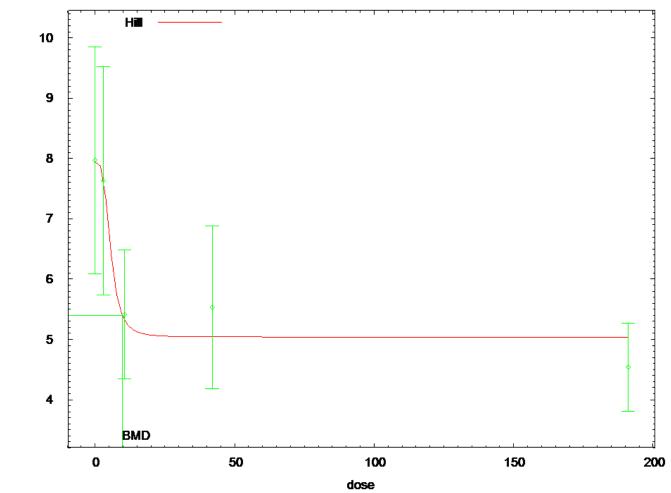
Test 1:	Do responses and/or variances differ among Dose levels?
	(A2 vs. R)
Test 2:	Are Variances Homogeneous? (Al vs A2)
Test 3:	Are variances adequately modeled? (A2 vs. A3)
Test 4:	Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:	When rho=0 the results of Test 3 and Test 2 will be the
same.)	

## Tests of Interest

Test	-2*log(Likelihood	Ratio)	Test df	p-value
IESL	-Z IUG(LIKEIII000	Ratio)	iest ui	p-varue

31.7865 8 4 Test 1 0.0001017 Test 2 12.065 0.01687 Test 3 12.065 4 0.01687 1 Test 4 1.23586 0.2663 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. Consider running a non-homogeneous variance model The p-value for Test 3 is less than .1. You may want to consider а different variance model 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 = Estimated standard deviations from the Risk Type control mean Confidence level = 0.95 BMD = 7.12804

BMDL computation failed.



09:34 06/22 2014

Mean Response

Hill Model

=== Hill Model. (Version: 2.17; Date: 01/28/2013) Input Data File: C:/Users/dmayfield/Desktop/Norm/WBC\_Historical-HLS 2001-White Blood Cell Count-HillNCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Norm/WBC\_Historical-HLS 2001-White Blood Cell Count-HillNCV-1SD-5d.plt Sun Jun 22 09:34:42 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = intercept + v\*dose^n/(k^n + dose^n) Dependent variable = MeanResponse Independent variable = Dose Power parameter restricted to be greater than 1 The variance is to be modeled as Var(i) = exp(lalpha + rho \* ln(mean(i))) Total number of dose groups = 5Total number of records with missing values = 0Maximum 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 = 1.40318 rho = 0 7.97 intercept = v = -3.43 n = 2.04485 k = 7.66914 Asymptotic Correlation Matrix of Parameter Estimates lalpha rho intercept v

n	k			
lalpha -0.076	1 0.0005	-0.99	0.31	-0.41
rho 0.076 -	-0.99 0.00025	1	-0.34	0.42
intercept -0.55	0.31 -0.57	-0.34	1	-0.93
v 0.61	-0.41 0.43	0.42	-0.93	1
n 1 0	-0.076 .51	0.076	-0.55	0.61
k 0.51	0.0005 1	-0.00025	-0.57	0.43

Parameter Estimates

			95.0%
Wald Confidence	Interval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Co	nf. Limit		
lalpha	-3.78741	2.04747	-
7.80039	0.225565		
rho	2.73058	1.12838	
0.518992	4.94217		
intercept	7.94128	0.756311	
6.45893	9.42362		
v	-2.89843	0.846166	-
4.55688	-1.23997		
n	3.53412	3.51116	-
3.34763	10.4159		
k	5.58094	3.3883	-
1.06001	12.2219		

Table of Data and Estimated Values of Interest

Dose Scaled R		Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 0.0357	10	7.97	7.94	2.63	2.55

2.9	10	7.63	7.68	2.65	2.43
-0.0655 10.6	9	5.41	5.31	1.39	1.47
0.194	9	5.41	5.51	1.39	1.4/
42	9	5.53	5.05	1.76	1.37
1.06					
191.1	10	4.54	5.04	1.02	1.37
-1.16					

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
Al	-55.036182	б	122.072364
A2	-49.003692	10	118.007385
A3	-49.214548	7	112.429095
fitted	-51.729259	б	115.458518
R	-64.896924	2	133.793848

## 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

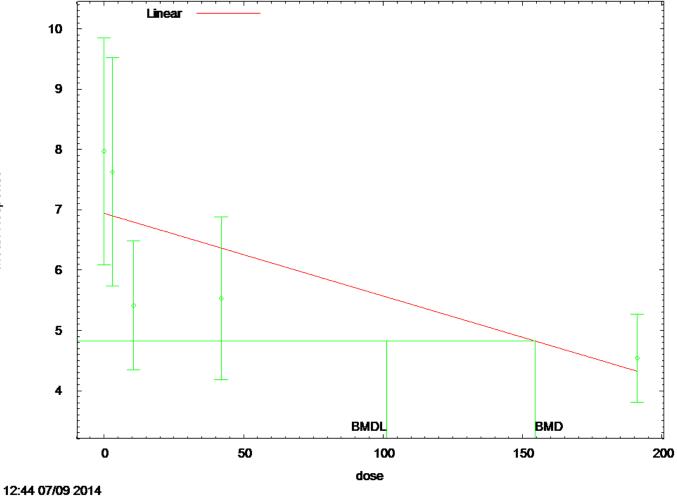
Test	-2*log(Likelihood	Patio)	Test df	aulevea
Iest	-Z"IOG(LIKEIIIIOOd	RALIO)	iest ai	p-value

3

Test 131.786580.0001017Test 212.06540.01687Test 30.42171130.9357Test 45.0294210.02492

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 = Estimated standard deviations from the Risk Type control mean Confidence level = 0.95 BMD = 9.78299

BMDL computation failed.



Mean Response

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_WBC\_Historical/WBC\_Historical-HLS 2001-White Blood Cell Count-LinearCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_WBC\_Historical/WBC\_Historical-HLS 2001-White Blood Cell Count-LinearCV-1SD-5d.plt Wed Jul 09 12:44:57 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse Independent variable = Dose rho is set to 0 Signs of the polynomial coefficients are not restricted A constant variance model is fit Total number of dose groups = 5Total number of records with missing values = 0Maximum 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 = 4.0681 rho = 0 Specified beta\_0 = 6.88046 beta\_1 = -0.0134724 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  $\)$ 

beta_1	beta_0	alpha	
-6.3e-008	3.5e-007	1	alpha
-0.56	1	3.5e-007	beta_0
1	-0.56	-6.3e-008	beta_1

## Parameter Estimates

			95.0%
Wald Confidence I	nterval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Con	f. Limit		
alpha	4.47635	0.913731	
2.68547	6.26723		
beta_0	6.93587	0.369654	
6.21136	7.66038		
beta_1	-0.0136993	0.00414278	-
0.021819	-0.0055796		

Table of Data and Estimated Values of Interest

Dose Scaled	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0	10	7.97	6.94	2.63	2.12
1.55					
2.9	10	7.63	6.9	2.65	2.12
1.1					
10.6	9	5.41	6.79	1.39	2.12
-1.96					
42	9	5.53	6.36	1.76	2.12
-1.18					
191.1	10	4.54	4.32	1.02	2.12
0.332					

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
Al	-55.036182	6	122.072364
A2	-49.003692	10	118.007385
A3	-55.036182	6	122.072364
fitted	-59.971358	3	125.942715
R	-64.896924	2	133.793848

### 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	31.7865	8	0.0001017
Test 2	12.065	4	0.01687
Test 3	12.065	4	0.01687
Test 4	9.87035	3	0.0197

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. Consider running a non-homogeneous variance model

The p-value for Test 3 is less than .1. You may want to consider a

different variance model

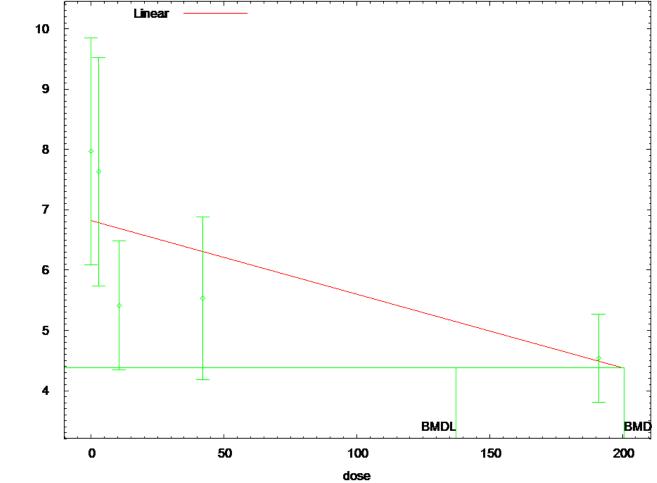
The p-value for Test 4 is less than .1. You may want to try a different model

Benchmark Dose Computation

Specified effect = 1 Risk Type = Estimated standard deviations from the control mean Confidence level = 0.95

BMD = 154.441

BMDL = 101.242



Mean Response

12:44 07/09 2014

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_WBC\_Historical/WBC\_Historical-HLS 2001-White Blood Cell Count-LinearNCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_WBC\_Historical/WBC\_Historical-HLS 2001-White Blood Cell Count-LinearNCV-1SD-5d.plt Wed Jul 09 12:44:58 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse Independent variable = Dose Signs of the polynomial coefficients are not restricted The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) \* rho) Total number of dose groups = 5Total number of records with missing values = 0Maximum 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 = 1.40318 rho = 0 beta\_0 = 6.88046  $beta_1 = -0.0134724$ Asymptotic Correlation Matrix of Parameter Estimates beta\_0 lalpha beta 1 rho -1 0.046 -0.054 lalpha 1

rho	-1	1	-0.046	0.055
beta_0	0.046	-0.046	1	-0.82
beta_1	-0.054	0.055	-0.82	1

Parameter Estimates

## 95.0%

Wald Con	fidence I	nterval		
V	ariable	Estimate	Std. Err.	Lower Conf.
Limit	Upper Con	f. Limit		
	lalpha	-6.96308	2.24713	-
11.3674		-2.55879		
	rho	4.55432	1.23325	
2.1372		6.97144		
	beta_0	6.82487	0.406771	
6.02761		7.62212		
	beta_1	-0.0121567	0.00273518	-
0.017517	5	-0.00679584		

Table of Data and Estimated Values of Interest

Dose Scaled	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 1.48	10	7.97	6.82	2.63	2.44
2.9	10	7.63	6.79	2.65	2.41
10.6 -1.65	9	5.41	6.7	1.39	2.34
42 -1.15	9	5.53	6.31	1.76	2.04
191.1 0.128	10	4.54	4.5	1.02	0.946

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<sup>2</sup>

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
Al	-55.036182	б	122.072364
A2	-49.003692	10	118.007385
A3	-49.214548	7	112.429095
fitted	-55.234090	4	118.468180
R	-64.896924	2	133.793848

#### Explanation of Tests

#### Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.7865	8	0.0001017
Test 2	12.065	4	0.01687
Test 3	0.421711	3	0.9357
Test 4	12.0391	3	0.00725

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

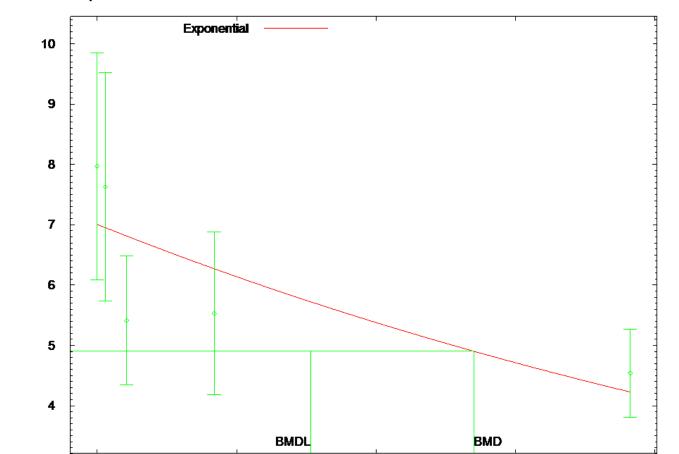
Benchmark Dose Computation

Specified effect = 1 Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 200.696

BMDL = 137.478



100

dose

1**50** 

200

50

# Exponential Model 2, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Level for BMDL

Mean Response

09:34 06/22 2014

0

=== Exponential Model. (Version: 1.9; Date: 01/29/2013) Input Data File: C:/Users/dmayfield/Desktop/Norm/WBC\_Historical-HLS 2001-White Blood Cell Count-ExpCV-1SD-5d.(d) Gnuplot Plotting File: Sun Jun 22 09:34:40 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function by Model: Model 2:  $Y[dose] = a * exp{sign * b * dose}$  $Y[dose] = a * exp\{sign * (b * dose)^d\}$ Model 3: Model 4:  $Y[dose] = a * [c-(c-1) * exp{-b * dose}]$  $Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]$ Model 5: 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 = MeanResponse 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 = 5Total 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	1.29317
rho(S)	0
a	5.42664
b	0.00232433
C	0
d	1

(S) = Specified

#### Parameter Estimates

Variable	Model 2
lnalpha	1.48734
rho	0
a	7.00671
b	0.00264475
С	0
d	1

# Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	10	7.97	2.626
2.9	10	7.63	2.653
10.6	9	5.41	1.392
42	9	5.53	1.756
191.1	10	4.54	1.019

## Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	7.007	2.104	1.448
2.9	6.953	2.104	1.017
10.6	6.813	2.104	-2.001
42	6.27	2.104	-1.055
191.1	4.227	2.104	0.4707

Other models for which likelihoods are calculated:

Model Al: Yij = Mu(i) + e(ij) Var{e(ij)} = Sigma^2

Model A2:	Yij = Var{e(ij)} =	Mu(i) + e(ij) Sigma(i)^2
Model A3:		Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R:	Yij = Var{e(ij)} =	

Likelihoods of Interest

AIC	Model	Log(likelihood)	DF
ALC			
100 0504	Al	-55.03618	6
122.0724	A2	-49.00369	10
118.0074	A3	-55.03618	6
122.0724	R	-64.89692	2
133.7938	2	-59.6961	3
125.3922			

Additive constant for all log-likelihoods = -44.11. This constant added to the above values gives the log-likelihood including the term that does not

depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A2 vs. A1) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 4: Does Model 2 fit the data? (A3 vs. 2)

Tests of Interest

Test p-value	-2*log(Likelihood Ratio)	D. F.
Test 1	31.79	8

0.0001017			
Test	2	12.06	4
0.01687			
Test	3	12.06	4
0.01687			
Test	4	9.32	3
0.02533			

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. Consider running a non-homogeneous variance model.

The p-value for Test 3 is less than .1. You may want to consider a different variance model.

The p-value for Test 4 is less than .1. Model 2 may not adequately

describe the data; you may want to consider another model.

Benchmark Dose Computations:

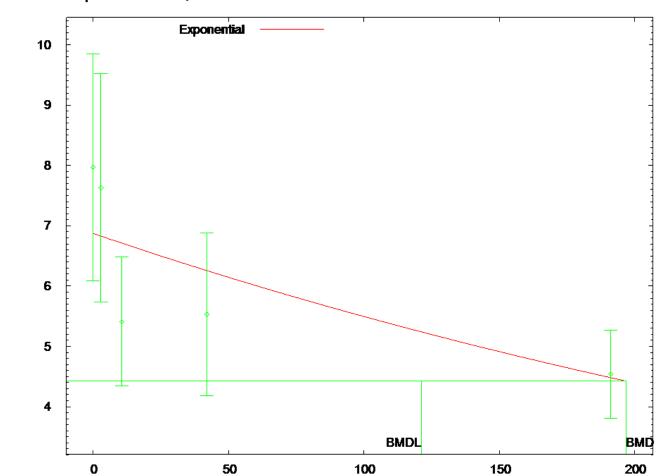
Specified Effect = 1.000000

Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

BMD = 134.987

BMDL = 76.6345



dose

# Exponential Model 2, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Level for BMDL

Mean Response

09:34 06/22 2014

```
______
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Norm/WBC_Historical-HLS 2001-White
Blood Cell Count-ExpNCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sun Jun 22 09:34:42 2014
_____
===
BMDS Model Run
~~~~
  The form of the response function by Model:
     Model 2:
                Y[dose] = a * exp{sign * b * dose}
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
     Model 4:
                Y[dose] = a * [c-(c-1) * exp{-b * dose}]
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  The variance is to be modeled as Var(i) = exp(lalpha + log
(mean(i)) * rho)
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 2
lnalpha	-4.88417
rho	3.3405
a	5.42664
b	0.00232433
C	0
d	1

#### Parameter Estimates

Variable	Model 2
lnalpha	-6.78632
rho	4.44974
a	6.87236
b	0.00223755
С	0
d	1

# Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	10	7.97	2.626
2.9	10	7.63	2.653
10.6	9	5.41	1.392
42	9	5.53	1.756
191.1	10	4.54	1.019

## Estimated Values of Interest

st Mean	Est Std	Scaled Residual
6.872	2.448	1.418
6.828	2.413	1.051
6.711	2.322	-1.681
6.256	1.986	-1.096
4.481	0.9455	0.1963
	6.872 6.828 6.711 6.256	6.8722.4486.8282.4136.7112.3226.2561.986

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:		Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R:	Yij = Var{e(ij)} =	

	Model	Log(likelihood)	DF
AIC			
	Al	-55.03618	6
122.0724	AL	-55.05010	0
110 0074	A2	-49.00369	10
118.0074	A3	-49.21455	7
112.4291	_		0
133.7938	R	-64.89692	2
133.7930	2	-54.95966	4
117.9193			

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

Likelihoods of Interest

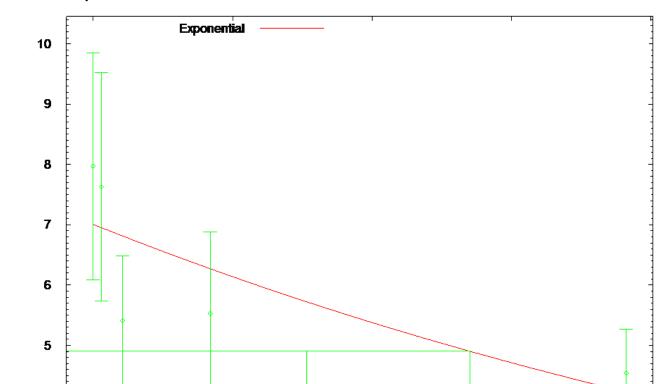
Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A2 vs. A1) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 4: Does Model 2 fit the data? (A3 vs. 2)

### Tests of Interest

Test p-value	-2*log(Likelihood Ratio)	D. F.
Test 1	31.79	8
0.0001017		
Test 2	12.06	4

0.01		0 4015	2
0.93	Test 3 57	0.4217	3
0.00	Test 4	11.49	3
0.00	200		
be a	The p-value for Test 1 is	less than .05.	There appears to
be u	difference between respons levels, it seems appropria		
	The p-value for Test 2 is variance model appears to		A non-homogeneous
	The p-value for Test 3 is variance appears to be app		. The modeled
The p-value for Test 4 is less than .1. Model 2 may not adequately			
uucq	describe the data; you may	want to consid	er another model.
В	enchmark Dose Computations:		
	Specified Effect = 1.00000	0	
cont	Risk Type = Estimat rol	ed standard dev	iations from
	Confidence Level = 0.95000	0	
	BMD = 19	6.821	

BMDL = 121.284



BMDL

100

dose

50

BMD

1**50** 

200

# Exponential Model 3, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Level for BMDL

Mean Response

09:34 06/22 2014

4

0

=== Exponential Model. (Version: 1.9; Date: 01/29/2013) Input Data File: C:/Users/dmayfield/Desktop/Norm/WBC\_Historical-HLS 2001-White Blood Cell Count-ExpCV-1SD-5d.(d) Gnuplot Plotting File: Sun Jun 22 09:34:40 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function by Model: Model 2:  $Y[dose] = a * exp{sign * b * dose}$  $Y[dose] = a * exp\{sign * (b * dose)^d\}$ Model 3: Model 4:  $Y[dose] = a * [c-(c-1) * exp{-b * dose}]$  $Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]$ Model 5: 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 = MeanResponse 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 = 5Total 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 3
lnalpha	1.29317
rho(S)	0
a	5.42664
b	0.00232433
C	0
d	1

(S) = Specified

#### Parameter Estimates

Variable	Model 3
lnalpha	1.48734
rho	0
a	7.00671
b	0.00264475
С	0
d	1

# Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	10	7.97	2.626
2.9	10	7.63	2.653
10.6	9	5.41	1.392
42	9	5.53	1.756
191.1	10	4.54	1.019

## Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	7.007	2.104	1.448
2.9	6.953	2.104	1.017
10.6	6.813	2.104	-2.001
42	6.27	2.104	-1.055
191.1	4.227	2.104	0.4707

Other models for which likelihoods are calculated:

Model Al: Yij = Mu(i) + e(ij) Var{e(ij)} = Sigma^2

Model A2:	Yij = Var{e(ij)} =	Mu(i) + e(ij) Sigma(i)^2
Model A3:		Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R:	Yij = Var{e(ij)} =	

Likelihoods of Interest

	Model	Log(likelihood)	DF
AIC			
100 0004	Al	-55.03618	6
122.0724	A2	-49.00369	10
118.0074	A3	-55.03618	6
122.0724	R	-64.89692	2
133.7938	3	-59.6961	3
125.3922			

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

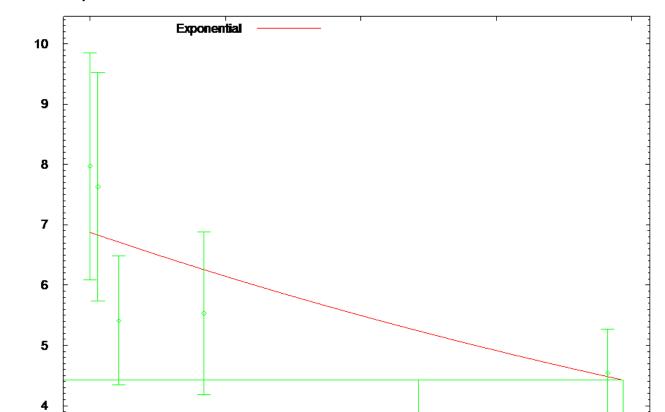
Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A2 vs. A1) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 5a: Does Model 3 fit the data? (A3 vs 3)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.
p-value		

Test 1 0.0001017	31.79	8
Test 2	12.06	4
0.01687		
Test 3	12.06	4
0.01687		
Test 5a	9.32	3
0.02533		

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. Consider running a non-homogeneous variance model. The p-value for Test 3 is less than .1. You may want to consider a different variance model. The p-value for Test 5a is less than .1. Model 3 may not adequately describe the data; you may want to consider another model. Benchmark Dose Computations: Specified Effect = 1.000000 Risk Type = Estimated standard deviations from control Confidence Level = 0.950000BMD = 134.987 BMDL = 76.6345



50

BMDL

1**50** 

100

dose

BMD

200

# Exponential Model 3, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Level for BMDL

Mean Response

09:34 06/22 2014

0

```
______
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Norm/WBC_Historical-HLS 2001-White
Blood Cell Count-ExpNCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sun Jun 22 09:34:42 2014
_____
===
BMDS Model Run
~~~~
  The form of the response function by Model:
     Model 2:
                Y[dose] = a * exp{sign * b * dose}
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
     Model 4:
                Y[dose] = a * [c-(c-1) * exp{-b * dose}]
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  The variance is to be modeled as Var(i) = exp(lalpha + log
(mean(i)) * rho)
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 3
lnalpha	-4.88417
rho	3.3405
a	5.42664
b	0.00232433
C	0
d	1

#### Parameter Estimates

Variable	Model 3
lnalpha	-6.78632
rho	4.44974
a	6.87236
b	0.00223755
С	0
d	1

# Table of Stats From Input Data

Dose	Ν	Obs Mean	Obs Std Dev
0	10	7.97	2.626
2.9	10	7.63	2.653
10.6	9	5.41	1.392
42	9	5.53	1.756
191.1	10	4.54	1.019

## Estimated Values of Interest

st Mean	Est Std	Scaled Residual
6.872	2.448	1.418
6.828	2.413	1.051
6.711	2.322	-1.681
6.256	1.986	-1.096
4.481	0.9455	0.1963
	6.872 6.828 6.711 6.256	6.8722.4486.8282.4136.7112.3226.2561.986

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:			Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R:	Yij = Var{e(ij)} =		

AIC	Model	Log(likelihood)	DF
122.0724	Al	-55.03618	6
122.0721	7.0	10 00360	1 0

122.0724			
118.0074	A2	-49.00369	10
	A3	-49.21455	7
112.4291	R	-64.89692	2
133.7938	2		4
	3	-54.95966	4

117.9193

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

Likelihoods of Interest

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 5a: Does Model 3 fit the data? (A3 vs 3)

#### Tests of Interest

Test p-value	-2*log(Likelihood Ratio)	D. F.
Test 1 0.0001017	31.79	8

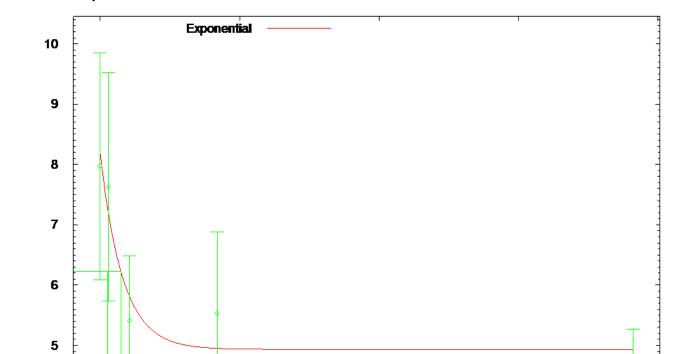
Test 2 0.01687	12.06	4
Test 3	0.4217	3
0.9357		-
Test 5a	11.49	3
0.00935		

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 5a is less than .1. Model 3 may not adequately describe the data; you may want to consider another model. Benchmark Dose Computations: Specified Effect = 1.000000

Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

BMD = 196.821 BMDL = 121.284



100

dose

1**50** 

200

# Exponential Model 4, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Level for BMDL

Mean Response

09:34 06/22 2014

4

BMDL

0

BMD

50

=== Exponential Model. (Version: 1.9; Date: 01/29/2013) Input Data File: C:/Users/dmayfield/Desktop/Norm/WBC\_Historical-HLS 2001-White Blood Cell Count-ExpCV-1SD-5d.(d) Gnuplot Plotting File: Sun Jun 22 09:34:40 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function by Model: Model 2:  $Y[dose] = a * exp{sign * b * dose}$  $Y[dose] = a * exp\{sign * (b * dose)^d\}$ Model 3: Model 4:  $Y[dose] = a * [c-(c-1) * exp{-b * dose}]$  $Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]$ Model 5: 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 = MeanResponse 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 = 5Total number of records with missing values = 0 Maximum number of iterations = 500 Relative Function Convergence has been set to: 1e-008 Parameter Convergence has been set to: 1e-008 MLE solution provided: Exact Initial Parameter Values

Variable	Model 4
lnalpha	1.29317
rho(S)	0
a	8.3685
b	0.0162762
С	0.516677
d	1

(S) = Specified

#### Parameter Estimates

Variable	Model 4
lnalpha	1.33935
rho	0
a	8.1813
b	0.124602
C	0.602967
d	1

# Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	10	7.97	2.626
2.9	10	7.63	2.653
10.6	9	5.41	1.392
42	9	5.53	1.756
191.1	10	4.54	1.019

## Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	8.181	1.954	-0.342
2.9	7.196	1.954	0.7021
10.6	5.8	1.954	-0.599
42	4.95	1.954	0.8901
191.1	4.933	1.954	-0.6362

Other models for which likelihoods are calculated:

Model Al: Yij = Mu(i) + e(ij) Var{e(ij)} = Sigma^2

Model A2	2:	Yij = Var{e(ij)} =	Mu(i) + e(ij) Sigma(i)^2
Model A3	3:		Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model H	R:	Yij = Var{e(ij)} =	

Likelihoods of Interest

AIC	Model	Log(likelihood) D	
	Al	-55.03618	б
122.0724	A2	-49.00369	10
118.0074	A3	-55.03618	6
122.0724	R	-64.89692	2
133.7938	4	-56.1443	4
120.2886			

Additive constant for all log-likelihoods = -44.11. This constant added to the above values gives the log-likelihood including the term that does not

depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A2 vs. A1) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 6a: Does Model 4 fit the data? (A3 vs 4)

Tests of Interest

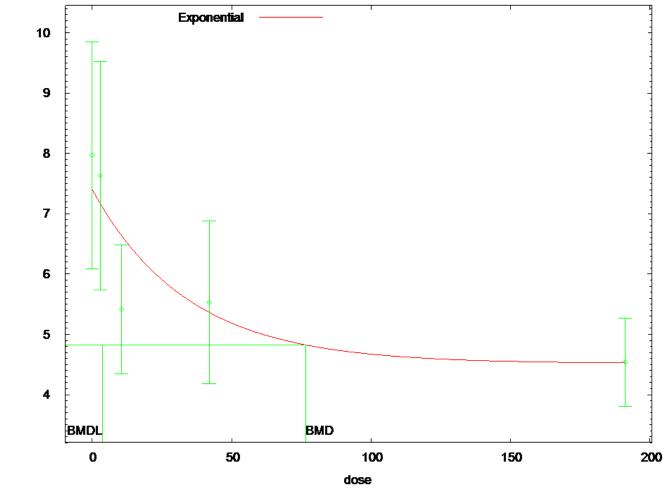
Test	-2*log(Likelihood Ratio)	D. F.
p-value		

Test 1 0.0001017	31.79	8
Test 2	12.06	4
0.01687 Test 3	12.06	4
0.01687 Test 6a	2.216	2
0.3302		

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. Consider running a non-homogeneous variance model. The p-value for Test 3 is less than .1. You may want to consider a different variance model. 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 = 7.38252 BMDL = 2.78564





09:34 06/22 2014

Mean Response

```
______
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Norm/WBC_Historical-HLS 2001-White
Blood Cell Count-ExpNCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sun Jun 22 09:34:42 2014
_____
===
BMDS Model Run
~~~~
  The form of the response function by Model:
     Model 2:
                Y[dose] = a * exp{sign * b * dose}
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
     Model 4:
                Y[dose] = a * [c-(c-1) * exp{-b * dose}]
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  The variance is to be modeled as Var(i) = exp(lalpha + log
(mean(i)) * rho)
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 4
lnalpha	-4.88417
rho	3.3405
a	8.3685
b	0.0162762
С	0.516677
d	1

#### Parameter Estimates

Variable	Model 4
lnalpha	-5.39586
rho	3.64125
a	7.40123
b	0.0291784
С	0.610206
d	1

# Table of Stats From Input Data

Dose	Ν	Obs Mean	Obs Std Dev
0	10	7.97	2.626
2.9	10	7.63	2.653
10.6	9	5.41	1.392
42	9	5.53	1.756
191.1	10	4.54	1.019

## Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	7.401	2.576	0.6982
2.9	7.167	2.43	0.6024
10.6	6.634	2.111	-1.739
42	5.363	1.433	0.3488
191.1	4.527	1.053	0.03843

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)

	<pre>Var{e(ij)} =</pre>	Sigma(i) <sup>2</sup>
Model A3:		Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R:	Yij = Var{e(ij)} =	

	Likelihoods of Int	erest
Model	Log(likelihood)	DF
Al	-55.03618	6
A2	-49.00369	10
Z 3	-49 21455	7
R	-64.89692	2
4	-52.81813	5
	Al A2 A3 R	A1 -55.03618 A2 -49.00369 A3 -49.21455 R -64.89692

Additive constant for all log-likelihoods = -44.11. This constant added to the above values gives the log-likelihood including the term that does not

depend on the model parameters.

### Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A2 vs. A1) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 6a: Does Model 4 fit the data? (A3 vs 4)

### Tests of Interest

Test p-value	-2*log(Likelihood Ratio)	D. F.
Test 1 0.0001017	31.79	8

Test 2 0.01687	12.06	4
Test 3	0.4217	З
0.9357	0.1217	5
Test ба	7.207	2
0.02723		

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data. The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate. The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here. The p-value for Test 6a is less than .1. Model 4 may not adequately describe the data; you may want to consider another model. Benchmark Dose Computations: Specified Effect = 1.000000

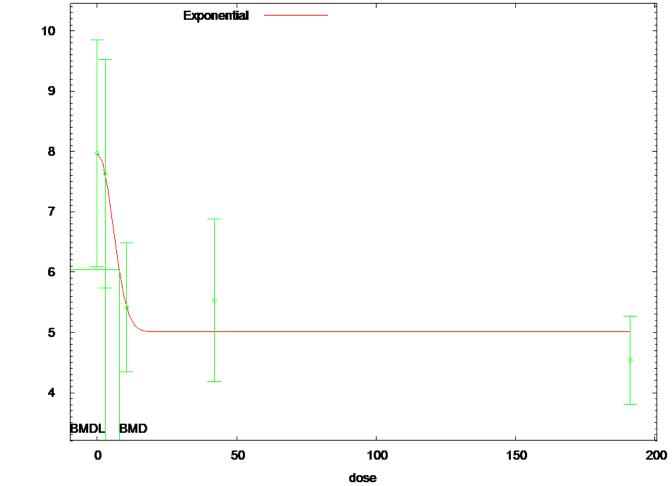
Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

BMD = 76.5897

BMDL = 3.58429





09:34 06/22 2014

Mean Response

=== Exponential Model. (Version: 1.9; Date: 01/29/2013) Input Data File: C:/Users/dmayfield/Desktop/Norm/WBC\_Historical-HLS 2001-White Blood Cell Count-ExpCV-1SD-5d.(d) Gnuplot Plotting File: Sun Jun 22 09:34:40 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function by Model: Model 2:  $Y[dose] = a * exp{sign * b * dose}$  $Y[dose] = a * exp\{sign * (b * dose)^d\}$ Model 3: Model 4:  $Y[dose] = a * [c-(c-1) * exp{-b * dose}]$  $Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]$ Model 5: 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 = MeanResponse 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 = 5Total 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	1.29317
rho(S)	0
a	8.3685
b	0.0162762
С	0.516677
d	1

(S) = Specified

### Parameter Estimates

Variable	Model 5
lnalpha	1.31937
rho	0
a	7.97
b	0.130055
С	0.628475
d	2.15774

## Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	10	7.97	2.626
2.9	10	7.63	2.653
10.6	9	5.41	1.392
42	9	5.53	1.756
191.1	10	4.54	1.019

## Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	7.97	1.934	7.975e-007
2.9	7.63	1.934	-1.085e-006
10.6	5.41	1.934	-4.854e-007
42	5.009	1.934	0.8082
191.1	5.009	1.934	-0.7667

Other models for which likelihoods are calculated:

Model Al: Yij = Mu(i) + e(ij) Var{e(ij)} = Sigma^2

Model A2:	Yij = Var{e(ij)} =	Mu(i) + e(ij) Sigma(i)^2
Model A3:		Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R:	Yij = Var{e(ij)} =	

Likelihoods of Interest

AIC	Model Log(likelihood)		DF
ALC			
100.0504	Al	-55.03618	6
122.0724	A2	-49.00369	10
118.0074	A3	-55.03618	б
122.0724	R	-64.89692	2
133.7938	5	-55.66483	5
121.3297			

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

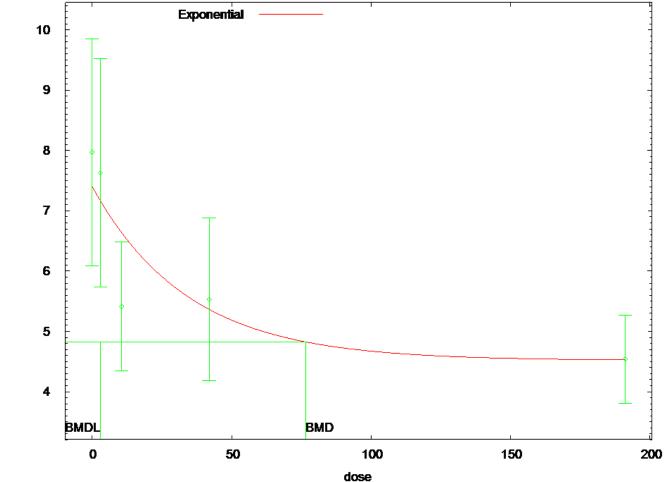
Test	-2*log(Likelihood Ratio)	D. F.
p-value		

Test 1 0.0001017	31.7	9 8
	10.0	с 1
Test 2	12.0	0 4
0.01687		
Test 3	12.0	б 4
0.01687		
Test 7a	1.25	7 1
0.2622		

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. Consider running a non-homogeneous variance model. The p-value for Test 3 is less than .1. You may want to consider a different variance model. 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 = 0.950000BMD = 7.89619

BMDL = 2.93169





Mean Response

09:34 06/22 2014

```
______
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Norm/WBC_Historical-HLS 2001-White
Blood Cell Count-ExpNCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sun Jun 22 09:34:42 2014
_____
===
BMDS Model Run
~~~~
  The form of the response function by Model:
     Model 2:
                Y[dose] = a * exp{sign * b * dose}
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
     Model 4:
                Y[dose] = a * [c-(c-1) * exp{-b * dose}]
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  The variance is to be modeled as Var(i) = exp(lalpha + log
(mean(i)) * rho)
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 5
lnalpha	-4.88417
rho	3.3405
a	8.3685
b	0.0162762
С	0.516677
d	1

### Parameter Estimates

Variable	Model 5
lnalpha	-5.39586
rho	3.64125
a	7.40123
b	0.0291784
С	0.610206
d	1

## Table of Stats From Input Data

Dose	Ν	Obs Mean	Obs Std Dev
0	10	7.97	2.626
2.9	10	7.63	2.653
10.6	9	5.41	1.392
42	9	5.53	1.756
191.1	10	4.54	1.019

## Estimated Values of Interest

Est Mean	Est Std	Scaled Residual
7.401	2.576	0.6982
7.167	2.43	0.6024
6.634	2.111	-1.739
5.363	1.433	0.3488
4.527	1.053	0.03844
	7.401 7.167 6.634 5.363	7.401       2.576         7.167       2.43         6.634       2.111         5.363       1.433

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)

	<pre>Var{e(ij)} =</pre>	Sigma(i) <sup>2</sup>
Model A3:		Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R:	Yij = Var{e(ij)} =	

		Likelihoods of Int	erest
AIC	Model	Log(likelihood)	DF
ALC			
	Al	-55.03618	6
122.0724	A2	-49.00369	10
118.0074	A3	-49.21455	7
112.4291			
133.7938	R	-64.89692	2
115.6363	5	-52.81813	5

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 p-value	-2*log(Likelihood Ratio)	D. F.
Test 1 0.0001017	31.79	8

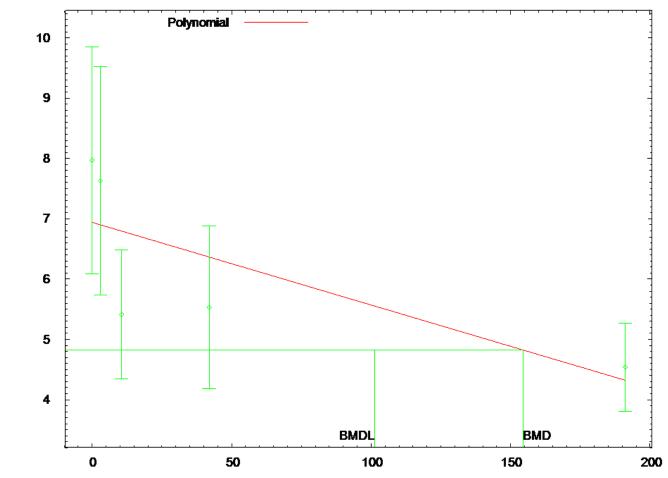
Test 2 0.01687	12.06	4
Test 3	0.4217	3
0.9357		
Test 7a	7.207	2
0.02723		

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 7a is less than .1. Model 5 may not adequately describe the data; you may want to consider another model. Benchmark Dose Computations: Specified Effect = 1.000000 Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

BMD = 76.5897

BMDL = 2.94249



# Polynomial Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

dose

Mean Response

12:44 07/09 2014

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_WBC\_Historical/WBC\_Historical-HLS 2001-White Blood Cell Count-Poly2CV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_WBC\_Historical/WBC\_Historical-HLS 2001-White Blood Cell Count-Poly2CV-1SD-5d.plt Wed Jul 09 12:44:57 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse 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 = 5Total 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 = 4.0681 Specified rho = 0  $beta_0 = 7.40214$  $beta_1 = -0.0643244$ beta\_2 = 0 Asymptotic Correlation Matrix of Parameter Estimates ( \*\*\* The model parameter(s) -rho -beta 2 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	-1.8e-007	3.5e-007
beta_0	-1.8e-007	1	-0.56
beta_1	3.5e-007	-0.56	1

## Parameter Estimates

			95.0%
Wald Confidence I	nterval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Con	f. Limit		
alpha	4.47634	0.91373	
2.68547	6.26722		
beta_0	6.93587	0.369654	
6.21136	7.66038		
beta_1	-0.0136993	0.00414278	-
0.021819	-0.0055796		
beta_2	0	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 Scaled	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 1.55	10	7.97	6.94	2.63	2.12
2.9 1.1	10	7.63	6.9	2.65	2.12
10.6 -1.96	9	5.41	6.79	1.39	2.12
42 -1.18	9	5.53	6.36	1.76	2.12
191.1 0.332	10	4.54	4.32	1.02	2.12

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<sup>2</sup>

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
Al	-55.036182	б	122.072364
A2	-49.003692	10	118.007385
A3	-55.036182	6	122.072364
fitted	-59.971358	3	125.942715
R	-64.896924	2	133.793848

### 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

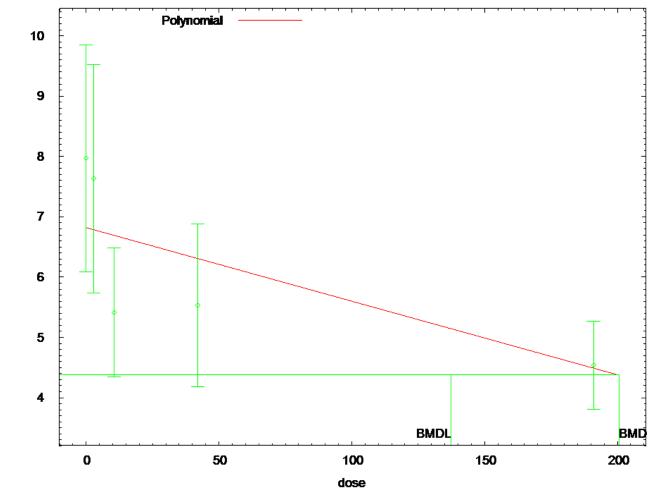
Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.7865	8	0.0001017
Test 2	12.065	4	0.01687
Test 3	12.065	4	0.01687
Test 4	9.87035	3	0.0197

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. Consider running a non-homogeneous variance model The p-value for Test 3 is less than .1. You may want to consider a different variance model 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 = 154.441

BMDL = 101.242



# Polynomial Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

12:44 07/09 2014

Mean Response

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_WBC\_Historical/WBC\_Historical-HLS 2001-White Blood Cell Count-Poly2NCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_WBC\_Historical/WBC\_Historical-HLS 2001-White Blood Cell Count-Poly2NCV-1SD-5d.plt Wed Jul 09 12:44:58 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse 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 = 5Total number of records with missing values = 0Maximum 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 = 1.40318 rho = 0  $beta_0 = 7.40214$  $beta_1 = -0.0643244$ 7.40214 beta\_2 = 0 Asymptotic Correlation Matrix of Parameter Estimates ( \*\*\* The model parameter(s) -beta\_2 have been estimated at a boundary point, or have been specified by the user,

and do not appear in the correlation matrix )

	lalpha	rho	beta_0	beta_1
lalpha	1	-1	0.046	-0.054
rho	-1	1	-0.046	0.055
beta_0	0.046	-0.046	1	-0.82
beta_1	-0.054	0.055	-0.82	1

Parameter Estimates

95	. (	)응

				90.0%
Wald Cor	fidence l	Interval		
V	/ariable	Estimate	Std. Err.	Lower Conf.
Limit	Upper Con	nf. Limit		
	lalpha	-6.96308	2.24713	-
11.3674	_	-2.55879		
	rho	4.55432	1.23325	
2.1372		6.97144		
	beta O	6.82487	0.406771	
6.02761	_	7.62212		
	beta 1	-0.0121567	0.00273518	_
0.017517	′5 —	-0.00679584		
	beta 2	0	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 Scaled	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 1.48	10	7.97	6.82	2.63	2.44
2.9	10	7.63	6.79	2.65	2.41
10.6	9	5.41	6.7	1.39	2.34
42 -1.15	9	5.53	6.31	1.76	2.04

191.1	10	4.54	4.5	1.02	0.946
0.128					

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)Var{e(ij)} = Sigma<sup>2</sup> Model A2: Yij = Mu(i) + e(ij)Var{e(ij)} = Sigma(i)<sup>2</sup>

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
Al	-55.036182	6	122.072364
A2	-49.003692	10	118.007385
A3	-49.214548	7	112.429095
fitted	-55.234090	4	118.468180
R	-64.896924	2	133.793848

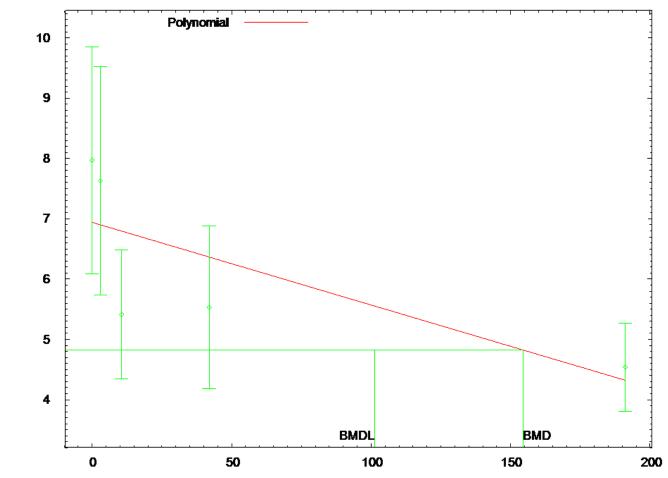
## Explanation of Tests

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	31.7865	8	0.0001017
Test 2	12.065	4	0.01687
Test 3	0.421711	3	0.9357
Test 4	12.0391	3	0.00725

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 = Estimated standard deviations from the Risk Type control mean Confidence level = 0.95 BMD = 200.696 BMDL = 137.478



# Polynomial Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

dose

Mean Response

12:44 07/09 2014

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_WBC\_Historical/WBC\_Historical-HLS 2001-White Blood Cell Count-Poly3CV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_WBC\_Historical/WBC\_Historical-HLS 2001-White Blood Cell Count-Poly3CV-1SD-5d.plt Wed Jul 09 12:44:57 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse 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 = 5Total 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 = 4.0681 Specified rho = 0 beta\_0 = 8.18961 beta\_1 = -0.328545 beta\_2 = 0  $beta_3 = -3.14654e - 005$ Asymptotic Correlation Matrix of Parameter Estimates ( \*\*\* The model parameter(s) -rho -beta\_2 -

beta\_3

have been estimated at a boundary point, or have been specified by the user,

and do not appear in the correlation matrix )

beta_1	beta_0	alpha	
-5.3e-008	-2.2e-008	1	alpha
-0.56	1	-2.2e-008	beta_0
1	-0.56	-5.3e-008	beta_1

Parameter Estimates

95.0%

				95.08
Wald Conf	idence In	terval		
Va	riable	Estimate	Std. Err.	Lower Conf.
Limit U	pper Conf	. Limit		
	alpha	4.47634	0.91373	
2.68547	_	6.26722		
	beta_0	6.93587	0.369654	
6.21136		7.66038		
	beta_1	-0.0136993	0.00414278	_
0.021819		0.00557961		
	beta_2	0	NA	
	beta_3	0	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 V	Values of	Interest
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Dose Scaled	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 1.55	10	7.97	6.94	2.63	2.12
2.9	10	7.63	6.9	2.65	2.12
10.6 -1.96	9	5.41	6.79	1.39	2.12
42	9	5.53	6.36	1.76	2.12
191.1	10	4.54	4.32	1.02	2.12

Model Descriptions for likelihoods calculated

Var{e(i)} = Sigma^2

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)

#### Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
Al	-55.036182	6	122.072364
A2	-49.003692	10	118.007385
A3	-55.036182	6	122.072364
fitted	-59.971358	3	125.942715
R	-64.896924	2	133.793848

## Explanation of Tests

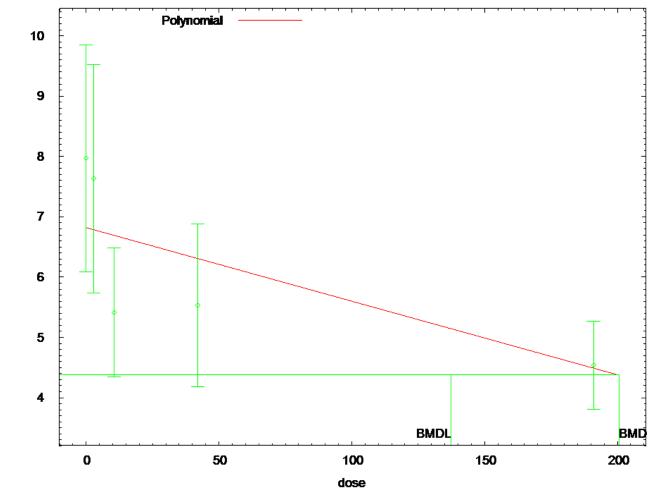
Test 1: Do responses and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A1 vs A2) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 4: Does the Model for the Mean Fit? (A3 vs. fitted) (Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

## Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.7865	8	0.0001017
Test 2	12.065	4	0.01687
Test 3	12.065	4	0.01687
Test 4	9.87035	3	0.0197

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. Consider running a non-homogeneous variance model The p-value for Test 3 is less than .1. You may want to consider а different variance model The p-value for Test 4 is less than .1. You may want to try a different model Benchmark Dose Computation Specified effect = 1 Estimated standard deviations from the Risk Type = control mean Confidence level = 0.95 154.441 BMD = BMDL = 101.242



# Polynomial Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

12:44 07/09 2014

Mean Response

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_WBC\_Historical/WBC\_Historical-HLS 2001-White Blood Cell Count-Poly3NCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_WBC\_Historical/WBC\_Historical-HLS 2001-White Blood Cell Count-Poly3NCV-1SD-5d.plt Wed Jul 09 12:44:58 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse 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 = 5Total number of records with missing values = 0Maximum 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 = 1.40318 rho = 0 beta\_0 = 8.18961 beta\_1 = -0.328545 beta\_2 = 0  $beta_3 = -3.14654e - 005$ Asymptotic Correlation Matrix of Parameter Estimates ( \*\*\* The model parameter(s) -beta\_2 -beta\_3

have been estimated at a boundary point, or have been specified by the user, and do not appear in the correlation matrix )

	lalpha	rho	beta_0	beta_1
lalpha	1	-1	0.046	-0.054
rho	-1	1	-0.046	0.055
beta_0	0.046	-0.046	1	-0.82
beta_1	-0.054	0.055	-0.82	1

Parameter Estimates

			95.0%
Wald Confidence I	Interval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Con	nf. Limit		
lalpha	-6.96308	2.24713	_
11.3674	-2.55879		
rho	4.55432	1.23325	
2.1372	6.97144		
beta_0	6.82487	0.406771	
6.02761	7.62212		
beta_1	-0.0121567	0.00273518	_
0.0175175	-0.00679584		
beta_2	0	NA	
beta_3	0	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 Scaled I	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 1.48	10	7.97	6.82	2.63	2.44
2.9	10	7.63	6.79	2.65	2.41
10.6 -1.65	9	5.41	6.7	1.39	2.34

42	9	5.53	6.31	1.76	2.04
-1.15					
191.1 0.128	10	4.54	4.5	1.02	0.946
0.128					

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
Al	-55.036182	б	122.072364
A2	-49.003692	10	118.007385
A3	-49.214548	7	112.429095
fitted	-55.234090	4	118.468180
R	-64.896924	2	133.793848

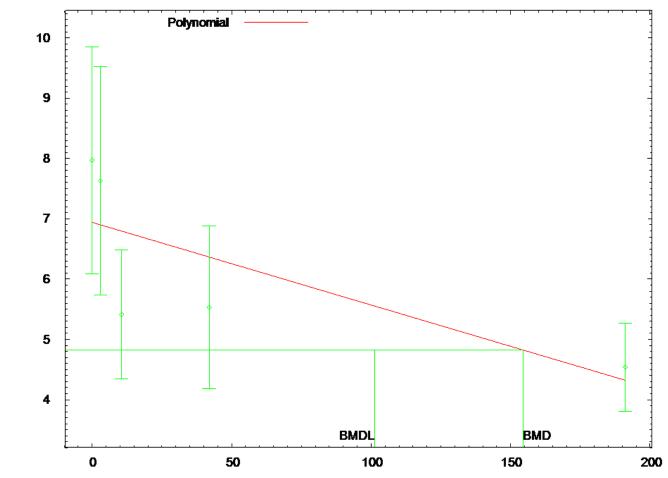
### Explanation of Tests

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	31.7865	8	0.0001017
Test 2	12.065	4	0.01687
Test 3	0.421711	3	0.9357

12.0391 3 0.00725 Test 4 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 = Estimated standard deviations from the Risk Type control mean Confidence level = 0.95 BMD = 200.696 BMDL = 137.478



# Polynomial Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

dose

Mean Response

12:44 07/09 2014

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_WBC\_Historical/WBC\_Historical-HLS 2001-White Blood Cell Count-Poly4CV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_WBC\_Historical/WBC\_Historical-HLS 2001-White Blood Cell Count-Poly4CV-1SD-5d.plt Wed Jul 09 12:44:56 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse 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 = 5Total 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 = 4.0681 rho = Specified 0 beta\_0 = 7.97  $beta_1 = -0.0490906$  $beta_2 = -0.0256112$ beta 3 = 0  $beta_4 = -3.15099e-006$ 

Asymptotic Correlation Matrix of Parameter Estimates

beta_1	beta_0	alpha	
7.6e-009	5.3e-008	1	alpha
-0.56	1	5.3e-008	beta_0
1	-0.56	7.6e-009	beta_1

Parameter Estimates

#### 95.0%

				95.08
Wald Cor	fidence	Interval		
V	/ariable	Estimate	Std. Err.	Lower Conf.
Limit	Upper Co	nf. Limit		
	alpha	4.47634	0.91373	
2.68547		6.26722		
	beta_0	6.93587	0.369654	
6.21136		7.66038		
	beta_1	-0.0136993	0.00414278	_
0.021819	)	-0.00557961		
	beta_2	0	NA	
	beta_3	0	NA	
	beta_4	0	NA	

NA - Indicates that this parameter has hit a bound implied by some inequality constraint and thus has no standard error.

Dose Scaled	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 1.55	10	7.97	6.94	2.63	2.12
2.9 1.1	10	7.63	6.9	2.65	2.12
10.6 -1.96	9	5.41	6.79	1.39	2.12
42	9	5.53	6.36	1.76	2.12

Table of Data and Estimated Values of Interest

-1.18 191.1 0.332	10	4.54	4.32	1.02	2.12
Model	Description	ns for likeli	noods calcula	ted	
Model		Yij = Mu(i) ij)} = Sigma^:			
Model		Yij = Mu(i) ij)} = Sigma(:			
Мс	Var{e(: odel A3 uses	Yij = Mu(i) ij)} = Sigma^: s any fixed va ed by the use:	2 ariance param	eters that	
Model		Yi = Mu + e (i)} = Sigma^:	. ,		

## Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
Al	-55.036182	6	122.072364
A2	-49.003692	10	118.007385
A3	-55.036182	б	122.072364
fitted	-59.971358	3	125.942715
R	-64.896924	2	133.793848

## 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.)

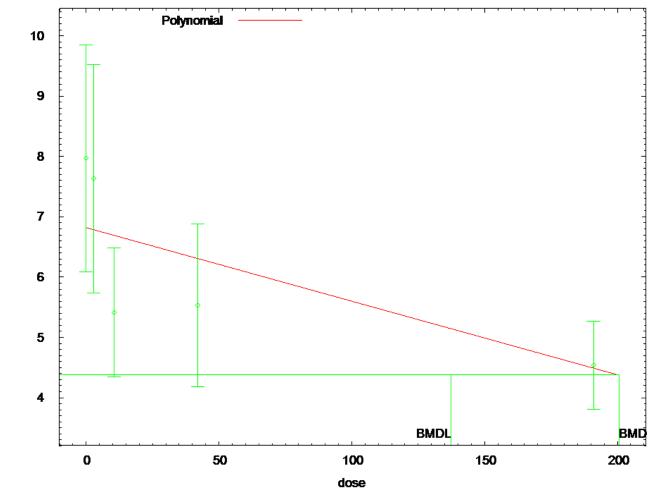
### Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.7865	8	0.0001017
Test 2	12.065	4	0.01687
Test 3	12.065	4	0.01687
Test 4	9.87035	3	0.0197

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. Consider running a non-homogeneous variance model The p-value for Test 3 is less than .1. You may want to consider а different variance model The p-value for Test 4 is less than .1. You may want to try a different model Benchmark Dose Computation Specified effect = 1 = Estimated standard deviations from the Risk Type control mean Confidence level = 0.95

BMD = 154.441

BMDL = 101.242



# Polynomial Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

12:44 07/09 2014

Mean Response

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_WBC\_Historical/WBC\_Historical-HLS 2001-White Blood Cell Count-Poly4NCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_WBC\_Historical/WBC\_Historical-HLS 2001-White Blood Cell Count-Poly4NCV-1SD-5d.plt Wed Jul 09 12:44:58 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse 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 = 5Total number of records with missing values = 0Maximum 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 = 1.40318 rho = 0 beta\_0 = 7.97  $beta_1 = -0.0490906$  $beta_2 = -0.0256112$ beta 3 = 0  $beta_4 = -3.15099e-006$ Asymptotic Correlation Matrix of Parameter Estimates

1

lalpha	1	-1	0.046	-0.054
rho	-1	1	-0.046	0.055
beta_0	0.046	-0.046	1	-0.82
beta_1	-0.054	0.055	-0.82	1

#### Parameter Estimates

### 95.0%

			95.06
Wald Confidence	e Interval		
Variable	e Estimate	Std. Err.	Lower Conf.
Limit Upper (	Conf. Limit		
lalpha	a -6.96308	2.24713	-
11.3674	-2.55879		
rho	o 4.55432	1.23325	
2.1372	6.97144		
beta_(	6.82487	0.406771	
6.02761	7.62213		
beta_i	1 -0.0121567	0.00273517	-
0.0175175	-0.00679584		
beta_2	2 0	NA	
beta_3	3 0	NA	
beta_4	4 0	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 Scaled R	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
	· <b></b>				
0 1.48	10	7.97	6.82	2.63	2.44
2.9	10	7.63	6.79	2.65	2.41

1.1					
10.6	9	5.41	6.7	1.39	2.34
-1.65					
42	9	5.53	6.31	1.76	2.04
-1.15					
191.1	10	4.54	4.5	1.02	0.946
0.128					

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<sup>2</sup>

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
Al	-55.036182	б	122.072364
A2	-49.003692	10	118.007385
A3	-49.214548	7	112.429095
fitted	-55.234090	4	118.468180
R	-64.896924	2	133.793848

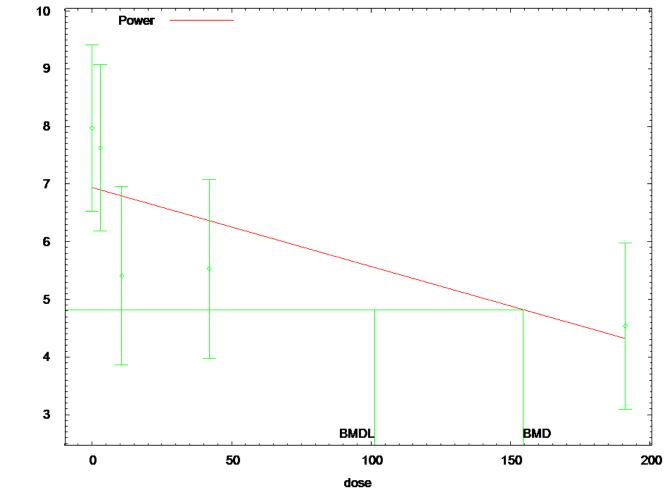
#### Explanation of Tests

#### Tests of Interest

Test	-2*log(Likelihood	Ratio	) Test df	p-value
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3

31.7865 8 0.0001017 4 0.01687 Test 2 Test 1 12.065 Test 3 0.421711 3 0.9357 Test 4 12.0391 3 0.00725 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 = Estimated standard deviations from the Risk Type control mean Confidence level = 0.95 BMD = 200.696 BMDL = 137.478



Power Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

09:34 06/22 2014

Mean Response

=== Power Model. (Version: 2.18; Date: 05/19/2014) Input Data File: C:/Users/dmayfield/Desktop/Norm/WBC\_Historical-HLS 2001-White Blood Cell Count-PowerCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Norm/WBC\_Historical-HLS 2001-White Blood Cell Count-PowerCV-1SD-5d.plt Sun Jun 22 09:34:41 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = control + slope \* dose^power Dependent variable = MeanResponse 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 = 5Total 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 = 4.0681 rho = Specified 0 4.54 control = slope = 3.7818 power = -0.420444Asymptotic 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	4e-009	-8.1e-010
control	4e-009	1	-0.56
slope	-8.1e-010	-0.56	1

#### Parameter Estimates

			95.0%
Wald Confidence I	nterval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Con	f. Limit		
alpha	4.47634	0.91373	
2.68547	6.26722		
control	6.93587	0.369654	
6.21136	7.66038		
slope	-0.0136993	0.00414278	_
0.021819	-0.00557961		
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 Scaled	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0	10	7.97	6.94	2.63	2.12
1.55 2.9 1.1	10	7.63	6.9	2.65	2.12
10.6 -1.96	9	5.41	6.79	1.39	2.12
-1.90 42 -1.18	9	5.53	6.36	1.76	2.12
191.1 0.332	10	4.54	4.32	1.02	2.12

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<sup>2</sup>

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
Al	-55.036182	б	122.072364
A2	-49.003692	10	118.007385
A3	-55.036182	6	122.072364
fitted	-59.971358	3	125.942715
R	-64.896924	2	133.793848

#### 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	31.7865	8	0.0001017
Test 2	12.065	4	0.01687
Test 3	12.065	4	0.01687
Test 4	9.87035	3	0.0197

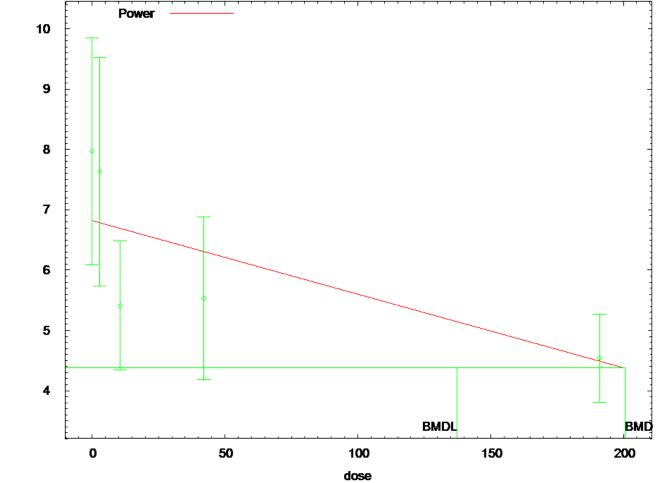
The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels It seems appropriate to model the data The p-value for Test 2 is less than .1. Consider running a non-homogeneous variance model The p-value for Test 3 is less than .1. You may want to consider a different variance model 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 = 154.441

BMDL = 101.242



Mean Response

09:34 06/22 2014

=== Power Model. (Version: 2.18; Date: 05/19/2014) Input Data File: C:/Users/dmayfield/Desktop/Norm/WBC\_Historical-HLS 2001-White Blood Cell Count-PowerNCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Norm/WBC\_Historical-HLS 2001-White Blood Cell Count-PowerNCV-1SD-5d.plt Sun Jun 22 09:34:42 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = control + slope \* dose^power Dependent variable = MeanResponse Independent variable = Dose The power is restricted to be greater than or equal to 1 The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) \* rho) Total number of dose groups = 5Total number of records with missing values = 0Maximum 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 = 1.40318 rho = 0 control = 4.54 slope = 3.7818 power = -0.420444Asymptotic Correlation Matrix of Parameter Estimates ( \*\*\* The model parameter(s) -power have been estimated at a boundary point, or have been specified by the user,

				,
	lalpha	rho	control	slope
lalpha	1	-1	0.42	-0.64
rho	-1	1	-0.48	0.67
control	0.42	-0.48	1	-0.82
slope	-0.64	0.67	-0.82	1

Parameter Estimates

and do not appear in the correlation matrix )

			95.08				
Wald Confidence Interval							
Variable	Estimate	Std. Err.	Lower Conf.				
Limit Upper Co	nf. Limit						
lalpha	-6.96308	2.98801	-				
12.8195	-1.10669						
rho	4.55432	1.6721					
1.27706	7.83158						
control	6.82487	0.408449					
6.02432	7.62541						
slope	-0.0121567	0.00273251	-				
0.0175123	-0.00680106						
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 Scaled 1	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 1.48	10	7.97	6.82	2.63	2.44
2.9	10	7.63	6.79	2.65	2.41
10.6 -1.65	9	5.41	6.7	1.39	2.34
42 -1.15	9	5.53	6.31	1.76	2.04

191.1	10	4.54	4.5	1.02	0.946
0.128					

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)Var{e(ij)} = Sigma<sup>2</sup> Model A2: Yij = Mu(i) + e(ij)Var{e(ij)} = Sigma(i)<sup>2</sup>

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
Al	-55.036182	6	122.072364
A2	-49.003692	10	118.007385
A3	-49.214548	7	112.429095
fitted	-55.234090	4	118.468180
R	-64.896924	2	133.793848

### Explanation of Tests

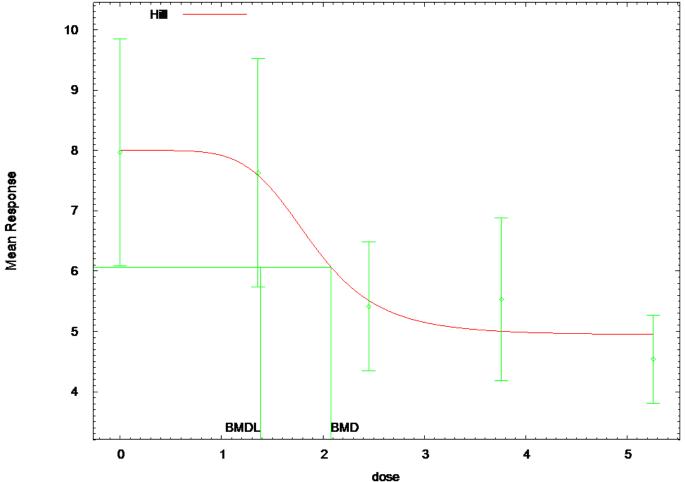
Test 1: Do responses and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A1 vs A2) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 4: Does the Model for the Mean Fit? (A3 vs. fitted) (Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

### Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.7865	8	0.0001017
Test 2	12.065	4	0.01687
Test 3	0.421711	3	0.9357
Test 4	12.0391	3	0.00725

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 = Estimated standard deviations from the Risk Type control mean Confidence level = 0.95 BMD = 200.696BMDL = 137.478

BMDS Model Results for White Blood Cell Count (Log-transformed Doses, Historical Controls)



09:40 06/22 2014

\_\_\_\_\_\_ === Hill Model. (Version: 2.17; Date: 01/28/2013) Input Data File: C:/Users/dmayfield/Desktop/Ln/WBC\_Historical\_Ln-HLS 2001-White Blood Cell Count-HillCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Ln/WBC Historical Ln-HLS 2001-White Blood Cell Count-HillCV-1SD-5d.plt Sun Jun 22 09:40:09 2014 \_\_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is:  $Y[dose] = intercept + v*dose^n/(k^n + dose^n)$ Dependent variable = MeanResponse 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 = 5Total 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 = 4.0681 Specified rho = 0 7.97 0 intercept = -3.43 v = \_ k = 4.25613 2.03611 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 )

anc	l do	not	appear	ın	the	correl	lation	matrix	)
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k		alpha	intercept	v	n
al 6.7e-00	pha 8	1	-5.9e-008	7.1e-008	5.5e-008
interc -0.4	ept	-5.9e-008	1	-0.78	-0.46
-0.02	v	7.1e-008	-0.78	1	0.68
-0.1	n	5.5e-008	-0.46	0.68	1
1	k	6.7e-008	-0.4	-0.02	-0.1

# Parameter Estimates

			95.0%
Wald Confidence Int	erval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Conf.	Limit		
alpha	3.7342	0.76224	
2.24023	5.22816		
intercept	8.0005	0.601995	
6.82061	9.18038		
v	-3.06445	0.884065	-
4.79718	-1.33171		
n	5.65284	5.65725	-
5.43517	16.7409		
k	1.88908	0.468465	
0.970902	2.80725		

### Table of Data and Estimated Values of Interest

Dose Scaled R		Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 -0.0499	10	7.97	8	2.63	1.93

1.361 0.0731	10	7.63	7.59	2.65	1.93
2.451	9	5.41	5.51	1.39	1.93
-0.152					
3.761 0.827	9	5.53	5	1.76	1.93
5.258	10	4.54	4.95	1.02	1.93
-0.663					

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
Al	-55.036182	6	122.072364
A2	-49.003692	10	118.007385
A3	-55.036182	6	122.072364
fitted	-55.620782	5	121.241565
R	-64.896924	2	133.793848

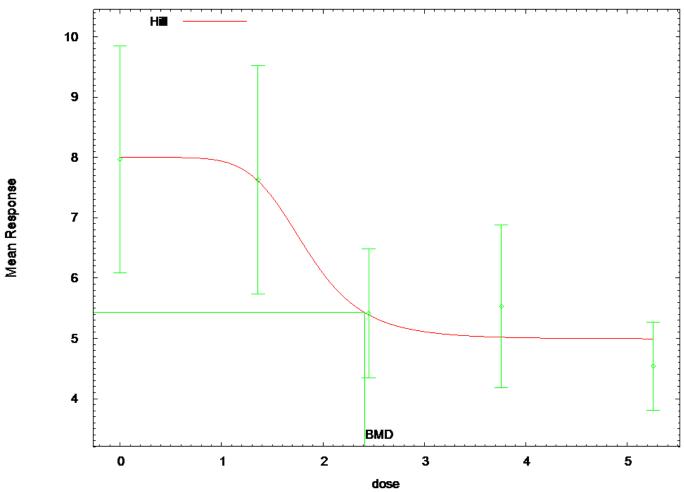
### Explanation of Tests

### Tests of Interest

Test	-2*log(Likelihood	Ratio)	Test df	p-value
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Test 131.786580.0001017Test 212.06540.01687Test 312.06540.01687Test 41.169210.2796

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. Consider running a non-homogeneous variance model The p-value for Test 3 is less than .1. You may want to consider а different variance model 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 = 2.0765 BMDL = 1.38411



09:40 06/22 2014

Hill Model

\_\_\_\_\_\_ === Hill Model. (Version: 2.17; Date: 01/28/2013) Input Data File: C:/Users/dmayfield/Desktop/Ln/WBC\_Historical\_Ln-HLS 2001-White Blood Cell Count-HillNCV-1SD-5d.  $(\overline{d})$ Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Ln/WBC Historical Ln-HLS 2001-White Blood Cell Count-HillNCV-1SD-5d.plt Sun Jun 22 09:40:10 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is:  $Y[dose] = intercept + v*dose^n/(k^n + dose^n)$ Dependent variable = MeanResponse Independent variable = Dose Power parameter restricted to be greater than 1 The variance is to be modeled as Var(i) = exp(lalpha + rho \* ln(mean(i))) Total number of dose groups = 5Total 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 = 1.40318 rho = 0 intercept = 7.97 -3.43 V = n = 4.25613 k = 2.03611 Asymptotic Correlation Matrix of Parameter Estimates intercept lalpha rho v

n	k			
lalpha -0.054	1 0.024	-0.99	0.3	-0.36
rho 0.053	-0.99 -0.023	1	-0.33	0.37
intercept -0.53	0.3-0.45	-0.33	1	-0.92
v 0.7	-0.36 0.27	0.37	-0.92	1
n 1 (	-0.054 ).17	0.053	-0.53	0.7
k 0.17	0.024 1	-0.023	-0.45	0.27

Parameter Estimates

				95.0%
Wald Con	fidence In	nterval		
V	ariable	Estimate	Std. Err.	Lower Conf.
Limit	Upper Con:	E. Limit		
	lalpha	-3.7714	2.03099	-
7.75207		0.209269		
	rho	2.72094	1.11924	
0.527268		4.91461		
in	tercept	8.00013	0.773538	
6.48402		9.51624		
	v	-3.00709	0.97751	-
4.92297		-1.09121		
	n	6.4198	7.51173	-
8.30292		21.1425		
	k	1.83415	0.387095	
1.07546		2.59284		

Table of Data and Estimated Values of Interest

Dose Scaled R		Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 -0.0371	10	7.97	8	2.63	2.57

1.361 0.0209	10	7.63	7.61	2.65	2.4
2.451	9	5.41	5.4	1.39	1.5
3.761 1.12	9	5.53	5.02	1.76	1.36
5.258 -1.07	10	4.54	5	1.02	1.35

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	-55.036182	6	122.072364
A2	-49.003692	10	118.007385
A3	-49.214548	7	112.429095
fitted	-51.685936	6	115.371872
R	-64.896924	2	133.793848

### 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
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Test 131.786580.0001017Test 212.06540.01687Test 30.42171130.9357Test 44.9427810.0262

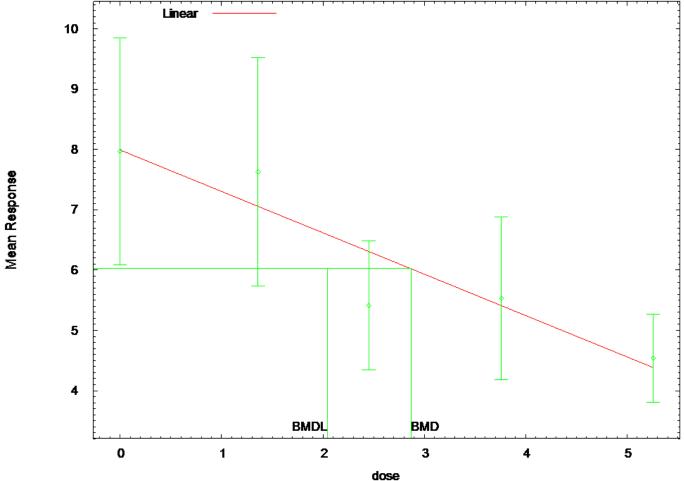
The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels It seems appropriate to model the data The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate The p-value for Test 3 is greater 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 = 2.41554

BMDL computation failed.



12:46 07/09 2014

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_WBC\_Historical\_Ln/WBC\_Historical\_L n-HLS 2001-White Blood Cell Count-LinearCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_WBC\_Historical\_Ln/WBC\_Historical\_L n-HLS 2001-White Blood Cell Count-LinearCV-1SD-5d.plt Wed Jul 09 12:46:34 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse Independent variable = Dose rho is set to 0 Signs of the polynomial coefficients are not restricted A constant variance model is fit Total number of dose groups = 5Total number of records with missing values = 0Maximum 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 = 4.0681 rho = 0 beta\_0 = 7.97189 beta\_1 = -0.684236 0 Specified 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	2.1e-008	-8.7e-010
beta_0	2.1e-008	1	-0.81
beta_1	-8.7e-010	-0.81	1

## Parameter Estimates

			95.0%
Wald Confidence In	nterval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Conf	. Limit		
alpha	3.87222	0.790413	
2.32303	5.4214		
beta_0	7.9913	0.481462	
7.04765	8.93494		
beta_1	-0.685697	0.152832	-
0.985242	-0.386152		

Table of Data and Estimated Values of Interest

Dose Scaled R	N.es.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 -0.0342	10	7.97	7.99	2.63	1.97
1.361 0.919	10	7.63	7.06	2.65	1.97
2.451 -1.37	9	5.41	6.31	1.39	1.97
3.761 0.179	9	5.53	5.41	1.76	1.97
5.258 0.248	10	4.54	4.39	1.02	1.97

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
Al	-55.036182	6	122.072364
A2	-49.003692	10	118.007385
A3	-55.036182	6	122.072364
fitted	-56.491842	3	118.983685
R	-64.896924	2	133.793848

### 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	31.7865	8	0.0001017
Test 2	12.065	4	0.01687
Test 3	12.065	4	0.01687
Test 4	2.91132	3	0.4055

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. Consider running a non-homogeneous variance model

The p-value for Test 3 is less than .1. You may want to consider a

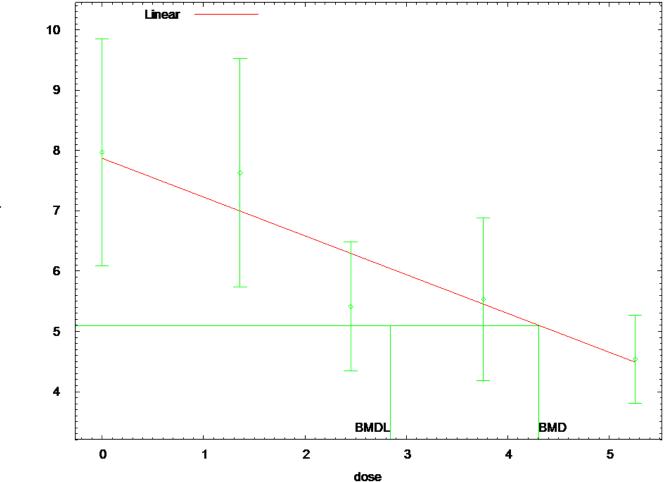
different variance model

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 = 2.86977

BMDL = 2.04395



Mean Response

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=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_WBC\_Historical\_Ln/WBC\_Historical\_L n-HLS 2001-White Blood Cell Count-LinearNCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_WBC\_Historical\_Ln/WBC\_Historical\_L n-HLS 2001-White Blood Cell Count-LinearNCV-1SD-5d.plt Wed Jul 09 12:46:35 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse Independent variable = Dose Signs of the polynomial coefficients are not restricted The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) \* rho) Total number of dose groups = 5Total number of records with missing values = 0Maximum 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 = 1.40318 rho = 0 rno = 0 beta\_0 = 7.97189 beta\_1 = -0.684236 Asymptotic Correlation Matrix of Parameter Estimates rho lalpha beta\_0 beta 1 -0.99 0.13 -0.15 lalpha 1

rho	-0.99	1	-0.13	0.15
beta_0	0.13	-0.13	1	-0.91
beta_1	-0.15	0.15	-0.91	1

Parameter Estimates

### 95.0%

Wald Confidence Interval					
Variable Estimate		Std. Err.	Lower Conf.		
Limit T	Upper Conf	. Limit			
	lalpha	-5.14645	1.9704	-	
9.00836		-1.28454			
	rho	3.48317	1.08261		
1.3613		5.60504			
	beta_0	7.86568	0.562534		
6.76313		8.96823			
	beta_1	-0.643285	0.134966	-	
0.907813		-0.378757			

Table of Data and Estimated Values of Interest

Dose Scaled	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 0.119	10	7.97	7.87	2.63	2.77
1.361 0.897	10	7.63	6.99	2.65	2.26
2.451 -1.41	9	5.41	6.29	1.39	1.88
3.761 0.172	9	5.53	5.45	1.76	1.46
5.258 0.172	10	4.54	4.48	1.02	1.04

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<sup>2</sup>

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
Al	-55.036182	б	122.072364
A2	-49.003692	10	118.007385
A3	-49.214548	7	112.429095
fitted	-51.789349	4	111.578698
R	-64.896924	2	133.793848

#### Explanation of Tests

#### Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.7865	8	0.0001017
Test 2	12.065	4	0.01687
Test 3	0.421711	3	0.9357
Test 4	5.1496	3	0.1612

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

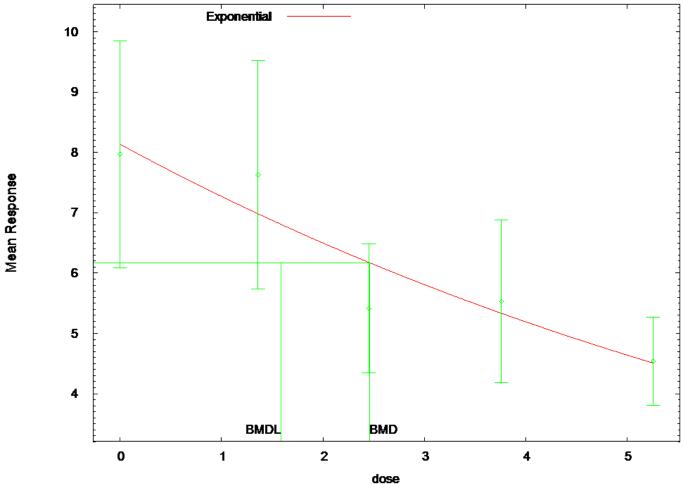
The p-value for Test 4 is greater than .1. The model chosen seems to adequately describe the data

# Benchmark Dose Computation

Specified effect = 1 Risk Type = Estimated standard deviations from the control mean Confidence level = 0.95

BMD = 4.30585

BMDL = 2.84002



09:40 06/22 2014

```
______
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Ln/WBC Historical Ln-HLS 2001-White
Blood Cell Count-ExpCV-1SD-5d. (d)
      Gnuplot Plotting File:
                                 Sun Jun 22 09:40:08 2014
______
===
BMDS Model Run
~~~~
  The form of the response function by Model:
                Y[dose] = a * exp{sign * b * dose}
     Model 2:
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
     Model 4:
                Y[dose] = a * [c-(c-1) * exp{-b * dose}]
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  rho is set to 0.
  A constant variance model is fit.
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 2
lnalpha	1.29317
rho(S)	0
a	4.59625
b	0.111233
C	0
d	1

(S) = Specified

### Parameter Estimates

Variable	Model 2
lnalpha	1.3495
rho	0
a	8.1349
b	0.112266
C	0
d	1

# Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	10	7.97	2.626
1.361	10	7.63	2.653
2.451	9	5.41	1.392
3.761	9	5.53	1.756
5.258	10	4.54	1.019

### Estimated Values of Interest

Est Mean	Est Std	Scaled Residual
8.135	1.964	-0.2656
6.982	1.964	1.043
6.178	1.964	-1.173
5.333	1.964	0.3008
4.508	1.964	0.05142
	8.135 6.982 6.178 5.333	8.135 1.964 6.982 1.964 6.178 1.964 5.333 1.964

Other models for which likelihoods are calculated:

Model A1: Yij = Mu(i) + e(ij) Var{e(ij)} = Sigma^2

Model A2:	Yij = Var{e(ij)} =	Mu(i) + e(ij) Sigma(i)^2
Model A3:	Yij = Var{e(ij)} =	Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R:	Yij = Var{e(ij)} =	Mu + e(i) Sigma^2

Likelihoods of Interest

AIC	Model	Log(likelihood)	DF
AIC			
100 0504	A1	-55.03618	6
122.0724	A2	-49.00369	10
118.0074	A3	-55.03618	6
122.0724	R	-64.89692	2
133.7938	2	-56.38802	3
118.776			

Additive constant for all log-likelihoods = -44.11. This constant added to the above values gives the log-likelihood including the term that does not

depend on the model parameters.

### Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A2 vs. A1) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 4: Does Model 2 fit the data? (A3 vs. 2)

Test p-value	-2*log(Likelihood Ratio)	D. F.
Test 1	31.79	8

0.0001017			
Test	2	12.06	4
0.01687			
Test	3	12.06	4
0.01687			
Test	4	2.704	3
0.4396			

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. Consider running a non-homogeneous variance model.

The p-value for Test 3 is less than .1. You may want to consider a different variance model.

The p-value for Test 4 is greater than .1. Model 2 seems to adequately describe the data.

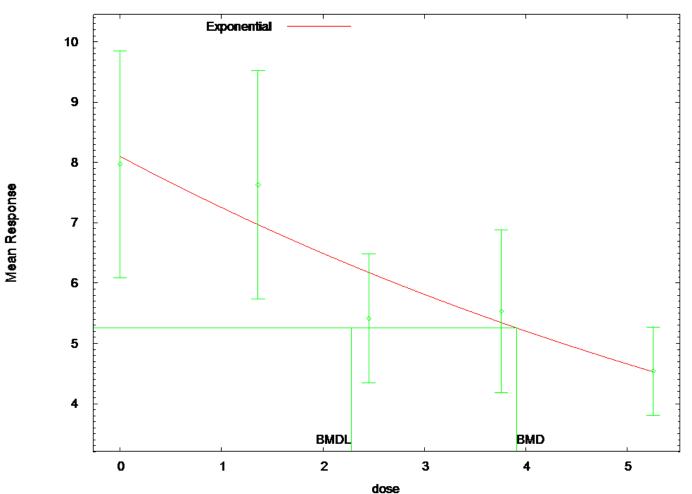
Benchmark Dose Computations:

Specified Effect = 1.000000

Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

BMD = 2.46063



Exponential Model 2, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Level for BMDL

09:40 06/22 2014

```
______
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Ln/WBC Historical Ln-HLS 2001-White
Blood Cell Count-ExpNCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sun Jun 22 09:40:09 2014
______
===
BMDS Model Run
~~~~
  The form of the response function by Model:
                Y[dose] = a * exp{sign * b * dose}
     Model 2:
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
                Y[dose] = a * [c-(c-1) * exp{-b * dose}]
     Model 4:
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  The variance is to be modeled as Var(i) = exp(lalpha + log
(mean(i)) * rho)
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 2
lnalpha	-4.88417
rho	3.3405
a	4.59625
b	0.111233
C	0
d	1

## Parameter Estimates

Variable	Model 2
lnalpha	-4.84136
rho	3.31356
a	8.10018
b	0.110606
С	0
d	1

# Table of Stats From Input Data

Dose	Ν	Obs Mean	Obs Std Dev
0	10	7.97	2.626
1.361	10	7.63	2.653
2.451	9	5.41	1.392
3.761	9	5.53	1.756
5.258	10	4.54	1.019

## Estimated Values of Interest

Est Mean	Est Std	Scaled Residual
8.1	2.844	-0.1448
6.968	2.216	0.9445
6.177	1.815	-1.267
5.344	1.427	0.3918
4.528	1.085	0.03447
	8.1 6.968 6.177 5.344	8.1       2.844         6.968       2.216         6.177       1.815         5.344       1.427

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)

		<pre>Var{e(ij)}</pre>	=	Sigma(i) <sup>2</sup>
Model A	3:	Yij Var{e(ij)}	=	Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model :	R:	Yij Var{e(ij)}	=	Mu + e(i) Sigma <sup>2</sup>

		Likelihoods of Int	erest
210	Model	Log(likelihood)	DF
AIC			
	A1	-55.03618	6
122.0724	A2	-49.00369	10
118.0074	A3	-49.21455	7
112.4291	R	-64.89692	2
133.7938			_
111.5818	2	-51.79089	4

Additive constant for all log-likelihoods = -44.11. This constant added to the above values gives the log-likelihood including the term that does not

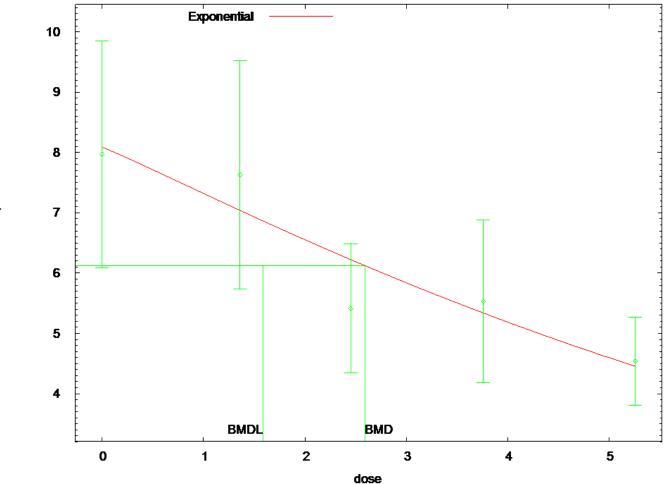
depend on the model parameters.

### Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A2 vs. A1) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 4: Does Model 2 fit the data? (A3 vs. 2)

Test p-value		-2*log(Likelihood Ratio)	D. F.
Test	1	31.79	8
0.0001017			
Test	2	12.06	4

0.01		0 4017	2	
Test 3 0.9357		0.4217	3	
0.95	Test 4	5.153	3	
0.16	1			
be a	The p-value for Test 1 is	less than .05.	There appears to	
be u	difference between respon levels, it seems appropri			
	The p-value for Test 2 is variance model appears to		A non-homogeneous	
	The p-value for Test 3 is variance appears to be ap	5	. The modeled	
	The p-value for Test 4 is to adequately describe th		. Model 2 seems	
В	enchmark Dose Computations	:		
	Specified Effect = 1.0000	00		
cont	Risk Type = Estima rol	ted standard dev	iations from	
	Confidence Level = 0.9500	00		
	BMD = 3	.90961		
	BMDL = 2	.28044		



Mean Response

09:40 06/22 2014

```
______
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Ln/WBC Historical Ln-HLS 2001-White
Blood Cell Count-ExpCV-1SD-5d. (d)
      Gnuplot Plotting File:
                                 Sun Jun 22 09:40:08 2014
______
===
BMDS Model Run
~~~~
  The form of the response function by Model:
                Y[dose] = a * exp{sign * b * dose}
     Model 2:
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
     Model 4:
                Y[dose] = a * [c-(c-1) * exp{-b * dose}]
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  rho is set to 0.
  A constant variance model is fit.
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 3
lnalpha	1.29317
rho(S)	0
a	4.59625
b	0.111233
С	0
d	1

(S) = Specified

### Parameter Estimates

Variable	Model 3
lnalpha	1.34879
rho	0
a	8.0841
b	0.117784
С	0
d	1.07945

# Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	10	7.97	2.626
1.361	10	7.63	2.653
2.451	9	5.41	1.392
3.761	9	5.53	1.756
5.258	10	4.54	1.019

### Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	8.084	1.963	-0.1838
1.361	7.038	1.963	0.9541
2.451	6.224	1.963	-1.243
3.761	5.337	1.963	0.295
5.258	4.454	1.963	0.1391

Other models for which likelihoods are calculated:

Model A1: Yij = Mu(i) + e(ij) Var{e(ij)} = Sigma^2

Model A2:	Yij = Var{e(ij)} =	Mu(i) + e(ij) Sigma(i)^2
Model A3:	Yij = Var{e(ij)} =	Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R:	Yij = Var{e(ij)} =	Mu + e(i) Sigma^2

Likelihoods of Interest

AIC	Model	Log(likelihood)	DF
AIC			
	A1	-55.03618	6
122.0724	A2	-49.00369	10
118.0074	A3	-55.03618	6
122.0724	R	-64.89692	2
133.7938	3	-56.37095	4
120.7419			

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.

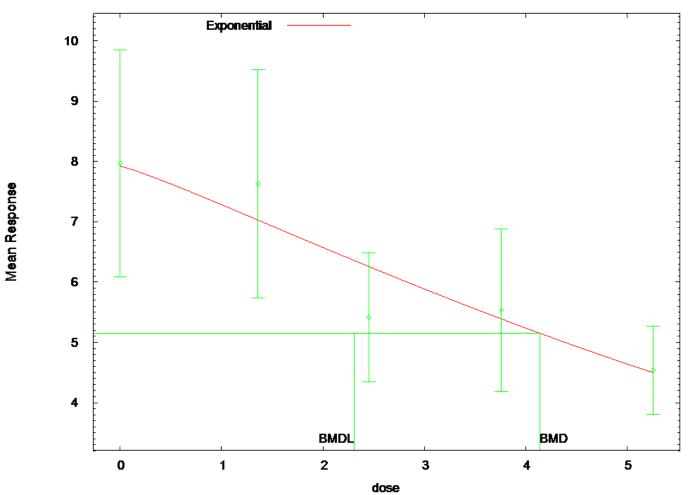
# Explanation of Tests

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 5a: Does Model 3 fit the data? (A3 vs 3)

Test	-2*log(Likelihood Ratio)	D. F.
p-value		

Test	1	31.79	8
0.0001017			
Test	2	12.06	4
0.01687			
Test	3	12.06	4
0.01687			
Test !	5a	2.67	2
0.2632			

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. Consider running a non-homogeneous variance model. The p-value for Test 3 is less than .1. You may want to consider a different variance model. The p-value for Test 5a is greater than .1. Model 3 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 = 2.59459



Exponential Model 3, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Level for BMDL

09:40 06/22 2014

```
______
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Ln/WBC Historical Ln-HLS 2001-White
Blood Cell Count-ExpNCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sun Jun 22 09:40:09 2014
______
===
BMDS Model Run
~~~~
  The form of the response function by Model:
                Y[dose] = a * exp{sign * b * dose}
     Model 2:
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
                Y[dose] = a * [c-(c-1) * exp{-b * dose}]
     Model 4:
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  The variance is to be modeled as Var(i) = exp(lalpha + log
(mean(i)) * rho)
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 3
lnalpha	-4.88417
rho	3.3405
a	4.59625
b	0.111233
С	0
d	1

# Parameter Estimates

Variable	Model 3
lnalpha	-4.99941
rho	3.39998
a	7.92142
b	0.115959
С	0
d	1.14918

# Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	10	7.97	2.626
1.361	10	7.63	2.653
2.451	9	5.41	1.392
3.761	9	5.53	1.756
5.258	10	4.54	1.019

## Estimated Values of Interest

Est Mean	Est Std	Scaled Residual
7.921	2.769	0.05548
7.027	2.259	0.8443
6.259	1.855	-1.372
5.388	1.438	0.2956
4.496	1.057	0.1309
	7.921 7.027 6.259 5.388	7.9212.7697.0272.2596.2591.8555.3881.438

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)

		<pre>Var{e(ij)}</pre>	=	Sigma(i) <sup>2</sup>
Model A	43:			Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model	R:	Yij Var{e(ij)}	=	Mu + e(i) Sigma^2

		Likelihoods of Int	erest
	Model	Log(likelihood)	DF
AIC			
	Al	-55.03618	6
122.0724	A2	-49.00369	10
118.0074	A3	-49.21455	7
112.4291	R	-64.89692	2
133.7938	3	-51.72531	5
113.4506	5	51,2551	5

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 5a: Does Model 3 fit the data? (A3 vs 3)

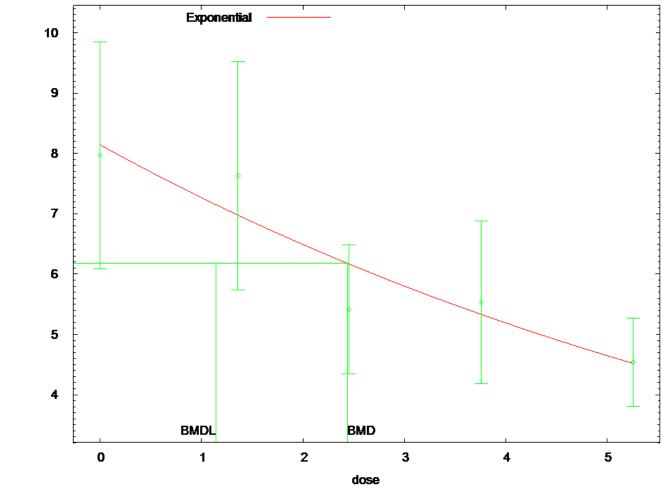
Test p-value	-2*log(Likelihood Ratio)	D. F.
Test 1 0.0001017	31.79	8

Test 2	12.06	4
0.01687		
Test 3	0.4217	3
0.9357		
Test 5a	5.022	2
0.08121		

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 5a is less than .1. Model 3 may not adequately describe the data; you may want to consider another model. Benchmark Dose Computations: Specified Effect = 1.000000 Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

BMD = 4.13868 BMDL = 2.30726



Mean Response

09:40 06/22 2014

```
______
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Ln/WBC Historical Ln-HLS 2001-White
Blood Cell Count-ExpCV-1SD-5d. (d)
      Gnuplot Plotting File:
                                 Sun Jun 22 09:40:08 2014
______
===
BMDS Model Run
~~~~
  The form of the response function by Model:
                Y[dose] = a * exp{sign * b * dose}
     Model 2:
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
     Model 4:
                Y[dose] = a * [c-(c-1) * exp{-b * dose}]
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  rho is set to 0.
  A constant variance model is fit.
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 4
lnalpha	1.29317
rho(S)	0
a	8.3685
b	0.188405
C	0.271255
d	1

(S) = Specified

### Parameter Estimates

Variable	Model 4
lnalpha	1.34948
rho	0
a	8.14254
b	0.119801
C	0.0476544
d	1

# Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	10	7.97	2.626
1.361	10	7.63	2.653
2.451	9	5.41	1.392
3.761	9	5.53	1.756
5.258	10	4.54	1.019

### Estimated Values of Interest

Est Mean	Est Std	Scaled Residual
8.143	1.964	-0.2779
6.976	1.964	1.053
6.169	1.964	-1.16
5.33	1.964	0.306
4.518	1.964	0.03482
	8.143 6.976 6.169 5.33	8.143 1.964 6.976 1.964 6.169 1.964 5.33 1.964

Other models for which likelihoods are calculated:

Model A1: Yij = Mu(i) + e(ij) Var{e(ij)} = Sigma^2

Model A2:	Yij = Var{e(ij)} =	Mu(i) + e(ij) Sigma(i)^2
Model A3:	Yij = Var{e(ij)} =	Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R:	Yij = Var{e(ij)} =	Mu + e(i) Sigma^2

Likelihoods of Interest

AIC	Model	Log(likelihood)	DF
AIC			
100 0504	A1	-55.03618	6
122.0724	A2	-49.00369	10
118.0074	A3	-55.03618	6
122.0724	R	-64.89692	2
133.7938	4	-56.3876	4
120.7752			

Additive constant for all log-likelihoods = -44.11. This constant added to the above values gives the log-likelihood including the term that does not

depend on the model parameters.

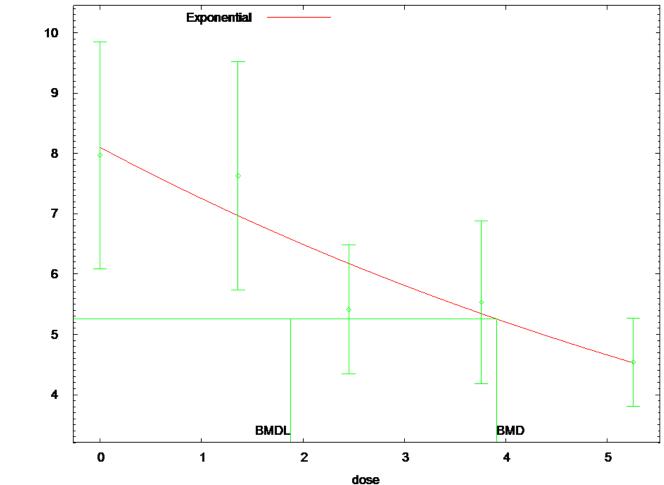
# Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A2 vs. A1) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 6a: Does Model 4 fit the data? (A3 vs 4)

Test	-2*log(Likelihood Ratio)	D. F.
p-value		

Test	1	31.79	8
0.0001017			
Test	2	12.06	4
0.01687			
Test	3	12.06	4
0.01687			
Test	ба	2.703	2
0.2589			
0.01687 Test 0.01687 Test	3	12.06	4 4 2

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. Consider running a non-homogeneous variance model. The p-value for Test 3 is less than .1. You may want to consider a different variance model. 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 = 2.43714



Mean Response

09:40 06/22 2014

```
______
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Ln/WBC Historical Ln-HLS 2001-White
Blood Cell Count-ExpNCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sun Jun 22 09:40:09 2014
______
===
BMDS Model Run
~~~~
  The form of the response function by Model:
                Y[dose] = a * exp{sign * b * dose}
     Model 2:
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
                Y[dose] = a * [c-(c-1) * exp{-b * dose}]
     Model 4:
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  The variance is to be modeled as Var(i) = exp(lalpha + log
(mean(i)) * rho)
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 4
lnalpha	-4.88417
rho	3.3405
a	8.3685
b	0.140289
С	0.108502
d	1

## Parameter Estimates

Variable	Model 4
lnalpha	-4.84136
rho	3.31356
a	8.10018
b	0.110606
С	0
d	1

# Table of Stats From Input Data

Dose	Ν	Obs Mean	Obs Std Dev
0	10	7.97	2.626
1.361	10	7.63	2.653
2.451	9	5.41	1.392
3.761	9	5.53	1.756
5.258	10	4.54	1.019

## Estimated Values of Interest

Est Mean	Est Std	Scaled Residual
8.1	2.844	-0.1448
6.968	2.216	0.9445
6.177	1.815	-1.267
5.344	1.427	0.3918
4.528	1.085	0.03447
	8.1 6.968 6.177 5.344	8.1         2.844           6.968         2.216           6.177         1.815           5.344         1.427

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)

		<pre>Var{e(ij)}</pre>	=	Sigma(i) <sup>2</sup>
Model A	43:			Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model	R:	Yij Var{e(ij)}	=	Mu + e(i) Sigma^2

		Likelihoods of Int	erest
2.50	Model	Log(likelihood)	DF
AIC			
	Al	-55.03618	6
122.0724	A2	-49.00369	10
118.0074	A3	-49.21455	7
112.4291	R	-64.89692	2
133.7938	4	-51.79089	4
111.5818	1	51.,5005	-

Additive constant for all log-likelihoods = -44.11. This constant added to the above values gives the log-likelihood including the term that does not

depend on the model parameters.

#### Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A2 vs. A1) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 6a: Does Model 4 fit the data? (A3 vs 4)

Test p-value	-2*log(Likelihood Ratio)	D. F.
Test 1 0.0001017	31.79	8

Test 2	12.06	4
0.01687		
Test 3	0.4217	3
0.9357		
Test 6a	5.153	3
0.161		

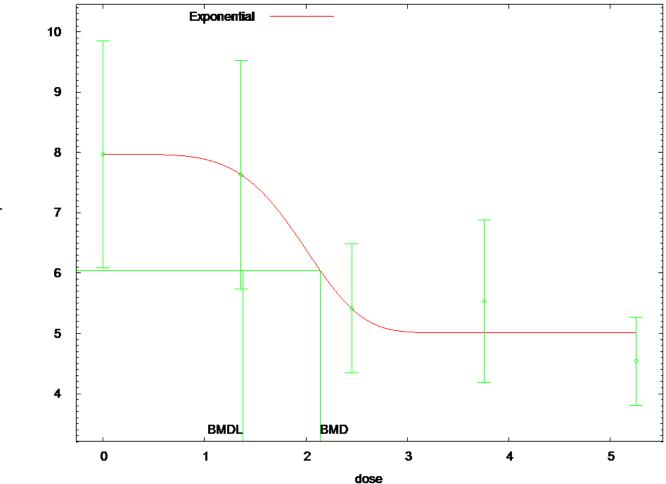
The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data. The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate. The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here. The p-value for Test 6a is greater than .1. Model 4 seems to adequately describe the data. Benchmark Dose Computations:

Specified Effect = 1.000000

Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

BMD = 3.90961



Mean Response

09:40 06/22 2014

```
______
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Ln/WBC Historical Ln-HLS 2001-White
Blood Cell Count-ExpCV-1SD-5d. (d)
      Gnuplot Plotting File:
                                 Sun Jun 22 09:40:08 2014
______
===
BMDS Model Run
~~~~
  The form of the response function by Model:
                Y[dose] = a * exp{sign * b * dose}
     Model 2:
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
     Model 4:
                Y[dose] = a * [c-(c-1) * exp{-b * dose}]
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  rho is set to 0.
  A constant variance model is fit.
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 5
lnalpha	1.29317
rho(S)	0
a	8.3685
b	0.188405
С	0.271255
d	1

(S) = Specified

### Parameter Estimates

Variable	Model 5
lnalpha	1.31937
rho	0
a	7.97001
b	0.471998
C	0.628474
d	4.754

# Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	10	7.97	2.626
1.361	10	7.63	2.653
2.451	9	5.41	1.392
3.761	9	5.53	1.756
5.258	10	4.54	1.019

### Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	7.97	1.934	-1.275e-005
1.361	7.63	1.934	1.8e-005
2.451	5.41	1.934	-1.795e-005
3.761	5.009	1.934	0.8082
5.258	5.009	1.934	-0.7667

Other models for which likelihoods are calculated:

Model A1: Yij = Mu(i) + e(ij) Var{e(ij)} = Sigma^2

Model A2:	Yij = Var{e(ij)} =	Mu(i) + e(ij) Sigma(i)^2
Model A3:		Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R:	Yij = Var{e(ij)} =	Mu + e(i) Sigma^2

Likelihoods of Interest

AIC	Model	Log(likelihood)	DF
AIC			
	A1	-55.03618	6
122.0724	A2	-49.00369	10
118.0074	A3	-55.03618	6
122.0724	R	-64.89692	2
133.7938	5	-55.66483	5
121.3297			

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.

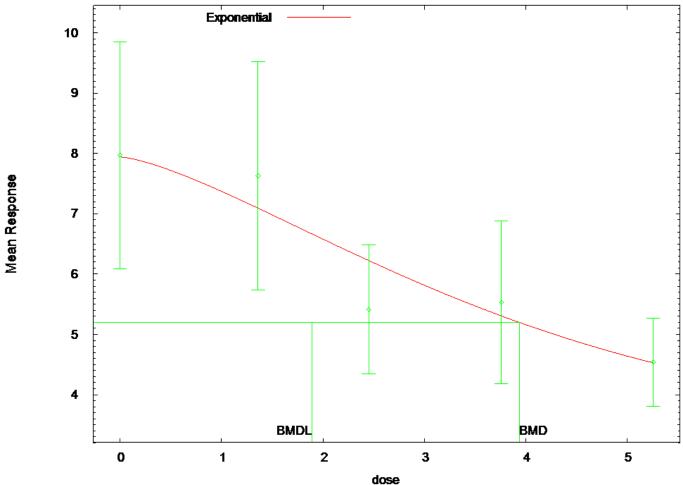
# Explanation of Tests

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)

Test	-2*log(Likelihood Ratio)	D. F.
p-value		

Test	1	31.79	8
0.0001017			
Test	2	12.06	4
0.01687			
Test	3	12.06	4
0.01687			
Test '	7a	1.257	1
0.2622			

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. Consider running a non-homogeneous variance model. The p-value for Test 3 is less than .1. You may want to consider a different variance model. 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 = 2.14436



09:40 06/22 2014

```
______
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Ln/WBC Historical Ln-HLS 2001-White
Blood Cell Count-ExpNCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sun Jun 22 09:40:09 2014
______
===
BMDS Model Run
~~~~
  The form of the response function by Model:
                Y[dose] = a * exp{sign * b * dose}
     Model 2:
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
                Y[dose] = a * [c-(c-1) * exp{-b * dose}]
     Model 4:
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  The variance is to be modeled as Var(i) = exp(lalpha + log
(mean(i)) * rho)
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 5
lnalpha	-4.88417
rho	3.3405
a	8.3685
b	0.140289
С	0.108502
d	1

# Parameter Estimates

Variable	Model 5
lnalpha	-4.83301
rho	3.30719
a	7.94216
b	0.240307
C	0.427483
d	1.40851

# Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	10	7.97	2.626
1.361	10	7.63	2.653
2.451	9	5.41	1.392
3.761	9	5.53	1.756
5.258	10	4.54	1.019

# Estimated Values of Interest

Est Mean	Est Std	Scaled Residual
7.942	2.746	0.03206
7.091	2.277	0.7483
6.224	1.835	-1.331
5.305	1.409	0.4781
4.527	1.084	0.03666
	7.942 7.091 6.224 5.305	7.9422.7467.0912.2776.2241.8355.3051.409

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)

		<pre>Var{e(ij)}</pre>	=	Sigma(i)^2	
Model A	.3:			Mu(i) + e(ij) exp(lalpha + log(mean(i)) *	rho)
Model	R:	Yij Var{e(ij)}	=	Mu + e(i) Sigma <sup>2</sup>	

		Likelihoods of Int	erest
2.50	Model	Log(likelihood)	DF
AIC			
	Al	-55.03618	6
122.0724	A2	-49.00369	10
118.0074	A3	-49.21455	7
112.4291	R	-64.89692	2
133.7938	5	-51.68357	6
115.3671	5	51.00007	Ũ

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)

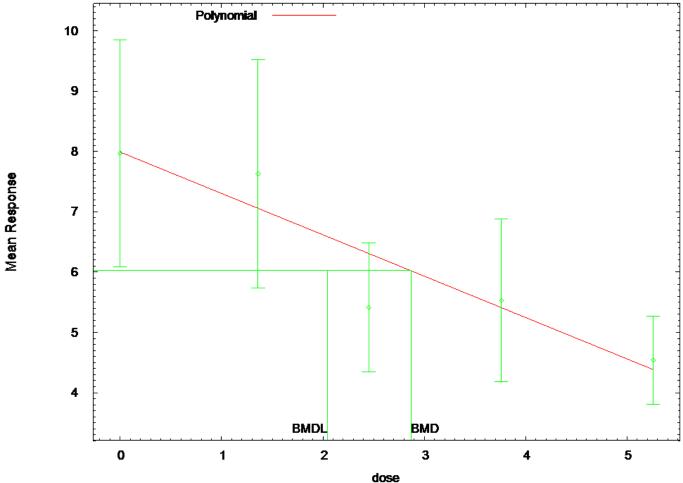
#### Tests of Interest

Test p-value	-2*log(Likelihood Ratio)	D. F.
Test 1 0.0001017	31.79	8

Test 2	12.06	4
0.01687 Test 3	0.4217	З
0.9357	0.4217	5
Test 7a	4.938	1
0.02627		

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 7a is less than .1. Model 5 may not adequately describe the data; you may want to consider another model. Benchmark Dose Computations: Specified Effect = 1.000000 Risk Type = Estimated standard deviations from control Confidence Level = 0.950000

> BMD = 3.9402 BMDL = 1.8945



12:46 07/09 2014

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_WBC\_Historical\_Ln/WBC\_Historical\_L n-HLS 2001-White Blood Cell Count-Poly2CV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_WBC\_Historical\_Ln/WBC\_Historical\_L n-HLS 2001-White Blood Cell Count-Poly2CV-1SD-5d.plt Wed Jul 09 12:46:34 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse 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 = 5Total 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 = 4.0681 Specified rho = 0 beta\_0 = 8.15662 beta\_1 = -0.952983 beta\_2 = 0 Asymptotic Correlation Matrix of Parameter Estimates ( \*\*\* The model parameter(s) -rho -beta 2 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	6.3e-008	-5.3e-008
beta_0	6.3e-008	1	-0.81
beta_1	-5.3e-008	-0.81	1

# Parameter Estimates

			95.0%
Wald Confidence In	terval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Conf	. Limit		
alpha	3.87221	0.790412	
2.32303	5.42139		
beta_0	7.9913	0.481462	
7.04765	8.93494		
beta_1	-0.685697	0.152832	-
0.985242	-0.386152		
beta_2	0	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
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Dose Scaled R	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 -0.0342	10	7.97	7.99	2.63	1.97
1.361 0.919	10	7.63	7.06	2.65	1.97
2.451 -1.37	9	5.41	6.31	1.39	1.97
3.761 0.179	9	5.53	5.41	1.76	1.97
5.258 0.248	10	4.54	4.39	1.02	1.97

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<sup>2</sup>

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
Al	-55.036182	б	122.072364
A2	-49.003692	10	118.007385
A3	-55.036182	6	122.072364
fitted	-56.491842	3	118.983685
R	-64.896924	2	133.793848

### 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

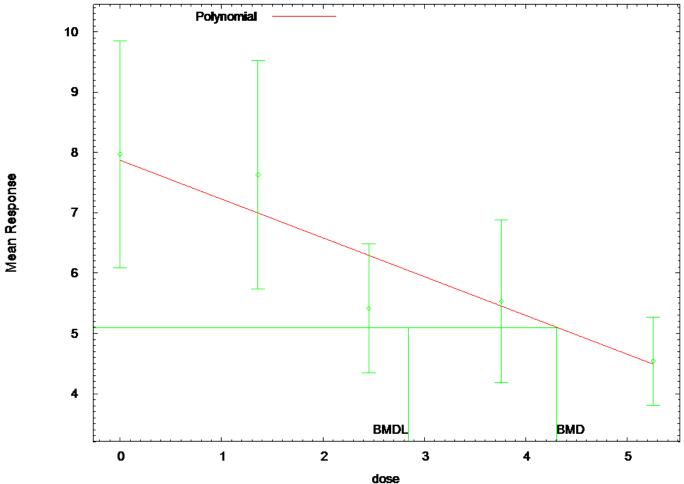
Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.7865	8	0.0001017
Test 2	12.065	4	0.01687
Test 3	12.065	4	0.01687
Test 4	2.91132	3	0.4055

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. Consider running a non-homogeneous variance model The p-value for Test 3 is less than .1. You may want to consider а different variance model 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 = Estimated standard deviations from the Risk Type control mean Confidence level = 0.95

BMD = 2.86977

BMDL = 2.04395



12:46 07/09 2014

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_WBC\_Historical\_Ln/WBC\_Historical\_L n-HLS 2001-White Blood Cell Count-Poly2NCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_WBC\_Historical\_Ln/WBC\_Historical\_L n-HLS 2001-White Blood Cell Count-Poly2NCV-1SD-5d.plt Wed Jul 09 12:46:35 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse 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 = 5Total number of records with missing values = 0Maximum 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 = 1.40318 rho = 0 beta\_0 = 8.15662 beta\_1 = -0.952983 beta\_2 = 0 Asymptotic Correlation Matrix of Parameter Estimates ( \*\*\* The model parameter(s) -beta\_2 have been estimated at a boundary point, or have been specified by the user,

	and	do	not	appear	in	the	correlation	matrix	)
--	-----	----	-----	--------	----	-----	-------------	--------	---

	lalpha	rho	beta_0	beta_1
lalpha	1	-0.99	0.13	-0.15
rho	-0.99	1	-0.13	0.15
beta_0	0.13	-0.13	1	-0.91
beta_1	-0.15	0.15	-0.91	1

Parameter Estimates

95.0%
-------

					95.	.0%
Wald Conf	idence Int	terval				
Va	riable	Estimate	e Std.	Err.	Lower	Conf.
Limit U	pper Conf	. Limit				
	lalpha	-5.14645	5 1	.9704		-
9.00836	_	-1.28454				
	rho	3.48317	1.	08261		
1.3613		5.60504				
	beta_0	7.86568	3 0.5	62534		
6.76313	_	8.96823				
	beta 1	-0.643285	5 0.1	34966		_
0.907813	_	-0.378757				
	beta_2	(	)	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 Scaled 1	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 0.119	10	7.97	7.87	2.63	2.77
1.361	10	7.63	6.99	2.65	2.26
2.451 -1.41	9	5.41	6.29	1.39	1.88
3.761 0.172	9	5.53	5.45	1.76	1.46

5.258	10	4.54	4.48	1.02	1.04
0.172					

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
Al	-55.036182	6	122.072364
A2	-49.003692	10	118.007385
A3	-49.214548	7	112.429095
fitted	-51.789349	4	111.578698
R	-64.896924	2	133.793848

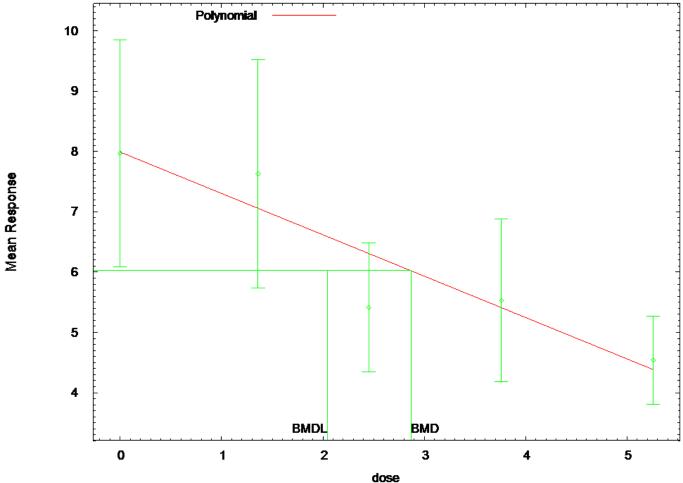
# Explanation of Tests

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	31.7865	8	0.0001017
Test 2	12.065	4	0.01687
Test 3	0.421711	3	0.9357
Test 4	5.1496	3	0.1612

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 = Estimated standard deviations from the Risk Type control mean Confidence level = 0.95 BMD = 4.30585 BMDL = 2.84002



12:46 07/09 2014

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_WBC\_Historical\_Ln/WBC\_Historical\_L n-HLS 2001-White Blood Cell Count-Poly3CV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_WBC\_Historical\_Ln/WBC\_Historical\_L n-HLS 2001-White Blood Cell Count-Poly3CV-1SD-5d.plt Wed Jul 09 12:46:34 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse 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 = 5Total 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 = 4.0681 Specified rho = 0  $r_{110} = 0$ beta\_0 = 8.07952 beta\_1 = -0.517572  $beta_2 = -0.184335$ beta 3 = 0 Asymptotic Correlation Matrix of Parameter Estimates ( \*\*\* The model parameter(s) -rho -beta\_2 -

and do not appear in the correlation matrix )

beta_1	beta_0	alpha	
-2.4e-008	1.5e-008	1	alpha
-0.81	1	1.5e-008	beta_0
1	-0.81	-2.4e-008	beta_1

Parameter Estimates

95.0%

Wald Confi	dence Interval			
Var	iable	Estimate	Std. Err.	Lower Conf.
Limit Up	per Conf. Limi	t		
	alpha	3.87222	0.790413	
2.32303	5.4	214		
b	oeta_0	7.9913	0.481462	
7.04765	8.93	494		
b	eta_1 -	0.685697	0.152832	-
0.985242	-0.38	6152		
b	eta_2	0	NA	
b	oeta_3	0	NA	
b 0.985242 b	Deta_1	0.685697	NA	-

NA - Indicates that this parameter has hit a bound implied by some inequality constraint and thus has no standard error.

Dose Scaled R	N Les.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 -0.0342	10	7.97	7.99	2.63	1.97
1.361 0.919	10	7.63	7.06	2.65	1.97
2.451 -1.37	9	5.41	6.31	1.39	1.97
3.761 0.179	9	5.53	5.41	1.76	1.97
5.258	10	4.54	4.39	1.02	1.97

Table of Data and Estimated Values of Interest

Model Descriptions for likelihoods calculated

Var{e(i)} = Sigma^2

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)

### Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
Al	-55.036182	б	122.072364
A2	-49.003692	10	118.007385
A3	-55.036182	6	122.072364
fitted	-56.491842	3	118.983685
R	-64.896924	2	133.793848

# Explanation of Tests

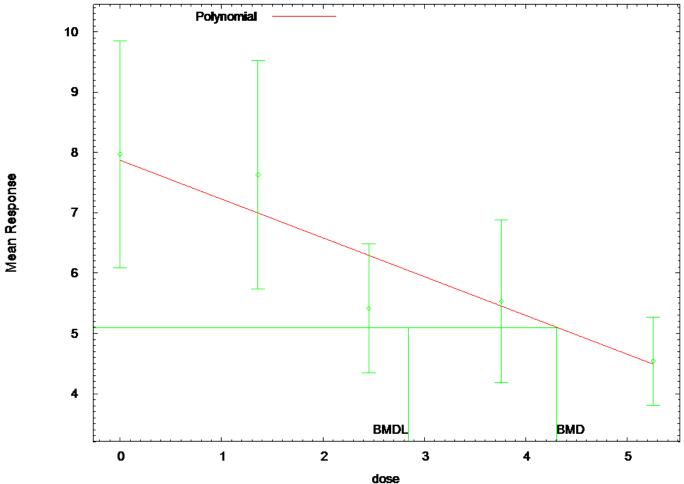
Test 1: Do responses and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A1 vs A2) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 4: Does the Model for the Mean Fit? (A3 vs. fitted) (Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

# Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.7865	8	0.0001017
Test 2	12.065	4	0.01687
Test 3	12.065	4	0.01687
Test 4	2.91132	3	0.4055

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. Consider running a non-homogeneous variance model The p-value for Test 3 is less than .1. You may want to consider а different variance model 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 Estimated standard deviations from the Risk Type = control mean Confidence level = 0.95 2.86977 BMD = BMDL = 2.04395



12:46 07/09 2014

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_WBC\_Historical\_Ln/WBC\_Historical\_L n-HLS 2001-White Blood Cell Count-Poly3NCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_WBC\_Historical\_Ln/WBC\_Historical\_L n-HLS 2001-White Blood Cell Count-Poly3NCV-1SD-5d.plt Wed Jul 09 12:46:35 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse 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 = 5Total number of records with missing values = 0Maximum 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 = 1.40318 rho = 0 8.07952 beta\_0 = 8.07952 beta\_1 = -0.517572  $beta_2 = -0.184335$ beta 3 = 0 Asymptotic Correlation Matrix of Parameter Estimates ( \*\*\* The model parameter(s) -beta\_2 -beta\_3

have been estimated at a boundary point, or have been specified by the user, and do not appear in the correlation matrix )

	lalpha	rho	beta_0	beta_1
lalpha	1	-0.99	0.13	-0.15
rho	-0.99	1	-0.13	0.15
beta_0	0.13	-0.13	1	-0.91
beta_1	-0.15	0.15	-0.91	1

Parameter Estimates

			95.0%
Wald Confidenc	e Interval		
Variabl	e Estimate	Std. Err.	Lower Conf.
Limit Upper	Conf. Limit		
lalph	a -5.14645	1.9704	_
9.00836	-1.28453		
rh	o 3.48317	1.08261	
1.3613	5.60504		
beta_	0 7.86568	0.562534	
6.76313	8.96823		
beta_	1 -0.643285	0.134966	_
0.907813	-0.378757		
beta_	2 0	NA	
beta_	3 0	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 Scaled	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 0.119	10	7.97	7.87	2.63	2.77
1.361	10	7.63	6.99	2.65	2.26
2.451 -1.41	9	5.41	6.29	1.39	1.88

3.761	9	5.53	5.45	1.76	1.46
0.172					
5.258	10	4.54	4.48	1.02	1.04
0.172					

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
Al	-55.036182	6	122.072364
A2	-49.003692	10	118.007385
A3	-49.214548	7	112.429095
fitted	-51.789349	4	111.578698
R	-64.896924	2	133.793848

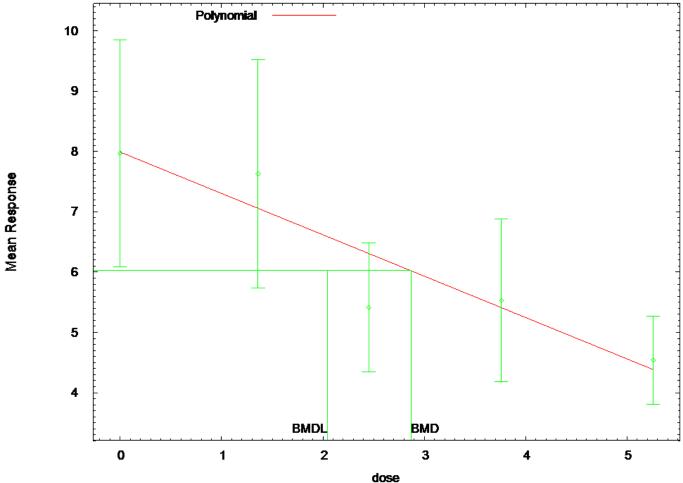
### Explanation of Tests

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	31.7865	8	0.0001017
Test 2	12.065	4	0.01687
Test 3	0.421711	3	0.9357

5.1496 3 0.1612 Test 4 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 = Estimated standard deviations from the Risk Type control mean Confidence level = 0.95 4.30585 BMD = 2.84002 BMDL =



12:46 07/09 2014

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_WBC\_Historical\_Ln/WBC\_Historical\_L n-HLS 2001-White Blood Cell Count-Poly4CV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_WBC\_Historical\_Ln/WBC\_Historical\_L n-HLS 2001-White Blood Cell Count-Poly4CV-1SD-5d.plt Wed Jul 09 12:46:34 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse 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 = 5Total 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 = 4.0681 rho = 0 Specified beta\_0 = 7.97 beta\_1 = 0  $beta_2 = -4.80701$ beta\_3 = 0  $beta_4 = -0.138078$ 

Asymptotic Correlation Matrix of Parameter Estimates

beta_1	bela_0	aipna	
-1.9e-009	-9.6e-009	1	alpha
-0.81	1	-9.6e-009	beta_0
1	-0.81	-1.9e-009	beta_1

Parameter Estimates

### 95.0%

Wald Confidence Int	cerval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Conf.	. Limit		
alpha	3.87222	0.790413	
2.32303	5.4214		
beta_0	7.9913	0.481462	
7.04765	8.93494		
beta_1	-0.685697	0.152832	_
0.985242	-0.386152		
beta_2	-1.61465e-138	NA	
beta_3	-1.41684e-143	NA	
beta_4	0	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 Intere	Table	of Data	ble of Data and	Estimated	Values	of	Interes
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Dose Scaled R	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0	10	7.97	7.99	2.63	1.97
-0.0342					
1.361 0.919	10	7.63	7.06	2.65	1.97
	0	Г <i>1</i> 1	C 21	1 20	1 07
2.451	9	5.41	6.31	1.39	1.97
-1.37 3.761	9	5.53	5.41	1.76	1.97

0.179 5.258 0.248	10	4.54	4.39	1.02	1.97
Model	Descriptio	ns for likeli	hoods calcula	ited	
Model		Yij = Mu(i) ij)} = Sigma^			
Model		Yij = Mu(i) ij)} = Sigma(			
Мс	Var{e( odel A3 use	Yij = Mu(i) ij)} = Sigma^ s any fixed v ed by the use	2 ariance param	eters that	
Model		Yi = Mu + e (i)} = Sigma^			

# Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-55.036182	6	122.072364
A2	-49.003692	10	118.007385
A3	-55.036182	б	122.072364
fitted	-56.491842	3	118.983685
R	-64.896924	2	133.793848

# 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.)

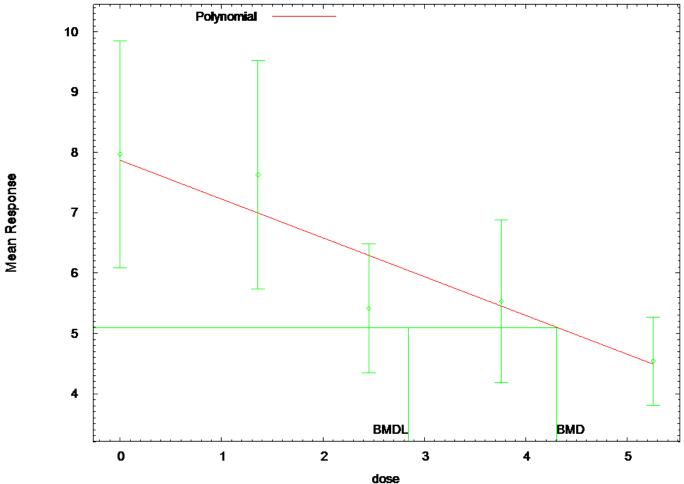
### Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.7865	8	0.0001017
Test 2	12.065	4	0.01687
Test 3	12.065	4	0.01687
Test 4	2.91132	3	0.4055

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. Consider running a non-homogeneous variance model The p-value for Test 3 is less than .1. You may want to consider а different variance model 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 = Estimated standard deviations from the Risk Type control mean Confidence level = 0.95

BMD = 2.86977

BMDL = 2.04395



12:46 07/09 2014

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_WBC\_Historical\_Ln/WBC\_Historical\_L n-HLS 2001-White Blood Cell Count-Poly4NCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_WBC\_Historical\_Ln/WBC\_Historical\_L n-HLS 2001-White Blood Cell Count-Poly4NCV-1SD-5d.plt Wed Jul 09 12:46:35 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse 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 = 5Total number of records with missing values = 0Maximum 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 = 1.40318 rho = 0 7.97 beta\_0 = beta\_1 = 0  $beta_2 = -4.80701$ beta\_3 = 0  $beta_4 = -0.138078$ 

Asymptotic Correlation Matrix of Parameter Estimates

	татрпа	1110	Deca_0	Deta_1
lalpha	1	-0.99	0.13	-0.15
rho	-0.99	1	-0.13	0.15
beta_0	0.13	-0.13	1	-0.91
beta_1	-0.15	0.15	-0.91	1

### Parameter Estimates

### 95.0%

Wald Conf	idence In	terval		23.00
	ariable	Estimate	Std. Err.	Lower Conf.
Limit U	Jpper Conf	. Limit		
	lalpha	-5.14645	1.9704	-
9.00837		-1.28453		
	rho	3.48317	1.08261	
1.3613		5.60505		
	beta_0	7.86568	0.562535	
6.76313		8.96823		
	beta_1	-0.643285	0.134966	_
0.907814		-0.378757		
	beta_2	0	NA	
	beta_3	0	NA	
	beta_4	-6.97218e-107	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 Scaled R	N Les.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
	· <b>_</b> _				
0 0.119	10	7.97	7.87	2.63	2.77
1.361	10	7.63	6.99	2.65	2.26

0.897	9	5.41	6.29	1.39	1.88
-1.41 3.761 0.172	9	5.53	5.45	1.76	1.46
5.258 0.172	10	4.54	4.48	1.02	1.04

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)Var $\{e(ij)\}$  = Sigma<sup>2</sup> Model A2: Yij = Mu(i) + e(ij)Var $\{e(ij)\}$  = Sigma(i)<sup>2</sup>

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
Al	-55.036182	6	122.072364
A2	-49.003692	10	118.007385
A3	-49.214548	7	112.429095
fitted	-51.789349	4	111.578698
R	-64.896924	2	133.793848

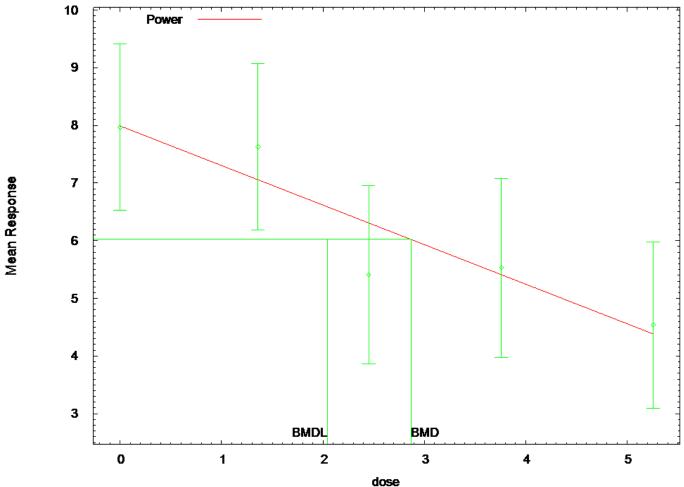
### Explanation of Tests

### Tests of Interest

Test	-2*log(Likelihood	Ratio	) Test df	p-value
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3

31.7865 8 4 Test 2 Test 1 0.0001017 12.065 0.01687 Test 3 0.421711 3 0.9357 Test 4 5.1496 3 0.1612 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 = 4.30586 2.84002 BMDL =



Power Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

09:40 06/22 2014

\_\_\_\_\_\_ === Power Model. (Version: 2.18; Date: 05/19/2014) Input Data File: C:/Users/dmayfield/Desktop/Ln/WBC\_Historical\_Ln-HLS 2001-White Blood Cell Count-PowerCV-1SD-5d.  $(\overline{d})$ Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Ln/WBC Historical Ln-HLS 2001-White Blood Cell Count-PowerCV-1SD-5d.plt Sun Jun 22 09:40:09 2014 \_\_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = control + slope \* dose^power Dependent variable = MeanResponse 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 = 5Total 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 = 4.0681 4.54 rho = Specified rho = 0 control = 4.54 slope = 3.75463 power = -1.18214 0 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	-2.6e-010	-1.7e-010
control	-2.6e-010	1	-0.81
slope	-1.7e-010	-0.81	1

### Parameter Estimates

			95.0%
Wald Confidence	Interval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Cc	onf. Limit		
alpha	3.87222	0.790413	
2.32303	5.4214		
control	7.9913	0.481462	
7.04765	8.93494		
slope	-0.685697	0.152832	_
0.985242	-0.386152		
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
---------------------------------------

Dose Scaled R	N Les.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 -0.0342	10	7.97	7.99	2.63	1.97
1.361 0.919	10	7.63	7.06	2.65	1.97
2.451	9	5.41	6.31	1.39	1.97
3.761 0.179	9	5.53	5.41	1.76	1.97
5.258 0.248	10	4.54	4.39	1.02	1.97

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<sup>2</sup>

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
Al	-55.036182	6	122.072364
A2	-49.003692	10	118.007385
A3	-55.036182	6	122.072364
fitted	-56.491842	3	118.983685
R	-64.896924	2	133.793848

#### Explanation of Tests

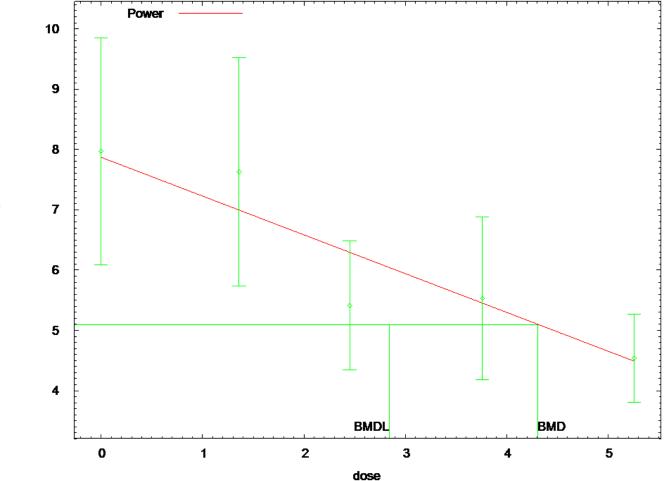
Test 1:	Do responses and/or variances differ among Dose levels?
	(A2 vs. R)
Test 2:	Are Variances Homogeneous? (A1 vs A2)
Test 3:	Are variances adequately modeled? (A2 vs. A3)
Test 4:	Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:	When rho=0 the results of Test 3 and Test 2 will be the
same.)	

### Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.7865	8	0.0001017
Test 2	12.065	4	0.01687
Test 3	12.065	4	0.01687
Test 4	2.91132	3	0.4055

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. Consider running a non-homogeneous variance model The p-value for Test 3 is less than .1. You may want to consider а different variance model 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 = Estimated standard deviations from the Risk Type control mean Confidence level = 0.95 BMD = 2.86977

BMDL = 2.04395



Mean Response

09:40 06/22 2014

\_\_\_\_\_\_ === Power Model. (Version: 2.18; Date: 05/19/2014) Input Data File: C:/Users/dmayfield/Desktop/Ln/WBC\_Historical\_Ln-HLS 2001-White Blood Cell Count-PowerNCV-1SD-5d. (d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Ln/WBC Historical Ln-HLS 2001-White Blood Cell Count-PowerNCV-1SD-5d.plt Sun Jun 22 09:40:10 2014 === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = control + slope \* dose^power Dependent variable = MeanResponse Independent variable = Dose The power is restricted to be greater than or equal to 1 The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) \* rho) Total number of dose groups = 5Total number of records with missing values = 0Maximum 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 = 1.40318 rho = 0 rho = 0 control = 4.54 slope = 3.75463 power = -1.18214 Asymptotic Correlation Matrix of Parameter Estimates ( \*\*\* The model parameter(s) -power have been estimated at a boundary point, or have been specified by the user,

and do not appear in the correlation matrix )

	lalpha	rho	control	slope
lalpha	1	-0.99	0.44	-0.56
rho	-0.99	1	-0.49	0.58
control	0.44	-0.49	1	-0.92
slope	-0.56	0.58	-0.92	1

Parameter Estimates

95	•	0응	

				95.0%
Wald (	Confidence I	Interval		
	Variable	Estimate	Std. Err.	Lower Conf.
Limit	Upper Con	ıf. Limit		
	lalpha	-5.14645	2.39809	-
9.846	62 -	-0.446281		
	rho	3.48317	1.33215	
0.872	197	6.09414		
	control	7.86568	0.565523	
6.7572	28	8.97409		
	slope	-0.643285	0.135832	-
0.909	_	-0.37706		
	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 Scaled 1	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 0.119	10	7.97	7.87	2.63	2.77
1.361 0.897	10	7.63	6.99	2.65	2.26
2.451	9	5.41	6.29	1.39	1.88
3.761 0.172	9	5.53	5.45	1.76	1.46

5.258	10	4.54	4.48	1.02	1.04
0.172					

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	-55.036182	6	122.072364
A2	-49.003692	10	118.007385
A3	-49.214548	7	112.429095
fitted	-51.789349	4	111.578698
R	-64.896924	2	133.793848

### Explanation of Tests

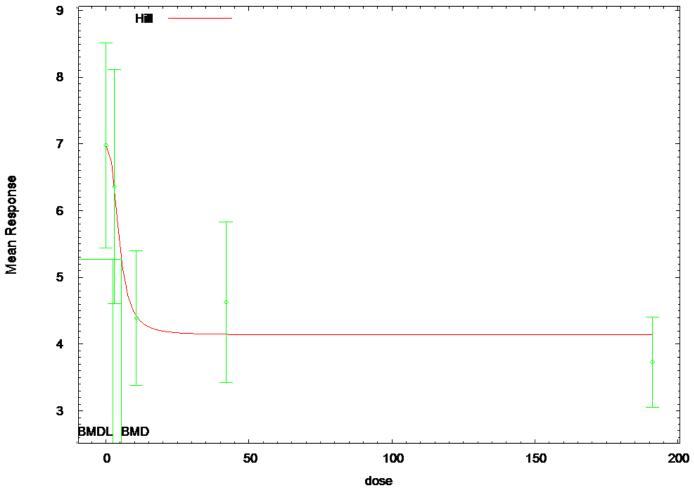
Test 1: Do responses and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A1 vs A2) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 4: Does the Model for the Mean Fit? (A3 vs. fitted) (Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

### Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.7865	8	0.0001017
Test 2	12.065	4	0.01687
Test 3	0.421711	3	0.9357
Test 4	5.1496	3	0.1612

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 = Estimated standard deviations from the Risk Type control mean Confidence level = 0.95 BMD = 4.30585BMDL = 2.84002

BMDS Model Results for Lymphocyte Count (Untransformed Doses, Concurrent Controls)



Hill Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

14:54 06/21 2014

\_\_\_\_\_\_ === Hill Model. (Version: 2.17; Date: 01/28/2013) Input Data File: C:/Users/dmayfield/Desktop/Ln/Lymphocyte\_Concurrent\_Normal-HLS 2001-Lymphocyte Count-HillCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Ln/Lymphocyte Concurrent Normal-HLS 2001-Lymphocyte Count-HillCV-1SD-5d.plt Sat Jun 21 14:54:12 2014 === BMDS Model Run ~~~~ The form of the response function is:  $Y[dose] = intercept + v*dose^n/(k^n + dose^n)$ Dependent variable = MeanResponse 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 = 5Total 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 = 3.18101 Specified rho = 0 intercept = 6.98 -3.25 v = n = 1.7748 k = 6.82817 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 )

k		alpha	intercept	v	n
al] -1.5e-0	oha 08	1	-4.7e-009	8.9e-009	5.4e-008
interce -0.39	ept	-4.7e-009	1	-0.8	-0.24
0.0044	v	8.9e-009	-0.8	1	0.5
-0.45	n	5.4e-008	-0.24	0.5	1
1	k	-1.5e-008	-0.39	0.0044	-0.45

Parameter Estimates

			95.0%
Wald Confidence Int	erval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Conf.	Limit		
alpha	2.92849	0.597775	
1.75687	4.1001		
intercept	6.98398	0.540843	
5.92395	8.04402		
v	-2.84388	0.694315	-
4.20471	-1.48305		
n	2.6779	2.57223	-
2.36358	7.71939		
k	4.63333	2.49765	-
0.261967	9.52864		

Table of Data and Estimated Values of Interest

Dose Scaled R		Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 -0.00736	10	6.98	6.98	2.15	1.71

2.9	10	6.36	6.35	2.45	1.71
0.0129					
10.6	9	4.39	4.42	1.31	1.71
-0.052					
42	9	4.63	4.15	1.56	1.71
0.845					
191.1	10	3.73	4.14	0.941	1.71
-0.758					

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	-49.132777	6	110.265553
A2	-43.798233	10	107.596466
A3	-49.132777	6	110.265553
fitted	-49.787657	5	109.575313
R	-59.677903	2	123.355807

# Explanation of Tests

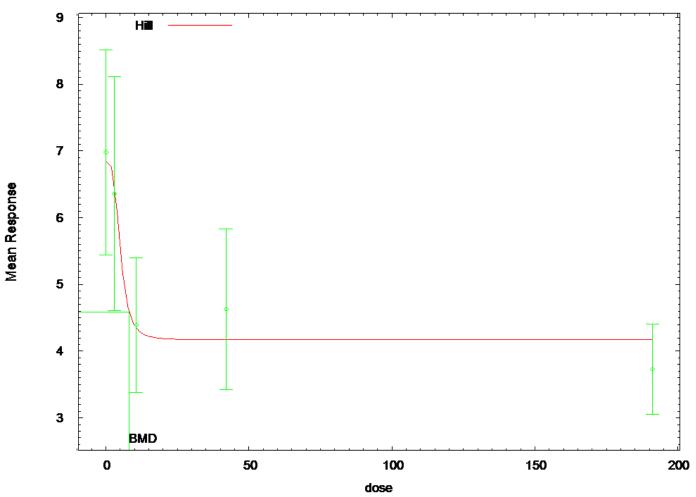
Test 1:	Do responses and/or variances differ among Dose levels?
	(A2 vs. R)
Test 2:	Are Variances Homogeneous? (A1 vs A2)
Test 3:	Are variances adequately modeled? (A2 vs. A3)
Test 4:	Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:	When rho=0 the results of Test 3 and Test 2 will be the
same.)	

### Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
------	--------------------------	---------	---------

Test 131.759380.0001029Test 210.669140.03055Test 310.669140.03055Test 41.3097610.2524

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. Consider running a non-homogeneous variance model The p-value for Test 3 is less than .1. You may want to consider а different variance model 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 = 5.40541 BMDL = 2.33184



14:54 06/21 2014

Hill Model

\_\_\_\_\_\_ === Hill Model. (Version: 2.17; Date: 01/28/2013) Input Data File: C:/Users/dmayfield/Desktop/Ln/Lymphocyte\_Concurrent\_Normal-HLS 2001-Lymphocyte Count-HillNCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Ln/Lymphocyte Concurrent Normal-HLS 2001-Lymphocyte Count-HillNCV-1SD-5d.plt Sat Jun 21 14:54:13 2014 === BMDS Model Run ~~~~ The form of the response function is:  $Y[dose] = intercept + v*dose^n/(k^n + dose^n)$ Dependent variable = MeanResponse Independent variable = Dose Power parameter restricted to be greater than 1 The variance is to be modeled as Var(i) = exp(lalpha + rho \* ln(mean(i))) Total number of dose groups = 5Total 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 = 1.1572 rho = 0 intercept = 6.98 -3.25 V = n = 1.7748 k = 6.82817 Asymptotic Correlation Matrix of Parameter Estimates intercept lalpha rho v

n	k			
lalpha -0.12	a 1 -0.068	-0.99	0.33	-0.42
rh0.12	o -0.99 0.068	1	-0.36	0.44
intercept -0.44	t 0.33 -0.52	-0.36	1	-0.92
0.55	v -0.42 0.36	0.44	-0.92	1
1	n -0.12 0.11	0.12	-0.44	0.55
]	k -0.068 1	0.068	-0.52	0.36

Parameter Estimates

				95.0%
Wald Con	fidence I	nterval		
V	ariable	Estimate	Std. Err.	Lower Conf.
Limit	Upper Con	f. Limit		
	lalpha	-2.89915	1.69974	-
6.23058		0.432275		
	rho	2.3509	1.03442	
0.323471		4.37834		
in	tercept	6.83523	0.682559	
5.49744		8.17302		
	v	-2.66512	0.760963	-
4.15658		-1.17366		
	n	3.59728	3.28848	-
2.84803		10.0426		
	k	5.0554	2.93561	-
0.698289		10.8091		

Table of Data and Estimated Values of Interest

Dose Scaled R		Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 0.204	10	6.98	6.84	2.15	2.25

2

2.9	10	6.36	6.52	2.45	2.12
-0.234 10.6	9	4.39	4.34	1.31	1.32
0.105	9	4.35	4.54	1.51	1.52
42	9	4.63	4.17	1.56	1.26
1.09					
191.1	10	3.73	4.17	0.941	1.26
-1.11					

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	-49.132777	6	110.265553
A2	-43.798233	10	107.596466
A3	-44.177523	7	102.355046
fitted	-46.479307	6	104.958615
R	-59.677903	2	123.355807

### 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 131.759380.0001029Test 210.669140.03055Test 30.7585830.8593Test 44.6035710.03191

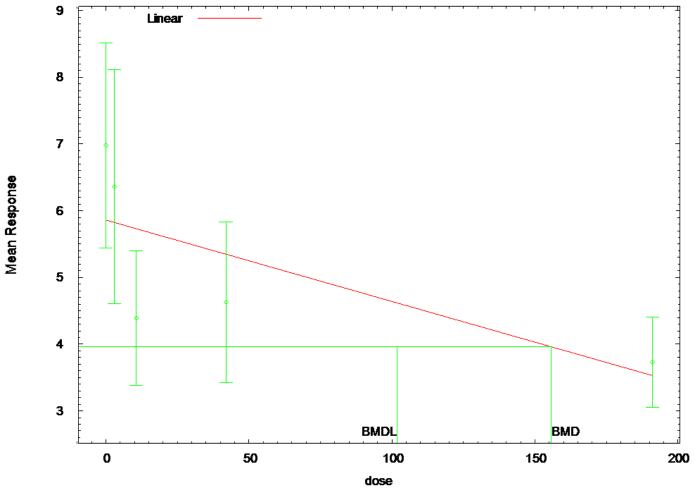
The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels It seems appropriate to model the data The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate The p-value for Test 3 is greater 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 = 8.07024

BMDL computation failed.



12:47 07/09 2014

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_Lymphocyte\_Concurrent/Lymphocyte\_C oncurrent\_Normal-HLS 2001-Lymphocyte Count-LinearCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_Lymphocyte\_Concurrent/Lymphocyte\_C oncurrent\_Normal-HLS 2001-Lymphocyte Count-LinearCV-1SD-5d.plt Wed Jul 09 12:47:23 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse Independent variable = Dose rho is set to 0 Signs of the polynomial coefficients are not restricted A constant variance model is fit Total number of dose groups = 5Total number of records with missing values = 0Maximum 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 = 3.18101 rho = 0 Specified  $r_{110} = 0$ beta\_0 = 5.80912  $beta_1 = -0.0119854$ Asymptotic Correlation Matrix of Parameter Estimates ( \*\*\* The model parameter(s) -rho have been estimated at a boundary point, or have been specified by the user,

and do not appear in the correlation matrix  $\)$ 

	alpha	beta_0	beta_1
alpha	1	5.7e-008	-1.1e-007
beta_0	5.7e-008	1	-0.56
beta_1	-1.1e-007	-0.56	1

### Parameter Estimates

			95.0%
Wald Confidence	Interval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Co	nf. Limit		
alpha	3.61273	0.737445	
2.16736	5.05809		
beta_0	5.86108	0.332087	
5.2102	6.51196		
beta_1	-0.0122035	0.00372175	-
0.019498	-0.00490895		

Table of Data and Estimated Values of Interest

Dose Scaled	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0	10	6.98	5.86	2.15	1.9
1.86					
2.9	10	6.36	5.83	2.45	1.9
0.889					
10.6	9	4.39	5.73	1.31	1.9
-2.12					
42	9	4.63	5.35	1.56	1.9
-1.13					
191.1	10	3.73	3.53	0.941	1.9
0.334					

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
Al	-49.132777	6	110.265553
A2	-43.798233	10	107.596466
A3	-49.132777	6	110.265553
fitted	-54.827112	3	115.654225
R	-59.677903	2	123.355807

### 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	31.7593	8	0.0001029
Test 2	10.6691	4	0.03055
Test 3	10.6691	4	0.03055
Test 4	11.3887	3	0.0098

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. Consider running a non-homogeneous variance model

The p-value for Test 3 is less than .1. You may want to consider a

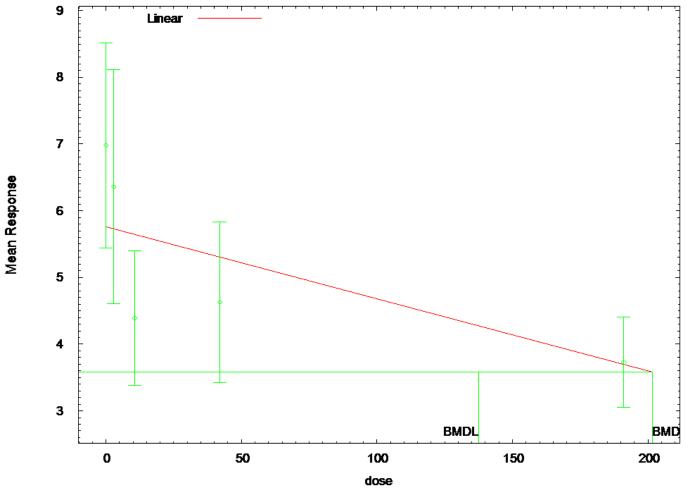
different variance model

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 = 155.752

BMDL = 101.835



Linear Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

12:47 07/09 2014

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_Lymphocyte\_Concurrent/Lymphocyte\_C oncurrent\_Normal-HLS 2001-Lymphocyte Count-LinearNCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_Lymphocyte\_Concurrent/Lymphocyte\_C oncurrent\_Normal-HLS 2001-Lymphocyte Count-LinearNCV-1SD-5d.plt Wed Jul 09 12:47:25 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse Independent variable = Dose Signs of the polynomial coefficients are not restricted The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) \* rho) Total number of dose groups = 5Total number of records with missing values = 0Maximum 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 = 1.1572 rho = 0  $beta_0 = 5.80912$  $beta_1 = -0.0119854$ Asymptotic Correlation Matrix of Parameter Estimates lalpha rho beta\_0 beta 1 -0.99 0.046 -0.055 lalpha 1

rho	-0.99	1	-0.047	0.056
beta_0	0.046	-0.047	1	-0.81
beta_1	-0.055	0.056	-0.81	1

Parameter Estimates

### 95.0%

Wald Confidence Interval						
Variabl	e Estimate	Std. Err.	Lower Conf.			
Limit Upper	Conf. Limit					
lalph	na -5.65714	1.90045	-			
9.38195	-1.93233					
rh	4.12209	1.15309				
1.86209	6.3821					
beta_	_0 5.76447	0.365011				
5.04907	6.47988					
beta_	_1 -0.0108344	0.00248095	_			
0.015697	-0.00597185					

Table of Data and Estimated Values of Interest

Dose Scaled	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 1.76	10	6.98	5.76	2.15	2.19
2.9	10	6.36	5.73	2.45	2.16
10.6 -1.8	9	4.39	5.65	1.31	2.1
42 -1.1	9	4.63	5.31	1.56	1.84
191.1 0.13	10	3.73	3.69	0.941	0.873

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<sup>2</sup>

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
Al	-49.132777	б	110.265553
A2	-43.798233	10	107.596466
A3	-44.177523	7	102.355046
fitted	-50.343208	4	108.686416
R	-59.677903	2	123.355807

### Explanation of Tests

#### Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.7593	8	0.0001029
Test 2	10.6691	4	0.03055
Test 3	0.75858	3	0.8593
Test 4	12.3314	3	0.00633

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

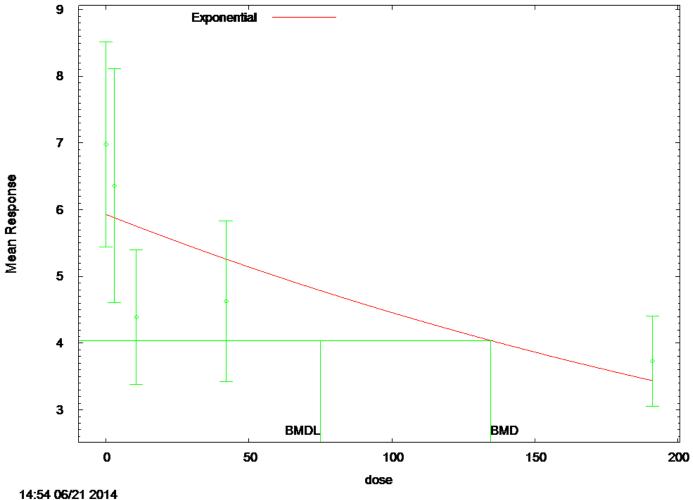
The p-value for Test 4 is less than .1. You may want to try a different model

Benchmark Dose Computation

Specified effect = 1 Risk Type = Estimated standard deviations from the control mean Confidence level = 0.95

BMD = 201.708

BMDL = 137.467



```
_____
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Ln/Lymphocyte Concurrent Normal-HLS
2001-Lymphocyte Count-ExpCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sat Jun 21 14:54:11 2014
______
===
BMDS Model Run
~~~~
  The form of the response function by Model:
                Y[dose] = a * exp{sign * b * dose}
     Model 2:
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
               Y[dose] = a * [c-(c-1) * exp{-b * dose}]
     Model 4:
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  rho is set to 0.
  A constant variance model is fit.
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 2
lnalpha	1.0472
rho(S)	0
a	4.506
b	0.00246217
С	0
d	1

(S) = Specified

#### Parameter Estimates

Variable	Model 2
lnalpha	1.27198
rho	0
a	5.93021
b	0.00285331
C	0
d	1

# Table of Stats From Input Data

Dose	Ν	Obs Mean	Obs Std Dev
0	10	6.98	2.146
2.9	10	6.36	2.452
10.6	9	4.39	1.308
42	9	4.63	1.564
191.1	10	3.73	0.941

### Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	5.93	1.889	1.757
2.9	5.881	1.889	0.8013
10.6	5.754	1.889	-2.166
42	5.26	1.889	-1.001
191.1	3.438	1.889	0.4894

Other models for which likelihoods are calculated:

Model A1: Yij = Mu(i) + e(ij) Var{e(ij)} = Sigma^2

Model A2:	Yij = Var{e(ij)} =	Mu(i) + e(ij) Sigma(i)^2
Model A3:	Yij = Var{e(ij)} =	Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R:	Yij = Var{e(ij)} =	Mu + e(i) Sigma^2

Likelihoods of Interest

AIC	Model	Log(likelihood)	DF
AIC			
	A1	-49.13278	6
110.2656	A2	-43.79823	10
107.5965	A3	-49.13278	6
110.2656	R	-59.6779	2
123.3558	2	-54.52762	3
115.0552	2	- 54.52702	5

Additive constant for all log-likelihoods = -44.11. This constant added to the above values gives the log-likelihood including the term that does not

depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A2 vs. A1) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 4: Does Model 2 fit the data? (A3 vs. 2)

Tests of Interest

Test p-value	-2*log(Likelihood Ratio)	D. F.
Test 1	31.76	8

0.0001029			
Test	2	10.67	4
0.03055			
Test	3	10.67	4
0.03055			
Test	4	10.79	3
0.01292			

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. Consider running a non-homogeneous variance model.

The p-value for Test 3 is less than .1. You may want to consider a different variance model.

The p-value for Test 4 is less than .1. Model 2 may not adequately

describe the data; you may want to consider another model.

Benchmark Dose Computations:

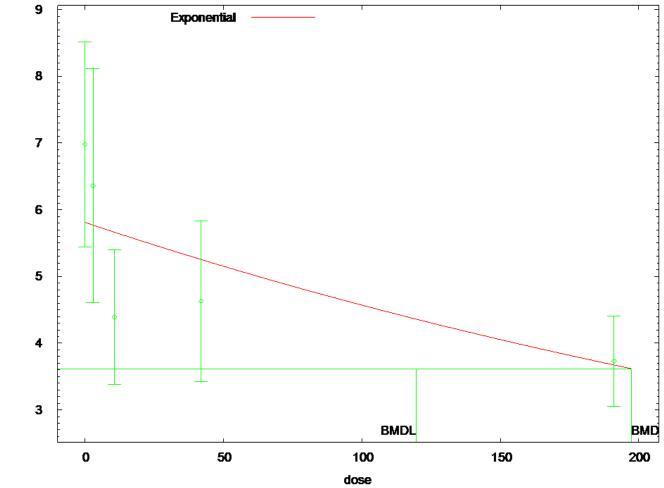
Specified Effect = 1.000000

Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

BMD = 134.402

BMDL = 74.8756



# Exponential Model 2, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Level for BMDL

Mean Response

14:54 06/21 2014

```
______
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Ln/Lymphocyte Concurrent Normal-HLS
2001-Lymphocyte Count-ExpNCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sat Jun 21 14:54:13 2014
______
===
BMDS Model Run
~~~~
  The form of the response function by Model:
                Y[dose] = a * exp{sign * b * dose}
     Model 2:
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
                Y[dose] = a * [c-(c-1) * exp{-b * dose}]
     Model 4:
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  The variance is to be modeled as Var(i) = exp(lalpha + log
(mean(i)) * rho)
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 2
lnalpha	-3.58873
rho	2.77965
a	4.506
b	0.00246217
С	0
d	1

### Parameter Estimates

Variable	Model 2
lnalpha	-5.4971
rho	4.01629
a	5.81037
b	0.00239974
С	0
d	1

# Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	10	6.98	2.146
2.9	10	6.36	2.452
10.6	9	4.39	1.308
42	9	4.63	1.564
191.1	10	3.73	0.941

### Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	5.81	2.193	1.687
2.9	5.77	2.162	0.8628
10.6	5.664	2.083	-1.835
42	5.253	1.791	-1.044
191.1	3.673	0.873	0.2059

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)

	<pre>Var{e(ij) } =</pre>	Sigma(i) <sup>2</sup>
Model A3	: Yij = Var{e(ij)} =	Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R	: Yij = Var{e(ij)} =	Mu + e(i) Sigma^2

		Likelihoods of Int	erest
210	Model	Log(likelihood)	DF
AIC			
	Al	-49.13278	6
110.2656	A2	-43.79823	10
107.5965			
102.355	A3	-44.17752	7
123.3558	R	-59.6779	2
	2	-50.053	4
108.106			

Additive constant for all log-likelihoods = -44.11. This constant added to the above values gives the log-likelihood including the term that does not

depend on the model parameters.

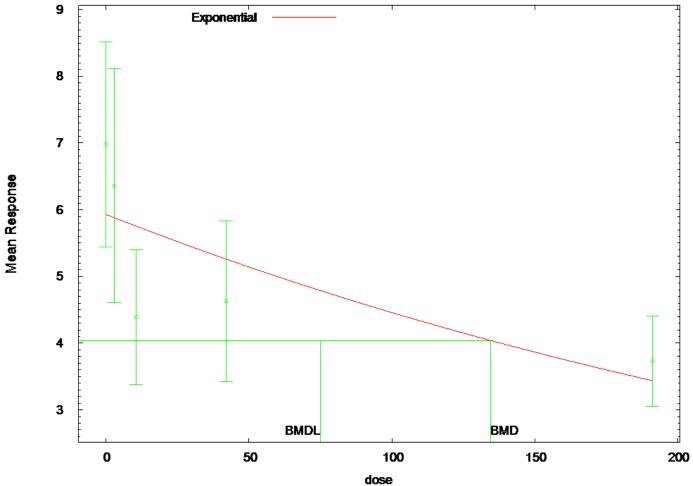
#### Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A2 vs. A1) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 4: Does Model 2 fit the data? (A3 vs. 2)

Test p-value		-2*log(Likelihood Ratio)	D. F.
	· _		
Test	1	31.76	8
0.0001029			
Test	2	10.67	4

```
0.03055
                                  0.7586
    Test 3
                                          3
0.8593
                                   11.75 3
    Test 4
0.008287
    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. Model 2 may not
adequately
    describe the data; you may want to consider another model.
  Benchmark Dose Computations:
    Specified Effect = 1.000000
           Risk Type = Estimated standard deviations from
control
    Confidence Level = 0.950000
                 BMD =
                          197.427
```

```
BMDL = 119.645
```



14:54 06/21 2014

```
_____
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Ln/Lymphocyte Concurrent Normal-HLS
2001-Lymphocyte Count-ExpCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sat Jun 21 14:54:11 2014
______
===
BMDS Model Run
~~~~
  The form of the response function by Model:
                Y[dose] = a * exp{sign * b * dose}
     Model 2:
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
               Y[dose] = a * [c-(c-1) * exp{-b * dose}]
     Model 4:
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  rho is set to 0.
  A constant variance model is fit.
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 3
lnalpha	1.0472
rho(S)	0
a	4.506
b	0.00246217
С	0
d	1

(S) = Specified

#### Parameter Estimates

Variable	Model 3
lnalpha	1.27198
rho	0
a	5.93021
b	0.00285331
C	0
d	1

# Table of Stats From Input Data

Dose	Ν	Obs Mean	Obs Std Dev
0	10	6.98	2.146
2.9	10	6.36	2.452
10.6	9	4.39	1.308
42	9	4.63	1.564
191.1	10	3.73	0.941

### Estimated Values of Interest

Est Mean	Est Std	Scaled Residual
5.93	1.889	1.757
5.881	1.889	0.8013
5.754	1.889	-2.166
5.26	1.889	-1.001
3.438	1.889	0.4894
	5.93 5.881 5.754 5.26	5.931.8895.8811.8895.7541.8895.261.889

Other models for which likelihoods are calculated:

Model A1: Yij = Mu(i) + e(ij) Var{e(ij)} = Sigma^2

Model A2:	Yij = Var{e(ij)} =	Mu(i) + e(ij) Sigma(i)^2
Model A3:	Yij = Var{e(ij)} =	Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R:	Yij = Var{e(ij)} =	Mu + e(i) Sigma^2

Likelihoods of Interest

AIC	Model	Log(likelihood)	DF
AIC			
	A1	-49.13278	6
110.2656	A2	-43.79823	10
107.5965	A3	-49.13278	6
110.2656			-
123.3558	R	-59.6779	2
115.0552	3	-54.52762	3

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.

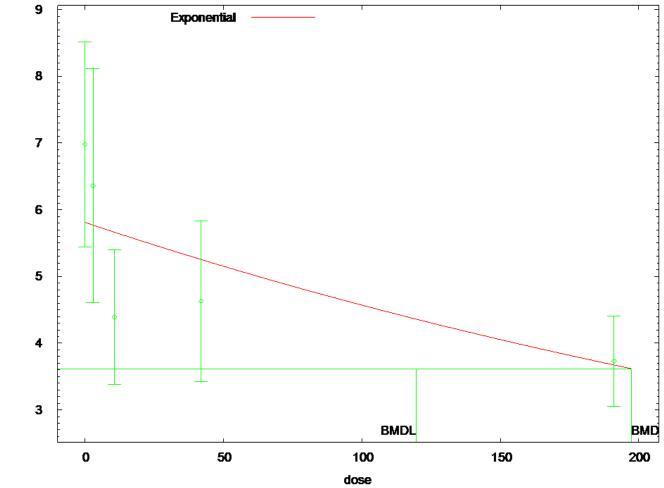
# Explanation of Tests

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 5a: Does Model 3 fit the data? (A3 vs 3)

Test	-2*log(Likelihood Ratio)	D. F.
p-value		

Test	1	31.76	8
0.0001029	2	10 67	4
Test 0.03055	2	10.67	4
0.03055 Test	2	10.67	Λ
0.03055	5	10.07	4
Test 5	ā	10.79	3
0.01292			

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. Consider running a non-homogeneous variance model. The p-value for Test 3 is less than .1. You may want to consider a different variance model. The p-value for Test 5a is less than .1. Model 3 may not adequately describe the data; you may want to consider another model. Benchmark Dose Computations: Specified Effect = 1.000000 Risk Type = Estimated standard deviations from control Confidence Level = 0.950000BMD = 134.402 BMDL = 74.8756



# Exponential Model 3, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Level for BMDL

Mean Response

14:54 06/21 2014

```
______
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Ln/Lymphocyte Concurrent Normal-HLS
2001-Lymphocyte Count-ExpNCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sat Jun 21 14:54:13 2014
______
===
BMDS Model Run
~~~~
  The form of the response function by Model:
                Y[dose] = a * exp{sign * b * dose}
     Model 2:
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
                Y[dose] = a * [c-(c-1) * exp{-b * dose}]
     Model 4:
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  The variance is to be modeled as Var(i) = exp(lalpha + log
(mean(i)) * rho)
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 3
lnalpha	-3.58873
rho	2.77965
a	4.506
b	0.00246217
C	0
d	1

### Parameter Estimates

Variable	Model 3
lnalpha	-5.4971
rho	4.01629
a	5.81037
b	0.00239974
C	0
d	1

# Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	10	6.98	2.146
2.9	10	6.36	2.452
10.6	9	4.39	1.308
42	9	4.63	1.564
191.1	10	3.73	0.941

### Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	5.81	2.193	1.687
2.9	5.77	2.162	0.8628
10.6	5.664	2.083	-1.835
42	5.253	1.791	-1.044
191.1	3.673	0.873	0.2059

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)

	<pre>Var{e(ij)} =</pre>	Sigma(i) <sup>2</sup>
Model A3	: Yij = Var{e(ij)} =	Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R	: Yij = Var{e(ij)} =	Mu + e(i) Sigma^2

		Likelihoods of Int	erest
210	Model	Log(likelihood)	DF
AIC			
	A1	-49.13278	6
110.2656	A2	-43.79823	10
107.5965	A3	-44.17752	7
102.355	R	-59.6779	2
123.3558			_
108.106	3	-50.053	4

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 5a: Does Model 3 fit the data? (A3 vs 3)

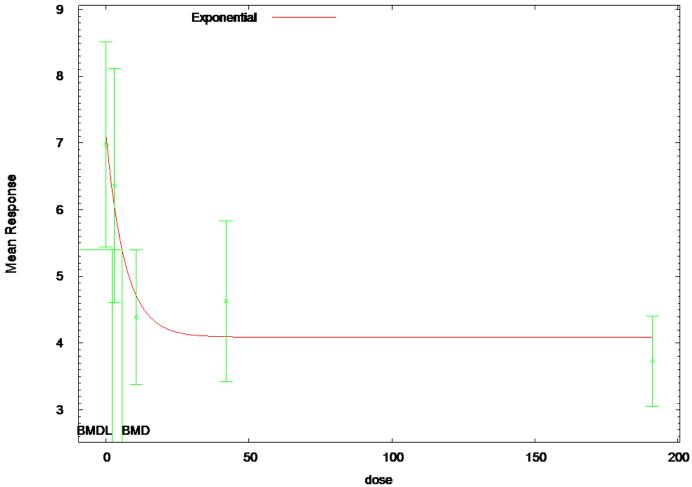
Test p-value	-2*log(Likelihood Ratio)	D. F.
Test 1 0.0001029	31.76	8

Test 2	10.67	4
0.03055		
Test 3	0.7586	3
0.8593		
Test 5a	11.75	3
0.008287		

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 5a is less than .1. Model 3 may not adequately describe the data; you may want to consider another model. Benchmark Dose Computations: Specified Effect = 1.000000 Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

BMD = 197.427 BMDL = 119.645



14:54 06/21 2014

```
_____
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Ln/Lymphocyte Concurrent Normal-HLS
2001-Lymphocyte Count-ExpCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sat Jun 21 14:54:11 2014
______
===
BMDS Model Run
~~~~
  The form of the response function by Model:
                Y[dose] = a * exp{sign * b * dose}
     Model 2:
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
               Y[dose] = a * [c-(c-1) * exp{-b * dose}]
     Model 4:
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  rho is set to 0.
  A constant variance model is fit.
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 4
lnalpha	1.0472
rho(S)	0
a	7.329
b	0.0170211
С	0.484702
d	1

(S) = Specified

#### Parameter Estimates

Variable	Model 4
lnalpha	1.08961
rho	0
a	7.12238
b	0.150285
C	0.574374
d	1

# Table of Stats From Input Data

Dose	Ν	Obs Mean	Obs Std Dev
0	10	6.98	2.146
2.9	10	6.36	2.452
10.6	9	4.39	1.308
42	9	4.63	1.564
191.1	10	3.73	0.941

### Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	7.122	1.724	-0.2611
2.9	6.051	1.724	0.5659
10.6	4.707	1.724	-0.5519
42	4.096	1.724	0.9284
191.1	4.091	1.724	-0.6619

Other models for which likelihoods are calculated:

Model A1: Yij = Mu(i) + e(ij) Var{e(ij)} = Sigma^2

Model A2:	Yij = Var{e(ij)} =	Mu(i) + e(ij) Sigma(i)^2
Model A3:	Yij = Var{e(ij)} =	Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R:	Yij = Var{e(ij)} =	Mu + e(i) Sigma^2

Likelihoods of Interest

AIC	Model	Log(likelihood)	DF
AIC			
	Al	-49.13278	6
110.2656	A2	-43.79823	10
107.5965	A3	-49.13278	6
110.2656	R	-59.6779	2
123.3558	4	-50.15058	4
108.3012			

Additive constant for all log-likelihoods = -44.11. This constant added to the above values gives the log-likelihood including the term that does not

depend on the model parameters.

# Explanation of Tests

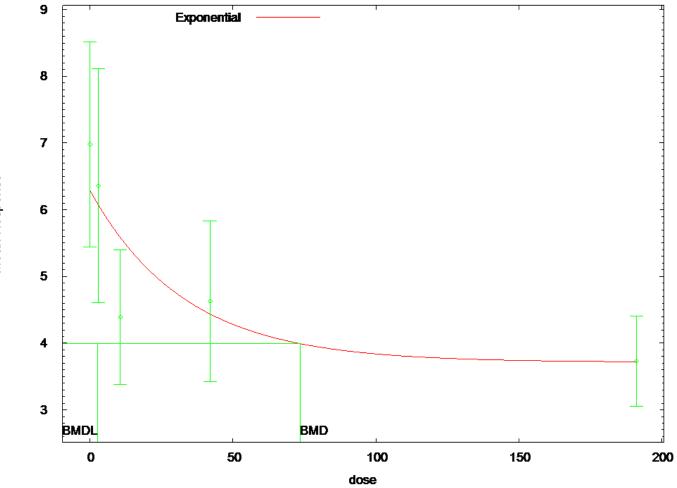
Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A2 vs. A1) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 6a: Does Model 4 fit the data? (A3 vs 4)

Test	-2*log(Likelihood Ratio)	D. F.
p-value		

Test	1	31.76	8
0.0001029			
Test	2	10.67	4
0.03055			
Test	3	10.67	4
0.03055			
Test 6	6a	2.036	2
0.3614			

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. Consider running a non-homogeneous variance model. The p-value for Test 3 is less than .1. You may want to consider a different variance model. 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 = 5.59708

BMDL = 2.23698



Mean Response

14:54 06/21 2014

```
______
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Ln/Lymphocyte Concurrent Normal-HLS
2001-Lymphocyte Count-ExpNCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sat Jun 21 14:54:13 2014
______
===
BMDS Model Run
~~~~
  The form of the response function by Model:
                Y[dose] = a * exp{sign * b * dose}
     Model 2:
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
                Y[dose] = a * [c-(c-1) * exp{-b * dose}]
     Model 4:
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  The variance is to be modeled as Var(i) = exp(lalpha + log
(mean(i)) * rho)
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 4
lnalpha	-3.58873
rho	2.77965
a	7.329
b	0.0170211
С	0.484702
d	1

# Parameter Estimates

Variable	Model 4
lnalpha	-4.3478
rho	3.2691
a	6.29097
b	0.0302436
С	0.590321
d	1

# Table of Stats From Input Data

Dose	Ν	Obs Mean	Obs Std Dev
0	10	6.98	2.146
2.9	10	6.36	2.452
10.6	9	4.39	1.308
42	9	4.63	1.564
191.1	10	3.73	0.941

### Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	6.291	2.298	0.948
2.9	6.075	2.171	0.4159
10.6	5.584	1.892	-1.894
42	4.437	1.299	0.445
191.1	3.722	0.9745	0.02708

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)

		<pre>Var{e(ij)}</pre>	=	Sigma(i) <sup>2</sup>	
Model A	A3:			Mu(i) + e(ij) exp(lalpha + log(mean(i)) *	rho)
Model	R:	Yij Var{e(ij)}	=	Mu + e(i) Sigma <sup>2</sup>	

		Likelihoods of Int	erest
210	Model	Log(likelihood)	DF
AIC			
	A1	-49.13278	6
110.2656	A2	-43.79823	10
107.5965	A3	-44.17752	7
102.355	R	-59.6779	2
123.3558			_
105.8113	4	-47.90566	5

Additive constant for all log-likelihoods = -44.11. This constant added to the above values gives the log-likelihood including the term that does not

depend on the model parameters.

#### Explanation of Tests

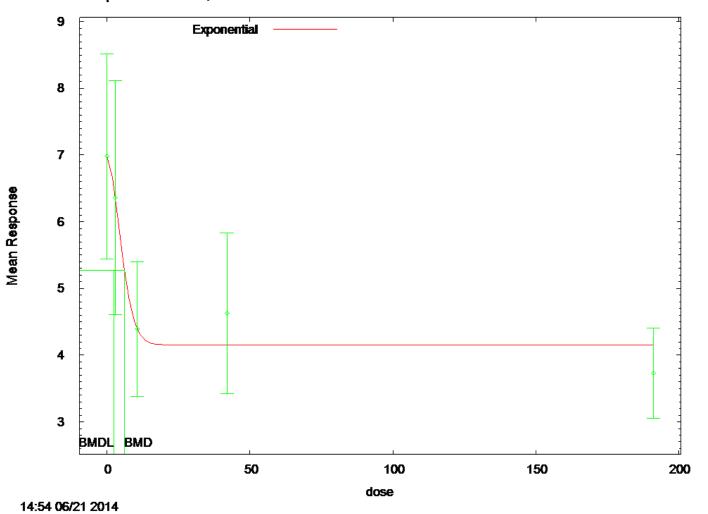
Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A2 vs. A1) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 6a: Does Model 4 fit the data? (A3 vs 4)

Test p-value	-2*log(Likelihood Ratio)	D. F.
Test 1 0.0001029	31.76	8

Test 2	10.67	4
0.03055		
Test 3	0.7586	3
0.8593		
Test 6a	7.456	2
0.02404		

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data. The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate. The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here. The p-value for Test 6a is less than .1. Model 4 may not adequately describe the data; you may want to consider another model. Benchmark Dose Computations: Specified Effect = 1.000000 Risk Type = Estimated standard deviations from control Confidence Level = 0.950000

> BMD = 73.5309 BMDL = 2.76278



```
_____
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Ln/Lymphocyte Concurrent Normal-HLS
2001-Lymphocyte Count-ExpCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sat Jun 21 14:54:11 2014
______
===
BMDS Model Run
~~~~
  The form of the response function by Model:
                Y[dose] = a * exp{sign * b * dose}
     Model 2:
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
               Y[dose] = a * [c-(c-1) * exp{-b * dose}]
     Model 4:
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  rho is set to 0.
  A constant variance model is fit.
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 5
lnalpha	1.0472
rho(S)	0
a	7.329
b	0.0170211
С	0.484702
d	1

(S) = Specified

#### Parameter Estimates

Variable	Model 5
lnalpha	1.07486
rho	0
a	6.98
b	0.157544
С	0.595461
d	1.78043

# Table of Stats From Input Data

Dose	Ν	Obs Mean	Obs Std Dev
0	10	6.98	2.146
2.9	10	6.36	2.452
10.6	9	4.39	1.308
42	9	4.63	1.564
191.1	10	3.73	0.941

### Estimated Values of Interest

Est Mean	Est Std	Scaled Residual
6.98	1.712	-4.535e-007
6.36	1.712	-4.619e-007
4.39	1.712	6.233e-007
4.156	1.712	0.8302
4.156	1.712	-0.7876
	6.98 6.36 4.39 4.156	6.981.7126.361.7124.391.7124.1561.712

Other models for which likelihoods are calculated:

Model A1: Yij = Mu(i) + e(ij) Var{e(ij)} = Sigma^2

Model A2:	Yij = Var{e(ij)} =	Mu(i) + e(ij) Sigma(i)^2
Model A3:	Yij = Var{e(ij)} =	Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R:	Yij = Var{e(ij)} =	Mu + e(i) Sigma^2

Likelihoods of Interest

	Model	Log(likelihood)	DF
AIC			
	A1	-49.13278	6
110.2656	A2	-43.79823	10
107.5965	A3	-49.13278	6
110.2656	R	-59.6779	2
123.3558			_
109.5934	5	-49.79672	5

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

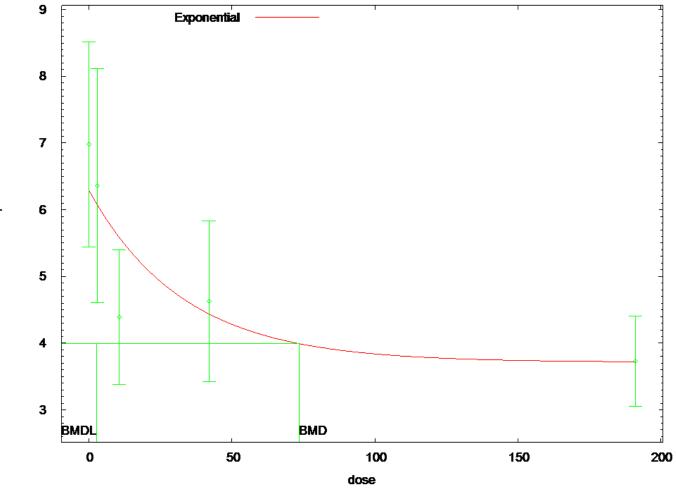
Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A2 vs. A1) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 7a: Does Model 5 fit the data? (A3 vs 5)

Test	-2*log(Likelihood Ratio)	D. F.
p-value		

Test	1	31.76	8
0.0001029			
Test	2	10.67	4
0.03055			
Test	3	10.67	4
0.03055			
Test '	7a	1.328	1
0.2492			

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. Consider running a non-homogeneous variance model. The p-value for Test 3 is less than .1. You may want to consider a different variance model. 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 = 6.10056

BMDL = 2.52044



Mean Response

14:54 06/21 2014

```
______
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Ln/Lymphocyte Concurrent Normal-HLS
2001-Lymphocyte Count-ExpNCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sat Jun 21 14:54:13 2014
______
===
BMDS Model Run
~~~~
  The form of the response function by Model:
                Y[dose] = a * exp{sign * b * dose}
     Model 2:
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
                Y[dose] = a * [c-(c-1) * exp{-b * dose}]
     Model 4:
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  The variance is to be modeled as Var(i) = exp(lalpha + log
(mean(i)) * rho)
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 5
lnalpha	-3.58873
rho	2.77965
a	7.329
b	0.0170211
C	0.484702
d	1

### Parameter Estimates

Variable	Model 5
lnalpha	-4.3478
rho	3.2691
a	6.29097
b	0.0302436
C	0.590321
d	1

# Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	10	6.98	2.146
2.9	10	6.36	2.452
10.6	9	4.39	1.308
42	9	4.63	1.564
191.1	10	3.73	0.941

### Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	6.291	2.298	0.948
2.9	6.075	2.171	0.4159
10.6	5.584	1.892	-1.894
42	4.437	1.299	0.445
191.1	3.722	0.9745	0.02708

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)

		<pre>Var{e(ij)}</pre>	=	Sigma(i) <sup>2</sup>	
Model A	A3:			Mu(i) + e(ij) exp(lalpha + log(mean(i)) *	rho)
Model	R:	Yij Var{e(ij)}	=	Mu + e(i) Sigma <sup>2</sup>	

		Likelihoods of Int	erest
210	Model	Log(likelihood)	DF
AIC			
	A1	-49.13278	6
110.2656	A2	-43.79823	10
107.5965	A3	-44.17752	7
102.355	R	-59.6779	2
123.3558			_
105.8113	5	-47.90566	5

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

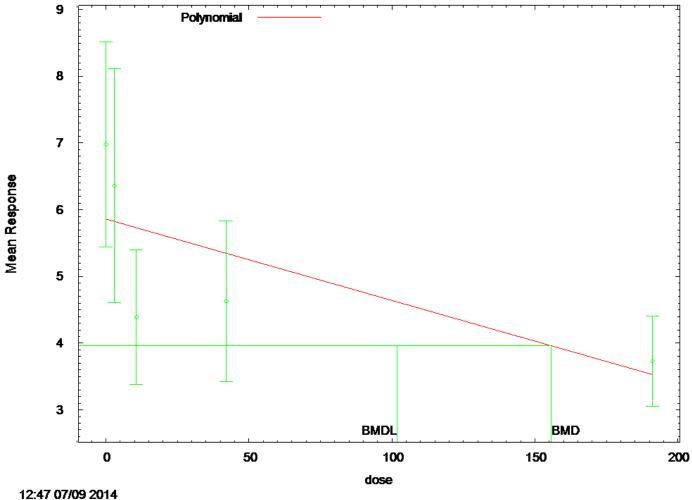
Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A2 vs. A1) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 7a: Does Model 5 fit the data? (A3 vs 5)

Test p-value	-2*log(Likelihood Ratio)	D. F.
Test 1 0.0001029	31.76	8

Test 2	10.67	4
0.03055		
Test 3	0.7586	3
0.8593		
Test 7a	7.456	2
0.02404		

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 7a is less than .1. Model 5 may not adequately describe the data; you may want to consider another model. Benchmark Dose Computations: Specified Effect = 1.000000 Risk Type = Estimated standard deviations from control Confidence Level = 0.950000

> BMD = 73.5309 BMDL = 2.76278



=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_Lymphocyte\_Concurrent/Lymphocyte\_C oncurrent\_Normal-HLS 2001-Lymphocyte Count-Poly2CV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_Lymphocyte\_Concurrent/Lymphocyte\_C oncurrent\_Normal-HLS 2001-Lymphocyte Count-Poly2CV-1SD-5d.plt Wed Jul 09 12:47:23 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse 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 = 5Total number of records with missing values = 0Maximum 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 = 3.18101 Specified rho = 0 beta\_0 = 6.28333 beta\_1 = -0.0582096 beta\_2 = Ο Asymptotic Correlation Matrix of Parameter Estimates ( \*\*\* The model parameter(s) -rho -beta 2 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	3.9e-007	-1.1e-006
beta_0	3.9e-007	1	-0.56
beta_1	-1.1e-006	-0.56	1

### Parameter Estimates

			95.0%
Wald Confidence	Interval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Co	nf. Limit		
alpha	3.61272	0.737443	
2.16736	5.05808		
beta_0	5.86108	0.332086	
5.2102	6.51196		
beta_1	-0.0122035	0.00372175	_
0.019498	-0.00490898		
beta_2	0	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 Scaled	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 1.86	10	6.98	5.86	2.15	1.9
2.9	10	6.36	5.83	2.45	1.9
10.6	9	4.39	5.73	1.31	1.9
42 -1.13	9	4.63	5.35	1.56	1.9
191.1 0.334	10	3.73	3.53	0.941	1.9

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<sup>2</sup>

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
Al	-49.132777	6	110.265553
A2	-43.798233	10	107.596466
A3	-49.132777	б	110.265553
fitted	-54.827112	3	115.654225
R	-59.677903	2	123.355807

#### 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

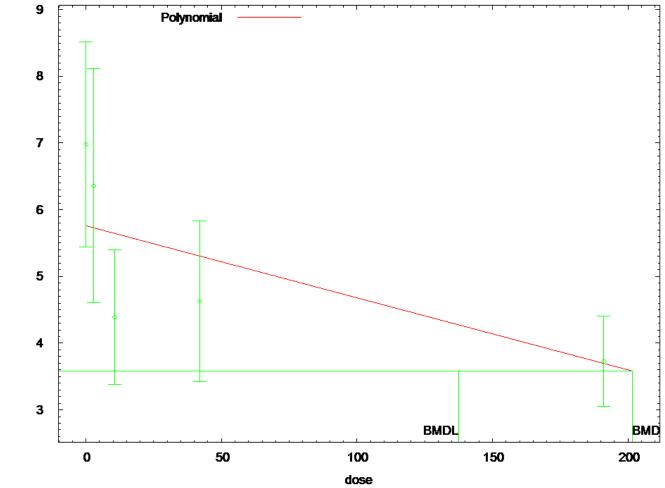
Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.7593	8	0.0001029
Test 2	10.6691	4	0.03055
Test 3	10.6691	4	0.03055
Test 4	11.3887	3	0.0098

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. Consider running a non-homogeneous variance model The p-value for Test 3 is less than .1. You may want to consider a different variance model The p-value for Test 4 is less than .1. You may want to try a different model

#### Benchmark Dose Computation

BMDL = 101.835

Specified effect = 1 Risk Type = Estimated standard deviations from the control mean Confidence level = 0.95 BMD = 155.752



Mean Response

12:47 07/09 2014

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_Lymphocyte\_Concurrent/Lymphocyte\_C oncurrent\_Normal-HLS 2001-Lymphocyte Count-Poly2NCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_Lymphocyte\_Concurrent/Lymphocyte\_C oncurrent\_Normal-HLS 2001-Lymphocyte Count-Poly2NCV-1SD-5d.plt Wed Jul 09 12:47:25 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse 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 = 5Total 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 = 1.1572 rho = 0  $beta_0 = 6.28333$  $beta_1 = -0.0582096$ beta\_2 = Ω Asymptotic Correlation Matrix of Parameter Estimates ( \*\*\* The model parameter(s) -beta\_2 have been estimated at a boundary point, or have been specified by the user,

and do not appear in the correlation matrix )

	lalpha	rho	beta_0	beta_1
lalpha	1	-0.99	0.046	-0.055
rho	-0.99	1	-0.047	0.056
beta_0	0.046	-0.047	1	-0.81
beta_1	-0.055	0.056	-0.81	1

Parameter Estimates

				95.08
Wald Con	fidence	Interval		
V	ariable	Estimate	Std. Err.	Lower Conf.
Limit	Upper Co	nf. Limit		
	lalpha	-5.65714	1.90045	_
9.38195	_	-1.93233		
	rho	4.12209	1.15308	
1.86209		6.3821		
	beta_0	5.76447	0.365011	
5.04907		6.47988		
	beta 1	-0.0108344	0.00248095	_
0.015697	—	-0.00597186		
	beta 2	0	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 Scaled	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 1.76	10	6.98	5.76	2.15	2.19
2.9	10	6.36	5.73	2.45	2.16
0.917 10.6	9	4.39	5.65	1.31	2.1
-1.8 42 -1.1	9	4.63	5.31	1.56	1.84

191.1	10	3.73	3.69	0.941	0.873
0.13					

Model A1: Yij = Mu(i) + e(ij)Var{e(ij)} = Sigma<sup>2</sup> Model A2: Yij = Mu(i) + e(ij)Var{e(ij)} = Sigma(i)<sup>2</sup>

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
Al	-49.132777	б	110.265553
A2	-43.798233	10	107.596466
A3	-44.177523	7	102.355046
fitted	-50.343208	4	108.686416
R	-59.677903	2	123.355807

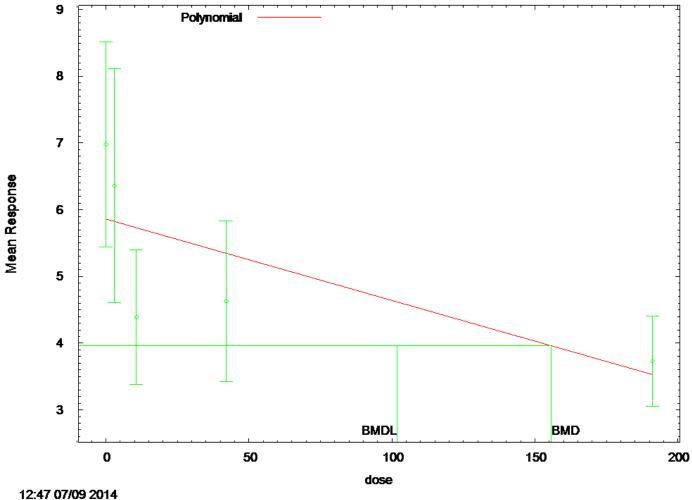
### Explanation of Tests

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	31.7593	8	0.0001029
Test 2	10.6691	4	0.03055
Test 3	0.75858	3	0.8593
Test 4	12.3314	3	0.00633

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 = Estimated standard deviations from the Risk Type control mean Confidence level = 0.95 BMD = 201.708 BMDL = 137.467



=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_Lymphocyte\_Concurrent/Lymphocyte\_C oncurrent\_Normal-HLS 2001-Lymphocyte Count-Poly3CV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_Lymphocyte\_Concurrent/Lymphocyte\_C oncurrent\_Normal-HLS 2001-Lymphocyte Count-Poly3CV-1SD-5d.plt Wed Jul 09 12:47:23 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse 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 = 5Total number of records with missing values = 0Maximum 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 = 3.18101 Specified rho = 0 beta\_0 = 7.08617 beta\_1 = -0.327588 beta\_2 = 0  $beta_3 = -3.20797e - 005$ Asymptotic Correlation Matrix of Parameter Estimates ( \*\*\* The model parameter(s) -rho -beta\_2 -

beta\_3

have been estimated at a boundary point, or have been specified by the user,

and do not appear in the correlation matrix )

beta_1	beta_0	alpha	
1.4e-006	-2.3e-007	1	alpha
-0.56	1	-2.3e-007	beta_0
1	-0.56	1.4e-006	beta_1

Parameter Estimates

95.0%

Wald Cont	Wald Confidence Interval						
Va	ariable	Estimate	Std. Err.	Lower Conf.			
Limit (	Upper Con	f. Limit					
	alpha	3.61273	0.737445				
2.16736		5.0581					
	beta_0	5.86108	0.332087	,			
5.2102		6.51196					
	beta_1	-0.0122034	0.00372175	-			
0.0194979	9	-0.00490893					
	beta_2	0	NA	L			
	beta_3	0	NA	L			

NA - Indicates that this parameter has hit a bound implied by some inequality constraint and thus has no standard error.

Table o	f Data	and	Estimated	Values	of	Interest	

Dose Scaled	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 1.86	10	6.98	5.86	2.15	1.9
2.9	10	6.36	5.83	2.45	1.9
10.6 -2.12	9	4.39	5.73	1.31	1.9
42	9	4.63	5.35	1.56	1.9
191.1	10	3.73	3.53	0.941	1.9

Var{e(i)} = Sigma^2

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)

### Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
Al	-49.132777	6	110.265553
A2	-43.798233	10	107.596466
A3	-49.132777	6	110.265553
fitted	-54.827112	3	115.654225
R	-59.677903	2	123.355807

### Explanation of Tests

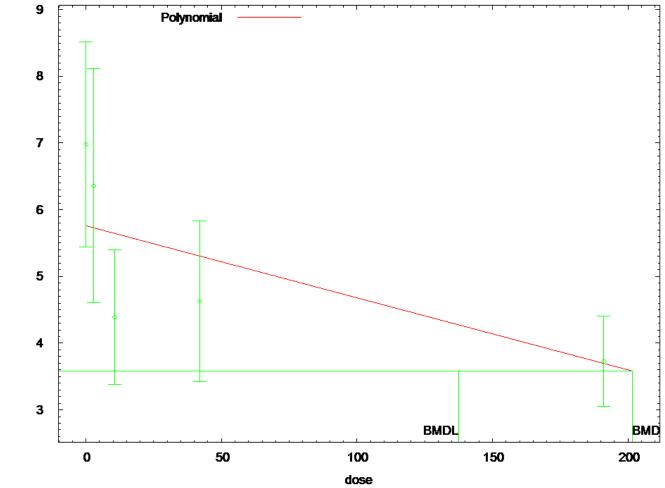
Test 1: Do responses and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A1 vs A2) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 4: Does the Model for the Mean Fit? (A3 vs. fitted) (Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

### Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.7593	8	0.0001029
Test 2	10.6691	4	0.03055
Test 3	10.6691	4	0.03055
Test 4	11.3887	3	0.0098

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. Consider running a non-homogeneous variance model The p-value for Test 3 is less than .1. You may want to consider а different variance model The p-value for Test 4 is less than .1. You may want to try a different model Benchmark Dose Computation Specified effect = 1 Estimated standard deviations from the Risk Type = control mean Confidence level = 0.95 155.753 BMD = BMDL = 101.835



Mean Response

12:47 07/09 2014

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_Lymphocyte\_Concurrent/Lymphocyte\_C oncurrent\_Normal-HLS 2001-Lymphocyte Count-Poly3NCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_Lymphocyte\_Concurrent/Lymphocyte\_C oncurrent\_Normal-HLS 2001-Lymphocyte Count-Poly3NCV-1SD-5d.plt Wed Jul 09 12:47:24 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse 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 = 5Total number of records with missing values = 0Maximum 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 = 1.1572 rho = 0 beta\_0 = 7.08617 beta\_1 = -0.327588 beta\_2 = 0  $beta_3 = -3.20797e - 005$ Asymptotic Correlation Matrix of Parameter Estimates ( \*\*\* The model parameter(s) -beta\_2 -beta\_3

have been estimated at a boundary point, or have been specified by the user, and do not appear in the correlation matrix )

	lalpha	rho	beta_0	beta_1
lalpha	1	-0.99	0.046	-0.055
rho	-0.99	1	-0.047	0.056
beta_0	0.046	-0.047	1	-0.81
beta_1	-0.055	0.056	-0.81	1

Parameter Estimates

			95.0%
Wald Confidence	Interval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Co	nf. Limit		
lalpha	-5.65713	1.90045	-
9.38194	-1.93232		
rho	4.12209	1.15308	
1.86209	6.38209		
beta_0	5.76447	0.365011	
5.04907	6.47988		
beta_1	-0.0108344	0.00248095	_
0.015697	-0.00597186		
beta_2	0	NA	
beta_3	0	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 Scaled	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 1.76	10	6.98	5.76	2.15	2.19
2.9	10	6.36	5.73	2.45	2.16
10.6 -1.8	9	4.39	5.65	1.31	2.1

42	9	4.63	5.31	1.56	1.84
-1.1					
191.1	10	3.73	3.69	0.941	0.873
0.13					

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
Al	-49.132777	б	110.265553
A2	-43.798233	10	107.596466
A3	-44.177523	7	102.355046
fitted	-50.343208	4	108.686416
R	-59.677903	2	123.355807

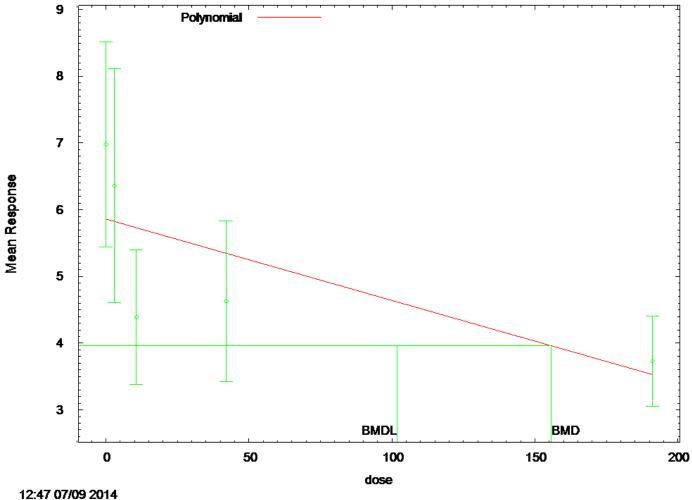
### Explanation of Tests

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	31.7593	8	0.0001029
Test 2	10.6691	4	0.03055
Test 3	0.75858	3	0.8593

12.3314 3 0.00633 Test 4 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 = Estimated standard deviations from the Risk Type control mean Confidence level = 0.95 201.708 BMD = BMDL = 137.467



=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_Lymphocyte\_Concurrent/Lymphocyte\_C oncurrent\_Normal-HLS 2001-Lymphocyte Count-Poly4CV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_Lymphocyte\_Concurrent/Lymphocyte\_C oncurrent\_Normal-HLS 2001-Lymphocyte Count-Poly4CV-1SD-5d.plt Wed Jul 09 12:47:23 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse 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 = 5Total number of records with missing values = 0Maximum 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 = 3.18101 Specified rho = 0 beta\_0 = 6.98 -0.192486 beta\_1 =  $beta_2 = -0.00831882$ beta\_3 = 0  $beta_4 = -1.52335e-006$ 

Asymptotic Correlation Matrix of Parameter Estimates

beta_1	Deta_U	alpha	
-9.4e-009	4.5e-008	1	alpha
-0.56	1	4.5e-008	beta_0
1	-0.56	-9.4e-009	beta_1

Parameter Estimates

#### 95.0%

				95.08
Wald Con	fidence	Interval		
V	ariable	Estimate	Std. Err.	Lower Conf.
Limit	Upper Co	nf. Limit		
	alpha	3.61273	0.737445	
2.16736		5.05809		
	beta_0	5.86108	0.332087	
5.2102		6.51196		
	beta_1	-0.0122035	0.00372175	_
0.019498		-0.00490895		
	beta_2	0	NA	
	beta_3	0	NA	
	beta_4	0	NA	

NA - Indicates that this parameter has hit a bound implied by some inequality constraint and thus has no standard error.

Dose Scaled	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 1.86	10	6.98	5.86	2.15	1.9
2.9	10	6.36	5.83	2.45	1.9
10.6	9	4.39	5.73	1.31	1.9
42	9	4.63	5.35	1.56	1.9

Table of Data and Estimated Values of Interest

-1.13					
191.1	10	3.73	3.53	0.941	1.9
0.334					

```
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<sup>2</sup>

## Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
Al	-49.132777	6	110.265553
A2	-43.798233	10	107.596466
A3	-49.132777	б	110.265553
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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.)

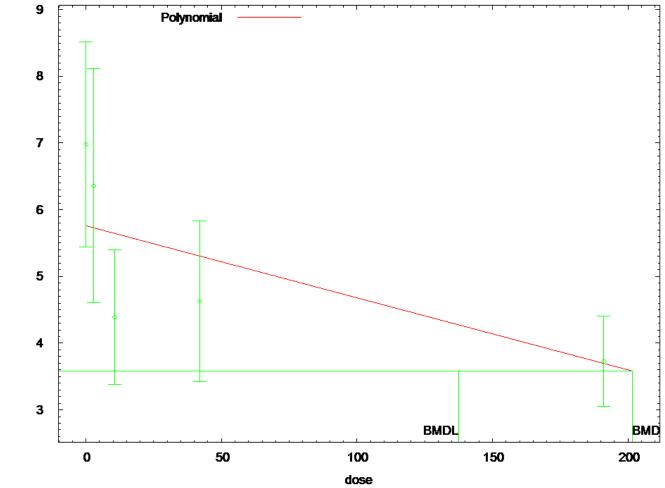
#### Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.7593	8	0.0001029
Test 2	10.6691	4	0.03055
Test 3	10.6691	4	0.03055
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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. Consider running a non-homogeneous variance model The p-value for Test 3 is less than .1. You may want to consider а different variance model The p-value for Test 4 is less than .1. You may want to try a different model Benchmark Dose Computation Specified effect = 1 = Estimated standard deviations from the Risk Type control mean Confidence level = 0.95

BMD = 155.752

BMDL = 101.835



Mean Response

12:47 07/09 2014

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_Lymphocyte\_Concurrent/Lymphocyte\_C oncurrent\_Normal-HLS 2001-Lymphocyte Count-Poly4NCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_Lymphocyte\_Concurrent/Lymphocyte\_C oncurrent\_Normal-HLS 2001-Lymphocyte Count-Poly4NCV-1SD-5d.plt Wed Jul 09 12:47:24 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse 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 = 5Total number of records with missing values = 0Maximum 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 = 1.1572 rho = 0 beta\_0 = 6.98 -0.192486 beta\_1 =  $beta_2 = -0.00831882$ beta\_3 = 0  $beta_4 = -1.52335e-006$ Asymptotic Correlation Matrix of Parameter Estimates

lalpha	1	-0.99	0.046	-0.055
rho	-0.99	1	-0.047	0.056
beta_0	0.046	-0.047	1	-0.81
beta_1	-0.055	0.056	-0.81	1

#### Parameter Estimates

#### 95.0%

				95.08
Wald Con	fidence	Interval		
V	ariable	Estimate	Std. Err.	Lower Conf.
Limit	Upper Co	nf. Limit		
	lalpha	-5.65714	1.90045	-
9.38195		-1.93233		
	rho	4.12209	1.15308	
1.86209		6.3821		
	beta_0	5.76447	0.365011	
5.04907		6.47988		
	beta_1	-0.0108344	0.00248095	-
0.015697		-0.00597186		
	beta_2	0	NA	
	beta_3	0	NA	
	beta_4	0	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 Scaled R		Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 1.76	10	6.98	5.76	2.15	2.19
2.9	10	6.36	5.73	2.45	2.16

0.917					
10.6	9	4.39	5.65	1.31	2.1
-1.8					
42	9	4.63	5.31	1.56	1.84
-1.1					
191.1	10	3.73	3.69	0.941	0.873
0.13					

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 R: Yi = Mu + e(i) $Var{e(i)} = Sigma^2$ 

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
Al	-49.132777	б	110.265553
A2	-43.798233	10	107.596466
A3	-44.177523	7	102.355046
fitted	-50.343208	4	108.686416
R	-59.677903	2	123.355807

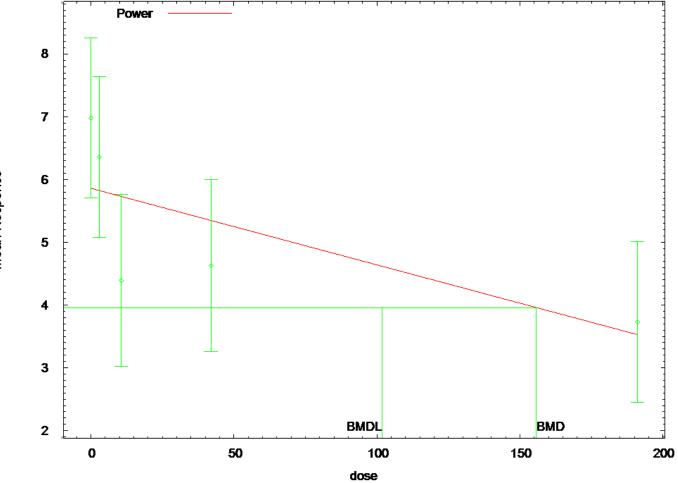
### Explanation of Tests

### Tests of Interest

Test	-2*log	(Likelihood	Ratio	) Test df	p-value
------	--------	-------------	-------	-----------	---------

3

31.7593 8 4 Test 1 0.0001029 Test 2 10.6691 0.03055 Test 3 0.75858 3 0.8593 Test 4 12.3314 3 0.00633 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 = 201.708 BMDL = 137.467



Mean Response

14:54 06/21 2014

\_\_\_\_\_ === Power Model. (Version: 2.18; Date: 05/19/2014) Input Data File: C:/Users/dmayfield/Desktop/Ln/Lymphocyte\_Concurrent\_Normal-HLS 2001-Lymphocyte Count-PowerCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Ln/Lymphocyte Concurrent Normal-HLS 2001-Lymphocyte Count-PowerCV-1SD-5d.plt Sat Jun 21 14:54:12 2014 === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = control + slope \* dose^power Dependent variable = MeanResponse 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 = 5Total 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 = 3.18101 rho = 0 control = 3.73 slope = 2.97763 power = -0.394692 Specified 0 3.73 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	-8.8e-009	2e-008
control	-8.8e-009	1	-0.56
slope	2e-008	-0.56	1

### Parameter Estimates

			95.0%
Wald Confidence	Interval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Co	onf. Limit		
alpha	3.61273	0.737445	
2.16736	5.05809		
control	5.86108	0.332087	
5.2102	6.51196		
slope	-0.0122035	0.00372175	-
0.019498	-0.00490895		
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
---------------------------------------

Dose Scaled	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 1.86	10	6.98	5.86	2.15	1.9
2.9	10	6.36	5.83	2.45	1.9
10.6	9	4.39	5.73	1.31	1.9
42 -1.13	9	4.63	5.35	1.56	1.9
191.1 0.334	10	3.73	3.53	0.941	1.9

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<sup>2</sup>

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-49.132777	6	110.265553
A2	-43.798233	10	107.596466
A3	-49.132777	6	110.265553
fitted	-54.827112	3	115.654225
R	-59.677903	2	123.355807

#### 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

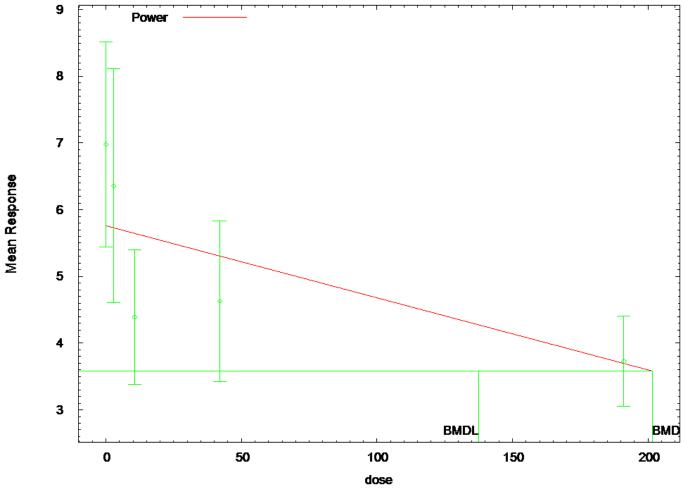
Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.7593	8	0.0001029
Test 2	10.6691	4	0.03055
Test 3	10.6691	4	0.03055
Test 4	11.3887	3	0.0098

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. Consider running a non-homogeneous variance model The p-value for Test 3 is less than .1. You may want to consider a different variance model 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 = 155.752

BMDL = 101.835



# Power Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

14:54 06/21 2014

\_\_\_\_\_\_ === Power Model. (Version: 2.18; Date: 05/19/2014) Input Data File: C:/Users/dmayfield/Desktop/Ln/Lymphocyte\_Concurrent\_Normal-HLS 2001-Lymphocyte Count-PowerNCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Ln/Lymphocyte Concurrent Normal-HLS 2001-Lymphocyte Count-PowerNCV-1SD-5d.plt Sat Jun 21 14:54:13 2014 === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = control + slope \* dose^power Dependent variable = MeanResponse Independent variable = Dose The power is restricted to be greater than or equal to 1 The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) \* rho) Total number of dose groups = 5Total 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 = 1.1572 3.73 rho = rho = 0 control = 3.73 slope = 2.97763 power = -0.394692 Asymptotic Correlation Matrix of Parameter Estimates ( \*\*\* The model parameter(s) -power have been estimated at a boundary point, or have been specified by the user,

and do not appear in the correlation matrix )

	lalpha	rho	control	slope
lalpha	1	-0.99	0.4	-0.63
rho	-0.99	1	-0.47	0.66
control	0.4	-0.47	1	-0.81
slope	-0.63	0.66	-0.81	1

Parameter Estimates

95	0응	

			95.0%
Wald Confidence	Interval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Co	onf. Limit		
lalpha	-5.65714	2.52061	-
10.5974	-0.716839		
rho	4.12209	1.56056	
1.06346	7.18072		
control	5.76447	0.366767	
5.04562	6.48332		
slope	-0.0108344	0.00248067	-
0.0156965	-0.0059724		
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 Scaled	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 1.76	10	6.98	5.76	2.15	2.19
2.9	10	6.36	5.73	2.45	2.16
10.6 -1.8	9	4.39	5.65	1.31	2.1
42 -1.1	9	4.63	5.31	1.56	1.84

191.1	10	3.73	3.69	0.941	0.873
0.13					

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	-49.132777	6	110.265553
A2	-43.798233	10	107.596466
A3	-44.177523	7	102.355046
fitted	-50.343208	4	108.686416
R	-59.677903	2	123.355807

### Explanation of Tests

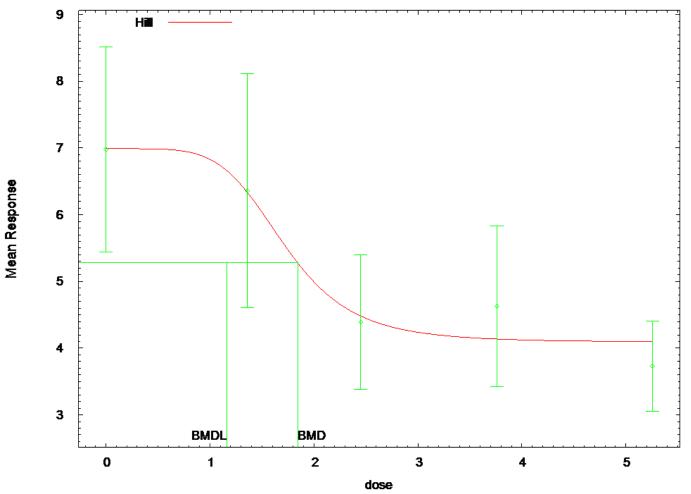
Test 1: Do responses and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A1 vs A2) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 4: Does the Model for the Mean Fit? (A3 vs. fitted) (Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

#### Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.7593	8	0.0001029
Test 2	10.6691	4	0.03055
Test 3	0.75858	3	0.8593
Test 4	12.3314	3	0.00633

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 Estimated standard deviations from the Risk Type = control mean Confidence level = 0.95 BMD = 201.708BMDL = 137.467

**BMDS Model Results for Lymphocyte Count** (Log-transformed Doses, Concurrent Controls)



Hill Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

15:00 06/21 2014

\_\_\_\_\_\_ === Hill Model. (Version: 2.17; Date: 01/28/2013) Input Data File: C:/Users/dmayfield/Desktop/Ln/Lymphocyte\_Concurrent\_Normal-HLS 2001-Lymphocyte Count-HillCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Ln/Lymphocyte Concurrent Normal-HLS 2001-Lymphocyte Count-HillCV-1SD-5d.plt Sat Jun 21 15:00:53 2014 === BMDS Model Run ~~~~ The form of the response function is:  $Y[dose] = intercept + v*dose^n/(k^n + dose^n)$ Dependent variable = MeanResponse 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 = 5Total 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 = 3.18101 Specified rho = 0 rho = intercept = 6.98 -3.25 V = n = 3.73558 k = 1.91707 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 )

k		alpha	intercept	v	n
al -5.7e-0	pha 09	1	-5.5e-009	2.3e-010	-3e-009
interc -0.35	ept	-5.5e-009	1	-0.76	-0.27
-0.15	v	2.3e-010	-0.76	1	0.63
-0.46	n	-3e-009	-0.27	0.63	1
1	k	-5.7e-009	-0.35	-0.15	-0.46

# Parameter Estimates

95.0%

Wald Confidence Int	erval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Conf.	Limit		
alpha	2.92519	0.597102	
1.75489	4.09549		
intercept	6.99164	0.538504	
5.93619	8.04709		
v	-2.90088	0.770715	-
4.41146	-1.39031		
n	5.25235	5.26679	-
5.07036	15.5751		
k	1.72188	0.43844	
0.862555	2.58121		

# Table of Data and Estimated Values of Interest

Dose Scaled R		Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 -0.0215	10	6.98	6.99	2.15	1.71

1.361	10	6.36	6.34	2.45	1.71
0.0403 2.451	9	4.39	4.48	1.31	1.71
-0.164 3.761	9	4.63	4.14	1.56	1.71
0.863	9	4.05	4.14	1.50	1./1
5.258 -0.682	10	3.73	4.1	0.941	1.71

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
Al	-49.132777	6	110.265553
A2	-43.798233	10	107.596466
A3	-49.132777	6	110.265553
fitted	-49.760637	5	109.521275
R	-59.677903	2	123.355807

# Explanation of Tests

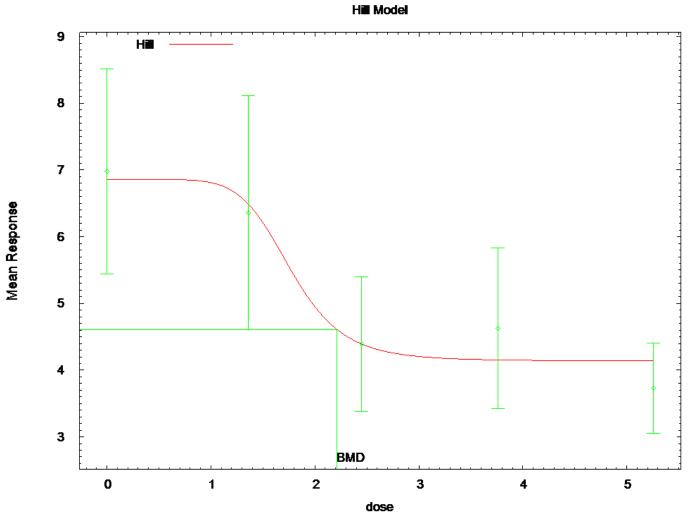
Test 1:	Do responses and/or variances differ among Dose levels?
	(A2 vs. R)
Test 2:	Are Variances Homogeneous? (A1 vs A2)
Test 3:	Are variances adequately modeled? (A2 vs. A3)
Test 4:	Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:	When rho=0 the results of Test 3 and Test 2 will be the
same.)	

### Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
------	--------------------------	---------	---------

Test 131.759380.0001029Test 210.669140.03055Test 310.669140.03055Test 41.2557210.2625

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. Consider running a non-homogeneous variance model The p-value for Test 3 is less than .1. You may want to consider а different variance model 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 = 1.84483 BMDL = 1.16494



15:00 06/21 2014

\_\_\_\_\_\_ === Hill Model. (Version: 2.17; Date: 01/28/2013) Input Data File: C:/Users/dmayfield/Desktop/Ln/Lymphocyte\_Concurrent\_Normal-HLS 2001-Lymphocyte Count-HillNCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Ln/Lymphocyte Concurrent Normal-HLS 2001-Lymphocyte Count-HillNCV-1SD-5d.plt Sat Jun 21 15:00:54 2014 === BMDS Model Run ~~~~ The form of the response function is:  $Y[dose] = intercept + v*dose^n/(k^n + dose^n)$ Dependent variable = MeanResponse Independent variable = Dose Power parameter restricted to be greater than 1 The variance is to be modeled as Var(i) = exp(lalpha + rho \* ln(mean(i))) Total number of dose groups = 5Total 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 = 1.1572 rho = 0 intercept = 6.98 -3.25 V = 3.73558 n = k = 1.91707 Asymptotic Correlation Matrix of Parameter Estimates intercept lalpha rho v

n	k			
lalpha -0.11	1 -0.05	-0.99	0.33	-0.4
rho 0.11	-0.99 0.05	1	-0.36	0.42
intercept -0.47	0.33 -0.46	-0.36	1	-0.92
v 0.64	-0.4 0.27	0.42	-0.92	1
n 1 0.0	-0.11	0.11	-0.47	0.64
k 0.037	-0.05 1	0.05	-0.46	0.27

Parameter Estimates

				95.0%
Wald Con:	fidence In	nterval		
Va	ariable	Estimate	Std. Err.	Lower Conf.
Limit 1	Upper Conf	. Limit		
	lalpha	-2.88611	1.69349	-
6.20529		0.433065		
	rho	2.34243	1.03058	
0.322528		4.36233		
in	tercept	6.86104	0.687328	
5.5139		8.20818		
	v	-2.71896	0.819674	-
4.32549		-1.11243		
	n	7.0209	7.30818	-
7.30287		21.3447		
	k	1.76898	0.407522	
0.970252		2.56771		

Table of Data and Estimated Values of Interest

Dose Scaled R		Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 0.167	10	6.98	6.86	2.15	2.25

1.361 -0.193	10	6.36	6.49	2.45	2.11
2.451	9	4.39	4.39	1.31	1.34
-0.00499	-		1.05	1.01	2101
3.761	9	4.63	4.16	1.56	1.25
1.14					
5.258	10	3.73	4.14	0.941	1.25
-1.05					

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	-49.132777	6	110.265553
A2	-43.798233	10	107.596466
A3	-44.177523	7	102.355046
fitted	-46.454509	6	104.909018
R	-59.677903	2	123.355807

### 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 131.759380.0001029Test 210.669140.03055Test 30.7585830.8593Test 44.5539710.03284

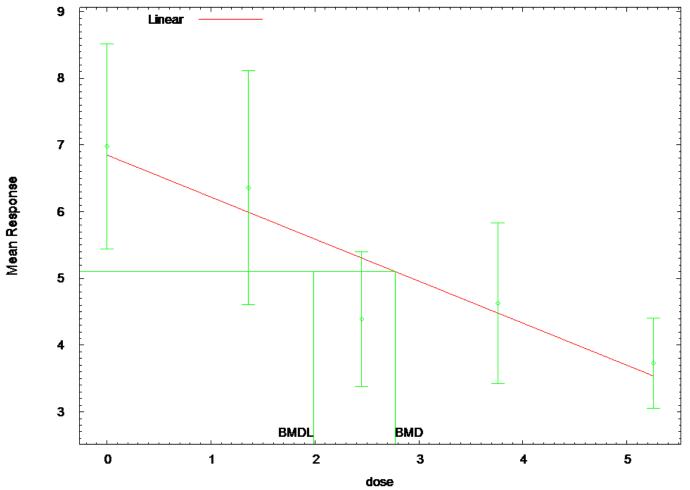
The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels It seems appropriate to model the data The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate The p-value for Test 3 is greater 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 = 2.21464

BMDL computation failed.



Linear Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

12:48 07/09 2014

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_Lymphocyte\_Concurrent\_Ln/Lymphocyt e\_Concurrent\_LN-HLS 2001-Lymphocyte Count-LinearCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_Lymphocyte\_Concurrent\_Ln/Lymphocyt e\_Concurrent\_LN-HLS 2001-Lymphocyte Count-LinearCV-1SD-5d.plt Wed Jul 09 12:48:52 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse Independent variable = Dose rho is set to 0 Signs of the polynomial coefficients are not restricted A constant variance model is fit Total number of dose groups = 5Total 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 = 3.18101 rho = 0 beta\_0 = 6.83073 beta\_1 = -0.628452 0 Specified 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	1.2e-008	1.2e-010
beta_0	1.2e-008	1	-0.81
beta_1	1.2e-010	-0.81	1

# Parameter Estimates

				95.0%
Wald Cor	nfidence I	nterval		
Z	/ariable	Estimate	Std. Err.	Lower Conf.
Limit	Upper Con	f. Limit		
	alpha	3.05049	0.622679	
1.83006		4.27092		
	beta_0	6.85042	0.427333	
6.01286		7.68798		
	beta_1	-0.630151	0.13565	-
0.89602		-0.364283		

Table of Data and Estimated Values of Interest

Dose Scaled	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0	10	6.98	6.85	2.15	1.75
0.235 1.361 0.665	10	6.36	5.99	2.45	1.75
2.451	9	4.39	5.31	1.31	1.75
3.761	9	4.63	4.48	1.56	1.75
5.258 0.349	10	3.73	3.54	0.941	1.75

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
Al	-49.132777	6	110.265553
A2	-43.798233	10	107.596466
A3	-49.132777	б	110.265553
fitted	-50.767279	3	107.534558
R	-59.677903	2	123.355807

### 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	31.7593	8	0.0001029
Test 2	10.6691	4	0.03055
Test 3	10.6691	4	0.03055
Test 4	3.269	3	0.352

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. Consider running a non-homogeneous variance model

The p-value for Test 3 is less than .1. You may want to consider a

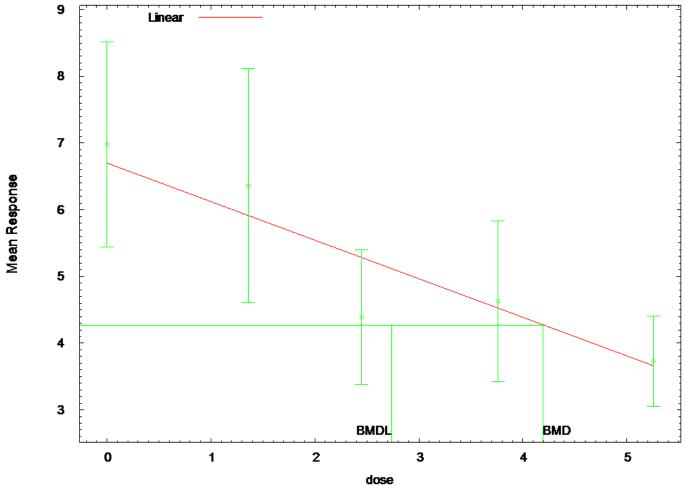
different variance model

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 = 2.77166

BMDL = 1.99011



12:48 07/09 2014

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_Lymphocyte\_Concurrent\_Ln/Lymphocyt e\_Concurrent\_LN-HLS 2001-Lymphocyte Count-LinearNCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_Lymphocyte\_Concurrent\_Ln/Lymphocyt e\_Concurrent\_LN-HLS 2001-Lymphocyte Count-LinearNCV-1SD-5d.plt Wed Jul 09 12:48:53 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse Independent variable = Dose Signs of the polynomial coefficients are not restricted The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) \* rho) Total number of dose groups = 5Total number of records with missing values = 0Maximum 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 = 1.1572 rho = 0 beta\_0 = 6.83073 beta\_1 = -0.628452 Asymptotic Correlation Matrix of Parameter Estimates beta\_0 lalpha rho beta 1 -0.99 0.17 -0.2 lalpha 1

rho	-0.99	1	-0.17	0.2
beta_0	0.17	-0.17	1	-0.91
beta_1	-0.2	0.2	-0.91	1

Parameter Estimates

# 95.0%

Wald Con	fidence In	terval		
V	ariable	Estimate	Std. Err.	Lower Conf.
Limit 1	Upper Conf	. Limit		
	lalpha	-4.00629	1.70369	-
7.34546		-0.667114		
	rho	3.03769	1.03603	
1.0071		5.06828		
	beta_0	6.69816	0.5031	
5.7121		7.68422		
	beta_1	-0.577576	0.122436	_
0.817545		-0.337606		

Table of Data and Estimated Values of Interest

Dose Scaled	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 0.368	10	6.98	6.7	2.15	2.42
1.361 0.706	10	6.36	5.91	2.45	2.01
2.451 -1.58	9	4.39	5.28	1.31	1.69
3.761 0.234	9	4.63	4.53	1.56	1.34
5.258 0.224	10	3.73	3.66	0.941	0.969

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<sup>2</sup>

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
Al	-49.132777	6	110.265553
A2	-43.798233	10	107.596466
A3	-44.177523	7	102.355046
fitted	-46.826872	4	101.653745
R	-59.677903	2	123.355807

#### Explanation of Tests

#### Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.7593	8	0.0001029
Test 2	10.6691	4	0.03055
Test 3	0.75858	3	0.8593
Test 4	5.2987	3	0.1512

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

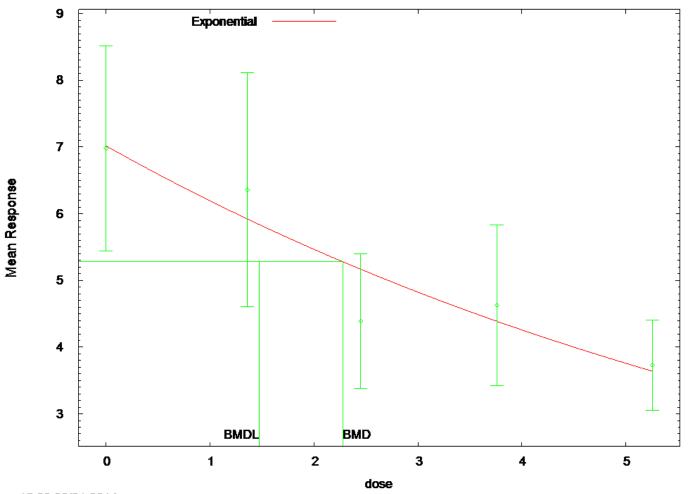
to be appropriate here

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 = 4.19696

BMDL = 2.73754



# Exponential Model 2, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Level for BMDL

15:00 06/21 2014

```
_____
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Ln/Lymphocyte Concurrent Normal-HLS
2001-Lymphocyte Count-ExpCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sat Jun 21 15:00:52 2014
______
===
BMDS Model Run
~~~~
  The form of the response function by Model:
                Y[dose] = a * exp{sign * b * dose}
     Model 2:
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
               Y[dose] = a * [c-(c-1) * exp{-b * dose}]
     Model 4:
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  rho is set to 0.
  A constant variance model is fit.
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 2
lnalpha	1.0472
rho(S)	0
a	3.75105
b	0.120756
С	0
d	1

(S) = Specified

#### Parameter Estimates

Variable	Model 2
lnalpha	1.10399
rho	0
a	7.01811
b	0.12488
C	0
d	1

# Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	10	6.98	2.146
1.361	10	6.36	2.452
2.451	9	4.39	1.308
3.761	9	4.63	1.564
5.258	10	3.73	0.941

### Estimated Values of Interest

Est Mean	Est Std	Scaled Residual
7.018	1.737	-0.0694
5.921	1.737	0.7991
5.168	1.737	-1.343
4.388	1.737	0.4184
3.64	1.737	0.1646
	7.018 5.921 5.168 4.388	7.018       1.737         5.921       1.737         5.168       1.737         4.388       1.737

Other models for which likelihoods are calculated:

Model A1: Yij = Mu(i) + e(ij) Var{e(ij)} = Sigma^2

Model A2:	Yij = Var{e(ij)} =	Mu(i) + e(ij) Sigma(i)^2
Model A3:	Yij = Var{e(ij)} =	Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R:	Yij = Var{e(ij)} =	Mu + e(i) Sigma^2

Likelihoods of Interest

AIC	Model	Log(likelihood)	DF
AIC			
	A1	-49.13278	6
110.2656	A2	-43.79823	10
107.5965	A3	-49.13278	6
110.2656	R	-59.6779	2
123.3558	2	-50.49569	3
106.9914	Δ.	- 20.49209	5

Additive constant for all log-likelihoods = -44.11. This constant added to the above values gives the log-likelihood including the term that does not

depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A2 vs. A1) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 4: Does Model 2 fit the data? (A3 vs. 2)

Tests of Interest

Test p-value	-2*log(Likelihood Ratio)	D. F.
Test 1	31.76	8

0.0001029			
Test	2	10.67	4
0.03055			
Test	3	10.67	4
0.03055			
Test	4	2.726	3
0.4359			

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. Consider running a non-homogeneous variance model.

The p-value for Test 3 is less than .1. You may want to consider a different variance model.

The p-value for Test 4 is greater than .1. Model 2 seems to adequately describe the data.

Benchmark Dose Computations:

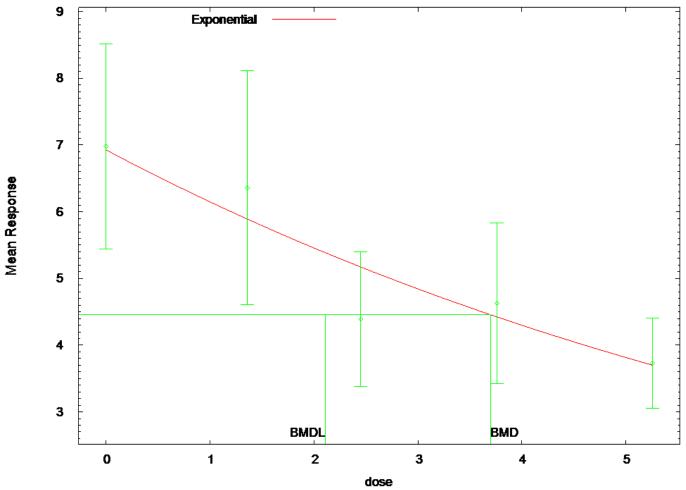
Specified Effect = 1.000000

Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

BMD = 2.2766

BMDL = 1.47441



Exponential Model 2, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Level for BMDL

15:00 06/21 2014

```
______
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Ln/Lymphocyte Concurrent Normal-HLS
2001-Lymphocyte Count-ExpNCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sat Jun 21 15:00:54 2014
______
===
BMDS Model Run
~~~~
  The form of the response function by Model:
                Y[dose] = a * exp{sign * b * dose}
     Model 2:
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
                Y[dose] = a * [c-(c-1) * exp{-b * dose}]
     Model 4:
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  The variance is to be modeled as Var(i) = exp(lalpha + log
(mean(i)) * rho)
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 2
lnalpha	-3.58873
rho	2.77965
a	3.75105
b	0.120756
C	0
d	1

# Parameter Estimates

Variable	Model 2
lnalpha	-3.68376
rho	2.83845
a	6.92765
b	0.119268
С	0
d	1

# Table of Stats From Input Data

Dose	Ν	Obs Mean	Obs Std Dev
0	10	6.98	2.146
1.361	10	6.36	2.452
2.451	9	4.39	1.308
3.761	9	4.63	1.564
5.258	10	3.73	0.941

## Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	6.928	2.472	0.06697
1.361	5.89	1.963	0.7575
2.451	5.172	1.633	-1.436
3.761	4.424	1.308	0.4734
5.258	3.7	1.015	0.09256

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)

	<pre>Var{e(ij)} =</pre>	=	Sigma(i) <sup>2</sup>
Model A3:			Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R:	Yij = Var{e(ij)} =	=	Mu + e(i) Sigma^2

		Likelihoods of Int	erest
210	Model	Log(likelihood)	DF
AIC			
	Al	-49.13278	6
110.2656	A2	-43.79823	10
107.5965			
102.355	A3	-44.17752	7
123.3558	R	-59.6779	2
	2	-46.77567	4
101.5513			

Additive constant for all log-likelihoods = -44.11. This constant added to the above values gives the log-likelihood including the term that does not

depend on the model parameters.

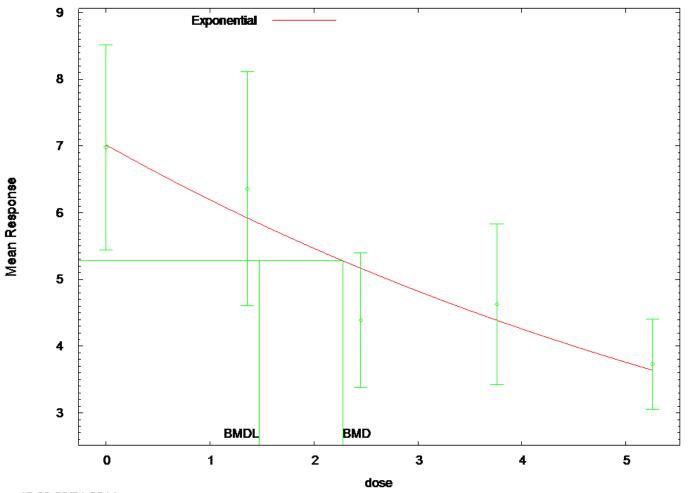
### Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A2 vs. A1) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 4: Does Model 2 fit the data? (A3 vs. 2)

### Tests of Interest

Test p-value	-2*1	og(Likelihood Ratio)	D. F.
Test	1	31.76	8
0.0001029			
Test	2	10.67	4

```
0.03055
                                 0.7586
    Test 3
                                          3
0.8593
                                  5.196 3
    Test 4
0.158
     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 = 3.70064
                BMDL =
                           2.11166
```



# Exponential Model 3, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Level for BMDL

15:00 06/21 2014

```
_____
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Ln/Lymphocyte Concurrent Normal-HLS
2001-Lymphocyte Count-ExpCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sat Jun 21 15:00:52 2014
______
===
BMDS Model Run
~~~~
  The form of the response function by Model:
                Y[dose] = a * exp{sign * b * dose}
     Model 2:
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
               Y[dose] = a * [c-(c-1) * exp{-b * dose}]
     Model 4:
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  rho is set to 0.
  A constant variance model is fit.
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 3
lnalpha	1.0472
rho(S)	0
a	3.75105
b	0.120756
C	0
d	1

(S) = Specified

#### Parameter Estimates

Variable	Model 3
lnalpha	1.10399
rho	0
a	7.01811
b	0.12488
С	0
d	1

# Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	10	6.98	2.146
1.361	10	6.36	2.452
2.451	9	4.39	1.308
3.761	9	4.63	1.564
5.258	10	3.73	0.941

### Estimated Values of Interest

Est Mean	Est Std	Scaled Residual
7.018	1.737	-0.0694
5.921	1.737	0.7991
5.168	1.737	-1.343
4.388	1.737	0.4184
3.64	1.737	0.1646
	7.018 5.921 5.168 4.388	7.018       1.737         5.921       1.737         5.168       1.737         4.388       1.737

Other models for which likelihoods are calculated:

Model A1: Yij = Mu(i) + e(ij) Var{e(ij)} = Sigma^2

Model A2:	Yij = Var{e(ij)} =	Mu(i) + e(ij) Sigma(i)^2
Model A3:	Yij = Var{e(ij)} =	Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R:	Yij = Var{e(ij)} =	Mu + e(i) Sigma^2

Likelihoods of Interest

AIC	Model	Log(likelihood)	DF
ALC			
	Al	-49.13278	6
110.2656	A2	-43.79823	10
107.5965	A3	-49.13278	6
110.2656	R	-59.6779	2
123.3558	3	-50.49569	3
106.9914	5	30.19909	5

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

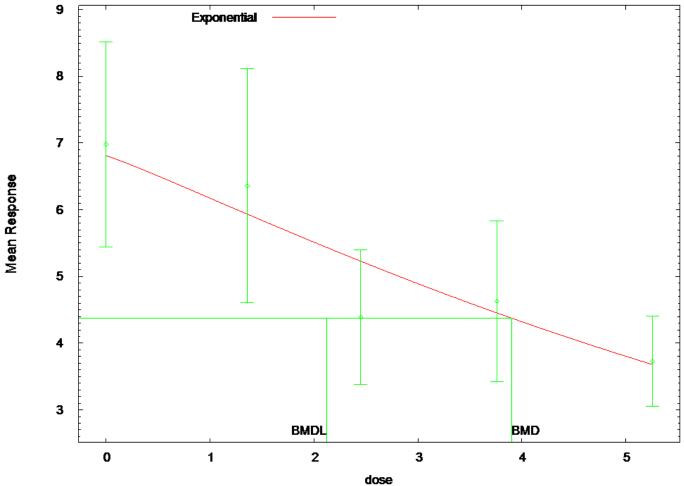
Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A2 vs. A1) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 5a: Does Model 3 fit the data? (A3 vs 3)

Test	-2*log(Likelihood Ratio)	D. F.
p-value		

Test	1	31.76	8
0.0001029			
Test	2	10.67	4
0.03055			
Test	3	10.67	4
0.03055			
Test !	5a	2.726	3
0.4359			

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. Consider running a non-homogeneous variance model. The p-value for Test 3 is less than .1. You may want to consider a different variance model. The p-value for Test 5a is greater than .1. Model 3 seems to adequately describe the data. Benchmark Dose Computations: Specified Effect = 1.000000 Risk Type = Estimated standard deviations from control Confidence Level = 0.950000 2.2766 BMD =

BMDL = 1.47441



15:00 06/21 2014

```
______
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Ln/Lymphocyte Concurrent Normal-HLS
2001-Lymphocyte Count-ExpNCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sat Jun 21 15:00:54 2014
______
===
BMDS Model Run
~~~~
  The form of the response function by Model:
                Y[dose] = a * exp{sign * b * dose}
     Model 2:
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
                Y[dose] = a * [c-(c-1) * exp{-b * dose}]
     Model 4:
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  The variance is to be modeled as Var(i) = exp(lalpha + log
(mean(i)) * rho)
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 3
lnalpha	-3.58873
rho	2.77965
a	3.75105
b	0.120756
C	0
d	1

## Parameter Estimates

Variable	Model 3
lnalpha	-3.804
rho	2.9112
a	6.80909
b	0.122743
С	0
d	1.10799

# Table of Stats From Input Data

Dose	Ν	Obs Mean	Obs Std Dev
0	10	6.98	2.146
1.361	10	6.36	2.452
2.451	9	4.39	1.308
3.761	9	4.63	1.564
5.258	10	3.73	0.941

## Estimated Values of Interest

Est Mean	Est Std	Scaled Residual
6.809	2.436	0.2219
5.933	1.993	0.6771
5.228	1.658	-1.516
4.453	1.313	0.4044
3.679	0.9942	0.1617
	6.809 5.933 5.228 4.453	6.8092.4365.9331.9935.2281.6584.4531.313

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)

	<pre>Var{e(ij) } =</pre>	Sigma(i) <sup>2</sup>
Model A3	: Yij = Var{e(ij)} =	Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R	: Yij = Var{e(ij)} =	Mu + e(i) Sigma^2

		Likelihoods of Int	erest
210	Model	Log(likelihood)	DF
AIC			
	A1	-49.13278	6
110.2656	A2	-43.79823	10
107.5965	A3	-44.17752	7
102.355	R	-59.6779	2
123.3558	3	-46.74085	5
103.4817	2	-40./4005	5

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 5a: Does Model 3 fit the data? (A3 vs 3)

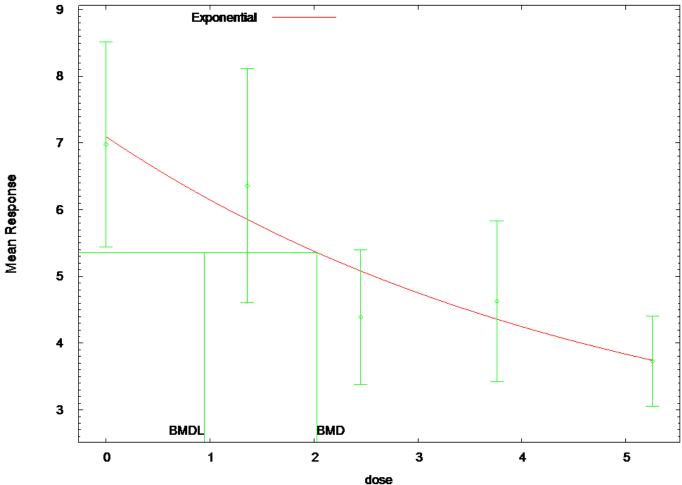
Test p-value	-2*log(Likelihood Ratio)	D. F.
Test 1 0.0001029	31.76	8

Test 2	10.67	4
0.03055		
Test 3	0.7586	3
0.8593		
Test 5a	5.127	2
0.07705		

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 5a is less than .1. Model 3 may not adequately describe the data; you may want to consider another model. Benchmark Dose Computations: Specified Effect = 1.000000 Risk Type = Estimated standard deviations from control Confidence Level = 0.950000

> BMD = 3.90494 BMDL = 2.12529

> > 4



15:00 06/21 2014

```
_____
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Ln/Lymphocyte Concurrent Normal-HLS
2001-Lymphocyte Count-ExpCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sat Jun 21 15:00:52 2014
______
===
BMDS Model Run
~~~~
  The form of the response function by Model:
                Y[dose] = a * exp{sign * b * dose}
     Model 2:
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
               Y[dose] = a * [c-(c-1) * exp{-b * dose}]
     Model 4:
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  rho is set to 0.
  A constant variance model is fit.
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 4
lnalpha	1.0472
rho(S)	0
a	7.329
b	0.208885
С	0.254469
d	1

(S) = Specified

### Parameter Estimates

Variable	Model 4
lnalpha	1.10181
rho	0
a	7.09555
b	0.208122
C	0.289709
d	1

# Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	10	6.98	2.146
1.361	10	6.36	2.452
2.451	9	4.39	1.308
3.761	9	4.63	1.564
5.258	10	3.73	0.941

## Estimated Values of Interest

Est Mean	Est Std	Scaled Residual
7.096	1.735	-0.2106
5.852	1.735	0.9254
5.082	1.735	-1.196
4.36	1.735	0.4676
3.743	1.735	-0.02344
	7.096 5.852 5.082 4.36	7.096       1.735         5.852       1.735         5.082       1.735         4.36       1.735

Other models for which likelihoods are calculated:

Model A1: Yij = Mu(i) + e(ij) Var{e(ij)} = Sigma^2

Model A2:	Yij = Var{e(ij)} =	Mu(i) + e(ij) Sigma(i)^2
Model A3:	Yij = Var{e(ij)} =	Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R:	Yij = Var{e(ij)} =	Mu + e(i) Sigma^2

Likelihoods of Interest

AIC	Model	Log(likelihood)	DF
AIC			
	Al	-49.13278	6
110.2656	A2	-43.79823	10
107.5965	A3	-49.13278	6
110.2656	R	-59.6779	2
123.3558			_
108.8867	4	-50.44333	4

Additive constant for all log-likelihoods = -44.11. This constant added to the above values gives the log-likelihood including the term that does not

depend on the model parameters.

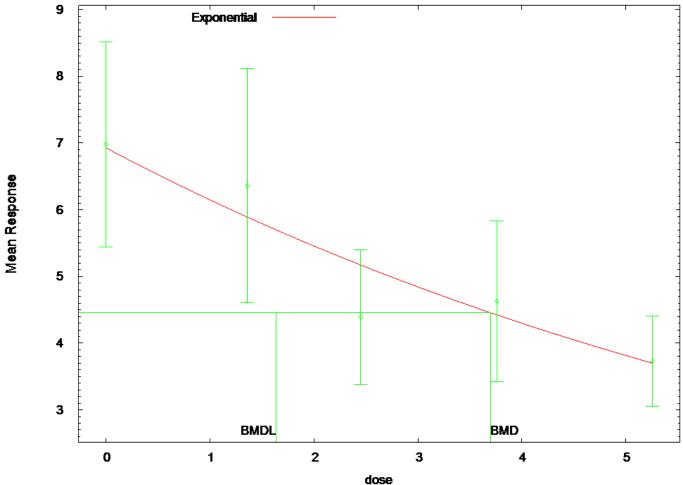
# Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A2 vs. A1) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 6a: Does Model 4 fit the data? (A3 vs 4)

Test	-2*log(Likelihood Ratio)	D. F.
p-value		

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. Consider running a non-homogeneous variance model. The p-value for Test 3 is less than .1. You may want to consider a different variance model. 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 = 2.02729

BMDL = 0.94493



15:00 06/21 2014

```
______
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Ln/Lymphocyte Concurrent Normal-HLS
2001-Lymphocyte Count-ExpNCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sat Jun 21 15:00:54 2014
______
===
BMDS Model Run
~~~~
  The form of the response function by Model:
                Y[dose] = a * exp{sign * b * dose}
     Model 2:
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
                Y[dose] = a * [c-(c-1) * exp{-b * dose}]
     Model 4:
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  The variance is to be modeled as Var(i) = exp(lalpha + log
(mean(i)) * rho)
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 4
lnalpha	-3.58873
rho	2.77965
a	7.329
b	0.208885
С	0.254469
d	1

## Parameter Estimates

Variable	Model 4
lnalpha	-3.68376
rho	2.83845
a	6.92765
b	0.119268
С	0
d	1

# Table of Stats From Input Data

Dose	Ν	Obs Mean	Obs Std Dev
0	10	6.98	2.146
1.361	10	6.36	2.452
2.451	9	4.39	1.308
3.761	9	4.63	1.564
5.258	10	3.73	0.941

## Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	6.928	2.472	0.06697
1.361	5.89	1.963	0.7575
2.451	5.172	1.633	-1.436
3.761	4.424	1.308	0.4734
5.258	3.7	1.015	0.09256

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) <sup>2</sup>	
Model A		= Mu(i) + e(ij) = exp(lalpha + log(mean(i))	* rho)
Model :	R: Yij Var{e(ij)}	= Mu + e(i) = Sigma <sup>2</sup>	

		Likelihoods of Int	erest
210	Model	Log(likelihood)	DF
AIC			
	A1	-49.13278	6
110.2656	A2	-43.79823	10
107.5965	A3	-44.17752	7
102.355	R	-59.6779	2
123.3558			_
101.5513	4	-46.77567	4

Additive constant for all log-likelihoods = -44.11. This constant added to the above values gives the log-likelihood including the term that does not

depend on the model parameters.

### Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A2 vs. A1) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 6a: Does Model 4 fit the data? (A3 vs 4)

Test p-value	-2*log(Likelihood Ratio)	D. F.
Test 1 0.0001029	31.76	8

Test 2	10.67	4
0.03055		
Test 3	0.7586	3
0.8593		
Test 6a	5.196	3
0.158		

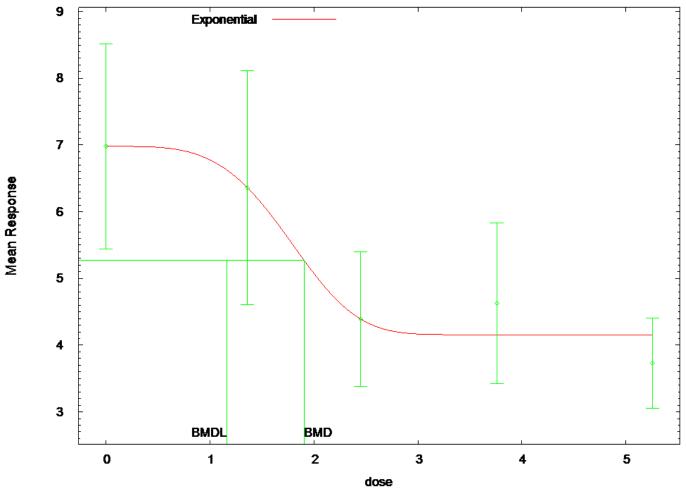
The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data. The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate. The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here. The p-value for Test 6a is greater than .1. Model 4 seems to adequately describe the data. Benchmark Dose Computations: Specified Effect = 1.000000 Risk Type = Estimated standard deviations from

control

Confidence Level = 0.950000

BMD = 3.70064

BMDL = 1.6333



Exponential Model 5, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Level for BMDL

15:00 06/21 2014

```
_____
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Ln/Lymphocyte Concurrent Normal-HLS
2001-Lymphocyte Count-ExpCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sat Jun 21 15:00:52 2014
______
===
BMDS Model Run
~~~~
  The form of the response function by Model:
                Y[dose] = a * exp{sign * b * dose}
     Model 2:
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
               Y[dose] = a * [c-(c-1) * exp{-b * dose}]
     Model 4:
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  rho is set to 0.
  A constant variance model is fit.
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 5
lnalpha	1.0472
rho(S)	0
a	7.329
b	0.208885
С	0.254469
d	1

(S) = Specified

### Parameter Estimates

Variable	Model 5
lnalpha	1.07486
rho	0
a	6.98002
b	0.514905
C	0.595454
d	3.92235

# Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	10	6.98	2.146
1.361	10	6.36	2.452
2.451	9	4.39	1.308
3.761	9	4.63	1.564
5.258	10	3.73	0.941

## Estimated Values of Interest

Est Mean	Est Std	Scaled Residual
6.98	1.712	-3.861e-005
6.36	1.712	6.283e-005
4.39	1.712	-0.0001466
4.156	1.712	0.8303
4.156	1.712	-0.7876
	6.98 6.36 4.39 4.156	6.981.7126.361.7124.391.7124.1561.712

Other models for which likelihoods are calculated:

Model A1: Yij = Mu(i) + e(ij) Var{e(ij)} = Sigma^2

Model A2:	Yij = Var{e(ij)} =	Mu(i) + e(ij) Sigma(i)^2
Model A3:	Yij = Var{e(ij)} =	Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R:	Yij = Var{e(ij)} =	Mu + e(i) Sigma^2

Likelihoods of Interest

<b></b>	Model	Log(likelihood)	DF
AIC			
	A1	-49.13278	6
110.2656	AI	-49.15270	0
	A2	-43.79823	10
107.5965	A3	-49.13278	6
110.2656	AS	-49.15270	0
	R	-59.6779	2
123.3558	5	-49.79671	5
109.5934	5	-49.79071	5

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

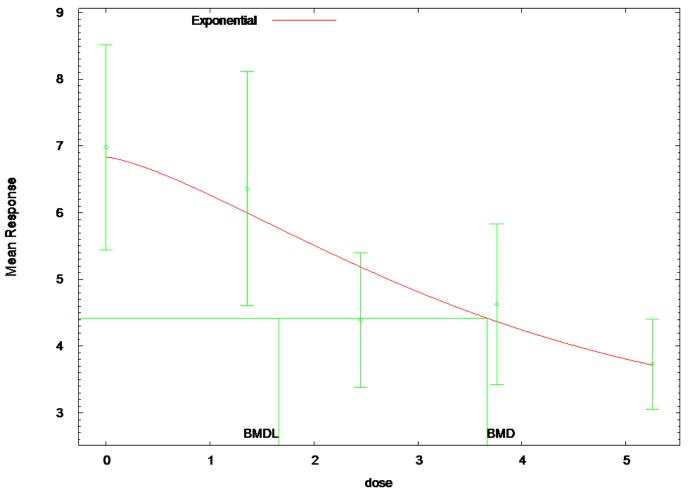
Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A2 vs. A1) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 7a: Does Model 5 fit the data? (A3 vs 5)

Test	-2*log(Likelihood Ratio)	D. F.
p-value		

Test	1	31.76	8
0.0001029			
Test	2	10.67	4
0.03055			
Test	3	10.67	4
0.03055			
Test	7a	1.328	1
0.2492			

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. Consider running a non-homogeneous variance model. The p-value for Test 3 is less than .1. You may want to consider a different variance model. The p-value for Test 7a is greater than .1. Model 5 seems to adequately describe the data. Benchmark Dose Computations: Specified Effect = 1.000000 Risk Type = Estimated standard deviations from control Confidence Level = 0.950000 BMD = 1.90743

BMDL = 1.16077



Exponential Model 5, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Level for BMDL

15:00 06/21 2014

```
______
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Ln/Lymphocyte Concurrent Normal-HLS
2001-Lymphocyte Count-ExpNCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sat Jun 21 15:00:54 2014
______
===
BMDS Model Run
~~~~
  The form of the response function by Model:
                Y[dose] = a * exp{sign * b * dose}
     Model 2:
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
                Y[dose] = a * [c-(c-1) * exp{-b * dose}]
     Model 4:
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  The variance is to be modeled as Var(i) = exp(lalpha + log
(mean(i)) * rho)
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 5
lnalpha	-3.58873
rho	2.77965
a	7.329
b	0.208885
С	0.254469
d	1

## Parameter Estimates

Variable	Model 5
lnalpha	-3.65305
rho	2.81765
a	6.83365
b	0.262032
С	0.422483
d	1.38992

# Table of Stats From Input Data

Dose	Ν	Obs Mean	Obs Std Dev
0	10	6.98	2.146
1.361	10	6.36	2.452
2.451	9	4.39	1.308
3.761	9	4.63	1.564
5.258	10	3.73	0.941

## Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	6.834	2.413	0.1918
1.361	5.996	2.007	0.5734
2.451	5.186	1.636	-1.46
3.761	4.368	1.285	0.6107
5.258	3.715	1.023	0.04492

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)

	<pre>Var{e(ij) } =</pre>	Sigma(i) <sup>2</sup>
Model A3	: Yij = Var{e(ij)} =	Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R	: Yij = Var{e(ij)} =	Mu + e(i) Sigma^2

		Likelihoods of Int	erest
210	Model	Log(likelihood)	DF
AIC			
	A1	-49.13278	6
110.2656	A2	-43.79823	10
107.5965	A3	-44.17752	7
102.355	R	-59.6779	2
123.3558			_
105.3823	5	-46.69115	6

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

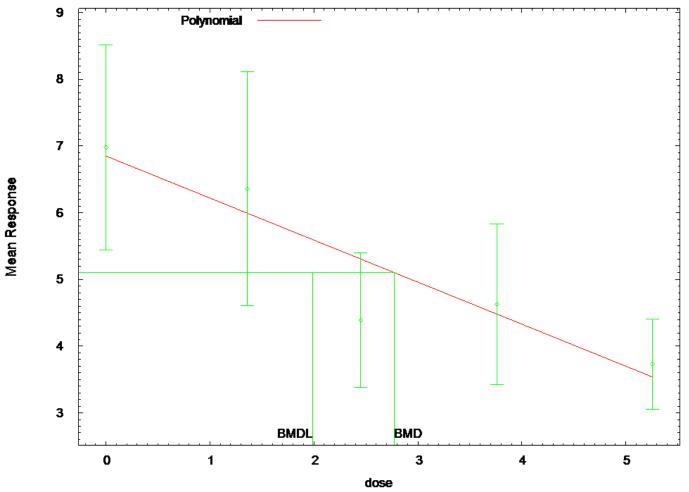
Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A2 vs. A1) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 7a: Does Model 5 fit the data? (A3 vs 5)

Test p-value	-2*log(Likelihood Ratio)	D. F.
Test 1 0.0001029	31.76	8

Test 2	10.67	4
0.03055		
Test 3	0.7586	3
0.8593		
Test 7a	5.027	1
0.02495		

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 7a is less than .1. Model 5 may not adequately describe the data; you may want to consider another model. Benchmark Dose Computations: Specified Effect = 1.000000 Risk Type = Estimated standard deviations from control Confidence Level = 0.950000

> BMD = 3.66557 BMDL = 1.66159



12:48 07/09 2014

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_Lymphocyte\_Concurrent\_Ln/Lymphocyt e\_Concurrent\_LN-HLS 2001-Lymphocyte Count-Poly2CV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_Lymphocyte\_Concurrent\_Ln/Lymphocyt e\_Concurrent\_LN-HLS 2001-Lymphocyte Count-Poly2CV-1SD-5d.plt Wed Jul 09 12:48:52 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse 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 = 5Total number of records with missing values = 0Maximum 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 = 3.18101 Specified rho = 0 beta\_0 = beta\_1 = 7.10002 -1.02021 beta\_2 = 0 Asymptotic Correlation Matrix of Parameter Estimates ( \*\*\* The model parameter(s) -rho -beta 2 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	1e-007	-1.1e-007
beta_0	1e-007	1	-0.81
beta_1	-1.1e-007	-0.81	1

### Parameter Estimates

				95.0%
Wald Con	fidence I	nterval		
V	ariable	Estimate	Std. Err.	Lower Conf.
Limit	Upper Con	f. Limit		
	alpha	3.05049	0.622679	)
1.83006		4.27092		
	beta_0	6.85042	0.427333	
6.01286		7.68798		
	beta_1	-0.630151	0.13565	-
0.89602		-0.364283		
	beta_2	0	NZ	<u>\</u>

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 Scaled	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 0.235	10	6.98	6.85	2.15	1.75
1.361 0.665	10	6.36	5.99	2.45	1.75
2.451 -1.57	9	4.39	5.31	1.31	1.75
3.761 0.257	9	4.63	4.48	1.56	1.75
5.258 0.349	10	3.73	3.54	0.941	1.75

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<sup>2</sup>

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
Al	-49.132777	6	110.265553
A2	-43.798233	10	107.596466
A3	-49.132777	6	110.265553
fitted	-50.767279	3	107.534558
R	-59.677903	2	123.355807

### 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

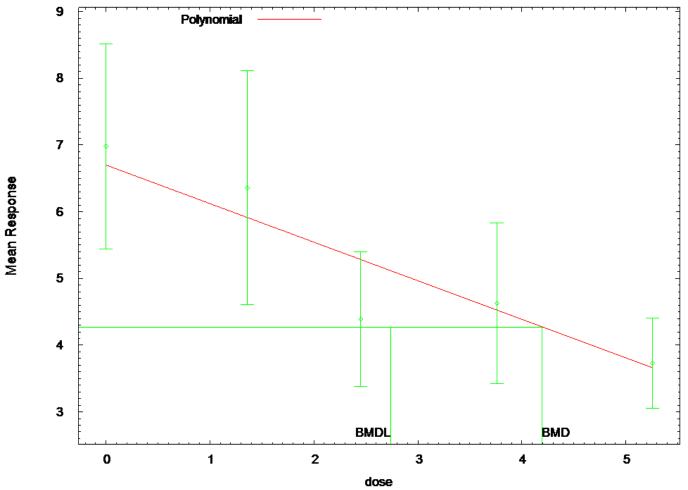
Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.7593	8	0.0001029
Test 2	10.6691	4	0.03055
Test 3	10.6691	4	0.03055
Test 4	3.269	3	0.352

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. Consider running a non-homogeneous variance model The p-value for Test 3 is less than .1. You may want to consider a different variance model 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 = 2.77166

BMDL = 1.99011



Polynomial Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

12:48 07/09 2014

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_Lymphocyte\_Concurrent\_Ln/Lymphocyt e\_Concurrent\_LN-HLS 2001-Lymphocyte Count-Poly2NCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_Lymphocyte\_Concurrent\_Ln/Lymphocyt e\_Concurrent\_LN-HLS 2001-Lymphocyte Count-Poly2NCV-1SD-5d.plt Wed Jul 09 12:48:53 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse 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 = 5Total number of records with missing values = 0Maximum 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 = 1.1572 rho = 0 7.10002 beta\_0 = beta\_0 = beta\_1 = -1.02021 beta\_2 = 0 Asymptotic Correlation Matrix of Parameter Estimates ( \*\*\* The model parameter(s) -beta\_2 have been estimated at a boundary point, or have been specified by the user,

and do not appear in the correlation matrix )

	lalpha	rho	beta_0	beta_1
lalpha	1	-0.99	0.17	-0.2
rho	-0.99	1	-0.17	0.2
beta_0	0.17	-0.17	1	-0.91
beta_1	-0.2	0.2	-0.91	1

Parameter Estimates

			95.0%
Wald Confidence 1	Interval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Cor	nf. Limit		
lalpha	-4.00629	1.70369	_
7.34546	-0.667115		
rho	3.03769	1.03603	
1.0071	5.06828		
beta_0	6.69816	0.5031	
5.7121	7.68422		
beta_1	-0.577576	0.122436	_
0.817545	-0.337606		
beta_2	0	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 Scaled	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 0.368	10	6.98	6.7	2.15	2.42
1.361 0.706	10	6.36	5.91	2.45	2.01
2.451 -1.58	9	4.39	5.28	1.31	1.69
3.761 0.234	9	4.63	4.53	1.56	1.34

5.258	10	3.73	3.66	0.941	0.969
0.224					

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

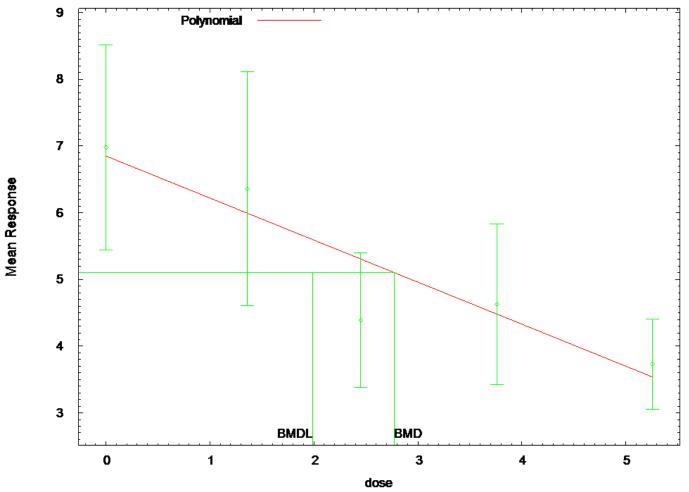
Model	Log(likelihood)	# Param's	AIC
Al	-49.132777	б	110.265553
A2	-43.798233	10	107.596466
A3	-44.177523	7	102.355046
fitted	-46.826872	4	101.653745
R	-59.677903	2	123.355807

### 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.)

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.7593	8	0.0001029
Test 2	10.6691	4	0.03055
Test 3	0.75858	3	0.8593
Test 4	5.2987	3	0.1512

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 = Estimated standard deviations from the Risk Type control mean Confidence level = 0.95 BMD = 4.19696 BMDL = 2.73754



12:48 07/09 2014

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_Lymphocyte\_Concurrent\_Ln/Lymphocyt e\_Concurrent\_LN-HLS 2001-Lymphocyte Count-Poly3CV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_Lymphocyte\_Concurrent\_Ln/Lymphocyt e\_Concurrent\_LN-HLS 2001-Lymphocyte Count-Poly3CV-1SD-5d.plt Wed Jul 09 12:48:52 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse 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 = 5Total 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 = 3.18101 Specified rho = 0 beta\_0 = 7.07831beta\_1 = -0.897602beta\_2 = 0 beta 3 = 0 Asymptotic Correlation Matrix of Parameter Estimates ( \*\*\* The model parameter(s) -rho -beta\_2 -

beta\_3

have been estimated at a boundary point, or have been specified by the user,

and do not appear in the correlation matrix )

beta_1	beta_0	alpha	
-1.3e-008	-3e-008	1	alpha
-0.81	1	-3e-008	beta_0
1	-0.81	-1.3e-008	beta_1

Parameter Estimates

95.0%

Wald Conf	idence Int	cerval				
Va	riable	Estimate	Std.	Err.	Lower	Conf.
Limit U	pper Conf	. Limit				
	alpha	3.05049	0.62	2679		
1.83006		4.27092				
	beta_0	6.85042	0.42	27333		
6.01286		7.68798				
	beta_1	-0.630151	0.1	3565		_
0.89602	-	-0.364283				
	beta_2	0		NA		
	beta_3	0		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 Scaled	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 0.235	10	6.98	6.85	2.15	1.75
1.361 0.665	10	6.36	5.99	2.45	1.75
2.451 -1.57	9	4.39	5.31	1.31	1.75
3.761	9	4.63	4.48	1.56	1.75
5.258	10	3.73	3.54	0.941	1.75

Model Descriptions for likelihoods calculated

Var{e(i)} = Sigma^2

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)

### Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
Al	-49.132777	6	110.265553
A2	-43.798233	10	107.596466
A3	-49.132777	6	110.265553
fitted	-50.767279	3	107.534558
R	-59.677903	2	123.355807

# Explanation of Tests

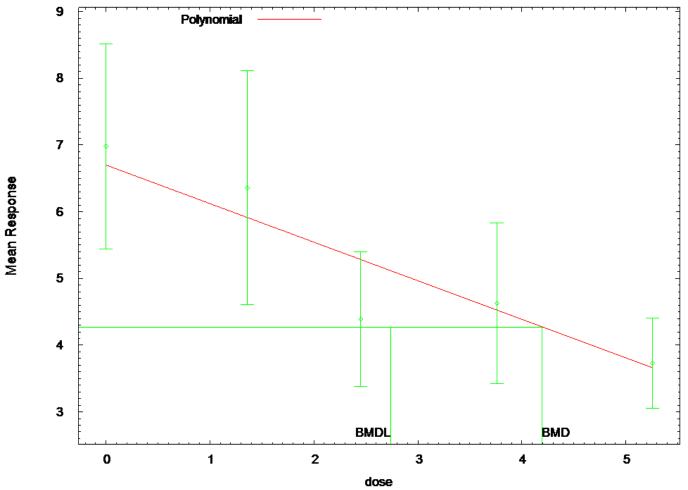
Test 1: Do responses and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A1 vs A2) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 4: Does the Model for the Mean Fit? (A3 vs. fitted) (Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

# Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.7593	8	0.0001029
Test 2	10.6691	4	0.03055
Test 3	10.6691	4	0.03055
Test 4	3.269	3	0.352

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. Consider running a non-homogeneous variance model The p-value for Test 3 is less than .1. You may want to consider а different variance model 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 Estimated standard deviations from the Risk Type = control mean Confidence level = 0.95 2.77166 BMD = BMDL = 1.99011



Polynomial Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

12:48 07/09 2014

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_Lymphocyte\_Concurrent\_Ln/Lymphocyt e\_Concurrent\_LN-HLS 2001-Lymphocyte Count-Poly3NCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_Lymphocyte\_Concurrent\_Ln/Lymphocyt e\_Concurrent\_LN-HLS 2001-Lymphocyte Count-Poly3NCV-1SD-5d.plt Wed Jul 09 12:48:53 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse 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 = 5Total number of records with missing values = 0Maximum 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 = 1.1572 rho = 0 beta\_0 = 7.07831 beta\_1 = -0.897602 7.07831 beta\_2 = 0 beta 3 = 0 Asymptotic Correlation Matrix of Parameter Estimates ( \*\*\* The model parameter(s) -beta\_2 -beta\_3

have been estimated at a boundary point, or have been specified by the user, and do not appear in the correlation matrix )

	lalpha	rho	beta_0	beta_1
lalpha	1	-0.99	0.17	-0.2
rho	-0.99	1	-0.17	0.2
beta_0	0.17	-0.17	1	-0.91
beta_1	-0.2	0.2	-0.91	1

Parameter Estimates

			95.0%
Wald Confidence In	nterval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Cont	E. Limit		
lalpha	-4.00629	1.70369	-
7.34547	-0.667116		
rho	3.03769	1.03603	
1.0071	5.06828		
beta_0	6.69816	0.5031	
5.7121	7.68422		
beta_1	-0.577575	0.122436	-
0.817545	-0.337606		
beta_2	0	NA	
beta_3	0	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 Scaled I	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 0.368	10	6.98	6.7	2.15	2.42
1.361 0.706	10	6.36	5.91	2.45	2.01
2.451 -1.58	9	4.39	5.28	1.31	1.69

3.761	9	4.63	4.53	1.56	1.34
0.234					
5.258	10	3.73	3.66	0.941	0.969
0.224					

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
Al	-49.132777	б	110.265553
A2	-43.798233	10	107.596466
A3	-44.177523	7	102.355046
fitted	-46.826872	4	101.653745
R	-59.677903	2	123.355807

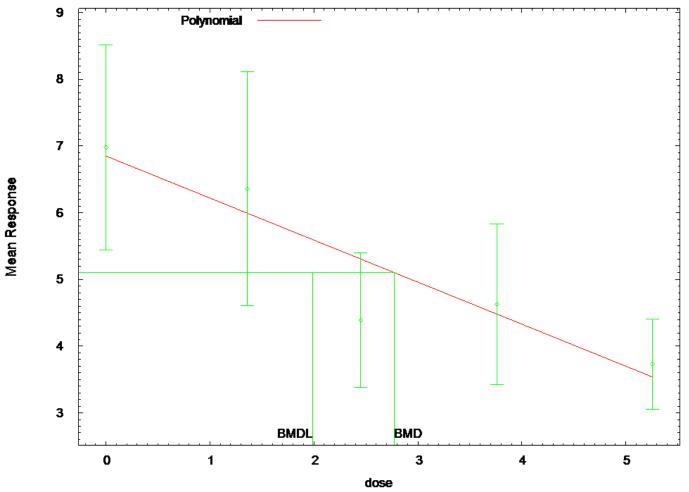
### Explanation of Tests

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	31.7593	8	0.0001029
Test 2	10.6691	4	0.03055
Test 3	0.75858	3	0.8593

5.2987 3 0.1512 Test 4 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 = Estimated standard deviations from the Risk Type control mean Confidence level = 0.95 4.19697 BMD = BMDL = 2.73754



12:48 07/09 2014

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_Lymphocyte\_Concurrent\_Ln/Lymphocyt e\_Concurrent\_LN-HLS 2001-Lymphocyte Count-Poly4CV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_Lymphocyte\_Concurrent\_Ln/Lymphocyt e\_Concurrent\_LN-HLS 2001-Lymphocyte Count-Poly4CV-1SD-5d.plt Wed Jul 09 12:48:52 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse 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 = 5Total number of records with missing values = 0Maximum 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 = 3.18101 rho = 0 Specified beta\_0 = 6.98 beta\_1 = 0  $beta_2 = -4.14163$ beta\_3 = 0  $beta_4 = -0.123946$ 

Asymptotic Correlation Matrix of Parameter Estimates

peta_1	beta_U	alpha	
4.2e-008	-3.4e-008	1	alpha
-0.81	1	-3.4e-008	beta_0
1	-0.81	4.2e-008	beta_1

Parameter Estimates

#### 95.0%

Wald Cor	nfidence 1	Interval		
V	/ariable	Estimate	Std. Err	. Lower Conf.
Limit	Upper Cor	nf. Limit		
	alpha	3.05049	0.62267	9
1.83006		4.27092		
	beta_0	6.85042	0.42733	3
6.01286		7.68798		
	beta_1	-0.630151	0.1356	5 –
0.89602		-0.364282		
	beta_2	0	N	A
	beta_3	0	N	A
	beta_4	0	N.	A

NA - Indicates that this parameter has hit a bound implied by some inequality constraint and thus has no standard error.

Dose Scaled	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 0.235	10	6.98	6.85	2.15	1.75
1.361 0.665	10	6.36	5.99	2.45	1.75
2.451 -1.57	9	4.39	5.31	1.31	1.75
3.761	9	4.63	4.48	1.56	1.75

Table of Data and Estimated Values of Interest

0.257 5.258 0.349	10	3.73	3.54	0.941	1.75
Model	Descriptio	ns for likeli	hoods calcul	ated	
Model	A1: Var{e(	Yij = Mu(i) ij)} = Sigma^			

Model A2: Yij = Mu(i) + e(ij) $Var{e(ij)} = Sigma(i)^2$ 

Model R: Yi = Mu + e(i)Var $\{e(i)\}$  = Sigma<sup>2</sup>

# Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-49.132777	б	110.265553
A2	-43.798233	10	107.596466
A3	-49.132777	б	110.265553
fitted	-50.767279	3	107.534558
R	-59.677903	2	123.355807

# Explanation of Tests

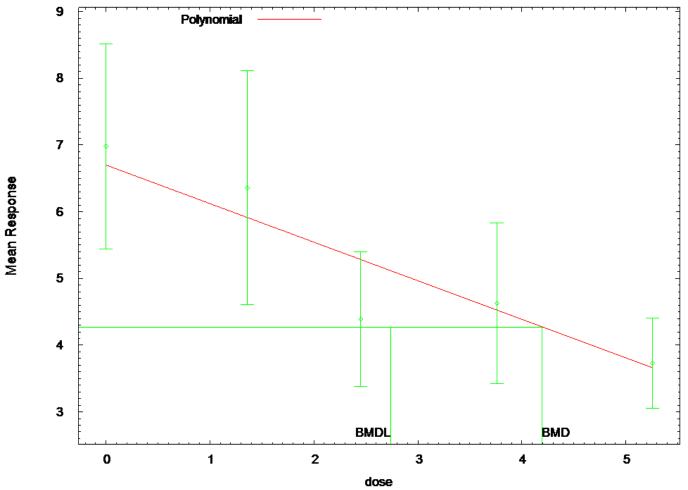
## Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.7593	8	0.0001029
Test 2	10.6691	4	0.03055
Test 3	10.6691	4	0.03055
Test 4	3.269	3	0.352

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. Consider running a non-homogeneous variance model The p-value for Test 3 is less than .1. You may want to consider а different variance model 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 = Estimated standard deviations from the Risk Type control mean Confidence level = 0.95

BMD = 2.77166

BMDL = 1.99011



Polynomial Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

12:48 07/09 2014

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_Lymphocyte\_Concurrent\_Ln/Lymphocyt e\_Concurrent\_LN-HLS 2001-Lymphocyte Count-Poly4NCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_Lymphocyte\_Concurrent\_Ln/Lymphocyt e\_Concurrent\_LN-HLS 2001-Lymphocyte Count-Poly4NCV-1SD-5d.plt Wed Jul 09 12:48:53 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse 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 = 5Total number of records with missing values = 0Maximum 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 = 1.1572 rho = 0 6.98 beta\_0 = beta\_1 = 0  $beta_2 = -4.14163$ beta\_3 = 0  $beta_4 = -0.123946$ 

Asymptotic Correlation Matrix of Parameter Estimates

lalpha	1	-0.99	0.17	-0.2
rho	-0.99	1	-0.17	0.2
beta_0	0.17	-0.17	1	-0.91
beta_1	-0.2	0.2	-0.91	1

#### Parameter Estimates

### 95.0%

				95.06
Wald Con	fidence I	nterval		
V	ariable	Estimate	Std. Err.	Lower Conf.
Limit	Upper Con	f. Limit		
	lalpha	-4.00629	1.70369	-
7.34547		-0.667111		
	rho	3.03769	1.03604	
1.0071		5.06828		
	beta_0	6.69816	0.503101	
5.7121		7.68422		
	beta_1	-0.577575	0.122436	_
0.817545		-0.337606		
	beta_2	-0	NA	
	beta_3	-2.72589e-104	NA	
	beta_4	- 0	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 Scaled R	N es.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 0.368	10	6.98	6.7	2.15	2.42
1.361	10	6.36	5.91	2.45	2.01

0.706 2.451	9	4.39	5.28	1.31	1.69
-1.58 3.761 0.234	9	4.63	4.53	1.56	1.34
5.258 0.224	10	3.73	3.66	0.941	0.969

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<sup>2</sup>

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
Al	-49.132777	б	110.265553
A2	-43.798233	10	107.596466
A3	-44.177523	7	102.355046
fitted	-46.826872	4	101.653745
R	-59.677903	2	123.355807

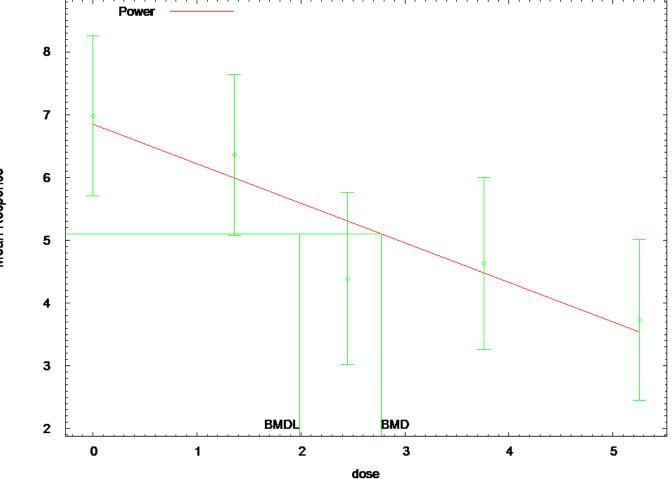
## Explanation of Tests

# Tests of Interest

Test	-2*log	(Likelihood	Ratio	) Test df	p-value
------	--------	-------------	-------	-----------	---------

3

31.7593 8 4 Test 1 0.0001029 Test 2 10.6691 0.03055 Test 3 0.75858 3 0.8593 5.2987 Test 4 3 0.1512 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 4.19697 BMD = 2.73754 BMDL =



Mean Response

15:00 06/21 2014

\_\_\_\_\_ === Power Model. (Version: 2.18; Date: 05/19/2014) Input Data File: C:/Users/dmayfield/Desktop/Ln/Lymphocyte\_Concurrent\_Normal-HLS 2001-Lymphocyte Count-PowerCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Ln/Lymphocyte Concurrent Normal-HLS 2001-Lymphocyte Count-PowerCV-1SD-5d.plt Sat Jun 21 15:00:53 2014 === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = control + slope \* dose^power Dependent variable = MeanResponse 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 = 5Total 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 = 3.18101 rho = 0 control = 3.73 slope = 3.0162 power = -1.13303 Specified 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	3.7e-011	-3.5e-011
control	3.7e-011	1	-0.81
slope	-3.5e-011	-0.81	1

# Parameter Estimates

				95.0%
Wald Con:				
Va	ariable	Estimate	Std. Err.	Lower Conf.
Limit 1	Upper Con	f. Limit		
	alpha	3.05049	0.622679	
1.83006		4.27092		
(	control	6.85042	0.427333	
6.01286		7.68798		
	slope	-0.630151	0.13565	-
0.89602		-0.364283		
	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
---------------------------------------

Dose Scaled	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 0.235	10	6.98	6.85	2.15	1.75
1.361 0.665	10	6.36	5.99	2.45	1.75
2.451 -1.57	9	4.39	5.31	1.31	1.75
3.761 0.257	9	4.63	4.48	1.56	1.75
5.258 0.349	10	3.73	3.54	0.941	1.75

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<sup>2</sup>

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-49.132777	6	110.265553
A2	-43.798233	10	107.596466
A3	-49.132777	6	110.265553
fitted	-50.767279	3	107.534558
R	-59.677903	2	123.355807

#### Explanation of Tests

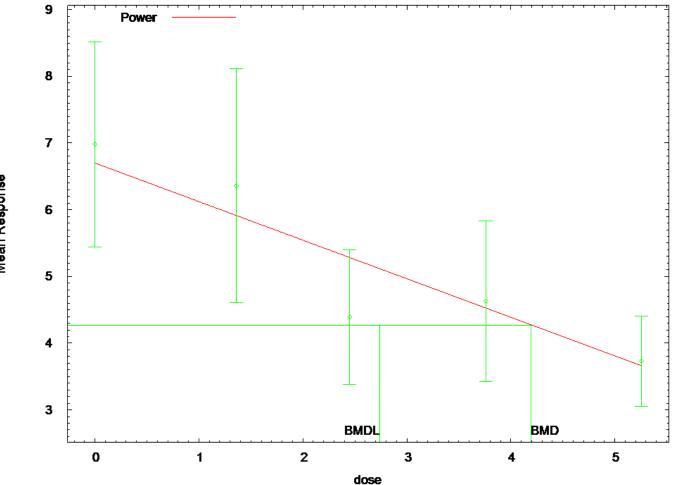
Test 1:	Do responses and/or variances differ among Dose levels?
	(A2 vs. R)
Test 2:	Are Variances Homogeneous? (A1 vs A2)
Test 3:	Are variances adequately modeled? (A2 vs. A3)
Test 4:	Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:	When rho=0 the results of Test 3 and Test 2 will be the
same.)	

# Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.7593	8	0.0001029
Test 2	10.6691	4	0.03055
Test 3	10.6691	4	0.03055
Test 4	3.269	3	0.352

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. Consider running a non-homogeneous variance model The p-value for Test 3 is less than .1. You may want to consider а different variance model 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 = Estimated standard deviations from the Risk Type control mean Confidence level = 0.95 BMD = 2.77166

BMDL = 1.99011



Mean Response

15:00 06/21 2014

\_\_\_\_\_\_ === Power Model. (Version: 2.18; Date: 05/19/2014) Input Data File: C:/Users/dmayfield/Desktop/Ln/Lymphocyte\_Concurrent\_Normal-HLS 2001-Lymphocyte Count-PowerNCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Ln/Lymphocyte Concurrent Normal-HLS 2001-Lymphocyte Count-PowerNCV-1SD-5d.plt Sat Jun 21 15:00:54 2014 === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = control + slope \* dose^power Dependent variable = MeanResponse Independent variable = Dose The power is restricted to be greater than or equal to 1 The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) \* rho) Total number of dose groups = 5Total 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 = 1.1572 rho = rho = 0 control = 3.73 slope = 3.0162 power = -1.13303 0 3.73 0 Asymptotic Correlation Matrix of Parameter Estimates ( \*\*\* The model parameter(s) -power have been estimated at a boundary point, or have been specified by the user,

and do not appear in the correlation matr:
--

	lalpha	rho	control	slope
lalpha	1	-0.99	0.43	-0.55
rho	-0.99	1	-0.48	0.58
control	0.43	-0.48	1	-0.91
slope	-0.55	0.58	-0.91	1

Parameter Estimates

95.0%

			90.00
Wald Confidence	e Interval		
Variable	e Estimate	Std. Err.	Lower Conf.
Limit Upper C	Conf. Limit		
lalpha	-4.00629	2.05361	-
8.03128	0.0187019		
rho	3.03769	1.26122	
0.565751	5.50963		
control	6.69816	0.505256	
5.70788	7.68845		
slope	-0.577575	0.122984	-
0.81862	-0.33653		
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 Scaled	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 0.368	10	6.98	6.7	2.15	2.42
1.361 0.706	10	6.36	5.91	2.45	2.01
2.451 -1.58	9	4.39	5.28	1.31	1.69
3.761 0.234	9	4.63	4.53	1.56	1.34

5.258	10	3.73	3.66	0.941	0.969
0.224					

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	-49.132777	6	110.265553
A2	-43.798233	10	107.596466
A3	-44.177523	7	102.355046
fitted	-46.826872	4	101.653745
R	-59.677903	2	123.355807

# Explanation of Tests

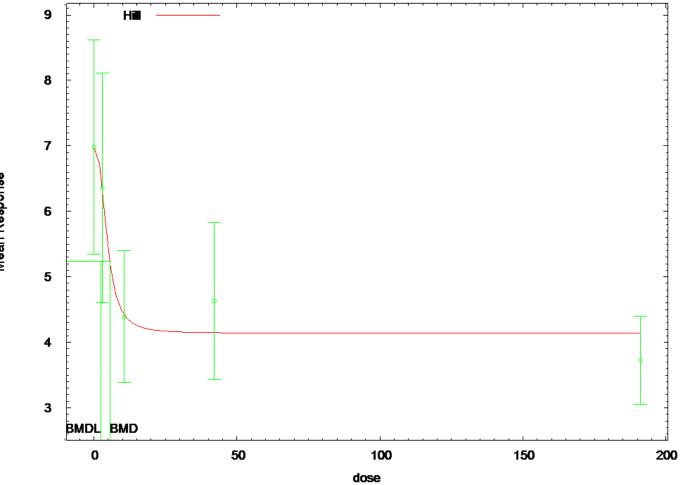
Test 1: Do responses and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A1 vs A2) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 4: Does the Model for the Mean Fit? (A3 vs. fitted) (Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

### Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.7593	8	0.0001029
Test 2	10.6691	4	0.03055
Test 3	0.75858	3	0.8593
Test 4	5.2987	3	0.1512

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 = Estimated standard deviations from the Risk Type control mean Confidence level = 0.95 BMD = 4.19697BMDL = 2.73754

BMDS Model Results for Lymphocyte Count (Untransformed Doses, Historical Controls)



Mean Response

10:03 06/22 2014

\_\_\_\_\_\_ === Hill Model. (Version: 2.17; Date: 01/28/2013) Input Data File: C:/Users/dmayfield/Desktop/Ln/Lymphocyte\_Historical\_Normal-HLS 2001-Lymphocyte Count-HillCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Ln/Lymphocyte Historical Normal-HLS 2001-Lymphocyte Count-HillCV-1SD-5d.plt Sun Jun 22 10:03:59 2014 === BMDS Model Run ~~~~ The form of the response function is:  $Y[dose] = intercept + v*dose^n/(k^n + dose^n)$ Dependent variable = MeanResponse 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 = 5Total 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 = 3.31423 Specified rho = 0 intercept = 6.98 -3.25 v = n = 1.7748 k = 6.82817 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,

k	alpha	intercept	v	n
alpha 1.5e-007	1	-1.4e-007	-2.7e-007	2e-007
intercept	-1.4e-007	1	-0.8	-0.24

-0.8

k 1.5e-007 -0.39 0.0043 -0.45

n 2e-007 -0.24 0.5

-0.39

0.0043

-0.45

1

v -2.7e-007

and do not appear in the correlation matrix )

Parameter	Estimates
rarameter	L'ALTINALES

1

0.5

1

			95.0%
Wald Confidence In	nterval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Con:	f. Limit		
alpha	3.04783	0.622135	
1.82847	4.26719		
intercept	6.98398	0.551753	
5.90257	8.0654		
v	-2.84388	0.708322	-
4.23217	-1.45559		
n	2.67791	2.62413	-
2.4653	7.82111		
k	4.63334	2.54804	-
0.360729	9.6274		

Table of Data and Estimated Values of Interest

Dose Scaled Rea	N s.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0	10	6.98	6.98	2.29	1.75

2.9	10	6.36	6.35	2.45	1.75
0.0127					
10.6	9	4.39	4.42	1.31	1.75
-0.051					
42	9	4.63	4.15	1.56	1.75
0.829					
191.1	10	3.73	4.14	0.941	1.75
-0.743					

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
Al	-50.117411	6	112.234822
A2	-44.445511	10	108.891023
A3	-50.117411	6	112.234822
fitted	-50.746309	5	111.492618
R	-60.317047	2	124.634093

# Explanation of Tests

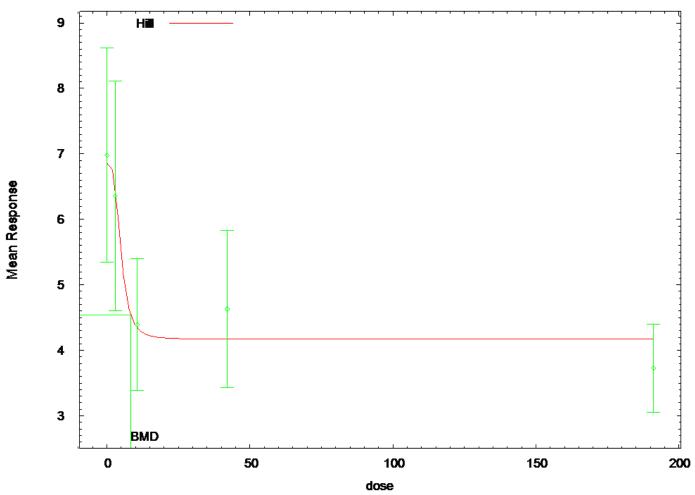
Test 1:	Do responses and/or variances differ among Dose levels?
	(A2 vs. R)
Test 2:	Are Variances Homogeneous? (A1 vs A2)
Test 3:	Are variances adequately modeled? (A2 vs. A3)
Test 4:	Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:	When rho=0 the results of Test 3 and Test 2 will be the
same.)	

# Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
------	--------------------------	---------	---------

Test 131.743180.0001035Test 211.343840.02296Test 311.343840.02296Test 41.257810.2621

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. Consider running a non-homogeneous variance model The p-value for Test 3 is less than .1. You may want to consider а different variance model 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 = 5.50919 BMDL = 2.35382



10:04 06/22 2014

Hill Model

\_\_\_\_\_\_ === Hill Model. (Version: 2.17; Date: 01/28/2013) Input Data File: C:/Users/dmayfield/Desktop/Ln/Lymphocyte\_Historical\_Normal-HLS 2001-Lymphocyte Count-HillNCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Ln/Lymphocyte Historical Normal-HLS 2001-Lymphocyte Count-HillNCV-1SD-5d.plt Sun Jun 22 10:04:00 2014 === BMDS Model Run ~~~~ The form of the response function is:  $Y[dose] = intercept + v*dose^n/(k^n + dose^n)$ Dependent variable = MeanResponse Independent variable = Dose Power parameter restricted to be greater than 1 The variance is to be modeled as Var(i) = exp(lalpha + rho \* ln(mean(i))) Total number of dose groups = 5Total 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 = 1.19823 rho = 0 intercept = 6.98 -3.25 v = n = 1.7748 k = 6.82817 Asymptotic Correlation Matrix of Parameter Estimates intercept lalpha rho v

n k			
lalpha -0.1 -0.045	1 -0.99	0.34	-0.43
rho -0 0.1 0.045	).99 1	-0.37	0.45
intercept ( -0.39 -0.5	-0.37	1	-0.93
v -0 0.52 0.33	0.43 0.45	-0.93	1
n - 1 -0.0023	-0.1 0.1	-0.39	0.52
k -0.	.045 0.045	-0.5	0.33

Parameter Estimates

			95.0%
Wald Confidence	Interval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Co	nf. Limit		
lalpha	-3.08024	1.71715	-
6.4458	0.285316		
rho	2.47594	1.04624	
0.425339	4.52653		
intercept	6.86429	0.699318	
5.49365	8.23493		
v	-2.69337	0.77583	-
4.21397	-1.17277		
n	3.47624	3.09597	-
2.59174	9.54423		
k	4.89095	2.7048	-
0.410352	10.1923		

Table of Data and Estimated Values of Interest

Dose Scaled R		Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 0.157	10	6.98	6.86	2.29	2.33

2

2.9	10	6.36	6.49	2.45	2.17
-0.186	9	4.39	4.34	1 0 1	1 2 2
10.6 0.108	9	4.39	4.34	1.31	1.32
42	9	4.63	4.17	1.56	1.26
1.09					
191.1	10	3.73	4.17	0.941	1.26
-1.11					

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
Al	-50.117411	6	112.234822
A2	-44.445511	10	108.891023
A3	-44.702636	7	103.405272
fitted	-47.027008	6	106.054017
R	-60.317047	2	124.634093

## 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.)	

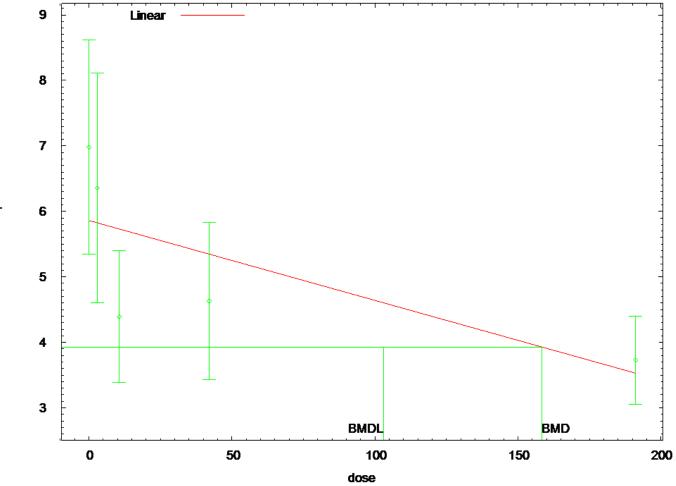
### Tests of Interest

Test	-2*log(Likelihood H	Ratio) Test	df	p-value
------	---------------------	-------------	----	---------

Test 131.743180.0001035Test 211.343840.02296Test 30.51424930.9157Test 44.6487410.03108

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 = Estimated standard deviations from the Risk Type control mean Confidence level = 0.95 BMD = 8.32507

BMDL computation failed.



Mean Response

12:50 07/09 2014

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_Lymphocyte\_Historical/Lymphocyte\_H istorical\_Normal-HLS 2001-Lymphocyte Count-LinearCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_Lymphocyte\_Historical/Lymphocyte\_H istorical\_Normal-HLS 2001-Lymphocyte Count-LinearCV-1SD-5d.plt Wed Jul 09 12:50:23 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse Independent variable = Dose rho is set to 0 Signs of the polynomial coefficients are not restricted A constant variance model is fit Total number of dose groups = 5Total number of records with missing values = 0Maximum 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 = 3.31423 rho = 0 Specified  $r_{110} = 0$ beta\_0 = 5.80912  $beta_1 = -0.0119854$ 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 )

beta_1	beta_0	alpha	
-6.9e-009	-2.7e-007	1	alpha
-0.56	1	-2.7e-007	beta_0
1	-0.56	-6.9e-009	beta_1

# Parameter Estimates

			95.0%
Wald Confidence I	nterval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Con	f. Limit		
alpha	3.73207	0.761805	
2.23896	5.22518		
beta_0	5.86108	0.337527	
5.19954	6.52262		
beta_1	-0.0122035	0.00378272	-
0.0196175	-0.00478945		

Table of Data and Estimated Values of Interest

Dose Scaled	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
	1.0	<	5.00	0.00	1 0 0
0	10	6.98	5.86	2.29	1.93
1.83					
2.9	10	6.36	5.83	2.45	1.93
0.875					
10.6	9	4.39	5.73	1.31	1.93
-2.08					
42	9	4.63	5.35	1.56	1.93
-1.12	-				
191.1	10	3.73	3.53	0.941	1.93
0.329					

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
Al	-50.117411	6	112.234822
A2	-44.445511	10	108.891023
A3	-50.117411	6	112.234822
fitted	-55.607114	3	117.214227
R	-60.317047	2	124.634093

### 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	31.7431	8	0.0001035
Test 2	11.3438	4	0.02296
Test 3	11.3438	4	0.02296
Test 4	10.9794	3	0.01184

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. Consider running a non-homogeneous variance model

The p-value for Test 3 is less than .1. You may want to consider a

different variance model

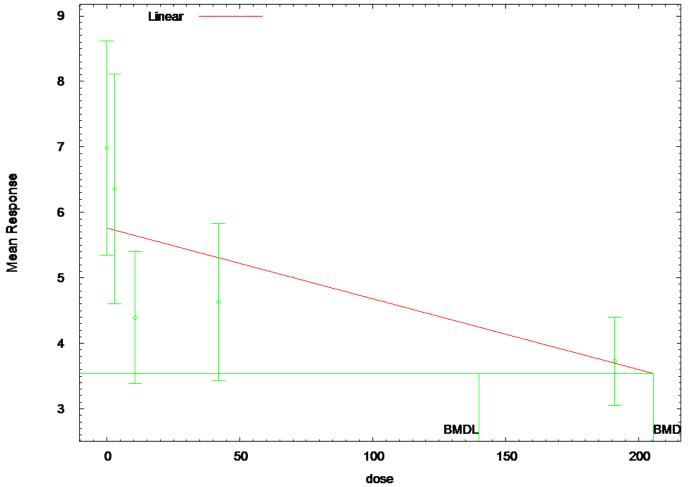
The p-value for Test 4 is less than .1. You may want to try a different model

Benchmark Dose Computation

Specified effect = 1 Risk Type = Estimated standard deviations from the control mean Confidence level = 0.95

BMD = 158.304

BMDL = 102.979



Linear Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

12:50 07/09 2014

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_Lymphocyte\_Historical/Lymphocyte\_H istorical\_Normal-HLS 2001-Lymphocyte Count-LinearNCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_Lymphocyte\_Historical/Lymphocyte\_H istorical\_Normal-HLS 2001-Lymphocyte Count-LinearNCV-1SD-5d.plt Wed Jul 09 12:50:25 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse Independent variable = Dose Signs of the polynomial coefficients are not restricted The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) \* rho) Total number of dose groups = 5Total number of records with missing values = 0Maximum 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 = 1.19823 rho = 0 beta\_0 = 5.80912  $beta_1 = -0.0119854$ Asymptotic Correlation Matrix of Parameter Estimates lalpha rho beta\_0 beta 1 -0.99 0.041 -0.047 lalpha 1

rho	-0.99	1	-0.042	0.048
beta_0	0.041	-0.042	1	-0.82
beta_1	-0.047	0.048	-0.82	1

Parameter Estimates

# 95.0%

Wald Confidence I	Interval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Con	nf. Limit		
lalpha	-5.79277	1.89821	_
9.51319	-2.07234		
rho	4.22044	1.15187	
1.96281	6.47806		
beta_0	5.76177	0.371198	
5.03424	6.48931		
beta_1	-0.0108106	0.00250705	-
0.0157243	-0.00589687		

Table of Data and Estimated Values of Interest

Dose Scaled	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 1.73	10	6.98	5.76	2.29	2.22
2.9 0.906	10	6.36	5.73	2.45	2.2
10.6 -1.77	9	4.39	5.65	1.31	2.13
42 -1.09	9	4.63	5.31	1.56	1.87
191.1 0.124	10	3.73	3.7	0.941	0.871

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<sup>2</sup>

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
Al	-50.117411	б	112.234822
A2	-44.445511	10	108.891023
A3	-44.702636	7	103.405272
fitted	-50.932591	4	109.865181
R	-60.317047	2	124.634093

#### Explanation of Tests

#### Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.7431	8	0.0001035
Test 2	11.3438	4	0.02296
Test 3	0.514249	3	0.9157
Test 4	12.4599	3	0.005963

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

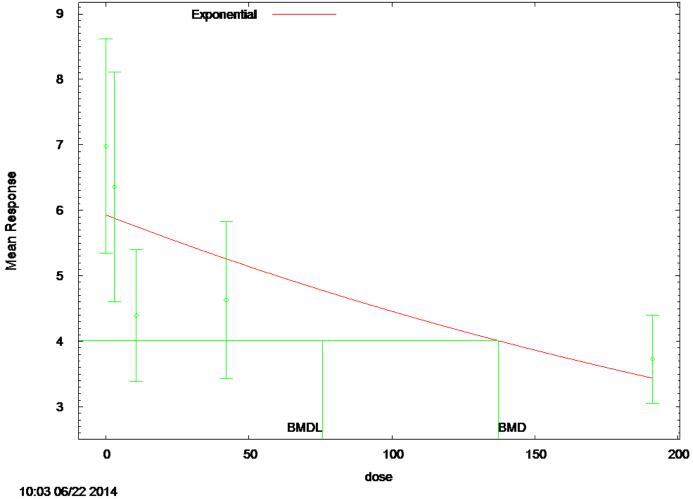
The p-value for Test 4 is less than .1. You may want to try a different model

Benchmark Dose Computation

Specified effect = 1 Risk Type = Estimated standard deviations from the control mean Confidence level = 0.95

BMD = 205.687

BMDL = 139.91



```
_____
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Ln/Lymphocyte Historical Normal-HLS
2001-Lymphocyte Count-ExpCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sun Jun 22 10:03:58 2014
______
===
BMDS Model Run
~~~~
  The form of the response function by Model:
                Y[dose] = a * exp{sign * b * dose}
     Model 2:
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
                Y[dose] = a * [c-(c-1) * exp{-b * dose}]
     Model 4:
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  rho is set to 0.
  A constant variance model is fit.
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 2
lnalpha	1.08823
rho(S)	0
a	4.506
b	0.00246217
C	0
d	1

(S) = Specified

#### Parameter Estimates

Variable	Model 2
lnalpha	1.30489
rho	0
a	5.93021
b	0.00285331
С	0
d	1

# Table of Stats From Input Data

Dose	Ν	Obs Mean	Obs Std Dev
0	10	6.98	2.289
2.9	10	6.36	2.452
10.6	9	4.39	1.308
42	9	4.63	1.564
191.1	10	3.73	0.941

## Estimated Values of Interest

Est Mean	Est Std	Scaled Residual
5.93	1.92	1.729
5.881	1.92	0.7883
5.754	1.92	-2.13
5.26	1.92	-0.985
3.438	1.92	0.4814
	5.93 5.881 5.754 5.26	5.931.925.8811.925.7541.925.261.92

Other models for which likelihoods are calculated:

Model A1: Yij = Mu(i) + e(ij) Var{e(ij)} = Sigma^2

Model A2:	Yij = Var{e(ij)} =	Mu(i) + e(ij) Sigma(i)^2
Model A3:	Yij = Var{e(ij)} =	Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R:	Yij = Var{e(ij)} =	Mu + e(i) Sigma^2

Likelihoods of Interest

AIC	Model	Log(likelihood)	DF
ALC			
110 0240	Al	-50.11741	6
112.2348	A2	-44.44551	10
108.891	A3	-50.11741	6
112.2348	R	-60.31705	2
124.6341	2	-55.31726	3
116.6345			

Additive constant for all log-likelihoods = -44.11. This constant added to the above values gives the log-likelihood including the term that does not

depend on the model parameters.

### Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A2 vs. A1) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 4: Does Model 2 fit the data? (A3 vs. 2)

#### Tests of Interest

Test p-value	-2*log(Likelihood Ratio)	D. F.
Test 1	31.74	8

0.0001035			
Test	2	11.34	4
0.02296			
Test	3	11.34	4
0.02296			
Test	4	10.4	3
0.01546			

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. Consider running

a non-homogeneous variance model.

The p-value for Test 3 is less than .1. You may want to consider a different variance model.

The p-value for Test 4 is less than .1. Model 2 may not adequately

describe the data; you may want to consider another model.

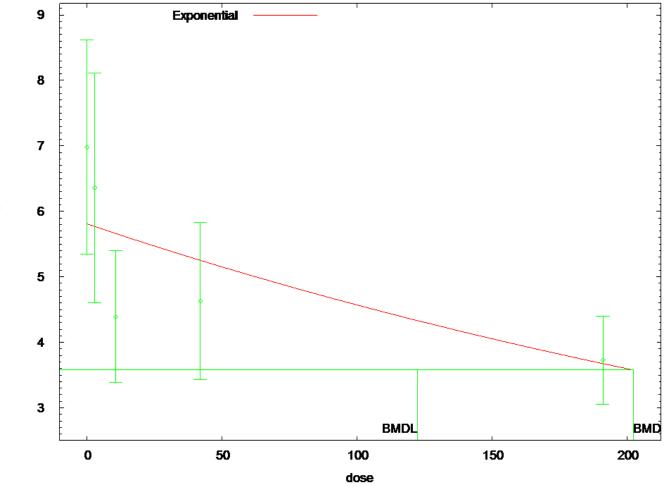
Benchmark Dose Computations:

Specified Effect = 1.000000

Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

BMD = 137.129 BMDL = 75.742



# Exponential Model 2, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Level for BMDL

Mean Response

10:04 06/22 2014

```
______
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Ln/Lymphocyte Historical Normal-HLS
2001-Lymphocyte Count-ExpNCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sun Jun 22 10:03:59 2014
______
===
BMDS Model Run
~~~~
  The form of the response function by Model:
                Y[dose] = a * exp{sign * b * dose}
     Model 2:
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
                Y[dose] = a * [c-(c-1) * exp{-b * dose}]
     Model 4:
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  The variance is to be modeled as Var(i) = exp(lalpha + log
(mean(i)) * rho)
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 2
lnalpha	-3.80501
rho	2.92874
a	4.506
b	0.00246217
C	0
d	1

# Parameter Estimates

Variable	Model 2
lnalpha	-5.63395
rho	4.11509
a	5.80788
b	0.00239458
C	0
d	1

# Table of Stats From Input Data

Dose	Ν	Obs Mean	Obs Std Dev
0	10	6.98	2.289
2.9	10	6.36	2.452
10.6	9	4.39	1.308
42	9	4.63	1.564
191.1	10	3.73	0.941

# Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	5.808	2.232	1.661
2.9	5.768	2.2	0.8514
10.6	5.662	2.118	-1.802
42	5.252	1.814	-1.029
191.1	3.675	0.8704	0.1991

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)

		<pre>Var{e(ij)}</pre>	=	Sigma(i) <sup>2</sup>
Model A	3:	Yij Var{e(ij)}	=	Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model :	R:	Yij Var{e(ij)}	=	Mu + e(i) Sigma <sup>2</sup>

		Likelihoods of Int	erest
210	Model	Log(likelihood)	DF
AIC			
	A1	-50.11741	6
112.2348	A2	-44.44551	10
108.891	A3	-44.70264	7
103.4053	R	-60.31705	2
124.6341	2	-50.63837	_
109.2767	2	- 50 . 0 5 0 3 7	4

Additive constant for all log-likelihoods = -44.11. This constant added to the above values gives the log-likelihood including the term that does not

depend on the model parameters.

### Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A2 vs. A1) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 4: Does Model 2 fit the data? (A3 vs. 2)

# Tests of Interest

Test p-value		-2*log(Likelihood Ratio)	D. F.
Test	1	31.74	8
0.0001035			
Test	2	11.34	4

0.02290	6									
Te	est 3					(	0.5142	2		3
0.9157										
Te	est 4						11.8	7		3
0.00783	37									
Tl be a	he p-value	for	Test	1	is	less	than	.05.	There	appears

difference between response and/or variances among the dose levels, it seems appropriate to model the data.

to

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. Model 2 may not adequately

describe the data; you may want to consider another model.

Benchmark Dose Computations:

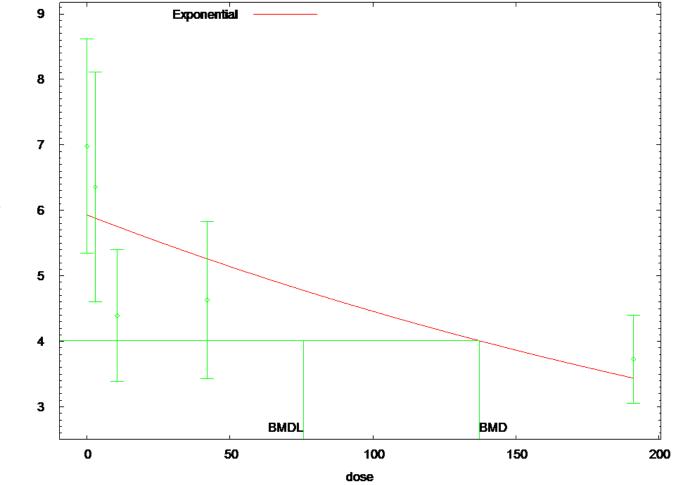
Specified Effect = 1.000000

Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

BMDL =

BMD = 202.488 122.382



Mean Response

10:03 06/22 2014

```
_____
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Ln/Lymphocyte Historical Normal-HLS
2001-Lymphocyte Count-ExpCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sun Jun 22 10:03:58 2014
______
===
BMDS Model Run
~~~~
  The form of the response function by Model:
                Y[dose] = a * exp{sign * b * dose}
     Model 2:
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
                Y[dose] = a * [c-(c-1) * exp{-b * dose}]
     Model 4:
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  rho is set to 0.
  A constant variance model is fit.
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 3
lnalpha	1.08823
rho(S)	0
a	4.506
b	0.00246217
C	0
d	1

(S) = Specified

#### Parameter Estimates

Variable	Model 3
lnalpha	1.30489
rho	0
a	5.93021
b	0.00285331
C	0
d	1

# Table of Stats From Input Data

Dose	Ν	Obs Mean	Obs Std Dev
0	10	6.98	2.289
2.9	10	6.36	2.452
10.6	9	4.39	1.308
42	9	4.63	1.564
191.1	10	3.73	0.941

## Estimated Values of Interest

Est Mean	Est Std	Scaled Residual
5.93	1.92	1.729
5.881	1.92	0.7883
5.754	1.92	-2.13
5.26	1.92	-0.985
3.438	1.92	0.4814
	5.93 5.881 5.754 5.26	5.931.925.8811.925.7541.925.261.92

Other models for which likelihoods are calculated:

Model A1: Yij = Mu(i) + e(ij) Var{e(ij)} = Sigma^2

Model A2:	Yij = Var{e(ij)} =	Mu(i) + e(ij) Sigma(i)^2
Model A3:	Yij = Var{e(ij)} =	Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R:	Yij = Var{e(ij)} =	Mu + e(i) Sigma^2

Likelihoods of Interest

AIC	Model	Log(likelihood)	DF
ALC			
	A1	-50.11741	6
112.2348	A2	-44.44551	10
108.891	A3	-50.11741	6
112.2348	R	-60.31705	2
124.6341	3	-55.31726	3
116.6345			

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

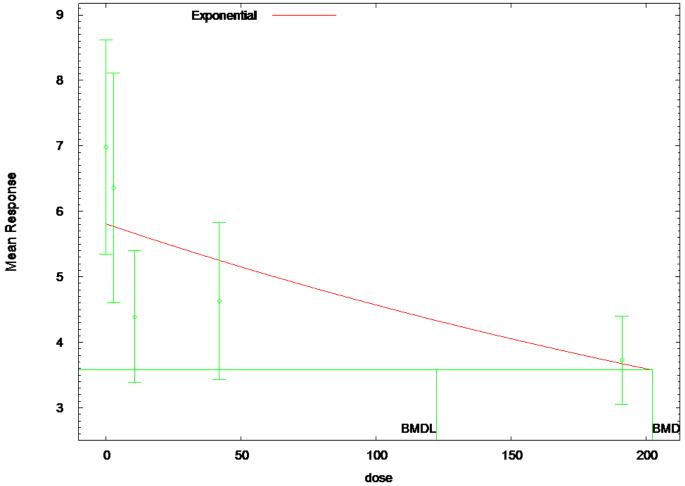
Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A2 vs. A1) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 5a: Does Model 3 fit the data? (A3 vs 3)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.
p-value		

Test	1	31.74	8
0.0001035			
Test	2	11.34	4
0.02296			
Test	3	11.34	4
0.02296			
Test	5a	10.4	3
0.01546			

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. Consider running a non-homogeneous variance model. The p-value for Test 3 is less than .1. You may want to consider a different variance model. The p-value for Test 5a is less than .1. Model 3 may not adequately describe the data; you may want to consider another model. Benchmark Dose Computations: Specified Effect = 1.000000 Risk Type = Estimated standard deviations from control Confidence Level = 0.950000BMD = 137.129 BMDL = 75.742



# Exponential Model 3, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Level for BMDL

10:04 06/22 2014

```
______
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Ln/Lymphocyte Historical Normal-HLS
2001-Lymphocyte Count-ExpNCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sun Jun 22 10:03:59 2014
______
===
BMDS Model Run
~~~~
  The form of the response function by Model:
                Y[dose] = a * exp{sign * b * dose}
     Model 2:
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
                Y[dose] = a * [c-(c-1) * exp{-b * dose}]
     Model 4:
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  The variance is to be modeled as Var(i) = exp(lalpha + log
(mean(i)) * rho)
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 3
lnalpha	-3.80501
rho	2.92874
a	4.506
b	0.00246217
C	0
d	1

# Parameter Estimates

Variable	Model 3
lnalpha	-5.63395
rho	4.11509
a	5.80788
b	0.00239458
C	0
d	1

# Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	10	6.98	2.289
2.9	10	6.36	2.452
10.6	9	4.39	1.308
42	9	4.63	1.564
191.1	10	3.73	0.941

# Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	5.808	2.232	1.661
2.9	5.768	2.2	0.8514
10.6	5.662	2.118	-1.802
42	5.252	1.814	-1.029
191.1	3.675	0.8704	0.1991

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)

		<pre>Var{e(ij)}</pre>	=	Sigma(i) <sup>2</sup>	
Model A	43:			Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rh	10)
Model	R:	Yij Var{e(ij)}	=	Mu + e(i) Sigma <sup>2</sup>	

		Likelihoods of Int	erest
AIC	Model	Log(likelihood)	DF
1110			
	Al	-50.11741	6
112.2348	A2	-44.44551	10
108.891	A3	-44.70264	7
103.4053	R	-60.31705	2
124.6341	3	-50.63837	4
109.2767			

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 5a: Does Model 3 fit the data? (A3 vs 3)

#### Tests of Interest

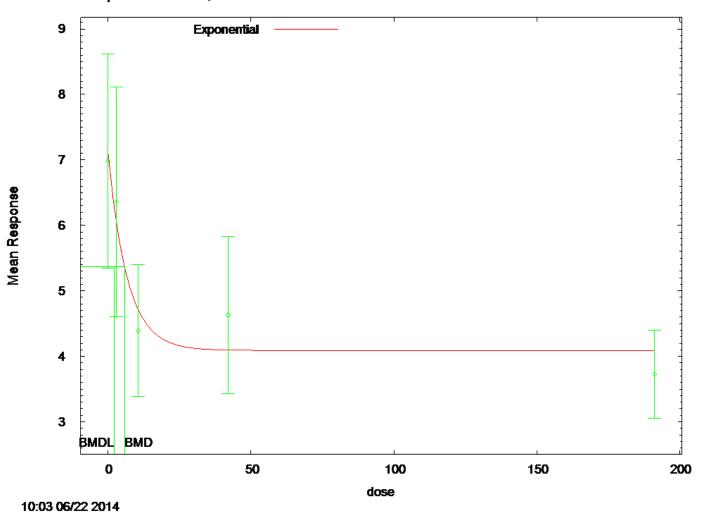
Test p-value	-2*log(Likelihood Ratio)	D. F.
Test 1 0.0001035	31.74	8

Test 2	11.34	4
0.02296		
Test 3	0.5142	3
0.9157		
Test 5a	11.87	3
0.007837		

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 5a is less than .1. Model 3 may not adequately describe the data; you may want to consider another model. Benchmark Dose Computations: Specified Effect = 1.000000 Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

BMD = 202.488 BMDL = 122.382



```
_____
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Ln/Lymphocyte Historical Normal-HLS
2001-Lymphocyte Count-ExpCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sun Jun 22 10:03:58 2014
______
===
BMDS Model Run
~~~~
  The form of the response function by Model:
                Y[dose] = a * exp{sign * b * dose}
     Model 2:
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
                Y[dose] = a * [c-(c-1) * exp{-b * dose}]
     Model 4:
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  rho is set to 0.
  A constant variance model is fit.
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 4
lnalpha	1.08823
rho(S)	0
a	7.329
b	0.0170211
C	0.484702
d	1

(S) = Specified

### Parameter Estimates

Variable	Model 4
lnalpha	1.12896
rho	0
a	7.12238
b	0.150285
C	0.574374
d	1

# Table of Stats From Input Data

Dose	Ν	Obs Mean	Obs Std Dev
0	10	6.98	2.289
2.9	10	6.36	2.452
10.6	9	4.39	1.308
42	9	4.63	1.564
191.1	10	3.73	0.941

## Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	7.122	1.759	-0.256
2.9	6.051	1.759	0.5549
10.6	4.707	1.759	-0.5412
42	4.096	1.759	0.9103
191.1	4.091	1.759	-0.649

Other models for which likelihoods are calculated:

Model A1: Yij = Mu(i) + e(ij) Var{e(ij)} = Sigma^2

Model A2:	Yij = Var{e(ij)} =	Mu(i) + e(ij) Sigma(i)^2
Model A3:	Yij = Var{e(ij)} =	Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R:	Yij = Var{e(ij)} =	Mu + e(i) Sigma^2

Likelihoods of Interest

AIC	Model	Log(likelihood)	DF
AIC			
110 0040	Al	-50.11741	6
112.2348	A2	-44.44551	10
108.891	A3	-50.11741	6
112.2348	R	-60.31705	2
124.6341	4	-51.09512	4
110.1902			

Additive constant for all log-likelihoods = -44.11. This constant added to the above values gives the log-likelihood including the term that does not

depend on the model parameters.

# Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A2 vs. A1) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 6a: Does Model 4 fit the data? (A3 vs 4)

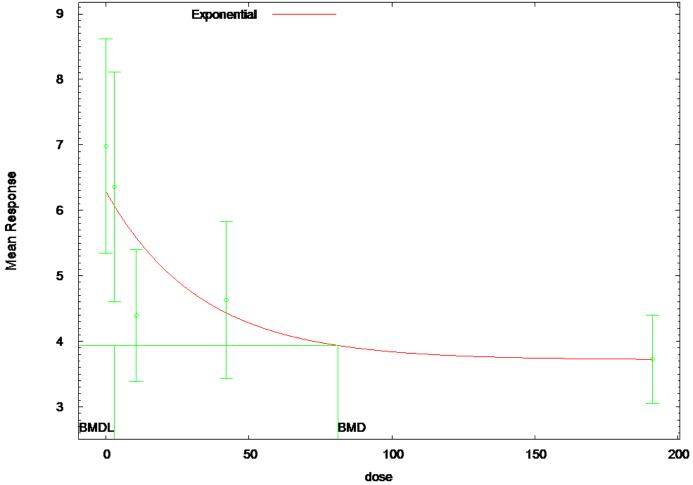
Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.
p-value		

Test	1	31.74	8
0.0001035			
Test	2	11.34	4
0.02296			
Test	3	11.34	4
0.02296			
Test (	ба	1.955	2
0.3762			

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. Consider running a non-homogeneous variance model. The p-value for Test 3 is less than .1. You may want to consider a different variance model. 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 = 5.77383

BMDL = 2.26317



10:04 06/22 2014

```
______
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Ln/Lymphocyte Historical Normal-HLS
2001-Lymphocyte Count-ExpNCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sun Jun 22 10:03:59 2014
______
===
BMDS Model Run
~~~~
  The form of the response function by Model:
                Y[dose] = a * exp{sign * b * dose}
     Model 2:
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
                Y[dose] = a * [c-(c-1) * exp{-b * dose}]
     Model 4:
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  The variance is to be modeled as Var(i) = exp(lalpha + log
(mean(i)) * rho)
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 4
lnalpha	-3.80501
rho	2.92874
a	7.329
b	0.0170211
C	0.484702
d	1

## Parameter Estimates

Variable	Model 4
lnalpha	-4.52284
rho	3.39008
a	6.28865
b	0.0303979
C	0.591176
d	1

# Table of Stats From Input Data

Dose	Ν	Obs Mean	Obs Std Dev
0	10	6.98	2.289
2.9	10	6.36	2.452
10.6	9	4.39	1.308
42	9	4.63	1.564
191.1	10	3.73	0.941

## Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	6.289	2.352	0.9295
2.9	6.072	2.216	0.4113
10.6	5.58	1.921	-1.859
42	4.435	1.301	0.4498
191.1	3.725	0.9684	0.01497

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)

		<pre>Var{e(ij)}</pre>	=	Sigma(i) <sup>2</sup>	
Model A	43:			Mu(i) + e(ij) exp(lalpha + log(mean(i)) *	rho)
Model	R:	Yij Var{e(ij)}	=	Mu + e(i) Sigma <sup>2</sup>	

		Likelihoods of Int	erest
210	Model	Log(likelihood)	DF
AIC			
	A1	-50.11741	6
112.2348	A2	-44.44551	10
108.891	A3	-44.70264	7
103.4053	R	-60.31705	2
124.6341		-48.43541	5
106.8708	4	-40.43541	5

Additive constant for all log-likelihoods = -44.11. This constant added to the above values gives the log-likelihood including the term that does not

depend on the model parameters.

### Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A2 vs. A1) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 6a: Does Model 4 fit the data? (A3 vs 4)

#### Tests of Interest

Test p-value	-2*log(Likelihood Ratio)	D. F.
Test 1 0.0001035	31.74	8

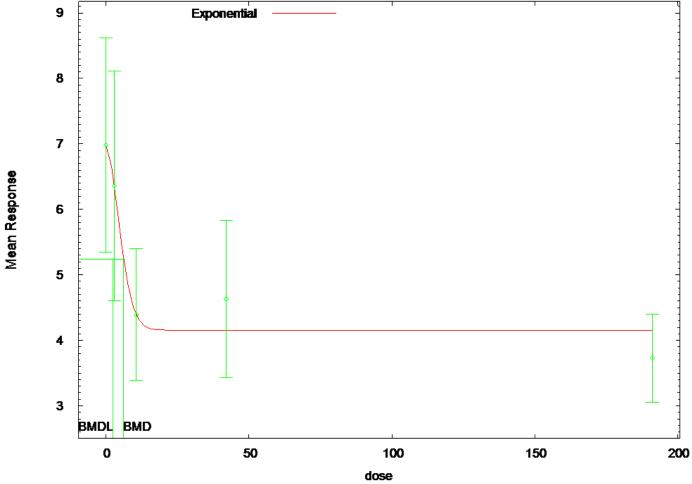
Test 2	11.34	4
0.02296		
Test 3	0.5142	3
0.9157		
Test 6a	7.466	2
0.02393		

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data. The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate. The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here. The p-value for Test 6a is less than .1. Model 4 may not adequately describe the data; you may want to consider another model. Benchmark Dose Computations: Specified Effect = 1.000000 Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

BMD = 81.0526

BMDL = 2.80644



10:03 06/22 2014

```
_____
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Ln/Lymphocyte Historical Normal-HLS
2001-Lymphocyte Count-ExpCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sun Jun 22 10:03:58 2014
______
===
BMDS Model Run
~~~~
  The form of the response function by Model:
                Y[dose] = a * exp{sign * b * dose}
     Model 2:
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
                Y[dose] = a * [c-(c-1) * exp{-b * dose}]
     Model 4:
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  rho is set to 0.
  A constant variance model is fit.
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 5	
lnalpha	1.08823	
rho(S)	0	
a	7.329	
b	0.0170211	
C	0.484702	
d	1	

(S) = Specified

### Parameter Estimates

Variable	Model 5
lnalpha	1.11479
rho	0
a	6.98
b	0.157544
С	0.595461
d	1.78044

# Table of Stats From Input Data

Dose	Ν	Obs Mean	Obs Std Dev
0	10	6.98	2.289
2.9	10	6.36	2.452
10.6	9	4.39	1.308
42	9	4.63	1.564
191.1	10	3.73	0.941

## Estimated Values of Interest

Est Mean	Est Std	Scaled Residual
6.98	1.746	6.523e-007
6.36	1.746	-6.948e-007
4.39	1.746	-2.243e-007
4.156	1.746	0.8138
4.156	1.746	-0.7721
	6.98 6.36 4.39 4.156	6.98 1.746 6.36 1.746 4.39 1.746 4.156 1.746

Other models for which likelihoods are calculated:

Model A1: Yij = Mu(i) + e(ij) Var{e(ij)} = Sigma^2

Model A2:	Yij = Var{e(ij)} =	Mu(i) + e(ij) Sigma(i)^2
Model A3:		Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R:	Yij = Var{e(ij)} =	Mu + e(i) Sigma^2

Likelihoods of Interest

AIC	Model Log(likelihoo		DF
AIC			
112 2240	Al	-50.11741	6
112.2348	A2	-44.44551	10
108.891	A3	-50.11741	6
112.2348	R	-60.31705	2
124.6341	5	-50.75502	5
111.51			

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)

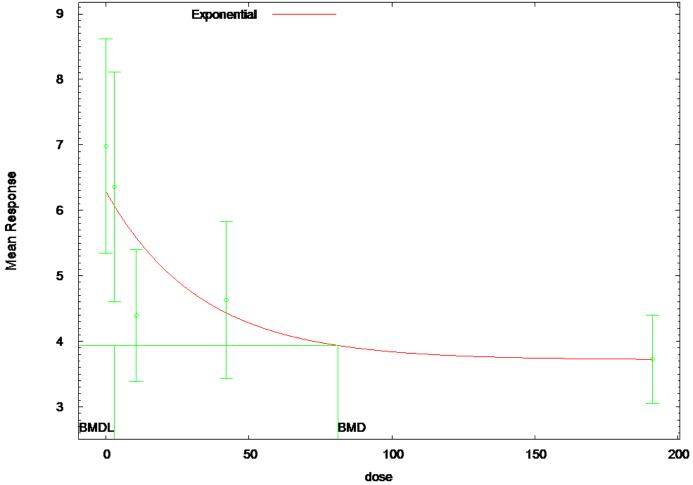
Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.
p-value		

Test	1	31.74	8
0.0001035			
Test	2	11.34	4
0.02296			
Test	3	11.34	4
0.02296			
Test '	7a	1.275	1
0.2588			

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. Consider running a non-homogeneous variance model. The p-value for Test 3 is less than .1. You may want to consider a different variance model. 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 = 6.21566

BMDL = 2.54297



10:04 06/22 2014

```
______
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Ln/Lymphocyte Historical Normal-HLS
2001-Lymphocyte Count-ExpNCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sun Jun 22 10:03:59 2014
______
===
BMDS Model Run
~~~~
  The form of the response function by Model:
                Y[dose] = a * exp{sign * b * dose}
     Model 2:
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
                Y[dose] = a * [c-(c-1) * exp{-b * dose}]
     Model 4:
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  The variance is to be modeled as Var(i) = exp(lalpha + log
(mean(i)) * rho)
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 5
lnalpha	-3.80501
rho	2.92874
a	7.329
b	0.0170211
C	0.484702
d	1

## Parameter Estimates

Variable	Model 5
lnalpha	-4.52284
rho	3.39008
a	6.28866
b	0.0303979
С	0.591176
d	1

# Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	10	6.98	2.289
2.9	10	6.36	2.452
10.6	9	4.39	1.308
42	9	4.63	1.564
191.1	10	3.73	0.941

## Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	6.289	2.352	0.9295
2.9	6.072	2.216	0.4113
10.6	5.58	1.921	-1.859
42	4.435	1.301	0.4498
191.1	3.725	0.9684	0.01497

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)

		<pre>Var{e(ij)}</pre>	=	Sigma(i) <sup>2</sup>	
Model A	43:			Mu(i) + e(ij) exp(lalpha + log(mean(i)) *	rho)
Model	R:	Yij Var{e(ij)}	=	Mu + e(i) Sigma <sup>2</sup>	

		Likelihoods of Int	erest
210	Model	Log(likelihood)	DF
AIC			
	A1	-50.11741	6
112.2348	A2	-44.44551	10
108.891	A3	-44.70264	7
103.4053	R	-60.31705	2
124.6341		-48.43541	5
106.8708	5	-40.43541	5

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)

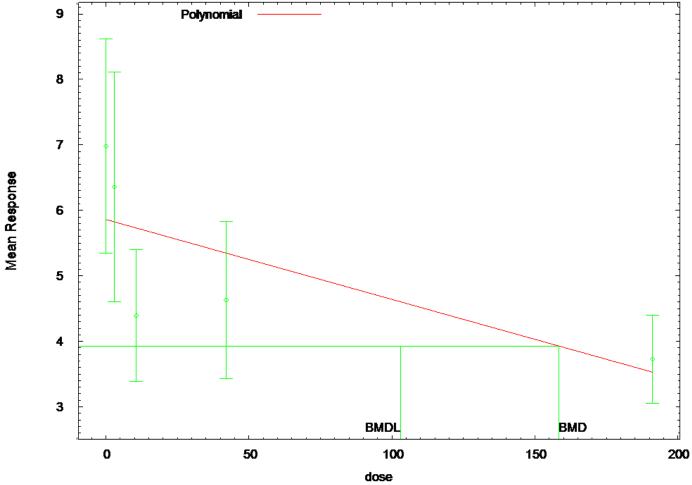
#### Tests of Interest

Test p-value	-2*log(Likelihood Ratio)	D. F.
Test 1 0.0001035	31.74	8

Test 2	11.34	4
0.02296		
Test 3	0.5142	3
0.9157		
Test 7a	7.466	2
0.02393		

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 7a is less than .1. Model 5 may not adequately describe the data; you may want to consider another model. Benchmark Dose Computations: Specified Effect = 1.000000 Risk Type = Estimated standard deviations from control Confidence Level = 0.950000

> BMD = 81.0527 BMDL = 2.80644



# Polynomial Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

12:50 07/09 2014

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_Lymphocyte\_Historical/Lymphocyte\_H istorical\_Normal-HLS 2001-Lymphocyte Count-Poly2CV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_Lymphocyte\_Historical/Lymphocyte\_H istorical\_Normal-HLS 2001-Lymphocyte Count-Poly2CV-1SD-5d.plt Wed Jul 09 12:50:23 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse 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 = 5Total number of records with missing values = 0Maximum 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 = 3.31423 Specified rho = 0 beta\_0 = 6.28333 beta\_1 = -0.0582096 beta\_2 = Ο Asymptotic Correlation Matrix of Parameter Estimates ( \*\*\* The model parameter(s) -rho -beta 2 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	8.6e-008	-1.1e-007
beta_0	8.6e-008	1	-0.56
beta_1	-1.1e-007	-0.56	1

## Parameter Estimates

			95.0%
Wald Confidence I	nterval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Con	f. Limit		
alpha	3.73207	0.761805	
2.23896	5.22518		
beta_0	5.86108	0.337527	
5.19954	6.52262		
beta_1	-0.0122035	0.00378272	-
0.0196175	-0.00478945		
beta_2	0	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 Scaled	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 1.83	10	6.98	5.86	2.29	1.93
2.9 0.875	10	6.36	5.83	2.45	1.93
10.6	9	4.39	5.73	1.31	1.93
42 -1.12	9	4.63	5.35	1.56	1.93
191.1 0.329	10	3.73	3.53	0.941	1.93

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<sup>2</sup>

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
Al	-50.117411	б	112.234822
A2	-44.445511	10	108.891023
A3	-50.117411	б	112.234822
fitted	-55.607114	3	117.214227
R	-60.317047	2	124.634093

### 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

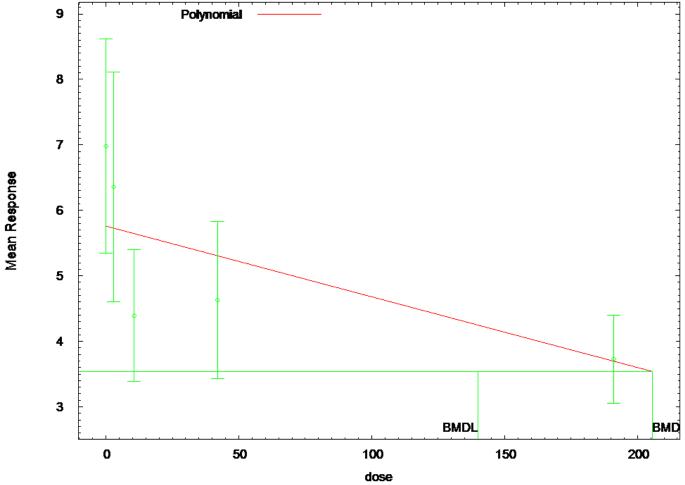
Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.7431	8	0.0001035
Test 2	11.3438	4	0.02296
Test 3	11.3438	4	0.02296
Test 4	10.9794	3	0.01184

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. Consider running a non-homogeneous variance model The p-value for Test 3 is less than .1. You may want to consider a different variance model 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 = 158.304

BMDL = 102.979



# Polynomial Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

12:50 07/09 2014

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_Lymphocyte\_Historical/Lymphocyte\_H istorical\_Normal-HLS 2001-Lymphocyte Count-Poly2NCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_Lymphocyte\_Historical/Lymphocyte\_H istorical\_Normal-HLS 2001-Lymphocyte Count-Poly2NCV-1SD-5d.plt Wed Jul 09 12:50:25 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse 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 = 5Total number of records with missing values = 0Maximum 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 = 1.19823 rho = 0  $beta_0 = 6.28333$  $beta_1 = -0.0582096$ beta\_2 = Ω Asymptotic Correlation Matrix of Parameter Estimates ( \*\*\* The model parameter(s) -beta\_2 have been estimated at a boundary point, or have

been specified by the user,

and do not appear in the correlation matrix )

	lalpha	rho	beta_0	beta_1
lalpha	1	-0.99	0.041	-0.047
rho	-0.99	1	-0.042	0.048
beta_0	0.041	-0.042	1	-0.82
beta_1	-0.047	0.048	-0.82	1

Parameter Estimates

				90.0%
Wald Cor	nfidence I	Interval		
7	/ariable	Estimate	Std. Err.	Lower Conf.
Limit	Upper Cor	nf. Limit		
	lalpha	-5.79277	1.89821	-
9.51319		-2.07234		
	rho	4.22044	1.15187	
1.96281		6.47807		
	beta_0	5.76177	0.371198	
5.03424		6.48931		
	beta_1	-0.0108106	0.00250705	-
0.015724	43	-0.00589687		
	beta_2	0	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 Scaled	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 1.73	10	6.98	5.76	2.29	2.22
2.9	10	6.36	5.73	2.45	2.2
0.906 10.6 -1.77	9	4.39	5.65	1.31	2.13
42 -1.09	9	4.63	5.31	1.56	1.87

191.1	10	3.73	3.7	0.941	0.871
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)} = 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
Al	-50.117411	6	112.234822
A2	-44.445511	10	108.891023
A3	-44.702636	7	103.405272
fitted	-50.932591	4	109.865181
R	-60.317047	2	124.634093

### Explanation of Tests

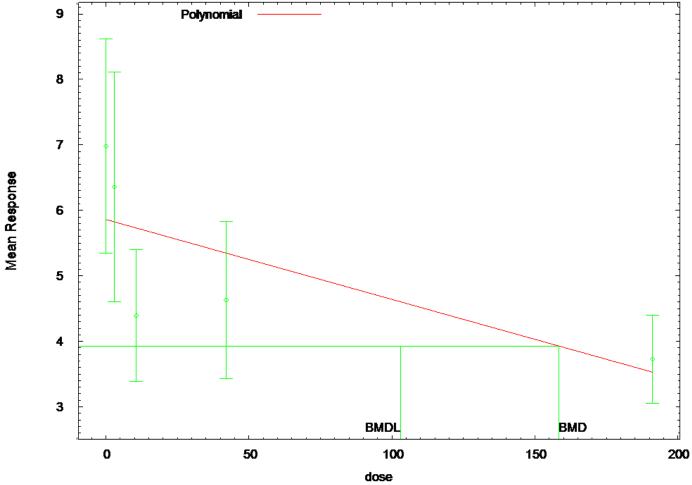
Test 1: Do responses and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A1 vs A2) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 4: Does the Model for the Mean Fit? (A3 vs. fitted) (Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

### Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.7431	8	0.0001035
Test 2	11.3438	4	0.02296
Test 3	0.514249	3	0.9157
Test 4	12.4599	3	0.005963

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 = Estimated standard deviations from the Risk Type control mean Confidence level = 0.95 BMD = 205.687

BMDL = 139.91



# Polynomial Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

12:50 07/09 2014

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_Lymphocyte\_Historical/Lymphocyte\_H istorical\_Normal-HLS 2001-Lymphocyte Count-Poly3CV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_Lymphocyte\_Historical/Lymphocyte\_H istorical\_Normal-HLS 2001-Lymphocyte Count-Poly3CV-1SD-5d.plt Wed Jul 09 12:50:23 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse 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 = 5Total number of records with missing values = 0Maximum 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 = 3.31423 Specified rho = 0 beta\_0 = 7.08617 beta\_1 = -0.327588 beta\_2 = 0  $beta_3 = -3.20797e - 005$ Asymptotic Correlation Matrix of Parameter Estimates ( \*\*\* The model parameter(s) -rho -beta\_2 -

beta\_3

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	-8.7e-009	2e-009
beta_0	-8.7e-009	1	-0.56
beta_1	2e-009	-0.56	1

Parameter Estimates

95.0%

Wald Confidence Interval					
Estimate	Std. Err.	Lower Conf.			
f. Limit					
3.73207	0.761806				
5.22518					
5.86108	0.337527				
6.52262					
-0.0122035	0.00378272	-			
-0.00478945					
0	NA				
0	NA				
	Estimate f. Limit 3.73207 5.22518 5.86108 6.52262 -0.0122035	Estimate Std. Err. f. Limit 3.73207 0.761806 5.22518 5.86108 0.337527 6.52262 -0.0122035 0.00378272 -0.00478945 0 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 Intere
--

Dose Scaled	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev		
0 1.83	10	6.98	5.86	2.29	1.93		
2.9	10	6.36	5.83	2.45	1.93		
10.6	9	4.39	5.73	1.31	1.93		
42 -1.12	9	4.63	5.35	1.56	1.93		
191.1	10	3.73	3.53	0.941	1.93		

Model Descriptions for likelihoods calculated

Var{e(i)} = Sigma^2

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)

## Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
Al	-50.117411	б	112.234822
A2	-44.445511	10	108.891023
A3	-50.117411	6	112.234822
fitted	-55.607114	3	117.214227
R	-60.317047	2	124.634093

### Explanation of Tests

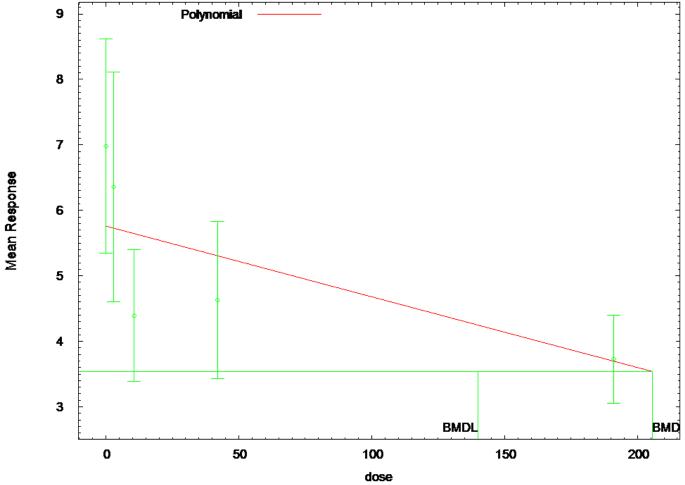
Test 1: Do responses and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A1 vs A2) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 4: Does the Model for the Mean Fit? (A3 vs. fitted) (Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

### Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.7431	8	0.0001035
Test 2	11.3438	4	0.02296
Test 3	11.3438	4	0.02296
Test 4	10.9794	3	0.01184

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. Consider running a non-homogeneous variance model The p-value for Test 3 is less than .1. You may want to consider а different variance model The p-value for Test 4 is less than .1. You may want to try a different model Benchmark Dose Computation Specified effect = 1 Estimated standard deviations from the Risk Type = control mean Confidence level = 0.95 158.304 BMD = BMDL = 102.979



# Polynomial Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

12:50 07/09 2014

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_Lymphocyte\_Historical/Lymphocyte\_H istorical\_Normal-HLS 2001-Lymphocyte Count-Poly3NCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_Lymphocyte\_Historical/Lymphocyte\_H istorical\_Normal-HLS 2001-Lymphocyte Count-Poly3NCV-1SD-5d.plt Wed Jul 09 12:50:24 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse 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 = 5Total number of records with missing values = 0Maximum 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 = 1.19823 rho = 0 beta\_0 = 7.08617 beta\_1 = -0.327588 beta\_2 = 0  $beta_3 = -3.20797e - 005$ Asymptotic Correlation Matrix of Parameter Estimates ( \*\*\* The model parameter(s) -beta\_2 -beta\_3

have been estimated at a boundary point, or have been specified by the user, and do not appear in the correlation matrix )

	lalpha	rho	beta_0	beta_1
lalpha	1	-0.99	0.041	-0.047
rho	-0.99	1	-0.042	0.048
beta_0	0.041	-0.042	1	-0.82
beta_1	-0.047	0.048	-0.82	1

Parameter Estimates

			95.0%
Wald Confidence I	nterval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Con	f. Limit		
lalpha	-5.79278	1.89821	-
9.5132	-2.07236		
rho	4.22045	1.15187	
1.96282	6.47807		
beta_0	5.76177	0.371198	
5.03424	6.48931		
beta_1	-0.0108106	0.00250705	-
0.0157243	-0.00589686		
beta_2	0	NA	
beta_3	0	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 Scaled	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 1.73	10	6.98	5.76	2.29	2.22
2.9	10	6.36	5.73	2.45	2.2
10.6 -1.77	9	4.39	5.65	1.31	2.13

42	9	4.63	5.31	1.56	1.87
-1.09 191.1 0.124	10	3.73	3.7	0.941	0.871
Model	Descriptic	ns for likeli	hoods calcul	ated	
Model		Yij = Mu(i) ij)} = Sigma^			
Model		Yij = Mu(i) ij)} = Sigma(			
M	Var{e( odel A3 use	Yij = Mu(i) ij)} = exp(la s any fixed v ed by the use	lpha + rho*l ariance para		

Model R: Yi = Mu + e(i) $Var{e(i)} = Sigma^2$ 

# Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
Al	-50.117411	б	112.234822
A2	-44.445511	10	108.891023
A3	-44.702636	7	103.405272
fitted	-50.932591	4	109.865181
R	-60.317047	2	124.634093

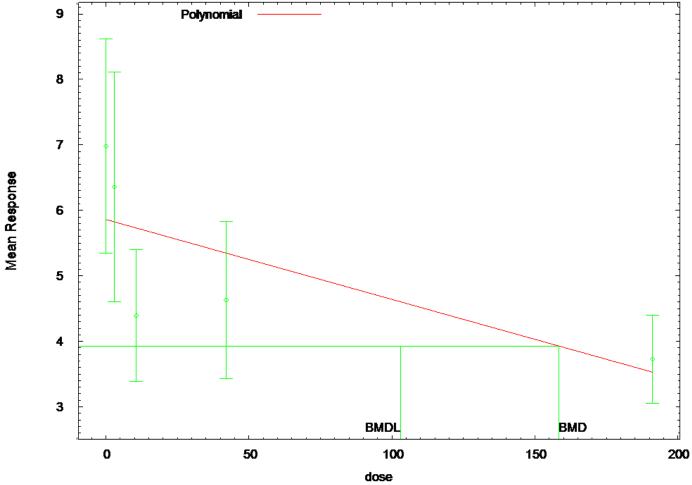
## Explanation of Tests

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	31.7431	8	0.0001035
Test 2	11.3438	4	0.02296
Test 3	0.514249	3	0.9157

12.4599 3 0.005963 Test 4 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 = Estimated standard deviations from the Risk Type control mean Confidence level = 0.95 BMD = 205.687 BMDL = 139.91



# Polynomial Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

12:50 07/09 2014

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_Lymphocyte\_Historical/Lymphocyte\_H istorical\_Normal-HLS 2001-Lymphocyte Count-Poly4CV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_Lymphocyte\_Historical/Lymphocyte\_H istorical\_Normal-HLS 2001-Lymphocyte Count-Poly4CV-1SD-5d.plt Wed Jul 09 12:50:23 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse 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 = 5Total number of records with missing values = 0Maximum 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 = 3.31423 Specified rho = 0 beta\_0 = 6.98 -0.192486 beta\_1 =  $beta_2 = -0.00831882$ beta 3 = 0  $beta_4 = -1.52335e-006$ 

Asymptotic Correlation Matrix of Parameter Estimates

beta_l	beta_0	alpha	
6.5e-008	8e-007	1	alpha
-0.56	1	8e-007	beta_0
1	-0.56	6.5e-008	beta_1

Parameter Estimates

#### 95.0%

Wald Con	ifidence :	Interval		
V	/ariable	Estimate	Std. Err.	Lower Conf.
Limit	Upper Con	nf. Limit		
	alpha	3.73207	0.761806	
2.23896		5.22518		
	beta_0	5.86108	0.337527	
5.19954		6.52262		
	beta_1	-0.0122035	0.00378272	-
0.019617	75	-0.00478945		
	beta_2	-0	NA	
	beta_3	0	NA	
	beta_4	-7.39728e-104	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 Scaled	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 1.83	10	6.98	5.86	2.29	1.93
2.9 0.875	10	6.36	5.83	2.45	1.93
10.6	9	4.39	5.73	1.31	1.93
42	9	4.63	5.35	1.56	1.93

-1.12					
191.1	10	3.73	3.53	0.941	1.93
0.329					

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<sup>2</sup>

# Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
Al	-50.117411	6	112.234822
A2	-44.445511	10	108.891023
A3	-50.117411	б	112.234822
fitted	-55.607114	3	117.214227
R	-60.317047	2	124.634093

### Explanation of Tests

### Tests of Interest

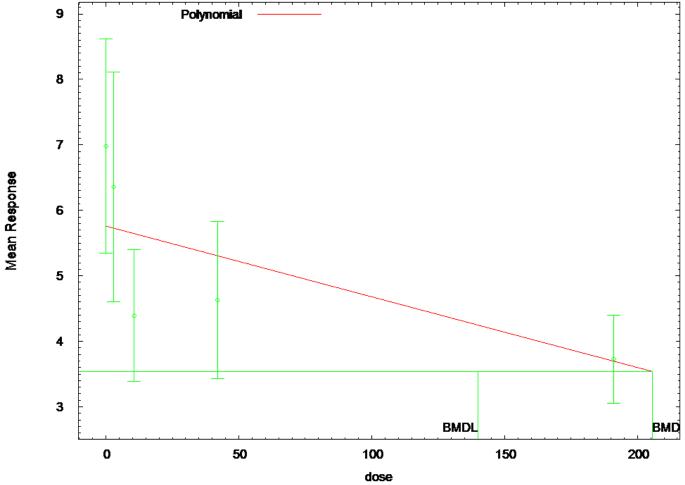
Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.7431	8	0.0001035
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Test 3	11.3438	4	0.02296
Test 4	10.9794	3	0.01184

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. Consider running a non-homogeneous variance model The p-value for Test 3 is less than .1. You may want to consider а different variance model The p-value for Test 4 is less than .1. You may want to try a different model Benchmark Dose Computation Specified effect = 1 = Estimated standard deviations from the control mean Confidence level = 0.95

Risk Type

BMD = 158.304

BMDL = 102.979



# Polynomial Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

12:50 07/09 2014

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_Lymphocyte\_Historical/Lymphocyte\_H istorical\_Normal-HLS 2001-Lymphocyte Count-Poly4NCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_Lymphocyte\_Historical/Lymphocyte\_H istorical\_Normal-HLS 2001-Lymphocyte Count-Poly4NCV-1SD-5d.plt Wed Jul 09 12:50:24 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse 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 = 5Total number of records with missing values = 0Maximum 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 = 1.19823 rho = 0 beta\_0 = 6.98 -0.192486 beta\_1 =  $beta_2 = -0.00831882$ beta\_3 = 0  $beta_4 = -1.52335e-006$ Asymptotic Correlation Matrix of Parameter Estimates

lalpha	1	-0.99	0.041	-0.047
rho	-0.99	1	-0.042	0.048
beta_0	0.041	-0.042	1	-0.82
beta_1	-0.047	0.048	-0.82	1

#### Parameter Estimates

### 95.0%

				95.06
Wald Con	fidence I	Interval		
V	'ariable	Estimate	Std. Err.	Lower Conf.
Limit	Upper Con	nf. Limit		
	lalpha	-5.79277	1.89821	-
9.51319		-2.07234		
	rho	4.22044	1.15187	
1.96281		6.47807		
	beta_0	5.76177	0.371198	
5.03424		6.48931		
	beta_1	-0.0108106	0.00250705	-
0.015724	:3	-0.00589687		
	beta_2	0	NA	
	beta_3	0	NA	
	beta_4	0	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 Scaled F	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 1.73	10	6.98	5.76	2.29	2.22
2.9	10	6.36	5.73	2.45	2.2

0.906 10.6	9	4.39	5.65	1.31	2.13
-1.77 42 -1.09	9	4.63	5.31	1.56	1.87
191.1 0.124	10	3.73	3.7	0.941	0.871

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
Al	-50.117411	б	112.234822
A2	-44.445511	10	108.891023
A3	-44.702636	7	103.405272
fitted	-50.932591	4	109.865181
R	-60.317047	2	124.634093

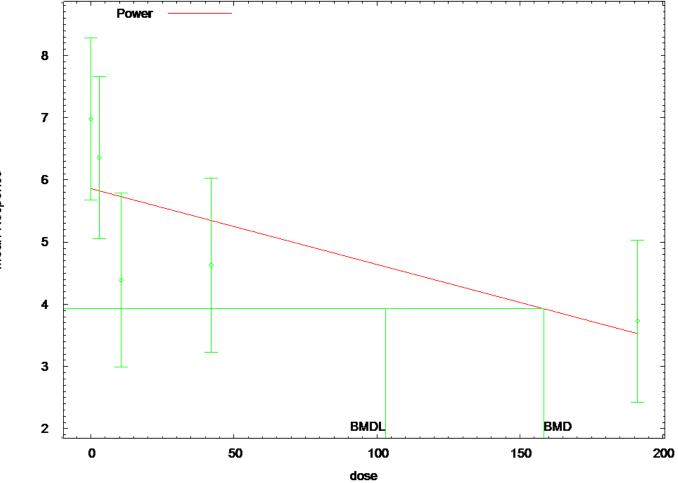
### Explanation of Tests

### Tests of Interest

Test	-2*log(I	ikelihood	Ratio)	Test df	p-value
------	----------	-----------	--------	---------	---------

3

31.7431 11.3438 8 4 Test 1 0.0001035 Test 2 0.02296 Test 3 0.514249 3 0.9157 Test 4 12.4599 3 0.005963 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 = 205.687 BMDL = 139.91



Mean Response

10:03 06/22 2014

\_\_\_\_\_ === Power Model. (Version: 2.18; Date: 05/19/2014) Input Data File: C:/Users/dmayfield/Desktop/Ln/Lymphocyte\_Historical\_Normal-HLS 2001-Lymphocyte Count-PowerCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Ln/Lymphocyte Historical Normal-HLS 2001-Lymphocyte Count-PowerCV-1SD-5d.plt Sun Jun 22 10:03:59 2014 === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = control + slope \* dose^power Dependent variable = MeanResponse 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 = 5Total 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 = 3.31423 rho = 0 control = 3.73 slope = 2.97763 power = -0.394692 Specified 0 3.73 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	-5.8e-008	8.1e-008
control	-5.8e-008	1	-0.56
slope	8.1e-008	-0.56	1

# Parameter Estimates

			95.0%
Wald Confidence	Interval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Co	onf. Limit		
alpha	3.73207	0.761806	
2.23896	5.22518		
control	5.86108	0.337527	
5.19954	6.52262		
slope	-0.0122034	0.00378272	-
0.0196175	-0.00478945		
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 Scaled	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 1.83	10	6.98	5.86	2.29	1.93
2.9	10	6.36	5.83	2.45	1.93
10.6	9	4.39	5.73	1.31	1.93
42 -1.12	9	4.63	5.35	1.56	1.93
191.1 0.329	10	3.73	3.53	0.941	1.93

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<sup>2</sup>

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
Al	-50.117411	6	112.234822
A2	-44.445511	10	108.891023
A3	-50.117411	6	112.234822
fitted	-55.607114	3	117.214227
R	-60.317047	2	124.634093

#### 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

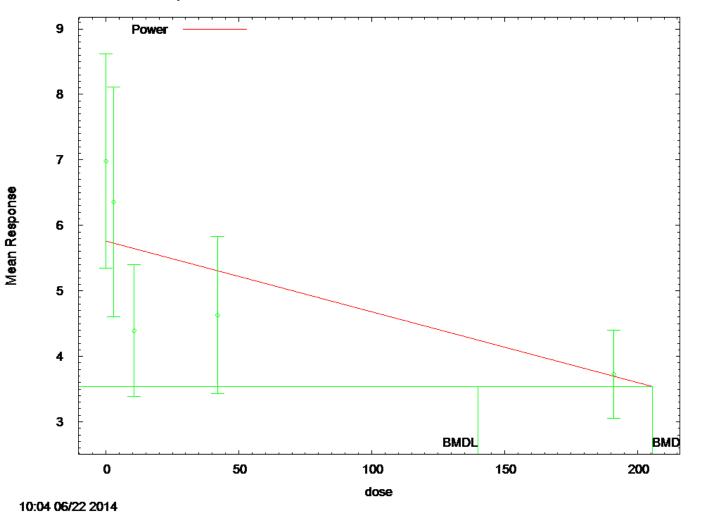
Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.7431	8	0.0001035
Test 2	11.3438	4	0.02296
Test 3	11.3438	4	0.02296
Test 4	10.9794	3	0.01184

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. Consider running a non-homogeneous variance model The p-value for Test 3 is less than .1. You may want to consider a different variance model 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 = 158.304

BMDL = 102.979



# Power Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

\_\_\_\_\_\_ === Power Model. (Version: 2.18; Date: 05/19/2014) Input Data File: C:/Users/dmayfield/Desktop/Ln/Lymphocyte\_Historical\_Normal-HLS 2001-Lymphocyte Count-PowerNCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Ln/Lymphocyte Historical Normal-HLS 2001-Lymphocyte Count-PowerNCV-1SD-5d.plt Sun Jun 22 10:04:00 2014 === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = control + slope \* dose^power Dependent variable = MeanResponse Independent variable = Dose The power is restricted to be greater than or equal to 1 The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) \* rho) Total number of dose groups = 5Total 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 = 1.19823 rho = rho = 0 control = 3.73 slope = 2.97763 power = -0.394692 0 Asymptotic Correlation Matrix of Parameter Estimates ( \*\*\* The model parameter(s) -power have been estimated at a boundary point, or have been specified by the user,

en specified		appear in th	e correlation	n matrix )
	lalpha	rho	control	slope
lalpha	1	-0.99	0.41	-0.64
rho	-0.99	1	-0.48	0.67
control	0.41	-0.48	1	-0.82
slope	-0.64	0.67	-0.82	1

Parameter Estimates

				95.06	
Wald Confidence Interval					
Ţ	/ariable	Estimate	Std. Err.	Lower Conf.	
Limit	Upper Co	nf. Limit			
	lalpha	-5.79276	2.54456	-	
10.78		-0.805511			
	rho	4.22044	1.57816		
1.12729		7.31358			
	control	5.76177	0.372822		
5.03106		6.49249			
	slope	-0.0108106	0.00250309	-	
0.015716	56 -	-0.00590465			
	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 Scaled	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
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42 -1.09	9	4.63	5.31	1.56	1.87

191.1	10	3.73	3.7	0.941	0.871
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)} = 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	-50.117411	6	112.234822
A2	-44.445511	10	108.891023
A3	-44.702636	7	103.405272
fitted	-50.932591	4	109.865181
R	-60.317047	2	124.634093

## Explanation of Tests

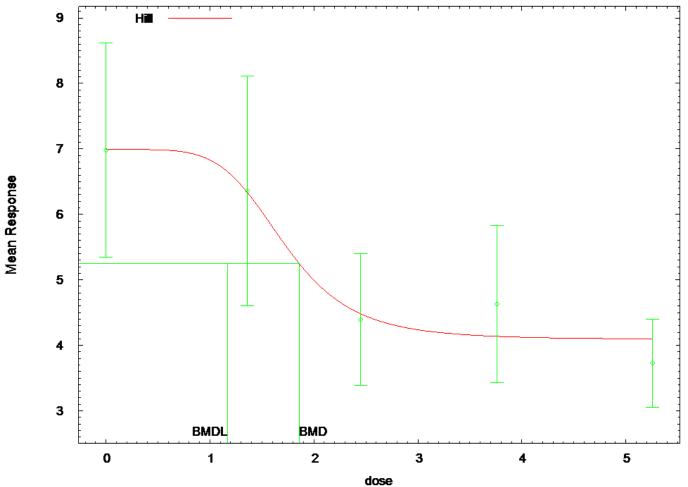
Test 1: Do responses and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A1 vs A2) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 4: Does the Model for the Mean Fit? (A3 vs. fitted) (Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

### Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.7431	8	0.0001035
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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 Estimated standard deviations from the Risk Type = control mean Confidence level = 0.95 BMD = 205.687BMDL = 139.91

BMDS Model Results for Lymphocyte Count (Log-transformed Doses, Historical Controls)



10:10 06/22 2014

\_\_\_\_\_\_ === Hill Model. (Version: 2.17; Date: 01/28/2013) Input Data File: C:/Users/dmayfield/Desktop/Ln/Lymphocyte\_Historical\_LN-HLS 2001-Lymphocyte Count-HillCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Ln/Lymphocyte Historical LN-HLS 2001-Lymphocyte Count-HillCV-1SD-5d.plt Sun Jun 22 10:10:17 2014 \_\_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is:  $Y[dose] = intercept + v*dose^n/(k^n + dose^n)$ Dependent variable = MeanResponse 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 = 5Total 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 = 3.31423 Specified rho = 0 rno = intercept = 6.98 -3.25 v = n = 3.73558 k = 1.91707 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,

k	alpha	intercept	v	n
alpha -1.4e-007	1	4.7e-008	6.8e-008	1.5e-007
intercept -0.35	4.7e-008	1	-0.76	-0.27
v -0.15	6.8e-008	-0.76	1	0.63

n 1.5e-007 -0.27 0.63 1

1

k -1.4e-007 -0.35 -0.15 -0.46

and do not appear in the correlation matrix )

Parameter Estimates

				95.0%
Wald Conf:	idence Int	erval		
Vai	riable	Estimate	Std. Err.	Lower Conf.
Limit Up	oper Conf.	Limit		
	alpha	3.04453	0.621463	
1.82649		4.26258		
inte	ercept	6.99164	0.54938	
5.91488		8.06841		
	v	-2.90088	0.78628	-
4.44196		-1.3598		
	n	5.25235	5.37316	-
5.27884		15.7836		
	k	1.72188	0.447295	
0.8452		2.59856		

Table of Data and Estimated Values of Interest

Dose Scaled R		Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 -0.0211	10	6.98	6.99	2.29	1.74

1.361	10	6.36	6.34	2.45	1.74
0.0395 2.451	9	4.39	4.48	1.31	1.74
-0.161	9	4.39	4.40	1.31	1./4
3.761	9	4.63	4.14	1.56	1.74
0.846					
5.258	10	3.73	4.1	0.941	1.74
-0.669					

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
Al	-50.117411	6	112.234822
A2	-44.445511	10	108.891023
A3	-50.117411	6	112.234822
fitted	-50.720349	5	111.440698
R	-60.317047	2	124.634093

# Explanation of Tests

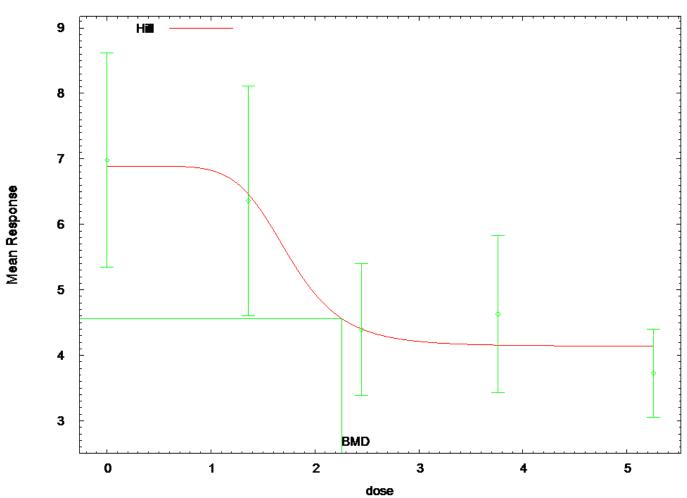
Test 1:	Do responses and/or variances differ among Dose levels?
	(A2 vs. R)
Test 2:	Are Variances Homogeneous? (A1 vs A2)
Test 3:	Are variances adequately modeled? (A2 vs. A3)
Test 4:	Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:	When rho=0 the results of Test 3 and Test 2 will be the
same.)	

## Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
------	--------------------------	---------	---------

Test 131.743180.0001035Test 211.343840.02296Test 311.343840.02296Test 41.2058810.2722

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. Consider running a non-homogeneous variance model The p-value for Test 3 is less than .1. You may want to consider а different variance model 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 = 1.86228 BMDL = 1.17035



10:10 06/22 2014

Hill Model

\_\_\_\_\_\_ === Hill Model. (Version: 2.17; Date: 01/28/2013) Input Data File: C:/Users/dmayfield/Desktop/Ln/Lymphocyte\_Historical\_LN-HLS 2001-Lymphocyte Count-HillNCV-ISD-5d. (d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Ln/Lymphocyte Historical LN-HLS 2001-Lymphocyte Count-HillNCV-1SD-5d.plt Sun Jun 22 10:10:18 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is:  $Y[dose] = intercept + v*dose^n/(k^n + dose^n)$ Dependent variable = MeanResponse Independent variable = Dose Power parameter restricted to be greater than 1 The variance is to be modeled as Var(i) = exp(lalpha + rho \* ln(mean(i))) Total number of dose groups = 5Total 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 = 1.19823 rho = 0 intercept = 6.98 -3.25 v = 3.73558 n = k = 1.91707 Asymptotic Correlation Matrix of Parameter Estimates intercept lalpha rho v

n	k			
lalph -0.09	a 1 -0.032	-0.99	0.33	-0.4
rh 0.09	.o -0.99 0.033	1	-0.37	0.42
intercep -0.44	t 0.33 -0.43	-0.37	1	-0.92
0.62	v -0.4 0.23	0.42	-0.92	1
	n -0.09 -0.05	0.09	-0.44	0.62
-0.05	k -0.032 1	0.033	-0.43	0.23

Parameter Estimates

				95.0%
Wald Con:	fidence In	nterval		
Va	ariable	Estimate	Std. Err.	Lower Conf.
Limit 1	Upper Cont	E. Limit		
	lalpha	-3.0691	1.70987	-
6.42039		0.282182		
	rho	2.46856	1.04176	
0.426739		4.51038		
in	tercept	6.89077	0.705601	
5.50782		8.27372		
	v	-2.75193	0.840902	-
4.40007		-1.10379		
	n	6.70247	6.94921	-
6.91773		20.3227		
	k	1.74805	0.392584	
0.978601		2.5175		

Table of Data and Estimated Values of Interest

Dose Scaled R		Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 0.121	10	6.98	6.89	2.29	2.33

2

1.361 -0.143	10	6.36	6.46	2.45	2.15
2.451	9	4.39	4.4	1.31	1.34
3.761	9	4.63	4.15	1.56	1.25
5.258 -1.04	10	3.73	4.14	0.941	1.25

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
Al	-50.117411	6	112.234822
A2	-44.445511	10	108.891023
A3	-44.702636	7	103.405272
fitted	-46.998934	6	105.997868
R	-60.317047	2	124.634093

# 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.)	

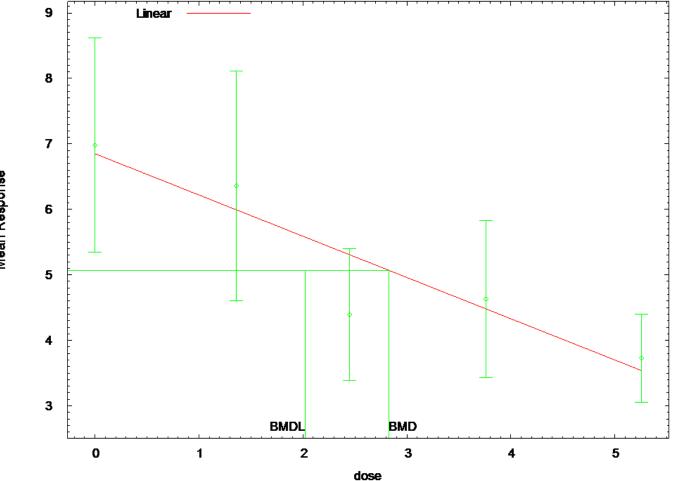
## Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
------	--------------------------	---------	---------

Test 131.743180.0001035Test 211.343840.02296Test 30.51424930.9157Test 44.592610.03211

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 = Estimated standard deviations from the Risk Type control mean Confidence level = 0.95 BMD = 2.26002

BMDL computation failed.



Mean Response

12:48 07/09 2014

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_Lymphocyte\_Historical\_Ln/Lymphocyt e\_Historical\_LN-HLS 2001-Lymphocyte Count-LinearCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_Lymphocyte\_Historical\_Ln/Lymphocyt e\_Historical\_LN-HLS 2001-Lymphocyte Count-LinearCV-1SD-5d.plt Wed Jul 09 12:48:07 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse Independent variable = Dose rho is set to 0 Signs of the polynomial coefficients are not restricted A constant variance model is fit Total number of dose groups = 5Total number of records with missing values = 0Maximum 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 = 3.31423 rho = 0 beta\_0 = 6.83073 beta\_1 = -0.628452 0 Specified 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  $\)$ 

beta_	beta_0	alpha	
-8.6e-01	2.2e-008	1	alpha
-0.8	1	2.2e-008	beta_0
	-0.81	-8.6e-010	beta_1

## Parameter Estimates

				95.0%
Wald Cont	fidence In	terval		
Va	ariable	Estimate	Std. Err.	Lower Conf.
Limit (	Upper Conf	. Limit		
	alpha	3.16984	0.64704	
1.90166		4.43801		
	beta_0	6.85042	0.435612	
5.99664		7.70421		
	beta_1	-0.630151	0.138278	_
0.901171		-0.359132		

Table of Data and Estimated Values of Interest

Dose Scaled	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0	10	6.98	6.85	2.29	1.78
0.23 1.361	10	6.36	5.99	2.45	1.78
0.652 2.451	9	4.39	5.31	1.31	1.78
-1.54 3.761	9	4.63	4.48	1.56	1.78
0.252 5.258 0.343	10	3.73	3.54	0.941	1.78

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
Al	-50.117411	6	112.234822
A2	-44.445511	10	108.891023
A3	-50.117411	6	112.234822
fitted	-51.688316	3	109.376631
R	-60.317047	2	124.634093

## 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	31.7431	8	0.0001035
Test 2	11.3438	4	0.02296
Test 3	11.3438	4	0.02296
Test 4	3.14181	3	0.3703

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. Consider running a non-homogeneous variance model

The p-value for Test 3 is less than .1. You may want to consider a

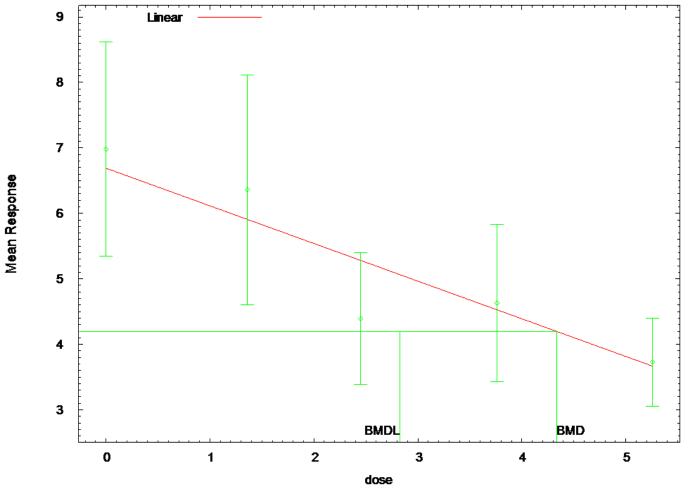
different variance model

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 = 2.82536

BMDL = 2.0197



Linear Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

12:48 07/09 2014

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_Lymphocyte\_Historical\_Ln/Lymphocyt e\_Historical\_LN-HLS 2001-Lymphocyte Count-LinearNCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_Lymphocyte\_Historical\_Ln/Lymphocyt e\_Historical\_LN-HLS 2001-Lymphocyte Count-LinearNCV-1SD-5d.plt Wed Jul 09 12:48:08 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse Independent variable = Dose Signs of the polynomial coefficients are not restricted The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) \* rho) Total number of dose groups = 5Total number of records with missing values = 0Maximum 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 = 1.19823 rho = 0 beta\_0 = 6.83073 beta\_1 = -0.628452 Asymptotic Correlation Matrix of Parameter Estimates beta\_0 lalpha rho beta 1 -0.99 0.16 -0.19 lalpha 1

rho	-0.99	1	-0.16	0.19
beta_0	0.16	-0.16	1	-0.91
beta_1	-0.19	0.19	-0.91	1

Parameter Estimates

95.0%

Wald Con	fidence I	nterval		
V	ariable	Estimate	Std. Err.	Lower Conf.
Limit	Upper Con:	f. Limit		
	lalpha	-4.22724	1.68476	-
7.5293		-0.925178		
	rho	3.18577	1.02462	
1.17755		5.19399		
	beta_0	6.68829	0.512021	
5.68475		7.69183		
	beta_1	-0.574737	0.123483	_
0.816759		-0.332715		

Table of Data and Estimated Values of Interest

Dose Scaled	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 0.37	10	6.98	6.69	2.29	2.49
1.361 0.702	10	6.36	5.91	2.45	2.04
2.451 -1.56	9	4.39	5.28	1.31	1.71
3.761	9	4.63	4.53	1.56	1.34
5.258 0.21	10	3.73	3.67	0.941	0.957

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<sup>2</sup>

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
Al	-50.117411	6	112.234822
A2	-44.445511	10	108.891023
A3	-44.702636	7	103.405272
fitted	-47.300760	4	102.601521
R	-60.317047	2	124.634093

#### Explanation of Tests

#### Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.7431	8	0.0001035
Test 2	11.3438	4	0.02296
Test 3	0.514249	3	0.9157
Test 4	5.19625	3	0.158

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

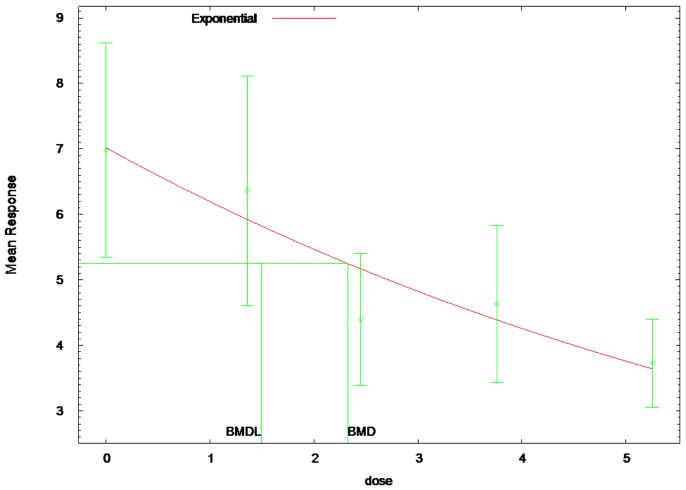
to be appropriate here

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 = 4.33739

BMDL = 2.82692



# Exponential Model 2, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Level for BMDL

10:10 06/22 2014

```
______
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Ln/Lymphocyte_Historical_LN-HLS 2001-
Lymphocyte Count-ExpCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sun Jun 22 10:10:17 2014
______
===
BMDS Model Run
~~~~
  The form of the response function by Model:
                Y[dose] = a * exp\{sign * b * dose\}
     Model 2:
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
                Y[dose] = a * [c-(c-1) * exp{-b * dose}]
     Model 4:
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  rho is set to 0.
  A constant variance model is fit.
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 2
lnalpha	1.08823
rho(S)	0
a	3.75105
b	0.120756
С	0
d	1

(S) = Specified

#### Parameter Estimates

Variable	Model 2
lnalpha	1.14279
rho	0
a	7.01811
b	0.12488
C	0
d	1

# Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	10	6.98	2.289
1.361	10	6.36	2.452
2.451	9	4.39	1.308
3.761	9	4.63	1.564
5.258	10	3.73	0.941

## Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	7.018	1.771	-0.06806
1.361	5.921	1.771	0.7837
2.451	5.168	1.771	-1.317
3.761	4.388	1.771	0.4104
5.258	3.64	1.771	0.1614

Other models for which likelihoods are calculated:

Model A1: Yij = Mu(i) + e(ij) Var{e(ij)} = Sigma^2

Model A2:	Yij = Var{e(ij)} =	Mu(i) + e(ij) Sigma(i)^2
Model A3:	Yij = Var{e(ij)} =	Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R:	Yij = Var{e(ij)} =	Mu + e(i) Sigma^2

Likelihoods of Interest

AIC	Model	Log(likelihood)	DF
ALC			
	A1	-50.11741	6
112.2348	A2	-44.44551	10
108.891	A3	-50.11741	6
112.2348	R	-60.31705	2
124.6341	2	-51.427	3
108.854			

Additive constant for all log-likelihoods = -44.11. This constant added to the above values gives the log-likelihood including the term that does not

depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A2 vs. A1) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 4: Does Model 2 fit the data? (A3 vs. 2)

Tests of Interest

Test p-value	-2*log(Likelihood Ratio)	D. F.
Test 1	31.74	8

0.0001035			
Test	2	11.34	4
0.02296			
Test	3	11.34	4
0.02296			
Test	4	2.619	3
0.4541			

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. Consider running a non-homogeneous variance model.

The p-value for Test 3 is less than .1. You may want to consider a different variance model.

The p-value for Test 4 is greater than .1. Model 2 seems to adequately describe the data.

Benchmark Dose Computations:

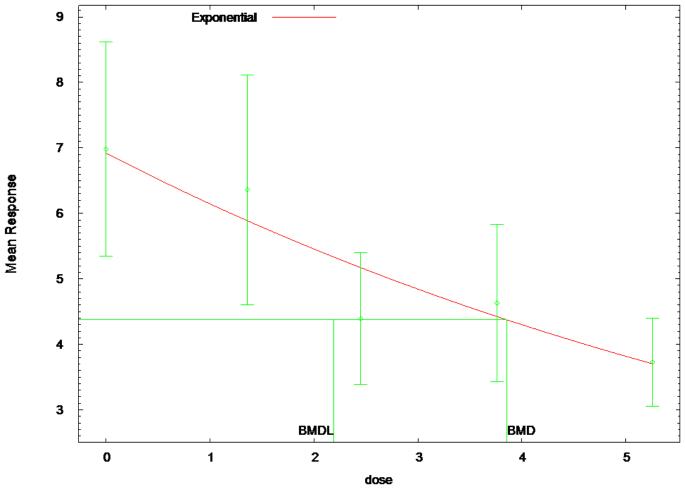
Specified Effect = 1.000000

Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

BMD = 2.32836

BMDL = 1.49734



# Exponential Model 2, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Level for BMDL

10:10 06/22 2014

```
______
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Ln/Lymphocyte_Historical_LN-HLS 2001-
Lymphocyte Count-ExpNCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sun Jun 22 10:10:18 2014
______
===
BMDS Model Run
~~~~
  The form of the response function by Model:
                Y[dose] = a * exp\{sign * b * dose\}
     Model 2:
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
                Y[dose] = a * [c-(c-1) * exp{-b * dose}]
     Model 4:
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  The variance is to be modeled as Var(i) = exp(lalpha + log
(mean(i)) * rho)
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 2
lnalpha	-3.80501
rho	2.92874
a	3.75105
b	0.120756
C	0
d	1

## Parameter Estimates

Variable	Model 2
lnalpha	-3.90258
rho	2.98432
a	6.92193
b	0.118985
C	0
d	1

# Table of Stats From Input Data

Dose	Ν	Obs Mean	Obs Std Dev
0	10	6.98	2.289
1.361	10	6.36	2.452
2.451	9	4.39	1.308
3.761	9	4.63	1.564
5.258	10	3.73	0.941

## Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	6.922	2.549	0.07205
1.361	5.887	2.002	0.7472
2.451	5.171	1.649	-1.42
3.761	4.425	1.307	0.4713
5.258	3.703	1.002	0.08605

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)

		<pre>Var{e(ij)}</pre>	=	Sigma(i) <sup>2</sup>
Model A	3:	Yij Var{e(ij)}	=	Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model :	R:	Yij Var{e(ij)}	=	Mu + e(i) Sigma <sup>2</sup>

		Likelihoods of Int	erest
210	Model	Log(likelihood)	DF
AIC			
	A1	-50.11741	6
112.2348	A2	-44.44551	10
108.891	A3	-44.70264	7
103.4053	R	-60.31705	2
124.6341	2	-47.23015	4
102.4603	2	-47.23013	4

Additive constant for all log-likelihoods = -44.11. This constant added to the above values gives the log-likelihood including the term that does not

depend on the model parameters.

### Explanation of Tests

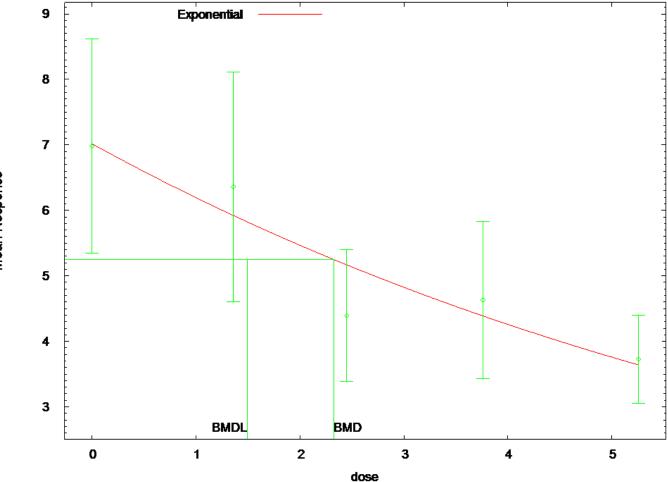
Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A2 vs. A1) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 4: Does Model 2 fit the data? (A3 vs. 2)

### Tests of Interest

Test p-value		-2*log(Likelihood Ratio)	D. F.
Test	1	31.74	8
0.0001035			
Test	2	11.34	4

0.02		0 5140	2	
Test 3 0.9157		0.5142	3	
0.91	Test 4	5.055	3	
0.16	78			
be a	The p-value for Test 1 is les	ss than .05. The	re appears to	
200	difference between response a levels, it seems 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.			
B	enchmark Dose Computations:			
Specified Effect = 1.000000				
Risk Type = Estimated standard deviations from control				
	Confidence Level = 0.950000			
	BMD = 3.859	924		

BMDL = 2.19242



Mean Response

10:10 06/22 2014

```
______
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Ln/Lymphocyte_Historical_LN-HLS 2001-
Lymphocyte Count-ExpCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sun Jun 22 10:10:17 2014
______
===
BMDS Model Run
~~~~
  The form of the response function by Model:
                Y[dose] = a * exp\{sign * b * dose\}
     Model 2:
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
                Y[dose] = a * [c-(c-1) * exp{-b * dose}]
     Model 4:
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  rho is set to 0.
  A constant variance model is fit.
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 3
lnalpha	1.08823
rho(S)	0
a	3.75105
b	0.120756
С	0
d	1

(S) = Specified

#### Parameter Estimates

Variable	Model 3
lnalpha	1.14279
rho	0
a	7.01811
b	0.12488
C	0
d	1

# Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	10	6.98	2.289
1.361	10	6.36	2.452
2.451	9	4.39	1.308
3.761	9	4.63	1.564
5.258	10	3.73	0.941

## Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	7.018	1.771	-0.06806
1.361	5.921	1.771	0.7837
2.451	5.168	1.771	-1.317
3.761	4.388	1.771	0.4104
5.258	3.64	1.771	0.1614

Other models for which likelihoods are calculated:

Model A1: Yij = Mu(i) + e(ij) Var{e(ij)} = Sigma^2

Model A2:	Yij = Var{e(ij)} =	Mu(i) + e(ij) Sigma(i)^2
Model A3:	Yij = Var{e(ij)} =	Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R:	Yij = Var{e(ij)} =	Mu + e(i) Sigma^2

Likelihoods of Interest

AIC	Model	Log(likelihood)	DF
ALC			
110 0240	Al	-50.11741	6
112.2348	A2	-44.44551	10
108.891	A3	-50.11741	6
112.2348	R	-60.31705	2
124.6341	3	-51.427	3
108.854			

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 5a: Does Model 3 fit the data? (A3 vs 3)

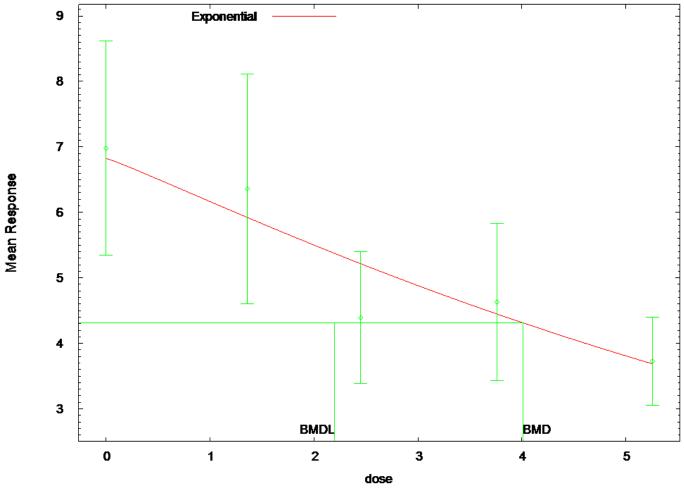
Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.
p-value		

Test	1	31.74	8
0.0001035			
Test	2	11.34	4
0.02296			
Test	3	11.34	4
0.02296			
Test !	5a	2.619	3
0.4541			

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. Consider running a non-homogeneous variance model. The p-value for Test 3 is less than .1. You may want to consider a different variance model. The p-value for Test 5a is greater than .1. Model 3 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 = 2.32836

BMDL = 1.49734



# Exponential Model 3, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Level for BMDL

10:10 06/22 2014

```
______
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Ln/Lymphocyte_Historical_LN-HLS 2001-
Lymphocyte Count-ExpNCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sun Jun 22 10:10:18 2014
______
===
BMDS Model Run
~~~~
  The form of the response function by Model:
                Y[dose] = a * exp\{sign * b * dose\}
     Model 2:
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
                Y[dose] = a * [c-(c-1) * exp{-b * dose}]
     Model 4:
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  The variance is to be modeled as Var(i) = exp(lalpha + log
(mean(i)) * rho)
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 3
lnalpha	-3.80501
rho	2.92874
a	3.75105
b	0.120756
C	0
d	1

# Parameter Estimates

Variable	Model 3
lnalpha	-3.99515
rho	3.04054
a	6.82645
b	0.121704
С	0
d	1.08473

# Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	10	6.98	2.289
1.361	10	6.36	2.452
2.451	9	4.39	1.308
3.761	9	4.63	1.564
5.258	10	3.73	0.941

## Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	6.826	2.516	0.193
1.361	5.921	2.027	0.6844
2.451	5.215	1.671	-1.482
3.761	4.448	1.312	0.4168
5.258	3.686	0.9859	0.14

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)

		<pre>Var{e(ij)}</pre>	=	Sigma(i)^2	
Model A	43:			Mu(i) + e(ij) exp(lalpha + log(mean(i)) *	rho)
Model	R:	Yij Var{e(ij)}	=	Mu + e(i) Sigma <sup>2</sup>	

		Likelihoods of Int	erest
210	Model	Log(likelihood)	DF
AIC			
	A1	-50.11741	6
112.2348	A2	-44.44551	10
108.891	A3	-44.70264	7
103.4053	R	-60.31705	2
124.6341	3	-47.20826	5
104.4165	2	····	J

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 5a: Does Model 3 fit the data? (A3 vs 3)

#### Tests of Interest

Test p-value	-2*log(Likelihood Ratio)	D. F.
Test 1 0.0001035	31.74	8

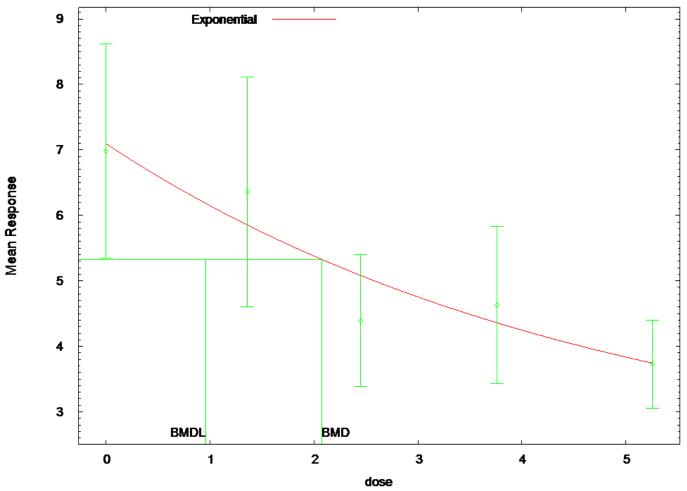
Test 2	11.34	4
0.02296		
Test 3	0.5142	3
0.9157		
Test 5a	5.011	2
0.08162		

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 5a is less than .1. Model 3 may not adequately describe the data; you may want to consider another model. Benchmark Dose Computations: Specified Effect = 1.000000

Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

BMD = 4.01364 BMDL = 2.20133



# Exponential Model 4, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Level for BMDL

10:10 06/22 2014

```
______
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Ln/Lymphocyte_Historical_LN-HLS 2001-
Lymphocyte Count-ExpCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sun Jun 22 10:10:17 2014
______
===
BMDS Model Run
~~~~
  The form of the response function by Model:
                Y[dose] = a * exp\{sign * b * dose\}
     Model 2:
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
                Y[dose] = a * [c-(c-1) * exp{-b * dose}]
     Model 4:
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  rho is set to 0.
  A constant variance model is fit.
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 4
lnalpha	1.08823
rho(S)	0
a	7.329
b	0.208885
С	0.254469
d	1

(S) = Specified

#### Parameter Estimates

Variable	Model 4
lnalpha	1.14069
rho	0
a	7.09555
b	0.208122
C	0.289708
d	1

# Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	10	6.98	2.289
1.361	10	6.36	2.452
2.451	9	4.39	1.308
3.761	9	4.63	1.564
5.258	10	3.73	0.941

## Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	7.096	1.769	-0.2066
1.361	5.852	1.769	0.9075
2.451	5.082	1.769	-1.173
3.761	4.36	1.769	0.4586
5.258	3.743	1.769	-0.02299

Other models for which likelihoods are calculated:

Model A1: Yij = Mu(i) + e(ij) Var{e(ij)} = Sigma^2

Model A2:	Yij = Var{e(ij)} =	Mu(i) + e(ij) Sigma(i)^2
Model A3:		Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R:	Yij = Var{e(ij)} =	

Likelihoods of Interest

AIC	Model	Log(likelihood)	DF
ALC			
	A1	-50.11741	6
112.2348	A2	-44.44551	10
108.891	A3	-50.11741	6
112.2348	R	-60.31705	2
124.6341	4	-51.37665	4
110.7533			

Additive constant for all log-likelihoods = -44.11. This constant added to the above values gives the log-likelihood including the term that does not

depend on the model parameters.

# Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A2 vs. A1) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 6a: Does Model 4 fit the data? (A3 vs 4)

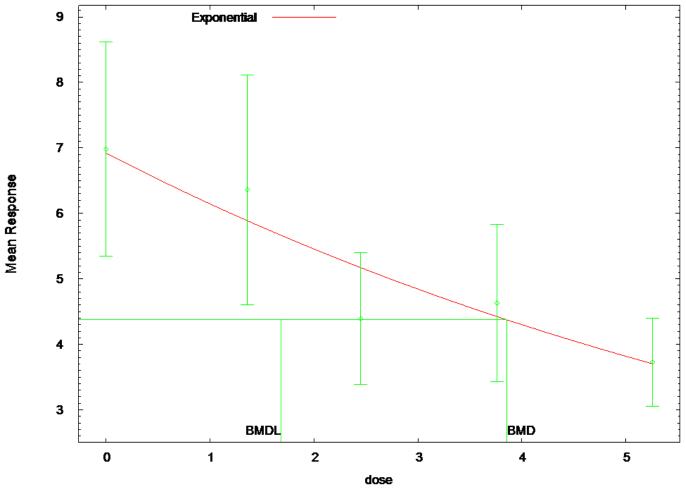
Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.
p-value		

Test	1	31.74	8
0.0001035			
Test	2	11.34	4
0.02296			
Test	3	11.34	4
0.02296			
Test (	ба	2.518	2
0.2839			

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. Consider running a non-homogeneous variance model. The p-value for Test 3 is less than .1. You may want to consider a different variance model. 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 = 2.07707

BMDL = 0.956572



Exponential Model 4, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Level for BMDL

10:10 06/22 2014

```
______
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Ln/Lymphocyte_Historical_LN-HLS 2001-
Lymphocyte Count-ExpNCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sun Jun 22 10:10:18 2014
______
===
BMDS Model Run
~~~~
  The form of the response function by Model:
                Y[dose] = a * exp\{sign * b * dose\}
     Model 2:
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
                Y[dose] = a * [c-(c-1) * exp{-b * dose}]
     Model 4:
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  The variance is to be modeled as Var(i) = exp(lalpha + log
(mean(i)) * rho)
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 4
lnalpha	-3.80501
rho	2.92874
a	7.329
b	0.208885
C	0.254469
d	1

## Parameter Estimates

Variable	Model 4
lnalpha	-3.90257
rho	2.98431
a	6.92193
b	0.118985
С	0
d	1

# Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	10	6.98	2.289
1.361	10	6.36	2.452
2.451	9	4.39	1.308
3.761	9	4.63	1.564
5.258	10	3.73	0.941

### Estimated Values of Interest

Est Mean	Est Std	Scaled Residual
6.922	2.549	0.07205
5.887	2.002	0.7472
5.171	1.649	-1.42
4.425	1.307	0.4713
3.703	1.002	0.08604
	6.922 5.887 5.171 4.425	6.9222.5495.8872.0025.1711.6494.4251.307

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)

		<pre>Var{e(ij)}</pre>	=	Sigma(i) <sup>2</sup>
Model A	43:			Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model	R:	Yij Var{e(ij)}	=	Mu + e(i) Sigma^2

		Likelihoods of Int	erest
AIC	Model	Log(likelihood)	DF
	Al	-50.11741	6
112.2348	A2	-44.44551	10
108.891	A3	-44.70264	7
103.4053	R	-60.31705	2
124.6341	4	-47.23015	4
102.4603	-		-

Additive constant for all log-likelihoods = -44.11. This constant added to the above values gives the log-likelihood including the term that does not

depend on the model parameters.

### Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A2 vs. A1) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 6a: Does Model 4 fit the data? (A3 vs 4)

#### Tests of Interest

Test p-value	-2*log(Likelihood Ratio)	D. F.
Test 1 0.0001035	31.74	8

Test 2	11.34	4
0.02296		
Test 3	0.5142	3
0.9157		
Test 6a	5.055	3
0.1678		

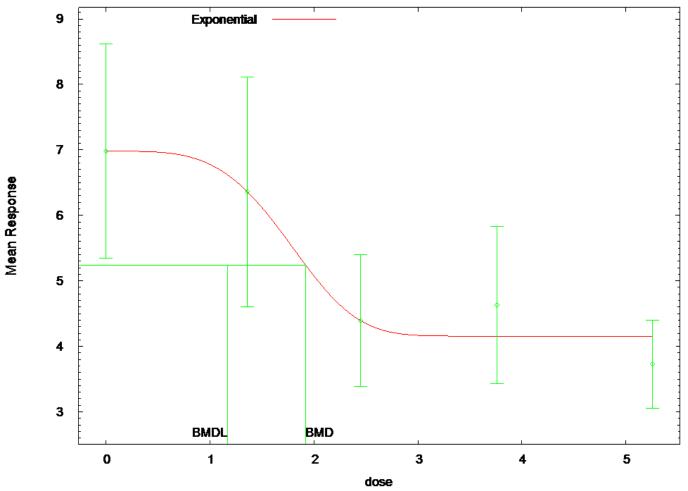
The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data. The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate. The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here. The p-value for Test 6a is greater than .1. Model 4 seems to adequately describe the data. Benchmark Dose Computations: Specified Effect = 1.000000

Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

BMD = 3.85925

BMDL = 1.683



# Exponential Model 5, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Level for BMDL

10:10 06/22 2014

```
______
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Ln/Lymphocyte_Historical_LN-HLS 2001-
Lymphocyte Count-ExpCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sun Jun 22 10:10:17 2014
______
===
BMDS Model Run
~~~~
  The form of the response function by Model:
                Y[dose] = a * exp\{sign * b * dose\}
     Model 2:
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
                Y[dose] = a * [c-(c-1) * exp{-b * dose}]
     Model 4:
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  rho is set to 0.
  A constant variance model is fit.
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 5
lnalpha	1.08823
rho(S)	0
a	7.329
b	0.208885
С	0.254469
d	1

(S) = Specified

### Parameter Estimates

Variable	Model 5
lnalpha	1.11479
rho	0
a	6.98002
b	0.514905
C	0.595454
d	3.92235

# Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	10	6.98	2.289
1.361	10	6.36	2.452
2.451	9	4.39	1.308
3.761	9	4.63	1.564
5.258	10	3.73	0.941

### Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	6.98	1.746	-3.704e-005
1.361	6.36	1.746	6.068e-005
2.451	4.39	1.746	-0.0001435
3.761	4.156	1.746	0.8139
5.258	4.156	1.746	-0.772

Other models for which likelihoods are calculated:

Model A1: Yij = Mu(i) + e(ij) Var{e(ij)} = Sigma^2

Model A2:	Yij = Var{e(ij)} =	Mu(i) + e(ij) Sigma(i)^2
Model A3:		Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R:	Yij = Var{e(ij)} =	Mu + e(i) Sigma^2

Likelihoods of Interest

AIC	Model	Log(likelihood)	DF
AIC			
110 0240	Al	-50.11741	6
112.2348	A2	-44.44551	10
108.891	A3	-50.11741	6
112.2348	R	-60.31705	2
124.6341	5	-50.75501	5
111.51			

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)

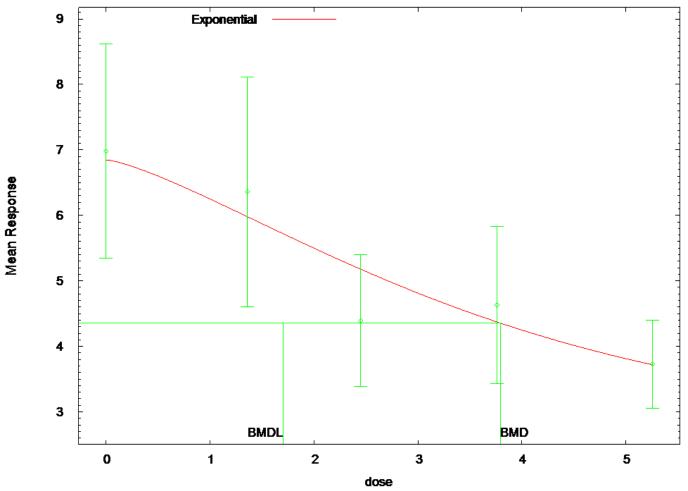
Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.
p-value		

Test	1	31.74	8
0.0001035			
Test	2	11.34	4
0.02296			
Test	3	11.34	4
0.02296			
Test '	7a	1.275	1
0.2588			

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. Consider running a non-homogeneous variance model. The p-value for Test 3 is less than .1. You may want to consider a different variance model. The p-value for Test 7a is greater than .1. Model 5 seems to adequately describe the data. Benchmark Dose Computations: Specified Effect = 1.000000 Risk Type = Estimated standard deviations from control Confidence Level = 0.950000 BMD = 1.92368

BMDL = 1.16803



# Exponential Model 5, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Level for BMDL

10:10 06/22 2014

```
______
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Ln/Lymphocyte_Historical_LN-HLS 2001-
Lymphocyte Count-ExpNCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sun Jun 22 10:10:18 2014
______
===
BMDS Model Run
~~~~
  The form of the response function by Model:
                Y[dose] = a * exp\{sign * b * dose\}
     Model 2:
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
                Y[dose] = a * [c-(c-1) * exp{-b * dose}]
     Model 4:
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  The variance is to be modeled as Var(i) = exp(lalpha + log
(mean(i)) * rho)
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 5
lnalpha	-3.80501
rho	2.92874
a	7.329
b	0.208885
С	0.254469
d	1

### Parameter Estimates

Variable	Model 5
lnalpha	-3.85928
rho	2.95639
a	6.84831
b	0.255151
C	0.408943
d	1.34247

# Table of Stats From Input Data

Dose	Ν	Obs Mean	Obs Std Dev
0	10	6.98	2.289
1.361	10	6.36	2.452
2.451	9	4.39	1.308
3.761	9	4.63	1.564
5.258	10	3.73	0.941

### Estimated Values of Interest

9
9
1
2
4
9 1 2

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)

		<pre>Var{e(ij)}</pre>	=	Sigma(i) <sup>2</sup>
Model A	43:			Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model	R:	Yij Var{e(ij)}	=	Mu + e(i) Sigma^2

		Likelihoods of Int	erest
2.50	Model	Log(likelihood)	DF
AIC			
	A1	-50.11741	6
112.2348	A2	-44.44551	10
108.891	A3	-44.70264	7
103.4053	R	-60.31705	2
124.6341			6
106.3334	5	-47.16672	0

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)

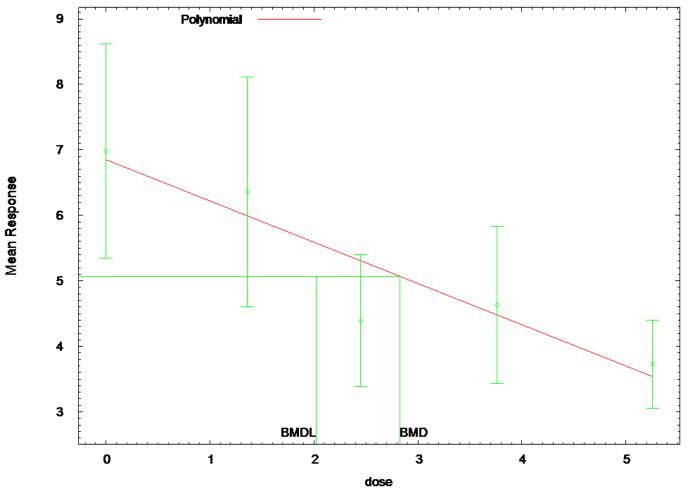
### Tests of Interest

Test p-value	-2*log(Likelihood Ratio)	D. F.
Test 1 0.0001035	31.74	8

Test 2	11.34	4
0.02296 Test 3	0.5142	З
0.9157	0.5142	2
Test 7a	4.928	1
0.02642		

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 7a is less than .1. Model 5 may not adequately describe the data; you may want to consider another model. Benchmark Dose Computations: Specified Effect = 1.000000 Risk Type = Estimated standard deviations from control Confidence Level = 0.950000

> BMD = 3.79695 BMDL = 1.70114



Polynomial Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

12:48 07/09 2014

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_Lymphocyte\_Historical\_Ln/Lymphocyt e\_Historical\_LN-HLS 2001-Lymphocyte Count-Poly2CV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_Lymphocyte\_Historical\_Ln/Lymphocyt e\_Historical\_LN-HLS 2001-Lymphocyte Count-Poly2CV-1SD-5d.plt Wed Jul 09 12:48:07 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse 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 = 5Total number of records with missing values = 0Maximum 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 = 3.31423 Specified rho = 0 beta\_0 = beta\_1 = 7.10002 -1.02021 beta\_2 = 0 Asymptotic Correlation Matrix of Parameter Estimates ( \*\*\* The model parameter(s) -rho -beta 2 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	-1.3e-007	1.2e-007
beta_0	-1.3e-007	1	-0.81
beta_1	1.2e-007	-0.81	1

### Parameter Estimates

			95.0%
Wald Confidence In	iterval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Conf	. Limit		
alpha	3.16984	0.64704	
1.90166	4.43801		
beta_0	6.85042	0.435612	
5.99664	7.70421		
beta_1	-0.630151	0.138278	_
0.901171	-0.359132		
beta_2	0	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 Scaled	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 0.23	10	6.98	6.85	2.29	1.78
1.361 0.652	10	6.36	5.99	2.45	1.78
2.451 -1.54	9	4.39	5.31	1.31	1.78
3.761 0.252	9	4.63	4.48	1.56	1.78
5.258 0.343	10	3.73	3.54	0.941	1.78

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<sup>2</sup>

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
Al	-50.117411	6	112.234822
A2	-44.445511	10	108.891023
A3	-50.117411	6	112.234822
fitted	-51.688316	3	109.376631
R	-60.317047	2	124.634093

#### 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

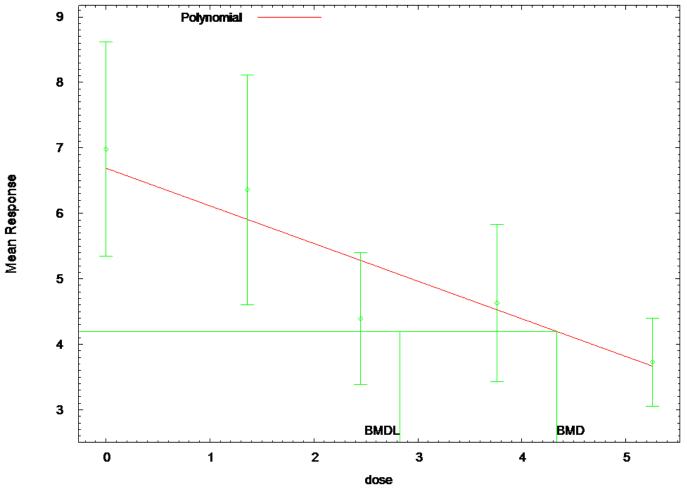
Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.7431	8	0.0001035
Test 2	11.3438	4	0.02296
Test 3	11.3438	4	0.02296
Test 4	3.14181	3	0.3703

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. Consider running a non-homogeneous variance model The p-value for Test 3 is less than .1. You may want to consider а different variance model 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 = Estimated standard deviations from the Risk Type control mean Confidence level = 0.95

BMD = 2.82536

BMDL = 2.0197



Polynomial Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

12:48 07/09 2014

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_Lymphocyte\_Historical\_Ln/Lymphocyt e\_Historical\_LN-HLS 2001-Lymphocyte Count-Poly2NCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_Lymphocyte\_Historical\_Ln/Lymphocyt e\_Historical\_LN-HLS 2001-Lymphocyte Count-Poly2NCV-1SD-5d.plt Wed Jul 09 12:48:08 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse 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 = 5Total number of records with missing values = 0Maximum 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 = 1.19823 rho = 0 beta\_0 = beta\_1 = 7.10002 -1.02021 beta\_2 = 0 Asymptotic Correlation Matrix of Parameter Estimates ( \*\*\* The model parameter(s) -beta\_2 have been estimated at a boundary point, or have been specified by the user,

and do not appear	in the	correlation	matrix	)
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	lalpha	rho	beta_0	beta_1
lalpha	1	-0.99	0.16	-0.19
rho	-0.99	1	-0.16	0.19
beta_0	0.16	-0.16	1	-0.91
beta_1	-0.19	0.19	-0.91	1

Parameter Estimates

			95.0%
Wald Confidence	Interval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Co	nf. Limit		
lalpha	-4.22724	1.68476	_
7.5293	-0.925178		
rho	3.18577	1.02462	
1.17755	5.19399		
beta_0	6.68829	0.512021	
5.68475	7.69183		
beta_1	-0.574737	0.123483	_
0.816759	-0.332715		
beta_2	0	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 Scaled	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 0.37	10	6.98	6.69	2.29	2.49
1.361 0.702	10	6.36	5.91	2.45	2.04
2.451 -1.56	9	4.39	5.28	1.31	1.71
3.761 0.232	9	4.63	4.53	1.56	1.34

5.258	10	3.73	3.67	0.941	0.957
0.21					

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
Al	-50.117411	б	112.234822
A2	-44.445511	10	108.891023
A3	-44.702636	7	103.405272
fitted	-47.300760	4	102.601521
R	-60.317047	2	124.634093

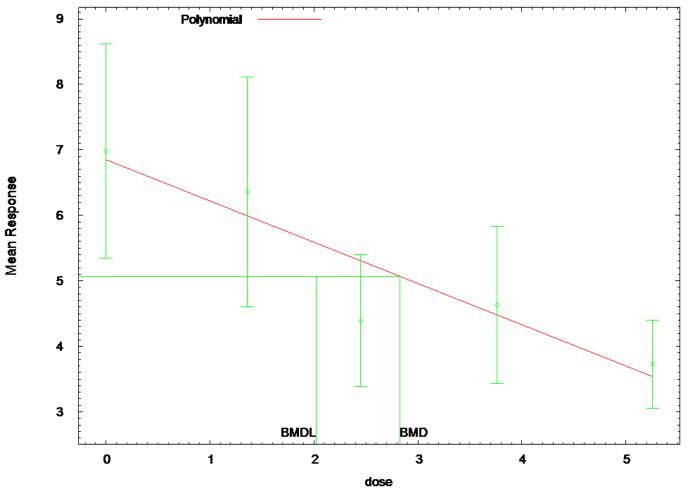
### Explanation of Tests

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	31.7431	8	0.0001035
Test 2	11.3438	4	0.02296
Test 3	0.514249	3	0.9157
Test 4	5.19625	3	0.158

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 = Estimated standard deviations from the Risk Type control mean Confidence level = 0.95 BMD = 4.33739 BMDL = 2.82692



Polynomial Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

12:48 07/09 2014

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_Lymphocyte\_Historical\_Ln/Lymphocyt e\_Historical\_LN-HLS 2001-Lymphocyte Count-Poly3CV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_Lymphocyte\_Historical\_Ln/Lymphocyt e\_Historical\_LN-HLS 2001-Lymphocyte Count-Poly3CV-1SD-5d.plt Wed Jul 09 12:48:07 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse 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 = 5Total number of records with missing values = 0Maximum 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 = 3.31423 Specified rho = 0 beta\_0 = 7.07831beta\_1 = -0.8976027.07831 beta\_2 = 0 beta 3 = 0 Asymptotic Correlation Matrix of Parameter Estimates ( \*\*\* The model parameter(s) -rho -beta\_2 -

	alpha	beta_0	beta_1
alpha	1	4.6e-008	3.4e-009
beta_0	4.6e-008	1	-0.81
beta_1	3.4e-009	-0.81	1

Parameter Estimates

95.0%

Wald Confidence Interval					
Variable	Estimate	Std. Err.	Lower Conf.		
Limit Upper Conf	. Limit				
alpha	3.16984	0.64704			
1.90166	4.43801				
beta_0	6.85042	0.435612			
5.99664	7.70421				
beta_1	-0.630151	0.138278	-		
0.901171	-0.359132				
beta_2	0	NA			
beta_3	0	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 Scaled	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 0.23	10	6.98	6.85	2.29	1.78
1.361 0.652	10	6.36	5.99	2.45	1.78
2.451 -1.54	9	4.39	5.31	1.31	1.78
3.761	9	4.63	4.48	1.56	1.78
5.258	10	3.73	3.54	0.941	1.78

2

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
Al	-50.117411	6	112.234822
A2	-44.445511	10	108.891023
A3	-50.117411	6	112.234822
fitted	-51.688316	3	109.376631
R	-60.317047	2	124.634093

### Explanation of Tests

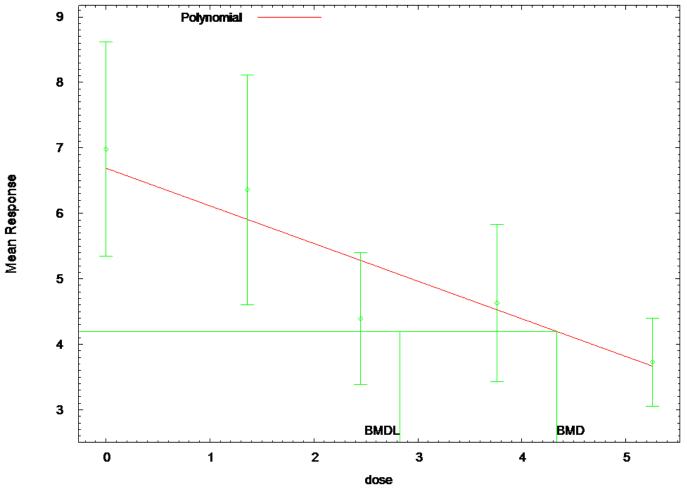
Test 1: Do responses and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A1 vs A2) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 4: Does the Model for the Mean Fit? (A3 vs. fitted) (Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

### Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.7431	8	0.0001035
Test 2	11.3438	4	0.02296
Test 3	11.3438	4	0.02296
Test 4	3.14181	3	0.3703

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. Consider running a non-homogeneous variance model The p-value for Test 3 is less than .1. You may want to consider а different variance model 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 Estimated standard deviations from the Risk Type = control mean Confidence level = 0.95 2.82536 BMD = BMDL = 2.0197



Polynomial Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

12:48 07/09 2014

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_Lymphocyte\_Historical\_Ln/Lymphocyt e\_Historical\_LN-HLS 2001-Lymphocyte Count-Poly3NCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_Lymphocyte\_Historical\_Ln/Lymphocyt e\_Historical\_LN-HLS 2001-Lymphocyte Count-Poly3NCV-1SD-5d.plt Wed Jul 09 12:48:08 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse 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 = 5Total number of records with missing values = 0Maximum 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 = 1.19823 rho = 0 beta\_0 = 7.07831 beta\_1 = -0.897602 7.07831 beta\_2 = 0 beta 3 = 0 Asymptotic Correlation Matrix of Parameter Estimates ( \*\*\* The model parameter(s) -beta\_2 -beta\_3

have been estimated at a boundary point, or have been specified by the user, and do not appear in the correlation matrix )

	lalpha	rho	beta_0	beta_1
lalpha	1	-0.99	0.16	-0.19
rho	-0.99	1	-0.16	0.19
beta_0	0.16	-0.16	1	-0.91
beta_1	-0.19	0.19	-0.91	1

Parameter Estimates

			95.0%
Wald Confidence	Interval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Co:	nf. Limit		
lalpha	-4.22724	1.68476	_
7.5293	-0.925179		
rho	3.18577	1.02462	
1.17755	5.19399		
beta_0	6.68829	0.512021	
5.68475	7.69183		
beta_1	-0.574737	0.123483	-
0.816759	-0.332715		
beta_2	0	NA	
beta_3	0	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 Scaled 1	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 0.37	10	6.98	6.69	2.29	2.49
1.361 0.702	10	6.36	5.91	2.45	2.04
2.451 -1.56	9	4.39	5.28	1.31	1.71

3.761	9	4.63	4.53	1.56	1.34
0.232					
5.258	10	3.73	3.67	0.941	0.957
0.21					

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
Al	-50.117411	б	112.234822
A2	-44.445511	10	108.891023
A3	-44.702636	7	103.405272
fitted	-47.300760	4	102.601521
R	-60.317047	2	124.634093

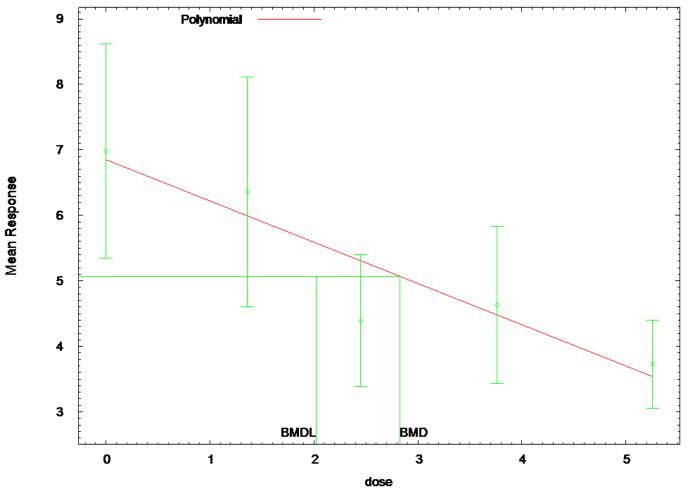
#### Explanation of Tests

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	31.7431	8	0.0001035
Test 2	11.3438	4	0.02296
Test 3	0.514249	3	0.9157

Test 4 5.19625 3 0.158 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 Estimated standard deviations from the Risk Type = control mean Confidence level = 0.95 4.33739 BMD = BMDL = 2.82692



Polynomial Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

12:48 07/09 2014

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_Lymphocyte\_Historical\_Ln/Lymphocyt e\_Historical\_LN-HLS 2001-Lymphocyte Count-Poly4CV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_Lymphocyte\_Historical\_Ln/Lymphocyt e\_Historical\_LN-HLS 2001-Lymphocyte Count-Poly4CV-1SD-5d.plt Wed Jul 09 12:48:07 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse 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 = 5Total 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 = 3.31423 rho = 0 Specified  $beta_0 =$ 6.98 beta\_1 = 0 beta\_2 = -4.14163 beta\_3 = 0  $beta_4 = -0.123946$ 

Asymptotic Correlation Matrix of Parameter Estimates

	alpha	beta_0	beta_1
alpha	1	-1.1e-006	8.5e-007
beta_0	-1.1e-006	1	-0.81
beta_1	8.5e-007	-0.81	1

Parameter Estimates

#### 95.0%

Wald Conf	fidence In	nterval		
Va	ariable	Estimate	Std. Err.	Lower Conf.
Limit (	Jpper Cont	f. Limit		
	alpha	3.16984	0.64704	
1.90166		4.43801		
	beta_0	6.85042	0.435612	
5.99663		7.7042		
	beta_1	-0.630151	0.138278	_
0.90117		-0.359131		
	beta_2	-8.26857e-102	NA	
	beta_3	-1.22857e-104	NA	
	beta_4	-0	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 Intere	Table	of Data	ble of Data and	Estimated	Values	of	Interes
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Dose Scaled	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 0.23	10	6.98	6.85	2.29	1.78
1.361	10	6.36	5.99	2.45	1.78
0.652 2.451 -1.54	9	4.39	5.31	1.31	1.78
-1.54 3.761	9	4.63	4.48	1.56	1.78

0.252 5.258 0.343	10 3	8.73	3.54	0.943	L	1.78
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<sup>2</sup>

# Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
Al	-50.117411	6	112.234822
A2	-44.445511	10	108.891023
A3	-50.117411	6	112.234822
fitted	-51.688316	3	109.376631
R	-60.317047	2	124.634093

### 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.)

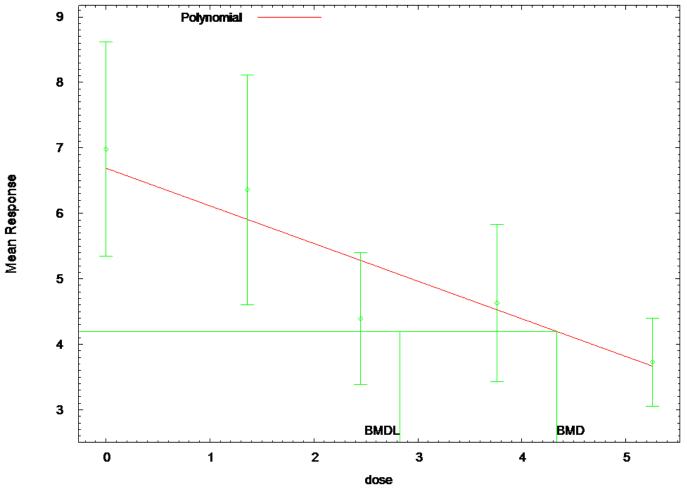
### Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.7431	8	0.0001035
Test 2	11.3438	4	0.02296
Test 3	11.3438	4	0.02296
Test 4	3.14181	3	0.3703

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. Consider running a non-homogeneous variance model The p-value for Test 3 is less than .1. You may want to consider а different variance model 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 = Estimated standard deviations from the Risk Type control mean Confidence level = 0.95

BMD = 2.82536

BMDL = 2.0197



Polynomial Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

12:48 07/09 2014

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_Lymphocyte\_Historical\_Ln/Lymphocyt e\_Historical\_LN-HLS 2001-Lymphocyte Count-Poly4NCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_Lymphocyte\_Historical\_Ln/Lymphocyt e\_Historical\_LN-HLS 2001-Lymphocyte Count-Poly4NCV-1SD-5d.plt Wed Jul 09 12:48:08 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse 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 = 5Total number of records with missing values = 0Maximum 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 = 1.19823 rho = 0 beta\_0 = 6.98 beta\_1 = 0  $beta_2 = -4.14163$ beta\_3 = 0  $beta_4 = -0.123946$ 

Asymptotic Correlation Matrix of Parameter Estimates

Deca_1	Deca_0	1110	Tatpila	
-0.19	0.16	-0.99	1	lalpha
0.19	-0.16	1	-0.99	rho
-0.91	1	-0.16	0.16	beta_0
1	-0.91	0.19	-0.19	beta_1

### Parameter Estimates

### 95.0%

Wald Confi	idence Int	erizal			23.0	0
			<u>a</u> , 1		T O	
	riable	Estimate	Sta	l. Err.	Lower C	oni.
Limit Up	pper Conf.	Limit				
1	lalpha	-4.22724	1	.68476		-
7.52931		-0.92518				
	rho	3.18577	1	.02462		
1.17755		5.19399				
k	oeta_0	6.68829	0.	512022		
5.68475		7.69183				
k	oeta_1	-0.574737	0.	123483	_	
0.816759		-0.332715				
k	oeta_2	0		NA		
k	beta_3	0		NA		
k	peta_4	0		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 Scaled R	N es.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 0.37	10	6.98	6.69	2.29	2.49
1.361	10	6.36	5.91	2.45	2.04

0.702 2.451	9	4.39	5.28	1.31	1.71
-1.56 3.761 0.231	9	4.63	4.53	1.56	1.34
5.258 0.21	10	3.73	3.67	0.941	0.957

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 R: Yi = Mu + e(i) $Var{e(i)} = Sigma^2$ 

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
Al	-50.117411	б	112.234822
A2	-44.445511	10	108.891023
A3	-44.702636	7	103.405272
fitted	-47.300760	4	102.601521
R	-60.317047	2	124.634093

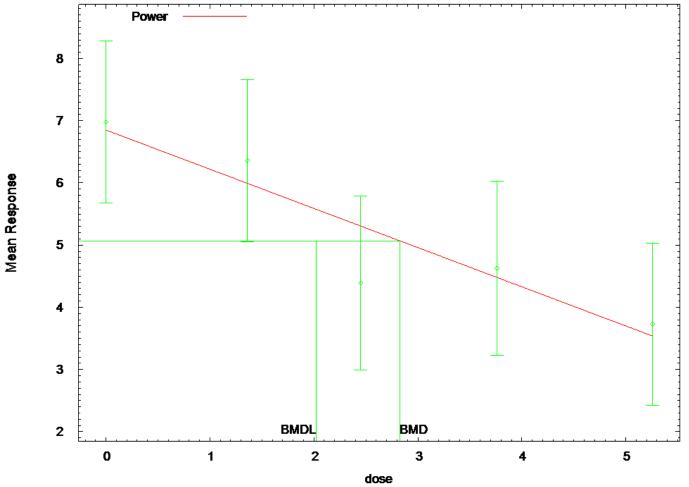
### Explanation of Tests

### Tests of Interest

Test	-2*log(Likelihood	Ratio	) Test df	p-value
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3

8 4 31.7431 11.3438 Test 1 0.0001035 Test 2 0.02296 Test 3 0.514249 3 0.9157 Test 4 5.19625 3 0.158 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 = 4.33739 2.82692 BMDL =



Power Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

10:10 06/22 2014

\_\_\_\_\_ === Power Model. (Version: 2.18; Date: 05/19/2014) Input Data File: C:/Users/dmayfield/Desktop/Ln/Lymphocyte\_Historical\_LN-HLS 2001-Lymphocyte Count-PowerCV-1SD-5d. (d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Ln/Lymphocyte Historical LN-HLS 2001-Lymphocyte Count-PowerCV-1SD-5d.plt Sun Jun 22 10:10:17 2014 \_\_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = control + slope \* dose^power Dependent variable = MeanResponse 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 = 5Total 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 = 3.31423 rho = 0 control = 3.73 slope = 3.0162 power = -1.13303 0 Specified 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	-7.3e-008	9.3e-009
control	-7.3e-008	1	-0.81
slope	9.3e-009	-0.81	1

# Parameter Estimates

			95.0%
Wald Confidence	Interval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Cc	nf. Limit		
alpha	3.16984	0.64704	
1.90166	4.43801		
control	6.85042	0.435612	
5.99664	7.70421		
slope	-0.630151	0.138278	-
0.901171	-0.359132		
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
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Dose Scaled	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 0.23	10	6.98	6.85	2.29	1.78
1.361 0.652	10	6.36	5.99	2.45	1.78
2.451 -1.54	9	4.39	5.31	1.31	1.78
3.761 0.252	9	4.63	4.48	1.56	1.78
5.258 0.343	10	3.73	3.54	0.941	1.78

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<sup>2</sup>

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-50.117411	6	112.234822
A2	-44.445511	10	108.891023
A3	-50.117411	6	112.234822
fitted	-51.688316	3	109.376631
R	-60.317047	2	124.634093

#### Explanation of Tests

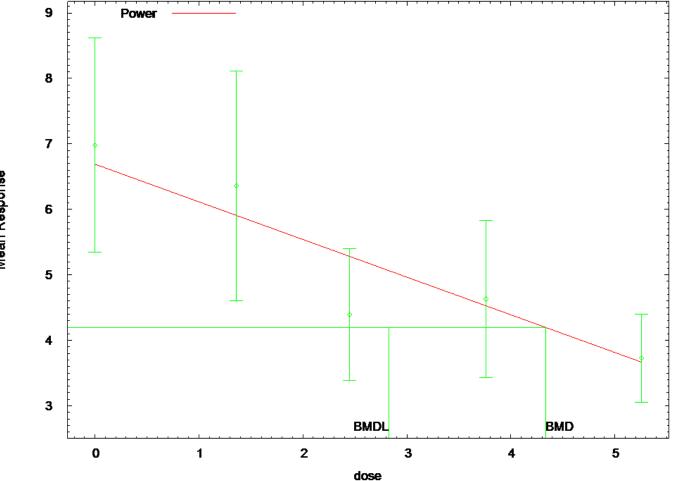
Test 1:	Do responses and/or variances differ among Dose levels?
	(A2 vs. R)
Test 2:	Are Variances Homogeneous? (A1 vs A2)
Test 3:	Are variances adequately modeled? (A2 vs. A3)
Test 4:	Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:	When rho=0 the results of Test 3 and Test 2 will be the
same.)	

# Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.7431	8	0.0001035
Test 2	11.3438	4	0.02296
Test 3	11.3438	4	0.02296
Test 4	3.14181	3	0.3703

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. Consider running a non-homogeneous variance model The p-value for Test 3 is less than .1. You may want to consider а different variance model 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 = Estimated standard deviations from the Risk Type control mean Confidence level = 0.95 BMD = 2.82536

BMDL = 2.0197



Mean Response

10:10 06/22 2014

\_\_\_\_\_\_ === Power Model. (Version: 2.18; Date: 05/19/2014) Input Data File: C:/Users/dmayfield/Desktop/Ln/Lymphocyte\_Historical\_LN-HLS 2001-Lymphocyte Count-PowerNCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Ln/Lymphocyte Historical LN-HLS 2001-Lymphocyte Count-PowerNCV-1SD-5d.plt Sun Jun 22 10:10:19 2014 === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = control + slope \* dose^power Dependent variable = MeanResponse Independent variable = Dose The power is restricted to be greater than or equal to 1 The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) \* rho) Total number of dose groups = 5Total number of records with missing values = 0Maximum 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 = 1.19823 rho = 0 control = 3.73 slope = 3.0162 power = -1.13303 rho = Asymptotic Correlation Matrix of Parameter Estimates ( \*\*\* The model parameter(s) -power have been estimated at a boundary point, or have been specified by the user,

				,
	lalpha	rho	control	slope
lalpha	1	-0.99	0.45	-0.57
rho	-0.99	1	-0.5	0.6
control	0.45	-0.5	1	-0.91
slope	-0.57	0.6	-0.91	1

Parameter Estimates

and do not appear in the correlation matrix )

95	0응	

			95.08
Wald Confiden	ce Interval		
Variab	le Estimat	e Std. Err.	Lower Conf.
Limit Upper	Conf. Limit		
lalp	ha -4.2272	5 2.06914	-
8.28268	-0.17181		
r	ho 3.1857	7 1.27347	
0.689823	5.68172		
contr	ol 6.6882	9 0.515026	
5.67886	7.69772		
slo	pe -0.57473	7 0.124269	-
0.8183	-0.331174		
pow	ver	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 Scaled :	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0	10	6.98	6.69	2.29	2.49
0.37					
1.361	10	6.36	5.91	2.45	2.04
0.702					
2.451	9	4.39	5.28	1.31	1.71
-1.56					
3.761	9	4.63	4.53	1.56	1.34
0.232					

5.258	10	3.73	3.67	0.941	0.957
0.21					

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

Mode	Log(likelihood)	# Param's	AIC
A1	-50.117411	6	112.234822
A2	-44.445511	10	108.891023
A3	-44.702636	7	103.405272
fitted	-47.300760	4	102.601521
R	-60.317047	2	124.634093

# Explanation of Tests

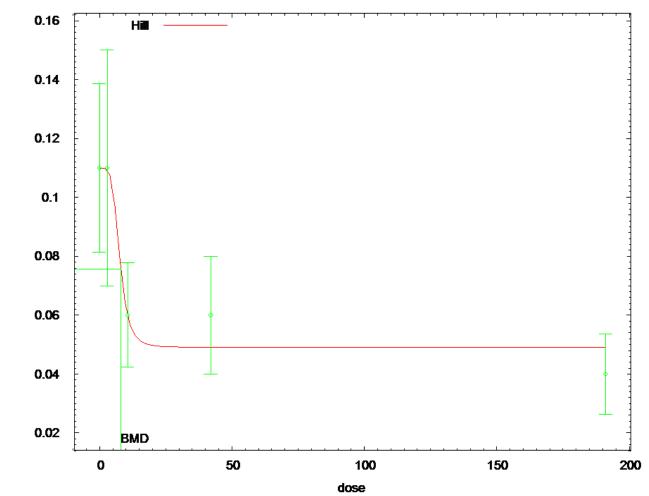
Test 1: Do responses and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A1 vs A2) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 4: Does the Model for the Mean Fit? (A3 vs. fitted) (Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

### Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.7431	8	0.0001035
Test 2	11.3438	4	0.02296
Test 3	0.514249	3	0.9157
Test 4	5.19625	3	0.158

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 = Estimated standard deviations from the Risk Type control mean Confidence level = 0.95 BMD = 4.33739BMDL = 2.82692

BMDS Model Results for Large Unstained Cells Count (Untransformed Doses, Concurrent Controls)



15:22 06/21 2014

Mean Response

Hill Model

\_\_\_\_\_\_ === Hill Model. (Version: 2.17; Date: 01/28/2013) Input Data File: C:/Users/dmayfield/Desktop/Norm/LUC concurrent-HLS 2001-LUC count-HillCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Norm/LUC concurrent-HLS 2001-LUC count-HillCV-1SD-5d.plt Sat Jun 21 15:22:11 2014 === BMDS Model Run ~~~~ The form of the response function is:  $Y[dose] = intercept + v*dose^n/(k^n + dose^n)$ Dependent variable = MeanResponse 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 = 5Total 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 = 0.001291 0 Specified rho = intercept = 0.11 -0.07 V = n = 5.34555 k = 8.29 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 )

and do not app	pear in the	correlation	matrix )	)
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k		alpha	intercept	v	n
a 1.1e-0	lpha 06	1	-7.9e-007	5.9e-007	1.1e-006
inter -0.71	cept	-7.9e-007	1	-0.82	-0.71
0.56	v	5.9e-007	-0.82	1	0.62
0.97	n	1.1e-006	-0.71	0.62	1
1	k	1.1e-006	-0.71	0.56	0.97

# Parameter Estimates

95.0%

Wald Confiden	ce In	terval		
Variab	le	Estimate	Std. Err.	Lower Conf.
Limit Upper	Conf	. Limit		
alp	ha	0.00119596	0.000244124	
0.000717485		0.00167443		
interce	pt	0.110304	0.0110773	
0.0885926		0.132015		
	v	-0.0608572	0.0140877	-
0.0884685		-0.0332458		
	n	4.73776	20.3397	-
35.1273		44.6028		
	k	7.63214	10.8067	-
13.5485		28.8128		

# Table of Data and Estimated Values of Interest

Dose Scaled R		Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 -0.0278	10	0.11	0.11	0.04	0.0346

2.9	10	0.11	0.11	0.056	0.0346
0.0285					
10.6	9	0.06	0.06	0.023	0.0346
-0.00405					
42	9	0.06	0.0495	0.026	0.0346
0.914					
191.1	10	0.04	0.0494	0.019	0.0346
-0.864					

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
Al	138.296137	6	-264.592275
A2	146.083690	10	-272.167381
A3	138.296137	6	-264.592275
fitted	137.491343	5	-264.982687
R	125.105720	2	-246.211439

# Explanation of Tests

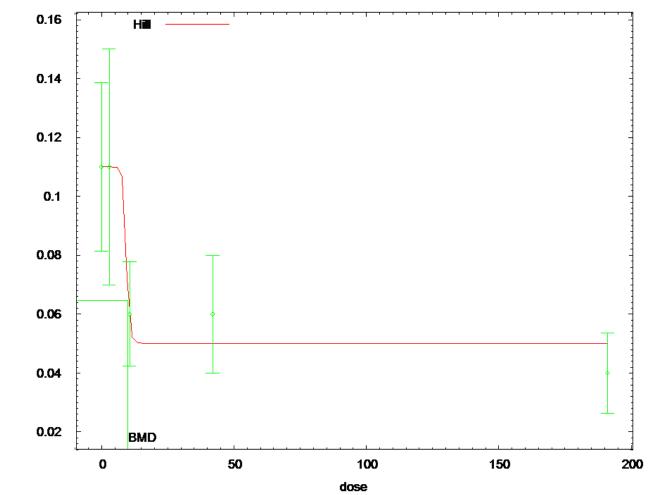
# Tests of Interest

Test -2\*log(Likelihood Ratio) Test df p-value

3

Test 1 Test 2 41.95598<.0001</th>15.575140.003646 4 Test 3 15.5751 0.003646 1 Test 4 1.60959 0.2045 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. Consider running a non-homogeneous variance model The p-value for Test 3 is less than .1. You may want to consider а different variance model 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 = Estimated standard deviations from the Risk Type control mean Confidence level = 0.95 BMD = 8.08783

BMDL computation failed.



15:22 06/21 2014

Mean Response

Hill Model

\_\_\_\_\_\_ === Hill Model. (Version: 2.17; Date: 01/28/2013) Input Data File: C:/Users/dmayfield/Desktop/Norm/LUC concurrent-HLS 2001-LUC count-HillNCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Norm/LUC concurrent-HLS 2001-LUC count-HillNCV-1SD-5d.plt Sat Jun 21 15:22:13 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is:  $Y[dose] = intercept + v*dose^n/(k^n + dose^n)$ Dependent variable = MeanResponse Independent variable = Dose Power parameter restricted to be greater than 1 The variance is to be modeled as Var(i) = exp(lalpha + rho \* ln(mean(i))) Total number of dose groups = 5Total 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 = -6.65234 rho = rno = 0 intercept = 0.11 v = -0.07 n = 5.34555 0 k = 8.29 Asymptotic Correlation Matrix of Parameter Estimates intercept lalpha rho v

n	k			
lalpha 2.7e-005	1 -0.00015	0.99	-0.38	0.47
rho 3.2e-005	0.99 -0.00015	1	-0.34	0.46
intercept -0.00027	-0.38 -0.00043	-0.34	1	-0.9
v 0.00028	0.47 3.3e-005	0.46	-0.9	1
n 1	2.7e-005 1	3.2e-005	-0.00027	0.00028
k 1	-0.00015 1	-0.00015	-0.00043	3.3e-005

Parameter Estimates

			95.0%				
Wald Confidence 1	Wald Confidence Interval						
Variable	Estimate	Std. Err.	Lower Conf.				
Limit Upper Conf. Limit							
lalpha	-2.17483	1.65823	_				
5.4249	1.07524						
rho	1.81244	0.62408					
0.589269	3.03562						
intercept	0.110329	0.0101805					
0.0903753	0.130282						
v	-0.0599397	0.01149	-				
0.0824597	-0.0374198						
n	15.5198	5275.25	-				
10323.8	10354.8						
k	9.30751	411.378	-				
796.979	815.594						

Table of Data and Estimated Values of Interest

Dose Scaled R		Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 -0.0227	10	0.11	0.11	0.04	0.0457

2.9	10	0.11	0.11	0.056	0.0457
-0.0227					
10.6	9	0.06	0.0574	0.023	0.0253
0.306					
42	9	0.06	0.0504	0.026	0.0225
1.28					
191.1	10	0.04	0.0504	0.019	0.0225
-1.46					

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	138.296137	6	-264.592275
A2	146.083690	10	-272.167381
A3	145.492300	7	-276.984600
fitted	142.899629	6	-273.799258
R	125.105720	2	-246.211439

### 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 H	Ratio) Test	df	p-value
------	---------------------	-------------	----	---------

Test 141.95598<.0001</th>Test 215.575140.003646Test 31.1827830.7571Test 45.1853410.02278

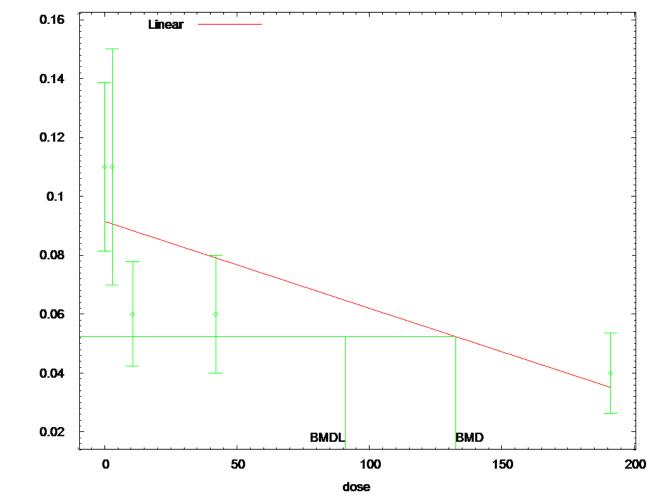
The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels It seems appropriate to model the data The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate The p-value for Test 3 is greater 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 = 10.0356

BMDL computation failed.



Linear Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

12:40 07/09 2014

Mean Response

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_LUC\_Concurrent/LUC\_concurrent-HLS 2001-LUC count-LinearCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_LUC\_Concurrent/LUC\_concurrent-HLS 2001-LUC count-LinearCV-1SD-5d.plt Wed Jul 09 12:40:22 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse Independent variable = Dose rho is set to 0 Signs of the polynomial coefficients are not restricted A constant variance model is fit Total number of dose groups = 5Total number of records with missing values = 0Maximum 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 = 0.001291 rho = 0 Specified  $beta_0 = 0.0903263$  $beta_1 = -0.000290477$ 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 )

beta_1	beta_0	alpha	
1.9e-007	-4.4e-008	1	alpha
-0.56	1	-4.4e-008	beta_0
1	-0.56	1.9e-007	beta_1

# Parameter Estimates

			95.0%
Wald Confidence In	terval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Conf	. Limit		
alpha	0.00153024	0.000312359	
0.000918027	0.00214245		
beta_0	0.091509	0.0068346	
0.0781134	0.104905		
beta_1	-0.000295197	7.65966e-005	-
0.000445324	-0.000145071		

Table of Data and Estimated Values of Interest

Dose Scaled	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0	10	0.11	0.0915	0.04	0.0391
1.49 2.9	10	0.11	0.0907	0.056	0.0391
1.56 10.6	9	0.06	0.0884	0.023	0.0391
-2.18 42 -1.47	9	0.06	0.0791	0.026	0.0391
191.1 0.396	10	0.04	0.0351	0.019	0.0391

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
Al	138.296137	б	-264.592275
A2	146.083690	10	-272.167381
A3	138.296137	б	-264.592275
fitted	131.575968	3	-257.151936
R	125.105720	2	-246.211439

# 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	41.9559	8	<.0001
Test 2	15.5751	4	0.003646
Test 3	15.5751	4	0.003646
Test 4	13.4403	3	0.003775

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. Consider running a non-homogeneous variance model

The p-value for Test 3 is less than .1. You may want to consider a

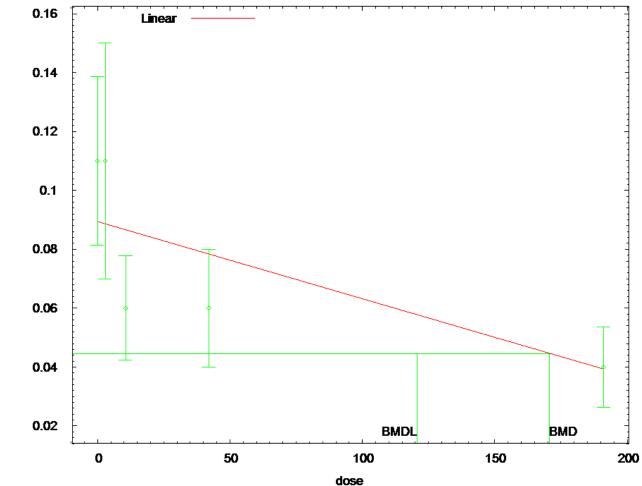
different variance model

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 = 132.516

BMDL = 90.8103



12:40 07/09 2014

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_LUC\_Concurrent/LUC\_concurrent-HLS 2001-LUC count-LinearNCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_LUC\_Concurrent/LUC\_concurrent-HLS 2001-LUC count-LinearNCV-1SD-5d.plt Wed Jul 09 12:40:25 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse Independent variable = Dose Signs of the polynomial coefficients are not restricted The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) \* rho) Total number of dose groups = 5Total number of records with missing values = 0Maximum 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 = -6.65234 rho = 0  $beta_0 = 0.0903263$  $beta_1 = -0.000290477$ Asymptotic Correlation Matrix of Parameter Estimates lalpha beta\_0 beta 1 rho 0.99 -0.052 0.061 lalpha 1

rho	0.99	1	-0.052	0.06
beta_0	-0.052	-0.052	1	-0.82
beta_1	0.061	0.06	-0.82	1

Parameter Estimates

# 95.0%

Wald Confidence Interval						
	Variable	Estimate	Std. Err.	Lower Conf.		
Limit	Upper Conf	. Limit				
	lalpha	-0.716057	1.62767	-		
3.90623		2.47412				
	rho	2.2765	0.616544			
1.0681		3.48491				
	beta_0	0.08936	0.00749719			
0.07466	58	0.104054				
	beta_1	-0.00026225	5.03908e-005	-		
0.00036	1014	-0.000163486				

Table of Data and Estimated Values of Interest

Dose Scaled	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 1.46	10	0.11	0.0894	0.04	0.0447
2.9 1.53	10	0.11	0.0886	0.056	0.0443
10.6 -1.85	9	0.06	0.0866	0.023	0.0432
42 -1.43	9	0.06	0.0783	0.026	0.0385
191.1 0.136	10	0.04	0.0392	0.019	0.0175

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<sup>2</sup>

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
Al	138.296137	б	-264.592275
A2	146.083690	10	-272.167381
A3	145.492300	7	-276.984600
fitted	136.270966	4	-264.541933
R	125.105720	2	-246.211439

#### Explanation of Tests

### Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	41.9559	8	<.0001
Test 2	15.5751	4	0.003646
Test 3	1.18278	3	0.7571
Test 4	18.4427	3	0.0003564

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

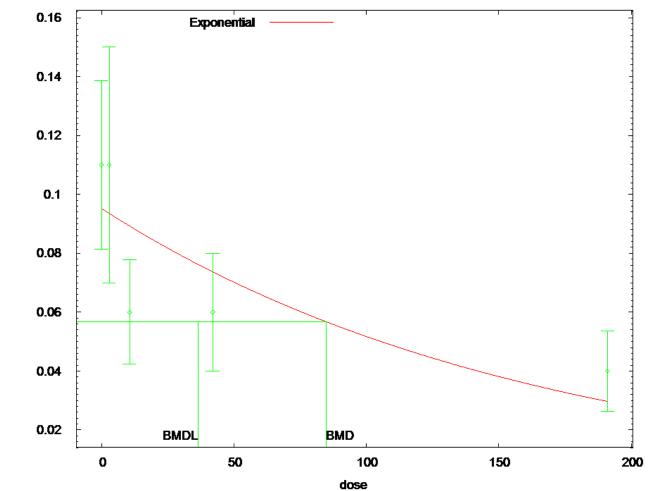
The p-value for Test 4 is less than .1. You may want to try a different model

Benchmark Dose Computation

Specified effect = 1 Risk Type = Estimated standard deviations from the control mean Confidence level = 0.95

BMD = 170.581

BMDL = 120.78



15:22 06/21 2014

Mean Response

```
______
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Norm/LUC concurrent-HLS 2001-LUC
count-ExpCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sat Jun 21 15:22:11 2014
______
===
BMDS Model Run
~~~~
  The form of the response function by Model:
                Y[dose] = a * exp{sign * b * dose}
     Model 2:
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
               Y[dose] = a * [c-(c-1) * exp{-b * dose}]
     Model 4:
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  rho is set to 0.
  A constant variance model is fit.
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 2
lnalpha	-6.76234
rho(S)	0
a	0.0567269
b	0.00445872
C	0
d	1

(S) = Specified

#### Parameter Estimates

Variable	Model 2
lnalpha	-6.51823
rho	0
a	0.0951988
b	0.00609925
C	0
d	1

# Table of Stats From Input Data

Dose	Ν	Obs Mean	Obs Std Dev
0	10	0.11	0.04
2.9	10	0.11	0.056
10.6	9	0.06	0.023
42	9	0.06	0.026
191.1	10	0.04	0.019

### Estimated Values of Interest

Other models for which likelihoods are calculated:

Model A1: Yij = Mu(i) + e(ij) Var{e(ij)} = Sigma^2

Model A2	Yij = Var{e(ij)} =	Mu(i) + e(ij) Sigma(i)^2
Model A3	Yij = Var{e(ij)} =	Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R	Yij = Var{e(ij)} =	Mu + e(i) Sigma^2

Likelihoods of Interest

AIC	Model	Log(likelihood)	DF	
AIC				
	A1	138.2961	6	-
264.5923	A2	146.0837	10	-
272.1674	A3	138.2961	6	_
264.5923	R	125.1057	2	_
246.2114	2	132.4375	3	_
258.875	2	192.1979	5	

Additive constant for all log-likelihoods = -44.11. This constant added to the above values gives the log-likelihood including the term that does not

depend on the model parameters.

### Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A2 vs. A1) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 4: Does Model 2 fit the data? (A3 vs. 2)

Test p-value	-2*log(Likelihood Ratio)	D. F.
Test 1	41.96	8

< 0.0001			
Test	2	15.58	4
0.003646			
Test	3	15.58	4
0.003646			
Test	4	11.72	3
0.008417			

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. Consider running a non-homogeneous variance model.

The p-value for Test 3 is less than .1. You may want to consider a different variance model.

The p-value for Test 4 is less than .1. Model 2 may not adequately

describe the data; you may want to consider another model.

Benchmark Dose Computations:

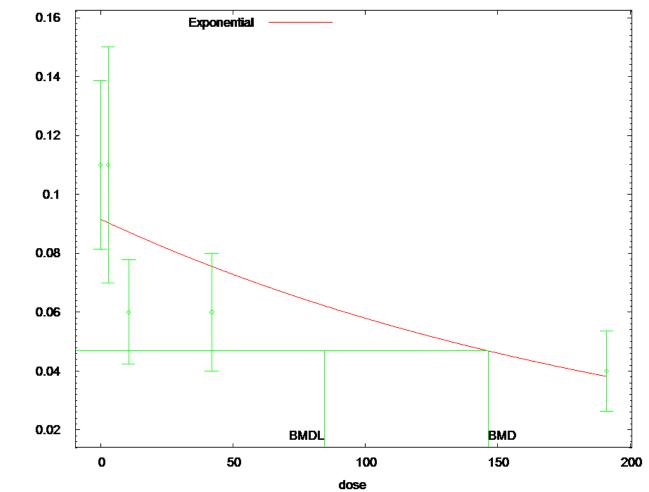
Specified Effect = 1.000000

Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

BMD = 84.7394

BMDL = 36.554



Mean Response

15:22 06/21 2014

```
_____
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Norm/LUC concurrent-HLS 2001-LUC
count-ExpNCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sat Jun 21 15:22:12 2014
______
===
BMDS Model Run
~~~~
  The form of the response function by Model:
                Y[dose] = a * exp{sign * b * dose}
     Model 2:
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
                Y[dose] = a * [c-(c-1) * exp{-b * dose}]
     Model 4:
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  The variance is to be modeled as Var(i) = exp(lalpha + log
(mean(i)) * rho)
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 2
lnalpha	-1.95665
rho	1.89965
a	0.0567269
b	0.00445872
С	0
d	1

## Parameter Estimates

Variable	Model 2
lnalpha	-1.07085
rho	2.15178
a	0.0915571
b	0.00457633
C	0
d	1

# Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	10	0.11	0.04
2.9	10	0.11	0.056
10.6	9	0.06	0.023
42	9	0.06	0.026
191.1	10	0.04	0.019

## Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	0.09156	0.04471	1.305
2.9	0.09035	0.04407	1.41
10.6	0.08722	0.04243	-1.925
42	0.07555	0.03635	-1.283
191.1	0.03818	0.01745	0.3291

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)

		<pre>Var{e(ij)}</pre>	=	Sigma(i) <sup>2</sup>
Model A	A3:	Yij Var{e(ij)}	=	Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model	R:	Yij Var{e(ij)}	= =	Mu + e(i) Sigma^2

Likelihoods of Interest Model Log(likelihood) DF AIC \_ \_ \_ \_ \_ \_ \_ ----- ----\_ \_ \_ \_ \_ \_ \_ \_ \_ \_ \_ \_ \_ \_ \_ \_ \_ \_ 6 138.2961 A1 \_ 264.5923 10 146.0837 A2 272.1674 145.4923 7 A3 276.9846 R 125.1057 2 -246.2114 137.0503 4 -2 266.1006

Additive constant for all log-likelihoods = -44.11. This constant added to the above values gives the log-likelihood including the term that does not

depend on the model parameters.

#### Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A2 vs. A1) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 4: Does Model 2 fit the data? (A3 vs. 2)

Test p-value	-2*log(Likelihood	Ratio) D.	F.
Test < 0.0001	1	41.96	8
Test	2	15.58	4

0.003646			
Test	3	1.183	3
0.7571			
Test	4	16.88	3
0.0007466			

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. Model 2 may not adequately describe the data; you may want to consider another model. Benchmark Dose Computations: Specified Effect = 1.000000

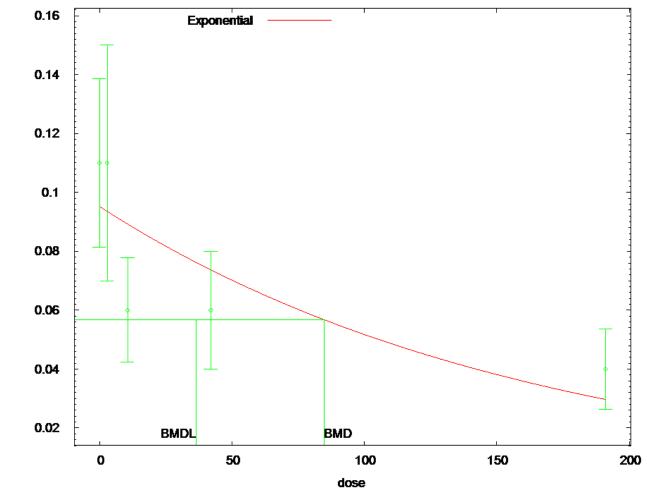
Risk Type = Estimated standard deviations from

control

Confidence Level = 0.950000

BMD = 146.401

BMDL = 84.5804



Mean Response

15:22 06/21 2014

```
______
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Norm/LUC concurrent-HLS 2001-LUC
count-ExpCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sat Jun 21 15:22:11 2014
______
===
BMDS Model Run
~~~~
  The form of the response function by Model:
                Y[dose] = a * exp{sign * b * dose}
     Model 2:
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
               Y[dose] = a * [c-(c-1) * exp{-b * dose}]
     Model 4:
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  rho is set to 0.
  A constant variance model is fit.
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 3
lnalpha	-6.76234
rho(S)	0
a	0.0567269
b	0.00445872
С	0
d	1

(S) = Specified

#### Parameter Estimates

Variable	Model 3
lnalpha	-6.51823
rho	0
a	0.0951988
b	0.00609925
C	0
d	1

# Table of Stats From Input Data

Dose	Ν	Obs Mean	Obs Std Dev
0	10	0.11	0.04
2.9	10	0.11	0.056
10.6	9	0.06	0.023
42	9	0.06	0.026
191.1	10	0.04	0.019

### Estimated Values of Interest

Est Mean	Est Std	Scaled Residual
0.0952	0.03842	1.218
0.09353	0.03842	1.356
0.08924	0.03842	-2.283
0.07368	0.03842	-1.069
0.02968	0.03842	0.8495
	0.0952 0.09353 0.08924 0.07368	0.0952 0.03842 0.09353 0.03842 0.08924 0.03842 0.07368 0.03842

Other models for which likelihoods are calculated:

Model A1: Yij = Mu(i) + e(ij) Var{e(ij)} = Sigma^2

Model A2:	Yij = Var{e(ij)} =	Mu(i) + e(ij) Sigma(i)^2
Model A3:		Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R:	Yij = Var{e(ij)} =	

Likelihoods of Interest

AIC	Model	Log(likelihood)	DF	
AIC				
264.5923	A1	138.2961	6	-
272.1674	A2	146.0837	10	-
264.5923	A3	138.2961	6	-
	R	125.1057	2	-
246.2114	3	132.4375	3	-
258.875				

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.

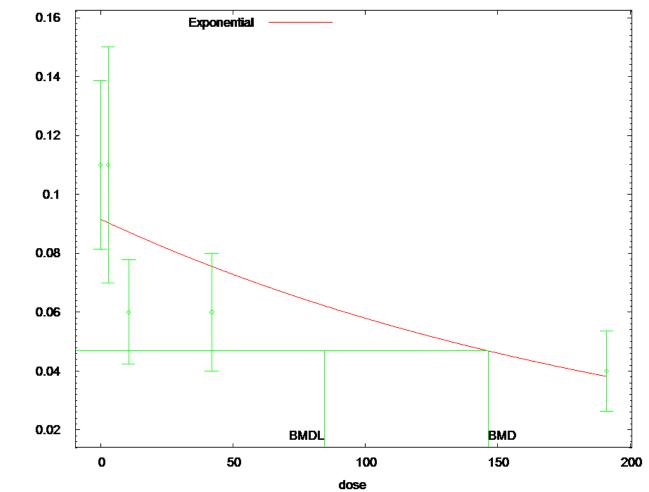
# Explanation of Tests

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 5a: Does Model 3 fit the data? (A3 vs 3)

Test	-2*log(Likelihood Ratio)	D. F.
p-value		

Test 1 < 0.0001	41.96	8
Test 2	15.58	4
0.003646 Test 3	15.58	4
0.003646 Test 5a	11.72	3
0.008417	11.72	5

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. Consider running a non-homogeneous variance model. The p-value for Test 3 is less than .1. You may want to consider a different variance model. The p-value for Test 5a is less than .1. Model 3 may not adequately describe the data; you may want to consider another model. Benchmark Dose Computations: Specified Effect = 1.000000 Risk Type = Estimated standard deviations from control Confidence Level = 0.950000BMD = 84.7394 BMDL = 36.554



Mean Response

15:22 06/21 2014

```
_____
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Norm/LUC concurrent-HLS 2001-LUC
count-ExpNCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sat Jun 21 15:22:12 2014
______
===
BMDS Model Run
~~~~
  The form of the response function by Model:
                Y[dose] = a * exp{sign * b * dose}
     Model 2:
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
                Y[dose] = a * [c-(c-1) * exp{-b * dose}]
     Model 4:
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  The variance is to be modeled as Var(i) = exp(lalpha + log
(mean(i)) * rho)
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 3
lnalpha	-1.95665
rho	1.89965
a	0.0567269
b	0.00445872
С	0
d	1

## Parameter Estimates

Variable	Model 3
lnalpha	-1.07085
rho	2.15178
a	0.0915571
b	0.00457634
C	0
d	1

# Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	10	0.11	0.04
2.9	10	0.11	0.056
10.6	9	0.06	0.023
42	9	0.06	0.026
191.1	10	0.04	0.019

## Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	0.09156	0.04471	1.305
2.9	0.09035	0.04407	1.41
10.6	0.08722	0.04243	-1.925
42	0.07555	0.03635	-1.283
191.1	0.03818	0.01745	0.3291

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) <sup>2</sup>	
Model .	A3:			Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rł	ho)
Model	R:	Yij Var{e(ij)}	=	Mu + e(i) Sigma^2	

		Likelihoods of Int	erest	
	Model	Log(likelihood)	DF	
AIC				
	A1	138.2961	6	-
264.5923	A2	146.0837	10	-
272.1674	A3	145.4923	7	-
276.9846	R	125.1057	2	-
246.2114	3	137.0503	4	_
266.1006				

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

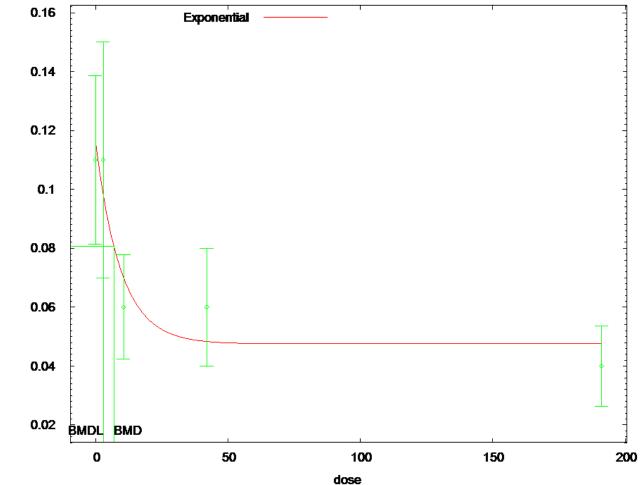
Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A2 vs. A1) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 5a: Does Model 3 fit the data? (A3 vs 3)

Test p-value	-2*log(Likelihood Ratio)	D. F.
Test 1 < 0.0001	41.96	8

Test 2	2	15.58	4
0.003646			
Test 3	3	1.183	3
0.7571			
Test 5a	a	16.88	3
0.0007466			

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 5a is less than .1. Model 3 may not adequately describe the data; you may want to consider another model. Benchmark Dose Computations: Specified Effect = 1.000000 Risk Type = Estimated standard deviations from control Confidence Level = 0.950000

> BMD = 146.4 BMDL = 84.5804



15:22 06/21 2014

```
______
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Norm/LUC concurrent-HLS 2001-LUC
count-ExpCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sat Jun 21 15:22:11 2014
______
===
BMDS Model Run
~~~~
  The form of the response function by Model:
                Y[dose] = a * exp{sign * b * dose}
     Model 2:
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
               Y[dose] = a * [c-(c-1) * exp{-b * dose}]
     Model 4:
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  rho is set to 0.
  A constant variance model is fit.
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 4
lnalpha	-6.76234
rho(S)	0
a	0.1155
b	0.0201693
C	0.329829
d	1

(S) = Specified

#### Parameter Estimates

Variable	Model 4
lnalpha	-6.68465
rho	0
a	0.116057
b	0.10556
C	0.409529
d	1

# Table of Stats From Input Data

Dose	Ν	Obs Mean	Obs Std Dev
0	10	0.11	0.04
2.9	10	0.11	0.056
10.6	9	0.06	0.023
42	9	0.06	0.026
191.1	10	0.04	0.019

### Estimated Values of Interest

Est Mean	Est Std	Scaled Residual
0.1161	0.03535	-0.5418
0.09799	0.03535	1.075
0.06991	0.03535	-0.8411
0.04834	0.03535	0.9892
0.04753	0.03535	-0.6734
	0.1161 0.09799 0.06991 0.04834	0.1161 0.03535 0.09799 0.03535 0.06991 0.03535 0.04834 0.03535

Other models for which likelihoods are calculated:

Model A1: Yij = Mu(i) + e(ij) Var{e(ij)} = Sigma^2

Model A2:	Yij = Var{e(ij)} =	Mu(i) + e(ij) Sigma(i)^2
Model A3:		Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R:	Yij = Var{e(ij)} =	

Likelihoods of Interest

AIC	Model	Log(likelihood)	DF	
AIC				
264 5000	Al	138.2961	6	-
264.5923	A2	146.0837	10	-
272.1674	A3	138.2961	6	-
264.5923	R	125.1057	2	-
246.2114	4	136.4317	4	-
264.8634				

Additive constant for all log-likelihoods = -44.11. This constant added to the above values gives the log-likelihood including the term that does not

depend on the model parameters.

# Explanation of Tests

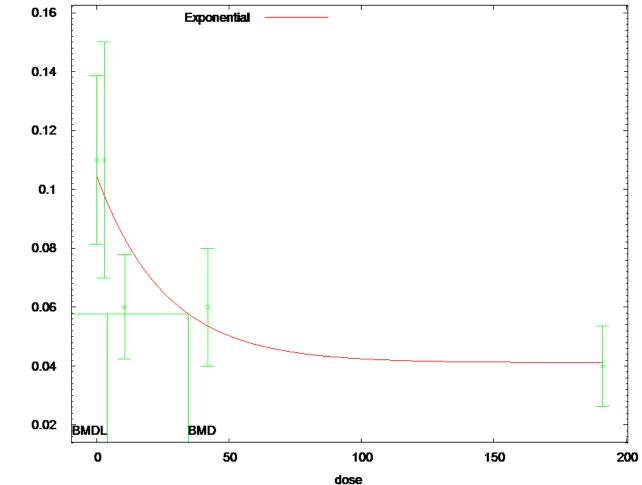
Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A2 vs. A1) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 6a: Does Model 4 fit the data? (A3 vs 4)

Test	-2*log(Likelihood Ratio)	D. F.
p-value		

Test 1	41.96	8
< 0.0001 Test 2	15.58	1
0.003646	13.30	Ŧ
Test 3	15.58	4
0.003646		
Test 6a	3.729	2
0.155		

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. Consider running a non-homogeneous variance model. The p-value for Test 3 is less than .1. You may want to consider a different variance model. 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 = 6.87276

BMDL = 2.97343



Mean Response

15:22 06/21 2014

```
_____
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Norm/LUC concurrent-HLS 2001-LUC
count-ExpNCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sat Jun 21 15:22:12 2014
______
===
BMDS Model Run
~~~~
  The form of the response function by Model:
                Y[dose] = a * exp{sign * b * dose}
     Model 2:
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
                Y[dose] = a * [c-(c-1) * exp{-b * dose}]
     Model 4:
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  The variance is to be modeled as Var(i) = exp(lalpha + log
(mean(i)) * rho)
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 4
lnalpha	-1.95665
rho	1.89965
a	0.1155
b	0.0201693
C	0.329829
d	1

## Parameter Estimates

Variable	Model 4
lnalpha	-1.60402
rho	1.99902
a	0.104728
b	0.0388147
C	0.392968
d	1

# Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	10	0.11	0.04
2.9	10	0.11	0.056
10.6	9	0.06	0.023
42	9	0.06	0.026
191.1	10	0.04	0.019

## Estimated Values of Interest

Est Mean	Est Std	Scaled Residual
0.1047	0.04701	0.3546
0.09796	0.04398	0.8658
0.08328	0.03739	-1.868
0.05361	0.02407	0.7966
0.04119	0.0185	-0.2039
	0.1047 0.09796 0.08328 0.05361	0.1047 0.04701 0.09796 0.04398 0.08328 0.03739 0.05361 0.02407

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)

		<pre>Var{e(ij)}</pre>	=	Sigma(i) <sup>2</sup>
Model A	A3:	Yij Var{e(ij)}	=	Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model	R:	Yij Var{e(ij)}	= =	Mu + e(i) Sigma^2

		Likelihoods of Int	erest	
210	Model	Log(likelihood)	DF	
AIC				
	Al	138.2961	6	-
264.5923	A2	146.0837	10	-
272.1674	A3	145.4923	7	-
276.9846	R	125.1057	2	-
246.2114	4	140.8295	5	-
271.659				

Additive constant for all log-likelihoods = -44.11. This constant added to the above values gives the log-likelihood including the term that does not

depend on the model parameters.

#### Explanation of Tests

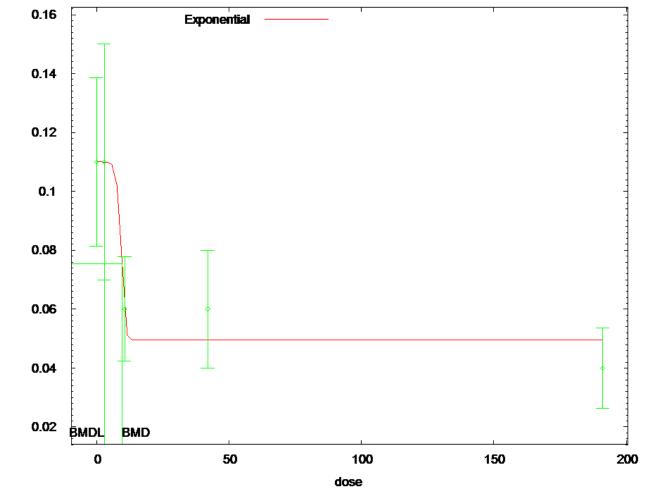
Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A2 vs. A1) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 6a: Does Model 4 fit the data? (A3 vs 4)

Test p-value	-2*log(Likelihood Ratio)	D. F.
Test 1	41.96	8
< 0.0001		

Test 2	15.58	4
0.003646		
Test 3	1.183	3
0.7571		
Test 6a	9.326	2
0.00944		

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data. The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate. The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here. The p-value for Test 6a is less than .1. Model 4 may not adequately describe the data; you may want to consider another model. Benchmark Dose Computations: Specified Effect = 1.000000 Risk Type = Estimated standard deviations from control Confidence Level = 0.950000

> BMD = 34.6593 BMDL = 3.93988



15:22 06/21 2014

Mean Response

```
______
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Norm/LUC concurrent-HLS 2001-LUC
count-ExpCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sat Jun 21 15:22:11 2014
______
===
BMDS Model Run
~~~~
  The form of the response function by Model:
                Y[dose] = a * exp{sign * b * dose}
     Model 2:
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
               Y[dose] = a * [c-(c-1) * exp{-b * dose}]
     Model 4:
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  rho is set to 0.
  A constant variance model is fit.
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 5
lnalpha	-6.76234
rho(S)	0
a	0.1155
b	0.0201693
C	0.329829
d	1

(S) = Specified

#### Parameter Estimates

Variable	Model 5
lnalpha	-6.72878
rho	0
a	0.110002
b	0.101245
С	0.449753
d	7.91531

# Table of Stats From Input Data

Dose	Ν	Obs Mean	Obs Std Dev
0	10	0.11	0.04
2.9	10	0.11	0.056
10.6	9	0.06	0.023
42	9	0.06	0.026
191.1	10	0.04	0.019

### Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	0.11	0.03458	-0.0001696
2.9	0.11	0.03458	0.0001695
10.6	0.06	0.03458	-3.376e-008
42	0.04947	0.03458	0.9131
191.1	0.04947	0.03458	-0.8663

Other models for which likelihoods are calculated:

Model A1: Yij = Mu(i) + e(ij) Var{e(ij)} = Sigma^2

Model A2:	Yij = Var{e(ij)} =	Mu(i) + e(ij) Sigma(i)^2
Model A3:	Yij = Var{e(ij)} =	Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R:	Yij = Var{e(ij)} =	Mu + e(i) Sigma^2

Likelihoods of Interest

AIC	Model	Log(likelihood)	DF	
AIC				
264 5000	Al	138.2961	6	-
264.5923	A2	146.0837	10	-
272.1674	A3	138.2961	6	-
264.5923	R	125.1057	2	-
246.2114	5	137.4907	5	-
264.9813				

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

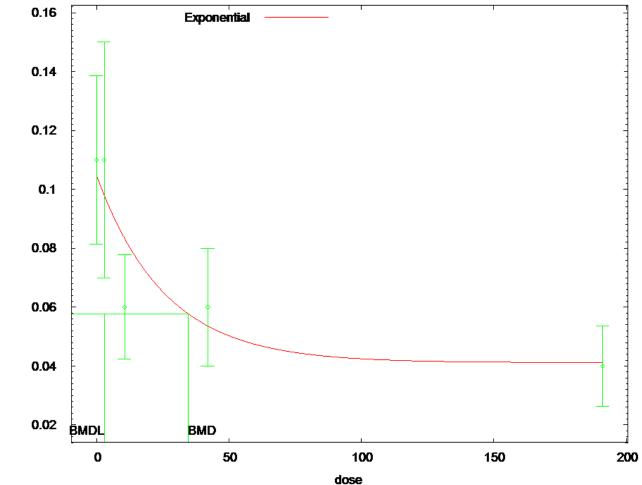
Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A2 vs. A1) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 7a: Does Model 5 fit the data? (A3 vs 5)

Test	-2*log(Likelihood Ratio)	D. F.
p-value		

Test	1	41.96	8
< 0.0001			
Test	2	15.58	4
0.003646			
Test	3	15.58	4
0.003646			
Test 7	'a	1.611	1
0.2044			

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. Consider running a non-homogeneous variance model. The p-value for Test 3 is less than .1. You may want to consider a different variance model. 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 = 9.67214

BMDL = 2.99175



15:22 06/21 2014

Mean Response

```
_____
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Norm/LUC concurrent-HLS 2001-LUC
count-ExpNCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sat Jun 21 15:22:12 2014
______
===
BMDS Model Run
~~~~
  The form of the response function by Model:
                Y[dose] = a * exp{sign * b * dose}
     Model 2:
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
                Y[dose] = a * [c-(c-1) * exp{-b * dose}]
     Model 4:
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  The variance is to be modeled as Var(i) = exp(lalpha + log
(mean(i)) * rho)
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 5
lnalpha	-1.95665
rho	1.89965
a	0.1155
b	0.0201693
С	0.329829
d	1

# Parameter Estimates

Variable	Model 5
lnalpha	-1.60402
rho	1.99902
a	0.104728
b	0.0388146
C	0.392968
d	1

# Table of Stats From Input Data

Dose	Ν	Obs Mean	Obs Std Dev
0	10	0.11	0.04
2.9	10	0.11	0.056
10.6	9	0.06	0.023
42	9	0.06	0.026
191.1	10	0.04	0.019

# Estimated Values of Interest

Est Mean	Est Std	Scaled Residual
0.1047	0.04701	0.3546
0.09796	0.04398	0.8658
0.08328	0.03739	-1.868
0.05361	0.02407	0.7966
0.04119	0.0185	-0.2039
	0.1047 0.09796 0.08328 0.05361	0.1047 0.04701 0.09796 0.04398 0.08328 0.03739 0.05361 0.02407

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)

		<pre>Var{e(ij)}</pre>	=	Sigma(i) <sup>2</sup>
Model A	A3:	Yij Var{e(ij)}	=	Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model	R:	Yij Var{e(ij)}	= =	Mu + e(i) Sigma^2

		Likelihoods of Int	erest	
	Model	Log(likelihood)	DF	
AIC				
	Al	138.2961	6	-
264.5923	A2	146.0837	10	_
272.1674	A3	145.4923	7	-
276.9846	R	125.1057	2	-
246.2114	5	140.8295	5	-
271.659				

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)

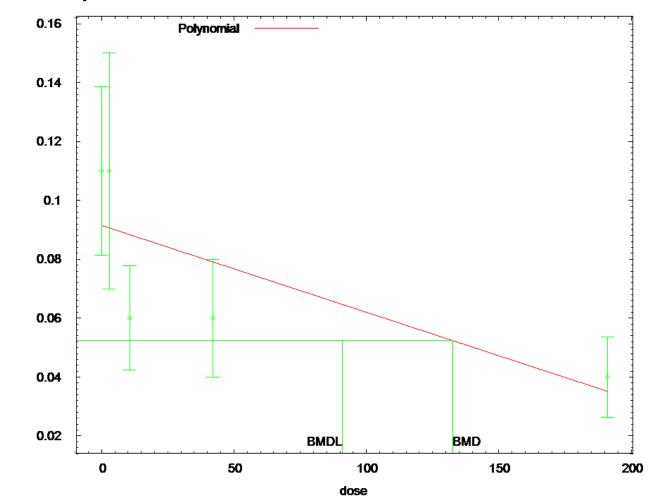
## Tests of Interest

Test p-value	-2*log(Likelihood Ratio)	D. F.
Test 1	41.96	8
< 0.0001		

Test 2	15.58	4
0.003646		
Test 3	1.183	3
0.7571		
Test 7a	9.326	2
0.00944		

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 7a is less than .1. Model 5 may not adequately describe the data; you may want to consider another model. Benchmark Dose Computations: Specified Effect = 1.000000 Risk Type = Estimated standard deviations from control Confidence Level = 0.950000

> BMD = 34.6593 BMDL = 2.96623



12:40 07/09 2014

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_LUC\_Concurrent/LUC\_concurrent-HLS 2001-LUC count-Poly2CV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_LUC\_Concurrent/LUC\_concurrent-HLS 2001-LUC count-Poly2CV-1SD-5d.plt Wed Jul 09 12:40:22 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse 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 = 5Total 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 = 0.001291 Specified rho = 0  $beta_0 = 0.101799$  $beta_1 = -0.00140875$ beta\_2 = 0 Asymptotic Correlation Matrix of Parameter Estimates ( \*\*\* The model parameter(s) -rho -beta 2 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	-2.9e-010	-2e-011
beta_0	-2.9e-010	1	-0.56
beta_1	-2e-011	-0.56	1

## Parameter Estimates

			95.0%
Wald Confidence In	terval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Conf	. Limit		
alpha	0.00153024	0.000312359	
0.000918027	0.00214245		
beta_0	0.091509	0.0068346	
0.0781134	0.104905		
beta_1	-0.000295198	7.65966e-005	-
0.000445324	-0.000145071		
beta_2	0	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 Scaled	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 1.49	10	0.11	0.0915	0.04	0.0391
2.9 1.56	10	0.11	0.0907	0.056	0.0391
10.6	9	0.06	0.0884	0.023	0.0391
42 -1.47	9	0.06	0.0791	0.026	0.0391
191.1 0.396	10	0.04	0.0351	0.019	0.0391

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<sup>2</sup>

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	138.296137	6	-264.592275
A2	146.083690	10	-272.167381
A3	138.296137	б	-264.592275
fitted	131.575968	3	-257.151936
R	125.105720	2	-246.211439

### 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	41.9559	8	<.0001
Test 2	15.5751	4	0.003646
Test 3	15.5751	4	0.003646
Test 4	13.4403	3	0.003775

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

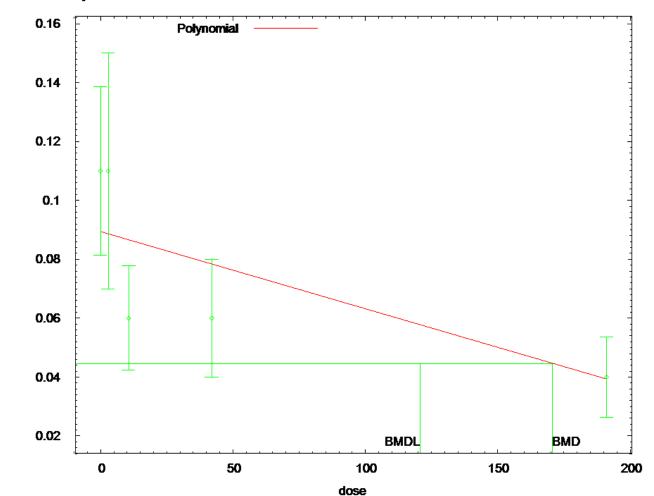
The p-value for Test 2 is less than .1. Consider running a non-homogeneous variance model The p-value for Test 3 is less than .1. You may want to consider а different variance model The p-value for Test 4 is less than .1. You may want to try a different model

### Benchmark Dose Computation

BMDL =

Specified effect = 1 = Estimated standard deviations from the Risk Type control mean Confidence level = 0.95 BMD = 132.516 90.8103

4



Mean Response

12:40 07/09 2014

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_LUC\_Concurrent/LUC\_concurrent-HLS 2001-LUC count-Poly2NCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_LUC\_Concurrent/LUC\_concurrent-HLS 2001-LUC count-Poly2NCV-1SD-5d.plt Wed Jul 09 12:40:25 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse 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 = 5Total number of records with missing values = 0Maximum 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 = -6.65234 rho = 0 beta\_0 = 0.101799  $beta_1 = -0.00140875$ beta\_2 = 0 Asymptotic Correlation Matrix of Parameter Estimates ( \*\*\* The model parameter(s) -beta\_2 have been estimated at a boundary point, or have been specified by the user,

and do not appear in the correlation matrix )

	lalpha	rho	beta_0	beta_1
lalpha	1	0.99	-0.052	0.061
rho	0.99	1	-0.052	0.06
beta_0	-0.052	-0.052	1	-0.82
beta_1	0.061	0.06	-0.82	1

Parameter Estimates

			95.00
Wald Confidence In	terval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Conf	. Limit		
lalpha	-0.716054	1.62767	-
3.90623	2.47412		
rho	2.2765	0.616544	
1.0681	3.48491		
beta_0	0.08936	0.00749719	
0.0746658	0.104054		
beta_1	-0.00026225	5.03908e-005	_
0.000361014	-0.000163486		
beta_2	0	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 Scaled 1	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 1.46	10	0.11	0.0894	0.04	0.0447
2.9	10	0.11	0.0886	0.056	0.0443
10.6	9	0.06	0.0866	0.023	0.0432
42 -1.43	9	0.06	0.0783	0.026	0.0385

191.1	10	0.04	0.0392	0.019	0.0175
0.136					

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
Al	138.296137	6	-264.592275
A2	146.083690	10	-272.167381
A3	145.492300	7	-276.984600
fitted	136.270966	4	-264.541933
R	125.105720	2	-246.211439

## Explanation of Tests

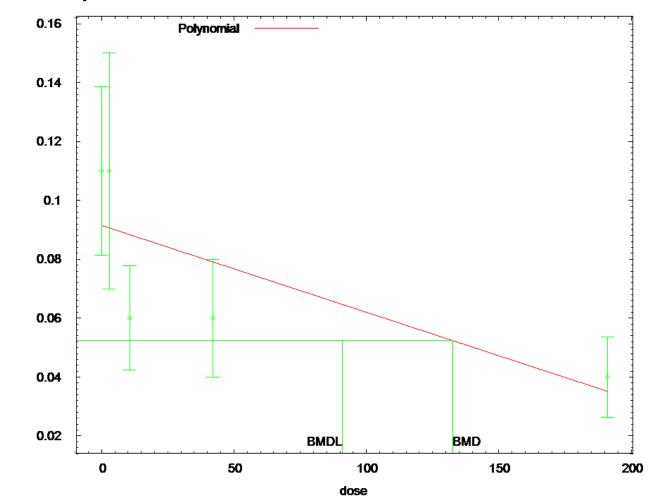
Test 1: Do responses and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A1 vs A2) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 4: Does the Model for the Mean Fit? (A3 vs. fitted) (Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

## Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	41.9559	8	<.0001
Test 2	15.5751	4	0.003646
Test 3	1.18278	3	0.7571
Test 4	18.4427	3	0.0003564

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 = Estimated standard deviations from the Risk Type control mean Confidence level = 0.95 BMD = 170.581

BMDL = 120.78



12:40 07/09 2014

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_LUC\_Concurrent/LUC\_concurrent-HLS 2001-LUC count-Poly3CV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_LUC\_Concurrent/LUC\_concurrent-HLS 2001-LUC count-Poly3CV-1SD-5d.plt Wed Jul 09 12:40:22 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse 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 = 5Total 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 = 0.001291 Specified rho = 0  $beta_0 = 0.117085$  $beta_1 = -0.00653781$ beta\_2 = 0  $beta_3 = -6.10808e - 007$ Asymptotic Correlation Matrix of Parameter Estimates ( \*\*\* The model parameter(s) -rho -beta\_2 -

beta\_3

have been estimated at a boundary point, or have been specified by the user,

and do not appear in the correlation matrix )

beta_1	beta_0	alpha	
-4.3e-011	-3.8e-011	1	alpha
-0.56	1	-3.8e-011	beta_0
1	-0.56	-4.3e-011	beta_1

Parameter Estimates

95.0%

		95.08
terval		
Estimate	Std. Err.	Lower Conf.
. Limit		
0.00153024	0.000312359	
0.00214245		
0.091509	0.0068346	
0.104905		
-0.000295198	7.65966e-005	-
-0.000145071		
-0	NA	
0	NA	
	Estimate . Limit 0.00153024 0.00214245 0.091509 0.104905 -0.000295198 -0.000145071 -0	Estimate Std. Err. . Limit 0.00153024 0.000312359 0.00214245 0.091509 0.0068346 0.104905 -0.000295198 7.65966e-005 -0.000145071 -0 NA

NA - Indicates that this parameter has hit a bound implied by some inequality constraint and thus has no standard error.

Table c	сf	Data	and	Estimated	Values	of	Interest
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Dose Scaled	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 1.49	10	0.11	0.0915	0.04	0.0391
2.9 1.56	10	0.11	0.0907	0.056	0.0391
10.6	9	0.06	0.0884	0.023	0.0391
42 -1.47	9	0.06	0.0791	0.026	0.0391
191.1	10	0.04	0.0351	0.019	0.0391

Model Descriptions for likelihoods calculated

Var{e(i)} = Sigma^2

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)

## Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
Al	138.296137	б	-264.592275
A2	146.083690	10	-272.167381
A3	138.296137	б	-264.592275
fitted	131.575968	3	-257.151936
R	125.105720	2	-246.211439

## Explanation of Tests

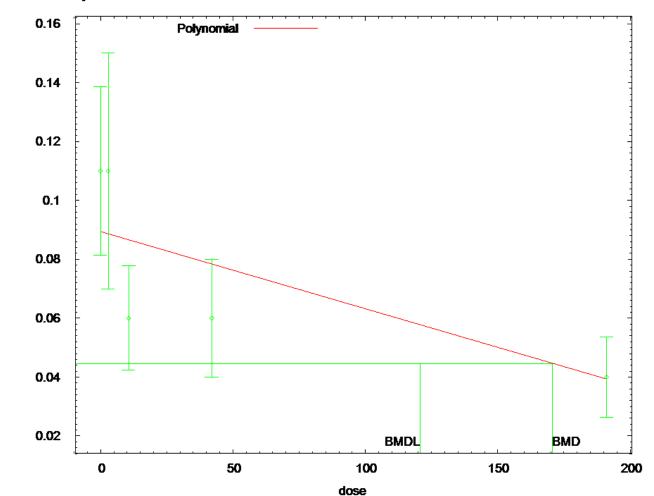
Test 1: Do responses and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A1 vs A2) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 4: Does the Model for the Mean Fit? (A3 vs. fitted) (Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

## Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1 Test 2 Test 3	41.9559 15.5751 15.5751	8 4 4	<.0001 0.003646 0.003646
Test 4	13.4403	3	0.003775

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. Consider running a non-homogeneous variance model The p-value for Test 3 is less than .1. You may want to consider а different variance model The p-value for Test 4 is less than .1. You may want to try a different model Benchmark Dose Computation Specified effect = 1 Estimated standard deviations from the Risk Type = control mean Confidence level = 0.95 132.516 BMD = BMDL = 90.8103



Mean Response

12:40 07/09 2014

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_LUC\_Concurrent/LUC\_concurrent-HLS 2001-LUC count-Poly3NCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_LUC\_Concurrent/LUC\_concurrent-HLS 2001-LUC count-Poly3NCV-1SD-5d.plt Wed Jul 09 12:40:25 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse 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 = 5Total number of records with missing values = 0Maximum 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 = -6.65234 rho = 0 beta\_0 = 0.117085  $beta_1 = -0.00653781$ beta\_2 = 0  $beta_3 = -6.10808e - 007$ Asymptotic Correlation Matrix of Parameter Estimates ( \*\*\* The model parameter(s) -beta\_2 -beta\_3

have been estimated at a boundary point, or have been specified by the user, and do not appear in the correlation matrix )

	lalpha	rho	beta_0	beta_1
lalpha	1	0.99	-0.052	0.061
rho	0.99	1	-0.052	0.06
beta_0	-0.052	-0.052	1	-0.82
beta_1	0.061	0.06	-0.82	1

Parameter Estimates

95.0%

terval		
Estimate	Std. Err.	Lower Conf.
. Limit		
-0.716063	1.62767	-
2.47411		
2.2765	0.616544	
3.4849		
0.08936	0.00749719	
0.104054		
-0.00026225	5.03908e-005	-
-0.000163486		
0	NA	
0	NA	
	Estimate . Limit -0.716063 2.47411 2.2765 3.4849 0.08936 0.104054 -0.00026225 -0.000163486	Estimate Std. Err. . Limit -0.716063 1.62767 2.47411 2.2765 0.616544 3.4849 0.08936 0.00749719 0.104054 -0.00026225 5.03908e-005 -0.000163486 0 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 Scaled	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 1.46	10	0.11	0.0894	0.04	0.0447
2.9	10	0.11	0.0886	0.056	0.0443
10.6 -1.85	9	0.06	0.0866	0.023	0.0432

42	9	0.06	0.0783	0.026	0.0385
-1.43					
191.1	10	0.04	0.0392	0.019	0.0175
0.136					

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	138.296137	б	-264.592275
A2	146.083690	10	-272.167381
A3	145.492300	7	-276.984600
fitted	136.270966	4	-264.541933
R	125.105720	2	-246.211439

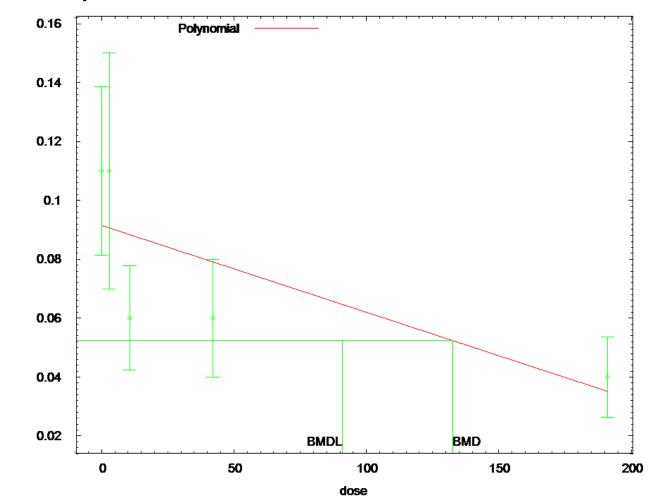
### Explanation of Tests

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	41.9559	8	<.0001
Test 2	15.5751	4	0.003646
Test 3	1.18278	3	0.7571

18.4427 3 0.0003564 Test 4 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 = Estimated standard deviations from the Risk Type control mean Confidence level = 0.95 BMD = 170.581 BMDL = 120.78



12:40 07/09 2014

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_LUC\_Concurrent/LUC\_concurrent-HLS 2001-LUC count-Poly4CV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_LUC\_Concurrent/LUC\_concurrent-HLS 2001-LUC count-Poly4CV-1SD-5d.plt Wed Jul 09 12:40:22 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse 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 = 5Total 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 = 0.001291 Specified rho = 0 beta\_0 = 0.11 beta\_1 = 0  $beta_2 = -0.000923644$ beta\_3 = 0  $beta_4 = -1.01654e-007$ 

Asymptotic Correlation Matrix of Parameter Estimates

	alpha	beta_0	beta_1
alpha	1	8.5e-009	-5e-008
beta_0	8.5e-009	1	-0.56
beta_1	-5e-008	-0.56	1

Parameter Estimates

$\sim$	Γ.	<u>0</u>	
9	С	06	5

Wald Confidence In	terval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Conf	. Limit		
alpha	0.00153024	0.000312359	
0.000918027	0.00214245		
beta_0	0.091509	0.0068346	
0.0781134	0.104905		
beta_1	-0.000295198	7.65966e-005	-
0.000445324	-0.000145071		
beta_2	0	NA	
beta_3	0	NA	
beta_4	0	NA	

NA - Indicates that this parameter has hit a bound implied by some inequality constraint and thus has no standard error.

Dose Scaled	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 1.49	10	0.11	0.0915	0.04	0.0391
2.9 1.56	10	0.11	0.0907	0.056	0.0391
10.6 -2.18	9	0.06	0.0884	0.023	0.0391
42	9	0.06	0.0791	0.026	0.0391

Table of Data and Estimated Values of Interest

-1.47 191.1 0.396	10	0.04	0.0351	0.019	0.0391
Model	Descriptio	ns for like	lihoods calcul	ated	
Model		Yij = Mu(i ij)} = Sigm			
Model		Yij = Mu(i ij)} = Sigm			
Мо	Var{e( odel A3 use	Yij = Mu(i ij)} = Sigm s any fixed ed by the u	a^2 variance para	meters that	
Model		Yi = Mu + (i)} = Sigm	( <i>)</i>		

# Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
Al	138.296137	6	-264.592275
A2	146.083690	10	-272.167381
A3	138.296137	б	-264.592275
fitted	131.575968	3	-257.151936
R	125.105720	2	-246.211439

## 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

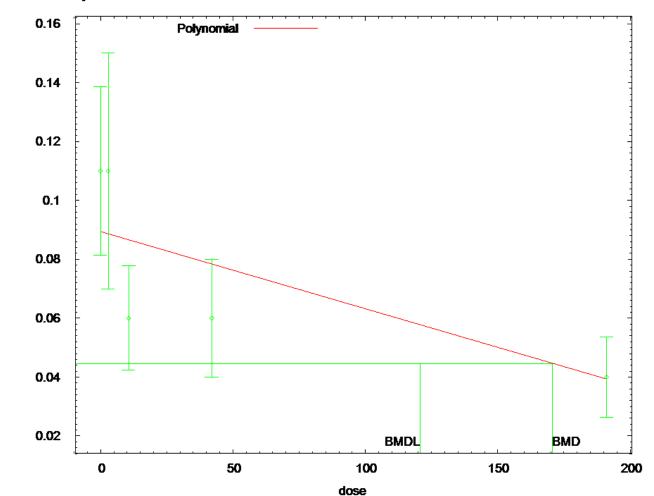
Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	41.9559	8	<.0001
Test 2	15.5751	4	0.003646
Test 3	15.5751	4	0.003646
Test 4	13.4403	3	0.003775

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. Consider running a non-homogeneous variance model The p-value for Test 3 is less than .1. You may want to consider а different variance model The p-value for Test 4 is less than .1. You may want to try a different model Benchmark Dose Computation Specified effect = 1 = Estimated standard deviations from the Risk Type control mean

Confidence level = 0.95

BMD = 132.516

BMDL = 90.8103



Mean Response

12:40 07/09 2014

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_LUC\_Concurrent/LUC\_concurrent-HLS 2001-LUC count-Poly4NCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_LUC\_Concurrent/LUC\_concurrent-HLS 2001-LUC count-Poly4NCV-1SD-5d.plt Wed Jul 09 12:40:24 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse 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 = 5Total number of records with missing values = 0Maximum 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 = -6.65234 rho = 0 0.11 beta\_0 = beta\_1 = 0  $beta_2 = -0.000923644$ beta\_3 = 0  $beta_4 = -1.01654e - 007$ Asymptotic Correlation Matrix of Parameter Estimates

1

0.061	-0.052	0.99	1	lalpha
0.06	-0.052	1	0.99	rho
-0.82	1	-0.052	-0.052	beta_0
1	-0.82	0.06	0.061	beta_1

## Parameter Estimates

# 95.0%

Wald Confidence Interval					
Variab	le Estimate	Std. Err.	Lower Conf.		
Limit Upper	Conf. Limit				
lalpl	na -0.716065	1.62767	_		
3.90624	2.47411				
rl	no 2.2765	0.616544			
1.0681	3.4849				
beta	_0 0.08936	0.00749719			
0.0746658	0.104054				
beta	_1 -0.00026225	5.03908e-005	_		
0.000361015	-0.000163486				
beta	_2 0	NA			
beta	_3 0	NA			
beta	_4 0	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 Scaled H	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 1.46	10	0.11	0.0894	0.04	0.0447
2.9	10	0.11	0.0886	0.056	0.0443

1.53					
10.6	9	0.06	0.0866	0.023	0.0432
-1.85					
42	9	0.06	0.0783	0.026	0.0385
-1.43					
191.1	10	0.04	0.0392	0.019	0.0175
0.136					

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
Al	138.296137	б	-264.592275
A2	146.083690	10	-272.167381
A3	145.492300	7	-276.984600
fitted	136.270966	4	-264.541933
R	125.105720	2	-246.211439

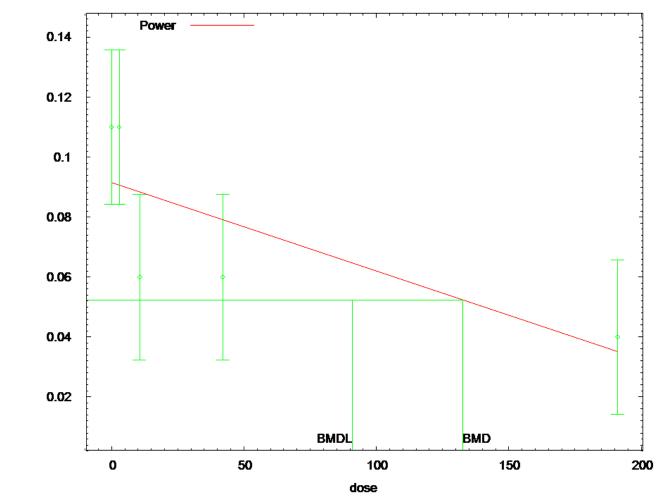
## Explanation of Tests

## Tests of Interest

Test	-2*log	(Likelihood	Ratio	) Test df	p-value
------	--------	-------------	-------	-----------	---------

3

8 Test 1 41.9559 <.0001 o 4 Test 2 0.003646 15.5751 Test 3 1.18278 3 0.7571 Test 4 18.4427 3 0.0003564 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 = 170.581 120.78 BMDL =



Power Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

15:22 06/21 2014

\_\_\_\_\_\_ === Power Model. (Version: 2.18; Date: 05/19/2014) Input Data File: C:/Users/dmayfield/Desktop/Norm/LUC concurrent-HLS 2001-LUC count-PowerCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Norm/LUC concurrent-HLS 2001-LUC count-PowerCV-1SD-5d.plt Sat Jun 21 15:22:12 2014 === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = control + slope \* dose^power Dependent variable = MeanResponse 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 = 5Total 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 = 0.001291 rho = 0 control = 0.11 slope = -0.800207 power = -0.463824 Specified 0 0.11 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	1.5e-007	1.8e-008
control	1.5e-007	1	-0.56
slope	1.8e-008	-0.56	1

### Parameter Estimates

			95.0%
Wald Confidence In	terval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Conf	. Limit		
alpha	0.00153024	0.000312359	
0.000918027	0.00214245		
control	0.091509	0.0068346	
0.0781134	0.104905		
slope	-0.000295198	7.65966e-005	-
0.000445324	-0.000145071		
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 Intere	Table	of	Data	and	Estimated	Values	of	Interest
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Dose Scaled	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 1.49	10	0.11	0.0915	0.04	0.0391
2.9	10	0.11	0.0907	0.056	0.0391
10.6	9	0.06	0.0884	0.023	0.0391
42 -1.47	9	0.06	0.0791	0.026	0.0391
191.1 0.396	10	0.04	0.0351	0.019	0.0391

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<sup>2</sup>

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	138.296137	6	-264.592275
A2	146.083690	10	-272.167381
A3	138.296137	6	-264.592275
fitted	131.575968	3	-257.151936
R	125.105720	2	-246.211439

#### 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

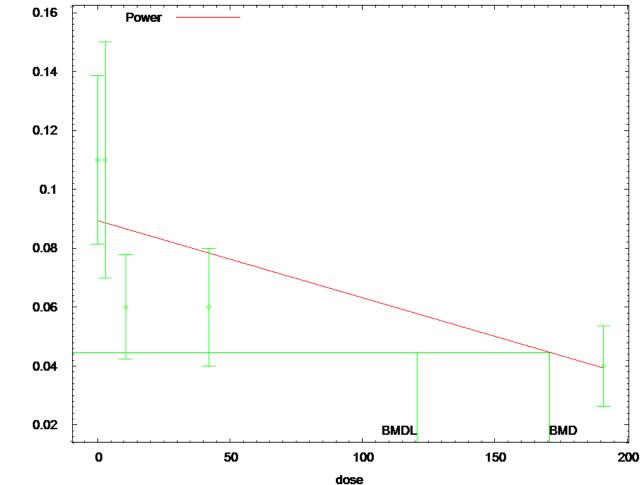
Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	41.9559	8	<.0001
Test 2	15.5751	4	0.003646
Test 3	15.5751	4	0.003646
Test 4	13.4403	3	0.003775

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. Consider running a non-homogeneous variance model The p-value for Test 3 is less than .1. You may want to consider a different variance model 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 = 132.516

BMDL = 90.8103



15:22 06/21 2014

Mean Response

\_\_\_\_\_\_ === Power Model. (Version: 2.18; Date: 05/19/2014) Input Data File: C:/Users/dmayfield/Desktop/Norm/LUC concurrent-HLS 2001-LUC count-PowerNCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Norm/LUC concurrent-HLS 2001-LUC count-PowerNCV-1SD-5d.plt Sat Jun 21 15:22:14 2014 === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = control + slope \* dose^power Dependent variable = MeanResponse Independent variable = Dose The power is restricted to be greater than or equal to 1 The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) \* rho) Total number of dose groups = 5Total 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 = -6.65234 rho = rho = 0 control = 0.11 slope = -0.800207 power = -0.463824 0 Asymptotic Correlation Matrix of Parameter Estimates ( \*\*\* The model parameter(s) -power have been estimated at a boundary point, or have been specified by the user,

and do not appear in the correlation matrix )

	lalpha	rho	control	slope
lalpha	1	0.99	-0.45	0.64
rho	0.99	1	-0.39	0.62
control	-0.45	-0.39	1	-0.82
slope	0.64	0.62	-0.82	1

Parameter Estimates

## 95.0%

			90.00
Wald Confidence Inte			
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Conf.	Limit		
lalpha	-0.716057	2.16724	-
4.96376	3.53165		
rho	2.2765	0.815964	
0.677244	3.87576		
control	0.08936	0.00757597	
0.0745113	0.104209		
slope	-0.00026225	5.08149e-005	-
0.000361845	-0.000162655		
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 Scaled 1	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0	10	0.11	0.0894	0.04	0.0447
1.46					
2.9	10	0.11	0.0886	0.056	0.0443
1.53					
10.6	9	0.06	0.0866	0.023	0.0432
-1.85					
42	9	0.06	0.0783	0.026	0.0385
-1.43					

191.1	10	0.04	0.0392	0.019	0.0175
0.136					

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	138.296137	6	-264.592275
A2	146.083690	10	-272.167381
A3	145.492300	7	-276.984600
fitted	136.270966	4	-264.541933
R	125.105720	2	-246.211439

### Explanation of Tests

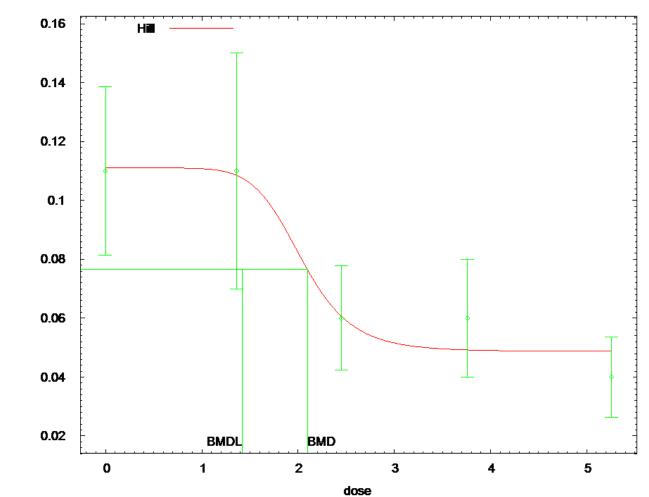
Test 1: Do responses and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A1 vs A2) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 4: Does the Model for the Mean Fit? (A3 vs. fitted) (Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

#### Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	41.9559	8	<.0001
Test 2	15.5751	4	0.003646
Test 3	1.18278	3	0.7571
Test 4	18.4427	3	0.0003564

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 Estimated standard deviations from the Risk Type = control mean Confidence level = 0.95 BMD = 170.581BMDL = 120.78

BMDS Model Results for Large Unstained Cells Count (Log-transformed Doses, Concurrent Controls)



Hill Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

Mean Response

15:31 06/21 2014

\_\_\_\_\_\_ === Hill Model. (Version: 2.17; Date: 01/28/2013) Input Data File: C:/Users/dmayfield/Desktop/Ln/LUC concurrent-HLS 2001-LUC count-HillCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Ln/LUC concurrent-HLS 2001-LUC count-HillCV-1SD-5d.plt Sat Jun 21 15:31:12 2014 === BMDS Model Run ~~~~ The form of the response function is:  $Y[dose] = intercept + v*dose^n/(k^n + dose^n)$ Dependent variable = MeanResponse 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 = 5Total 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 = 0.001291 Specified rho = 0 intercept = 0.11 -0.07 v = n = 16.2187 k = 2.124 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 )

k		alpha	intercept	v	n
a] -2.6e-0	lpha 006	1	2e-006	-1.5e-006	-2.5e-006
intero -0.57	cept	2e-006	1	-0.81	-0.6
0.35	v	-1.5e-006	-0.81	1	0.67
0.65	n	-2.5e-006	-0.6	0.67	1
	k	-2.6e-006	-0.57	0.35	0.65

# 1

## Parameter Estimates

95.0%

Wald Confiden	an Tri			
Wald Confidence	ce III	Leival		
Variab	le	Estimate	Std. Err.	Lower Conf.
Limit Upper	Conf	. Limit		
alpl	ha	0.00119497	0.000243923	
0.000716893		0.00167305		
interce	ot	0.111175	0.010299	
0.0909893	-	0.131361		
	v	-0.0623099	0.0149175	_
0.0915477		-0.0330721		
	n	7.84542	11.0062	-
13.7263		29.4172		
	k	2.04202	0.46892	
1.12296		2.96109		

# Table of Data and Estimated Values of Interest

Dose Scaled R		Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 -0.107	10	0.11	0.111	0.04	0.0346

1.361	10	0.11	0.109	0.056	0.0346
0.119 2.451	9	0.06	0.0609	0.023	0.0346
-0.076					
3.761 0.922	9	0.06	0.0494	0.026	0.0346
5.258	10	0.04	0.0489	0.019	0.0346
-0.814					

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	138.296137	6	-264.592275
A2	146.083690	10	-272.167381
A3	138.296137	6	-264.592275
fitted	137.511155	5	-265.022309
R	125.105720	2	-246.211439

## Explanation of Tests

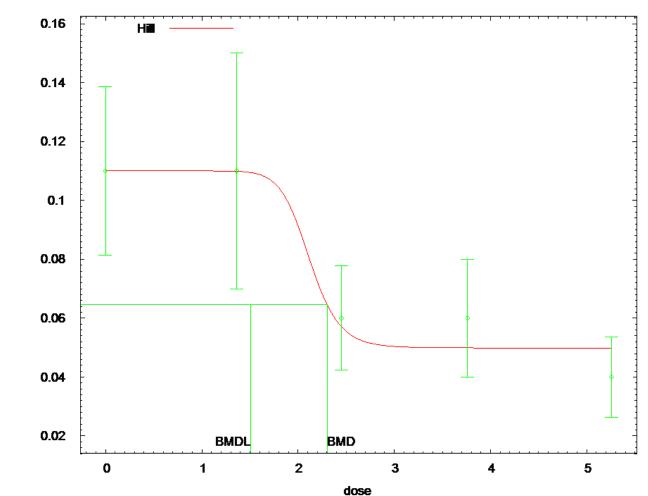
### Tests of Interest

Test -2\*log(Likelihood Ratio) Test df p-value

3

Test 141.95598<.0001</th>Test 215.575140.003646Test 315.575140.003646Test 41.5699710.2102

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. Consider running a non-homogeneous variance model The p-value for Test 3 is less than .1. You may want to consider а different variance model 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 = 2.1001 BMDL = 1.41795



Hill Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

15:31 06/21 2014

\_\_\_\_\_\_ === Hill Model. (Version: 2.17; Date: 01/28/2013) Input Data File: C:/Users/dmayfield/Desktop/Ln/LUC concurrent-HLS 2001-LUC count-HillNCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Ln/LUC concurrent-HLS 2001-LUC count-HillNCV-1SD-5d.plt Sat Jun 21 15:31:13 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is:  $Y[dose] = intercept + v*dose^n/(k^n + dose^n)$ Dependent variable = MeanResponse Independent variable = Dose Power parameter restricted to be greater than 1 The variance is to be modeled as Var(i) = exp(lalpha + rho \* ln(mean(i))) Total number of dose groups = 5Total 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 = -6.65234 rho = 0 intercept = 0.11 -0.07 v = n = 16.2187 k = 2.124 Asymptotic Correlation Matrix of Parameter Estimates intercept lalpha rho v

n	k			
lalpha 0.027	1 0.011	0.99	-0.38	0.46
rho 0.028	0.99 0.012	1	-0.34	0.45
intercept -0.2	-0.38	-0.34	1	-0.9
v 0.27	0.46 0.25	0.45	-0.9	1
n 1 0.	0.027 98	0.028	-0.2	0.27
k 0.98	0.011	0.012	-0.21	0.25

Parameter Estimates

			95.0%
Wald Confidence Int	erval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Conf.	Limit		
lalpha	-2.17641	1.65816	-
5.42635	1.07352		
rho	1.81184	0.624065	
0.588697	3.03499		
intercept	0.110395	0.0104058	
0.0900003	0.13079		
v	-0.060051	0.0119329	-
0.0834391	-0.0366628		
n	13.7775	54.3009	-
92.6503	120.205		
k	2.11962	1.16519	-
0.164118	4.40336		

Table of Data and Estimated Values of Interest

Dose Scaled R		Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 -0.0273	10	0.11	0.11	0.04	0.0457

1.361 -0.0181	10	0.11	0.11	0.056	0.0457
2.451 0.297	9	0.06	0.0575	0.023	0.0253
3.761	9	0.06	0.0504	0.026	0.0225
1.29 5.258	10	0.04	0.0503	0.019	0.0225
-1.46					

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
Al	138.296137	6	-264.592275
A2	146.083690	10	-272.167381
A3	145.492300	7	-276.984600
fitted	142.900991	6	-273.801982
R	125.105720	2	-246.211439

#### 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"Tog (LIRETINOOU RACTO) Test ut p-vatu	Test	-2*log(Likelihood	Ratio)	Test df	p-valu
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Test 141.95598<.0001</th>Test 215.575140.003646Test 31.1827830.7571Test 45.1826210.02281

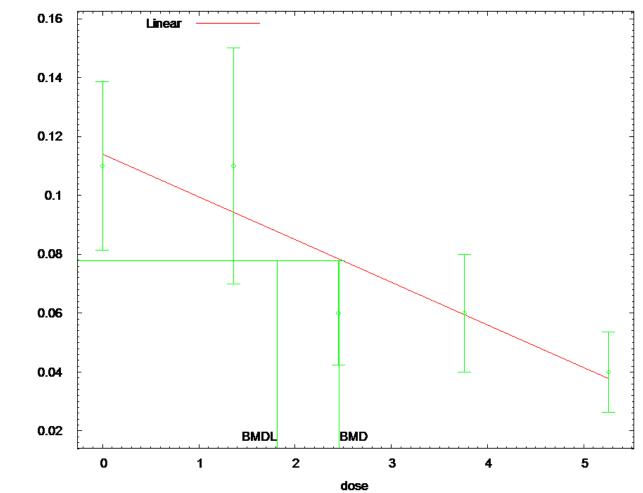
The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels It seems appropriate to model the data The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate

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 = 2.30628 BMDL = 1.50553



Mean Response

12:53 07/09 2014

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_LUC\_Concurren\_Ln/LUC\_concurrent-HLS 2001-LUC count-LinearCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_LUC\_Concurren\_Ln/LUC\_concurrent-HLS 2001-LUC count-LinearCV-1SD-5d.plt Wed Jul 09 12:53:08 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse Independent variable = Dose rho is set to 0 Signs of the polynomial coefficients are not restricted A constant variance model is fit Total number of dose groups = 5Total number of records with missing values = 0Maximum 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 = 0.001291 rho = 0 Specified beta\_0 = 0.113195 beta\_1 = -0.0144941 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	7.4e-009	-7.8e-009
beta_0	7.4e-009	1	-0.81
beta_1	-7.8e-009	-0.81	1

## Parameter Estimates

			95.0%
Wald Confidence I	nterval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Con	f. Limit		
alpha	0.00127623	0.000260509	
0.000765639	0.00178682		
beta_0	0.113585	0.00874069	
0.0964537	0.130717		
beta_1	-0.0145136	0.00277459	-
0.0199517	-0.00907554		

Table of Data and Estimated Values of Interest

Dose Scaled 1	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 -0.317	10	0.11	0.114	0.04	0.0357
-0.317 1.361 1.43	10	0.11	0.0938	0.056	0.0357
2.451	9	0.06	0.078	0.023	0.0357
3.761	9	0.06	0.059	0.026	0.0357
5.258 0.241	10	0.04	0.0373	0.019	0.0357

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
Al	138.296137	б	-264.592275
A2	146.083690	10	-272.167381
A3	138.296137	б	-264.592275
fitted	135.932325	3	-265.864651
R	125.105720	2	-246.211439

## 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	41.9559	8	<.0001
Test 2	15.5751	4	0.003646
Test 3	15.5751	4	0.003646
Test 4	4.72762	3	0.1929

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. Consider running a non-homogeneous variance model

The p-value for Test 3 is less than .1. You may want to consider a

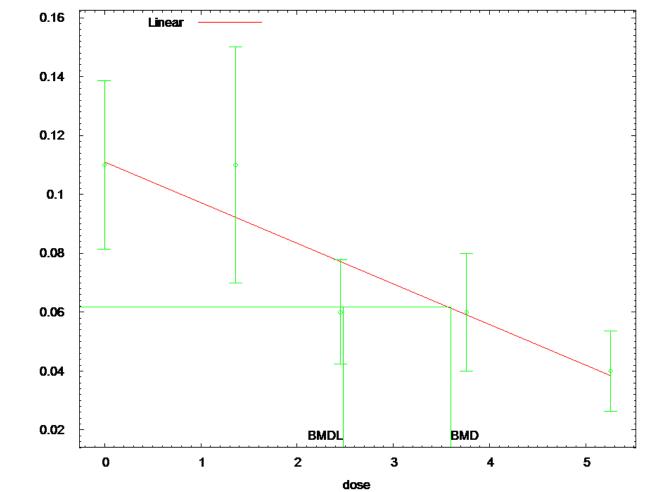
different variance model

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 = 2.46143

BMDL = 1.81322



Mean Response

12:53 07/09 2014

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_LUC\_Concurren\_Ln/LUC\_concurrent-HLS 2001-LUC count-LinearNCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_LUC\_Concurren\_Ln/LUC\_concurrent-HLS 2001-LUC count-LinearNCV-1SD-5d.plt Wed Jul 09 12:53:09 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse Independent variable = Dose Signs of the polynomial coefficients are not restricted The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) \* rho) Total number of dose groups = 5Total number of records with missing values = 0Maximum 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 = -6.65234 rho = 0 beta\_0 = 0.113195 beta\_1 = -0.0144941 Asymptotic Correlation Matrix of Parameter Estimates lalpha beta\_0 beta 1 rho 0.99 -0.073 0.086 lalpha 1

rho	0.99	1	-0.073	0.087
beta_0	-0.073	-0.073	1	-0.92
beta_1	0.086	0.087	-0.92	1

Parameter Estimates

## 95.0%

Wald Confidence Interval					
Variable	Estimate	Std. Err.	Lower Conf.		
Limit Upper Co:	nf. Limit				
lalpha	-1.68251	1.47799	-		
4.57931	1.21429				
rho	1.97135	0.555285			
0.883008	3.05969				
beta_0	0.111471	0.0102095			
0.0914608	0.131481				
beta_1	-0.0137839	0.00240468	-		
0.018497	-0.00907084				

Table of Data and Estimated Values of Interest

Dose Scaled R	N .es.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 -0.0938	10	0.11	0.111	0.04	0.0496
1.361	10	0.11	0.0927	0.056	0.0414
2.451	9	0.06	0.0777	0.023	0.0347
3.761 0.0415	9	0.06	0.0596	0.026	0.0268
5.258 0.18	10	0.04	0.039	0.019	0.0176

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<sup>2</sup>

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
Al	138.296137	б	-264.592275
A2	146.083690	10	-272.167381
A3	145.492300	7	-276.984600
fitted	141.105082	4	-274.210164
R	125.105720	2	-246.211439

#### Explanation of Tests

#### Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	41.9559	8	<.0001
Test 2	15.5751	4	0.003646
Test 3	1.18278	3	0.7571
Test 4	8.77444	3	0.03245

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

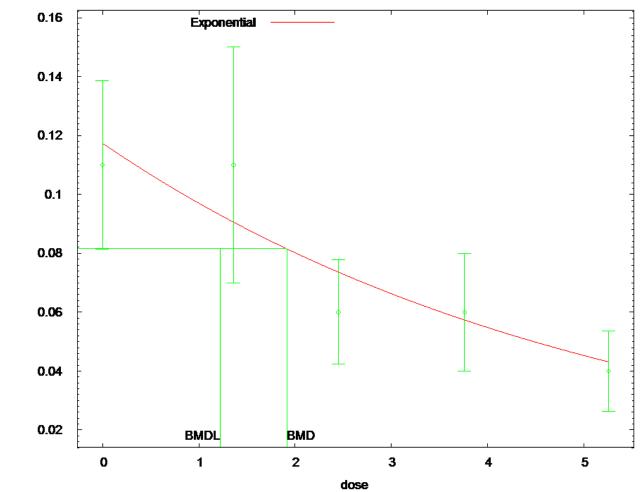
The p-value for Test 4 is less than .1. You may want to try a different model

Benchmark Dose Computation

Specified effect = 1 Risk Type = Estimated standard deviations from the control mean Confidence level = 0.95

BMD = 3.59823

BMDL = 2.47874



Mean Response

15:31 06/21 2014

```
_____
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Ln/LUC concurrent-HLS 2001-LUC count-
ExpCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sat Jun 21 15:31:12 2014
______
===
BMDS Model Run
~~~~
  The form of the response function by Model:
                Y[dose] = a * exp{sign * b * dose}
     Model 2:
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
               Y[dose] = a * [c-(c-1) * exp{-b * dose}]
     Model 4:
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  rho is set to 0.
  A constant variance model is fit.
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 2
lnalpha	-6.76234
rho(S)	0
a	0.0423932
b	0.202634
С	0
d	1

(S) = Specified

#### Parameter Estimates

Variable	Model 2
lnalpha	-6.65741
rho	0
a	0.117357
b	0.190434
C	0
d	1

## Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	10	0.11	0.04
1.361	10	0.11	0.056
2.451	9	0.06	0.023
3.761	9	0.06	0.026
5.258	10	0.04	0.019

## Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	0.1174	0.03584	-0.6491
1.361	0.09056	0.03584	1.715
2.451	0.07359	0.03584	-1.137
3.761	0.05734	0.03584	0.2227
5.258	0.04312	0.03584	-0.275

Other models for which likelihoods are calculated:

Model A1: Yij = Mu(i) + e(ij) Var{e(ij)} = Sigma^2

Model A2	Yij = Var{e(ij)} =	Mu(i) + e(ij) Sigma(i)^2
Model A3	Yij = Var{e(ij)} =	Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R	Yij = Var{e(ij)} =	Mu + e(i) Sigma^2

Likelihoods of Interest

AIC	Model	Log(likelihood)	DF	
ALC				
264 5000	Al	138.2961	6	-
264.5923	A2	146.0837	10	-
272.1674	A3	138.2961	6	-
264.5923	R	125.1057	2	-
246.2114	2	135.7778	3	-
265.5555				

Additive constant for all log-likelihoods = -44.11. This constant added to the above values gives the log-likelihood including the term that does not

depend on the model parameters.

### Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A2 vs. A1) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 4: Does Model 2 fit the data? (A3 vs. 2)

#### Tests of Interest

Test p-value	-2*log(Likelihood Ratio)	D. F.
Test 1	41.96	8

< 0.0001			
Test	2	15.58	4
0.003646			
Test	3	15.58	4
0.003646			
Test	4	5.037	3
0.1691			

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. Consider running

a non-homogeneous variance model.

The p-value for Test 3 is less than .1. You may want to consider a different variance model.

The p-value for Test 4 is greater than .1. Model 2 seems to adequately describe the data.

Benchmark Dose Computations:

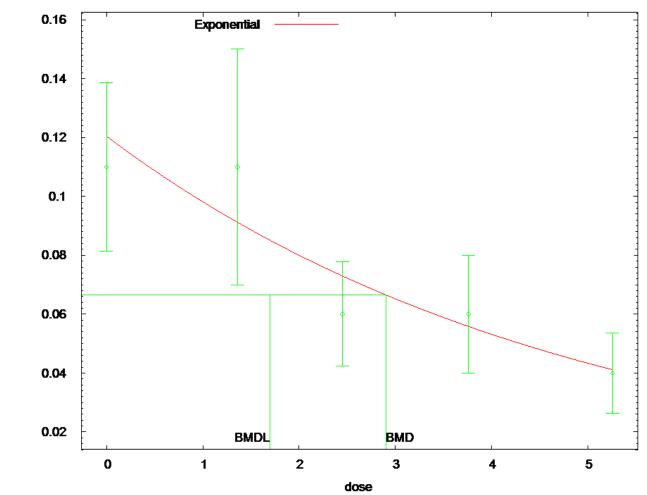
Specified Effect = 1.000000

Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

BMD = 1.91354

BMDL = 1.22128



Mean Response

15:31 06/21 2014

```
______
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Ln/LUC concurrent-HLS 2001-LUC count-
ExpNCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sat Jun 21 15:31:13 2014
______
===
BMDS Model Run
~~~~
  The form of the response function by Model:
                Y[dose] = a * exp{sign * b * dose}
     Model 2:
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
               Y[dose] = a * [c-(c-1) * exp{-b * dose}]
     Model 4:
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  The variance is to be modeled as Var(i) = exp(lalpha + log
(mean(i)) * rho)
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 2
lnalpha	-1.95665
rho	1.89965
a	0.0423932
b	0.202634
С	0
d	1

### Parameter Estimates

Variable	Model 2
lnalpha	-1.63386
rho	1.9875
a	0.12042
b	0.204379
С	0
d	1

# Table of Stats From Input Data

Dose	Ν	Obs Mean	Obs Std Dev
0	10	0.11	0.04
1.361	10	0.11	0.056
2.451	9	0.06	0.023
3.761	9	0.06	0.026
5.258	10	0.04	0.019

### Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	0.1204	0.05391	-0.6113
1.361	0.09118	0.04089	1.456
2.451	0.07297	0.03277	-1.187
3.761	0.05583	0.02511	0.4981
5.258	0.04111	0.01853	-0.1902

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)

		<pre>Var{e(ij)}</pre>	=	Sigma(i) <sup>2</sup>
Model A	A3:	Yij Var{e(ij)}	=	Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model	R:	Yij Var{e(ij)}	= =	Mu + e(i) Sigma^2

Likelihoods of Interest Model Log(likelihood) DF AIC \_ \_ \_ \_ \_ \_ \_ ----- ----\_ \_ \_ \_ \_ \_ \_ \_ \_ \_ \_ \_ \_ \_ \_ \_ \_ \_ 6 138.2961 A1 \_ 264.5923 10 146.0837 A2 272.1674 145.4923 7 A3 276.9846 R 125.1057 2 -246.2114 4 – 2 140.9803 273.9606

Additive constant for all log-likelihoods = -44.11. This constant added to the above values gives the log-likelihood including the term that does not

depend on the model parameters.

#### Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A2 vs. A1) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 4: Does Model 2 fit the data? (A3 vs. 2)

Test p-value	-2*log(Likelihood Ratio)	D. F.
Test 1	41.96	8
< 0.0001 Test 2	15.58	4

0.003646			
Test	3	1.183	3
0.7571			
Test	4	9.024	3
0.02897			

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. Model 2 may not adequately

describe the data; you may want to consider another model.

Benchmark Dose Computations:

Specified Effect = 1.000000

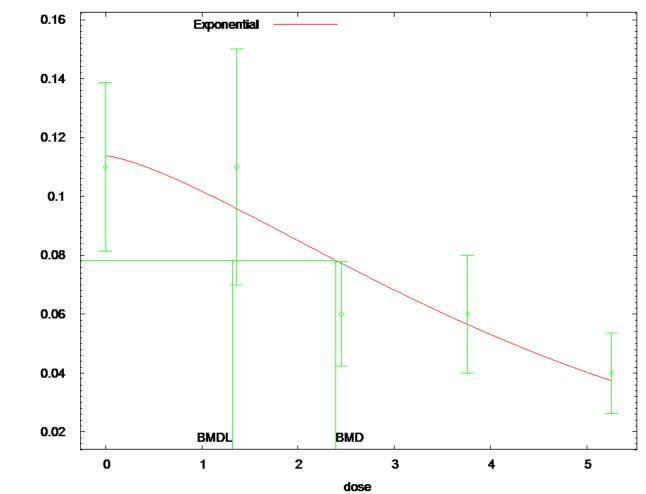
Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

BMDL =

BMD = 2.90447

1.69873



Mean Response

15:31 06/21 2014

```
_____
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Ln/LUC concurrent-HLS 2001-LUC count-
ExpCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sat Jun 21 15:31:12 2014
______
===
BMDS Model Run
~~~~
  The form of the response function by Model:
                Y[dose] = a * exp{sign * b * dose}
     Model 2:
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
               Y[dose] = a * [c-(c-1) * exp{-b * dose}]
     Model 4:
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  rho is set to 0.
  A constant variance model is fit.
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 3
lnalpha	-6.76234
rho(S)	0
a	0.134683
b	0.131222
С	0
d	2

(S) = Specified

#### Parameter Estimates

Variable	Model 3
lnalpha	-6.676
rho	0
a	0.113757
b	0.205456
C	0
d	1.3856

# Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	10	0.11	0.04
1.361	10	0.11	0.056
2.451	9	0.06	0.023
3.761	9	0.06	0.026
5.258	10	0.04	0.019

### Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	0.1138	0.03551	-0.3346
1.361	0.09587	0.03551	1.258
2.451	0.07729	0.03551	-1.461
3.761	0.05651	0.03551	0.2946
5.258	0.03738	0.03551	0.2334

Other models for which likelihoods are calculated:

Model A1: Yij = Mu(i) + e(ij) Var{e(ij)} = Sigma^2

Model A2:	Yij = Var{e(ij)} =	Mu(i) + e(ij) Sigma(i)^2
Model A3:	Yij = Var{e(ij)} =	Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R:	Yij = Var{e(ij)} =	Mu + e(i) Sigma^2

Likelihoods of Interest

AIC	Model	Log(likelihood)	DF	
AIC				
	A1	138.2961	6	-
264.5923	A2	146.0837	10	-
272.1674	A3	138.2961	6	-
264.5923	R	125.1057	2	_
246.2114	3	136.2241	4	-
264.4482				

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

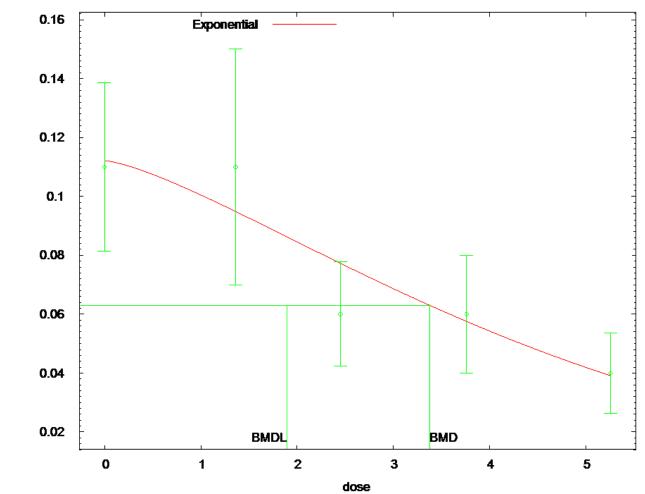
Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A2 vs. A1) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 5a: Does Model 3 fit the data? (A3 vs 3)

Test	-2*log(Likelihood Ratio)	D. F.
p-value		

Test 1	41.96	8
< 0.0001		
Test 2	15.58	4
0.003646		
Test 3	15.58	4
0.003646		
Test 5a	4.144	2
0.1259		

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. Consider running a non-homogeneous variance model. The p-value for Test 3 is less than .1. You may want to consider a different variance model. The p-value for Test 5a is greater than .1. Model 3 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 = 2.3942

BMDL = 1.31419



Mean Response

15:31 06/21 2014

```
______
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Ln/LUC concurrent-HLS 2001-LUC count-
ExpNCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sat Jun 21 15:31:13 2014
______
===
BMDS Model Run
~~~~
  The form of the response function by Model:
                Y[dose] = a * exp{sign * b * dose}
     Model 2:
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
               Y[dose] = a * [c-(c-1) * exp{-b * dose}]
     Model 4:
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  The variance is to be modeled as Var(i) = exp(lalpha + log
(mean(i)) * rho)
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 3
lnalpha	-1.95665
rho	1.89965
a	0.134683
b	0.131222
С	0
d	2

### Parameter Estimates

Variable	Model 3
lnalpha	-1.78769
rho	1.93751
a	0.112162
b	0.197578
С	0
d	1.36103

# Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	10	0.11	0.04
1.361	10	0.11	0.056
2.451	9	0.06	0.023
3.761	9	0.06	0.026
5.258	10	0.04	0.019

### Estimated Values of Interest

Est Mean	Est Std	Scaled Residual
0.1122	0.04913	-0.1392
0.09488	0.04178	1.145
0.07726	0.03424	-1.513
0.05754	0.02573	0.2874
0.03912	0.01771	0.1568
	0.1122 0.09488 0.07726 0.05754	0.1122 0.04913 0.09488 0.04178 0.07726 0.03424 0.05754 0.02573

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)

		<pre>Var{e(ij)}</pre>	=	Sigma(i) <sup>2</sup>
Model A	A3:	Yij Var{e(ij)}	=	Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model	R:	Yij Var{e(ij)}	= =	Mu + e(i) Sigma^2

		Likelihoods of Int	erest	
	Model	Log(likelihood)	DF	
AIC				
	A1	138.2961	6	-
264.5923	A2	146.0837	10	-
272.1674	A3	145.4923	7	_
276.9846	R	125.1057	2	-
246.2114	3	141.5335	5	_
273.067				

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 5a: Does Model 3 fit the data? (A3 vs 3)

Test p-value	-2*log(Likelihood Ratio)	D. F.
Test 1	41.96	8
< 0.0001		

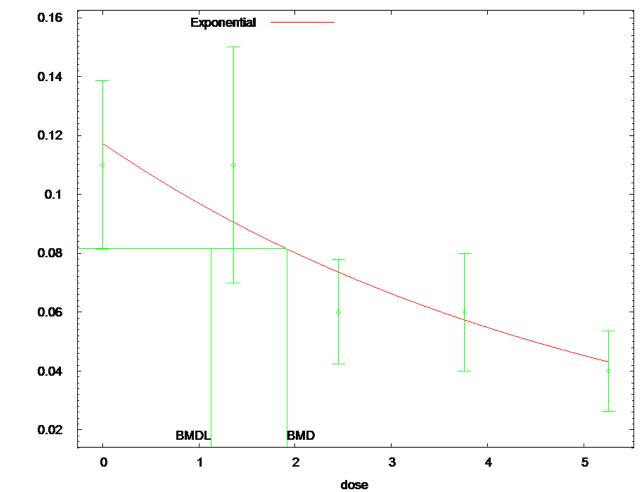
Test 2	15.58	4
0.003646		
Test 3	1.183	3
0.7571		
Test 5a	7.918	2
0.01909		

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 5a is less than .1. Model 3 may not adequately describe the data; you may want to consider another model. Benchmark Dose Computations: Specified Effect = 1.000000 Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

BMD = 3.37592

BMDL = 1.89841



Mean Response

15:31 06/21 2014

```
_____
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Ln/LUC concurrent-HLS 2001-LUC count-
ExpCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sat Jun 21 15:31:12 2014
______
===
BMDS Model Run
~~~~
  The form of the response function by Model:
                Y[dose] = a * exp{sign * b * dose}
     Model 2:
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
               Y[dose] = a * [c-(c-1) * exp{-b * dose}]
     Model 4:
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  rho is set to 0.
  A constant variance model is fit.
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 4
lnalpha	-6.76234
rho(S)	0
a	0.1155
b	0.19568
С	0.00034632
d	1

(S) = Specified

#### Parameter Estimates

Variable	Model 4
lnalpha	-6.65741
rho	0
a	0.117357
b	0.190434
C	0
d	1

# Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	10	0.11	0.04
1.361	10	0.11	0.056
2.451	9	0.06	0.023
3.761	9	0.06	0.026
5.258	10	0.04	0.019

### Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	0.1174	0.03584	-0.6491
1.361	0.09056	0.03584	1.715
2.451	0.07359	0.03584	-1.137
3.761	0.05734	0.03584	0.2227
5.258	0.04312	0.03584	-0.275

Other models for which likelihoods are calculated:

Model A1: Yij = Mu(i) + e(ij) Var{e(ij)} = Sigma^2

Model A2:	Yij = Var{e(ij)} =	Mu(i) + e(ij) Sigma(i)^2
Model A3:		Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R:	Yij = Var{e(ij)} =	

Likelihoods of Interest

AIC	Model	Log(likelihood)	DF	
AIC				
	A1	138.2961	6	-
264.5923	A2	146.0837	10	-
272.1674	A3	138.2961	6	_
264.5923	R	125.1057	2	_
246.2114	4	135.7778	3	_
265.5555	-	2001.110	5	

Additive constant for all log-likelihoods = -44.11. This constant added to the above values gives the log-likelihood including the term that does not

depend on the model parameters.

# Explanation of Tests

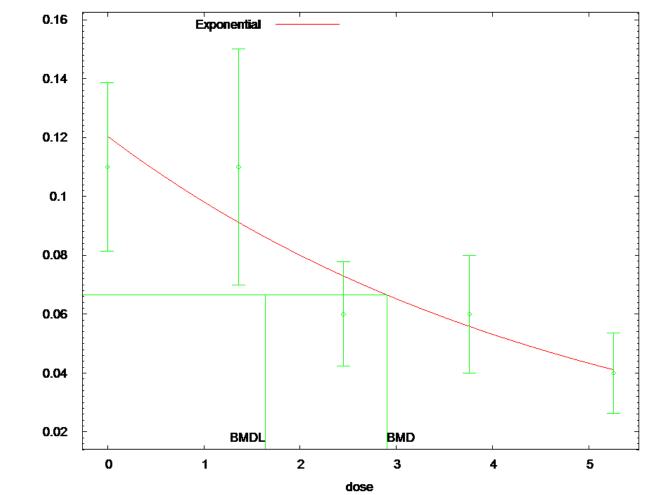
Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A2 vs. A1) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 6a: Does Model 4 fit the data? (A3 vs 4)

Test	-2*log(Likelihood Ratio)	D. F.
p-value		

Test 1 < 0.0001	41.96	8
Test 2	15.58	4
0.003646 Test 3	15.58	4
0.003646 Test 6a	5.037	3
0.1691		

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. Consider running a non-homogeneous variance model. The p-value for Test 3 is less than .1. You may want to consider a different variance model. The p-value for Test 6a is greater than .1. Model 4 seems to adequately describe the data. Benchmark Dose Computations: Specified Effect = 1.000000 Risk Type = Estimated standard deviations from control Confidence Level = 0.950000 BMD = 1.91354

BMDL = 1.12587



Mean Response

15:31 06/21 2014

```
______
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Ln/LUC concurrent-HLS 2001-LUC count-
ExpNCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sat Jun 21 15:31:13 2014
______
===
BMDS Model Run
~~~~
  The form of the response function by Model:
                Y[dose] = a * exp{sign * b * dose}
     Model 2:
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
               Y[dose] = a * [c-(c-1) * exp{-b * dose}]
     Model 4:
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  The variance is to be modeled as Var(i) = exp(lalpha + log
(mean(i)) * rho)
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 4
lnalpha	-1.95665
rho	1.89965
a	0.1155
b	0.19568
С	0.00034632
d	1

## Parameter Estimates

Variable	Model 4
lnalpha	-1.63385
rho	1.9875
a	0.12042
b	0.204378
С	0
d	1

# Table of Stats From Input Data

Dose	Ν	Obs Mean	Obs Std Dev
0	10	0.11	0.04
1.361	10	0.11	0.056
2.451	9	0.06	0.023
3.761	9	0.06	0.026
5.258	10	0.04	0.019

### Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	0.1204	0.05391	-0.6113
1.361	0.09118	0.04089	1.456
2.451	0.07297	0.03277	-1.187
3.761	0.05583	0.02511	0.4981
5.258	0.04111	0.01853	-0.1902

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)

		<pre>Var{e(ij)}</pre>	=	Sigma(i) <sup>2</sup>
Model A	A3:	Yij Var{e(ij)}	=	Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model	R:	Yij Var{e(ij)}	= =	Mu + e(i) Sigma^2

		Likelihoods of Int	cerest	
	Model	Log(likelihood)	DF	
AIC				
	A1	138.2961	6	-
264.5923	A2	146.0837	10	-
272.1674	A3	145.4923	7	_
276.9846	R	125.1057	2	-
246.2114	4	140.9803	4	_
273.9606				

Additive constant for all log-likelihoods = -44.11. This constant added to the above values gives the log-likelihood including the term that does not

depend on the model parameters.

#### Explanation of Tests

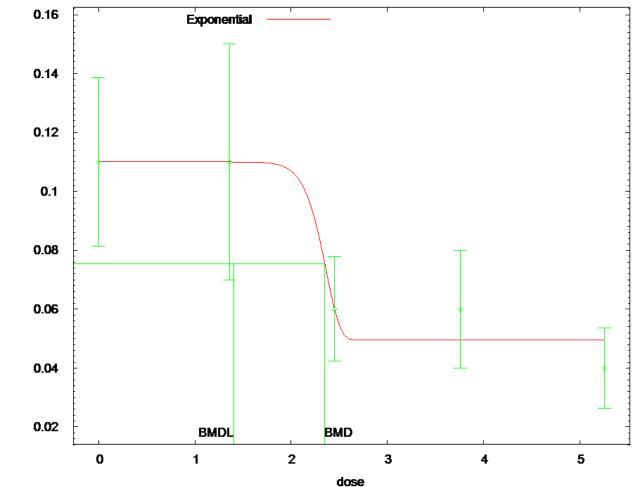
Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A2 vs. A1) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 6a: Does Model 4 fit the data? (A3 vs 4)

Test p-value	-2*log(Likelihood Ratio)	D. F.
Test 1 < 0.0001	41.96	8

Test 2	15.58	4
0.003646		
Test 3	1.183	3
0.7571		
Test 6a	9.024	3
0.02897		

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data. The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate. The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here. The p-value for Test 6a is less than .1. Model 4 may not adequately describe the data; you may want to consider another model. Benchmark Dose Computations: Specified Effect = 1.000000 Risk Type = Estimated standard deviations from control Confidence Level = 0.950000

> BMD = 2.90448 BMDL = 1.63628



15:31 06/21 2014

```
_____
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Ln/LUC concurrent-HLS 2001-LUC count-
ExpCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sat Jun 21 15:31:12 2014
______
===
BMDS Model Run
~~~~
  The form of the response function by Model:
                Y[dose] = a * exp{sign * b * dose}
     Model 2:
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
               Y[dose] = a * [c-(c-1) * exp{-b * dose}]
     Model 4:
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  rho is set to 0.
  A constant variance model is fit.
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 5
lnalpha	-6.76234
rho(S)	0
a	0.1155
b	0.19568
C	0.00034632
d	1

(S) = Specified

#### Parameter Estimates

Variable	Model 5
lnalpha	-6.72878
rho	0
a	0.110002
b	0.421364
C	0.449753
d	17.3452

# Table of Stats From Input Data

Dose	Ν	Obs Mean	Obs Std Dev
0	10	0.11	0.04
1.361	10	0.11	0.056
2.451	9	0.06	0.023
3.761	9	0.06	0.026
5.258	10	0.04	0.019

### Estimated Values of Interest

dual
1
4
8
1
3

Other models for which likelihoods are calculated:

Model A1: Yij = Mu(i) + e(ij) Var{e(ij)} = Sigma^2

Model A2:	Yij = Var{e(ij)} =	Mu(i) + e(ij) Sigma(i)^2
Model A3:	Yij = Var{e(ij)} =	Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R:	Yij = Var{e(ij)} =	Mu + e(i) Sigma^2

Likelihoods of Interest

AIC	Model	Log(likelihood)	DF	
AIC				
264 5000	Al	138.2961	6	-
264.5923	A2	146.0837	10	-
272.1674	A3	138.2961	6	-
264.5923	R	125.1057	2	-
246.2114	5	137.4907	5	-
264.9813				

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

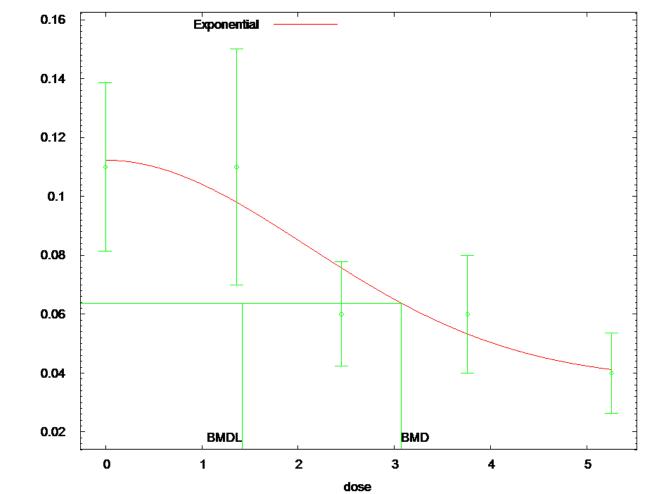
Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A2 vs. A1) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 7a: Does Model 5 fit the data? (A3 vs 5)

Test	-2*log(Likelihood Ratio)	D. F.
p-value		

Test 1	1	41.96	8
< 0.0001	-		
Test 2	2	15.58	4
0.003646			
Test 3	3	15.58	4
0.003646			
Test 7a	a	1.611	1
0.2044			

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. Consider running a non-homogeneous variance model. The p-value for Test 3 is less than .1. You may want to consider a different variance model. 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 = 2.35065

BMDL = 1.40406



Mean Response

15:31 06/21 2014

```
______
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Ln/LUC concurrent-HLS 2001-LUC count-
ExpNCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sat Jun 21 15:31:13 2014
______
===
BMDS Model Run
~~~~
  The form of the response function by Model:
                Y[dose] = a * exp{sign * b * dose}
     Model 2:
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
               Y[dose] = a * [c-(c-1) * exp{-b * dose}]
     Model 4:
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  The variance is to be modeled as Var(i) = exp(lalpha + log
(mean(i)) * rho)
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 5
lnalpha	-1.95665
rho	1.89965
a	0.1155
b	0.19568
С	0.00034632
d	1

## Parameter Estimates

Variable	Model 5
lnalpha	-1.86635
rho	1.91354
a	0.112314
b	0.332923
С	0.333365
d	1.95986

# Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	10	0.11	0.04
1.361	10	0.11	0.056
2.451	9	0.06	0.023
3.761	9	0.06	0.026
5.258	10	0.04	0.019

### Estimated Values of Interest

Est Mean	Est Std	Scaled Residual
0.1123	0.04855	-0.1507
0.09801	0.04262	0.8893
0.0757	0.03329	-1.415
0.05327	0.02378	0.8484
0.04118	0.01859	-0.2013
	0.1123 0.09801 0.0757 0.05327	0.1123 0.04855 0.09801 0.04262 0.0757 0.03329 0.05327 0.02378

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)

		<pre>Var{e(ij)}</pre>	=	Sigma(i) <sup>2</sup>
Model A	A3:	Yij Var{e(ij)}	=	Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model	R:	Yij Var{e(ij)}	= =	Mu + e(i) Sigma^2

		Likelihoods of Int	cerest	
AIC	Model	Log(likelihood)	DF	
ALC				
	Al	138.2961	6	-
264.5923	A2	146.0837	10	-
272.1674	A3	145.4923	7	-
276.9846	R	125.1057	2	-
246.2114	5	141.9263	6	-
271.8527				

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

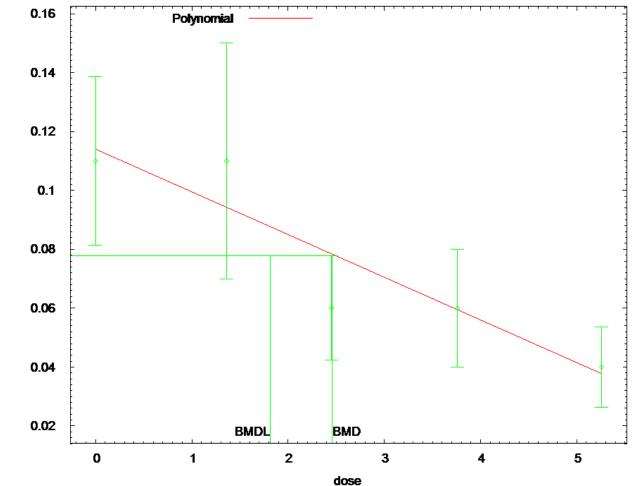
Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A2 vs. A1) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 7a: Does Model 5 fit the data? (A3 vs 5)

Test p-value	-2*log(Likelihood Ratio)	D. F.
Test 1 < 0.0001	41.96	8

Test 2	15.58	4
0.003646		
Test 3	1.183	3
0.7571		
Test 7a	7.132	1
0.007572		

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 7a is less than .1. Model 5 may not adequately describe the data; you may want to consider another model. Benchmark Dose Computations: Specified Effect = 1.000000 Risk Type = Estimated standard deviations from control Confidence Level = 0.950000

> BMD = 3.07261 BMDL = 1.42137



Polynomial Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

12:53 07/09 2014

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_LUC\_Concurren\_Ln/LUC\_concurrent-HLS 2001-LUC count-Poly2CV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_LUC\_Concurren\_Ln/LUC\_concurrent-HLS 2001-LUC count-Poly2CV-1SD-5d.plt Wed Jul 09 12:53:07 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse 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 = 5Total 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 = 0.001291 Specified rho = 0 beta\_0 = 0.115396 beta\_1 = -0.0176965 0.115396 beta\_2 = 0 Asymptotic Correlation Matrix of Parameter Estimates ( \*\*\* The model parameter(s) -rho -beta 2 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	-6.6e-009	2.1e-008
beta_0	-6.6e-009	1	-0.81
beta_1	2.1e-008	-0.81	1

# Parameter Estimates

			95.0%
Wald Confidence I	nterval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Con	f. Limit		
alpha	0.00127623	0.000260509	
0.000765639	0.00178682		
beta_0	0.113585	0.00874069	
0.0964537	0.130717		
beta_1	-0.0145136	0.00277459	-
0.0199517	-0.00907554		
beta_2	0	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 Scaled H	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 -0.317	10	0.11	0.114	0.04	0.0357
1.361 1.43	10	0.11	0.0938	0.056	0.0357
2.451	9	0.06	0.078	0.023	0.0357
3.761	9	0.06	0.059	0.026	0.0357
5.258 0.241	10	0.04	0.0373	0.019	0.0357

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<sup>2</sup>

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	138.296137	6	-264.592275
A2	146.083690	10	-272.167381
A3	138.296137	6	-264.592275
fitted	135.932325	3	-265.864651
R	125.105720	2	-246.211439

### 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

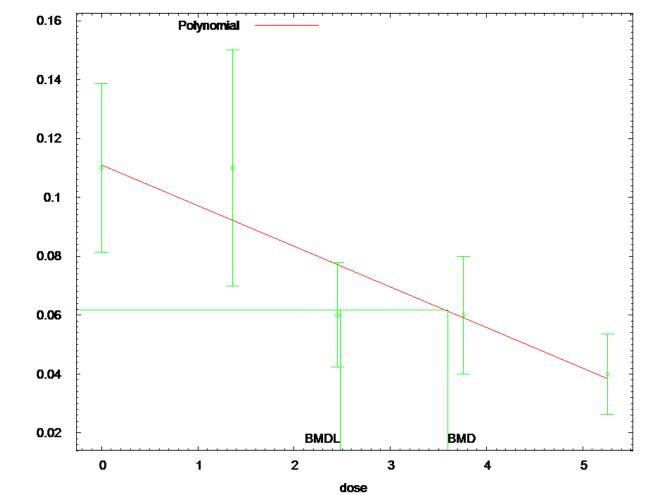
Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	41.9559	8	<.0001
Test 2	15.5751	4	0.003646
Test 3	15.5751	4	0.003646
Test 4	4.72762	3	0.1929

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. Consider running a non-homogeneous variance model The p-value for Test 3 is less than .1. You may want to consider a different variance model 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 = 2.46143

BMDL = 1.81322



Polynomial Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

Mean Response

12:53 07/09 2014

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_LUC\_Concurren\_Ln/LUC\_concurrent-HLS 2001-LUC count-Poly2NCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_LUC\_Concurren\_Ln/LUC\_concurrent-HLS 2001-LUC count-Poly2NCV-1SD-5d.plt Wed Jul 09 12:53:09 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse 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 = 5Total number of records with missing values = 0Maximum 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 = -6.65234 rho = 0 beta\_0 = 0.115396 beta\_1 = -0.0176965 beta\_2 = 0 Asymptotic Correlation Matrix of Parameter Estimates ( \*\*\* The model parameter(s) -beta\_2 have been estimated at a boundary point, or have been specified by the user,

and do not appear in the correlation matrix )

	lalpha	rho	beta_0	beta_1
lalpha	1	0.99	-0.073	0.086
rho	0.99	1	-0.073	0.087
beta_0	-0.073	-0.073	1	-0.92
beta_1	0.086	0.087	-0.92	1

Parameter Estimates

9	5	0	÷

			95.08
Wald Confidence 1	Interval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Cor	nf. Limit		
lalpha	-1.68251	1.47799	-
4.57931	1.21429		
rho	1.97135	0.555285	
0.883008	3.05969		
beta_0	0.111471	0.0102095	
0.0914608	0.131481		
beta 1	-0.0137839	0.00240468	-
0.018497	-0.00907084		
beta_2	0	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 Scaled R	N es.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 -0.0938	10	0.11	0.111	0.04	0.0496
1.361 1.32	10	0.11	0.0927	0.056	0.0414
2.451 -1.53	9	0.06	0.0777	0.023	0.0347
3.761 0.0415	9	0.06	0.0596	0.026	0.0268

5.258	10	0.04	0.039	0.019	0.0176
0.18					

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
Al	138.296137	б	-264.592275
A2	146.083690	10	-272.167381
A3	145.492300	7	-276.984600
fitted	141.105082	4	-274.210164
R	125.105720	2	-246.211439

# Explanation of Tests

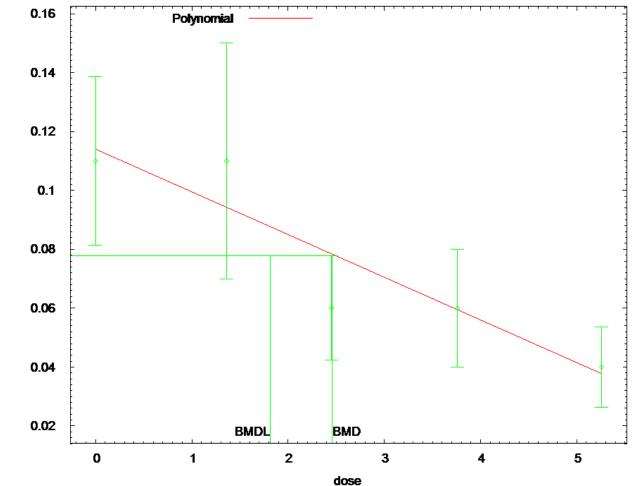
Test 1: Do responses and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A1 vs A2) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 4: Does the Model for the Mean Fit? (A3 vs. fitted) (Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

### Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	41.9559	8	<.0001
Test 2	15.5751	4	0.003646
Test 3	1.18278	3	0.7571
Test 4	8.77444	3	0.03245

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 = Estimated standard deviations from the Risk Type control mean Confidence level = 0.95 BMD = 3.59823

BMDL = 2.47874



Polynomial Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

12:53 07/09 2014

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_LUC\_Concurren\_Ln/LUC\_concurrent-HLS 2001-LUC count-Poly3CV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_LUC\_Concurren\_Ln/LUC\_concurrent-HLS 2001-LUC count-Poly3CV-1SD-5d.plt Wed Jul 09 12:53:07 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse 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 = 5Total 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 = 0.001291 Specified rho = 0 beta\_0 = 0.112441 beta\_1 = -0.0010106  $beta_2 = -0.00840676$ beta 3 = 0 Asymptotic Correlation Matrix of Parameter Estimates ( \*\*\* The model parameter(s) -rho -beta\_2 -

beta\_3

have been estimated at a boundary point, or have been specified by the user,

and do not appear in the correlation matrix )

beta_1	beta_0	alpha	
-8.2e-014	3.3e-012	1	alpha
-0.81	1	3.3e-012	beta_0
1	-0.81	-8.2e-014	beta_1

Parameter Estimates

95.0%

			95.08
Wald Confidence I			
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Con	f. Limit		
alpha	0.00127623	0.000260509	
0.000765639	0.00178682		
beta_0	0.113585	0.00874069	
0.0964537	0.130717		
beta_1	-0.0145136	0.00277459	_
0.0199517	-0.00907554		
beta_2	-1.86999e-027	NA	
beta_3	0	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
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Dose Scaled H	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 -0.317	10	0.11	0.114	0.04	0.0357
1.361 1.43	10	0.11	0.0938	0.056	0.0357
2.451 -1.51	9	0.06	0.078	0.023	0.0357
3.761	9	0.06	0.059	0.026	0.0357
5.258	10	0.04	0.0373	0.019	0.0357

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
Al	138.296137	б	-264.592275
A2	146.083690	10	-272.167381
A3	138.296137	б	-264.592275
fitted	135.932325	3	-265.864651
R	125.105720	2	-246.211439

# Explanation of Tests

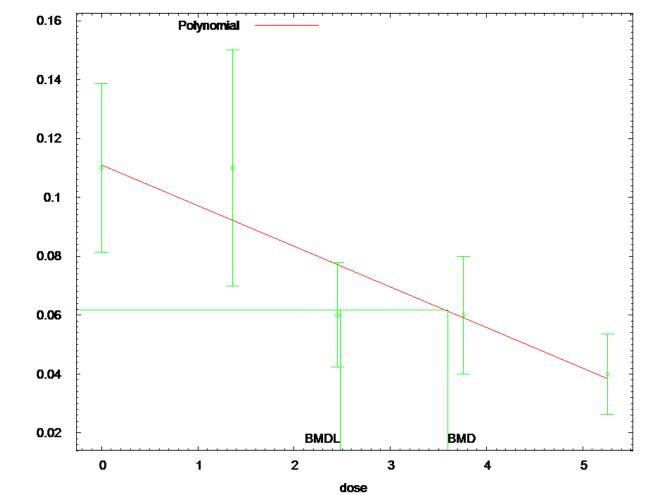
Test 1: Do responses and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A1 vs A2) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 4: Does the Model for the Mean Fit? (A3 vs. fitted) (Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

### Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	41.9559	8	<.0001
Test 2	15.5751	4	0.003646
Test 3	15.5751	4	0.003646
Test 4	4.72762	3	0.1929

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. Consider running a non-homogeneous variance model The p-value for Test 3 is less than .1. You may want to consider а different variance model 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 Estimated standard deviations from the Risk Type = control mean Confidence level = 0.95 2.46143 BMD = BMDL = 1.81322



Polynomial Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

Mean Response

12:53 07/09 2014

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_LUC\_Concurren\_Ln/LUC\_concurrent-HLS 2001-LUC count-Poly3NCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_LUC\_Concurren\_Ln/LUC\_concurrent-HLS 2001-LUC count-Poly3NCV-1SD-5d.plt Wed Jul 09 12:53:09 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse 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 = 5Total number of records with missing values = 0Maximum 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 = -6.65234 rho = 0 beta\_0 = 0.112441 beta\_1 = -0.0010106  $beta_2 = -0.00840676$ beta 3 = 0 Asymptotic Correlation Matrix of Parameter Estimates ( \*\*\* The model parameter(s) -beta\_2 -beta\_3

have been estimated at a boundary point, or have been specified by the user, and do not appear in the correlation matrix )

	lalpha	rho	beta_0	beta_1
lalpha	1	0.99	-0.073	0.086
rho	0.99	1	-0.073	0.087
beta_0	-0.073	-0.073	1	-0.92
beta_1	0.086	0.087	-0.92	1

Parameter Estimates

95.0%

			23.00
Wald Confidence	Interval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Con	nf. Limit		
lalpha	-1.68252	1.47799	-
4.57932	1.21429		
rho	1.97134	0.555285	
0.883005	3.05968		
beta_0	0.111471	0.0102095	
0.0914608	0.131481		
beta_1	-0.0137839	0.00240468	-
0.018497	-0.00907085		
beta_2	-9.34995e-028	NA	
beta_3	0	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 Scaled R	N es.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 -0.0938	10	0.11	0.111	0.04	0.0496
1.361	10	0.11	0.0927	0.056	0.0414
1.32 2.451 -1.53	9	0.06	0.0777	0.023	0.0347

2

3.761 0.0415	9	0.06	0.0596	0.026	0.0268
5.258 0.18	10	0.04	0.039	0.019	0.0176

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
Al	138.296137	6	-264.592275
A2	146.083690	10	-272.167381
A3	145.492300	7	-276.984600
fitted	141.105082	4	-274.210164
R	125.105720	2	-246.211439

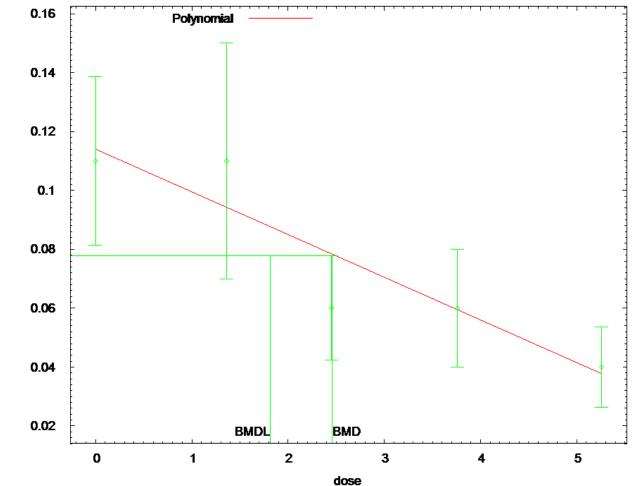
### Explanation of Tests

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	41.9559	8	<.0001
Test 2	15.5751	4	0.003646
Test 3	1.18278	3	0.7571

8.77444 3 0.03245 Test 4 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 = Estimated standard deviations from the Risk Type control mean Confidence level = 0.95 BMD = 3.59822 2.47874 BMDL =



Polynomial Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

12:53 07/09 2014

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_LUC\_Concurren\_Ln/LUC\_concurrent-HLS 2001-LUC count-Poly4CV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_LUC\_Concurren\_Ln/LUC\_concurrent-HLS 2001-LUC count-Poly4CV-1SD-5d.plt Wed Jul 09 12:53:07 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse 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 = 5Total 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 = 0.001291 rho = Specified 0 beta\_0 = 0.11 beta\_1 = 0  $beta_2 = -0.111453$ beta 3 = 0  $beta_4 = -0.00307798$ 

Asymptotic Correlation Matrix of Parameter Estimates

beta_1	beta_0	alpha	
-6.8e-009	1.2e-008	1	alpha
-0.81	1	1.2e-008	beta_0
1	-0.81	-6.8e-009	beta_1

Parameter Estimates

9	5	08	5

Wald Confidence I	Interval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Con	f. Limit		
alpha	0.00127623	0.000260509	
0.000765639	0.00178682		
beta_0	0.113585	0.00874069	
0.0964537	0.130717		
beta_1	-0.0145136	0.00277459	_
0.0199517	-0.00907554		
beta_2	0	NA	
beta_3	0	NA	
beta_4	0	NA	

NA - Indicates that this parameter has hit a bound implied by some inequality constraint and thus has no standard error.

Dose Scaled	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 -0.317	10	0.11	0.114	0.04	0.0357
1.361 1.43	10	0.11	0.0938	0.056	0.0357
2.451	9	0.06	0.078	0.023	0.0357
3.761	9	0.06	0.059	0.026	0.0357

Table of Data and Estimated Values of Interest

0.084 5.258 0.241	10	0.04	0.0373	0.019	0.0357
Model	Descriptio	ns for like	lihoods calcul	ated	
Model		Yij = Mu(i ij)} = Sigm			
Model		Yij = Mu(i ij)} = Sigm			
Mo	Var{e( odel A3 use	Yij = Mu(i ij)} = Sigm s any fixed ed by the u	a^2 variance para	meters that	
Model		Yi = Mu + (i)} = Sigm			

# Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
Al	138.296137	б	-264.592275
A2	146.083690	10	-272.167381
A3	138.296137	б	-264.592275
fitted	135.932325	3	-265.864651
R	125.105720	2	-246.211439

# 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.)

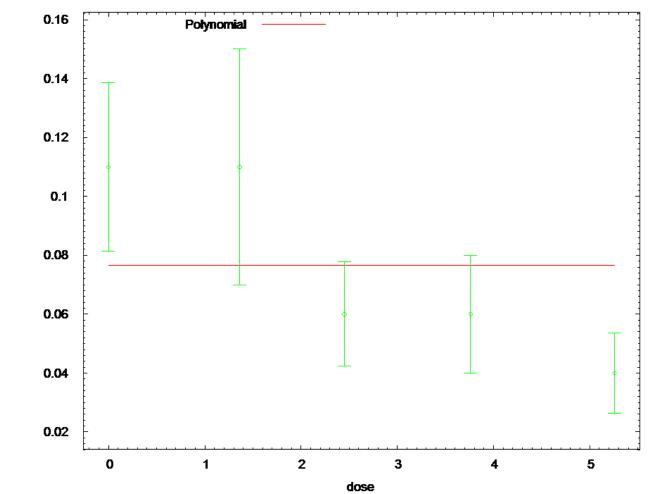
# Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	41.9559	8	<.0001
Test 2	15.5751	4	0.003646
Test 3	15.5751	4	0.003646
Test 4	4.72762	3	0.1929

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. Consider running a non-homogeneous variance model The p-value for Test 3 is less than .1. You may want to consider а different variance model 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 = Estimated standard deviations from the Risk Type control mean Confidence level = 0.95

BMD = 2.46143

BMDL = 1.81322



Mean Response

12:53 07/09 2014

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_LUC\_Concurren\_Ln/LUC\_concurrent-HLS 2001-LUC count-Poly4NCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_LUC\_Concurren\_Ln/LUC\_concurrent-HLS 2001-LUC count-Poly4NCV-1SD-5d.plt Wed Jul 09 12:53:08 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse 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 = 5Total number of records with missing values = 0Maximum 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 = -6.65234 rho = 0 beta\_0 = 0.11 beta\_1 = 0  $beta_2 = -0.111453$ beta 3 = 0  $beta_4 = -0.00307798$ 

Asymptotic Correlation Matrix of Parameter Estimates

	lalpha	rho	beta_0
lalpha	NA	NA	NA
rho	NA	NA	NA
beta_0	NA	NA	1

Parameter Estimates

#### 95.0%

Wald (	Confidence Int	erval		
	Variable	Estimate	Std. Err.	Lower Conf.
Limit	Upper Conf.	Limit		
	lalpha	-244.198	NA	
NA		NA		
	rho	-92.6629	NA	
NA		NA		
	beta_0	0.0766667	NA	
NA		NA		
	beta_1	0	NA	
	beta_2	0	NA	
	beta_3	0	NA	
	beta_4	0	NA	

At least some variance estimates are negative. THIS USUALLY MEANS THE MODEL HAS NOT CONVERGED! Try again from another starting point.

Dose Scaled	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 2.35	10	0.11	0.0767	0.04	0.0448
1.361	10	0.11	0.0767	0.056	0.0448
2.35 2.451 -1.12	9	0.06	0.0767	0.023	0.0448

Table of Data and Estimated Values of Interest

3.761 -1.12	9	0.06	0.0767	0.026	0.0448
5.258	10	0.04	0.0767	0.019	0.0448
2.55					
		6 1.11			
Model	Descriptio	ns for like	elihoods calcul	ated	
Model		Yij = Mu(i			
	Var{e(	ij)} = Sign	na^2		
Model		Yij = Mu(i ij)} = Sign	, , ,		
		- ) ) 0190			

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<sup>2</sup>

### Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
Al	138.296137	6	-264.592275
A2	146.083690	10	-272.167381
A3	145.492300	7	-276.984600
fitted	125.105720	3	-244.211439
R	125.105720	2	-246.211439

# 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.)

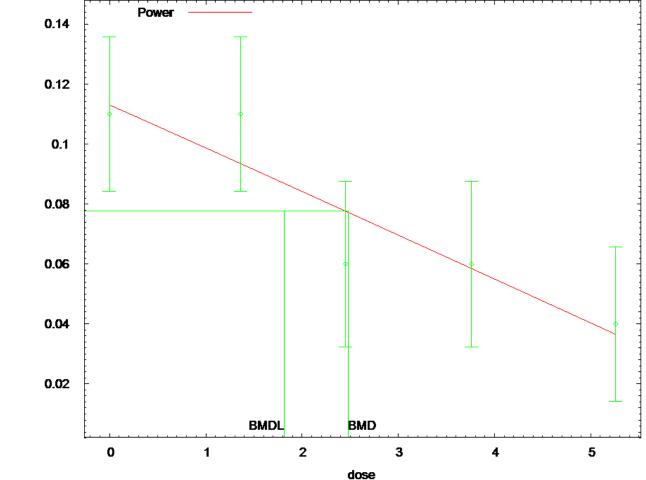
#### Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	41.9559	8	<.0001
Test 2	15.5751	4	0.003646
Test 3	1.18278	3	0.7571

40.7732 4 <.0001 Test 4 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 BMD computation failed for BMR = 0.0319035 Setting BMD = 100\*(maximum dose) Benchmark Dose Computation 1 Specified effect = Risk Type Estimated standard deviations from the = control mean Confidence level = 0.95 -9999 BMD =

BMDL computation failed.





15:31 06/21 2014

\_\_\_\_\_\_ === Power Model. (Version: 2.18; Date: 05/19/2014) Input Data File: C:/Users/dmayfield/Desktop/Ln/LUC concurrent-HLS 2001-LUC count-PowerCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Ln/LUC concurrent-HLS 2001-LUC count-PowerCV-1SD-5d.plt Sat Jun 21 15:31:12 2014 === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = control + slope \* dose^power Dependent variable = MeanResponse 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 = 5Total 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 = 0.001291 rho = 0 control = 0.11 slope = -0.592187 Specified 0 0.11 power = -1.28654 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

and	do	not	appear	in	the	correlation	matrix	)

	alpha	control	slope	power
alpha	1	3.7e-007	-5.2e-007	-5.1e-007
control	3.7e-007	1	-0.73	-0.56
slope	-5.2e-007	-0.73	1	0.96
power	-5.1e-007	-0.56	0.96	1

Parameter Estimates

95.0%

				95.0%
Wald Conf	idence Int	terval		
Va	riable	Estimate	Std. Err.	Lower Conf.
Limit U	pper Conf	. Limit		
	alpha	0.00127621	0.000260506	
0.0007656	31	0.0017868		
C	ontrol	0.113451	0.0105385	
0.092796		0.134106		
	slope	-0.0143078	0.0094404	-
0.0328106		0.00419509		
	power	1.00832	0.367697	
0.287652		1.729		

Table of Data and Estimated Values of Interest

Dose Scaled 1	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 -0.305	10	0.11	0.113	0.04	0.0357
1.361 1.42	10	0.11	0.0939	0.056	0.0357
2.451	9	0.06	0.0781	0.023	0.0357
3.761 0.0804	9	0.06	0.059	0.026	0.0357
5.258 0.25	10	0.04	0.0372	0.019	0.0357

Model Descriptions for likelihoods calculated

Yij = Mu(i) + e(ij)Model A1:  $Var\{e(ij)\} = Sigma^2$ Model A2: Yij = Mu(i) + e(ij)Var{e(ij)} = Sigma(i)<sup>2</sup> 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<sup>2</sup>

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
Al	138.296137	6	-264.592275
A2	146.083690	10	-272.167381
A3	138.296137	6	-264.592275
fitted	135.932584	4	-263.865168
R	125.105720	2	-246.211439

### 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

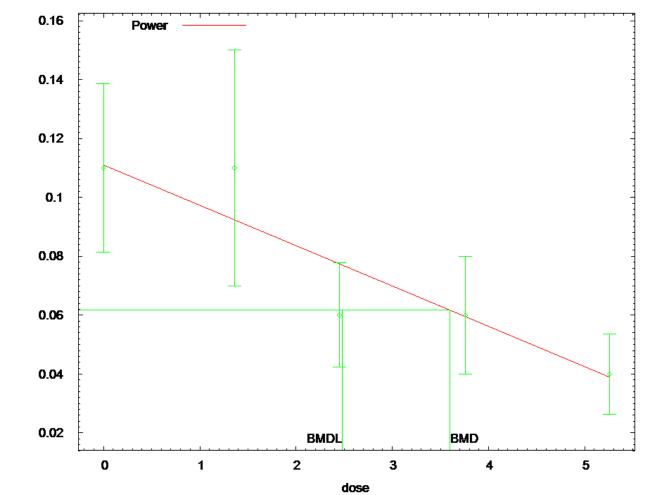
-2*log(Likelihood Ratio)	Test df	p-value
41.9559	8	<.0001
15.5751	4	0.003646
15.5751	4	0.003646
4.72711	2	0.09409
	41.9559 15.5751 15.5751	15.5751 4 15.5751 4

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. Consider running a non-homogeneous variance model The p-value for Test 3 is less than .1. You may want to consider а different variance model The p-value for Test 4 is less than .1. You may want to try a different model Benchmark Dose Computation Specified effect = 1 = Estimated standard deviations from the Risk Type control mean Confidence level = 0.95 BMD = 2.47805

BMDL = 1.81327



Power Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

Mean Response

15:31 06/21 2014

\_\_\_\_\_\_ === Power Model. (Version: 2.18; Date: 05/19/2014) Input Data File: C:/Users/dmayfield/Desktop/Ln/LUC concurrent-HLS 2001-LUC count-PowerNCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Ln/LUC concurrent-HLS 2001-LUC count-PowerNCV-1SD-5d.plt Sat Jun 21 15:31:13 2014 === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = control + slope \* dose^power Dependent variable = MeanResponse Independent variable = Dose The power is restricted to be greater than or equal to 1 The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) \* rho) Total number of dose groups = 5Total 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 = -6.65234 rho = 0 control = 0.11 slope = -0.592187 power = -1.28654 Asymptotic Correlation Matrix of Parameter Estimates lalpha rho control slope power

lalpha 0.058	1	0.99	-0.39	0.19
rho 0.06	0.99	1	-0.35	0.19
control -0.67	-0.39	-0.35	1	-0.82
slope 0.97	0.19	0.19	-0.82	1
power 1	0.058	0.06	-0.67	0.97

#### Parameter Estimates

			95.0%
Wald Confidence Int	erval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Conf.	Limit		
lalpha	-1.68197	1.81421	-
5.23774	1.87381		
rho	1.97156	0.68144	
0.635958	3.30715		
control	0.111423	0.0137997	
0.0843765	0.13847		
slope	-0.0137341	0.00995796	-
0.0332514	0.0057831		
power	1.00182	0.353281	
0.309397	1.69423		

## Table of Data and Estimated Values of Interest

Dose Scaled R	N Les.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 -0.0908	10	0.11	0.111	0.04	0.0496
1.361 1.32	10	0.11	0.0927	0.056	0.0414
2.451 -1.53	9	0.06	0.0777	0.023	0.0348
3.761 0.0398	9	0.06	0.0596	0.026	0.0268

5.258	10	0.04	0.039	0.019	0.0176
0.181					

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	138.296137	6	-264.592275
A2	146.083690	10	-272.167381
A3	145.492300	7	-276.984600
fitted	141.105095	5	-272.210190
R	125.105720	2	-246.211439

## Explanation of Tests

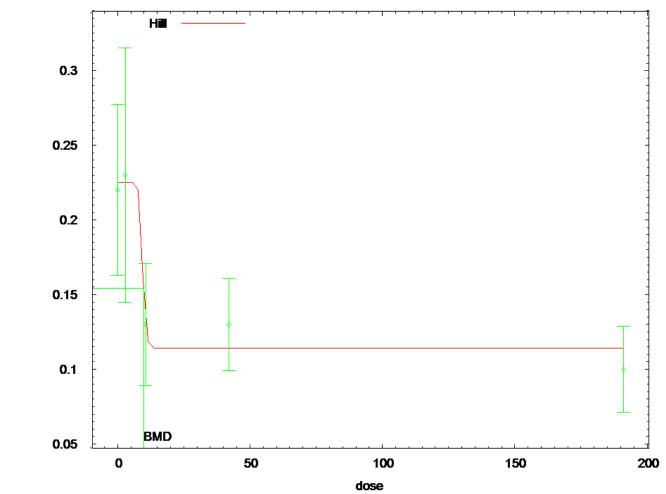
Test 1: Do responses and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A1 vs A2) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 4: Does the Model for the Mean Fit? (A3 vs. fitted) (Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

#### Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	41.9559	8	<.0001
Test 2	15.5751	4	0.003646
Test 3	1.18278	3	0.7571
Test 4	8.77441	2	0.01244

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 Estimated standard deviations from the Risk Type = control mean Confidence level = 0.95 BMD = 3.6015BMDL = 2.47875

**BMDS Model Results for Monocyte Count** (Untransformed Doses, Concurrent Controls)



09:00 06/22 2014

Mean Response

Hill Model

=== Hill Model. (Version: 2.17; Date: 01/28/2013) Input Data File: C:/Users/dmayfield/Desktop/Norm/Monocyte\_Concurrent\_Normal-HLS 2001-Monocyte Count-HillCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Norm/Monocyte\_Concurrent\_Normal-HLS 2001-Monocyte Count-HillCV-1SD-5d.plt Sun Jun 22 09:00:28 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = intercept + v\*dose^n/(k^n + dose^n) Dependent variable = MeanResponse 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 = 5Total 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 = 0.00545863Specified rho = 0 intercept = 0.22 -0.12 v = n = 2.57326 k = 8.29 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 )

k	alpha	intercept	v	n
alpha -2.6e-005	1	-2.2e-008	2.7e-008	-2.6e-005
intercept -0.00059	-2.2e-008	1	-0.7	-0.00038
v -0.00048	2.7e-008	-0.7	1	0.00031
n 1	-2.6e-005	-0.00038	0.00031	1
k 1	-2.6e-005	-0.00059	-0.00048	1

Parameter Estimates

95.0%

Wald Confidence I	nterval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Con	f. Limit		
alpha	0.00498925	0.00101843	
0.00299317	0.00698533		
intercept	0.225	0.0157944	
0.194044	0.255956		
v	-0.110789	0.0226286	_
0.155141	-0.0664382		
n	15.3673	6667.32	_
13052.3	13083.1		
k	9.43171	477.861	_
927.159	946.023		

Table of Data and Estimated Values of Interest

Dose Scaled R		Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 -0.224	10	0.22	0.225	0.08	0.0706

2.9	10	0.23	0.225	0.119	0.0706
0.224					
10.6	9	0.13	0.13	0.053	0.0706
2.12e-0	07				
42	9	0.13	0.114	0.04	0.0706
0.671					
191.1	10	0.1	0.114	0.04	0.0706
-0.636					

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<sup>2</sup>

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
Al	103.693409	б	-195.386818
A2	112.779870	10	-205.559741
A3	103.693409	6	-195.386818
fitted	103.211257	5	-196.422513
R	92.681036	2	-181.362073

### Explanation of Tests

Test 1:	Do responses and/or variances differ among Dose levels? (A2 vs. R)
	Are Variances Homogeneous? (A1 vs A2) Are variances adequately modeled? (A2 vs. A3)
Test 4:	Does the Model for the Mean Fit? (A3 vs. fitted) When rho=0 the results of Test 3 and Test 2 will be the
same.)	

#### Tests of Interest

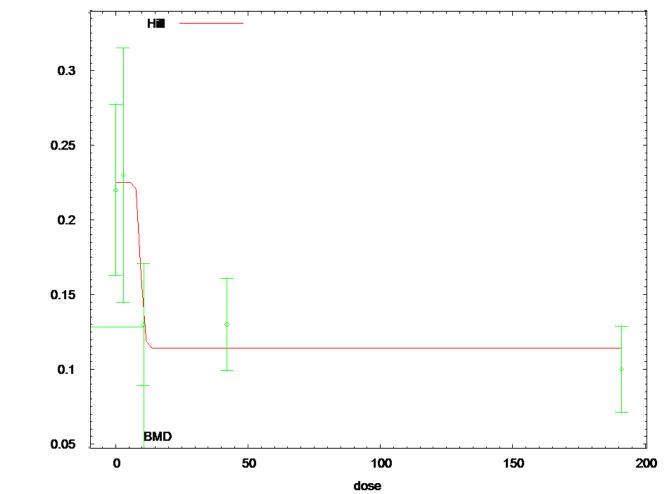
Test	-2*log(Likelihood Rati	o) Test df	p-value
TCDC	a rog(hriterritood itaer	O, ICDC al	p varac

3

Test 1 Test 2 40.1977 18.1729 8 4 <.0001 0.001142 0.001142 Test 3 18.1729 4 1 Test 4 0.964305 0.3261 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. Consider running a non-homogeneous variance model The p-value for Test 3 is less than .1. You may want to consider а different variance model 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 = Estimated standard deviations from the Risk Type control mean

Confidence level = 0.95 BMD = 9.78479

BMDL computation failed.



09:00 06/22 2014

Mean Response

Hill Model

=== Hill Model. (Version: 2.17; Date: 01/28/2013) Input Data File: C:/Users/dmayfield/Desktop/Norm/Monocyte\_Concurrent\_Normal-HLS 2001-Monocyte Count-HillNCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Norm/Monocyte\_Concurrent\_Normal-HLS 2001-Monocyte Count-HillNCV-1SD-5d.plt Sun Jun 22 09:00:29 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = intercept + v\*dose^n/(k^n + dose^n) Dependent variable = MeanResponse Independent variable = Dose Power parameter restricted to be greater than 1 The variance is to be modeled as Var(i) = exp(lalpha + rho \* ln(mean(i))) Total number of dose groups = 5Total number of records with missing values = 0Maximum number of iterations = 500 Relative Function Convergence has been set to: 1e-008 Parameter Convergence has been set to: 1e-008 Default Initial Parameter Values lalpha = -5.21056 rho = 0 intercept = 0.22 -0.12 v = n = 2.57326 k = 8.29 Asymptotic Correlation Matrix of Parameter Estimates lalpha rho intercept v

n	k			
lalpha -2.8e-005	1 0.00016	0.99	-0.53	0.59
rho -2.4e-005	0.99 0.00016	1	-0.47	0.56
intercept -0.00011	-0.53 -0.00052	-0.47	1	-0.92
v 0.00014	0.59 0.0002	0.56	-0.92	1
n 1	-2.8e-005 1	-2.4e-005	-0.00011	0.00014
k 1	0.00016	0.00016	-0.00052	0.0002

Parameter Estimates

			95.0%
Wald Confidence	e Interval		
Variable	e Estimate	Std. Err.	Lower Conf.
Limit Upper (	Conf. Limit		
lalpha	a -0.920071	1.51601	_
3.89139	2.05125		
rho	2.51647	0.795521	
0.957276	4.07566		
intercept	0.22479	0.0215475	
0.182558	0.267022		
7	<i>r</i> -0.110884	0.0235358	_
0.157013	-0.0647546		
1	ı 15.4349	4108.6	_
8037.27	8068.14		
]	s 9.49312	278.689	_
536.728	555.714		

Table of Data and Estimated Values of Interest

Dose Scaled R		Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 -0.157	10	0.22	0.225	0.08	0.0965

2.9	10	0.23	0.225	0.119	0.0965
0.171	9	0 1 2	0.131		0.0489
10.6 -0.0614	9	0.13	0.131	0.053	0.0489
42	9	0.13	0.114	0.04	0.041
1.18					
191.1	10	0.1	0.114	0.04	0.041
-1.07					

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
Al	103.693409	б	-195.386818
A2	112.779870	10	-205.559741
A3	111.990624	7	-209.981248
fitted	110.593061	6	-209.186122
R	92.681036	2	-181.362073

### Explanation of Tests

#### Tests of Interest

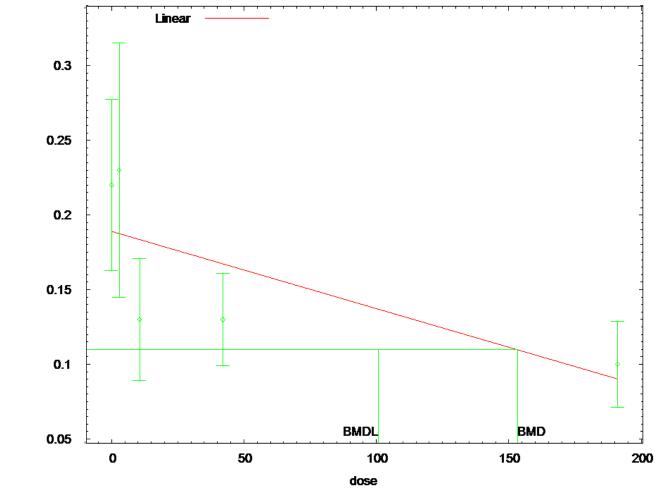
Test -2\*log(Likelihood Ratio) Test df p-value

3

8 Test 1 40.1977 <.0001 Test 2 4 0.001142 18.1729 Test 3 1.57849 3 0.6643 1 Test 4 2.79513 0.09455

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 = 10.7399

BMDL computation failed.



Mean Response

12:45 07/09 2014

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_Monocyte\_Concurrent/Monocyte\_Concu rrent\_Normal-HLS 2001-Monocyte Count-LinearCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_Monocyte\_Concurrent/Monocyte\_Concu rrent Normal-HLS 2001-Monocyte Count-LinearCV-1SD-5d.plt Wed Jul 09 12:45:45 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse Independent variable = Dose rho is set to 0 Signs of the polynomial coefficients are not restricted A constant variance model is fit Total number of dose groups = 5Total number of records with missing values = 0Maximum 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 = 0.00545863rho = 0 Specified beta 0 = 0.187061 $beta_1 = -0.000508131$ 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 1	.6e-008	-3.5e-008
peta_0 1.	6e-008	1	-0.56
oeta_1 -3.	5e-008	-0.56	1

## Parameter Estimates

			95.0%
Wald Confidence In	nterval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Conf	. Limit		
alpha	0.00628416	0.00128275	
0.00377002	0.0087983		
beta_0	0.189334	0.0138502	
0.162188	0.21648		
beta_1	-0.000517126	0.000155222	-
0.000821356	-0.000212897		

Table of Data and Estimated Values of Interest

Dose Scaled	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 1.22	10	0.22	0.189	0.08	0.0793
2.9 1.68	10	0.23	0.188	0.119	0.0793
10.6	9	0.13	0.184	0.053	0.0793
42 -1.42	9	0.13	0.168	0.04	0.0793
191.1 0.379	10	0.1	0.0905	0.04	0.0793

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
Al	103.693409	б	-195.386818
A2	112.779870	10	-205.559741
A3	103.693409	6	-195.386818
fitted	97.673375	3	-189.346749
R	92.681036	2	-181.362073

### 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	40.1977	8	<.0001
Test 2	18.1729	4	0.001142
Test 3	18.1729	4	0.001142
Test 4	12.0401	3	0.007247

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. Consider running a non-homogeneous variance model

The p-value for Test 3 is less than .1. You may want to consider a

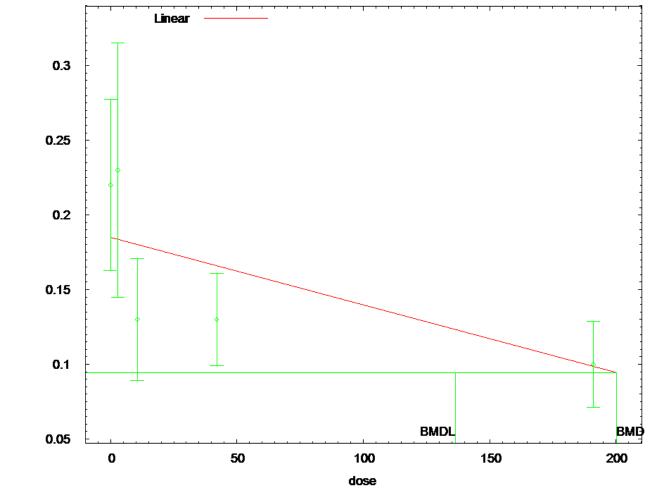
different variance model

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 = 153.295

BMDL = 100.721



Mean Response

12:45 07/09 2014

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_Monocyte\_Concurrent/Monocyte\_Concu rrent\_Normal-HLS 2001-Monocyte Count-LinearNCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_Monocyte\_Concurrent/Monocyte\_Concu rrent\_Normal-HLS 2001-Monocyte Count-LinearNCV-1SD-5d.plt Wed Jul 09 12:45:48 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse Independent variable = Dose Signs of the polynomial coefficients are not restricted The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) \* rho) Total number of dose groups = 5Total number of records with missing values = 0Maximum number of iterations = 500 Relative Function Convergence has been set to: 1e-008 Parameter Convergence has been set to: 1e-008 Default Initial Parameter Values lalpha = -5.21056 rho = 0 beta\_0 = 0.187061  $beta_1 = -0.000508131$ Asymptotic Correlation Matrix of Parameter Estimates lalpha beta\_0 beta 1 rho 0.99 -0.037 0.035 lalpha 1

rho	0.99	1	-0.036	0.033
beta_0	-0.037	-0.036	1	-0.81
beta_1	0.035	0.033	-0.81	1

Parameter Estimates

## 95.0%

Wald Confid	lence Int	erval		
Vari	able	Estimate	Std. Err.	Lower Conf.
Limit Upp	per Conf.	Limit		
la	alpha	0.0784577	1.48211	-
2.82642		2.98334		
	rho	2.89289	0.795215	
1.3343		4.45148		
be	eta_0	0.184882	0.015175	
0.15514		0.214625		
be	eta_1	-0.000451919	0.000103729	-
0.000655225	5	-0.000248614		

Table of Data and Estimated Values of Interest

Dose Scaled	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 1.23	10	0.22	0.185	0.08	0.0905
2.9	10	0.23	0.184	0.119	0.0896
10.6 -1.72	9	0.13	0.18	0.053	0.0871
42 -1.39	9	0.13	0.166	0.04	0.0774
191.1 0.128	10	0.1	0.0985	0.04	0.0364

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<sup>2</sup>

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
Al	103.693409	б	-195.386818
A2	112.779870	10	-205.559741
A3	111.990624	7	-209.981248
fitted	102.275742	4	-196.551485
R	92.681036	2	-181.362073

#### Explanation of Tests

#### Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	40.1977	8	<.0001
Test 2	18.1729	4	0.001142
Test 3	1.57849	3	0.6643
Test 4	19.4298	3	0.0002228

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

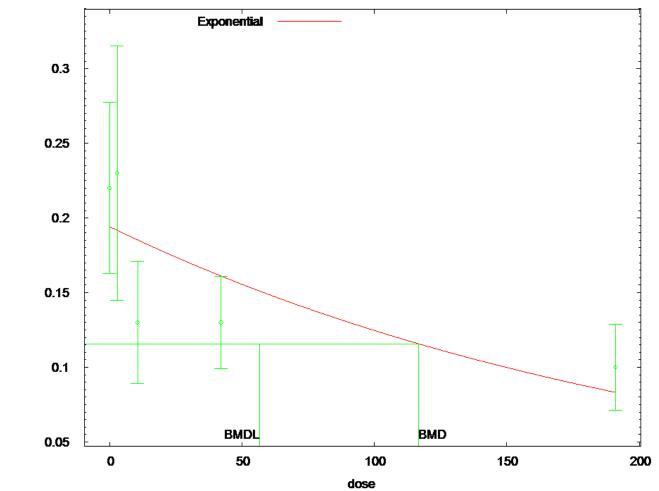
Benchmark Dose Computation

Specified effect = 1 Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 200.254

BMDL = 136.469



Mean Response

09:00 06/22 2014

```
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Norm/Monocyte_Concurrent_Normal-HLS
2001-Monocyte Count-ExpCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sun Jun 22 09:00:28 2014
_____
===
BMDS Model Run
~~~~
  The form of the response function by Model:
     Model 2:
                Y[dose] = a * exp{sign * b * dose}
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
     Model 4:
               Y[dose] = a * [c-(c-1) * exp{-b * dose}]
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  rho is set to 0.
  A constant variance model is fit.
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 2
lnalpha	-5.32056
rho(S)	0
a	0.129933
b	0.00346714
C	0
d	1

(S) = Specified

#### Parameter Estimates

Variable	Model 2
lnalpha	-5.09159
rho	0
a	0.194195
b	0.00443287
C	0
d	1

## Table of Stats From Input Data

Dose	Ν	Obs Mean	Obs Std Dev
0	10	0.22	0.08
2.9	10	0.23	0.119
10.6	9	0.13	0.053
42	9	0.13	0.04
191.1	10	0.1	0.04

## Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	0.1942	0.07841	1.041
2.9	0.1917	0.07841	1.544
10.6	0.1853	0.07841	-2.115
42	0.1612	0.07841	-1.194
191.1	0.08324	0.07841	0.6759

Other models for which likelihoods are calculated:

Model Al: Yij = Mu(i) + e(ij) Var{e(ij)} = Sigma^2

Model A2:	Yij = Var{e(ij)} =	Mu(i) + e(ij) Sigma(i)^2
Model A3:		Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R:	Yij = Var{e(ij)} =	

Likelihoods of Interest

AIC	Model	Log(likelihood)	DF	
ALC				
105 2060	A1	103.6934	6	_
195.3868	A2	112.7799	10	_
205.5597	A3	103.6934	6	_
195.3868	R	92.68104	2	_
181.3621	2	98.19822	3	_
190.3964	_		-	

Additive constant for all log-likelihoods = -44.11. This constant added to the above values gives the log-likelihood including the term that does not

depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A2 vs. A1) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 4: Does Model 2 fit the data? (A3 vs. 2)

Tests of Interest

Test p-value	-2*log(Likelihood Ratio)	D. F.
Test 1	40.2	8

< 0.0001			
Test	2	18.17	4
0.001142			
Test	3	18.17	4
0.001142			
Test	4	10.99	3
0.01178			

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. Consider running a non-homogeneous variance model.

The p-value for Test 3 is less than .1. You may want to consider a different variance model.

The p-value for Test 4 is less than .1. Model 2 may not adequately

describe the data; you may want to consider another model.

Benchmark Dose Computations:

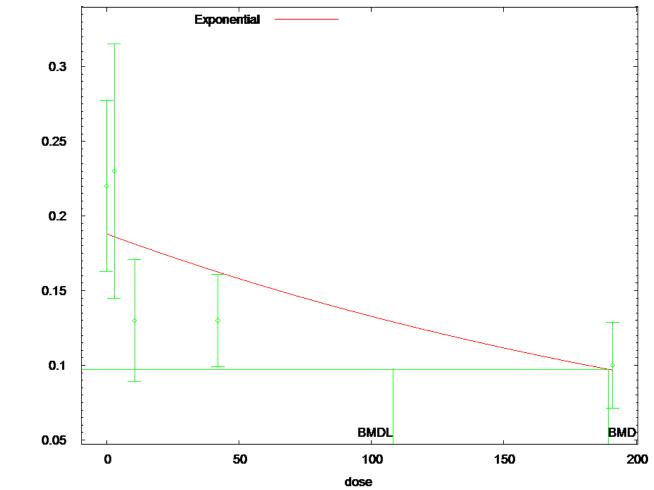
Specified Effect = 1.000000

Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

BMD = 116.658

BMDL = 56.7657



## Exponential Model 2, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Level for BMDL

09:00 06/22 2014

```
______
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Norm/Monocyte_Concurrent_Normal-HLS
2001-Monocyte Count-ExpNCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sun Jun 22 09:00:29 2014
_____
===
BMDS Model Run
~~~~
  The form of the response function by Model:
     Model 2:
                Y[dose] = a * exp{sign * b * dose}
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
     Model 4:
                Y[dose] = a * [c-(c-1) * exp{-b * dose}]
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  The variance is to be modeled as Var(i) = exp(lalpha + log
(mean(i)) * rho)
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 2
lnalpha	-1.08858
rho	2.4145
a	0.129933
b	0.00346714
С	0
d	1

#### Parameter Estimates

Variable	Model 2
lnalpha	-0.168436
rho	2.77209
a	0.188
b	0.00347346
C	0
d	1

## Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	10	0.22	0.08
2.9	10	0.23	0.119
10.6	9	0.13	0.053
42	9	0.13	0.04
191.1	10	0.1	0.04

## Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	0.188	0.09065	1.116
2.9	0.1861	0.08939	1.552
10.6	0.1812	0.08614	-1.783
42	0.1625	0.07406	-1.316
191.1	0.0968	0.03613	0.28

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)

	<pre>Var{e(ij)} =</pre>	Sigma(i)^2
Model A3	: Yij = Var{e(ij)} =	Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R	: Yij = Var{e(ij)} =	

Likelihoods of Interest

AIC	Model	Log(likelihood)	DF	
AIC				
195.3868	A1	103.6934	б	-
	A2	112.7799	10	-
205.5597	A3	111.9906	7	-
	R	92.68104	2	-
181.3621	2	102.8544	4	-
197.7087				

Additive constant for all log-likelihoods = -44.11. This constant added to the

above values gives the log-likelihood including the term that does not

depend on the model parameters.

#### Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A2 vs. A1) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 4: Does Model 2 fit the data? (A3 vs. 2)

## Tests of Interest

Test p-value	-2*log(Likelihood Ratio)	D. F.
Test 1	40.2	8
< 0.0001		
Test 2	18.17	4

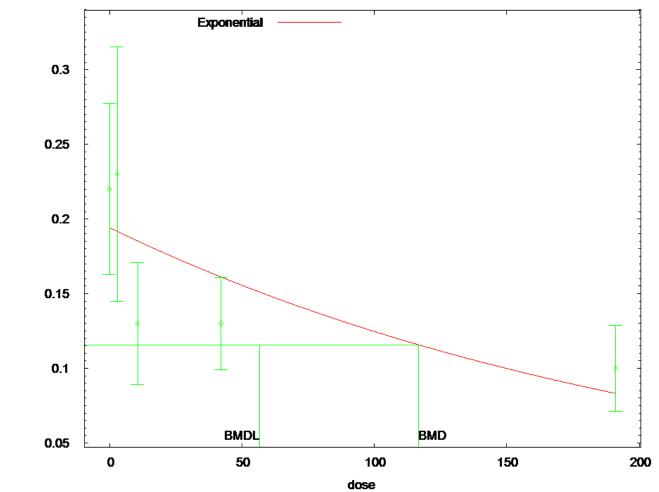
0.001142			
Test	3	1.578	3
0.6643			
Test	4	18.27	3
0.0003864			

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. Model 2 may not adequately describe the data; you may want to consider another model. Benchmark Dose Computations: Specified Effect = 1.000000

Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

BMD = 189.478 BMDL = 108.159



Mean Response

09:00 06/22 2014

```
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Norm/Monocyte_Concurrent_Normal-HLS
2001-Monocyte Count-ExpCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sun Jun 22 09:00:28 2014
_____
===
BMDS Model Run
~~~~
  The form of the response function by Model:
     Model 2:
                Y[dose] = a * exp{sign * b * dose}
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
     Model 4:
               Y[dose] = a * [c-(c-1) * exp{-b * dose}]
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  rho is set to 0.
  A constant variance model is fit.
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 3
lnalpha	-5.32056
rho(S)	0
a	0.129933
b	0.00346714
C	0
d	1

(S) = Specified

### Parameter Estimates

Variable	Model 3
lnalpha	-5.09159
rho	0
a	0.194195
b	0.00443287
C	0
d	1

# Table of Stats From Input Data

Dose	Ν	Obs Mean	Obs Std Dev
0	10	0.22	0.08
2.9	10	0.23	0.119
10.6	9	0.13	0.053
42	9	0.13	0.04
191.1	10	0.1	0.04

# Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	0.1942	0.07841	1.041
2.9	0.1917	0.07841	1.544
10.6	0.1853	0.07841	-2.115
42	0.1612	0.07841	-1.194
191.1	0.08324	0.07841	0.6759

Other models for which likelihoods are calculated:

Model Al: Yij = Mu(i) + e(ij) Var{e(ij)} = Sigma^2

Model A2:	Yij = Var{e(ij)} =	Mu(i) + e(ij) Sigma(i)^2
Model A3:		Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R:	Yij = Var{e(ij)} =	

Likelihoods of Interest

AIC	Model	Log(likelihood)	DF	
ALC				
105 2060	Al	103.6934	6	-
195.3868	A2	112.7799	10	_
205.5597	A3	103.6934	6	_
195.3868	R	92.68104	2	_
181.3621	3	98.19822	3	_
190.3964				

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.

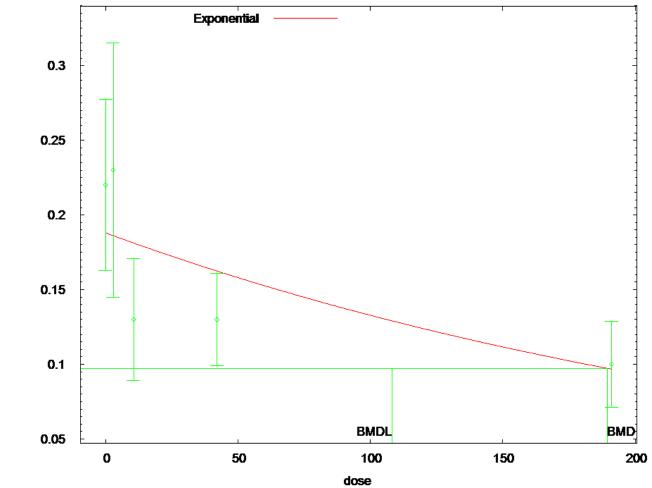
## Explanation of Tests

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 5a: Does Model 3 fit the data? (A3 vs 3)

Test	-2*log(Likelihood Ratio)	D. F.
p-value		

Test 1 < 0.0001	40.2	8
Test 2	18.17	4
0.001142 Test 3	18.17	4
0.001142	10.00	2
Test 5a 0.01178	10.99	3

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. Consider running a non-homogeneous variance model. The p-value for Test 3 is less than .1. You may want to consider a different variance model. The p-value for Test 5a is less than .1. Model 3 may not adequately describe the data; you may want to consider another model. Benchmark Dose Computations: Specified Effect = 1.000000 Risk Type = Estimated standard deviations from control Confidence Level = 0.950000BMD = 116.658 BMDL = 56.7657



# Exponential Model 3, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Level for BMDL

Mean Response

09:00 06/22 2014

```
______
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Norm/Monocyte_Concurrent_Normal-HLS
2001-Monocyte Count-ExpNCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sun Jun 22 09:00:29 2014
_____
===
BMDS Model Run
~~~~
  The form of the response function by Model:
     Model 2:
                Y[dose] = a * exp{sign * b * dose}
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
     Model 4:
                Y[dose] = a * [c-(c-1) * exp{-b * dose}]
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  The variance is to be modeled as Var(i) = exp(lalpha + log
(mean(i)) * rho)
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 3
lnalpha	-1.08858
rho	2.4145
a	0.32003
b	4.68914e-005
С	0
d	2

### Parameter Estimates

Variable	Model 3
lnalpha	-0.168453
rho	2.77208
a	0.188
b	0.00347346
C	0
d	1

# Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	10	0.22	0.08
2.9	10	0.23	0.119
10.6	9	0.13	0.053
42	9	0.13	0.04
191.1	10	0.1	0.04

# Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	0.188	0.09065	1.116
2.9	0.1861	0.08939	1.552
10.6	0.1812	0.08614	-1.783
42	0.1625	0.07406	-1.316
191.1	0.0968	0.03613	0.28

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)

	<pre>Var{e(ij)} =</pre>	=	Sigma(i)^2
Model A3:	5		Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R:	Yij = Var{e(ij)} =		

Likelihoods of Interest

AIC	Model	Log(likelihood)	DF	
ALC				
	Al	103.6934	6	-
195.3868	A2	112.7799	10	-
205.5597	A3	111.9906	7	_
209.9812	R	92.68104	2	_
181.3621	3	102.8544	4	_
197 7087	0		-	

197.7087

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 5a: Does Model 3 fit the data? (A3 vs 3)

Test p-value	-2*log(Likelihood Ratio)	D. F.
Test 1 < 0.0001	40.2	8

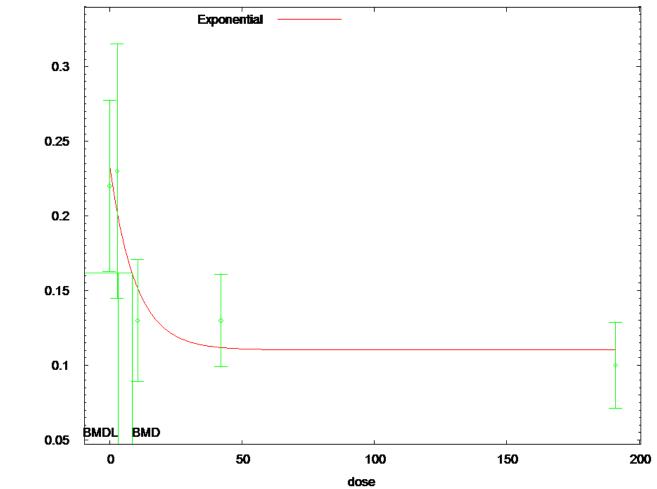
Test 2 0.001142	18.17	4
Test 3	1.578	3
0.6643	1.370	5
Test 5a	18.27	3
0.0003864		

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 5a is less than .1. Model 3 may not adequately describe the data; you may want to consider another model. Benchmark Dose Computations: Specified Effect = 1.000000

Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

BMD = 189.477 BMDL = 108.159



Mean Response

09:00 06/22 2014

```
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Norm/Monocyte_Concurrent_Normal-HLS
2001-Monocyte Count-ExpCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sun Jun 22 09:00:28 2014
_____
===
BMDS Model Run
~~~~
  The form of the response function by Model:
     Model 2:
                Y[dose] = a * exp{sign * b * dose}
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
     Model 4:
               Y[dose] = a * [c-(c-1) * exp{-b * dose}]
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  rho is set to 0.
  A constant variance model is fit.
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 4
lnalpha	-5.32056
rho(S)	0
a	0.2415
b	0.0190159
С	0.394361
d	1

(S) = Specified

### Parameter Estimates

Variable	Model 4
lnalpha	-5.24649
rho	0
a	0.23437
b	0.103831
C	0.470786
d	1

# Table of Stats From Input Data

Dose	Ν	Obs Mean	Obs Std Dev
0	10	0.22	0.08
2.9	10	0.23	0.119
10.6	9	0.13	0.053
42	9	0.13	0.04
191.1	10	0.1	0.04

# Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	0.2344	0.07257	-0.6262
2.9	0.2021	0.07257	1.215
10.6	0.1516	0.07257	-0.893
42	0.1119	0.07257	0.7474
191.1	0.1103	0.07257	-0.4505

Other models for which likelihoods are calculated:

Model Al: Yij = Mu(i) + e(ij) Var{e(ij)} = Sigma^2

Model A2:	Yij = Var{e(ij)} =	Mu(i) + e(ij) Sigma(i)^2
Model A3:		Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R:	Yij = Var{e(ij)} =	

Likelihoods of Interest

	Model	Log(likelihood)	DF	
AIC				
	A1	103.6934	6	_
195.3868	A2	112.7799	10	_
205.5597	A3	103.6934	6	_
195.3868	R	92.68104	2	_
181.3621	4	101.9157	4	_
195.8314				

Additive constant for all log-likelihoods = -44.11. This constant added to the above values gives the log-likelihood including the term that does not

depend on the model parameters.

### Explanation of Tests

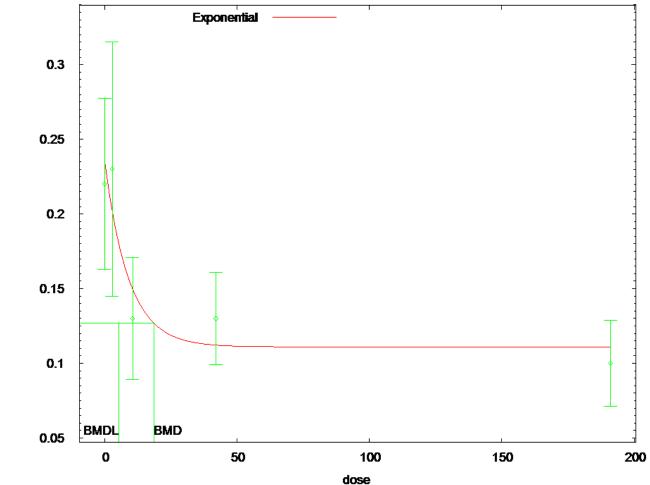
Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A2 vs. A1) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 6a: Does Model 4 fit the data? (A3 vs 4)

Test	-2*log(Likelihood Ratio)	D. F.
p-value		

Test 1 < 0.0001	40.2	8
Test 2	18.17	4
0.001142		
Test 3	18.17	4
0.001142		
Test ба	3.555	2
0.169		

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. Consider running a non-homogeneous variance model. The p-value for Test 3 is less than .1. You may want to consider a different variance model. 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 = 8.47184 BMDL = 3.37129



Exponential Model 4, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Level for BMDL

Mean Response

09:00 06/22 2014

```
______
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Norm/Monocyte_Concurrent_Normal-HLS
2001-Monocyte Count-ExpNCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sun Jun 22 09:00:29 2014
_____
===
BMDS Model Run
~~~~
  The form of the response function by Model:
     Model 2:
                Y[dose] = a * exp{sign * b * dose}
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
     Model 4:
                Y[dose] = a * [c-(c-1) * exp{-b * dose}]
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  The variance is to be modeled as Var(i) = exp(lalpha + log
(mean(i)) * rho)
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 4
lnalpha	-1.08858
rho	2.4145
a	0.2415
b	0.0190159
C	0.394361
d	1

### Parameter Estimates

Variable	Model 4
lnalpha	-0.648692
rho	2.61787
a	0.235853
b	0.110756
C	0.470676
d	1

# Table of Stats From Input Data

Dose	Ν	Obs Mean	Obs Std Dev
0	10	0.22	0.08
2.9	10	0.23	0.119
10.6	9	0.13	0.053
42	9	0.13	0.04
191.1	10	0.1	0.04

# Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	0.2359	0.1091	-0.4593
2.9	0.2016	0.08885	1.012
10.6	0.1496	0.06014	-0.9778
42	0.1122	0.04127	1.294
191.1	0.111	0.0407	-0.8555

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)

	<pre>Var{e(ij)} =</pre>	Sigma(i)^2
Model A3:		Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R:	Yij = Var{e(ij)} =	

Likelihoods of Interest

	Model	Model Log(likelihood) DF		
AIC				
105 2060	Al	103.6934	6	_
195.3868	A2	112.7799	10	-
205.5597	A3	111.9906	7	-
209.9812	R	92.68104	2	_
181.3621	4	108.3631	5	_
206.7262				

Additive constant for all log-likelihoods = -44.11. This constant added to the above values gives the log-likelihood including the term that does not

depend on the model parameters.

### Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A2 vs. A1) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 6a: Does Model 4 fit the data? (A3 vs 4)

Test p-value	-2*log(Likelihood Ratio)	D. F.
Test 1	40.2	8
< 0.0001		

Test 2 0.001142	18.17	4
Test 3	1.578	З
0.6643	1.570	5
Test 6a	7.255	2
0.02658		

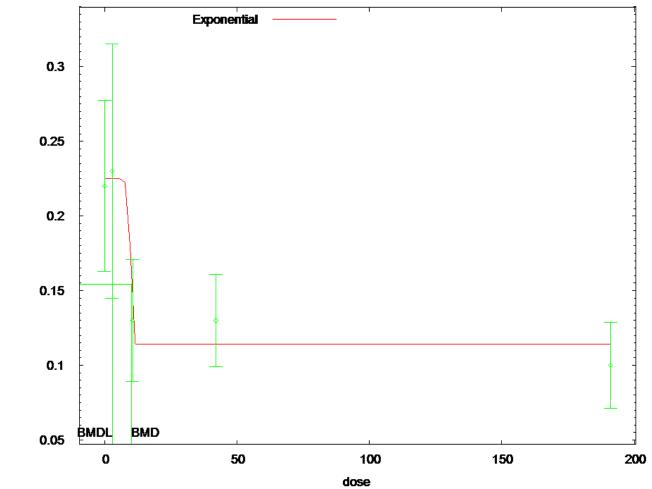
The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data. The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate. The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here. The p-value for Test 6a is less than .1. Model 4 may not adequately describe the data; you may want to consider another model. Benchmark Dose Computations: Specified Effect = 1.000000

Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

BMD = 18.7165 BMDL = 5.48116

```
DL = 5.48116
```



Mean Response

09:00 06/22 2014

```
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Norm/Monocyte_Concurrent_Normal-HLS
2001-Monocyte Count-ExpCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sun Jun 22 09:00:28 2014
_____
===
BMDS Model Run
~~~~
  The form of the response function by Model:
     Model 2:
                Y[dose] = a * exp{sign * b * dose}
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
     Model 4:
               Y[dose] = a * [c-(c-1) * exp{-b * dose}]
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  rho is set to 0.
  A constant variance model is fit.
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 5
lnalpha	-5.32056
rho(S)	0
a	0.2415
b	0.0190159
C	0.394361
d	1

(S) = Specified

### Parameter Estimates

Variable	Model 5
lnalpha	-5.30047
rho	0
a	0.225
b	0.0989556
С	0.507602
d	13.9617

# Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	10	0.22	0.08
2.9	10	0.23	0.119
10.6	9	0.13	0.053
42	9	0.13	0.04
191.1	10	0.1	0.04

# Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	0.225	0.07063	-0.2238
2.9	0.225	0.07063	0.2238
10.6	0.13	0.07063	3.526e-007
42	0.1142	0.07063	0.6706
191.1	0.1142	0.07063	-0.6362

Other models for which likelihoods are calculated:

Model Al: Yij = Mu(i) + e(ij) Var{e(ij)} = Sigma^2

Model A2:	Yij = Var{e(ij)} =	Mu(i) + e(ij) Sigma(i)^2
Model A3:		Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R:	Yij = Var{e(ij)} =	

Likelihoods of Interest

AIC	Model	Log(likelihood)	DF	
AIC				
105 2060	A1	103.6934	6	_
195.3868	A2	112.7799	10	-
205.5597	A3	103.6934	6	_
195.3868	R	92.68104	2	_
181.3621	5	103.2113	5	_
196.4225				

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

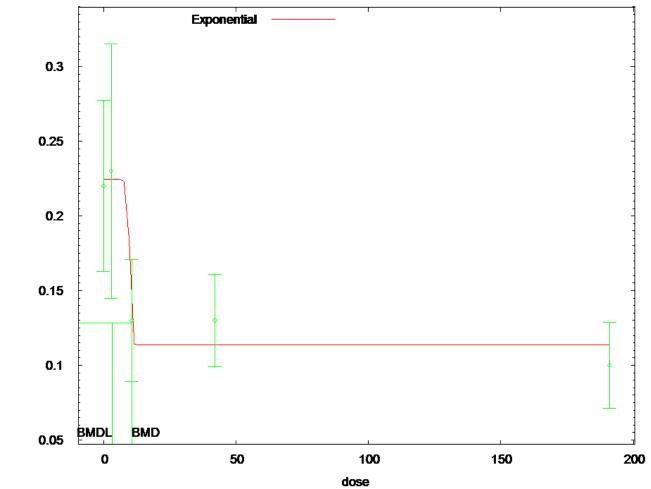
Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A2 vs. A1) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 7a: Does Model 5 fit the data? (A3 vs 5)

Test	-2*log(Likelihood Ratio)	D. F.
p-value		

Test 1 < 0.0001	40.2	8
Test 2 0.001142	18.17	4
Test 3	18.17	4
0.001142 Test 7a 0.3261	0.9643	1
0.3201		

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. Consider running a non-homogeneous variance model. The p-value for Test 3 is less than .1. You may want to consider a different variance model. 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 = 0.950000BMD = 10.1162

BMDL = 3.02618



Mean Response

09:00 06/22 2014

```
______
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Norm/Monocyte Concurrent Normal-HLS
2001-Monocyte Count-ExpNCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sun Jun 22 09:00:29 2014
______
===
BMDS Model Run
~~~~
  The form of the response function by Model:
                Y[dose] = a * exp{sign * b * dose}
     Model 2:
                Y[dose] = a * exp\{sign * (b * dose)^d\}
     Model 3:
     Model 4:
                Y[dose] = a * [c-(c-1) * exp{-b * dose}]
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  The variance is to be modeled as Var(i) = exp(lalpha + log
(mean(i)) * rho)
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 5
lnalpha	-1.08858
rho	2.4145
a	0.2415
b	0.0190159
C	0.394361
d	1

# Parameter Estimates

Variable	Model 5
lnalpha	-0.920072
rho	2.51647
a	0.22479
b	0.0983632
С	0.506722
d	14.9831

# Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	10	0.22	0.08
2.9	10	0.23	0.119
10.6	9	0.13	0.053
42	9	0.13	0.04
191.1	10	0.1	0.04

# Estimated Values of Interest

Est Mean	Est Std	Scaled Residual
0.2248	0.09651	-0.1569
0.2248	0.09651	0.1707
0.131	0.04893	-0.06137
0.1139	0.04103	1.177
0.1139	0.04103	-1.072
	0.2248 0.2248 0.131 0.1139	0.2248 0.09651 0.2248 0.09651 0.131 0.04893 0.1139 0.04103

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)

		<pre>Var{e(ij)}</pre>	=	Sigma(i) <sup>2</sup>	
Model	A3:			Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)	
Model	R:	Yij Var{e(ij)}	=	Mu + e(i) Sigma^2	

Likelihoods of Interest Model Log(likelihood) DF AIC ----- ----\_ 6 103.6934 A1 \_ 195.3868 10 A2 112.7799 205.5597 A3 111.9906 7 209.9812 R 92.68104 2 -181.3621 5 110.5931 6 -209.1861

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)

Test p-value	-2*log(Likelihood Ratio)	D. F.
Test 1 < 0.0001	40.2	8

Test 2	18.17	4
0.001142		
Test 3	1.578	3
0.6643		
Test 7a	2.795	1
0.09455		

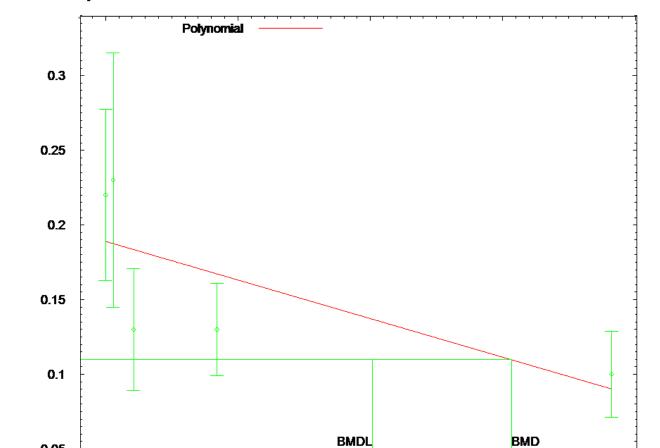
The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data. The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate. The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here. The p-value for Test 7a is less than .1. Model 5 may not adequately describe the data; you may want to consider another model. Benchmark Dose Computations: Specified Effect = 1.000000 Risk Type = Estimated standard deviations from

control

Confidence Level = 0.950000

BMD = 10.663

BMDL = 3.27746



100

dose

150

200

50

# Polynomial Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

Mean Response

12:45 07/09 2014

0.05

0

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_Monocyte\_Concurrent/Monocyte\_Concu rrent\_Normal-HLS 2001-Monocyte Count-Poly2CV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_Monocyte\_Concurrent/Monocyte\_Concu rrent\_Normal-HLS 2001-Monocyte Count-Poly2CV-1SD-5d.plt Wed Jul 09 12:45:45 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse 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 = 5Total number of records with missing values = 0Maximum 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 = 0.00545863Specified rho = 0  $beta_0 = 0.20922$  $beta_1 = -0.00266808$ beta\_2 = 0 Asymptotic Correlation Matrix of Parameter Estimates ( \*\*\* The model parameter(s) -rho -beta 2 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	4.2e-008	5.1e-009
beta_0	4.2e-008	1	-0.56
beta_1	5.1e-009	-0.56	1

# Parameter Estimates

			95.0%
Wald Confidence In	terval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Conf	. Limit		
alpha	0.00628415	0.00128275	
0.00377002	0.00879829		
beta_0	0.189334	0.0138502	
0.162188	0.21648		
beta_1	-0.000517126	0.000155222	-
0.000821356	-0.000212897		
beta_2	0	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 Scaled	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 1.22	10	0.22	0.189	0.08	0.0793
2.9	10	0.23	0.188	0.119	0.0793
10.6	9	0.13	0.184	0.053	0.0793
42 -1.42	9	0.13	0.168	0.04	0.0793
191.1 0.379	10	0.1	0.0905	0.04	0.0793

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<sup>2</sup>

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
Al	103.693409	б	-195.386818
A2	112.779870	10	-205.559741
A3	103.693409	б	-195.386818
fitted	97.673375	3	-189.346749
R	92.681036	2	-181.362073

### 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

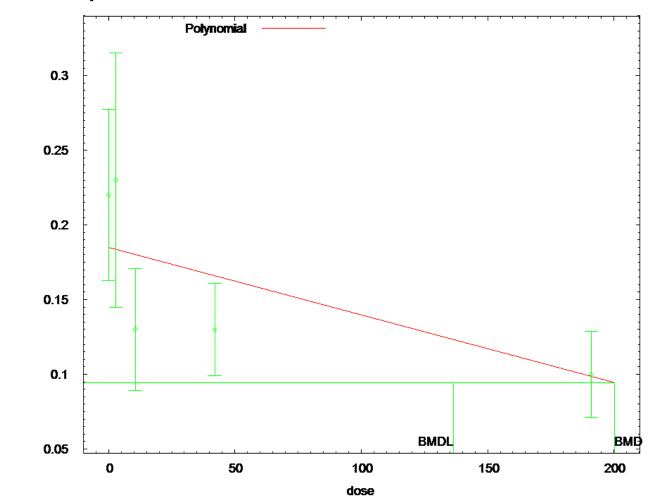
Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	40.1977	8	<.0001
Test 2	18.1729	4	0.001142
Test 3	18.1729	4	0.001142
Test 4	12.0401	3	0.007247

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. Consider running a non-homogeneous variance model The p-value for Test 3 is less than .1. You may want to consider a different variance model 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 = 153.295

BMDL = 100.721



# Polynomial Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

Mean Response

12:45 07/09 2014

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_Monocyte\_Concurrent/Monocyte\_Concu rrent\_Normal-HLS 2001-Monocyte Count-Poly2NCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_Monocyte\_Concurrent/Monocyte\_Concu rrent\_Normal-HLS 2001-Monocyte Count-Poly2NCV-1SD-5d.plt Wed Jul 09 12:45:48 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse 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 = 5Total number of records with missing values = 0Maximum number of iterations = 500 Relative Function Convergence has been set to: 1e-008 Parameter Convergence has been set to: 1e-008 Default Initial Parameter Values lalpha = -5.21056 rho = 0 beta\_0 = 0.20922  $beta_1 = -0.00266808$ beta\_2 = 0 Asymptotic Correlation Matrix of Parameter Estimates ( \*\*\* The model parameter(s) -beta\_2 have been estimated at a boundary point, or have

been specified by the user,

and do not appear in the correlation matrix )

	lalpha	rho	beta_0	beta_1
lalpha	1	0.99	-0.037	0.035
rho	0.99	1	-0.036	0.033
beta_0	-0.037	-0.036	1	-0.81
beta_1	0.035	0.033	-0.81	1

Parameter Estimates

9	5	•	08	5

				95.06
Wald Con	fidence I	nterval		
V	'ariable	Estimate	Std. Err.	Lower Conf.
Limit	Upper Con	f. Limit		
	lalpha	0.0784563	1.48211	-
2.82642		2.98333		
	rho	2.89289	0.795215	
1.3343		4.45148		
	beta_0	0.184882	0.015175	
0.15514		0.214625		
	beta 1	-0.000451919	0.000103729	_
0.000655	225	-0.000248614		
	beta_2	0	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 Scaled	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 1.23	10	0.22	0.185	0.08	0.0905
2.9	10	0.23	0.184	0.119	0.0896
10.6 -1.72	9	0.13	0.18	0.053	0.0871
42 -1.39	9	0.13	0.166	0.04	0.0774

191.1	10	0.1	0.0985	0.04	0.0364
0.128					

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
Al	103.693409	б	-195.386818
A2	112.779870	10	-205.559741
A3	111.990624	7	-209.981248
fitted	102.275742	4	-196.551485
R	92.681036	2	-181.362073

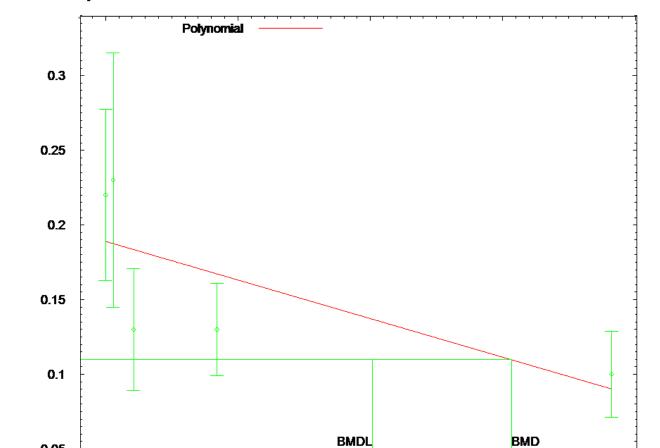
## Explanation of Tests

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	40.1977	8	<.0001
Test 2	18.1729	4	0.001142
Test 3	1.57849	3	0.6643
Test 4	19.4298	3	0.0002228

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 = Estimated standard deviations from the Risk Type control mean Confidence level = 0.95 BMD = 200.254 BMDL = 136.469



100

dose

150

200

50

# Polynomial Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

Mean Response

12:45 07/09 2014

0.05

0

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_Monocyte\_Concurrent/Monocyte\_Concu rrent\_Normal-HLS 2001-Monocyte Count-Poly3CV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_Monocyte\_Concurrent/Monocyte\_Concu rrent\_Normal-HLS 2001-Monocyte Count-Poly3CV-1SD-5d.plt Wed Jul 09 12:45:45 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse 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 = 5Total 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 = 0.00545863rho = 0 Specified beta\_0 = 0.236994 beta\_1 = -0.0119872 0.236994 beta\_2 = 0  $beta_3 = -1.10979e-006$ Asymptotic Correlation Matrix of Parameter Estimates ( \*\*\* The model parameter(s) -rho -beta\_2 -

beta\_3

have been estimated at a boundary point, or have been specified by the user,

and do not appear in the correlation matrix )

beta_1	beta_0	alpha	
-1.8e-010	-1.4e-009	1	alpha
-0.56	1	-1.4e-009	beta_0
1	-0.56	-1.8e-010	beta_1

Parameter Estimates

95.0%

			90.0%
Wald Confidence In	terval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Conf	. Limit		
alpha	0.00628415	0.00128275	
0.00377002	0.00879829		
beta_0	0.189334	0.0138502	
0.162188	0.21648		
beta_1	-0.000517126	0.000155222	_
0.000821356	-0.000212897		
beta_2	-0	NA	
beta_3	- 0	NA	

NA - Indicates that this parameter has hit a bound implied by some inequality constraint and thus has no standard error.

Dose Scaled	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 1.22	10	0.22	0.189	0.08	0.0793
2.9	10	0.23	0.188	0.119	0.0793
10.6	9	0.13	0.184	0.053	0.0793
-2.04 42 -1.42	9	0.13	0.168	0.04	0.0793
-1.42 191.1	10	0.1	0.0905	0.04	0.0793

Table of Data and Estimated Values of Interest

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
Al	103.693409	б	-195.386818
A2	112.779870	10	-205.559741
A3	103.693409	б	-195.386818
fitted	97.673375	3	-189.346749
R	92.681036	2	-181.362073

## Explanation of Tests

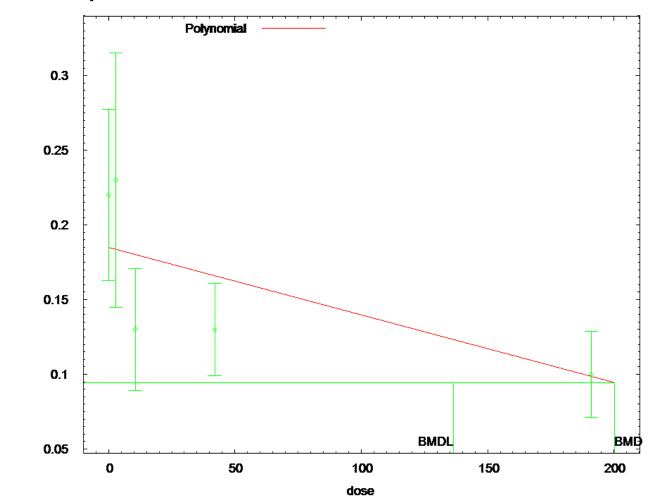
Test 1: Do responses and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A1 vs A2) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 4: Does the Model for the Mean Fit? (A3 vs. fitted) (Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

## Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	40.1977	8	<.0001
Test 2	18.1729	4	0.001142
Test 3	18.1729	4	0.001142
Test 4	12.0401	3	0.007247

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. Consider running a non-homogeneous variance model The p-value for Test 3 is less than .1. You may want to consider а different variance model The p-value for Test 4 is less than .1. You may want to try a different model Benchmark Dose Computation Specified effect = 1 Estimated standard deviations from the Risk Type = control mean Confidence level = 0.95 153.295 BMD = BMDL = 100.721



# Polynomial Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

Mean Response

12:45 07/09 2014

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_Monocyte\_Concurrent/Monocyte\_Concu rrent\_Normal-HLS 2001-Monocyte Count-Poly3NCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_Monocyte\_Concurrent/Monocyte\_Concu rrent Normal-HLS 2001-Monocyte Count-Poly3NCV-1SD-5d.plt Wed Jul 09 12:45:47 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse 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 = 5Total number of records with missing values = 0Maximum number of iterations = 500 Relative Function Convergence has been set to: 1e-008 Parameter Convergence has been set to: 1e-008 Default Initial Parameter Values lalpha = -5.21056 rho = 0 beta\_0 = 0.236994 beta\_1 = -0.0119872 beta\_2 = 0  $beta_3 = -1.10979e-006$ Asymptotic Correlation Matrix of Parameter Estimates ( \*\*\* The model parameter(s) -beta\_2 -beta\_3

have been estimated at a boundary point, or have been specified by the user, and do not appear in the correlation matrix )

	lalpha	rho	beta_0	beta_1
lalpha	1	0.99	-0.037	0.035
rho	0.99	1	-0.036	0.033
beta_0	-0.037	-0.036	1	-0.81
beta_1	0.035	0.033	-0.81	1

Parameter Estimates

			95.0%
Wald Confidence In	terval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Conf	. Limit		
lalpha	0.0784582	1.48211	-
2.82642	2.98333		
rho	2.89289	0.795215	
1.3343	4.45148		
beta_0	0.184882	0.015175	
0.15514	0.214625		
beta_1	-0.000451919	0.000103729	-
0.000655224	-0.000248614		
beta_2	0	NA	
beta_3	0	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 Scaled	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 1.23	10	0.22	0.185	0.08	0.0905
2.9	10	0.23	0.184	0.119	0.0896
1.64 10.6 -1.72	9	0.13	0.18	0.053	0.0871

42 -1.39	9	0.13	0.166	0.04	0.0774
191.1 0.128	10	0.1	0.0985	0.04	0.0364
Model	Descripti	ons for li	kelihoods cal	culated	
Model		Yij = Mu (ij)} = Si	(i) + e(ij) gma^2		
Model		Yij = Mu (ij)} = Si	(i) + e(ij) gma(i)^2		
Model	Var{e	(ij) = ex	(i) + e(ij) p(lalpha + rh	o*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<sup>2</sup>

## Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
Al	103.693409	6	-195.386818
A2	112.779870	10	-205.559741
A3	111.990624	7	-209.981248
fitted	102.275742	4	-196.551485
R	92.681036	2	-181.362073

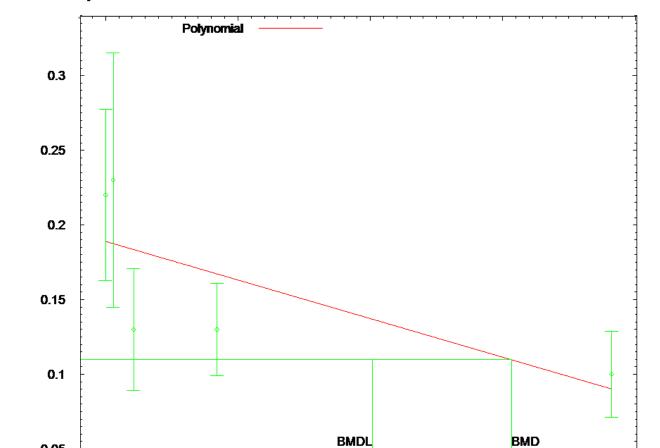
## Explanation of Tests

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	40.1977	8	<.0001
Test 2	18.1729	4	0.001142
Test 3	1.57849	3	0.6643

19.4298 3 0.0002228 Test 4 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 = Estimated standard deviations from the Risk Type control mean Confidence level = 0.95 200.254 BMD = BMDL = 136.469



100

dose

150

200

50

# Polynomial Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

Mean Response

12:45 07/09 2014

0.05

0

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_Monocyte\_Concurrent/Monocyte\_Concu rrent\_Normal-HLS 2001-Monocyte Count-Poly4CV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_Monocyte\_Concurrent/Monocyte\_Concu rrent\_Normal-HLS 2001-Monocyte Count-Poly4CV-1SD-5d.plt Wed Jul 09 12:45:45 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse 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 = 5Total 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 = 0.00545863rho = 0 Specified 0.22 beta\_0 = beta\_1 = 0  $beta_2 = -0.00230138$ beta 3 = 0  $beta_4 = -2.43829e-007$ 

Asymptotic Correlation Matrix of Parameter Estimates

beta_1	beta_0	alpha	
-2.1e-010	-1.9e-010	1	alpha
-0.56	1	-1.9e-010	beta_0
1	-0.56	-2.1e-010	beta_1

Parameter Estimates

9	5	0	ê	

Wald Confidence Interval					
Variable	Estimate	Std. Err.	Lower Conf.		
Limit Upper Conf	. Limit				
alpha	0.00628415	0.00128275			
0.00377002	0.00879829				
beta_0	0.189334	0.0138502			
0.162188	0.21648				
beta_1	-0.000517126	0.000155222	-		
0.000821356	-0.000212897				
beta_2	0	NA			
beta_3	-0	NA			
beta_4	-0	NA			

NA - Indicates that this parameter has hit a bound implied by some inequality constraint and thus has no standard error.

Dose Scaled	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 1.22	10	0.22	0.189	0.08	0.0793
2.9 1.68	10	0.23	0.188	0.119	0.0793
10.6	9	0.13	0.184	0.053	0.0793
42	9	0.13	0.168	0.04	0.0793

Table of Data and Estimated Values of Interest

-1.42 191.1 0.379	10	0.1	0.0905	0.04	0.0793
Model	Description	s for like	lihoods calcula	ted	
Model	Al: Var{e(i	Yij = Mu(i j)} = Sigm			
Model	A2: Var{e(i	Yij = Mu(i j)} = Sigm			
	Var{e(i	-	a^2 variance param	eters that	
Model		Yi = Mu + i)} = Sigm	· · ·		

## Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
Al	103.693409	б	-195.386818
A2	112.779870	10	-205.559741
A3	103.693409	б	-195.386818
fitted	97.673375	3	-189.346749
R	92.681036	2	-181.362073

## 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.)

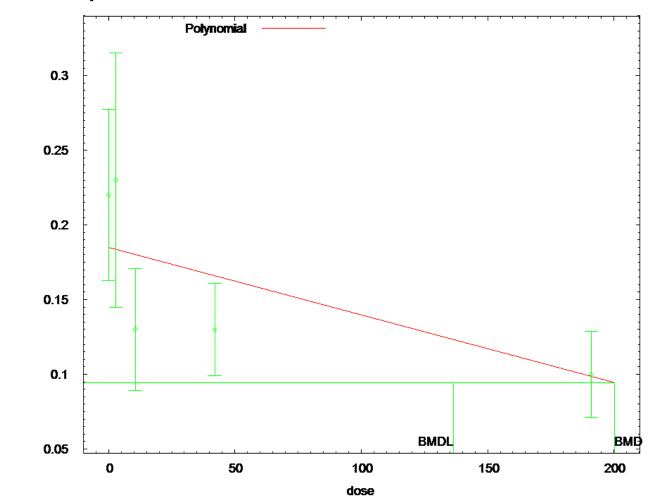
### Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	40.1977	8	<.0001
Test 2	18.1729	4	0.001142
Test 3	18.1729	4	0.001142
Test 4	12.0401	3	0.007247

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. Consider running a non-homogeneous variance model The p-value for Test 3 is less than .1. You may want to consider а different variance model The p-value for Test 4 is less than .1. You may want to try a different model Benchmark Dose Computation Specified effect = 1 = Estimated standard deviations from the Risk Type control mean Confidence level = 0.95

BMD = 153.295

BMDL = 100.721



# Polynomial Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

Mean Response

12:45 07/09 2014

=== Polynomial Model. (Version: 2.19; Date: 06/25/2014) Input Data File: C:/Users/dmayfield/Desktop/Rat\_Monocyte\_Concurrent/Monocyte\_Concu rrent\_Normal-HLS 2001-Monocyte Count-Poly4NCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Rat\_Monocyte\_Concurrent/Monocyte\_Concu rrent\_Normal-HLS 2001-Monocyte Count-Poly4NCV-1SD-5d.plt Wed Jul 09 12:45:47 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = beta\_0 + beta\_1\*dose + beta\_2\*dose^2 + ... Dependent variable = MeanResponse 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 = 5Total number of records with missing values = 0Maximum number of iterations = 500 Relative Function Convergence has been set to: 1e-008 Parameter Convergence has been set to: 1e-008 Default Initial Parameter Values lalpha = -5.21056 rho = 0 0.22 beta\_0 = beta\_1 = 0  $beta_2 = -0.00230138$ beta 3 = 0  $beta_4 = -2.43829e-007$ Asymptotic Correlation Matrix of Parameter Estimates

1

lalpha	1	0.99	-0.037	0.035
rho	0.99	1	-0.036	0.033
beta_0	-0.037	-0.036	1	-0.81
beta_1	0.035	0.033	-0.81	1

#### Parameter Estimates

### 95.0%

				95.06		
Wald Confidence Interval						
V	ariable	Estimate	Std. Err.	Lower Conf.		
Limit	Upper Conf	. Limit				
	lalpha	0.0784574	1.48211	-		
2.82642		2.98333				
	rho	2.89289	0.795214			
1.3343		4.45148				
	beta_0	0.184883	0.015175			
0.15514		0.214625				
	beta_1	-0.00045192	0.000103729	-		
0.000655	225	-0.000248615				
	beta_2	0	NA			
	beta_3	0	NA			
	beta_4	0	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 Scaled F	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 1.23	10	0.22	0.185	0.08	0.0905
2.9	10	0.23	0.184	0.119	0.0896

1.64 10.6	9	0.13	0.18	0.053	0.0871
-1.72 42 -1.39	9	0.13	0.166	0.04	0.0774
191.1 0.128	10	0.1	0.0985	0.04	0.0364

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<sup>2</sup>

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	103.693409	6	-195.386818
A2	112.779870	10	-205.559741
A3	111.990624	7	-209.981248
fitted	102.275742	4	-196.551485
R	92.681036	2	-181.362073

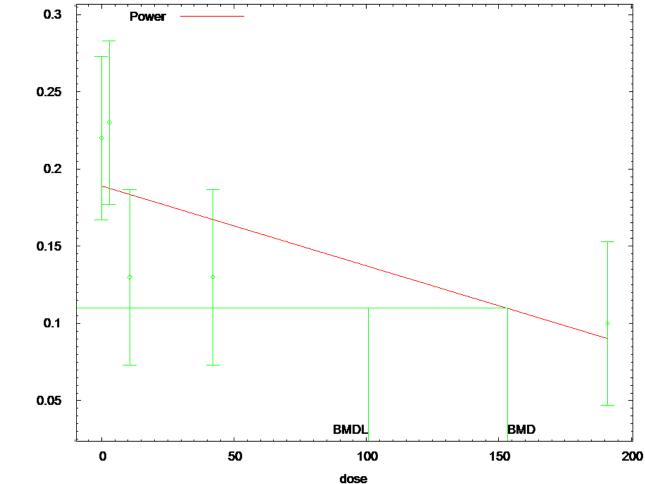
### Explanation of Tests

### Tests of Interest

Test	-2*log(Likelihood	Ratio)	Test df	p-value
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3

40.1977 8 Test 1 <.0001 o 4 Test 2 0.001142 18.1729 Test 3 1.57849 3 0.6643 Test 4 19.4298 3 0.0002228 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 = 200.254 BMDL = 136.469



Mean Response

09:00 06/22 2014

=== Power Model. (Version: 2.18; Date: 05/19/2014) Input Data File: C:/Users/dmayfield/Desktop/Norm/Monocyte\_Concurrent\_Normal-HLS 2001-Monocyte Count-PowerCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Norm/Monocyte\_Concurrent\_Normal-HLS 2001-Monocyte Count-PowerCV-1SD-5d.plt Sun Jun 22 09:00:28 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = control + slope \* dose^power Dependent variable = MeanResponse 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 = 5 Total number of records with missing values = 0 Maximum number of iterations = 500 Relative Function Convergence has been set to: 1e-008 Parameter Convergence has been set to: 1e-008 Default Initial Parameter Values alpha = 0.00545863rho = Specified 0 control = 0.1 slope = 0.178802 power = -0.542898 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	8.1e-009	-8.6e-009
control	8.1e-009	1	-0.56
slope	-8.6e-009	-0.56	1

## Parameter Estimates

			95.0%
Wald Confidence Ir	nterval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Conf	E. Limit		
alpha	0.00628415	0.00128275	
0.00377002	0.00879829		
control	0.189334	0.0138502	
0.162188	0.21648		
slope	-0.000517126	0.000155222	-
0.000821356	-0.000212897		
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
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Dose Scaled	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 1.22	10	0.22	0.189	0.08	0.0793
2.9	10	0.23	0.188	0.119	0.0793
10.6	9	0.13	0.184	0.053	0.0793
42	9	0.13	0.168	0.04	0.0793
191.1 0.379	10	0.1	0.0905	0.04	0.0793

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<sup>2</sup>

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
Al	103.693409	б	-195.386818
A2	112.779870	10	-205.559741
A3	103.693409	6	-195.386818
fitted	97.673375	3	-189.346749
R	92.681036	2	-181.362073

### 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

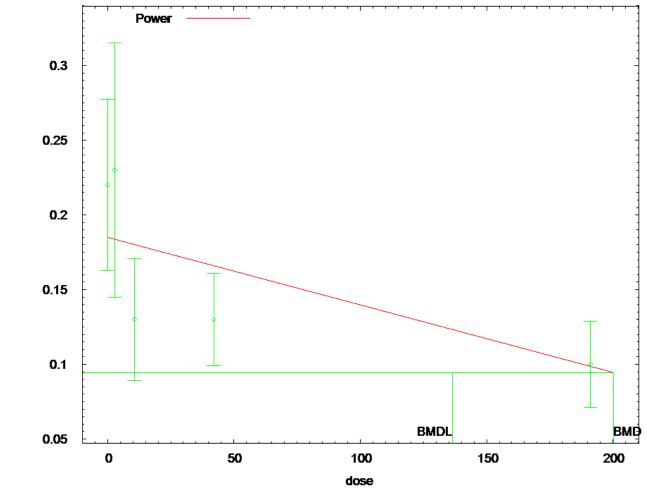
Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	40.1977	8	<.0001
Test 2	18.1729	4	0.001142
Test 3	18.1729	4	0.001142
Test 4	12.0401	3	0.007247

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. Consider running a non-homogeneous variance model The p-value for Test 3 is less than .1. You may want to consider a different variance model 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 = 153.295

BMDL = 100.721



Mean Response

09:00 06/22 2014

=== Power Model. (Version: 2.18; Date: 05/19/2014) Input Data File: C:/Users/dmayfield/Desktop/Norm/Monocyte\_Concurrent\_Normal-HLS 2001-Monocyte Count-PowerNCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Norm/Monocyte\_Concurrent\_Normal-HLS 2001-Monocyte Count-PowerNCV-1SD-5d.plt Sun Jun 22 09:00:31 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = control + slope \* dose^power Dependent variable = MeanResponse Independent variable = Dose The power is restricted to be greater than or equal to 1 The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) \* rho) Total number of dose groups = 5Total number of records with missing values = 0Maximum number of iterations = 500 Relative Function Convergence has been set to: 1e-008 Parameter Convergence has been set to: 1e-008 Default Initial Parameter Values lalpha = -5.21056 rho = 0 control = 0.1 slope = 0.1700---= -0.542898Asymptotic Correlation Matrix of Parameter Estimates ( \*\*\* The model parameter(s) -power have been estimated at a boundary point, or have been specified by the user,

en specified	and do not	appear in t	the correlation	matrix )
	lalpha	rho	control	slope
lalpha	1	0.99	-0.52	0.7
rho	0.99	1	-0.44	0.67
control	-0.52	-0.44	1	-0.82

slope 0.7 0.67 -0.82 1

Parameter Estimates

95.0%
-------

			22.00
Wald Confidence I	Interval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Con	nf. Limit		
lalpha	0.0784485	2.09108	-
4.01999	4.17689		
rho	2.89289	1.10377	
0.729543	5.05623		
control	0.184882	0.0153067	
0.154882	0.214883		
slope	-0.00045192	0.000103701	_
0.00065517	-0.000248669		
power	1	NA	
T			

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 Scaled 1	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 1.23	10	0.22	0.185	0.08	0.0905
2.9	10	0.23	0.184	0.119	0.0896
10.6 -1.72	9	0.13	0.18	0.053	0.0871
-1.72 42 -1.39	9	0.13	0.166	0.04	0.0774

191.1	10	0.1	0.0985	0.04	0.0364
0.128					

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
Al	103.693409	б	-195.386818
A2	112.779870	10	-205.559741
A3	111.990624	7	-209.981248
fitted	102.275742	4	-196.551485
R	92.681036	2	-181.362073

## 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.)

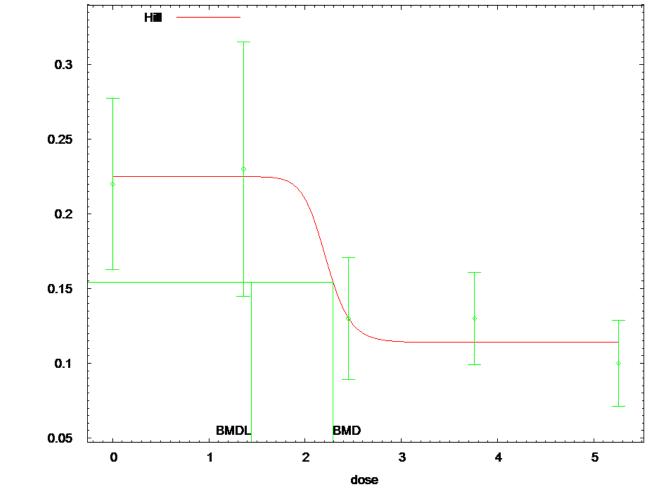
### Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	40.1977	8	<.0001
Test 2	18.1729	4	0.001142
Test 3	1.57849	3	0.6643
Test 4	19.4298	3	0.0002228

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 = Estimated standard deviations from the Risk Type control mean Confidence level = 0.95 BMD = 200.254BMDL = 136.469

**BMDS Model Results for Monocyte Count** (Log-transformed Doses, Concurrent Controls)





09:08 06/22 2014

Mean Response

=== Hill Model. (Version: 2.17; Date: 01/28/2013) Input Data File: C:/Users/dmayfield/Desktop/Norm/Monocyte\_Concurrent\_Ln-HLS 2001-Monocyte Count-HillCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Norm/Monocyte\_Concurrent\_Ln-HLS 2001-Monocyte Count-HillCV-1SD-5d.plt Sun Jun 22 09:08:08 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = intercept + v\*dose^n/(k^n + dose^n) Dependent variable = MeanResponse 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 = 5 Total number of records with missing values = 0 Maximum number of iterations = 500 Relative Function Convergence has been set to: 1e-008 Parameter Convergence has been set to: 1e-008 Default Initial Parameter Values alpha = 0.00545863Specified rho = 0 intercept = 0.22 v = -0.12 n = 4.79743 k = 2.124 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 )

k		alpha	intercept	v	n
al -1.5e-0	pha 06	1	1.6e-007	-2.1e-007	-1.5e-006
interc -0.079	ept	1.6e-007	1	-0.7	-0.072
0.081	v	-2.1e-007	-0.7	1	0.11
1	n	-1.5e-006	-0.072	0.11	1
1	k	-1.5e-006	-0.079	0.081	1

## Parameter Estimates

95.0%

terval		
Estimate	Std. Err.	Lower Conf.
. Limit		
0.00498924	0.00101842	
0.00698531		
0.225008	0.0158381	
0.25605		
-0.110809	0.0227564	-
0.0662072		
17.8909	242.727	-
493.627		
2.21732	2.99697	-
8.09127		
	. Limit 0.00498924 0.00698531 0.225008 0.25605 -0.110809 0.0662072 17.8909 493.627 2.21732	Estimate Std. Err. . Limit 0.00498924 0.00101842 0.00698531 0.225008 0.0158381 0.25605 -0.110809 0.0227564 0.0662072 17.8909 242.727 493.627 2.21732 2.99697

## Table of Data and Estimated Values of Interest

Dose Scaled R		Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 -0.224	10	0.22	0.225	0.08	0.0706

1.361	10	0.23	0.225	0.119	0.0706
0.224 2.451	9	0.13	0.13	0.053	0.0706
-0.00074 3.761	9	0.13	0.114	0.04	0.0706
0.671	9	0.15	0.114	0.04	0.0700
5.258 -0.636	10	0.1	0.114	0.04	0.0706

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	103.693409	б	-195.386818
A2	112.779870	10	-205.559741
A3	103.693409	б	-195.386818
fitted	103.211324	5	-196.422647
R	92.681036	2	-181.362073

## Explanation of Tests

### Tests of Interest

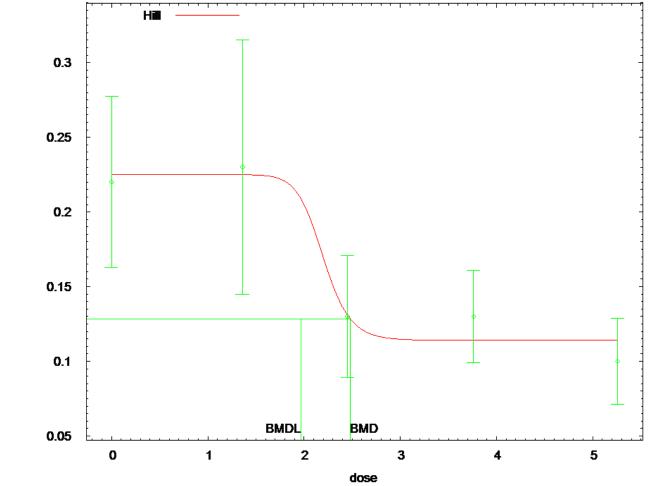
Test -2\*log(Likelihood Ratio) Test df p-value

3

Test 140.19778<.0001</th>Test 218.172940.001142Test 318.172940.001142Test 40.96417110.3261

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. Consider running a non-homogeneous variance model The p-value for Test 3 is less than .1. You may want to consider а different variance model 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 = Estimated standard deviations from the Risk Type control mean Confidence level = 0.95 BMD = 2.28837 BMDL = 1.43897





Mean Response

09:08 06/22 2014

=== Hill Model. (Version: 2.17; Date: 01/28/2013) Input Data File: C:/Users/dmayfield/Desktop/Norm/Monocyte\_Concurrent\_Ln-HLS 2001-Monocyte Count-HillNCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Norm/Monocyte\_Concurrent\_Ln-HLS 2001-Monocyte Count-HillNCV-1SD-5d.plt Sun Jun 22 09:08:09 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = intercept + v\*dose^n/(k^n + dose^n) Dependent variable = MeanResponse Independent variable = Dose Power parameter restricted to be greater than 1 The variance is to be modeled as Var(i) = exp(lalpha + rho \* ln(mean(i))) Total number of dose groups = 5Total number of records with missing values = 0Maximum number of iterations = 500 Relative Function Convergence has been set to: 1e-008 Parameter Convergence has been set to: 1e-008 Default Initial Parameter Values lalpha = -5.21056 rho = 0 intercept = 0.22 v = -0.12 n = 4.79743 k = 2.124 Asymptotic Correlation Matrix of Parameter Estimates lalpha rho intercept v

n	k			
lalpha -0.011	1-0.0022	0.99	-0.53	0.58
rho -0.011	0.99 -0.0021	1	-0.47	0.56
intercept -0.053	-0.53 -0.073	-0.47	1	-0.92
v 0.095	0.58 0.097	0.56	-0.92	1
n 1 (	-0.011	-0.011	-0.053	0.095
k 0.99	-0.0022 1	-0.0021	-0.073	0.097

Parameter Estimates

			95.0%
Wald Confidence I	nterval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Con	f. Limit		
lalpha	-0.919707	1.51609	-
3.8912	2.05178		
rho	2.51667	0.79556	
0.957403	4.07594		
intercept	0.224812	0.0215878	
0.182501	0.267124		
v	-0.110934	0.0236505	-
0.157288	-0.06458		
n	15.8793	87.1614	-
154.954	186.713		
k	2.20245	1.27621	-
0.298865	4.70378		

Table of Data and Estimated Values of Interest

Dose Scaled R		Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 -0.158	10	0.22	0.225	0.08	0.0965

1.361 0.172	10	0.23	0.225	0.119	0.0965
2.451	9	0.13	0.131	0.053	0.0489
-0.064 3.761	9	0.13	0.114	0.04	0.041
1.18 5.258	10	0.1	0.114	0.04	0.041
-1.07					

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
Al	103.693409	6	-195.386818
A2	112.779870	10	-205.559741
A3	111.990624	7	-209.981248
fitted	110.593587	б	-209.187174
R	92.681036	2	-181.362073

## Explanation of Tests

# Tests of Interest

Test -2\*log(Likelihood Ratio) Test df p-value

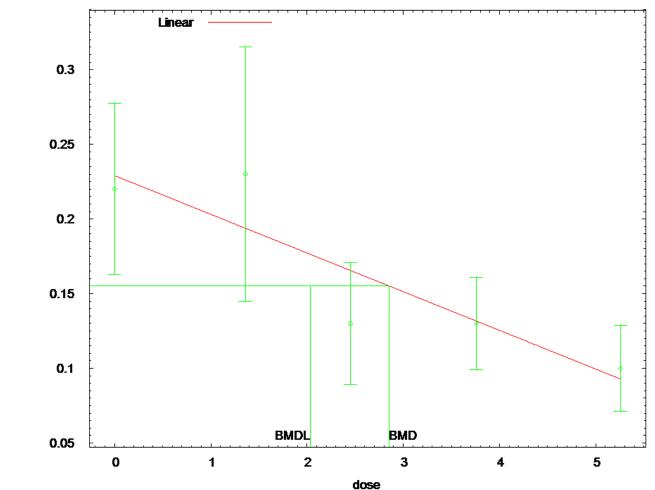
3

Test 1 40.1977 8 <.0001 4 Test 2 0.001142 18.1729 Test 3 1.57849 3 0.6643 1 Test 4 2.79407 0.09461

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 = 2.48276 BMDL = 1.96659



Linear Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

12:49 07/09 2014

```
===
      Polynomial Model. (Version: 2.19; Date: 06/25/2014)
      Input Data File:
C:/Users/dmayfield/Desktop/Rat_Monocyte_Concurrent
_Ln/Monocyte_Concurrent_Ln-HLS 2001-Monocyte Count-LinearCV-1SD-
5d.(d)
      Gnuplot Plotting File:
C:/Users/dmayfield/Desktop/Rat_Monocyte_Concurrent
_Ln/Monocyte_Concurrent_Ln-HLS 2001-Monocyte Count-LinearCV-1SD-
5d.plt
                                Wed Jul 09 12:49:38 2014
_____
===
BMDS Model Run
~~~~
  The form of the response function is:
  Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...
  Dependent variable = MeanResponse
  Independent variable = Dose
  rho is set to 0
  Signs of the polynomial coefficients are not restricted
  A constant variance model is fit
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
               Default Initial Parameter Values
                      alpha = 0.00545863
                       rho =
                                     0
                                         Specified
                     beta_0 =
                               0.228322
                     beta 1 = -0.0258442
         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  $\ensuremath{)}$ 

	alpha	beta_0	beta_1
alpha	1	-2.7e-008	3.1e-008
beta_0	-2.7e-008	1	-0.81
beta_1	3.1e-008	-0.81	1

#### Parameter Estimates

# 95.0%

Wald Confidence In	nterval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Cont	f. Limit		
alpha	0.00542838	0.00110806	
0.00325661	0.00760014		
beta_0	0.229102	0.0180267	
0.193771	0.264434		
beta_1	-0.0258556	0.00572228	_
0.037071	-0.0146401		

# Table of Data and Estimated Values of Interest

Dose Scaled R	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 -0.391	10	0.22	0.229	0.08	0.0737
1.361	10	0.23	0.194	0.119	0.0737
2.451	9	0.13	0.166	0.053	0.0737
3.761 -0.0757	9	0.13	0.132	0.04	0.0737
5.258 0.294	10	0.1	0.0932	0.04	0.0737

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:	$Yij = Mu(i) + e(ij)$ $Var{e(ij)} = Sigma^{2}$
	A3 uses any fixed variance parameters that specified by the user

Model R: Yi = Mu + e(i)Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
Al	103.693409	б	-195.386818
A2	112.779870	10	-205.559741
A3	103.693409	б	-195.386818
fitted	101.186766	3	-196.373532
R	92.681036	2	-181.362073

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

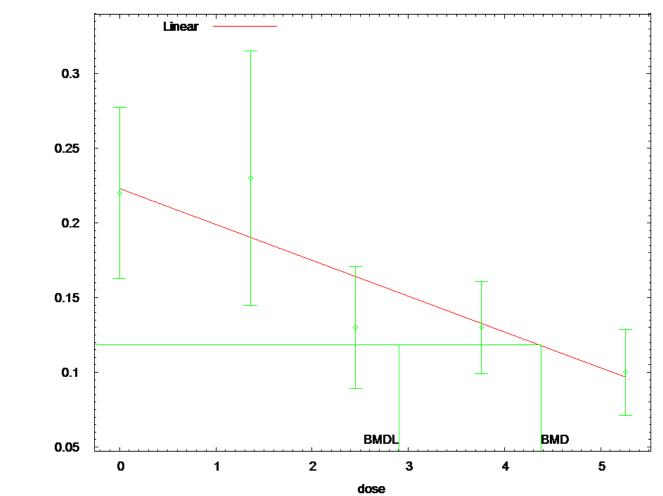
Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	40.1977	8	<.0001
Test 2	18.1729	4	0.001142
Test 3	18.1729	4	0.001142
Test 4	5.01329	3	0.1708

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. Consider running a non-homogeneous variance model

The p-value for Test 3 is less than .1. You may want to consider а different variance model 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 = 2.84958 BMDL = 2.03295



Mean Response

12:49 07/09 2014

```
===
      Polynomial Model. (Version: 2.19; Date: 06/25/2014)
      Input Data File:
C:/Users/dmayfield/Desktop/Rat_Monocyte_Concurrent
_Ln/Monocyte_Concurrent_Ln-HLS 2001-Monocyte Count-LinearNCV-1SD-
5d.(d)
      Gnuplot Plotting File:
C:/Users/dmayfield/Desktop/Rat_Monocyte_Concurrent
_Ln/Monocyte_Concurrent_Ln-HLS 2001-Monocyte Count-LinearNCV-1SD-
5d.plt
                                Wed Jul 09 12:49:39 2014
_____
===
BMDS Model Run
~~~~
  The form of the response function is:
  Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...
  Dependent variable = MeanResponse
  Independent variable = Dose
  Signs of the polynomial coefficients are not restricted
  The variance is to be modeled as Var(i) = exp(lalpha + log
(mean(i)) * rho)
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
               Default Initial Parameter Values
                     lalpha = -5.21056
                       rho =
                                      0
                     beta_0 =
                              0.228322
                     beta 1 = -0.0258442
         Asymptotic Correlation Matrix of Parameter Estimates
                           rho
              lalpha
                                    beta_0
                                               beta_1
```

lalpha	1	0.99	-0.076	0.083
rho	0.99	1	-0.076	0.083
beta_0	-0.076	-0.076	1	-0.92
beta_1	0.083	0.083	-0.92	1

Parameter Estimates

# 95.0%

dence Int	erval		
iable	Estimate	Std. Err.	Lower Conf.
per Conf.	Limit		
alpha	-0.557382	1.30166	-
	1.99383		
rho	2.63613	0.691385	
	3.99122		
eta_0	0.22329	0.0212241	
	0.264888		
eta_1	-0.0239544	0.00497926	-
	-0.0141953		
	iable per Conf. alpha rho eta_0	per Conf. Limit alpha -0.557382 1.99383 rho 2.63613 3.99122 eta_0 0.22329 0.264888 eta_1 -0.0239544	iable Estimate Std. Err. per Conf. Limit alpha -0.557382 1.30166 1.99383 rho 2.63613 0.691385 3.99122 eta_0 0.22329 0.0212241 0.264888 eta_1 -0.0239544 0.00497926

# Table of Data and Estimated Values of Interest

Dose Scaled R	N es.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 -0.0992	10	0.22	0.223	0.08	0.105
1.361 1.46	10	0.23	0.191	0.119	0.0852
2.451	9	0.13	0.165	0.053	0.0702
3.761 -0.181	9	0.13	0.133	0.04	0.0531
5.258 0.24	10	0.1	0.0973	0.04	0.0351

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)

	<pre>Var{e(ij)} = Sigma^2</pre>
Model A2	: Yij = Mu(i) + e(ij) Var{e(ij)} = Sigma(i)^2
Model A3	5 - ( ) - ( 5)
	<pre>Var{e(ij)} = exp(lalpha + rho*ln(Mu(i))) l A3 uses any fixed variance parameters that specified by the user</pre>
Model R	: Yi = Mu + e(i) Var{e(i)} = Sigma^2

Model	Log(likelihood)	# Param's	AIC
Al	103.693409	б	-195.386818
A2	112.779870	10	-205.559741
A3	111.990624	7	-209.981248
fitted	107.004496	4	-206.008991
R	92.681036	2	-181.362073

# 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.)	

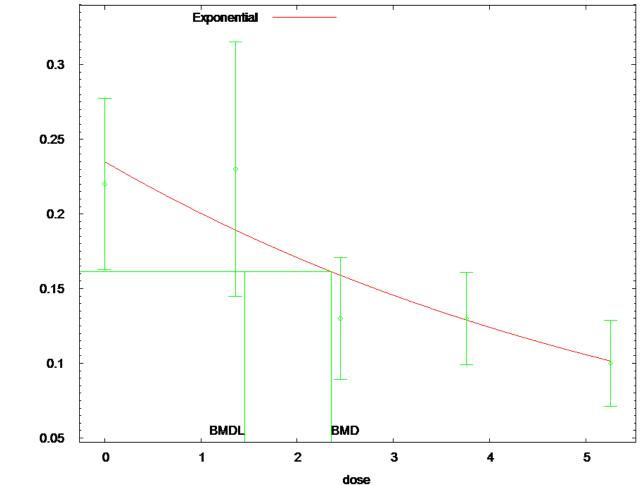
# Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	40.1977	8	<.0001
Test 2	18.1729	4	0.001142
Test 3	1.57849	3	0.6643
Test 4	9.97226	3	0.0188

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 = Estimated standard deviations from the Risk Type control mean Confidence level = 0.95 BMD = 4.37872 BMDL = 2.90647



Exponential Model 2, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Level for BMDL

09:08 06/22 2014

=== Exponential Model. (Version: 1.9; Date: 01/29/2013) Input Data File: C:/Users/dmayfield/Desktop/Norm/Monocyte\_Concurrent\_Ln-HLS 2001-Monocyte Count-ExpCV-1SD-5d.(d) Gnuplot Plotting File: Sun Jun 22 09:08:07 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function by Model: Model 2:  $Y[dose] = a * exp{sign * b * dose}$  $Y[dose] = a * exp\{sign * (b * dose)^d\}$ Model 3:  $Y[dose] = a * [c-(c-1) * exp{-b * dose}]$ Model 4:  $Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]$ Model 5: 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 = MeanResponse 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 = 5Total 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 rho(S)	-5.32056
1110(5)	0
a	0.101819
b	0.164384
C	0
d	1

(S) = Specified

#### Parameter Estimates

Variable	Model 2
lnalpha	-5.21349
rho	0
a	0.235092
b	0.159679
С	0
d	1

# Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	10	0.22	0.08
1.361	10	0.23	0.119
2.451	9	0.13	0.053
3.761	9	0.13	0.04
5.258	10	0.1	0.04

## Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	0.2351	0.07377	-0.6469
1.361	0.1892	0.07377	1.75
2.451	0.159	0.07377	-1.177
3.761	0.129	0.07377	0.0427
5.258	0.1015	0.07377	-0.06572

Other models for which likelihoods are calculated:

Model Al: Yij = Mu(i) + e(ij) Var{e(ij)} = Sigma^2

Model A2:	Yij = Var{e(ij)} =	Mu(i) + e(ij) Sigma(i)^2
Model A3:		Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R:	Yij = Var{e(ij)} =	

	Model	Log(likelihood)	DF	
AIC				
105 2060	Al	103.6934	6	_
195.3868	A2	112.7799	10	_
205.5597	A3	103.6934	6	_
195.3868	R	92.68104	2	_
181.3621	2	101.1239	3	_
196.2477				

Additive constant for all log-likelihoods = -44.11. This constant added to the above values gives the log-likelihood including the term that does not

depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A2 vs. A1) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 4: Does Model 2 fit the data? (A3 vs. 2)

Tests of Interest

Test p-value	-2*log(Likelihood Ratio)	D. F.
Test 1	40.2	8

< 0.0001			
Test	2	18.17	4
0.001142			
Test	3	18.17	4
0.001142			
Test	4	5.139	3
0.1619			

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. Consider running a non-homogeneous variance model.

The p-value for Test 3 is less than .1. You may want to consider a different variance model.

The p-value for Test 4 is greater than .1. Model 2 seems to adequately describe the data.

Benchmark Dose Computations:

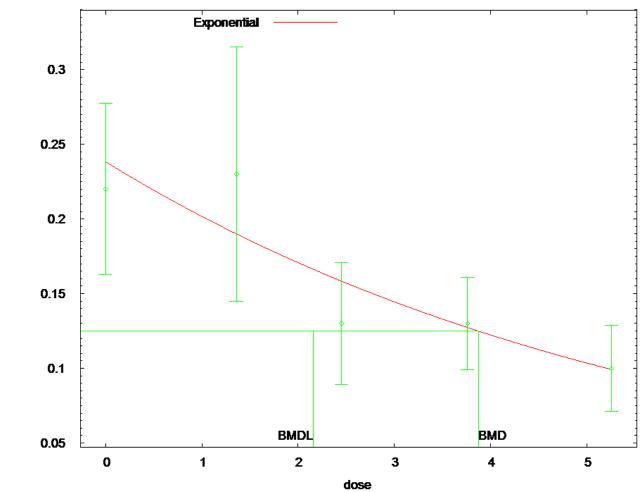
Specified Effect = 1.000000

Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

BMD = 2.35849

BMDL = 1.45524



Exponential Model 2, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Level for BMDL

09:08 06/22 2014

```
______
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Norm/Monocyte_Concurrent_Ln-HLS 2001-
Monocyte Count-ExpNCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sun Jun 22 09:08:08 2014
_____
===
BMDS Model Run
~~~~
  The form of the response function by Model:
     Model 2:
                Y[dose] = a * exp{sign * b * dose}
                Y[dose] = a * exp{sign * (b * dose)^d}
     Model 3:
     Model 4:
                Y[dose] = a * [c-(c-1) * exp{-b * dose}]
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  The variance is to be modeled as Var(i) = exp(lalpha + log
(mean(i)) * rho)
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 2
lnalpha	-1.08858
rho	2.4145
a	0.101819
b	0.164384
C	0
d	1

### Parameter Estimates

Variable	Model 2
lnalpha	-0.590628
rho	2.62295
a	0.238331
b	0.166716
C	0
d	1

# Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	10	0.22	0.08
1.361	10	0.23	0.119
2.451	9	0.13	0.053
3.761	9	0.13	0.04
5.258	10	0.1	0.04

# Estimated Values of Interest

Est Mean	Est Std	Scaled Residual
0.2383	0.1135	-0.5108
0.19	0.08428	1.503
0.1584	0.0664	-1.282
0.1273	0.04987	0.1617
0.09919	0.03595	0.07097
	0.2383 0.19 0.1584 0.1273	0.2383 0.1135 0.19 0.08428 0.1584 0.0664 0.1273 0.04987

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) <sup>2</sup>
Model A3	3: Yij = Var{e(ij)} =	Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R	<pre>X: Yij = Var{e(ij)} =</pre>	

	Model	Log(likelihood)	DF	
AIC				
	Al	103.6934	6	-
195.3868	A2	112.7799	10	_
205.5597	A3	111.9906	7	_
209.9812	R	92.68104	2	_
181.3621	2	107.1483	4	_
206.2965				

Additive constant for all log-likelihoods = -44.11. This constant added to the above values gives the log-likelihood including the term that

does not

depend on the model parameters.

#### Explanation of Tests

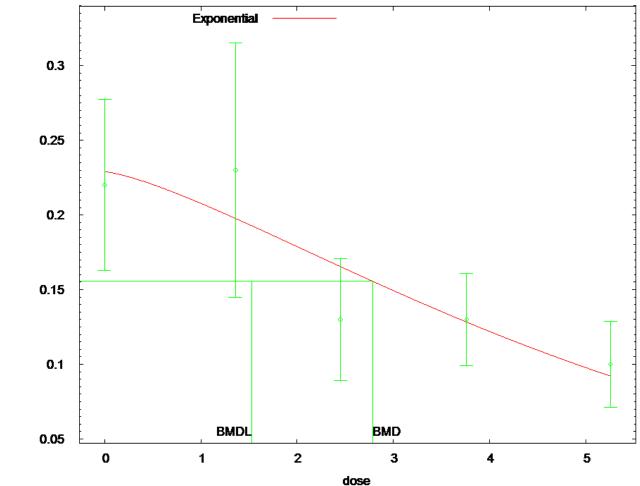
Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A2 vs. A1) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 4: Does Model 2 fit the data? (A3 vs. 2)

### Tests of Interest

Test p-value	-2*log(Likelihood Ratio)	D. F.
	40.2	0
Test 1 < 0.0001	40.2	8
Test 2	18.17	4

	1142 Test 3	1.578	3	
0.66	Test 4	9.685	3	
0.02	145			
be a	The p-value for Test 1 is less	than .05. Ther	e appears to	
be a	difference between response an levels, it seems appropriate t			
	The p-value for Test 2 is less variance model appears to be a		-homogeneous	
	The p-value for Test 3 is grea variance appears to be appropr		e modeled	
The p-value for Test 4 is less than .1. Model 2 may not adequately				
describe the data; you may want to consider another model.				
Benchmark Dose Computations:				
	Specified Effect = 1.000000			
cont	Risk Type = Estimated s rol	tandard deviatio	ons from	
	Confidence Level = 0.950000			
	BMD = 3.878	3		

BMDL = 2.16072



Exponential Model 3, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Level for BMDL

09:08 06/22 2014

=== Exponential Model. (Version: 1.9; Date: 01/29/2013) Input Data File: C:/Users/dmayfield/Desktop/Norm/Monocyte\_Concurrent\_Ln-HLS 2001-Monocyte Count-ExpCV-1SD-5d.(d) Gnuplot Plotting File: Sun Jun 22 09:08:07 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function by Model: Model 2:  $Y[dose] = a * exp{sign * b * dose}$  $Y[dose] = a * exp\{sign * (b * dose)^d\}$ Model 3:  $Y[dose] = a * [c-(c-1) * exp{-b * dose}]$ Model 4:  $Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]$ Model 5: 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 = MeanResponse 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 = 5Total 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 3
lnalpha	-5.32056
rho(S)	0
a	0.23917
b	0.0958051
С	0
d	2

(S) = Specified

#### Parameter Estimates

Variable	Model 3
lnalpha	-5.22632
rho	0
a	0.228926
b	0.177375
С	0
d	1.34953

# Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	10	0.22	0.08
1.361	10	0.23	0.119
2.451	9	0.13	0.053
3.761	9	0.13	0.04
5.258	10	0.1	0.04

## Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	0.2289	0.0733	-0.385
1.361	0.1977	0.0733	1.396
2.451	0.1654	0.0733	-1.449
3.761	0.1283	0.0733	0.06992
5.258	0.09213	0.0733	0.3394

Other models for which likelihoods are calculated:

Model Al: Yij = Mu(i) + e(ij) Var{e(ij)} = Sigma^2

Model A2:	Yij = Var{e(ij)} =	Mu(i) + e(ij) Sigma(i)^2
Model A3:		Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R:	Yij = Var{e(ij)} =	

AIC	Model	Log(likelihood)	DF	
ALC				
105 2060	Al	103.6934	6	-
195.3868	A2	112.7799	10	_
205.5597	A3	103.6934	6	_
195.3868	R	92.68104	2	_
181.3621	3	101.4317	4	_
194.8633				

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 5a: Does Model 3 fit the data? (A3 vs 3)

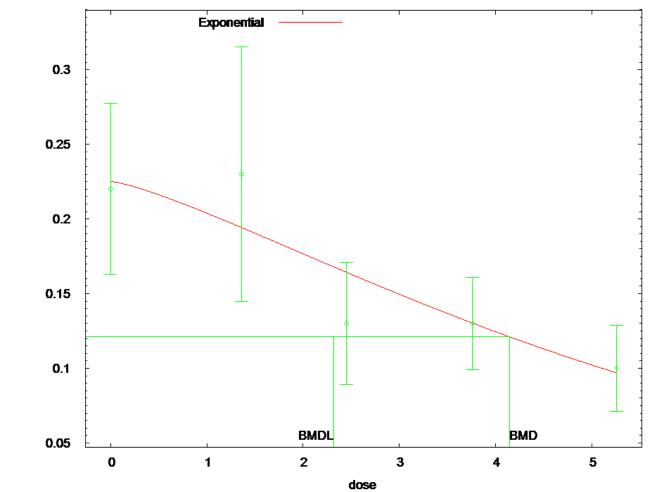
Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.
p-value		

Test 1 < 0.0001	40.2	8
Test 2	18.17	4
0.001142		
Test 3	18.17	4
0.001142		
Test 5a	4.523	2
0.1042		

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. Consider running a non-homogeneous variance model. The p-value for Test 3 is less than .1. You may want to consider a different variance model. The p-value for Test 5a is greater than .1. Model 3 seems to adequately describe the data. Benchmark Dose Computations: Specified Effect = 1.000000 Risk Type = Estimated standard deviations from control Confidence Level = 0.9500002.78443

BMD = 2.78443 BMDL = 1.53251



Mean Response

09:08 06/22 2014

```
______
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Norm/Monocyte_Concurrent_Ln-HLS 2001-
Monocyte Count-ExpNCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sun Jun 22 09:08:08 2014
_____
===
BMDS Model Run
~~~~
  The form of the response function by Model:
     Model 2:
                Y[dose] = a * exp{sign * b * dose}
                Y[dose] = a * exp{sign * (b * dose)^d}
     Model 3:
     Model 4:
                Y[dose] = a * [c-(c-1) * exp{-b * dose}]
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  The variance is to be modeled as Var(i) = exp(lalpha + log
(mean(i)) * rho)
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 3
lnalpha	-1.08858
rho	2.4145
a	0.23917
b	0.0958051
С	0
d	2

### Parameter Estimates

Variable	Model 3
lnalpha	-0.659547
rho	2.5928
a	0.225175
b	0.166469
С	0
d	1.28789

# Table of Stats From Input Data

Dose	Ν	Obs Mean	Obs Std Dev
0	10	0.22	0.08
1.361	10	0.23	0.119
2.451	9	0.13	0.053
3.761	9	0.13	0.04
5.258	10	0.1	0.04

# Estimated Values of Interest

Est Mean	Est Std	Scaled Residual
0.2252	0.1041	-0.1572
0.1942	0.08594	1.316
0.1643	0.06917	-1.487
0.1303	0.05121	-0.0169
0.09698	0.03492	0.2734
	0.2252 0.1942 0.1643 0.1303	0.2252 0.1041 0.1942 0.08594 0.1643 0.06917 0.1303 0.05121

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)

	<pre>Var{e(ij)} =</pre>	Sigma(i)^2
Model A3	: Yij = Var{e(ij)} =	Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R	: Yij = Var{e(ij)} =	

AIC	Model	Log(likelihood)	DF	
ALC				
	Al	103.6934	6	-
195.3868	A2	112.7799	10	_
205.5597	A3	111.9906	7	_
209.9812	R	92.68104	2	_
181.3621	3	107.4993	5	_
204 9986				

204.9986

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 5a: Does Model 3 fit the data? (A3 vs 3)

#### Tests of Interest

Test p-value	-2*log(Likelihood Ratio)	D. F.
Test 1 < 0.0001	40.2	8

Test 2	18.17	4
0.001142 Test 3	1.578	З
0.6643	1.370	5
Test 5a	8.983	2
0.01121		

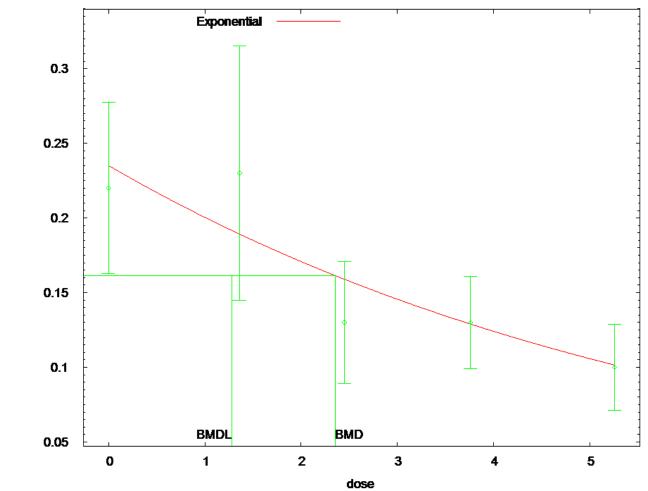
The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data. The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate. The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here. The p-value for Test 5a is less than .1. Model 3 may not adequately describe the data; you may want to consider another model. Benchmark Dose Computations:

Specified Effect = 1.000000

Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

BMD = 4.14625 BMDL = 2.32125



Exponential Model 4, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Level for BMDL

09:08 06/22 2014

=== Exponential Model. (Version: 1.9; Date: 01/29/2013) Input Data File: C:/Users/dmayfield/Desktop/Norm/Monocyte\_Concurrent\_Ln-HLS 2001-Monocyte Count-ExpCV-1SD-5d.(d) Gnuplot Plotting File: Sun Jun 22 09:08:07 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function by Model: Model 2:  $Y[dose] = a * exp{sign * b * dose}$  $Y[dose] = a * exp\{sign * (b * dose)^d\}$ Model 3:  $Y[dose] = a * [c-(c-1) * exp{-b * dose}]$ Model 4:  $Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]$ Model 5: 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 = MeanResponse 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 = 5Total number of records with missing values = 0 Maximum number of iterations = 500 Relative Function Convergence has been set to: 1e-008 Parameter Convergence has been set to: 1e-008 MLE solution provided: Exact Initial Parameter Values

Variable	Model 4
lnalpha	-5.32056
rho(S)	0
a	0.2415
b	0.172301
С	0.000414079
d	1

(S) = Specified

### Parameter Estimates

Variable	Model 4
lnalpha	-5.21349
rho	0
a	0.235092
b	0.159679
C	0
d	1

# Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	10	0.22	0.08
1.361	10	0.23	0.119
2.451	9	0.13	0.053
3.761	9	0.13	0.04
5.258	10	0.1	0.04

## Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	0.2351	0.07377	-0.6469
1.361	0.1892	0.07377	1.75
2.451	0.159	0.07377	-1.177
3.761	0.129	0.07377	0.0427
5.258	0.1015	0.07377	-0.06572

Other models for which likelihoods are calculated:

Model Al: Yij = Mu(i) + e(ij) Var{e(ij)} = Sigma^2

Model A2:	Yij = Var{e(ij)} =	Mu(i) + e(ij) Sigma(i)^2
Model A3:		Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R:	Yij = Var{e(ij)} =	

Likelihoods of Interest

AIC	Model	Log(likelihood)	DF	
ALC				
105 2060	Al	103.6934	6	-
195.3868	A2	112.7799	10	_
205.5597	A3	103.6934	6	_
195.3868	R	92.68104	2	_
181.3621	4	101.1239	3	_
196.2477				

Additive constant for all log-likelihoods = -44.11. This constant added to the above values gives the log-likelihood including the term that does not

depend on the model parameters.

### Explanation of Tests

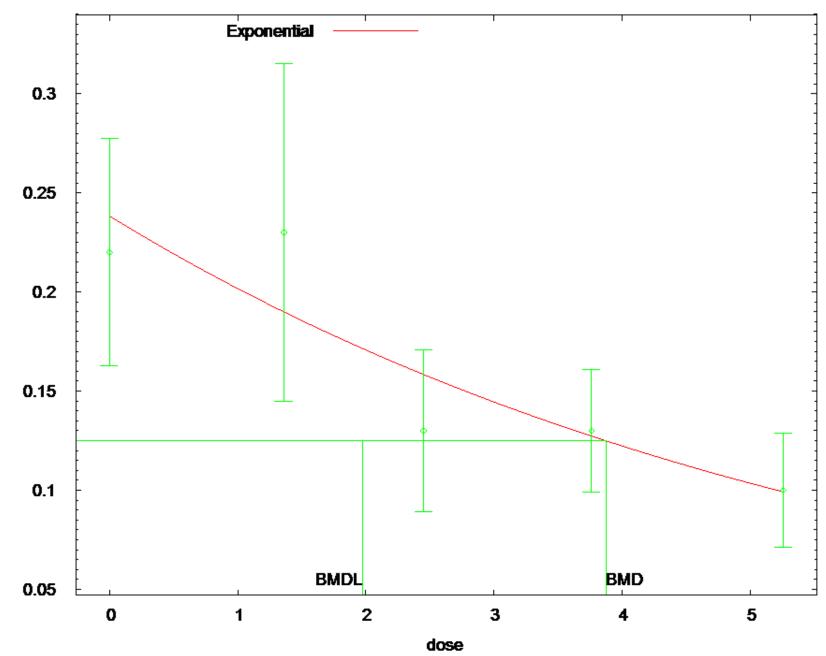
Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A2 vs. A1) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 6a: Does Model 4 fit the data? (A3 vs 4)

Test	-2*log(Likelihood Ratio)	D. F.
p-value		

Test 1 < 0.0001	40.2	8
Test 2	18.17	4
0.001142		
Test 3	18.17	4
0.001142		
Test ба	5.139	3
0.1619		

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. Consider running a non-homogeneous variance model. The p-value for Test 3 is less than .1. You may want to consider a different variance model. 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 = 2.35849 BMDL = 1.28226



Exponential Model 4, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Level for BMDL

09:08 06/22 2014

```
______
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Norm/Monocyte_Concurrent_Ln-HLS 2001-
Monocyte Count-ExpNCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sun Jun 22 09:08:08 2014
_____
===
BMDS Model Run
~~~~
  The form of the response function by Model:
     Model 2:
                Y[dose] = a * exp{sign * b * dose}
                Y[dose] = a * exp{sign * (b * dose)^d}
     Model 3:
     Model 4:
                Y[dose] = a * [c-(c-1) * exp{-b * dose}]
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  The variance is to be modeled as Var(i) = exp(lalpha + log
(mean(i)) * rho)
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 4
lnalpha	-1.08858
rho	2.4145
a	0.2415
b	0.172301
C	0.000414079
d	1

### Parameter Estimates

Variable	Model 4
lnalpha	-0.59063
rho	2.62295
a	0.238331
b	0.166716
С	0
d	1

# Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	10	0.22	0.08
1.361	10	0.23	0.119
2.451	9	0.13	0.053
3.761	9	0.13	0.04
5.258	10	0.1	0.04

## Estimated Values of Interest

Est Mean	Est Std	Scaled Residual
0.2383	0.1135	-0.5108
0.19	0.08428	1.503
0.1584	0.0664	-1.282
0.1273	0.04987	0.1617
0.09919	0.03595	0.07097
	0.2383 0.19 0.1584 0.1273	0.2383 0.1135 0.19 0.08428 0.1584 0.0664 0.1273 0.04987

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)

	<pre>Var{e(ij)} =</pre>	=	Sigma(i)^2
Model A3:	5		Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R:	Yij = Var{e(ij)} =		

Likelihoods of Interest

AIC	Model	Log(likelihood)	DF	
AIC				
105 2050	A1	103.6934	6	-
195.3868	A2	112.7799	10	_
205.5597	A3	111.9906	7	_
209.9812	R	92.68104	2	_
181.3621	4	107.1483	4	_
206 2965				

206.2965

Additive constant for all log-likelihoods = -44.11. This constant added to the above values gives the log-likelihood including the term that does not

depend on the model parameters.

#### Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A2 vs. A1) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 6a: Does Model 4 fit the data? (A3 vs 4)

Test p-value	-2*log(Likelihood Ratio)	D. F.
Test 1 < 0.0001	40.2	8

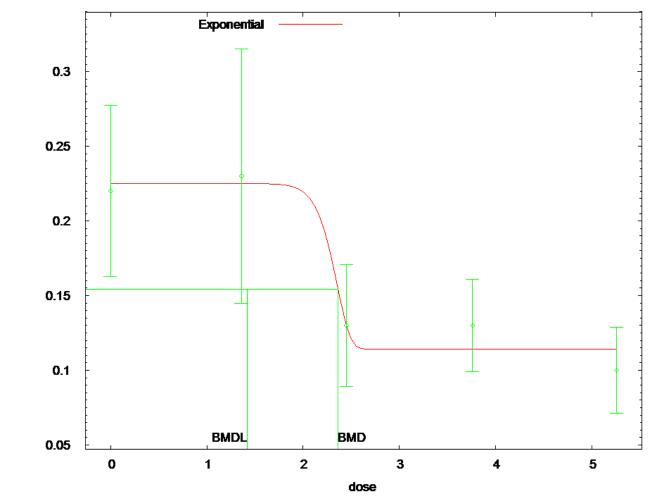
Test 2	18.17	4
0.001142 Test 3	1.578	З
0.6643	1.070	5
Test ба	9.685	3
0.02145		

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data. The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate. The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here. The p-value for Test 6a is less than .1. Model 4 may not adequately describe the data; you may want to consider another model. Benchmark Dose Computations: Specified Effect = 1.00000

Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

BMD = 3.8783 BMDL = 1.97412



Exponential Model 5, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Level for BMDL

09:08 06/22 2014

=== Exponential Model. (Version: 1.9; Date: 01/29/2013) Input Data File: C:/Users/dmayfield/Desktop/Norm/Monocyte\_Concurrent\_Ln-HLS 2001-Monocyte Count-ExpCV-1SD-5d.(d) Gnuplot Plotting File: Sun Jun 22 09:08:07 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function by Model: Model 2:  $Y[dose] = a * exp{sign * b * dose}$  $Y[dose] = a * exp\{sign * (b * dose)^d\}$ Model 3:  $Y[dose] = a * [c-(c-1) * exp{-b * dose}]$ Model 4:  $Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]$ Model 5: 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 = MeanResponse 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 = 5Total number of records with missing values = 0 Maximum number of iterations = 500 Relative Function Convergence has been set to: 1e-008 Parameter Convergence has been set to: 1e-008 MLE solution provided: Exact Initial Parameter Values

Variable	Model 5
lnalpha	-5.32056
rho(S)	0
a	0.2415
b	0.172301
C	0.000414079
d	1

(S) = Specified

#### Parameter Estimates

Variable	Model 5
lnalpha	-5.30047
rho	0
a	0.225003
b	0.423397
С	0.507595
d	18

# Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	10	0.22	0.08
1.361	10	0.23	0.119
2.451	9	0.13	0.053
3.761	9	0.13	0.04
5.258	10	0.1	0.04

## Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	0.225	0.07063	-0.224
1.361	0.225	0.07063	0.224
2.451	0.13	0.07063	-4.191e-005
3.761	0.1142	0.07063	0.6706
5.258	0.1142	0.07063	-0.6362

Other models for which likelihoods are calculated:

Model Al: Yij = Mu(i) + e(ij) Var{e(ij)} = Sigma^2

Model A2:	Yij = Var{e(ij)} =	Mu(i) + e(ij) Sigma(i)^2
Model A3:		Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R:	Yij = Var{e(ij)} =	

Likelihoods of Interest

	Model	Log(likelihood)	DF	
AIC				
	Al	103.6934	6	_
195.3868	A2	112.7799	10	_
205.5597	A3	103.6934	6	_
195.3868	R	92.68104	2	_
181.3621	5	103.2112	5	_
196.4224				

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

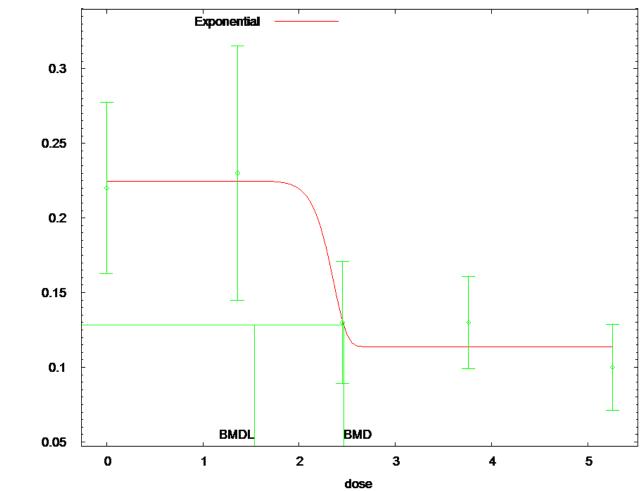
Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A2 vs. A1) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 7a: Does Model 5 fit the data? (A3 vs 5)

Test	-2*log(Likelihood Ratio)	D. F.
p-value		

Test 1 < 0.0001	40.2	8
Test 2 0.001142	18.17	4
Test 3	18.17	4
0.001142 Test 7a	0.9644	1
0.3261		

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. Consider running a non-homogeneous variance model. The p-value for Test 3 is less than .1. You may want to consider a different variance model. 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 = 2.36378 BMDL = 1.42021



Exponential Model 5, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Level for BMDL

Mean Response

09:08 06/22 2014

```
______
===
      Exponential Model. (Version: 1.9; Date: 01/29/2013)
      Input Data File:
C:/Users/dmayfield/Desktop/Norm/Monocyte_Concurrent_Ln-HLS 2001-
Monocyte Count-ExpNCV-1SD-5d.(d)
      Gnuplot Plotting File:
                                 Sun Jun 22 09:08:08 2014
_____
===
BMDS Model Run
~~~~
  The form of the response function by Model:
     Model 2:
                Y[dose] = a * exp{sign * b * dose}
                Y[dose] = a * exp{sign * (b * dose)^d}
     Model 3:
     Model 4:
                Y[dose] = a * [c-(c-1) * exp{-b * dose}]
               Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
     Model 5:
   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 = MeanResponse
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  The variance is to be modeled as Var(i) = exp(lalpha + log
(mean(i)) * rho)
  Total number of dose groups = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
  MLE solution provided: Exact
               Initial Parameter Values
```

Variable	Model 5
lnalpha	-1.08858
rho	2.4145
a	0.2415
b	0.172301
C	0.000414079
d	1

### Parameter Estimates

Variable	Model 5
lnalpha	-0.920058
rho	2.51647
a	0.224792
b	0.42243
С	0.506715
d	18

# Table of Stats From Input Data

Dose	Ν	Obs Mean	Obs Std Dev
0	10	0.22	0.08
1.361	10	0.23	0.119
2.451	9	0.13	0.053
3.761	9	0.13	0.04
5.258	10	0.1	0.04

## Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	0.2248	0.09652	-0.157
1.361	0.2248	0.09651	0.1708
2.451	0.131	0.04893	-0.06142
3.761	0.1139	0.04103	1.177
5.258	0.1139	0.04103	-1.072

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)

	<pre>Var{e(ij)} =</pre>	Sigma(i) <sup>2</sup>
Model A3		Mu(i) + e(ij) exp(lalpha + log(mean(i)) * rho)
Model R	: Yij = Var{e(ij)} =	

Likelihoods of Interest

AIC	Model	Log(likelihood)	DF	
ALC				
105 2060	Al	103.6934	6	_
195.3868	A2	112.7799	10	-
205.5597	A3	111.9906	7	_
209.9812	R	92.68104	2	_
181.3621	5	110.5929	б	_
209.1858				

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)

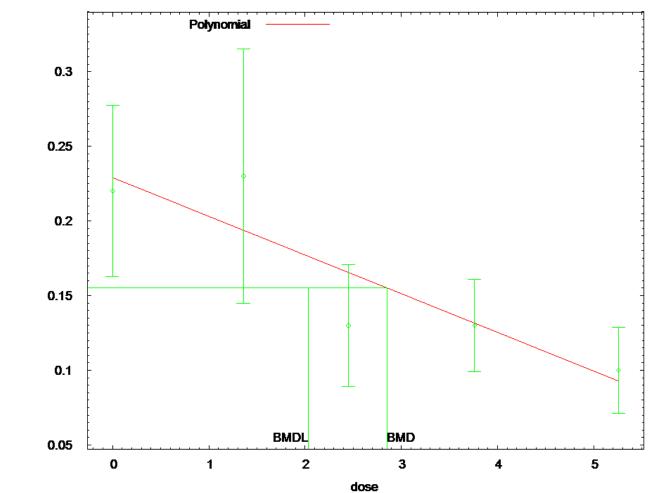
Test p-value	-2*log(Likelihood Ratio)	D. F.
Test 1	40.2	8
< 0.0001		

Test 2 0.001142	18.17	4
Test 3	1.578	З
0.6643	1.070	5
Test 7a	2.795	1
0.09454		

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 7a is less than .1. Model 5 may not adequately describe the data; you may want to consider another model. Benchmark Dose Computations: Specified Effect = 1.000000 Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

BMD = 2.46312 BMDL = 1.53813



Mean Response

12:49 07/09 2014

```
===
      Polynomial Model. (Version: 2.19; Date: 06/25/2014)
      Input Data File:
C:/Users/dmayfield/Desktop/Rat_Monocyte_Concurrent
_Ln/Monocyte_Concurrent_Ln-HLS 2001-Monocyte Count-Poly2CV-1SD-
5d.(d)
      Gnuplot Plotting File:
C:/Users/dmayfield/Desktop/Rat_Monocyte_Concurrent
_Ln/Monocyte_Concurrent_Ln-HLS 2001-Monocyte Count-Poly2CV-1SD-
5d.plt
                                Wed Jul 09 12:49:38 2014
_____
===
BMDS Model Run
~~~~
  The form of the response function is:
  Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...
  Dependent variable = MeanResponse
  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 = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
               Default Initial Parameter Values
                     alpha = 0.00545863
                       rho =
                                     0
                                         Specified
                     beta_0 =
                              0.232604
                     beta 1 = -0.0320749
                     beta_2 =
                                      0
```

```
Asymptotic Correlation Matrix of Parameter Estimates
```

	alpha	beta_0	beta_1
alpha	1	-1.7e-007	2.7e-007
beta_0	-1.7e-007	1	-0.81
beta_1	2.7e-007	-0.81	1

Parameter Estimates

95.0%

Wald Confidence I	nterval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Con	f. Limit		
alpha	0.00542838	0.00110806	
0.00325661	0.00760014		
beta_0	0.229102	0.0180267	
0.193771	0.264434		
beta_1	-0.0258556	0.00572228	-
0.037071	-0.0146401		
beta_2	0	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 Scaled R	N les.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 -0.391	10	0.22	0.229	0.08	0.0737
1.361	10	0.23	0.194	0.119	0.0737
2.451	9	0.13	0.166	0.053	0.0737
3.761 -0.0757	9	0.13	0.132	0.04	0.0737
5.258 0.294	10	0.1	0.0932	0.04	0.0737

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<sup>2</sup>

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
Al	103.693409	6	-195.386818
A2	112.779870	10	-205.559741
A3	103.693409	6	-195.386818
fitted	101.186766	3	-196.373532
R	92.681036	2	-181.362073

# Explanation of Tests

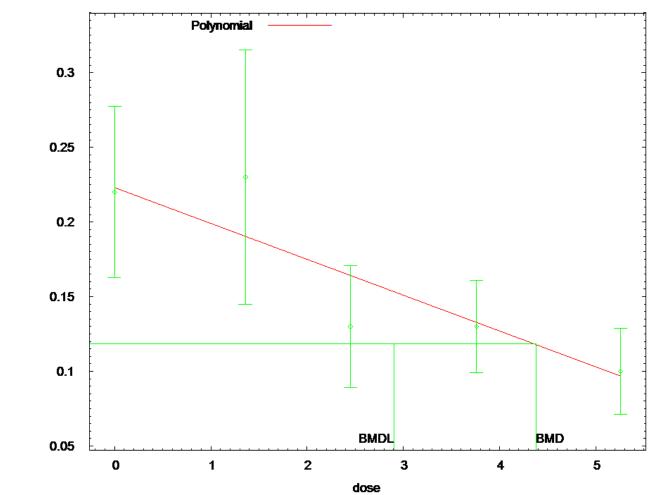
Test 1:	Do responses and/or variances differ among Dose levels?
	(A2 vs. R)
Test 2:	Are Variances Homogeneous? (A1 vs A2)
Test 3:	Are variances adequately modeled? (A2 vs. A3)
Test 4:	Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:	When rho=0 the results of Test 3 and Test 2 will be the
same.)	

#### Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	40.1977	8	<.0001
Test 2	18.1729	4	0.001142
Test 3	18.1729	4	0.001142
Test 4	5.01329	3	0.1708

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. Consider running a non-homogeneous variance model The p-value for Test 3 is less than .1. You may want to consider а different variance model 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 = Estimated standard deviations from the Risk Type control mean Confidence level = 0.95 BMD = 2.84958 BMDL = 2.03295



Polynomial Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

Mean Response

12:49 07/09 2014

```
===
      Polynomial Model. (Version: 2.19; Date: 06/25/2014)
      Input Data File:
C:/Users/dmayfield/Desktop/Rat_Monocyte_Concurrent
_Ln/Monocyte_Concurrent_Ln-HLS 2001-Monocyte Count-Poly2NCV-1SD-
5d.(d)
      Gnuplot Plotting File:
C:/Users/dmayfield/Desktop/Rat_Monocyte_Concurrent
_Ln/Monocyte_Concurrent_Ln-HLS 2001-Monocyte Count-Poly2NCV-1SD-
5d.plt
                                Wed Jul 09 12:49:39 2014
_____
===
BMDS Model Run
~~~~
  The form of the response function is:
  Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...
  Dependent variable = MeanResponse
  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 = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
               Default Initial Parameter Values
                     lalpha = -5.21056
                       rho =
                                     0
                     beta_0 =
                              0.232604
                     beta 1 = -0.0320749
                     beta_2 =
                                      0
```

1

Asymptotic Correlation Matrix of Parameter Estimates

( \*\*\* The model parameter(s) -beta\_2 have been estimated at a boundary point, or have been specified by the user, and do not appear in the correlation matrix ) lalpha rho beta\_0 beta\_1 lalpha 1 0.99 -0.076 0.083 0.99 1 -0.076 0.083 rho -0.076 -0.076 beta O 1 -0.92

0.083

## Parameter Estimates

-0.92

#### 95.0%

1

			95.0%
Wald Confidence In	nterval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Con:	f. Limit		
lalpha	-0.557387	1.30166	-
3.1086	1.99383		
rho	2.63613	0.691385	
1.28104	3.99122		
beta_0	0.22329	0.0212241	
0.181691	0.264888		
beta_1	-0.0239544	0.00497926	-
0.0337136	-0.0141953		
beta_2	0	NA	

NA - Indicates that this parameter has hit a bound implied by some inequality constraint and thus has no standard error.

0.083

beta\_1

	Table	of	Data	and	Estimated	Values	of	Interest
--	-------	----	------	-----	-----------	--------	----	----------

Dose Scaled R	N .es.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 -0.0992	10	0.22	0.223	0.08	0.105
1.361 1.46	10	0.23	0.191	0.119	0.0852
2.451 -1.48	9	0.13	0.165	0.053	0.0702

3.761 9 0.13 0.133 0.04 0.0531 -0.181 5.258 10 0.1 0.0973 0.04 0.0351 0.24 Model Descriptions for likelihoods calculated Model A1: Yij = Mu(i) + e(ij)Var{e(ij)} = Sigma^2 Yij = Mu(i) + e(ij)Model A2: 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

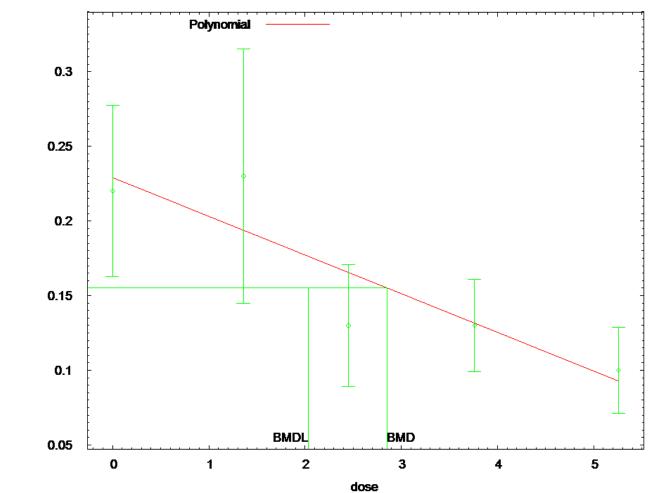
Model	Log(likelihood)	# Param's	AIC
A1	103.693409	6	-195.386818
A2	112.779870	10	-205.559741
A3	111.990624	7	-209.981248
fitted	107.004496	4	-206.008991
R	92.681036	2	-181.362073

#### 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.)

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	40.1977	8	<.0001
Test 2	18.1729	4	0.001142
Test 3	1.57849	3	0.6643

9.97226 3 0.0188 Test 4 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 = Estimated standard deviations from the Risk Type control mean Confidence level = 0.95 4.37872 BMD = 2.90647 BMDL =



Mean Response

12:49 07/09 2014

```
===
      Polynomial Model. (Version: 2.19; Date: 06/25/2014)
      Input Data File:
C:/Users/dmayfield/Desktop/Rat_Monocyte_Concurrent
_Ln/Monocyte_Concurrent_Ln-HLS 2001-Monocyte Count-Poly3CV-1SD-
5d.(d)
      Gnuplot Plotting File:
C:/Users/dmayfield/Desktop/Rat_Monocyte_Concurrent
_Ln/Monocyte_Concurrent_Ln-HLS 2001-Monocyte Count-Poly3CV-1SD-
5d.plt
                                Wed Jul 09 12:49:38 2014
_____
===
BMDS Model Run
~~~~
  The form of the response function is:
  Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...
  Dependent variable = MeanResponse
  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 = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
               Default Initial Parameter Values
                     alpha = 0.00545863
                       rho =
                                     0
                                         Specified
                     beta_0 = 0.224911
                     beta 1 =
                                     0
                     beta_2 = -0.0222894
                     beta_3 =
                                     0
```

Asymptotic Correlation Matrix of Parameter Estimates

	** The model	parameter(s)	-rho	-beta_2	-
beta_3	have been	estimated at	a boundar	v point.	or have
been specified	by the user	1		`	
	and do no	t appear in t	che correla	tion matr	ix )
	alpha	beta_0	beta_1		
alpha	1	1.1e-010	1.8e-010		
beta_0	1.1e-010	1	-0.81		

beta\_1 1.8e-010 -0.81 1

### Parameter Estimates

9	5	0%	

			95.06				
Wald Confidence I	Wald Confidence Interval						
Variable	Estimate	Std. Err.	Lower Conf.				
Limit Upper Con	f. Limit						
alpha	0.00542838	0.00110806					
0.00325661	0.00760014						
beta_0	0.229102	0.0180267					
0.193771	0.264434						
beta_1	-0.0258556	0.00572228	-				
0.037071	-0.0146401						
beta_2	- 0	NA					
beta_3	0	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 Scaled 1	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 -0.391	10	0.22	0.229	0.08	0.0737
1.361	10	0.23	0.194	0.119	0.0737
2.451	9	0.13	0.166	0.053	0.0737
3.761	9	0.13	0.132	0.04	0.0737

-0.0757 5.258 0.294	10	0.1	0.0932	0.04	0.0737		
Model Descriptions for likelihoods calculated							
Model 2	Al: Var{e(i	Yij = Mu(i j)} = Sigm					
Model 2	A2: Var{e(i	Yij = Mu(i j)} = Sigm	, , , ,				
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		Yi = Mu + i)} = Sigm					

# Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
Al	103.693409	6	-195.386818
A2	112.779870	10	-205.559741
A3	103.693409	б	-195.386818
fitted	101.186766	3	-196.373532
R	92.681036	2	-181.362073

### Explanation of Tests

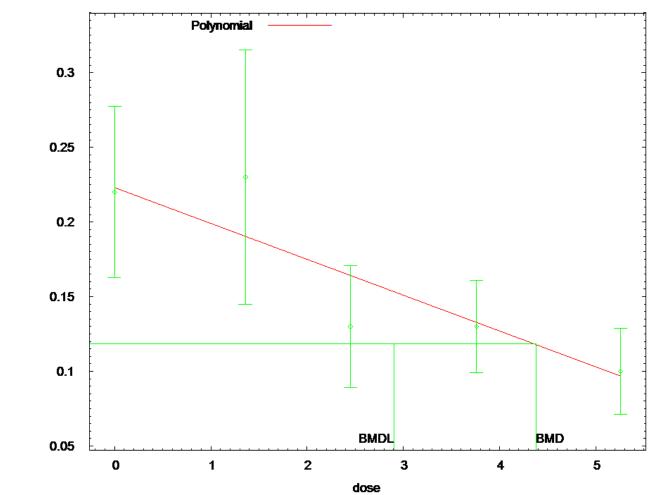
Test 1: Do responses and/or variances differ among Dose levels? (A2 vs. R) Test 2: Are Variances Homogeneous? (A1 vs A2) Test 3: Are variances adequately modeled? (A2 vs. A3) Test 4: Does the Model for the Mean Fit? (A3 vs. fitted) (Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	40.1977	8	<.0001
Test 2	18.1729	4	0.001142
Test 3	18.1729	4	0.001142
Test 4	5.01329	3	0.1708

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. Consider running a non-homogeneous variance model The p-value for Test 3 is less than .1. You may want to consider а different variance model 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 = Estimated standard deviations from the Risk Type control mean Confidence level = 0.95

BMD = 2.84958

BMDL = 2.03295



Polynomial Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

Mean Response

12:49 07/09 2014

```
===
      Polynomial Model. (Version: 2.19; Date: 06/25/2014)
      Input Data File:
C:/Users/dmayfield/Desktop/Rat_Monocyte_Concurrent
_Ln/Monocyte_Concurrent_Ln-HLS 2001-Monocyte Count-Poly3NCV-1SD-
5d.(d)
      Gnuplot Plotting File:
C:/Users/dmayfield/Desktop/Rat_Monocyte_Concurrent
_Ln/Monocyte_Concurrent_Ln-HLS 2001-Monocyte Count-Poly3NCV-1SD-
5d.plt
                                Wed Jul 09 12:49:39 2014
_____
===
BMDS Model Run
~~~~
  The form of the response function is:
  Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...
  Dependent variable = MeanResponse
  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 = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
               Default Initial Parameter Values
                     lalpha = -5.21056
                       rho =
                                     0
                    beta_0 = 0.224911
                     beta 1 =
                                     0
                     beta_2 = -0.0222894
                     beta_3 =
                                     0
```

Asymptotic Correlation Matrix of Parameter Estimates

<pre>( *** The model parameter(s) -beta_2 -beta_3</pre>						
		appear in ch	e corretacio	II MACLIX )		
	lalpha	rho	beta_0	beta_1		
lalpha	1	0.99	-0.076	0.083		
rho	0.99	1	-0.076	0.083		
beta_0	-0.076	-0.076	1	-0.92		
beta_1	0.083	0.083	-0.92	1		

### Parameter Estimates

95.0%
-------

		93.08
nterval		
Estimate	Std. Err.	Lower Conf.
. Limit		
-0.557383	1.30166	-
1.99383		
2.63613	0.691385	
3.99122		
0.22329	0.0212241	
0.264888		
-0.0239544	0.00497926	-
-0.0141953		
0	NA	
0	NA	
	Estimate E. Limit -0.557383 1.99383 2.63613 3.99122 0.22329 0.264888 -0.0239544	Estimate Std. Err. E. Limit -0.557383 1.30166 1.99383 2.63613 0.691385 3.99122 0.22329 0.0212241 0.264888 -0.0239544 0.00497926 -0.0141953 0 NA

NA - Indicates that this parameter has hit a bound implied by some inequality constraint and thus has no standard error.

Dose Scaled R	N es.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 -0.0992	10	0.22	0.223	0.08	0.105
1.361 1.46	10	0.23	0.191	0.119	0.0852

2.451	9	0.13	0.165	0.053	0.0702
-1.48					
3.761	9	0.13	0.133	0.04	0.0531
-0.181					
5.258	10	0.1	0.0973	0.04	0.0351
0.24					

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<sup>2</sup>

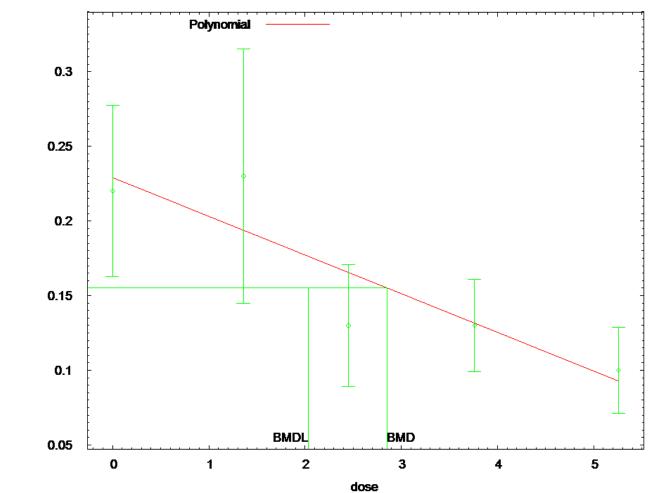
Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
Al	103.693409	б	-195.386818
A2	112.779870	10	-205.559741
A3	111.990624	7	-209.981248
fitted	107.004496	4	-206.008991
R	92.681036	2	-181.362073

## Explanation of Tests

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	40.1977	8	<.0001

18.1729 4 3 Test 2 0.001142 Test 3 1.57849 0.6643 Test 4 9.97226 3 0.0188 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 = 4.37872 BMDL = 2.90647



Mean Response

12:49 07/09 2014

```
===
      Polynomial Model. (Version: 2.19; Date: 06/25/2014)
      Input Data File:
C:/Users/dmayfield/Desktop/Rat_Monocyte_Concurrent
_Ln/Monocyte_Concurrent_Ln-HLS 2001-Monocyte Count-Poly4CV-1SD-
5d.(d)
      Gnuplot Plotting File:
C:/Users/dmayfield/Desktop/Rat_Monocyte_Concurrent
_Ln/Monocyte_Concurrent_Ln-HLS 2001-Monocyte Count-Poly4CV-1SD-
5d.plt
                                Wed Jul 09 12:49:38 2014
_____
===
BMDS Model Run
~~~~
  The form of the response function is:
  Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...
  Dependent variable = MeanResponse
  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 = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
               Default Initial Parameter Values
                     alpha = 0.00545863
                       rho =
                                     0
                                         Specified
                     beta_0 =
                                  0.22
                     beta_1 =
                                     0
                    beta_2 =
                                -0.22957
                     beta_3 =
                                     0
                     beta 4 = -0.00619142
```

Asymptotic Correlation Matrix of Parameter Estimates

	alpha	beta_0	beta_1
alpha	1	-6.5e-012	-1e-012
beta_0	-6.5e-012	1	-0.81
beta_1	-1e-012	-0.81	1

Parameter Estimates

a	Б	Ω	9
9	С	U	6

			95.08
Wald Confidence I	nterval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Con	f. Limit		
alpha	0.00542838	0.00110806	
0.00325661	0.00760014		
beta_0	0.229102	0.0180267	
0.193771	0.264434		
beta_1	-0.0258556	0.00572228	_
0.037071	-0.0146401		
beta_2	-2.80498e-027	NA	
beta_3	-1.77823e-028	NA	
beta_4	- 0	NA	

NA - Indicates that this parameter has hit a bound implied by some inequality constraint and thus has no standard error.

Dose Scaled R	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 -0.391	10	0.22	0.229	0.08	0.0737
1.361	10	0.23	0.194	0.119	0.0737
1.55 2.451	9	0.13	0.166	0.053	0.0737

-1.45					
3.761	9	0.13	0.132	0.04	0.0737
-0.0757					
5.258	10	0.1	0.0932	0.04	0.0737
0.294					

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

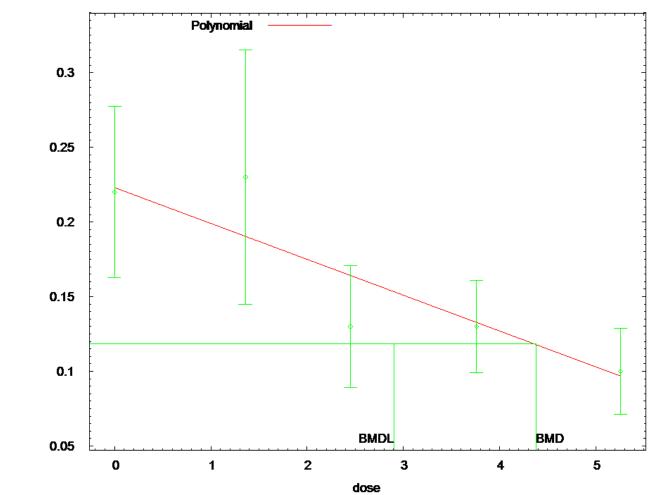
Model	Log(likelihood)	# Param's	AIC
Al	103.693409	б	-195.386818
A2	112.779870	10	-205.559741
A3	103.693409	6	-195.386818
fitted	101.186766	3	-196.373532
R	92.681036	2	-181.362073

### 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.)	

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	40.1977	8	<.0001
Test 2	18.1729	4	0.001142

Test 3 18.172940.0011425.0132930.1708 Test 4 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. Consider running a non-homogeneous variance model The p-value for Test 3 is less than .1. You may want to consider а different variance model 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 = Estimated standard deviations from the Risk Type control mean Confidence level = 0.95 BMD = 2.84958 BMDL = 2.03295



Polynomial Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

Mean Response

12:49 07/09 2014

```
===
      Polynomial Model. (Version: 2.19; Date: 06/25/2014)
      Input Data File:
C:/Users/dmayfield/Desktop/Rat_Monocyte_Concurrent
_Ln/Monocyte_Concurrent_Ln-HLS 2001-Monocyte Count-Poly4NCV-1SD-
5d.(d)
      Gnuplot Plotting File:
C:/Users/dmayfield/Desktop/Rat_Monocyte_Concurrent
_Ln/Monocyte_Concurrent_Ln-HLS 2001-Monocyte Count-Poly4NCV-1SD-
5d.plt
                                Wed Jul 09 12:49:39 2014
_____
===
BMDS Model Run
~~~~
  The form of the response function is:
  Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...
  Dependent variable = MeanResponse
  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 = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
               Default Initial Parameter Values
                     lalpha = -5.21056
                       rho =
                                     0
                     beta_0 =
                                  0.22
                     beta 1 =
                                     0
                    beta_2 =
                                -0.22957
                     beta_3 =
                                     0
                     beta 4 = -0.00619142
```

I	Asymptotic Corre	elation Matrix	of Paramet	er Estimates	
beta 4	( *** The model	<pre>parameter(s)</pre>	-beta_2	-beta_3 -	
have been estimated at a boundary point, or ha been specified by the user, and do not appear in the correlation matrix )					
	lalpha	rho	beta_0	beta_1	
lalpha	1	0.99	-0.076	0.083	
rho	0.99	1	-0.076	0.083	
beta_0	-0.076	-0.076	1	-0.92	
beta_1	0.083	0.083	-0.92	1	

Parameter Estimates

			95.0%
Wald Confidence	Interval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper C	onf. Limit		
lalpha	-0.557384	1.30166	-
3.1086	1.99383		
rho	2.63613	0.691385	
1.28104	3.99122		
beta_0	0.22329	0.0212241	
0.181691	0.264888		
beta_1	-0.0239544	0.00497926	_
0.0337136	-0.0141953		
beta_2	0	NA	
beta_3	0	NA	
beta_4	0	NA	

NA - Indicates that this parameter has hit a bound implied by some inequality constraint and thus has no standard error.

N s.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
-				
10	0.22	0.223	0.08	0.105
	s. 	s. 		s. 

-0.0992					
1.361	10	0.23	0.191	0.119	0.0852
1.46					
2.451	9	0.13	0.165	0.053	0.0702
-1.48					
3.761	9	0.13	0.133	0.04	0.0531
-0.181					
5.258	10	0.1	0.0973	0.04	0.0351
0.24					

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
Al	103.693409	б	-195.386818
A2	112.779870	10	-205.559741
A3	111.990624	7	-209.981248
fitted	107.004496	4	-206.008991
R	92.681036	2	-181.362073

# Explanation of Tests

Test 1:	Do responses and/or variances differ among Dose levels?
	(A2 vs. R)
Test 2:	Are Variances Homogeneous? (Al 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.)	

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	40.1977	8	<.0001
Test 2	18.1729	4	0.001142
Test 3	1.57849	3	0.6643
Test 4	9.97226	3	0.0188

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

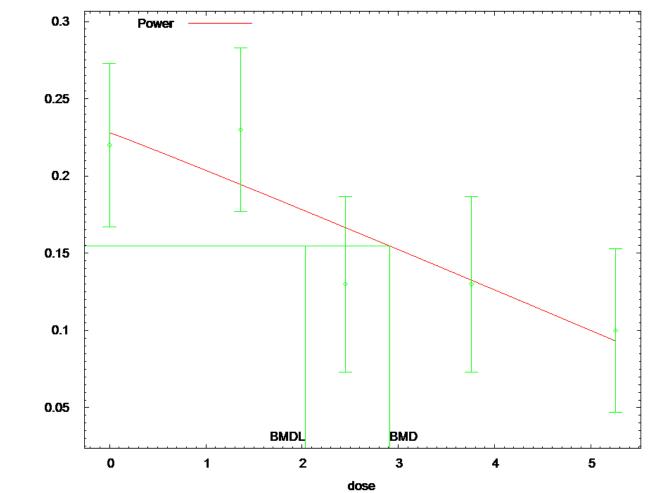
The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate

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 = control mean	= Es	timated standa	ard deviations	from the
Confidence level =	=	0.95		
BMD =	=	4.37872		
BMDL =	=	2.90647		



Mean Response

09:08 06/22 2014

=== Power Model. (Version: 2.18; Date: 05/19/2014) Input Data File: C:/Users/dmayfield/Desktop/Norm/Monocyte\_Concurrent\_Ln-HLS 2001-Monocyte Count-PowerCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Norm/Monocyte\_Concurrent\_Ln-HLS 2001-Monocyte Count-PowerCV-1SD-5d.plt Sun Jun 22 09:08:08 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = control + slope \* dose^power Dependent variable = MeanResponse 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 = 5 Total number of records with missing values = 0 Maximum number of iterations = 500 Relative Function Convergence has been set to: 1e-008 Parameter Convergence has been set to: 1e-008 Default Initial Parameter Values alpha = 0.00545863rho = Specified 0 control = 0.1 slope = 0.174099 power = -1.50587Asymptotic Correlation Matrix of Parameter Estimates ( \*\*\* The model parameter(s) -rho have been estimated at a boundary point, or have been specified by the user,

Sen Specifica	-	appear in	the correlat	ion matrix )
	alpha	control	slope	power
alpha	1	4e-008	-1.2e-007	-1.5e-007
control	4e-008	1	-0.72	-0.55
slope -	-1.2e-007	-0.72	1	0.96
power -	-1.5e-007	-0.55	0.96	1

Parameter Estimates

95.0%

Wald Confidence Int	erval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Conf.	Limit		
alpha	0.00542766	0.00110792	
0.00325618	0.00759914		
control	0.228176	0.0214028	
0.186228	0.270125		
slope	-0.0244404	0.018427	-
0.0605565	0.0116758		
power	1.03286	0.419442	
0.210769	1.85495		
0.210769	1.85495		

Dose Scaled R	N les.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 -0.351	10	0.22	0.228	0.08	0.0737
1.361	10	0.23	0.195	0.119	0.0737
2.451	9	0.13	0.166	0.053	0.0737
3.761 -0.0882	9	0.13	0.132	0.04	0.0737
5.258 0.323	10	0.1	0.0925	0.04	0.0737

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
Al	103.693409	б	-195.386818
A2	112.779870	10	-205.559741
A3	103.693409	б	-195.386818
fitted	101.189934	4	-194.379868
R	92.681036	2	-181.362073

#### 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

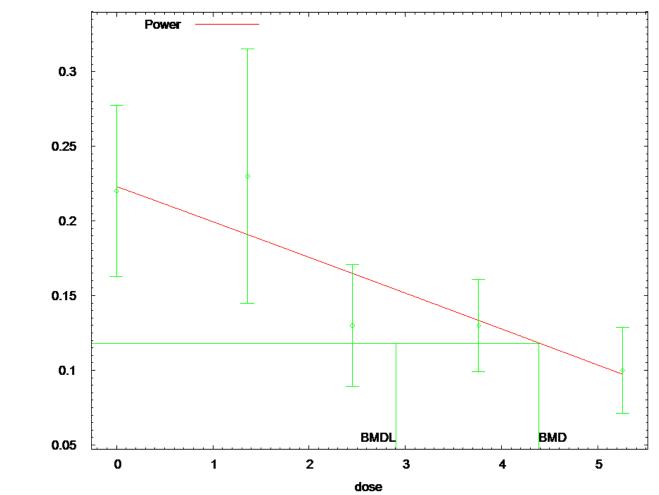
Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	40.1977	8	<.0001
Test 2	18.1729	4	0.001142
Test 3	18.1729	4	0.001142
Test 4	5.00695	2	0.0818

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. Consider running a non-homogeneous variance model The p-value for Test 3 is less than .1. You may want to consider а different variance model The p-value for Test 4 is less than .1. You may want to try a different model Benchmark Dose Computation Specified effect = 1 = Estimated standard deviations from the Risk Type control mean Confidence level = 0.95 BMD = 2.9104

BMDL = 2.03363



Mean Response

09:08 06/22 2014

=== Power Model. (Version: 2.18; Date: 05/19/2014) Input Data File: C:/Users/dmayfield/Desktop/Norm/Monocyte\_Concurrent\_Ln-HLS 2001-Monocyte Count-PowerNCV-1SD-5d.(d) Gnuplot Plotting File: C:/Users/dmayfield/Desktop/Norm/Monocyte\_Concurrent\_Ln-HLS 2001-Monocyte Count-PowerNCV-1SD-5d.plt Sun Jun 22 09:08:09 2014 \_\_\_\_\_ === BMDS Model Run ~~~~ The form of the response function is: Y[dose] = control + slope \* dose^power Dependent variable = MeanResponse Independent variable = Dose The power is restricted to be greater than or equal to 1 The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) \* rho) Total number of dose groups = 5Total number of records with missing values = 0Maximum number of iterations = 500 Relative Function Convergence has been set to: 1e-008 Parameter Convergence has been set to: 1e-008 Default Initial Parameter Values lalpha = -5.21056 rho = 0 control = 0.1 slope = 0.174099 power = -1.50587Asymptotic Correlation Matrix of Parameter Estimates lalpha rho control slope power

lalpha 0.081	1	0.99	-0.5	0.26
rho 0.081	0.99	1	-0.45	0.25
control -0.64	-0.5	-0.45	1	-0.81
slope 0.96	0.26	0.25	-0.81	1
power 1	0.081	0.081	-0.64	0.96

## Parameter Estimates

			95.0%
Wald Confidence In	terval		
Variable	Estimate	Std. Err.	Lower Conf.
Limit Upper Conf	. Limit		
lalpha	-0.553873	1.75668	-
3.9969	2.88915		
rho	2.63797	0.921616	
0.831639	4.44431		
control	0.222847	0.0276528	
0.168649	0.277045		
slope	-0.0235189	0.0181588	_
0.0591095	0.0120718		
power	1.00904	0.366939	
0.289854	1.72823		

Dose Scaled 1	N Res.	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev
0 -0.086	10	0.22	0.223	0.08	0.105
1.361 1.46	10	0.23	0.191	0.119	0.0852
2.451 -1.48	9	0.13	0.165	0.053	0.0703
3.761 -0.188	9	0.13	0.133	0.04	0.0532

5.258	10	0.1	0.0973	0.04	0.0351
0.242					

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

Mode	Log(likelihood)	# Param's	AIC
Al	103.693409	б	-195.386818
A2	112.779870	10	-205.559741
A3	111.990624	7	-209.981248
fitted	107.004802	5	-204.009605
R	92.681036	2	-181.362073

## 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.)

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	40.1977	8	<.0001
Test 2	18.1729	4	0.001142
Test 3	1.57849	3	0.6643
Test 4	9.97164	2	0.006834

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 = Estimated standard deviations from the Risk Type control mean Confidence level = 0.95 BMD = 4.39068BMDL = 2.90659