Appendix A

Output from BMDS

```
 ====================================================================
        $Revision: 2.2 $ $Date: 2001/03/14 01:17:00 $
       Input Data File: I:\NPB\LIVER\F0FEMHVC_GAMMA.(D)
       Gnuplot Plotting File:  I:\NPB\LIVER\F0FEMHVC_GAMMA.plt
                                        Wed Aug 08 16:14:09 2001
 ====================================================================
 Hepatocullular Vauolation, Centrilobular F0 Fem (Stump 2001)
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
   The form of the probability function is:
   P[response]= background+(1-background)*CumGamma[slope*dose,power],
   where CumGamma(.) is the cummulative Gamma distribution function

   Dependent variable = responder
   Independent variable = dose
   Power parameter is restricted as power >=1

   Total number of observations = 5
   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 =    0.0192308
                           Slope =    0.0113224
                           Power =      7.85558


      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
       Variable           Estimate             Std. Err.
     Background                  0                 NA
          Slope           0.0135675          0.00699159
          Power             9.26181             4.43562

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)  Deviance  Test DF     P-value
     Full model        -30.1125
   Fitted model        -30.3241      0.423245      3          0.9354
  Reduced model        -58.1592       56.0935      4         <.0001

           AIC:         64.6482
```

Female Liver Effects

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0	25	0
100.0000	0.0000	0.000	0	25	-0.01379
250.0000	0.0061	0.154	0	25	-0.3933
500.0000	0.2152	5.381	6	25	0.3014
750.0000	0.6554	16.384	16	25	-0.1617

Chi-square = 0.27 DF = 3 P-value = 0.9652

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk
Confidence level = 0.95
BMD = 415.541
BMDL = 319.798

```
 ======================================================================
        Logistic Model $Revision: 2.1 $ $Date: 2000/02/26 03:38:20 $
        Input Data File: I:\NPB\LIVER\F0FEMHVC_LOGISTIC.(D)
        Gnuplot Plotting File:  I:\NPB\LIVER\F0FEMHVC_LOGISTIC.plt
                                          Wed Aug 08 16:14:11 2001
 ======================================================================
 Hepatocullular Vauolation, Centrilobular F0 Fem (Stump 2001)
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
   The form of the probability function is:
   P[response] = 1/[1+EXP(-intercept-slope*dose)]

   Dependent variable = responder
   Independent variable = dose
   Slope parameter is not restricted

   Total number of observations = 5
   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 Parameter Values
                     background =            0   Specified
                      intercept =     -4.56003
                          slope =   0.00653633

           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 )

              intercept        slope
 intercept            1        -0.97
     slope        -0.97            1


                          Parameter Estimates

       Variable           Estimate             Std. Err.
      intercept            -6.09484             1.21884
          slope          0.00910019          0.00190446




                        Analysis of Deviance Table

       Model      Log(likelihood)  Deviance  Test DF     P-value
     Full model        -30.1125
   Fitted model        -31.2453       2.26567      3          0.5191
  Reduced model        -58.1592       56.0935      4         <.0001

           AIC:         66.4906
```

Female Liver Effects

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0022	0.056	0	25	-0.2374
100.0000	0.0056	0.139	0	25	-0.3742
250.0000	0.0215	0.537	0	25	-0.7405
500.0000	0.1758	4.396	6	25	0.8426
750.0000	0.6749	16.872	16	25	-0.3722

Chi-square = 1.59 DF = 3 P-value = 0.6609

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk
Confidence level = 0.95
BMD = 430.75
BMDL = 345.09

```
 ======================================================================
        Logistic Model $Revision: 2.1 $ $Date: 2000/02/26 03:38:20 $
        Input Data File: I:\NPB\LIVER\F0FEMHVC_LOGLOGISTIC.(D)
        Gnuplot Plotting File:  I:\NPB\LIVER\F0FEMHVC_LOGLOGISTIC.plt
                                          Wed Aug 08 16:14:12 2001
 ======================================================================
 Hepatocullular Vauolation, Centrilobular F0 Fem (Stump 2001)
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
    The form of the probability function is:
 P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]

   Dependent variable = responder
   Independent variable = dose
   Slope parameter is restricted as slope >= 1

   Total number of observations = 5
   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

   User has chosen the log transformed model
                  Default Initial Parameter Values
                     background =            0
                      intercept =     -15.0964
                          slope =      2.26228

           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 )

              intercept        slope
 intercept            1           -1
     slope           -1            1


                          Parameter Estimates

       Variable           Estimate             Std. Err.
     background                  0                 NA
      intercept            -31.2326            8.27966
          slope              4.8159            1.28779

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)  Deviance  Test DF     P-value
     Full model        -30.1125
   Fitted model        -30.4214      0.617795      3          0.8923
  Reduced model        -58.1592       56.0935      4         <.0001

           AIC:         64.8427
```

Female Liver Effects

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0	25	0
100.0000	0.0001	0.003	0	25	-0.05405
250.0000	0.0095	0.239	0	25	-0.4909
500.0000	0.2135	5.339	6	25	0.3227
750.0000	0.6568	16.420	16	25	-0.1768

Chi-square = 0.38 DF = 3 P-value = 0.9445

Benchmark Dose Computation

```
Specified effect =           0.1
Risk Type        =     Extra risk
Confidence level =          0.95
             BMD =       415.327
            BMDL =      319.737
```

```
 ==================================================================
        Probit Model $Revision: 2.1 $ $Date: 2000/02/26 03:38:53 $
        Input Data File: I:\NPB\LIVER\F0FEMHVC_PROBIT.(D)
        Gnuplot Plotting File:  I:\NPB\LIVER\F0FEMHVC_PROBIT.plt
                                          Wed Aug 08 16:14:15 2001
 ==================================================================
 Hepatocullular Vauolation, Centrilobular F0 Fem (Stump 2001)
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
   The form of the probability function is:
   P[response] = CumNorm(Intercept+Slope*Dose),
   where CumNorm(.) is the cumulative normal distribution function

   Dependent variable = responder
   Independent variable = dose
   Slope parameter is not restricted

   Total number of observations = 5
   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   Specified
                      intercept =     -2.87309
                          slope =   0.00412017

           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 )

              intercept        slope
 intercept            1        -0.96
     slope        -0.96            1

                              Parameter Estimates

       Variable           Estimate             Std. Err.
      intercept            -3.50382            0.686968
          slope          0.00525132          0.00109949



                        Analysis of Deviance Table

       Model      Log(likelihood)  Deviance  Test DF     P-value
     Full model        -30.1125
   Fitted model        -30.7482       1.27148      3          0.7359
  Reduced model        -58.1592       56.0935      4         <.0001

           AIC:         65.4964
```

Female Liver Effects

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0002	0.006	0	25	-0.07573
100.0000	0.0014	0.036	0	25	-0.1904
250.0000	0.0142	0.356	0	25	-0.6007
500.0000	0.1899	4.748	6	25	0.6383
750.0000	0.6681	16.702	16	25	-0.2984

Chi-square = 0.90 DF = 3 P-value = 0.8256

Benchmark Dose Computation

```
Specified effect =           0.1
Risk Type        =     Extra risk
Confidence level =          0.95
             BMD =       423.406
            BMDL =      334.385
```

```
 ==================================================================
        Probit Model $Revision: 2.1 $ $Date: 2000/02/26 03:38:53 $
        Input Data File: I:\NPB\LIVER\F0FEMHVC_LOGPROBIT.(D)
        Gnuplot Plotting File:  I:\NPB\LIVER\F0FEMHVC_LOGPROBIT.plt
                                          Wed Aug 08 16:14:13 2001
 ==================================================================
 Hepatocullular Vauolation, Centrilobular F0 Fem (Stump 2001)
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
   The form of the probability function is:
   P[response] = Background
               + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)),
   where CumNorm(.) is the cumulative normal distribution function

   Dependent variable = responder
   Independent variable = dose
   Slope parameter is restricted as slope >= 1

   Total number of observations = 5
   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

   User has chosen the log transformed model

                   Default Initial (and Specified) Parameter Values
                      background =            0
                       intercept =     -7.96265
                           slope =       1.1917

           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 )

              intercept        slope
 intercept            1           -1
     slope           -1            1


                          Parameter Estimates
       Variable           Estimate             Std. Err.
     background                  0                 NA
      intercept            -18.3053            4.91558
          slope             2.82354             0.7662

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)  Deviance  Test DF     P-value
     Full model        -30.1125
   Fitted model        -30.2191      0.213311      3          0.9754
  Reduced model        -58.1592       56.0935      4         <.0001
```

Female Liver Effects

AIC: 64.4382

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0	25	0
100.0000	0.0000	0.000	0	25	-0.001195
250.0000	0.0033	0.083	0	25	-0.2882
500.0000	0.2242	5.605	6	25	0.1894
750.0000	0.6505	16.263	16	25	-0.1105

Chi-square = 0.13 DF = 3 P-value = 0.9879

Benchmark Dose Computation

Specified effect = 0.1
Risk Type = Extra risk
Confidence level = 0.95
BMD = 415.388
BMDL = 322.058

```
 ======================================================================
        Multistage Model. $Revision: 2.1 $ $Date: 2000/08/21 03:38:21 $
        Input Data File: I:\NPB\LIVER\F0FEMHVC_MULTISTAGE.(D)
        Gnuplot Plotting File:  I:\NPB\LIVER\F0FEMHVC_MULTISTAGE.plt
                                          Wed Aug 08 16:14:14 2001
 ======================================================================
 Hepatocullular Vauolation, Centrilobular F0 Fem (Stump 2001)
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
-beta1*dose^1-beta2*dose^2-beta3*dose^3-beta4*dose^4)]

   The parameter betas are restricted to be positive

   Dependent variable = responder
   Independent variable = dose

 Total number of observations = 5
 Total number of records with missing values = 0
 Total number of parameters in model = 5
 Total number of specified parameters = 0
 Degree of polynomial = 4

 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
                        Beta(1) =            0
                        Beta(2) =            0
                        Beta(3) = 2.43889e-009
                        Beta(4) =            0


            Asymptotic Correlation Matrix of Parameter Estimates

( *** The model parameter(s)  -Background -Beta(1) -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(4)
   Beta(4)            1




                           Parameter Estimates

       Variable           Estimate             Std. Err.
     Background                  0                 NA
        Beta(1)                  0                 NA
        Beta(2)                  0                 NA
        Beta(3)                  0                 NA
        Beta(4)        3.43906e-012         1.0475e-012
```

Female Liver Effects

```
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)	Deviance	Test DF	P-value
Full model	-30.1125			
Fitted model	-30.6511	1.07728	4	0.8979
Reduced model	-58.1592	56.0935	4	<.0001

AIC: 63.3022

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Chi^2 Res.
0.0000	0.0000	0.000	0	25	0.000
100.0000	0.0003	0.009	0	25	-1.000
250.0000	0.0133	0.334	0	25	-1.014
500.0000	0.1934	4.835	6	25	0.299
750.0000	0.6632	16.579	16	25	-0.104

Chi-square = 0.75 DF = 4 P-value = 0.9444

Benchmark Dose Computation

```
Specified effect =            0.1
Risk Type        =      Extra risk
Confidence level =           0.95
             BMD =        418.369
            BMDL =        312.212
```

```
 ======================================================================
        Weibull Model $Revision: 2.2 $ $Date: 2000/03/17 22:27:16 $
        Input Data File: I:\NPB\LIVER\F0FEMHVC_WEIBULL.(D)
        Gnuplot Plotting File:  I:\NPB\LIVER\F0FEMHVC_WEIBULL.plt
                                          Wed Aug 08 16:14:15 2001
 ======================================================================
 Hepatocullular Vauolation, Centrilobular F0 Fem (Stump 2001)
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
   The form of the probability function is:
   P[response] = background + (1-background)*[1-EXP(-slope*dose^power)]

   Dependent variable = responder
   Independent variable = dose
   Power parameter is restricted as power >=1

   Total number of observations = 5
   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 =    0.0192308
                          Slope = 6.32563e-010
                          Power =      3.19763

           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.$          1.$
     Power          1.$          1.$


                          Parameter Estimates

       Variable           Estimate             Std. Err.
     Background                  0                 NA
          Slope        8.54532e-012             1.#QNAN
          Power             3.86009             1.#QNAN

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)  Deviance  Test DF     P-value
     Full model        -30.1125
   Fitted model        -30.6413       1.05766      3          0.7873
  Reduced model        -58.1592       56.0935      4         <.0001

           AIC:         65.2826
```

Female Liver Effects

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0	25	0
100.0000	0.0004	0.011	0	25	-0.1059
250.0000	0.0153	0.382	0	25	-0.6232
500.0000	0.2006	5.014	6	25	0.4923
750.0000	0.6573	16.432	16	25	-0.1819

Chi-square = 0.68 DF = 3 P-value = 0.8791

Benchmark Dose Computation

```
Specified effect =           0.1
Risk Type        =     Extra risk
Confidence level =          0.95
             BMD =       411.317
            BMDL =       310.499
```

```
 ==================================================================
        $Revision: 2.2 $ $Date: 2001/03/14 01:17:00 $
       Input Data File: I:\NPB\LIVER\F1FEMHVC_GAMMA.(D)
       Gnuplot Plotting File:  I:\NPB\LIVER\F1FEMHVC_GAMMA.plt
                                        Wed Aug 08 16:14:25 2001
 ==================================================================
 Hepatocellular Vacuolation, Centrilobular F1 Fem (Stump 2001
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
   The form of the probability function is:
   P[response]= background+(1-background)*CumGamma[slope*dose,power],
   where CumGamma(.) is the cummulative Gamma distribution function

   Dependent variable = responder
   Independent variable = dose
   Power parameter is restricted as power >=1

   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 =    0.0192308
                          Slope =   0.00206996
                          Power =      2.19869

           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

       Variable           Estimate             Std. Err.
     Background                  0                 NA
          Slope          0.00315149           0.0030946
          Power             2.80166             1.75659

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)  Deviance  Test DF     P-value
     Full model        -20.7462
   Fitted model        -20.9872      0.481856      2          0.7859
  Reduced model        -27.8769       14.2614      3         0.00257

           AIC:         45.9743
```

Female Liver Effects

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0	25	0
100.0000	0.0066	0.166	0	25	-0.409
250.0000	0.0618	1.545	2	25	0.3779
500.0000	0.2513	6.282	6	25	-0.1299

Chi-square = 0.33 DF = 2 P-value = 0.8492

Benchmark Dose Computation

```
Specified effect =           0.1
Risk Type        =     Extra risk
Confidence level =          0.95
             BMD =       311.571
            BMDL =      194.304
```

```
 ======================================================================
        Logistic Model $Revision: 2.1 $ $Date: 2000/02/26 03:38:20 $
        Input Data File: I:\NPB\LIVER\F1FEMHVC_LOGISTIC.(D)
        Gnuplot Plotting File:  I:\NPB\LIVER\F1FEMHVC_LOGISTIC.plt
                                          Wed Aug 08 16:14:26 2001
 ======================================================================
 Hepatocellular Vacuolation, Centrilobular F1 Fem (Stump 2001
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
   The form of the probability function is:
   P[response] = 1/[1+EXP(-intercept-slope*dose)]

   Dependent variable = responder
   Independent variable = dose
   Slope 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 Parameter Values
                     background =            0   Specified
                      intercept =     -4.11576
                          slope =    0.0061883

           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 )

              intercept        slope
 intercept            1        -0.95
     slope        -0.95            1

                          Parameter Estimates

       Variable           Estimate             Std. Err.
      intercept            -5.04723             1.26329
          slope          0.00794816           0.0028328




                        Analysis of Deviance Table

       Model      Log(likelihood)  Deviance  Test DF     P-value
     Full model        -20.7462
   Fitted model        -21.5707       1.64899      2          0.4385
  Reduced model        -27.8769       14.2614      3         0.00257

            AIC:         47.1415
```

Female Liver Effects

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0064	0.160	0	25	-0.4008
100.0000	0.0140	0.351	0	25	-0.5964
250.0000	0.0448	1.119	2	25	0.8515
500.0000	0.2548	6.370	6	25	-0.1699

Chi-square = 1.27 DF = 2 P-value = 0.5299

Benchmark Dose Computation

```
Specified effect =          0.1
Risk Type        =     Extra risk
Confidence level =         0.95
             BMD =      366.411
            BMDL =      288.128
```

```
 ======================================================================
        Logistic Model $Revision: 2.1 $ $Date: 2000/02/26 03:38:20 $
        Input Data File: I:\NPB\LIVER\F1FEMHVC_LOGLOGISTIC.(D)
        Gnuplot Plotting File:  I:\NPB\LIVER\F1FEMHVC_LOGLOGISTIC.plt
                                          Wed Aug 08 16:14:27 2001
 ======================================================================
 Hepatocellular Vacuolation, Centrilobular F1 Fem (WIL 2001)
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
   The form of the probability function is:
 P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]

   Dependent variable = responder
   Independent variable = dose
   Slope parameter is restricted as slope >= 1

   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

   User has chosen the log transformed model

                  Default Initial Parameter Values
                     background =            0
                      intercept =      -11.886
                          slope =      1.72149

            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 )

              intercept        slope
 intercept            1           -1
     slope           -1            1



                           Parameter Estimates

       Variable           Estimate             Std. Err.
     background                  0                NA
      intercept            -15.6064             6.2683
          slope             2.33466            1.04144

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)  Deviance  Test DF     P-value
     Full model        -20.7462
   Fitted model         -21.011      0.529472      2          0.7674
  Reduced model        -27.8769       14.2614      3         0.00257

            AIC:         46.0219
```

Female Liver Effects

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0	25	0
100.0000	0.0077	0.193	0	25	-0.4413
250.0000	0.0621	1.551	2	25	0.372
500.0000	0.2502	6.255	6	25	-0.118

Chi-square = 0.35 DF = 2 P-value = 0.8407

Benchmark Dose Computation

```
Specified effect =           0.1
Risk Type        =     Extra risk
Confidence level =          0.95
             BMD =       312.169
            BMDL =      191.279
```

```
=====================================================================
        Probit Model $Revision: 2.1 $ $Date: 2000/02/26 03:38:53 $
        Input Data File: I:\NPB\LIVER\F1FEMHVC_PROBIT.(D)
        Gnuplot Plotting File:  I:\NPB\LIVER\F1FEMHVC_PROBIT.plt
                                          Wed Aug 08 16:14:30 2001
 ====================================================================
 Hepatocellular Vacuolation, Centrilobular F1 Fem (Stump 2001
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
   The form of the probability function is:
   P[response] = CumNorm(Intercept+Slope*Dose),
   where CumNorm(.) is the cumulative normal distribution function

   Dependent variable = responder
   Independent variable = dose
   Slope 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   Specified
                      intercept =     -2.58533
                          slope =   0.00390053

           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 )

              intercept        slope
 intercept            1        -0.93
     slope        -0.93            1

                         Parameter Estimates
       Variable          Estimate            Std. Err.
      intercept           -2.68175            0.564027
          slope         0.00405994          0.00136227

                        Analysis of Deviance Table

       Model      Log(likelihood)  Deviance  Test DF     P-value
     Full model        -20.7462
   Fitted model        -21.3843       1.27609      2          0.5283
  Reduced model        -27.8769       14.2614      3         0.00257
            AIC:         46.7686


                              Goodness  of  Fit

                                                                  Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
  ---------------------------------------------------------------------
    0.0000      0.0037          0.092          0           25      -0.3031
  100.0000      0.0114          0.286          0           25      -0.5376
  250.0000      0.0478          1.195          2           25       0.7553
```

```
  500.0000      0.2573          6.432           6            25      -0.1976

 Chi-square =       0.99     DF = 2        P-value = 0.6095


   Benchmark Dose Computation

Specified effect =            0.1
Risk Type        =      Extra risk
Confidence level =           0.95
             BMD =        349.452
            BMDL =       270.662
```

```
 ======================================================================
        Probit Model $Revision: 2.1 $ $Date: 2000/02/26 03:38:53 $
        Input Data File: I:\NPB\LIVER\F1FEMHVC_LOGPROBIT.(D)
        Gnuplot Plotting File:  I:\NPB\LIVER\F1FEMHVC_LOGPROBIT.plt
                                          Wed Aug 08 16:14:28 2001
 ======================================================================
 Hepatocellular Vacuolation, Centrilobular F1 Fem (Stump 2001
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:
   P[response] = Background
               + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)),
   where CumNorm(.) is the cumulative normal distribution function

   Dependent variable = responder
   Independent variable = dose
   Slope parameter is restricted as slope >= 1

   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

   User has chosen the log transformed model

                  Default Initial (and Specified) Parameter Values
                      background =            0
                       intercept =     -6.85267
                           slope =            1

            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 )

              intercept        slope
 intercept            1           -1
     slope           -1            1


                         Parameter Estimates

       Variable           Estimate             Std. Err.
     background                  0                 NA
      intercept            -8.1756            3.07162
          slope            1.20711           0.517225

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

Female Liver Effects

Analysis of Deviance Table

Model	Log(likelihood)	Deviance	Test DF	P-value
Full model	-20.7462			
Fitted model	-20.9051	0.317653	2	0.8531
Reduced model	-27.8769	14.2614	3	0.00257

AIC: 45.8101

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0	25	0
100.0000	0.0044	0.111	0	25	-0.3339
250.0000	0.0654	1.636	2	25	0.2942
500.0000	0.2502	6.255	6	25	-0.1176

Chi-square = 0.21 DF = 2 P-value = 0.8995

Benchmark Dose Computation

```
Specified effect =           0.1
Risk Type        =      Extra risk
Confidence level =          0.95
             BMD =       302.236
            BMDL =       209.394
```

```
 ====================================================================
       Multistage Model. $Revision: 2.1 $ $Date: 2000/08/21 03:38:21 $
       Input Data File: I:\NPB\LIVER\F1FEMHVC_MULTISTAGE.(D)
       Gnuplot Plotting File:  I:\NPB\LIVER\F1FEMHVC_MULTISTAGE.plt
                                        Wed Aug 08 16:14:29 2001
 ====================================================================
 Hepatocellular Vacuolation, Centrilobular F1 Fem (Stump 2001
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
   The form of the probability function is:
   P[response] = background + (1-background)*[1-EXP(
-beta1*dose^1-beta2*dose^2-beta3*dose^3)]

   The parameter betas are restricted to be positive

   Dependent variable = responder
   Independent variable = dose
```

Female Liver Effects

```
Total number of observations = 4
Total number of records with missing values = 0
Total number of parameters in model = 4
Total number of specified parameters = 0
Degree of polynomial = 3
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
                       Beta(1) = 8.75512e-005
                       Beta(2) = 9.52285e-007
                       Beta(3) =            0

          Asymptotic Correlation Matrix of Parameter Estimates

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

               Beta(2)      Beta(3)
   Beta(2)           1        -0.99
   Beta(3)       -0.99            1


                              Parameter Estimates

       Variable           Estimate             Std. Err.
     Background                  0                 NA
        Beta(1)                  0                 NA
        Beta(2)        9.77092e-007         5.9749e-006
        Beta(3)        3.03674e-010        1.23787e-008

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

                        Analysis of Deviance Table

       Model      Log(likelihood)  Deviance  Test DF     P-value
     Full model        -20.7462
   Fitted model        -21.0522      0.612034      2          0.7364
  Reduced model        -27.8769       14.2614      3         0.00257

          AIC:         46.1045

                     Goodness  of  Fit

     Dose     Est._Prob.    Expected    Observed     Size     Chi^2 Res.
  ----------------------------------------------------------------------
    0.0000     0.0000         0.000         0          25       0.000
  100.0000     0.0100         0.251         0          25      -1.010
  250.0000     0.0637         1.592         2          25       0.273
  500.0000     0.2459         6.148         6          25      -0.032
 Chi-square =       0.37     DF = 2        P-value = 0.8314
```

Female Liver Effects

```
      Benchmark Dose Computation

Specified effect =            0.1
Risk Type        =      Extra risk
Confidence level =           0.95
             BMD =        313.462
            BMDL =        192.347
```

```
=====================================================================
        Weibull Model $Revision: 2.2 $ $Date: 2000/03/17 22:27:16 $
        Input Data File: I:\NPB\LIVER\F1FEMHVC_WEIBULL.(D)
        Gnuplot Plotting File:  I:\NPB\LIVER\F1FEMHVC_WEIBULL.plt
                                        Wed Aug 08 16:14:31 2001
 ====================================================================
 Hepatocellular Vacuolation, Centrilobular F1 Fem (Stump 2001
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
   The form of the probability function is:
   P[response] = background + (1-background)*[1-EXP(-slope*dose^power)]

   Dependent variable = responder
   Independent variable = dose
   Power parameter is restricted as power >=1

   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 =    0.0192308
                          Slope = 1.68226e-006
                          Power =      1.92765

           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           -1
     Power           -1            1

                          Parameter Estimates
       Variable           Estimate             Std. Err.
     Background                  0                 NA
          Slope        3.50772e-007        2.09065e-006
          Power             2.19095            0.984955

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)  Deviance  Test DF     P-value
     Full model        -20.7462
   Fitted model        -21.0362      0.579854      2          0.7483
  Reduced model        -27.8769       14.2614      3         0.00257

           AIC:         46.0723

                     Goodness  of  Fit

                                                                  Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
  ---------------------------------------------------------------------
```

```
    0.0000      0.0000          0.000          0           25            0
  100.0000      0.0084          0.210          0           25      -0.4606
  250.0000      0.0610          1.525          2           25       0.3974
  500.0000      0.2497          6.243          6           25      -0.1122

 Chi-square =       0.38     DF = 2        P-value = 0.8259


   Benchmark Dose Computation

Specified effect =            0.1
Risk Type        =      Extra risk
Confidence level =           0.95
             BMD =        316.321
            BMDL =       191.979
```

```
 ==================================================================
        $Revision: 2.2 $ $Date: 2001/03/14 01:17:00 $
       Input Data File: I:\NPB\LIVER\F0MHVC_GAMMA.(D)
       Gnuplot Plotting File:  I:\NPB\LIVER\F0MHVC_GAMMA.plt
                                        Wed Aug 08 16:14:16 2001
 ==================================================================
 Hepatocellular Vauolation, Centrilobular F0 Male Stump 2001
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
   The form of the probability function is:
   P[response]= background+(1-background)*CumGamma[slope*dose,power],
   where CumGamma(.) is the cummulative Gamma distribution function


   Dependent variable = responder
   Independent variable = dose
   Power parameter is restricted as power >=1

   Total number of observations = 5
   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 =    0.0192308
                          Slope =    0.0110334
                          Power =      4.15111

           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         0.97
     Power         0.97            1


                          Parameter Estimates
       Variable           Estimate             Std. Err.
     Background                  0                 NA
          Slope           0.0153502          0.00499637
          Power             5.43026            1.73485

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)  Deviance  Test DF     P-value
     Full model        -28.1956
   Fitted model        -28.9559       1.52058      3          0.6775
  Reduced model        -85.1938       113.996      4         <.0001

           AIC:         61.9117
```

Male Liver Effects

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0	25	0
100.0000	0.0113	0.282	0	25	-0.5341
250.0000	0.2685	6.712	7	25	0.1298
500.0000	0.8401	21.003	22	25	0.5443
750.0000	0.9836	24.590	24	25	-0.9289

Chi-square = 1.46 DF = 3 P-value = 0.6912

Benchmark Dose Computation

```
Specified effect =           0.1
Risk Type        =     Extra risk
Confidence level =          0.95
             BMD =       178.419
            BMDL =      130.265
```

```
=====================================================================
        Logistic Model $Revision: 2.1 $ $Date: 2000/02/26 03:38:20 $
        Input Data File: I:\NPB\LIVER\F0MHVC_LOGISTIC.(D)
        Gnuplot Plotting File:  I:\NPB\LIVER\F0MHVC_LOGISTIC.plt
                                        Wed Aug 08 16:14:18 2001
 ====================================================================
 Hepatocellular Vauolation, Centrilobular F0 Male Stump 2001
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
   The form of the probability function is:
   P[response] = 1/[1+EXP(-intercept-slope*dose)]

   Dependent variable = responder
   Independent variable = dose
   Slope parameter is not restricted

   Total number of observations = 5
   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 Parameter Values
                     background =            0   Specified
                      intercept =     -4.01599
                          slope =   0.00997963

           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 )

              intercept        slope
 intercept            1        -0.89
     slope        -0.89            1

                          Parameter Estimates
       Variable           Estimate             Std. Err.
      intercept            -4.32977            0.737463
          slope           0.0122019          0.00203944


                         Analysis of Deviance Table

       Model      Log(likelihood)  Deviance  Test DF     P-value
     Full model        -28.1956
   Fitted model        -30.7741       5.15711      3          0.1606
  Reduced model        -85.1938       113.996      4         <.0001
            AIC:         65.5482

                     Goodness  of  Fit

                                                                  Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
  ---------------------------------------------------------------------
    0.0000      0.0130          0.325          0           25      -0.5738
  100.0000      0.0427          1.068          0           25       -1.056
  250.0000      0.2177          5.442          7           25       0.7552
  500.0000      0.8546         21.365         22           25       0.3602
```

```
  750.0000      0.9920         24.800         24           25       -1.798

 Chi-square =       5.38     DF = 3        P-value = 0.1462


   Benchmark Dose Computation

Specified effect =            0.1
Risk Type        =      Extra risk
Confidence level =           0.95
             BMD =        184.911
            BMDL =       139.188
```

```
 ======================================================================
        Logistic Model $Revision: 2.1 $ $Date: 2000/02/26 03:38:20 $
        Input Data File: I:\NPB\LIVER\F0MHVC_LOGLOGISTIC.(D)
        Gnuplot Plotting File:  I:\NPB\LIVER\F0MHVC_LOGLOGISTIC.plt
                                          Wed Aug 08 16:14:19 2001
 ======================================================================
 Hepatocellular Vauolation, Centrilobular F0 Male Stump 2001
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
   The form of the probability function is:
 P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]

   Dependent variable = responder
   Independent variable = dose
   Slope parameter is restricted as slope >= 1

   Total number of observations = 5
   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

   User has chosen the log transformed model


                  Default Initial Parameter Values
                     background =            0
                      intercept =     -20.6001
                          slope =      3.60147

           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 )

              intercept        slope
 intercept            1           -1
     slope           -1            1
```

Male Liver Effects

Parameter Estimates

Variable	Estimate	Std. Err.
background	0	NA
intercept	-24.0668	4.62499
slope	4.17795	0.793578

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)	Deviance	Test DF	P-value
Full model	-28.1956			
Fitted model	-28.4871	0.58301	3	0.9003
Reduced model	-85.1938	113.996	4	<.0001

AIC: 60.9741

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0	25	0
100.0000	0.0079	0.199	0	25	-0.4476
250.0000	0.2693	6.731	7	25	0.1211
500.0000	0.8696	21.740	22	25	0.1542
750.0000	0.9732	24.330	24	25	-0.408

Chi-square = 0.41 DF = 3 P-value = 0.9391

Benchmark Dose Computation

Specified effect = 0.1
Risk Type = Extra risk
Confidence level = 0.95
BMD = 187.639
BMDL = 143.489

```
 ==================================================================
        Probit Model $Revision: 2.1 $ $Date: 2000/02/26 03:38:53 $
        Input Data File: I:\NPB\LIVER\F0MHVC_PROBIT.(D)
        Gnuplot Plotting File:  I:\NPB\LIVER\F0MHVC_PROBIT.plt
                                          Wed Aug 08 16:14:22 2001
 ==================================================================
 Hepatocellular Vauolation, Centrilobular F0 Male Stump 2001
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
   The form of the probability function is:
   P[response] = CumNorm(Intercept+Slope*Dose),
   where CumNorm(.) is the cumulative normal distribution function

   Dependent variable = responder
   Independent variable = dose
   Slope parameter is not restricted

   Total number of observations = 5
   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   Specified
                      intercept =     -2.51522
                          slope =    0.0061539

           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 )

              intercept        slope
 intercept            1        -0.87
     slope        -0.87            1

                          Parameter Estimates
       Variable           Estimate             Std. Err.
      intercept            -2.39622            0.364413
          slope          0.00656848         0.000945883


                        Analysis of Deviance Table

       Model      Log(likelihood)  Deviance  Test DF     P-value
     Full model        -28.1956
   Fitted model        -31.1724       5.95373      3          0.1139
  Reduced model        -85.1938       113.996      4         <.0001

           AIC:         66.3449

                     Goodness  of  Fit
```

Male Liver Effects

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0083	0.207	0	25	-0.4569
100.0000	0.0410	1.025	0	25	-1.034
250.0000	0.2254	5.635	7	25	0.6534
500.0000	0.8127	20.318	22	25	0.8621
750.0000	0.9943	24.857	24	25	-2.278

Chi-square = 7.64 DF = 3 P-value = 0.0542

Benchmark Dose Computation

```
Specified effect =           0.1
Risk Type        =     Extra risk
Confidence level =          0.95
             BMD =       175.998
            BMDL =      130.451
```

```
 ====================================================================
        Probit Model $Revision: 2.1 $ $Date: 2000/02/26 03:38:53 $
        Input Data File: I:\NPB\LIVER\F0MHVC_LOGPROBIT.(D)
        Gnuplot Plotting File:  I:\NPB\LIVER\F0MHVC_LOGPROBIT.plt
                                          Wed Aug 08 16:14:20 2001
 ====================================================================
 Hepatocellular Vauolation, Centrilobular F0 Male Stump 2001
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
   The form of the probability function is:
   P[response] = Background
               + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)),
   where CumNorm(.) is the cumulative normal distribution function

   Dependent variable = responder
   Independent variable = dose
   Slope parameter is restricted as slope >= 1

   Total number of observations = 5
   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

   User has chosen the log transformed model

                   Default Initial (and Specified) Parameter Values
                      background =            0
                       intercept =     -11.1762
                           slope =      1.95885

           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 )

              intercept        slope
 intercept            1           -1
     slope           -1            1



                         Parameter Estimates
       Variable          Estimate            Std. Err.
     background                 0               NA
      intercept           -13.5152            2.40506
          slope            2.34264           0.407194

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)  Deviance  Test DF     P-value
     Full model        -28.1956
   Fitted model        -28.4899      0.588675      3           0.899
  Reduced model        -85.1938       113.996      4         <.0001
```

Male Liver Effects

AIC: 60.9798

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0	25	0
100.0000	0.0032	0.080	0	25	-0.2831
250.0000	0.2808	7.020	7	25	-0.00909
500.0000	0.8516	21.290	22	25	0.3993
750.0000	0.9769	24.422	24	25	-0.5617

Chi-square = 0.56 DF = 3 P-value = 0.9066

Benchmark Dose Computation

```
Specified effect =           0.1
Risk Type        =     Extra risk
Confidence level =          0.95
             BMD =       185.336
            BMDL =       141.577
```

```
 ======================================================================
        Multistage Model. $Revision: 2.1 $ $Date: 2000/08/21 03:38:21 $
        Input Data File: I:\NPB\LIVER\F0MHVC_MULTISTAGE.(D)
        Gnuplot Plotting File:  I:\NPB\LIVER\F0MHVC_MULTISTAGE.plt
                                          Wed Aug 08 16:14:21 2001
 ======================================================================
 Hepatocellular Vauolation, Centrilobular F0 Male Stump 2001
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
   The form of the probability function is:
   P[response] = background + (1-background)*[1-EXP(
-beta1*dose^1-beta2*dose^2-beta3*dose^3-beta4*dose^4)]

   The parameter betas are restricted to be positive

   Dependent variable = responder
   Independent variable = dose

 Total number of observations = 5
 Total number of records with missing values = 0
 Total number of parameters in model = 5
 Total number of specified parameters = 0
 Degree of polynomial = 4

 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
                        Beta(1) =   0.00234536
                        Beta(2) =  3.0965e-006
                        Beta(3) =            0
                        Beta(4) =            0

           Asymptotic Correlation Matrix of Parameter Estimates
( *** The model parameter(s)  -Background    -Beta(1)    -Beta(4) have been
estimated at a boundary point, or have been specified by the user, and do not
appear in the correlation matrix )

                Beta(2)      Beta(3)
   Beta(2)            1        -0.96
   Beta(3)        -0.96            1

                          Parameter Estimates
       Variable           Estimate             Std. Err.
     Background                  0                 NA
        Beta(1)                  0                 NA
        Beta(2)        3.93284e-006        5.17885e-006
        Beta(3)        5.04198e-009        9.70032e-009
        Beta(4)                  0                 NA

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)  Deviance  Test DF     P-value
     Full model        -28.1956
```

```
   Fitted model        -30.3155       4.23994      3          0.2367
  Reduced model        -85.1938       113.996      4         <.0001

           AIC:         64.6311


                    Goodness  of  Fit

     Dose     Est._Prob.    Expected    Observed     Size     Chi^2 Res.
  ----------------------------------------------------------------------
    0.0000     0.0000         0.000         0          25       0.000
  100.0000     0.0434         1.085         0          25      -1.045
  250.0000     0.2772         6.929         7          25       0.014
  500.0000     0.8008        20.020        22          25       0.496
  750.0000     0.9870        24.674        24          25      -2.093
 Chi-square =       3.53     DF = 3        P-value = 0.3170


   Benchmark Dose Computation

Specified effect =           0.1
Risk Type        =      Extra risk
Confidence level =           0.95
             BMD =        149.905
            BMDL =         103.51
```

```
 ==================================================================
        Weibull Model $Revision: 2.2 $ $Date: 2000/03/17 22:27:16 $
        Input Data File: I:\NPB\LIVER\F0MHVC_WEIBULL.(D)
        Gnuplot Plotting File:  I:\NPB\LIVER\F0MHVC_WEIBULL.plt
                                          Wed Aug 08 16:14:23 2001
 ==================================================================
 Hepatocellular Vauolation, Centrilobular F0 Male Stump 2001
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
   The form of the probability function is:
   P[response] = background + (1-background)*[1-EXP(-slope*dose^power)]

   Dependent variable = responder
   Independent variable = dose
   Power parameter is restricted as power >=1

   Total number of observations = 5
   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 =    0.0192308
                          Slope = 1.40365e-005
                          Power =      1.84519

           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           -1
     Power           -1            1


                        Parameter Estimates

       Variable           Estimate             Std. Err.
     Background                  0                 NA
          Slope        5.78276e-007        1.36764e-006
          Power             2.39237            0.384308

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)  Deviance  Test DF     P-value
     Full model        -28.1956
   Fitted model         -30.013       3.63497      3          0.3037
  Reduced model        -85.1938       113.996      4         <.0001

           AIC:         64.0261

                     Goodness  of  Fit
```

Male Liver Effects

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0	25	0
100.0000	0.0346	0.865	0	25	-0.9468
250.0000	0.2705	6.763	7	25	0.1067
500.0000	0.8091	20.228	22	25	0.902
750.0000	0.9873	24.683	24	25	-1.222

Chi-square = 3.21 DF = 3 P-value = 0.3598

Benchmark Dose Computation

```
Specified effect =           0.1
Risk Type        =     Extra risk
Confidence level =          0.95
             BMD =       158.083
            BMDL =      110.075
```

```
 ==================================================================
         $Revision: 2.2 $ $Date: 2001/03/14 01:17:00 $
        Input Data File: I:\NPB\LIVER\F1MALHVC_GAMMA.(D)
        Gnuplot Plotting File:  I:\NPB\LIVER\F1MALHVC_GAMMA.plt
                                          Wed Aug 08 16:14:32 2001
 ==================================================================
 Hepatocellular Vacuolation, Centrilobular F1 Male Stump 2001
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
   The form of the probability function is:
   P[response]= background+(1-background)*CumGamma[slope*dose,power],
   where CumGamma(.) is the cummulative Gamma distribution function

   Dependent variable = responder
   Independent variable = dose
   Power parameter is restricted as power >=1

   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 =         0.02
                          Slope =    0.0159108
                          Power =      3.97245

           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

       Variable           Estimate             Std. Err.
     Background                  0                 NA
          Slope           0.0268365           0.0107971
          Power             6.85977             2.69098

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)  Deviance  Test DF     P-value
     Full model        -20.9822
   Fitted model        -22.1122          2.26      2           0.323
  Reduced model        -65.4379       88.9113      3         <.0001

           AIC:         48.2244
```

Male Liver Effects

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0	24	0
100.0000	0.0232	0.581	0	25	-0.7711
250.0000	0.5279	13.197	15	25	0.7222
500.0000	0.9820	23.569	23	24	-0.874

Chi-square = 1.88 DF = 2 P-value = 0.3906

Benchmark Dose Computation

```
Specified effect =           0.1
Risk Type        =     Extra risk
Confidence level =          0.95
             BMD =       141.202
            BMDL =      102.249
```

```
 ======================================================================
        Logistic Model $Revision: 2.1 $ $Date: 2000/02/26 03:38:20 $
        Input Data File: I:\NPB\LIVER\F1MALHVC_LOGISTIC.(D)
        Gnuplot Plotting File:  I:\NPB\LIVER\F1MALHVC_LOGISTIC.plt
                                          Wed Aug 08 16:14:34 2001
 ======================================================================
 Hepatocellular Vacuolation, Centrilobular F1 Male (WIL 2001)
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
   The form of the probability function is:
   P[response] = 1/[1+EXP(-intercept-slope*dose)]

   Dependent variable = responder
   Independent variable = dose
   Slope 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 Parameter Values
                     background =            0   Specified
                      intercept =     -4.27861
                          slope =    0.0146256

           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 )

              intercept        slope
 intercept            1        -0.95
     slope        -0.95            1


                        Parameter Estimates

       Variable           Estimate             Std. Err.
      intercept            -5.04406             1.19911
          slope           0.0203732          0.00502462




                        Analysis of Deviance Table

       Model      Log(likelihood)  Deviance  Test DF     P-value
     Full model        -20.9822
   Fitted model        -23.8565       5.74852      2         0.05646
  Reduced model        -65.4379       88.9113      3         <.0001

           AIC:          51.713
```

Male Liver Effects

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0064	0.154	0	24	-0.3934
100.0000	0.0471	1.178	0	25	-1.112
250.0000	0.5123	12.808	15	25	0.8772
500.0000	0.9942	23.861	23	24	-2.312

Chi-square = 7.50 DF = 2 P-value = 0.0235

Benchmark Dose Computation

```
Specified effect =           0.1
Risk Type        =     Extra risk
Confidence level =          0.95
             BMD =       142.802
            BMDL =      104.163
```

```
 ==================================================================
        Logistic Model $Revision: 2.1 $ $Date: 2000/02/26 03:38:20 $
        Input Data File: I:\NPB\LIVER\F1MALHVC_LOGLOGISTIC.(D)
        Gnuplot Plotting File:  I:\NPB\LIVER\F1MALHVC_LOGLOGISTIC.plt
                                          Wed Aug 08 16:14:36 2001
 ==================================================================
 Hepatocellular Vacuolation, Centrilobular F1 Male WIL 2001
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
   The form of the probability function is:
 P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]

   Dependent variable = responder
   Independent variable = dose
   Slope parameter is restricted as slope >= 1

   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

   User has chosen the log transformed model

                  Default Initial Parameter Values
                     background =            0
                      intercept =     -24.1469
                          slope =      4.40907

           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 )

              intercept        slope
 intercept            1           -1
     slope           -1            1


                          Parameter Estimates

       Variable           Estimate             Std. Err.
     background                  0                 NA
      intercept            -27.3003             7.55058
          slope             4.99462             1.36316

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)  Deviance  Test DF     P-value
     Full model        -20.9822
   Fitted model        -21.5153       1.06613      2          0.5868
  Reduced model        -65.4379       88.9113      3         <.0001

           AIC:         47.0306
```

Male Liver Effects

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0	24	0
100.0000	0.0134	0.335	0	25	-0.5827
250.0000	0.5689	14.222	15	25	0.3141
500.0000	0.9768	23.443	23	24	-0.6001

Chi-square = 0.80 DF = 2 P-value = 0.6709

Benchmark Dose Computation

```
Specified effect =           0.1
Risk Type        =     Extra risk
Confidence level =          0.95
             BMD =       152.325
            BMDL =      112.225
```

```
 ==================================================================
        Probit Model $Revision: 2.1 $ $Date: 2000/02/26 03:38:53 $
        Input Data File: I:\NPB\LIVER\F1MALHVC_PROBIT.(D)
        Gnuplot Plotting File:  I:\NPB\LIVER\F1MALHVC_PROBIT.plt
                                          Wed Aug 08 16:14:39 2001
 ==================================================================
 Hepatocellular Vacuolation, Centrilobular F1 Male WIL 2001
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
   The form of the probability function is:
   P[response] = CumNorm(Intercept+Slope*Dose),
   where CumNorm(.) is the cumulative normal distribution function

   Dependent variable = responder
   Independent variable = dose
   Slope 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   Specified
                       intercept =      -2.6892
                           slope =   0.00906518

           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 )

              intercept        slope
 intercept            1         -0.9
     slope         -0.9            1

                           Parameter Estimates

       Variable           Estimate             Std. Err.
      intercept            -2.57274            0.467065
          slope          0.00990244          0.00181579


                         Analysis of Deviance Table

       Model      Log(likelihood)  Deviance  Test DF     P-value
     Full model        -20.9822
   Fitted model          -24.32       6.67557      2         0.03552
  Reduced model        -65.4379       88.9113      3         <.0001

           AIC:           52.64

                      Goodness  of  Fit

                                                                  Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
  ---------------------------------------------------------------------
```

0.0000	0.0050	0.121	0	24	-0.3488
100.0000	0.0568	1.419	0	25	-1.227
250.0000	0.4613	11.533	15	25	1.391
500.0000	0.9913	23.791	23	24	-1.74

Chi-square = 6.59 DF = 2 P-value = 0.0371

Benchmark Dose Computation

Specified effect = 0.1
Risk Type = Extra risk
Confidence level = 0.95
BMD = 132.961
BMDL = 95.443

```
 ==================================================================
        Probit Model $Revision: 2.1 $ $Date: 2000/02/26 03:38:53 $
        Input Data File: I:\NPB\LIVER\F1MALHVC_LOGPROBIT.(D)
        Gnuplot Plotting File:  I:\NPB\LIVER\F1MALHVC_LOGPROBIT.plt
                                          Wed Aug 08 16:14:37 2001
 ==================================================================
 Hepatocellular Vacuolation, Centrilobular F1 Male WIL 2001
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
   The form of the probability function is:
   P[response] = Background
               + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)),
   where CumNorm(.) is the cumulative normal distribution function

   Dependent variable = responder
   Independent variable = dose
   Slope parameter is restricted as slope >= 1

   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

   User has chosen the log transformed model

                   Default Initial (and Specified) Parameter Values
                      background =            0
                       intercept =     -12.9511
                           slope =      2.37257

           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 )

              intercept        slope
 intercept            1           -1
     slope           -1            1


                          Parameter Estimates
       Variable           Estimate             Std. Err.
     background                  0                 NA
      intercept            -14.4311            3.13649
          slope             2.63923            0.56227

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)  Deviance  Test DF     P-value
     Full model        -20.9822
   Fitted model        -21.4914       1.01842      2           0.601
  Reduced model        -65.4379       88.9113      3         <.0001

           AIC:         46.9829
```

Male Liver Effects

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0	24	0
100.0000	0.0114	0.285	0	25	-0.5367
250.0000	0.5562	13.904	15	25	0.441
500.0000	0.9756	23.415	23	24	-0.549

Chi-square = 0.78 DF = 2 P-value = 0.6757

Benchmark Dose Computation

```
Specified effect =           0.1
Risk Type        =     Extra risk
Confidence level =          0.95
             BMD =       145.817
            BMDL =       110.332
```

```
 ==================================================================
        Multistage Model. $Revision: 2.1 $ $Date: 2000/08/21 03:38:21 $
        Input Data File: I:\NPB\LIVER\F1MALHVC_MULTISTAGE.(D)
        Gnuplot Plotting File:  I:\NPB\LIVER\F1MALHVC_MULTISTAGE.plt
                                          Wed Aug 08 16:14:38 2001
 ==================================================================
 Hepatocellular Vacuolation, Centrilobular F1 Male WIL 2001
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
   The form of the probability function is:
   P[response] = background + (1-background)*[1-EXP(
                  -beta1*dose^1-beta2*dose^2-beta3*dose^3)]

   The parameter betas are restricted to be positive

   Dependent variable = responder
   Independent variable = dose

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

 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
                        Beta(1) =  0.000666827
                        Beta(2) =  1.1676e-005
                        Beta(3) =            0

           Asymptotic Correlation Matrix of Parameter Estimates

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

                Beta(2)      Beta(3)
   Beta(2)            1        -0.94
   Beta(3)        -0.94            1


                              Parameter Estimates

       Variable           Estimate             Std. Err.
     Background                  0                 NA
        Beta(1)                  0                 NA
        Beta(2)         4.5088e-006        1.01213e-005
        Beta(3)        2.35347e-008        2.98289e-008

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

Male Liver Effects

Analysis of Deviance Table

Model	Log(likelihood)	Deviance	Test DF	P-value
Full model	-20.9822			
Fitted model	-23.7578	5.55111	2	0.06231
Reduced model	-65.4379	88.9113	3	<.0001

AIC: 51.5155

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Chi^2 Res.
0.0000	0.0000	0.000	0	24	0.000
100.0000	0.0663	1.658	0	25	-1.071
250.0000	0.4777	11.943	15	25	0.490
500.0000	0.9829	23.590	23	24	-1.463

Chi-square = 4.14 DF = 2 P-value = 0.1264

Benchmark Dose Computation

Specified effect = 0.1
Risk Type = Extra risk
Confidence level = 0.95
BMD = 119.888
BMDL = 76.4583

```
=====================================================================
        Weibull Model $Revision: 2.2 $ $Date: 2000/03/17 22:27:16 $
        Input Data File: I:\NPB\LIVER\F1MALHVC_WEIBULL.(D)
        Gnuplot Plotting File:  I:\NPB\LIVER\F1MALHVC_WEIBULL.plt
                                        Wed Aug 08 16:14:40 2001
 ====================================================================
 Hepatocellular Vacuolation, Centrilobular F1 Male WIL 2001
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

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


   Dependent variable = responder
   Independent variable = dose
   Power parameter is restricted as power >=1

   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 =         0.02
                          Slope = 3.68949e-005
                          Power =      1.80778


           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           -1
     Power           -1            1


                       Parameter Estimates
       Variable           Estimate             Std. Err.
     Background                  0                 NA
          Slope        5.16982e-007        1.37466e-006
          Power             2.55002            0.460749

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)  Deviance  Test DF     P-value
     Full model        -20.9822
   Fitted model        -23.4544       4.94434      2          0.0844
  Reduced model        -65.4379       88.9113      3         <.0001

           AIC:         50.9088
```

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0	24	0
100.0000	0.0630	1.575	0	25	-1.297
250.0000	0.4900	12.250	15	25	1.1
500.0000	0.9806	23.535	23	24	-0.7921

Chi-square = 3.52 DF = 2 P-value = 0.1721

Benchmark Dose Computation

```
Specified effect =           0.1
Risk Type        =     Extra risk
Confidence level =          0.95
             BMD =       120.789
            BMDL =      82.4206
```

```
=====================================================================
         $Revision: 2.2 $ $Date: 2001/03/14 01:17:00 $
        Input Data File: I:\NPB\90-DAY CLINTRIALS\MHPCNVAC_GAMMA.(D)
        Gnuplot Plotting File:  I:\NPB\90-DAY CLINTRIALS\MHPCNVAC_GAMMA.plt
                                          Wed Aug 08 16:18:13 2001
 ====================================================================
 Male Hepatocellular Centriolbular Vacuolation ClinTrial '97
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
   The form of the probability function is:
   P[response]= background+(1-background)*CumGamma[slope*dose,power],
   where CumGamma(.) is the cummulative Gamma distribution function

   Dependent variable = Centriolobular
   Independent variable = Hepatocellular
   Power parameter is restricted as power >=1

   Total number of observations = 5
   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 =      0.03125
                          Slope =   0.00424805
                          Power =      3.37069

           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
       Variable           Estimate             Std. Err.
     Background                  0                 NA
          Slope           0.0079761          0.00671147
          Power             5.49633             3.77971

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)  Deviance  Test DF     P-value
     Full model        -17.6012
   Fitted model        -17.9369       0.67144      3          0.8799
  Reduced model        -27.5194       19.8363      4        0.000538

           AIC:         39.8739
```

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0	15	0
100.0000	0.0005	0.008	0	15	-0.08806
200.0000	0.0121	0.181	0	15	-0.4286
400.0000	0.1536	2.304	3	15	0.498
600.0000	0.4313	6.470	6	15	-0.2451

Chi-square = 0.50 DF = 3 P-value = 0.9190

Benchmark Dose Computation

```
Specified effect =           0.1
Risk Type        =     Extra risk
Confidence level =          0.95
             BMD =       349.325
            BMDL =      227.418
```

```
 ==================================================================
        Logistic Model $Revision: 2.1 $ $Date: 2000/02/26 03:38:20 $
        Input Data File: I:\NPB\90-DAY CLINTRIALS\MHPCNVAC_LOGISTIC.(D)
 Gnuplot Plotting File:  I:\NPB\90-DAY CLINTRIALS\MHPCNVAC_LOGISTIC.plt
                                          Wed Aug 08 16:18:15 2001
 ==================================================================
 Male Hepatocellular Centriolbular Vacuolation ClinTrial '97
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
   The form of the probability function is:
   P[response] = 1/[1+EXP(-intercept-slope*dose)]

   Dependent variable = Centriolobular
   Independent variable = Hepatocellular
   Slope parameter is not restricted

   Total number of observations = 5
   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 Parameter Values
                     background =            0   Specified
                      intercept =     -3.89381
                          slope =   0.00578048

           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 )

              intercept        slope
 intercept            1        -0.96
     slope        -0.96            1


                              Parameter Estimates

       Variable           Estimate             Std. Err.
      intercept            -5.54196             1.51847
          slope          0.00886502          0.00289352




                        Analysis of Deviance Table

       Model      Log(likelihood)  Deviance  Test DF     P-value
     Full model        -17.6012
   Fitted model        -18.5977       1.99291      3          0.5739
  Reduced model        -27.5194       19.8363      4        0.000538

           AIC:         41.1953

                     Goodness  of  Fit
```

90 Day Clinical Trial Liver Effects

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0039	0.059	0	15	-0.2425
100.0000	0.0094	0.141	0	15	-0.3777
200.0000	0.0226	0.338	0	15	-0.5883
400.0000	0.1196	1.794	3	15	0.9592
600.0000	0.4445	6.667	6	15	-0.3468

Chi-square = 1.59 DF = 3 P-value = 0.6621

Benchmark Dose Computation

```
Specified effect =           0.1
Risk Type        =     Extra risk
Confidence level =          0.95
             BMD =       381.632
            BMDL =       287.14
```

```
 ==================================================================
        Logistic Model $Revision: 2.1 $ $Date: 2000/02/26 03:38:20 $
        Input Data File: I:\NPB\90-DAY CLINTRIALS\MHPCNVAC_LOGLOGISTIC.(D)
 Gnuplot Plotting File:  I:\NPB\90-DAY CLINTRIALS\MHPCNVAC_LOGLOGISTIC.plt
                                          Wed Aug 08 16:18:16 2001
 ==================================================================
 Male Hepatocellular Centriolbular Vacuolation ClinTrial '97
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
   The form of the probability function is:
 P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]

   Dependent variable = Centriolobular
   Independent variable = Hepatocellular
   Slope parameter is not restricted

   Total number of observations = 5
   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

   User has chosen the log transformed model

                  Default Initial Parameter Values
                     background =            0
                      intercept =     -12.1763
                          slope =      1.79642

            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 )

               intercept        slope
 intercept             1           -1
     slope            -1            1


                          Parameter Estimates

       Variable           Estimate             Std. Err.
     background                  0                 NA
      intercept            -22.9106            9.17041
          slope             3.53788            1.47418

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)  Deviance  Test DF     P-value
     Full model        -17.6012
   Fitted model        -18.0014      0.800332      3          0.8494
  Reduced model        -27.5194       19.8363      4        0.000538

           AIC:         40.0028
```

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0	15	0
100.0000	0.0013	0.020	0	15	-0.1416
200.0000	0.0153	0.229	0	15	-0.4824
400.0000	0.1527	2.291	3	15	0.5093
600.0000	0.4307	6.460	6	15	-0.24

Chi-square = 0.57 DF = 3 P-value = 0.9033

Benchmark Dose Computation

```
Specified effect =           0.1
Risk Type        =     Extra risk
Confidence level =          0.95
             BMD =       348.889
            BMDL =      223.951
```

```
 ==================================================================
        Probit Model $Revision: 2.1 $ $Date: 2000/02/26 03:38:53 $
        Input Data File: I:\NPB\90-DAY CLINTRIALS\MHPCNVAC_PROBIT.(D)
   Gnuplot Plotting File:  I:\NPB\90-DAY CLINTRIALS\MHPCNVAC_PROBIT.plt
                                          Wed Aug 08 16:18:19 2001
 ==================================================================
 Male Hepatocellular Centriolbular Vacuolation ClinTrial '97
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
   The form of the probability function is:
   P[response] = CumNorm(Intercept+Slope*Dose),
   where CumNorm(.) is the cumulative normal distribution function

   Dependent variable = Centriolobular
   Independent variable = Hepatocellular
   Slope parameter is not restricted

   Total number of observations = 5
   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   Specified
                      intercept =     -2.57869
                          slope =   0.00384964

           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 )

              intercept        slope
 intercept            1        -0.95
     slope        -0.95            1


                          Parameter Estimates

       Variable           Estimate             Std. Err.
      intercept            -3.09746             0.79085
          slope          0.00492788          0.00158225




                        Analysis of Deviance Table

       Model      Log(likelihood)  Deviance  Test DF     P-value
     Full model        -17.6012
   Fitted model        -18.2925       1.38259      3          0.7096
  Reduced model        -27.5194       19.8363      4        0.000538

           AIC:          40.585

                     Goodness  of  Fit
```

90 Day Clinical Trial Liver Effects

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0010	0.015	0	15	-0.1211
100.0000	0.0046	0.069	0	15	-0.2632
200.0000	0.0173	0.260	0	15	-0.5146
400.0000	0.1300	1.950	3	15	0.8059
600.0000	0.4440	6.661	6	15	-0.3433

Chi-square = 1.12 DF = 3 P-value = 0.7732

Benchmark Dose Computation

```
Specified effect =           0.1
Risk Type        =     Extra risk
Confidence level =          0.95
             BMD =        369.51
            BMDL =      273.389
```

```
=====================================================================
        Probit Model $Revision: 2.1 $ $Date: 2000/02/26 03:38:53 $
        Input Data File: I:\NPB\90-DAY CLINTRIALS\MHPCNVAC_LOGPROBIT.(D)
Gnuplot Plotting File:  I:\NPB\90-DAY CLINTRIALS\MHPCNVAC_LOGPROBIT.plt
                                          Wed Aug 08 16:18:17 2001
 ====================================================================
 Male Hepatocellular Centriolbular Vacuolation ClinTrial '97
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
   The form of the probability function is:
   P[response] = Background
               + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)),
   where CumNorm(.) is the cumulative normal distribution function

   Dependent variable = Centriolobular
   Independent variable = Hepatocellular
   Slope parameter is restricted as slope >= 1

   Total number of observations = 5
   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

   User has chosen the log transformed model

                   Default Initial (and Specified) Parameter Values
                      background =            0
                       intercept =     -6.78598
                           slope =            1

           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 )

              intercept        slope
 intercept            1           -1
     slope           -1            1


                          Parameter Estimates
       Variable           Estimate             Std. Err.
     background                  0                 NA
      intercept            -12.8607            5.17083
          slope            1.98179           0.836389

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)  Deviance  Test DF     P-value
     Full model        -17.6012
   Fitted model        -17.8389      0.475476      3          0.9242
  Reduced model        -27.5194       19.8363      4        0.000538

           AIC:         39.6779
```

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0	15	0
100.0000	0.0001	0.001	0	15	-0.03758
200.0000	0.0091	0.137	0	15	-0.3717
400.0000	0.1619	2.428	3	15	0.401
600.0000	0.4273	6.409	6	15	-0.2136

Chi-square = 0.35 DF = 3 P-value = 0.9512

Benchmark Dose Computation

```
Specified effect =           0.1
Risk Type        =     Extra risk
Confidence level =          0.95
             BMD =       344.726
            BMDL =       225.49
```

```
 ======================================================================
        Multistage Model. $Revision: 2.1 $ $Date: 2000/08/21 03:38:21 $
        Input Data File: I:\NPB\90-DAY CLINTRIALS\MHPCNVAC_MULTISTAGE.(D)
  Gnuplot Plotting File:  I:\NPB\90-DAY CLINTRIALS\MHPCNVAC_MULTISTAGE.plt
                                          Wed Aug 08 16:18:18 2001
 ======================================================================
 Male Hepatocellular Centriolbular Vacuolation ClinTrial '97
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
   The form of the probability function is:
   P[response] = background + (1-background)*[1-EXP(
                  -beta1*dose^1-beta2*dose^2-beta3*dose^3-beta4*dose^4)]

   The parameter betas are restricted to be positive

   Dependent variable = Centriolobular
   Independent variable = Hepatocellular

 Total number of observations = 5
 Total number of records with missing values = 0
 Total number of parameters in model = 5
 Total number of specified parameters = 0
 Degree of polynomial = 4

 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
                        Beta(1) =            0
                        Beta(2) = 1.47876e-006
                        Beta(3) =            0
                        Beta(4) =            0

           Asymptotic Correlation Matrix of Parameter Estimates

( *** The model parameter(s)  -Background    -Beta(1)    -Beta(2) -Beta(4)
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix )

                Beta(3)
   Beta(3)            1




                           Parameter Estimates

       Variable           Estimate             Std. Err.
     Background                  0                 NA
        Beta(1)                  0                 NA
        Beta(2)                  0                 NA
        Beta(3)        2.55015e-009        1.49016e-009
        Beta(4)                  0                 NA

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)	Deviance	Test DF	P-value
Full model	-17.6012			
Fitted model	-18.0947	0.986987	4	0.9118
Reduced model	-27.5194	19.8363	4	0.000538

AIC: 38.1894

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Chi^2 Res.
0.0000	0.0000	0.000	0	15	0.000
100.0000	0.0025	0.038	0	15	-1.003
200.0000	0.0202	0.303	0	15	-1.021
400.0000	0.1506	2.259	3	15	0.386
600.0000	0.4235	6.353	6	15	-0.096

Chi-square = 0.67 DF = 4 P-value = 0.9552

Benchmark Dose Computation

Specified effect = 0.1
Risk Type = Extra risk
Confidence level = 0.95
BMD = 345.704
BMDL = 226.133

```
 ==================================================================
        Weibull Model $Revision: 2.2 $ $Date: 2000/03/17 22:27:16 $
        Input Data File: I:\NPB\90-DAY CLINTRIALS\MHPCNVAC_WEIBULL.(D)
  Gnuplot Plotting File:  I:\NPB\90-DAY CLINTRIALS\MHPCNVAC_WEIBULL.plt
                                          Wed Aug 08 16:18:20 2001
 ==================================================================
 Male Hepatocellular Centriolbular Vacuolation ClinTrial '97
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
   The form of the probability function is:
   P[response] = background + (1-background)*[1-EXP(-slope*dose^power)]

   Dependent variable = Centriolobular
   Independent variable = Hepatocellular
   Power parameter is restricted as power >=1

   Total number of observations = 5
   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 =      0.03125
                          Slope = 1.79887e-007
                          Power =      2.31622

           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.$          1.$
     Power          1.$          1.$


                          Parameter Estimates

       Variable           Estimate             Std. Err.
     Background                  0                 NA
          Slope        1.17241e-009             1.#QNAN
          Power             3.12423             1.#QNAN

A - 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)  Deviance  Test DF     P-value
     Full model        -17.6012
   Fitted model        -18.0899      0.977308      3          0.8067
  Reduced model        -27.5194       19.8363      4        0.000538

           AIC:         40.1797
```

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0	15	0
100.0000	0.0021	0.031	0	15	-0.1766
200.0000	0.0180	0.269	0	15	-0.5236
400.0000	0.1461	2.192	3	15	0.5909
600.0000	0.4291	6.437	6	15	-0.228

Chi-square = 0.71 DF = 3 P-value = 0.8716

Benchmark Dose Computation

```
Specified effect =           0.1
Risk Type        =     Extra risk
Confidence level =          0.95
             BMD =       351.381
            BMDL =      221.776
```

```
 ====================================================================
        Hill Model. $Revision: 2.1 $ $Date: 2000/10/11 21:21:23 $
  Input Data File: I:\CYNTHIA\NPB\SPERMATOGENIC EFFECTS\F0MALES_HILL.(D)
Gnuplot Plotting File: I:\CYNTHIA\NPB\SPERMATOGENIC EFFECTS\F0MALES_HILL.plt
                                          Thu Aug 09 10:34:25 2001
 ====================================================================
 F0 Males Sperm Motility (WIL 2001)
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
   The form of the response function is:
   Y[dose] = intercept + v*dose^n/(k^n + dose^n)

   Dependent variable = MEAN
   Independent variable = Dose
   Power parameter restricted to be greater than 1
   The variance is to be modeled as Var(i) = alpha * mean(i) ^ rho

   Total number of dose groups = 5
   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 Parameter Values
                          alpha =            1
                            rho =     -3.39385
                      intercept =         86.8
                              v =          -37
                              n =      3.33298
                              k =       495.13

           Asymptotic Correlation Matrix of Parameter Estimates

           alpha        rho     intercept        v            n        k
  alpha      1        -0.99       -0.013       0.038        0.023    -0.038
   rho    -0.99          1        0.026      -0.033       -0.023     0.036
intercept -0.013       0.026        1        -0.36        -0.49       0.31
   v       0.038      -0.033      -0.36         1           0.91      -0.99
   n       0.023      -0.023      -0.49        0.91         1        -0.92
   k      -0.038       0.036       0.31       -0.99        -0.92        1


                      Parameter Estimates
       Variable           Estimate             Std. Err.
          alpha              149979              127854
            rho            -1.57152              0.2041
      intercept             88.1312             1.70741
              v             -72.272             52.5882
              n             2.84021             1.30088
              k             679.844             350.672


                   Table of Data and Estimated Values of Interest

Dose       N    Obs Mean    Obs Std Dev   Est Mean   Est Std Dev   Chi^2Res.
-----     ---   --------    -----------   --------   -----------  ----------
    0     25     86.8         11.9         88.1         11.5         -0.116
  100     25     88.8         7.22         87.8         11.5         0.0852
  250     25     83.4         10.4         84.1         11.9        -0.0628
```

500	25	68	17.4	66.8	14.3	0.0819
750	25	49.8	23.2	47	18.8	0.15

```
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)} = alpha*(Mu(i))^rho

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

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-399.452808	6	810.905616
A2	-379.868193	10	779.736387
A3	-382.809016	7	779.618031
fitted	-387.393129	6	786.786258
R	-442.883722	2	889.767444

Explanation of Tests

```
Test 1:  Does response 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)
```

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	126.031	8	<.0001
Test 2	39.1692	4	<.0001
Test 3	5.88164	3	0.1175
Test 4	9.16823	1	0.002463

The p-value for Test 1 is less than .05. There appears to be a 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 .05. A non-homogeneous variance model appears to be appropriate

The p-value for Test 3 is greater than .05. The modeled variance appears to be appropriate here

```
The p-value for Test 4 is less than .05.  You may want to try a different
model

      Benchmark Dose Computation

Specified effect =           1.1
Risk Type        =     Estimated standard deviations from the control mean
Confidence level =          0.95
             BMD =        393.44
            BMDL =       317.561

Warning:  optimum may not have been found.  Bad completion code in
Optimization routine.

BMDL computation failed for one or more point on the BMDL curve.
          The BMDL curve will not be plotted
```

```
=====================================================================
        Polynomial Model. $Revision: 2.1 $ $Date: 2000/10/11 17:51:39 $
        Input Data File: \NPB\SPERMATOGENIC EFFECTS\F0MALES_POLY.(D)
        Gnuplot Plotting File:  \NPB\SPERMATOGENIC EFFECTS\F0MALES_POLY.plt
                                          Thu Aug 09 10:34:29 2001
 ====================================================================
 F0 Males Sperm Motility (WIL 2001)
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
   The form of the response function is:
   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

   Dependent variable = MEAN
   Independent variable = Dose
   Signs of the polynomial coefficients are not restricted
   The variance is to be modeled as Var(i) = alpha*mean(i)^rho

   Total number of dose groups = 5
   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 Parameter Values
                          alpha =      228.621
                            rho =            0
                         beta_0 =      88.3096
                         beta_1 =  -0.00755941
                         beta_2 = -5.94946e-005


                          Parameter Estimates

       Variable           Estimate             Std. Err.
          alpha        1.31721e+007         2.2218e+007
            rho            -2.61657             0.39407
         beta_0              88.164             1.82653
         beta_1         -0.00266543           0.0156731
         beta_2       -6.94308e-005        2.33185e-005


            Asymptotic Correlation Matrix of Parameter Estimates

                  alpha          rho       beta_0       beta_1       beta_2
     alpha            1           -1       -0.038        0.078       -0.097
       rho           -1            1        0.039       -0.079        0.098
    beta_0       -0.038        0.039            1        -0.71         0.55
    beta_1        0.078       -0.079        -0.71            1        -0.94
    beta_2       -0.097        0.098         0.55        -0.94            1

                  Table of Data and Estimated Values of Interest

Dose       N    Obs Mean    Obs Std Dev   Est Mean   Est Std Dev   Chi^2Res.
-----     ---   --------    -----------   --------   -----------  ----------
    0    25       86.8         11.9         88.2         10.3           -3.3
  100    25       88.8         7.22         87.2         10.5            3.8
  250    25       83.4         10.4         83.2         11.2          0.541
  500    25         68         17.4         69.5         14.1          -2.61
  750    25       49.8         23.2         47.1         23.5           2.86
```

```
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)} = alpha*(Mu(i))^rho

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

                     Likelihoods of Interest
           Model     Log(likelihood)   DF        AIC
            A1        -399.452808       6     810.905616
            A2        -379.868193      10     779.736387
            A3        -382.809015       7     779.618030
          fitted      -385.332012       5     780.664024
             R        -442.383722       2     888.767444


                  Explanation of Tests
 Test 1:  Does response 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)

                    Tests of Interest
   Test    -2*log(Likelihood Ratio)  Test df        p-value
   Test 1             125.031          8          <.0001
   Test 2             39.1692          4          <.0001
   Test 3             5.88164          3          0.1175
   Test 4             5.04599          2         0.08022

The p-value for Test 1 is less than .05.  There appears
to be a
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 .05.  A
non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .05.  The
modeled variance appears  to be appropriate here

The p-value for Test 4 is greater than .05.  The model
chosen seems to adequately describe the data

 Benchmark Dose Computation
Specified effect =           1.1
Risk Type        =     Estimated standard deviations from the control mean
Confidence level =          0.95
```

Spermatogenic Effects

```
             BMD =        386.15
            BMDL =       283.381

BMDL computation failed for one or more point on the BMDL curve.

                  The BMDL curve will not be plotted
```

```
 ====================================================================
        Power Model. $Revision: 2.1 $ $Date: 2000/10/11 20:57:36 $
        Input Data File: \NPB\SPERMATOGENIC EFFECTS\F0MALES_POWER.(D)
        Gnuplot Plotting File:  \NPB\SPERMATOGENIC EFFECTS\F0MALES_POWER.plt
                                          Thu Aug 09 10:34:46 2001
 ====================================================================
 F0 Males Sperm Motility (WIL 2001)
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:
   Y[dose] = control + slope * dose^power

   Dependent variable = MEAN
   Independent variable = Dose
   The power is restricted to be greater than or equal to 1
   The variance is to be modeled as Var(i) = alpha*mean(i)^rho

   Total number of dose groups = 5
   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 Parameter Values
                          alpha =      228.621
                            rho =            0
                        control =         49.8
                          slope =      347.485
                          power =    -0.457288


            Asymptotic Correlation Matrix of Parameter Estimates

                  alpha          rho      control        slope        power
     alpha            1           -1         -0.1        -0.18        -0.21
       rho           -1            1         0.11         0.18         0.21
   control         -0.1         0.11            1        -0.52         -0.5
     slope        -0.18         0.18        -0.52            1            1
     power        -0.21         0.21         -0.5            1            1


                          Parameter Estimates
       Variable           Estimate             Std. Err.
          alpha        9.20798e+007        3.05994e+008
            rho            -3.06488            0.764179
        control             88.4203             1.48112
          slope        -0.000372103         0.000711517
          power             1.74656            0.293232


     Table of Data and Estimated Values of Interest

Dose       N    Obs Mean    Obs Std Dev   Est Mean   Est Std Dev   Chi^2Res.
-----     ---   --------    -----------   --------   -----------  ----------
    0     25     86.8         11.9         88.4         9.98         -0.162
  100     25     88.8         7.22         87.3         10.2          0.151
  250     25     83.4         10.4         82.7         11.1          0.065
```

500	25	68	17.4	69.2	14.5	-0.08
750	25	49.8	23.2	49.3	24.4	0.0195

```
 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)} = alpha*(Mu(i))^rho

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

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-398.952808	6	809.905616
A2	-379.868193	10	779.736387
A3	-382.809015	7	779.618030
fitted	-384.915826	5	779.831652
R	-442.383722	2	888.767444

```
                   Explanation of Tests
 Test 1:  Does response 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)
```

Tests of Interest

Test	-2*log(Likelihood Ratio)	d.f	p-value
Test 1	125.031	8	<.00001
Test 2	38.1692	4	<.00001
Test 3	5.88164	3	0.1175
Test 4	4.21362	2	0.1216

The p-value for Test 1 is less than .05. There appears to be a 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 .05. A non-homogeneous variance model appears to be appropriate

The p-value for Test 3 is greater than .05. The modeled variance appears to be appropriate here

The p-value for Test 4 is greater than .05. The model chosen seems to adequately describe the data

```
 Benchmark Dose Computation
Specified effect =           1.1
Risk Type        =     Estimated standard deviations from the control mean
```

Spermatogenic Effects

```
Confidence level =          0.95
             BMD =       362.428
            BMDL =       281.603
```

```
 ====================================================================
        Hill Model. $Revision: 2.1 $ $Date: 2000/10/11 21:21:23 $
        Input Data File: \NPB\SPERMATOGENIC EFFECTS\F1MALE_HILL.(D)
        Gnuplot Plotting File:  \NPB\SPERMATOGENIC EFFECTS\F1MALE_HILL.plt
                                          Wed Aug 08 16:06:15 2001
 ====================================================================
 F1 Males - Sperm Motility (WIL 2001)
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
   The form of the response function is:
   Y[dose] = intercept + v*dose^n/(k^n + dose^n)

   Dependent variable = MEAN
   Independent variable = Dose
   Power parameter restricted to be greater than 1
   The variance is to be modeled as Var(i) = alpha * mean(i) ^ rho

   Total number of dose groups = 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 Parameter Values
                          alpha =            1
                            rho =     -13.1049
                      intercept =         88.9
                              v =        -14.5
                              n =      2.42322
                              k =      325.721


            Asymptotic Correlation Matrix of Parameter Estimates

          alpha      rho    intercept            v            n           k
 alpha     1        -1        0.086        -0.11     2.1e-015     1.1e-016
 rho      -1         1       -0.084         0.11    -2.4e-015    -1.3e-016
intercept 0.086   -0.084       1          -0.86     7.3e-015       4e-016
   v     -0.11     0.11        -0.86         1      -1.2e-014    -6.3e-016
   n    2.1e-015 -2.4e-015    7.3e-015    -1.2e-014    1            1.1
   k    1.1e-016 -1.3e-016   4e-016       -6.3e-016   1.1            1
```

Spermatogenic Effects

Parameter Estimates

Variable	Estimate	Std. Err.
alpha	11896.2	28236.1
rho	-1.11556	0.539283
intercept	89.2723	1.81192
v	-7.45277	2.11724
n	3.78326	2.10141e+012
k	5e-006	5.44767e+007

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Obs Std Dev	Est Mean	Est Std Dev	Chi^2Res.
0	24	88.9	4.52	89.3	8.91	-0.0418
100	25	86.4	4.96	81.8	9.35	0.49
250	25	84.8	6.02	81.8	9.35	0.319
500	24	74.4	14.1	81.8	9.35	-0.794

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)} = alpha*(Mu(i))^rho

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

Degrees of freedom for Test A3 vs fitted <= 0

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-254.359931	5	518.719861
A2	-231.514646	8	479.029291
A3	-231.606238	6	475.212475
fitted	-267.065047	6	546.130094
R	-273.186516	2	550.373032

Explanation of Tests

Test 1: Does response 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)

Tests of Interest

Spermatogenic Effects

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	83.3437	6	<.0001
Test 2	45.6906	3	<.0001
Test 3	0.183184	2	0.9125
Test 4	70.9176	0	NA

The p-value for Test 1 is less than .05. There appears to be a 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 .05. A non-homogeneous variance model appears to be appropriate

The p-value for Test 3 is greater than .05. The modeled variance appears to be appropriate here

NA - Degrees of freedom for Test 4 are less than or equal to 0. The Chi-Square test for fit is not valid

BMD computation failed
BMR value is not in the range of the mean function

```
 ====================================================================
        Polynomial Model. $Revision: 2.1 $ $Date: 2000/10/11 17:51:39 $
        Input Data File: \NPB\SPERMATOGENIC EFFECTS\F1MALE_POLY.(D)
        Gnuplot Plotting File:  \NPB\SPERMATOGENIC EFFECTS\F1MALE_POLY.plt
                                          Wed Aug 08 16:06:16 2001
 ====================================================================
 F1 Males - Sperm Motility (WIL 2001)
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
   The form of the response function is:
   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

   Dependent variable = MEAN
   Independent variable = Dose
   Signs of the polynomial coefficients are not restricted
   The variance is to be modeled as Var(i) = alpha*mean(i)^rho

   Total number of dose groups = 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 Parameter Values
                          alpha =      68.9024
                            rho =            0
                         beta_0 =      88.4311
                         beta_1 =  -0.00622244
                         beta_2 = -4.32108e-005


                          Parameter Estimates

        Variable           Estimate            Std. Err.
           alpha        7.39579e+006        8.57251e+006
             rho            -2.67317            0.267958
          beta_0             88.7535             1.28534
          beta_1         -0.00331024           0.0143335
          beta_2       -5.82925e-005        2.79844e-005
```

Asymptotic Correlation Matrix of Parameter Estimates

	alpha	rho	beta_0	beta_1	beta_2
alpha	1	-0.99	-0.009	0.0013	-0.004
rho	-0.99	1	0.013	0.003	-0.0064
beta_0	-0.009	0.013	1	-0.71	0.56
beta_1	0.0013	0.003	-0.71	1	-0.95
beta_2	-0.004	-0.0064	0.56	-0.95	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Obs Std Dev	Est Mean	Est Std Dev	Chi^2Res.
0	24	88.9	4.52	88.8	6.77	0.519
100	25	86.4	4.96	87.8	6.86	-5.24
250	25	84.8	6.02	84.3	7.25	1.78
500	24	74.4	14.1	72.5	8.87	5.07

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)} = alpha*(Mu(i))^rho

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

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-254.359931	5	518.719861
A2	-231.514646	8	479.029291
A3	-231.606238	6	475.212475
fitted	-245.697626	5	501.395251
R	-273.186516	2	550.373032

Spermatogenic Effects

Explanation of Tests

```
 Test 1:  Does response 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)
```

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	83.3437	6	<.0001
Test 2	45.6906	3	<.0001
Test 3	0.183184	2	0.9125
Test 4	28.1828	1	<.0001

```
The p-value for Test 1 is less than .05.  There appears
to be a
difference between response and/or variances among the
dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .05.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .05.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is less than .05.  You may want to try a different
model

 Benchmark Dose Computation
Specified effect =           1.1
Risk Type        =     Estimated standard deviations from the control mean
Confidence level =          0.95
             BMD =       330.153
            BMDL =         130.7

 BMDL computation failed for one or more point on the BMDL curve.

                  The BMDL curve will not be plotted
```

```
 ==================================================================
        Power Model. $Revision: 2.1 $ $Date: 2000/10/11 20:57:36 $
        Input Data File: \NPB\SPERMATOGENIC EFFECTS\F1MALE_POWER.(D)
        Gnuplot Plotting File:  \NPB\SPERMATOGENIC EFFECTS\F1MALE_POWER.plt
                                          Wed Aug 08 16:06:19 2001
 ==================================================================
 F1 Males - Sperm Motility (WIL 2001)
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
   The form of the response function is:
   Y[dose] = control + slope * dose^power


   Dependent variable = MEAN
   Independent variable = Dose
   The power is restricted to be greater than or equal to 1
   The variance is to be modeled as Var(i) = alpha*mean(i)^rho

   Total number of dose groups = 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 Parameter Values
                          alpha =      68.9024
                            rho =            0
                        control =         88.9
                          slope =     -38.2716
                          power =    -0.156174

           Asymptotic Correlation Matrix of Parameter Estimates
                  alpha          rho      control        slope        power
     alpha            1           -1       -0.035        -0.32        -0.36
       rho           -1            1        0.038         0.32         0.36
   control       -0.035        0.038            1        -0.68        -0.66
     slope        -0.32         0.32        -0.68            1            1
     power        -0.36         0.36        -0.66            1            1
```

Spermatogenic Effects

Parameter Estimates

Variable	Estimate	Std. Err.
alpha	3.56746e+027	6.14102e+028
rho	-13.4895	3.8698
control	88.2997	0.888272
slope	-0.000380723	0.0013782
power	1.68485	0.589301

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Obs Std Dev	Est Mean	Est Std Dev	Chi^2Res.
0	24	88.9	4.52	88.3	4.48	0.134
100	25	86.4	4.96	87.4	4.8	-0.21
250	25	84.8	6.02	84.1	6.21	0.109
500	24	74.4	14.1	74.9	13.6	-0.0347

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)} = alpha*(Mu(i))^rho

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

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-254.359931	5	518.719861
A2	-231.514646	8	479.029291
A3	-231.606238	6	475.212475
fitted	-232.519320	5	475.038640
R	-273.186516	2	550.373032

Spermatogenic Effects

Explanation of Tests

Test 1: Does response 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)

Tests of Interest

Test	-2*log(Likelihood Ratio)	d.f	p-value
Test 1	83.3437	6	<.00001
Test 2	45.6906	3	<.00001
Test 3	0.183184	2	0.9125
Test 4	1.82616	1	0.1766

The p-value for Test 1 is less than .05. There appears to be a 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 .05. A non-homogeneous variance model appears to be appropriate

The p-value for Test 3 is greater than .05. The modeled variance appears to be appropriate here

The p-value for Test 4 is greater than .05. The model chosen seems to adequately describe the data

Benchmark Dose Computation

Specified effect = 1.1
Risk Type = Estimated standard deviations from the control mean
Confidence level = 0.95
BMD = 275.764
BMDL = 168.767