

Appendix A. BMDs Results for Frambozadrine

A1. Frambozadrine male response data: multistage model

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=====
2nd order Multistage Model. (Version: 2.8; Date: 02/20/2007)
  Input Data File: C:\BMDs\DATA\COOKE_2.(d)
  Gnuplot Plotting File: C:\BMDs\DATA\COOKE_2.plt
                                Tue Sep 25 08:06:24 2007
=====
```

BMDs MODEL RUN

The form of the probability function is:

$$P[\text{response}] = \text{background} + (1-\text{background}) * [1 - \text{EXP}(-\text{beta1} * \text{dose}^{1-\text{beta2} * \text{dose}^2})]$$

The parameter betas are restricted to be positive

Dependent variable = rm
Independent variable = dm

Total number of observations = 8
Total number of records with missing values = 4
Total number of parameters in model = 3
Total number of specified parameters = 0
Degree of polynomial = 2

Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

Background = 0.0833808
Beta(1) = 0
Beta(2) = 9.32742e-005

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -Beta(1)
have been estimated at a boundary point, or have been
specified by the user,
and do not appear in the correlation matrix)

Background Beta(2)

Background	1	-0.42
Beta(2)	-0.42	1

Parameter Estimates

Confidence Interval				95.0% Wald	
Limit	Variable	Estimate	Std. Err.	Lower	Conf.
	Upper			Conf.	
*	Background	0.0827757	*	*	*
*	Beta(1)	0	*	*	*
*	Beta(2)	9.29375e-005	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-71.9124	4			
Fitted model	-73.188	2	2.551	2	0.2793
Reduced model	-90.7357	1	37.6465	3	<.0001
AIC:	150.376				

Goodness of Fit

Scaled Residual	Dose	Est._Prob.	Expected	Observed	Size	

----	0.0000	0.0828	3.890	2	47	-1.001
	1.2000	0.0829	3.730	6	45	1.227
	15.0000	0.1018	4.477	4	44	-0.238
	82.0000	0.5090	23.923	24	47	0.022

Chi^2 = 2.56 d.f. = 2 P-value = 0.2774

Benchmark Dose Computation

Specified effect = 0.1
Risk Type = Extra risk
Confidence level = 0.95
BMD = 33.67
BMDL = 12.0408
BMDU = 41.9746

Taken together, (12.0408, 41.9746) is a 90 % two-sided confidence interval for the BMD

A2. Frambozadrine male response data: Weibull model

=====
Weibull Model using Weibull Model (Version: 2.7; Date:
2/20/2007)
Input Data File: C:\BMDS\DATA\COOKE_2.(d)
Gnuplot Plotting File: C:\BMDS\DATA\COOKE_2.plt
Thu Oct 04 08:44:04 2007
=====

BMDS MODEL RUN
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The form of the probability function is:

$$P[\text{response}] = \text{background} + (1-\text{background}) * [1 - \text{EXP}(-\text{slope} * \text{dose}^{\text{power}})]$$

Dependent variable = rm  
Independent variable = dm  
Power parameter is not restricted

Total number of observations = 4  
Total number of records with missing values = 0  
Maximum number of iterations = 250  
Relative Function Convergence has been set to: 1e-008  
Parameter Convergence has been set to: 1e-008

Default Initial (and Specified) Parameter Values  
Background = 0.0520833

Slope = 0.00101616  
 Power = 1.46987

Asymptotic Correlation Matrix of Parameter Estimates

|            | Background | Slope | Power |
|------------|------------|-------|-------|
| Background | 1          | -0.57 | 0.57  |
| Slope      | -0.57      | 1     | -1    |
| Power      | 0.57       | -1    | 1     |

Parameter Estimates

| Confidence Interval |                   |             | 95.0% Wald   |  |
|---------------------|-------------------|-------------|--------------|--|
| Variable            | Estimate          | Std. Err.   | Lower Conf.  |  |
| Limit               | Upper Conf. Limit |             |              |  |
| Background          | 0.0869172         | 0.0296776   | 0.0287501    |  |
| 0.145084            |                   |             |              |  |
| Slope               | 1.70594e-006      | 5.8638e-005 | -0.000113222 |  |
| 0.000116634         |                   |             |              |  |
| Power               | 2.90678           | 7.79422     | -12.3696     |  |
| 18.1832             |                   |             |              |  |

Analysis of Deviance Table

| Model         | Log(likelihood) | # Param's | Deviance | Test d.f. | P-value |
|---------------|-----------------|-----------|----------|-----------|---------|
| Full model    | -71.9124        | 4         |          |           |         |
| Fitted model  | -73.1516        | 3         | 2.47831  | 1         | 0.1154  |
| Reduced model | -90.7357        | 1         | 37.6465  | 3         | <.0001  |
| AIC:          | 152.303         |           |          |           |         |

Goodness of Fit

| Scaled Residual | Dose   | Est._Prob. | Expected | Observed | Size |        |
|-----------------|--------|------------|----------|----------|------|--------|
| -----           | 0.0000 | 0.0869     | 4.085    | 2        | 47   | -1.080 |
| -----           |        |            |          |          |      |        |

|         |        |        |    |    |        |
|---------|--------|--------|----|----|--------|
| 1.2000  | 0.0869 | 3.911  | 6  | 45 | 1.105  |
| 15.0000 | 0.0910 | 4.004  | 4  | 44 | -0.002 |
| 82.0000 | 0.5106 | 24.000 | 24 | 47 | 0.000  |

Chi^2 = 2.39      d.f. = 1      P-value = 0.1223

Benchmark Dose Computation

Specified effect = 0.1  
 Risk Type = Extra risk  
 Confidence level = 0.95  
 BMD = 44.4754  
 BMDL = 10.6727

**A3. Frambozadrine female response data: multistage model**

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=====
Multistage Model. (Version: 2.8; Date: 02/20/2007)
Input Data File: C:\BMDS\DATA\COOKE_2.(d)
Gnuplot Plotting File: C:\BMDS\DATA\COOKE_2.plt
                        Tue Sep 25 08:18:45 2007
=====
```

BMDS MODEL RUN

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The form of the probability function is:

$$P[\text{response}] = \text{background} + (1-\text{background}) * [1 - \text{EXP}(-\text{beta1} * \text{dose}^{1-\text{beta2}} * \text{dose}^2)]$$

The parameter betas are restricted to be positive

Dependent variable = rf
 Independent variable = df

Total number of observations = 8
 Total number of records with missing values = 4
 Total number of parameters in model = 3
 Total number of specified parameters = 0
 Degree of polynomial = 2

Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008

Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

Background = 0.0640802
Beta(1) = 0
Beta(2) = 9.21991e-005

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -Beta(1)
have been estimated at a boundary point, or have been
specified by the user,
and do not appear in the correlation matrix)

	Background	Beta(2)
Background	1	-0.34
Beta(2)	-0.34	1

Parameter Estimates

Confidence Interval			95.0% Wald	
Variable	Estimate	Std. Err.	Lower	Conf.
Limit	Upper	Conf.	Limit	
Background	0.0694834	*	*	*
Beta(1)	0	*	*	*
Beta(2)	8.92839e-005	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-68.3386	4			
Fitted model	-69.2093	2	1.74155	2	0.4186
Reduced model	-103.347	1	70.0176	3	<.0001

AIC: 142.419

Goodness of Fit

Scaled Dose Residual	Est._Prob.	Expected	Observed	Size	
0.0000	0.0695	3.335	3	48	-0.190
1.8000	0.0698	3.418	5	49	0.887
21.0000	0.1054	4.954	3	47	-0.928
109.0000	0.6779	32.538	33	48	0.143

Chi^2 = 1.71 d.f. = 2 P-value = 0.4262

Benchmark Dose Computation

Specified effect = 0.1
Risk Type = Extra risk
Confidence level = 0.95
BMD = 34.352
BMDL = 21.1513
BMDU = 40.8074

Taken together, (21.1513, 40.8074) is a 90 % two-sided confidence interval for the BMD

A4. Frambozadrine female response data: Weibull model

=====
Weibull Model using Weibull Model (Version: 2.7; Date:
2/20/2007)
Input Data File: C:\BMDS\DATA\COOKE_2.(d)
Gnuplot Plotting File: C:\BMDS\DATA\COOKE_2.plt
Thu Oct 04 09:31:47 2007
=====

BMDS MODEL RUN

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The form of the probability function is:

$P[\text{response}] = \text{background} + (1 - \text{background}) * [1 - \text{EXP}(-\text{slope} * \text{dose}^{\text{power}})]$

Dependent variable = rf  
 Independent variable = df  
 Power parameter is not restricted

Total number of observations = 4  
 Total number of records with missing values = 0  
 Maximum number of iterations = 250  
 Relative Function Convergence has been set to: 1e-008  
 Parameter Convergence has been set to: 1e-008

Default Initial (and Specified) Parameter Values

Background = 0.0714286  
 Slope = 0.000125709  
 Power = 1.93028

Asymptotic Correlation Matrix of Parameter Estimates

|            | Background | Slope | Power |
|------------|------------|-------|-------|
| Background | -1.\$      | -1.\$ | -1.\$ |
| Slope      | -1.\$      | -1.\$ | -1.\$ |
| Power      | -1.\$      | -1.\$ | -1.\$ |

Parameter Estimates

| Confidence Interval |              |           |         | 95.0% Wald |       |
|---------------------|--------------|-----------|---------|------------|-------|
| Variable            | Estimate     | Std. Err. | Lower   | Upper      | Conf. |
| Limit               | Upper        | Conf.     | Limit   | Limit      |       |
| Background          | 0.076389     | 1.#QNAN   | 1.#QNAN | 1.#QNAN    |       |
| Slope               | 4.14215e-021 | 1.#QNAN   | 1.#QNAN | 1.#QNAN    |       |
| Power               | 10.0213      | 1.#QNAN   | 1.#QNAN | 1.#QNAN    |       |

Analysis of Deviance Table

| Model         | Log(likelihood) | # Param's | Deviance | Test d.f. | P-value |
|---------------|-----------------|-----------|----------|-----------|---------|
| Full model    | -68.3386        | 4         |          |           |         |
| Fitted model  | -68.672         | 3         | 0.666833 | 1         | 0.4142  |
| Reduced model | -103.347        | 1         | 70.0176  | 3         | <.0001  |
| AIC:          | 143.344         |           |          |           |         |

Goodness of Fit

| Scaled Dose Residual | Est._Prob. | Expected | Observed | Size |        |
|----------------------|------------|----------|----------|------|--------|
| 0.0000               | 0.0764     | 3.667    | 3        | 48   | -0.362 |
| 1.8000               | 0.0764     | 3.743    | 5        | 49   | 0.676  |
| 21.0000              | 0.0764     | 3.590    | 3        | 47   | -0.324 |
| 109.0000             | 0.6875     | 33.000   | 33       | 48   | 0.000  |

Chi^2 = 0.69      d.f. = 1      P-value = 0.4050

Benchmark Dose Computation

Specified effect = 0.1  
Risk Type = Extra risk  
Confidence level = 0.95  
BMD = 86.3812  
BMDL = 25.2317

**A5. Frambozadrine pooled response data: multistage model**

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=====
Multistage Model. (Version: 2.8; Date: 02/20/2007)
Input Data File: C:\BMDS\DATA\COOKE_2C.(d)
Gnuplot Plotting File: C:\BMDS\DATA\COOKE_2C.plt
Tue Oct 02 14:50:11 2007
=====
```

BMDS MODEL RUN

The form of the probability function is:

$$P[\text{response}] = \text{background} + (1-\text{background}) * [1 - \text{EXP}(-\text{beta1} * \text{dose}^1 - \text{beta2} * \text{dose}^2)]$$

The parameter betas are restricted to be positive

Dependent variable = rm  
Independent variable = dm

Total number of observations = 8  
Total number of records with missing values = 0  
Total number of parameters in model = 3  
Total number of specified parameters = 0  
Degree of polynomial = 2

Maximum number of iterations = 250  
Relative Function Convergence has been set to: 1e-008  
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

Background = 0.0750485  
Beta(1) = 0  
Beta(2) = 9.20183e-005

Asymptotic Correlation Matrix of Parameter Estimates

( \*\*\* The model parameter(s) -Beta(1) have been estimated at a boundary point, or have been specified by the user, and do not appear in the correlation matrix )

|            | Background | Beta(2) |
|------------|------------|---------|
| Background | 1          | -0.37   |
| Beta(2)    | -0.37      | 1       |

Parameter Estimates

|                     |                   |           |           | 95.0% Wald  |  |
|---------------------|-------------------|-----------|-----------|-------------|--|
| Confidence Interval |                   | Estimate  | Std. Err. | Lower Conf. |  |
| Variable            | Upper Conf. Limit |           |           |             |  |
| Background          |                   | 0.0761237 | *         | *           |  |

\*

|   |         |              |   |   |
|---|---------|--------------|---|---|
|   | Beta(1) | 0            | * | * |
| * | Beta(2) | 9.07862e-005 | * | * |

\* - Indicates that this value is not calculated.

### Analysis of Deviance Table

| Model         | Log(likelihood) | # Param's | Deviance | Test d.f. | P-value |
|---------------|-----------------|-----------|----------|-----------|---------|
| Full model    | -140.251        | 8         |          |           |         |
| Fitted model  | -142.5          | 2         | 4.49751  | 6         | 0.6097  |
| Reduced model | -194.377        | 1         | 108.253  | 7         | <.0001  |
| AIC:          | 289             |           |          |           |         |

### Goodness of Fit

| Scaled Residual | Dose     | Est._Prob. | Expected | Observed | Size |        |
|-----------------|----------|------------|----------|----------|------|--------|
| -----           |          |            |          |          |      |        |
| -----           |          |            |          |          |      |        |
|                 | 0.0000   | 0.0761     | 3.578    | 2        | 47   | -0.868 |
|                 | 0.0000   | 0.0761     | 3.654    | 3        | 48   | -0.356 |
|                 | 1.2000   | 0.0762     | 3.431    | 6        | 45   | 1.443  |
|                 | 1.8000   | 0.0764     | 3.743    | 5        | 49   | 0.676  |
|                 | 15.0000  | 0.0948     | 4.171    | 4        | 44   | -0.088 |
|                 | 21.0000  | 0.1124     | 5.282    | 3        | 47   | -1.054 |
|                 | 82.0000  | 0.4982     | 23.417   | 24       | 47   | 0.170  |
|                 | 109.0000 | 0.6858     | 32.920   | 33       | 48   | 0.025  |

Chi^2 = 4.57      d.f. = 6      P-value = 0.6004

### Benchmark Dose Computation

Specified effect = 0.1  
Risk Type = Extra risk  
Confidence level = 0.95  
BMD = 34.0666  
BMDL = 22.865

BMDU = 38.8955

Taken together, (22.865 , 38.8955) is a 90 % two-sided confidence interval for the BMD

**A6. Frambozadrine pooled response data: Weibull model**

```
=====
Weibull Model using Weibull Model (Version: 2.7; Date:
2/20/2007)
Input Data File: C:\BMDS\DATA\COOKE_2C.(d)
Gnuplot Plotting File: C:\BMDS\DATA\COOKE_2C.plt
Wed Oct 03 08:05:30 2007
=====
```

BMDS MODEL RUN  
~~~~~

The form of the probability function is:

$$P[\text{response}] = \text{background} + (1 - \text{background}) * [1 - \text{EXP}(-\text{slope} * \text{dose}^{\text{power}})]$$

Dependent variable = rm
Independent variable = dm
Power parameter is restricted as power >=1

Total number of observations = 8
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial (and Specified) Parameter Values

Background = 0.0714286
Slope = 0.000182287
Power = 1.85106

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Slope	Power
Background	1	-0.26	0.25
Slope	-0.26	1	-1

Power 0.25 -1 1

Parameter Estimates

Confidence Interval		Estimate	Std. Err.	95.0% Wald
Variable	Upper Conf. Limit			Lower Conf.
Background	0.112873	0.0793053	0.0171268	0.0457374
Slope	9.00512e-005	1.16259e-005	4.00136e-005	-6.67994e-005
Power	3.92247	2.45043	0.751056	0.978388

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-140.251	8			
Fitted model	-142.269	3	4.03558	5	0.5443
Reduced model	-194.377	1	108.253	7	<.0001
AIC:	290.538				

Goodness of Fit

Scaled Residual	Dose	Est._Prob.	Expected	Observed	Size	

0.0000	0.0000	0.0793	3.727	2	47	-0.932
0.0000	0.0000	0.0793	3.807	3	48	-0.431
1.2000	1.2000	0.0793	3.569	6	45	1.341
1.8000	1.8000	0.0794	3.888	5	49	0.588
15.0000	15.0000	0.0874	3.847	4	44	0.082
21.0000	21.0000	0.0977	4.593	3	47	-0.782
82.0000	82.0000	0.4788	22.503	24	47	0.437
109.0000	109.0000	0.7064	33.907	33	48	-0.287

Chi^2 = 4.09 d.f. = 5 P-value = 0.5365

Benchmark Dose Computation

Specified effect = 0.1
Risk Type = Extra risk
Confidence level = 0.95
BMD = 41.2022
BMDL = 24.6057

Appendix B. BMDS Results for Nectorine

B1. Nectorine respiratory epithelial adenoma response data:
multistage model

```
=====
Multistage Cancer Model. (Version: 1.5; Date: 02/20/2007)
Input Data File: C:\BMDS\DATA\COOKE_3.(d)
Gnuplot Plotting File: C:\BMDS\DATA\COOKE_3.plt
                        Thu Oct 11 09:14:32 2007
=====
```

BMDS MODEL RUN

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The form of the probability function is:

$$P[\text{response}] = \text{background} + (1 - \text{background}) * [1 - \text{EXP}(-\text{beta}1 * \text{dose}^1)]$$

The parameter betas are restricted to be positive

Dependent variable = r1  
Independent variable = d

Total number of observations = 4  
Total number of records with missing values = 0  
Total number of parameters in model = 2  
Total number of specified parameters = 0  
Degree of polynomial = 1

Maximum number of iterations = 250  
Relative Function Convergence has been set to: 1e-008  
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

Background = 0.0278635  
Beta(1) = 0.00574599

Asymptotic Correlation Matrix of Parameter Estimates

( \*\*\* The model parameter(s) -Background  
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(1) 1

Parameter Estimates

| Confidence Interval |                   | Estimate   | Std. Err. | 95.0% Wald |       |
|---------------------|-------------------|------------|-----------|------------|-------|
| Limit               | Upper Conf. Limit |            |           | Lower      | Conf. |
| *                   | Background        | 0          | *         | *          |       |
| *                   | Beta(1)           | 0.00694724 | *         | *          |       |

\* - Indicates that this value is not calculated.

Analysis of Deviance Table

| Model         | Log(likelihood) | # Param's | Deviance | Test d.f. | P-value |
|---------------|-----------------|-----------|----------|-----------|---------|
| Full model    | -69.6561        | 4         |          |           |         |
| Fitted model  | -70.7964        | 1         | 2.2806   | 3         | 0.5162  |
| Reduced model | -81.8319        | 1         | 24.3516  | 3         | <.0001  |
| AIC:          | 143.593         |           |          |           |         |

Goodness of Fit

| Scaled Dose Residual | Est._Prob. | Expected | Observed | Size |        |
|----------------------|------------|----------|----------|------|--------|
| 0.0000               | 0.0000     | 0.000    | 0        | 49   | 0.000  |
| 10.0000              | 0.0671     | 3.289    | 6        | 49   | 1.548  |
| 30.0000              | 0.1881     | 9.030    | 8        | 48   | -0.381 |
| 60.0000              | 0.3409     | 16.362   | 15       | 48   | -0.415 |

Chi^2 = 2.71 d.f. = 3 P-value = 0.4380

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 15.1658

BMDL = 11.3242

BMDU = 22.7911

Taken together, (11.3242, 22.7911) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.00883061

**B2. Nectorine respiratory epithelial adenoma response data: Weibull model**

=====

Weibull Model using Weibull Model (Version: 2.7; Date: 2/20/2007)

Input Data File: C:\BMDS\DATA\COOKE\_3.(d)

Gnuplot Plotting File: C:\BMDS\DATA\COOKE\_3.plt

Thu Oct 11 09:28:06 2007

=====

BMDS MODEL RUN

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The form of the probability function is:

$P[\text{response}] = \text{background} + (1-\text{background}) * [1 - \text{EXP}(-\text{slope} * \text{dose}^{\text{power}})]$

Dependent variable = r1

Independent variable = d

Power parameter is not restricted

Total number of observations = 4

Total number of records with missing values = 0

Maximum number of iterations = 250

Relative Function Convergence has been set to: 1e-008

Parameter Convergence has been set to: 1e-008

Default Initial (and Specified) Parameter Values

Background = 0.01

Slope = 0.0069174

Power = 0.97209

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -Background
 have been estimated at a boundary point, or have been
 specified by the user,
 and do not appear in the correlation matrix)

	Slope	Power
Slope	1	-0.98
Power	-0.98	1

Parameter Estimates

Confidence Interval			95.0% Wald	
Variable	Estimate	Std. Err.	Lower Conf.	
Limit	Upper	Conf. Limit		
Background	0	NA		
Slope	0.0278097	0.0282953	-0.0276481	
Power	0.615358	0.283363	0.0599765	
0.0832674				
1.17074				

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

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-69.6561	4			
Fitted model	-69.9459	2	0.579582	2	0.7484
Reduced model	-81.8319	1	24.3516	3	<.0001
AIC:	143.892				

Goodness of Fit

Scaled

Dose	Est._Prob.	Expected	Observed	Size	Residual
0.0000	0.0000	0.000	0	49	0.000
10.0000	0.1084	5.310	6	49	0.317
30.0000	0.2019	9.691	8	48	-0.608
60.0000	0.2921	14.021	15	48	0.311

Chi^2 = 0.57 d.f. = 2 P-value = 0.7533

Benchmark Dose Computation

Specified effect = 0.1
Risk Type = Extra risk
Confidence level = 0.95
BMD = 8.71113
BMDL = 0.258966

**B3. Nectorine olfactory epithelial neuroblastoma response data:
multistage model**

```
=====
Multistage Cancer Model. (Version: 1.5; Date: 02/20/2007)
Input Data File: C:\BMDS\DATA\COOKE_3.(d)
Gnuplot Plotting File: C:\BMDS\DATA\COOKE_3.plt
Thu Oct 11 09:22:59 2007
=====
```

BMDS MODEL RUN

The form of the probability function is:

$$P[\text{response}] = \text{background} + (1-\text{background}) * [1 - \text{EXP}(-\text{beta1} * \text{dose}^1)]$$

The parameter betas are restricted to be positive

Dependent variable = r2
Independent variable = d

Total number of observations = 4
Total number of records with missing values = 0
Total number of parameters in model = 2

Total number of specified parameters = 0
 Degree of polynomial = 1

Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

Background = 0.00580029
 Beta(1) = 0.00128281

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -Background
 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(1) 1

Parameter Estimates

Confidence Interval				95.0% Wald
Limit	Variable	Estimate	Std. Err.	Lower Conf.
Upper	Conf. Limit			
*	Background	0	*	*
*	Beta(1)	0.00150273	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-24.9901	4			
Fitted model	-26.6168	1	3.25344	3	0.3542
Reduced model	-30.1258	1	10.2713	3	0.01639

AIC: 55.2337

Goodness of Fit

Scaled Dose Residual	Est._Prob.	Expected	Observed	Size	
0.0000	0.0000	0.000	0	49	0.000
10.0000	0.0149	0.731	0	49	-0.861
30.0000	0.0441	2.116	4	48	1.325
60.0000	0.0862	4.138	3	48	-0.585

Chi^2 = 2.84 d.f. = 3 P-value = 0.4170

Benchmark Dose Computation

Specified effect = 0.1
Risk Type = Extra risk
Confidence level = 0.95
BMD = 70.1129
BMDL = 39.9064
BMDU = 153.619

Taken together, (39.9064, 153.619) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.00250586

**B4. Nectorine olfactory epithelial neuroblastoma response data:
Weibull model**

=====
Weibull Model using Weibull Model (Version: 2.7; Date:
2/20/2007)
Input Data File: C:\BMDS\DATA\COOKE_3.(d)
Gnuplot Plotting File: C:\BMDS\DATA\COOKE_3.plt
Thu Oct 11 09:26:02 2007
=====

BMDS MODEL RUN

~~~~~

The form of the probability function is:

$$P[\text{response}] = \text{background} + (1 - \text{background}) * [1 - \text{EXP}(-\text{slope} * \text{dose}^{\text{power}})]$$

Dependent variable = r2  
Independent variable = d  
Power parameter is not restricted

Total number of observations = 4  
Total number of records with missing values = 0  
Maximum number of iterations = 250  
Relative Function Convergence has been set to: 1e-008  
Parameter Convergence has been set to: 1e-008

Default Initial (and Specified) Parameter Values

Background = 0.01  
Slope = 0.00175513  
Power = 0.878588

Asymptotic Correlation Matrix of Parameter Estimates

( \*\*\* The model parameter(s) -Background  
have been estimated at a boundary point, or have been  
specified by the user,  
and do not appear in the correlation matrix )

|       | Slope | Power |
|-------|-------|-------|
| Slope | 1     | -0.99 |
| Power | -0.99 | 1     |

Parameter Estimates

| Confidence Interval |          |            |             | 95.0% Wald  |
|---------------------|----------|------------|-------------|-------------|
| Variable            | Estimate | Std. Err.  | Lower Conf. |             |
| Limit               | Upper    | Limit      |             |             |
| Background          | 0        | NA         |             |             |
| 0.00902584          | Slope    | 0.00154299 | 0.00381785  | -0.00593986 |
| 2.2888              | Power    | 0.992853   | 0.661211    | -0.303096   |

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

Analysis of Deviance Table

| Model         | Log(likelihood) | # Param's | Deviance | Test d.f. | P-value |
|---------------|-----------------|-----------|----------|-----------|---------|
| Full model    | -24.9901        | 4         |          |           |         |
| Fitted model  | -26.6168        | 2         | 3.25332  | 2         | 0.1966  |
| Reduced model | -30.1258        | 1         | 10.2713  | 3         | 0.01639 |
| AIC:          | 57.2336         |           |          |           |         |

Goodness of Fit

| Scaled Residual | Dose   | Est._Prob. | Expected | Observed | Size | P-value |
|-----------------|--------|------------|----------|----------|------|---------|
| 0.0000          | 0.0000 | 0.0000     | 0.000    | 0        | 49   | 0.000   |
| 10.0000         | 0.0151 | 0.0151     | 0.738    | 0        | 49   | -0.866  |
| 30.0000         | 0.0442 | 0.0442     | 2.120    | 4        | 48   | 1.320   |
| 60.0000         | 0.0860 | 0.0860     | 4.127    | 3        | 48   | -0.580  |

Chi^2 = 2.83      d.f. = 2      P-value = 0.2430

Benchmark Dose Computation

Specified effect = 0.1  
 Risk Type = Extra risk  
 Confidence level = 0.95  
 BMD = 70.3914  
 BMDL = 39.8991

Appendix C. BMDS Results for Persimonate

C1. Persimonate BC63F1 male mice response data: multistage model

```
=====
Multistage Cancer Model. (Version: 1.5; Date: 02/20/2007)
Input Data File: C:\BMDS\DATA\COOKE_4.(d)
Gnuplot Plotting File: C:\BMDS\DATA\COOKE_4.plt
                               Mon Sep 24 07:26:36 2007
=====
```

BMDS MODEL RUN

~~~~~

The form of the probability function is:

$$P[\text{response}] = \text{background} + (1-\text{background}) * [1 - \text{EXP}(-\text{beta1} * \text{dose}^1)]$$

The parameter betas are restricted to be positive

Dependent variable = r1
Independent variable = met1

Total number of observations = 6
Total number of records with missing values = 3
Total number of parameters in model = 2
Total number of specified parameters = 0
Degree of polynomial = 1

Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

Background = 0.317949
Beta(1) = 0.0304484

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Beta(1)
Background	1	-0.64
Beta(1)	-0.64	1

Parameter Estimates

Confidence Interval		Variable	Estimate	Std. Err.	95.0% Wald	
Limit	Upper Conf. Limit				Lower	Conf.
*		Background	0.341285	*		*
*		Beta(1)	0.0284828	*		*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-85.3426	3			
Fitted model	-85.5783	2	0.471435	1	0.4923
Reduced model	-97.664	1	24.6428	2	<.0001
AIC:	175.157				

Goodness of Fit

Scaled Residual	Dose	Est._Prob.	Expected	Observed	Size	
0.0000		0.3413	16.723	17	49	0.083
27.0000		0.6947	32.651	31	47	-0.523
41.0000		0.7951	39.755	41	50	0.436

Chi^2 = 0.47 d.f. = 1 P-value = 0.4926

Benchmark Dose Computation

Specified effect = 0.1
 Risk Type = Extra risk
 Confidence level = 0.95
 BMD = 3.69909

BMDL = 2.71242

BMDU = 5.5735

Taken together, (2.71242, 5.5735) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.0368674

C2. Persimonate Crj:BDF1 male mice response data: multistage model

```
=====
Multistage Model. (Version: 2.8; Date: 02/20/2007)
Input Data File: C:\BMDS\DATA\COOKE_4B.(d)
Gnuplot Plotting File: C:\BMDS\DATA\COOKE_4B.plt
                                Fri Oct 05 13:29:26 2007
=====
```

BMDS MODEL RUN

~~~~~

The form of the probability function is:

$$P[\text{response}] = \text{background} + (1-\text{background}) * [1 - \text{EXP}(-\text{beta1} * \text{dose}^{1-\text{beta2}} * \text{dose}^2)]$$

The parameter betas are not restricted

Dependent variable = r  
Independent variable = met

Total number of observations = 4  
Total number of records with missing values = 0  
Total number of parameters in model = 3  
Total number of specified parameters = 0  
Degree of polynomial = 2

Maximum number of iterations = 250  
Relative Function Convergence has been set to: 1e-008  
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values  
Background = 0.349225  
Beta(1) = -0.00758195  
Beta(2) = 0.0011817

Asymptotic Correlation Matrix of Parameter Estimates

|            | Background | Beta(1) | Beta(2) |
|------------|------------|---------|---------|
| Background | 1          | -0.71   | 0.58    |
| Beta(1)    | -0.71      | 1       | -0.95   |
| Beta(2)    | 0.58       | -0.95   | 1       |

Parameter Estimates

| Confidence Interval |             |           |       | 95.0% Wald |       |
|---------------------|-------------|-----------|-------|------------|-------|
| Variable            | Estimate    | Std. Err. | Lower | Upper      | Conf. |
| Background          | 0.34497     | *         | *     | *          | *     |
| Beta(1)             | -0.00425233 | *         | *     | *          | *     |
| Beta(2)             | 0.00106195  | *         | *     | *          | *     |

\* - Indicates that this value is not calculated.

Analysis of Deviance Table

| Model         | Log(likelihood) | # Param's | Deviance | Test d.f. | P-value |
|---------------|-----------------|-----------|----------|-----------|---------|
| Full model    | -116.442        | 4         |          |           |         |
| Fitted model  | -117.778        | 3         | 2.67277  | 1         | 0.1021  |
| Reduced model | -132.99         | 1         | 33.0977  | 3         | <.0001  |
| AIC:          | 241.556         |           |          |           |         |

Goodness of Fit

| Scaled Residual | Dose | Est._Prob. | Expected | Observed | Size |        |
|-----------------|------|------------|----------|----------|------|--------|
| 0.0000          |      | 0.3450     | 15.869   | 13       | 46   | -0.890 |
| 3.4000          |      | 0.3435     | 16.833   | 21       | 49   | 1.253  |

|         |        |        |    |    |        |
|---------|--------|--------|----|----|--------|
| 14.0000 | 0.4354 | 20.900 | 19 | 48 | -0.553 |
| 36.0000 | 0.8072 | 39.554 | 40 | 49 | 0.161  |

Chi^2 = 2.69      d.f. = 1      P-value = 0.1007

Benchmark Dose Computation

Specified effect = 0.1  
Risk Type = Extra risk  
Confidence level = 0.95  
BMD = 12.162  
BMDL = 3.45475  
BMDU = 22.2207

Taken together, (3.45475, 22.2207) is a 90 % two-sided confidence interval for the BMD

**C3. Persimonate Crj:BDF1 male mice response data: Weibull model**

=====  
Weibull Model using Weibull Model (Version: 2.7; Date: 2/20/2007)  
Input Data File: C:\BMDS\DATA\COOKE\_4B.(d)  
Gnuplot Plotting File: C:\BMDS\DATA\COOKE\_4B.plt  
Fri Oct 05 13:40:08 2007  
=====

BMDS MODEL RUN  
~~~~~

The form of the probability function is:

$$P[\text{response}] = \text{background} + (1-\text{background}) * [1 - \text{EXP}(-\text{slope} * \text{dose}^{\text{power}})]$$

Dependent variable = r
Independent variable = met
Power parameter is not restricted

Total number of observations = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial (and Specified) Parameter Values

Background = 0.287234
 Slope = 0.000581165
 Power = 2.15702

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Slope	Power
Background	1	-0.58	0.57
Slope	-0.58	1	-1
Power	0.57	-1	1

Parameter Estimates

Confidence Interval				95.0% Wald
Variable	Estimate	Std. Err.	Lower	Conf.
Limit	Upper	Conf.	Limit	
Background	0.356441	0.0512024	0.256086	
0.456796				
Slope	1.91438e-005	0.000164445	-0.000303162	
0.00034145				
Power	3.09445	2.39428	-1.59825	
7.78716				

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-116.442	4			
Fitted model	-117.542	3	2.20118	1	
0.1379					
Reduced model	-132.99	1	33.0977	3	
<.0001					
AIC:	241.084				

Goodness of Fit

Scaled

Dose	Est._Prob.	Expected	Observed	Size	Residual
0.0000	0.3564	16.396	13	46	-1.046
3.4000	0.3570	17.492	21	49	1.046
14.0000	0.3984	19.123	19	48	-0.036
36.0000	0.8162	39.992	40	49	0.003

Chi^2 = 2.19 d.f. = 1 P-value = 0.1391

Benchmark Dose Computation

Specified effect = 0.1
Risk Type = Extra risk
Confidence level = 0.95
BMD = 16.1742
BMDL = 4.59798

C4. Persimonate pooled response data: multistage model

```
=====
Multistage Model. (Version: 2.8; Date: 02/20/2007)
Input Data File: C:\BMDS\DATA\COOKE_4.(d)
Gnuplot Plotting File: C:\BMDS\DATA\COOKE_4.plt
Tue Oct 02 14:47:09 2007
=====
```

BMDS MODEL RUN

The form of the probability function is:

$$P[\text{response}] = \text{background} + (1-\text{background}) * [1 - \text{EXP}(-\text{beta1} * \text{dose}^1)]$$

The parameter betas are restricted to be positive

Dependent variable = r
Independent variable = met

Total number of observations = 7
Total number of records with missing values = 0
Total number of parameters in model = 2
Total number of specified parameters = 0

Degree of polynomial = 1

Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

Background = 0.278339
Beta(1) = 0.0331573

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Beta(1)
Background	1	-0.59
Beta(1)	-0.59	1

Parameter Estimates

Confidence Interval				95.0% Wald
Variable	Estimate	Std. Err.	Lower Conf.	
Limit	Upper Conf.	Limit		
*	Background	0.308802	*	*
*	Beta(1)	0.0292731	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-201.784	7			
Fitted model	-205.034	2	6.49916	5	0.2606
Reduced model	-233.283	1	62.997	6	<.0001
AIC:	414.068				

Goodness of Fit

Scaled Dose Residual	Est._Prob.	Expected	Observed	Size	
0.0000	0.3088	14.205	13	46	-0.385
0.0000	0.3088	15.131	17	49	0.578
3.4000	0.3743	18.340	21	49	0.785
14.0000	0.5412	25.978	19	48	-2.021
27.0000	0.6864	32.262	31	47	-0.397
36.0000	0.7590	37.193	40	49	0.938
41.0000	0.7919	39.593	41	50	0.490

Chi^2 = 6.46 d.f. = 5 P-value = 0.2640

Benchmark Dose Computation

Specified effect = 0.1
Risk Type = Extra risk
Confidence level = 0.95
BMD = 3.59923
BMDL = 2.85892
BMDU = 4.731

Taken together, (2.85892, 4.731) is a 90 % two-sided confidence interval for the BMD

C5. Persimonate pooled response data: Weibull model

```
=====
Weibull Model using Weibull Model (Version: 2.7; Date:
2/20/2007)
Input Data File: C:\BMDS\DATA\COOKE_4C.(d)
Gnuplot Plotting File: C:\BMDS\DATA\COOKE_4C.plt
Fri Oct 05 14:00:27 2007
=====
```

BMDS MODEL RUN

~~~~~  
The form of the probability function is:

P[response] = background + (1-background)\*[1-EXP(-slope\*dose^power)]

Dependent variable = r  
 Independent variable = met  
 Power parameter is not restricted

Total number of observations = 7  
 Total number of records with missing values = 0  
 Maximum number of iterations = 250  
 Relative Function Convergence has been set to: 1e-008  
 Parameter Convergence has been set to: 1e-008

Default Initial (and Specified) Parameter Values

Background = 0.35  
 Slope = 0.00144995  
 Power = 1.82013

Asymptotic Correlation Matrix of Parameter Estimates

|            | Background | Slope | Power |
|------------|------------|-------|-------|
| Background | 1          | -0.43 | 0.41  |
| Slope      | -0.43      | 1     | -1    |
| Power      | 0.41       | -1    | 1     |

Parameter Estimates

| Confidence Interval |                   |            |             | 95.0% Wald |
|---------------------|-------------------|------------|-------------|------------|
| Variable            | Estimate          | Std. Err.  | Lower Conf. |            |
| Limit               | Upper Conf. Limit |            |             |            |
| Background          | 0.344205          | 0.0401171  | 0.265577    |            |
| 0.422833            |                   |            |             |            |
| Slope               | 0.00066921        | 0.00167598 | -0.00261565 |            |
| 0.00395407          |                   |            |             |            |
| Power               | 2.06878           | 0.696739   | 0.703192    |            |
| 3.43436             |                   |            |             |            |

Analysis of Deviance Table

| Model         | Log(likelihood) | # Param's | Deviance | Test d.f. | P-value |
|---------------|-----------------|-----------|----------|-----------|---------|
| Full model    | -201.784        | 7         |          |           |         |
| Fitted model  | -203.336        | 3         | 3.10325  | 4         | 0.5407  |
| Reduced model | -233.283        | 1         | 62.997   | 6         | <.0001  |
| AIC:          | 412.672         |           |          |           |         |

Goodness of Fit

| Scaled Dose | Est._Prob. | Expected | Observed | Size | Residual |
|-------------|------------|----------|----------|------|----------|
| 0.0000      | 0.3442     | 15.833   | 13       | 46   | -0.879   |
| 0.0000      | 0.3442     | 16.866   | 17       | 49   | 0.040    |
| 3.4000      | 0.3497     | 17.135   | 21       | 49   | 1.158    |
| 14.0000     | 0.4396     | 21.103   | 19       | 48   | -0.611   |
| 27.0000     | 0.6444     | 30.286   | 31       | 47   | 0.218    |
| 36.0000     | 0.7838     | 38.407   | 40       | 49   | 0.553    |
| 41.0000     | 0.8465     | 42.326   | 41       | 50   | -0.520   |

Chi^2 = 3.11      d.f. = 4      P-value = 0.5391

Benchmark Dose Computation

Specified effect = 0.1  
Risk Type = Extra risk  
Confidence level = 0.95  
BMD = 11.5355  
BMDL = 4.27128