Appendix 8: BMD Analysis of Pup Mortality Data

Dimethoate: Issues Related to the Hazard and Dose Response Assessment

Analysis of variance (ANOVA) is typically used to identify statistically significant difference between various dose groups within a toxicity study. Although the group means and standard deviations can be used to characterize the response of the experimental dose groups, ANOVA does not characterize the entire dose-response relationship. Benchmark dose (BMD) analysis attempts to model the dose-response relationship with a dose-response curve that can be described by a mathematical function. The dose-response curve which is estimated based on the experimental observations interpolates the magnitude of the response for any dose within the experimental dosing range. Various mathematical models can be used to model this dose-response curve. Once a BMD model has been selected, the dose resulting in a specified response (i.e. benchmark response, BMR) is determined. For quantal data, the BMR is expressed as additional or extra risk above the control group response (i.e., background). The dose resulting in the BMR is termed the "benchmark dose". Generally, the dose resulting in a BMR of X% risk is referred to as the BMD_X. The corresponding lower 95% confidence limit on the BMD_X is the BMDL_X.

A BMD analysis of the pup mortality data from the dimethoate developmental neurotoxicity (DNT) study was performed using EPA's Benchmark Dose Software (BMDS). The BMDS software, user's manual, and technical guidance can be obtained at www.epa.gov/ncea/bmds.htm. For the dimethoate DNT study, pup mortality was modeled using the available BMDS nested models: NLogistic, NCTR, and RaiVR. These three models are termed "nested" because one can (via model options) model intralitter correlation (i.e. the tendency of pups within a litter to respond similarly) and/or include litter-specific covariates (i.e. explanatory variables other than dose that may help predict pup response) such as litter size or number of implantation sites. For all nested model runs presented, intralitter correlation was specified (litter-effect was taken into account). The *Benchmark Dose Technical Guidance Document* (http://oaspub.epa.gov/eims/eimscomm.getfile?p_download_id=4727) suggests that covariates affected by dose not be used as a litter-specific covariate. Since an evaluation of pup mortality presupposes litter size is affected by dose, it was not included as a litter-specific covariate.

Separate BMD analyses were performed for the two post-natal day (PND) periods: PND 1-4 and PND 5-11. A culling event on PND 4 artificially reduced the sizes of the litters, making the PND 1-4 and PND 5-11 study periods incomparable. For the initial BMD model runs to select an appropriate model, the BMR was set at an "extra risk" of 10%, as oppose to an "additional risk" 10% (see definitions in *Help Manual for Benchmark Dose Software Version 1.3* at www.epa.gov/ncea/bnchmrk/pdfhelp1-3.exe for details).

Table A8.1 contains summary information for the various model runs for the PND 1-4 and PND 5-11 study periods. For both study periods, all three models produce very similar BMD values. All of the BMDs from PND 1-4 were lower than those from PND 5-11. In fact, all BMD_{10} estimates for PND 5-11 were slightly outside the experimental dose range. As with any model fitted to experimental observations, estimates extrapolated outside the range of data are less reliable than those that are interpolated.

Consistent with the *Benchmark Dose Technical Guidance Document* (http://oaspub.epa.gov/eims/eimscomm.getfile?p_download_id=4727), the minimal Akaike Information Criterion (AIC) was used to identify the most appropriate model among the three nested models. The AICs for the RaiVR model was not reported in the text output files. The AIC for all of the models was calculated as

$$AIC = -2L + 2p$$

where is L is the log-likelihood of the fitted model and p is the number of parameters whose estimates do not fall on a bound. As noted in the technical guidance, the AIC is only an approximate criterion for selecting a model. For both study periods, the differences in the AICs of the models were negligible. Since the Nlogistic model produced the smallest BMD values, its estimates were used for further comparison with brain ChEI BMD values. The nested models were also run based on a BMR of 5% (extra risk). The BMD_5 values are provided in Table A8.2 for comparison. The text and graphical output[1] from the BMDS models are included at the end of this appendix. The output files are identified by the study period and model name.

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[1] The confidence intervals for the proportion of pups affected are not correct (i.e. too short) for the RaiVR and NCTR models. This problem has been submitted to the BMDS development team and will be fixed in the next version of BMDS.

PND 1-4 : NLogisitic

```
 ====================================================================
        NLogistic Model. $Revision: 2.8 $ $Date: 2003/05/06 16:33:47 $
        Input Data File: C:\HOME\BMD_WORKGROUP\DIMETH_DNT_PRE.(d)
                                          Mon Aug 30 13:58:17 2004
 ====================================================================

 BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

 The probability function is:


 Prob. = alpha + theta1*Rij + [1 - alpha - theta1*Rij]/

                       [1+exp(-beta-theta2*Rij-rho*log(Dose))],

          where Rij is the litter specific covariate.

 Restrict Power rho >= 1.



 Total number of observations = 94
 Total number of records with missing values = 0
 Total number of parameters in model = 9
 Total number of specified parameters = 2


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

 User specifies the following parameters:
          theta1 =          0
          theta2 =          0
```

```
                  Default Initial Parameter Values
                          alpha =    0.0392155
                           beta =     -8.55764
                         theta1 =            0   Specified
                         theta2 =            0   Specified
                            rho =       6.6578
                           phi1 =    0.0400623
                           phi2 =     0.124621
                           phi3 =     0.342834
                           phi4 =     0.633774
```

```
                                 Parameter Estimates

                 Variable           Estimate             Std. Err.
                    alpha           0.0259287           0.00816164
                     beta            -2.18984             0.353674
                      rho                   1              Bounded
                     phi1           0.0242811             0.215005
                     phi2            0.112448             0.258862
                     phi3            0.425418                    0
                     phi4            0.643375                    0


                               Analysis of Deviance Table

                 Model      Log(likelihood)  Deviance  Test DF     P-value
               Full model        -156.049
             Fitted model        -237.909      163.72      88      1.7462425e-006
            Reduced model        -412.865     513.631      93          <.0001

                     AIC:          487.818


                                      Litter Data


                     Lit.-Spec.                Litter                          chi-squared
              Dose      Cov.      Est._Prob.    Size     Expected   Observed   Residual
            -------------------------------------------------------------------------
              0.0000   10.0000       0.026       10        0.259          0      -0.4674
              0.0000   11.0000       0.026       11        0.285          0      -0.4854
              0.0000   12.0000       0.026       12        0.311          0      -0.5021
              0.0000   12.0000       0.026       12        0.311          0      -0.5021
              0.0000   13.0000       0.026       13        0.337          0      -0.5177
              0.0000   13.0000       0.026       13        0.337          0      -0.5177
              0.0000   13.0000       0.026       13        0.337          1       1.0181
```

```
              0.0000   14.0000       0.026       14        0.363          3       3.8662
              0.0000   14.0000       0.026       14        0.363          0      -0.5322
              0.0000   14.0000       0.026       14        0.363          0      -0.5322
              0.0000   14.0000       0.026       14        0.363          0      -0.5322
              0.0000   15.0000       0.026       15        0.389          0      -0.5459
              0.0000   15.0000       0.026       15        0.389          0      -0.5459
              0.0000   15.0000       0.026       15        0.389          1       0.8577
              0.0000   16.0000       0.026       16        0.415          0      -0.5587
              0.0000   16.0000       0.026       16        0.415          0      -0.5587
              0.0000   16.0000       0.026       16        0.415          2       2.1349
              0.0000   17.0000       0.026       17        0.441          0      -0.5709
              0.0000   17.0000       0.026       17        0.441          0      -0.5709
              0.0000   17.0000       0.026       17        0.441          1       0.7243
```

```
0.0000   18.0000       0.026          18         0.467          0      -0.5824
0.0000   18.0000       0.026          18         0.467          1       0.6654
0.0000   22.0000       0.026          22         0.570          1       0.4690

0.1000   11.0000       0.037          11         0.404          1       0.6558
0.1000   12.0000       0.037          12         0.441          0      -0.4522
0.1000   13.0000       0.037          13         0.477          0      -0.4592
0.1000   14.0000       0.037          14         0.514          2       1.3461
0.1000   14.0000       0.037          14         0.514          1       0.4403
0.1000   14.0000       0.037          14         0.514          0      -0.4655
0.1000   14.0000       0.037          14         0.514          0      -0.4655
0.1000   14.0000       0.037          14         0.514          0      -0.4655
0.1000   15.0000       0.037          15         0.551          0      -0.4712
0.1000   15.0000       0.037          15         0.551          0      -0.4712
0.1000   15.0000       0.037          15         0.551          0      -0.4712
0.1000   15.0000       0.037          15         0.551          0      -0.4712
0.1000   15.0000       0.037          15         0.551          0      -0.4712
0.1000   15.0000       0.037          15         0.551          0      -0.4712
0.1000   15.0000       0.037          15         0.551          1       0.3845
0.1000   16.0000       0.037          16         0.587          0      -0.4764
0.1000   16.0000       0.037          16         0.587          0      -0.4764
0.1000   16.0000       0.037          16         0.587          0      -0.4764
0.1000   16.0000       0.037          16         0.587          0      -0.4764
0.1000   16.0000       0.037          16         0.587          0      -0.4764
0.1000   17.0000       0.037          17         0.624          3       1.8315
0.1000   17.0000       0.037          17         0.624          0      -0.4811
0.1000   18.0000       0.037          18         0.661          0      -0.4854

0.5000    9.0000       0.078           9         0.698          0      -0.4145
0.5000   13.0000       0.078          13         1.008          0      -0.4231
0.5000   13.0000       0.078          13         1.008          0      -0.4231
0.5000   13.0000       0.078          13         1.008          0      -0.4231
0.5000   14.0000       0.078          14         1.086          1      -0.0335
0.5000   14.0000       0.078          14         1.086          0      -0.4245
0.5000   14.0000       0.078          14         1.086          0      -0.4245
0.5000   14.0000       0.078          14         1.086          0      -0.4245
0.5000   14.0000       0.078          14         1.086          0      -0.4245
```

```
0.5000   14.0000       0.078          14         1.086          0      -0.4245
0.5000   15.0000       0.078          15         1.163          0      -0.4258
0.5000   15.0000       0.078          15         1.163          0      -0.4258
0.5000   15.0000       0.078          15         1.163          2       0.3062
0.5000   16.0000       0.078          16         1.241          0      -0.4269
0.5000   16.0000       0.078          16         1.241          0      -0.4269
0.5000   16.0000       0.078          16         1.241          1      -0.0829
0.5000   16.0000       0.078          16         1.241          2       0.2612
0.5000   16.0000       0.078          16         1.241          1      -0.0829
0.5000   17.0000       0.078          17         1.318          0      -0.4279
0.5000   17.0000       0.078          17         1.318          2       0.2212
0.5000   17.0000       0.078          17         1.318          0      -0.4279
0.5000   17.0000       0.078          17         1.318         17       5.0893
```

```
  0.5000   17.0000       0.078          17        1.318          0       -0.4279
  0.5000   18.0000       0.078          18        1.396          5        1.1069

  3.0000    8.0000       0.271           8        2.166          0       -0.7347
  3.0000   12.0000       0.271          12        3.250          0       -0.7428
  3.0000   13.0000       0.271          13        3.520         13        2.0036
  3.0000   13.0000       0.271          13        3.520          0       -0.7440
  3.0000   13.0000       0.271          13        3.520          0       -0.7440
  3.0000   14.0000       0.271          14        3.791          1       -0.5486
  3.0000   14.0000       0.271          14        3.791         14        2.0065
  3.0000   14.0000       0.271          14        3.791          0       -0.7451
  3.0000   14.0000       0.271          14        3.791          0       -0.7451
  3.0000   15.0000       0.271          15        4.062          0       -0.7461
  3.0000   15.0000       0.271          15        4.062          0       -0.7461
  3.0000   15.0000       0.271          15        4.062          1       -0.5624
  3.0000   16.0000       0.271          16        4.333          0       -0.7469
  3.0000   16.0000       0.271          16        4.333         16        2.0113
  3.0000   16.0000       0.271          16        4.333          1       -0.5745
  3.0000   16.0000       0.271          16        4.333          9        0.8046
  3.0000   17.0000       0.271          17        4.604          4       -0.0980
  3.0000   17.0000       0.271          17        4.604          1       -0.5852
  3.0000   17.0000       0.271          17        4.604          1       -0.5852
  3.0000   17.0000       0.271          17        4.604          1       -0.5852
  3.0000   18.0000       0.271          18        4.874          0       -0.7483
  3.0000   18.0000       0.271          18        4.874          0       -0.7483
  3.0000   19.0000       0.271          19        5.145          1       -0.6033
  3.0000   19.0000       0.271          19        5.145          9        0.5611


Combine litters with adjacent levels of the litter-specific covariate
within dose groups until the expected count exceeds 3.0, to help improve
the fit of the X^2 statistic to chi-squared.

                              Grouped Data

```

```
                  Mean                                    chi-squared
    Dose    Lit.-Spec. Cov.      Expected  Observed        Residual
 -------------------------------------------------------------
  0.0000        12.6000            3.267         4          0.3625
  0.0000        15.5000            3.215         3         -0.1045
  0.0000        18.4000            2.385         3          0.3375

  0.1000        13.1429            3.377         4          0.2239
  0.1000        14.8333            3.267         0         -1.1518
  0.1000        15.6667            3.451         1         -0.8256
  0.1000        17.0000            2.496         3          0.1940

  0.5000        12.0000            3.723         0         -0.8352
```

```
   0.5000       14.0000            6.515         1     -0.8803
   0.5000       15.0000            3.490         2     -0.3149
   0.5000       16.0000            6.204         4     -0.3392
   0.5000       17.0000            6.592        19      1.8008
   0.5000       18.0000            1.396         5      1.1069

   3.0000       10.0000            5.416         0     -1.0266
   3.0000       13.0000           10.561        13      0.2976
   3.0000       14.0000           15.165        15     -0.0162
   3.0000       15.0000           12.186         1     -1.1862
   3.0000       16.0000           17.331        26      0.7472
   3.0000       17.0000           18.414         7     -0.9269
   3.0000       18.0000            9.749         0     -1.0583
   3.0000       19.0000           10.290        10     -0.0299

 Chi-square =      13.60   DF = 14    P-value = 0.4803


To calculate the BMD and BMDL, the litter specific covariate is fixed
 at the mean litter specific covariate of all the data: 15.010638

   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =       0.992644

            BMDL =      0.572876
```

PND 1-4 : NCTR

```
 ====================================================================
        NCTR Model. $Revision: 1.9 $ $Date: 2000/03/01 15:36:12 $
        Input Data File: C:\HOME\BMD_WORKGROUP\DIMETH_DNT_PRE.(d)
        Gnuplot Plotting File:  C:\HOME\BMD_WORKGROUP\DIMETH_DNT_PRE.plt
```

```
                                          Mon Aug 30 15:13:49 2004
 ====================================================================

 BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

 The probability function is:


 Prob. = 1 - exp[-(alpha + th1*Rij) - (beta + th2*Rij)*Dose^rho],

          where Rij is the centralized litter specific covariate.
```

```
 Restrict Power rho >= 1.



 Total number of observations = 94
 Total number of records with missing values = 0
 Total number of parameters in model = 9
 Total number of specified parameters = 2


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

****  We are sorry but Relative Function and Parameter Convergence    ****
****  are currently unavailable in this model.  Please keep checking  ****
****  the web sight for model updates which will eventually           ****
****  incorporate these convergence criterion.  Default values used.  ****

 User specifies the following paramters:
          theta1 =           0
          theta2 =           0



                 Default Initial Parameter Values
                         alpha =    0.0267795
                          beta =    0.0979922
                           rho =            1
                          phi1 =    0.0245305
                          phi2 =      0.10874
                          phi3 =     0.415627
                          phi4 =     0.645474

Warning: Maximum iteration may be not large enough. Iterations reach the
maxmimum.
Warning: Maximum iteration may be not large enough. Iterations reach the
```

```
maxmimum.

                                 Parameter Estimates

       Variable            Estimate                Std. Err.
          alpha            0.0267795              0.00968363
           beta            0.0979922               0.0395913
            rho                    1                0.382079
           phi1            0.0245305               0.0330719
           phi2              0.10874                0.109592
           phi3             0.415627               0.0701499
           phi4             0.645474               0.0794038
```

```
                          Analysis of Deviance Table

       Model      Log(likelihood)     Deviance  Test DF     P-value
     Full model        -156.049
   Fitted model        -237.983          163.869    89          <.0001
  Reduced model        -412.865          513.631    93          <.0001

           AIC:         485.967


                       Goodness  of  Fit



     Dose    Litter_Size   Est._Prob.    Expected    Observed
  -----------------------------------------------------------
   0.0000         10         0.026          0.264         0
   0.0000         11         0.026          0.291         0
   0.0000         12         0.026          0.634         0
   0.0000         13         0.026          1.031         1
   0.0000         14         0.026          1.480         3
   0.0000         15         0.026          1.189         1
   0.0000         16         0.026          1.268         2
   0.0000         17         0.026          1.348         1
   0.0000         18         0.026          0.951         1
   0.0000         22         0.026          0.581         1

   0.1000         11         0.036          0.395         1
   0.1000         12         0.036          0.431         0
   0.1000         13         0.036          0.467         0
   0.1000         14         0.036          2.514         3
   0.1000         15         0.036          3.771         1
   0.1000         16         0.036          2.873         0
   0.1000         17         0.036          1.221         3
   0.1000         18         0.036          0.647         0
```

```
   0.5000          9         0.073          0.657         0
   0.5000         13         0.073          2.846         0
   0.5000         14         0.073          6.130         1
   0.5000         15         0.073          3.284         2
   0.5000         16         0.073          5.838         4
   0.5000         17         0.073          6.203        19
   0.5000         18         0.073          1.314         5

   3.0000          8         0.274          2.195         0
   3.0000         12         0.274          3.293         0
   3.0000         13         0.274         10.702        13
   3.0000         14         0.274         15.366        15
```

```
   3.0000        15        0.274         12.348        1
   3.0000        16        0.274         17.562       26
   3.0000        17        0.274         18.659        7
   3.0000        18        0.274          9.878        0
   3.0000        19        0.274         10.427       10

 Chi-square =      18.75   DF = 29    P-value = 0.9276


To calculate the BMD and BMDL, the litter specific covariate is fixed at the
overall mean of the litter specific covariates: 15.010638

   Benchmark Dose Computation

Specified effect =           0.1

Risk Type        =      Extra risk

Confidence level =      0.950000

             BMD =       1.07519

            BMDL =      0.663683
```

PND 1-4 : RaiVR

```
 ====================================================================
        RaiVR Model. $Revision: 1.8 $ $Date: 1999/11/22 18:51:37 $
        Input Data File: C:\HOME\BMD_WORKGROUP\DIMETH_DNT_PRE.(d)
        Gnuplot Plotting File:  C:\HOME\BMD_WORKGROUP\DIMETH_DNT_PRE.plt
                                          Wed Sep 01 15:16:27 2004
 ====================================================================

 BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

 The probability function is:


 Prob. = [1-exp(-Alpha-Beta*Dose^Rho)]*exp(-(Th1+Th2*Dose)*Rij),

           where Rij is the litter specific covariate.

 Restrict Power rho >= 1.



 Total number of observations = 94
 Total number of records with missing values = 0
 Total number of parameters in model = 9
 Total number of specified parameters = 2


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

****  We are sorry but Relative Function and Parameter Convergence    ****
****  are currently unavailable in this model.  Please keep checking  ****
****  the web sight for model updates which will eventually           ****
****  incorporate these convergence criterion.  Default values used.  ****
```

```
 User specifies the following parameters:
          theta1 =           0
          theta2 =           0



                  Default Initial Parameter Values
                          alpha =    0.0267795
                           beta =    0.0979922
                            rho =            1
                           phi1 =    0.0245305
                           phi2 =      0.10874
```

```
                         phi3 =     0.415627
                         phi4 =     0.645474


                        Parameter Estimates

     Variable              Estimate             Std. Err.
        alpha              0.0267795          0.00968363
         beta              0.0979922           0.0395913
          rho                      1            0.382079
         phi1              0.0245305           0.0330719
         phi2                0.10874            0.109592
         phi3               0.415627           0.0701499
         phi4               0.645474           0.0794038


                      Analysis of Deviance Table

     Model      Log(likelihood)     Deviance  Test DF     P-value
   Full model      -156.049
 Fitted model      -237.983          163.869    89          <.0001
Reduced model      -412.865          513.631    93          <.0001


                   Goodness  of  Fit



   Dose   Litter_Size   Est._Prob.   Expected    Observed
-----------------------------------------------------------
 0.0000         10          0.026         0.264          0
 0.0000         11          0.026         0.291          0
 0.0000         12          0.026         0.634          0
 0.0000         13          0.026         1.031          1
 0.0000         14          0.026         1.480          3
```

```
 0.0000         15          0.026         1.189          1
 0.0000         16          0.026         1.268          2
 0.0000         17          0.026         1.348          1
 0.0000         18          0.026         0.951          1
 0.0000         22          0.026         0.581          1

 0.1000         11          0.036         0.395          1
 0.1000         12          0.036         0.431          0
 0.1000         13          0.036         0.467          0
 0.1000         14          0.036         2.514          3
 0.1000         15          0.036         3.771          1
 0.1000         16          0.036         2.873          0
 0.1000         17          0.036         1.221          3
```

```
   0.1000        18        0.036          0.647         0

   0.5000         9        0.073          0.657         0
   0.5000        13        0.073          2.846         0
   0.5000        14        0.073          6.130         1
   0.5000        15        0.073          3.284         2
   0.5000        16        0.073          5.838         4
   0.5000        17        0.073          6.203        19
   0.5000        18        0.073          1.314         5

   3.0000         8        0.274          2.195         0
   3.0000        12        0.274          3.293         0
   3.0000        13        0.274         10.702        13
   3.0000        14        0.274         15.366        15
   3.0000        15        0.274         12.348         1
   3.0000        16        0.274         17.562        26
   3.0000        17        0.274         18.659         7
   3.0000        18        0.274          9.878         0
   3.0000        19        0.274         10.427        10

 Chi-square =      18.75    DF = 28    P-value = 0.9058


To calculate the BMD and BMDL, the litter specific covariate is fixed at the
mean of litter specific covariate: 15.010638

   Benchmark Dose Computation

Specified effect =           0.1

Risk Type        =      Extra risk

Confidence level =      0.950000

             BMD =       1.07519

            BMDL =      0.663683
```

```
 BMDL curve computation failed for BMR = 0.300000 .
 The BMDL curve appearing in the graph may not accurate.
```

PND 5-11 : NLogistic

```
====================================================================
       NLogistic Model. $Revision: 2.8 $ $Date: 2003/05/06 16:33:47 $
       Input Data File: C:\HOME\BMD_WORKGROUP\DIMETH_DNT_POST.(d)
                                         Wed Sep 01 14:45:48 2004
====================================================================

BMDS MODEL RUN
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The probability function is:


Prob. = alpha + theta1*Rij + [1 - alpha - theta1*Rij]/

                      [1+exp(-beta-theta2*Rij-rho*log(Dose))],

         where Rij is the litter specific covariate.

Restrict Power rho >= 1.



Total number of observations = 90
Total number of records with missing values = 0
Total number of parameters in model = 9
Total number of specified parameters = 2


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

User specifies the following parameters:
         theta1 =          0
         theta2 =          0
```

```
                 Default Initial Parameter Values
                         alpha =    0.0281834
                          beta =     -14.3853
                        theta1 =            0   Specified
                        theta2 =            0   Specified
                           rho =      10.8683
                          phi1 =    0.0407047
                          phi2 =     0.215684
                          phi3 =     0.382769
                          phi4 =     0.422581
```

```
                            Parameter Estimates

         Variable            Estimate              Std. Err.
            alpha            0.0281834            0.0102475
             beta            -14.3853              0.658931
              rho             10.8683              0.306772
             phi1            0.0407047             0.289263
             phi2             0.215684              0.26325
             phi3             0.382769                    0
             phi4             0.422581                    0


                          Analysis of Deviance Table

         Model      Log(likelihood)  Deviance  Test DF     P-value
       Full model        -60.6438
     Fitted model        -105.591       89.8954     83          0.2835
    Reduced model         -142.88       164.472     89         <.0001

            AIC:          225.183


                                 Litter Data


            Lit.-Spec.                Litter                             chi-squared
   Dose        Cov.      Est._Prob.    Size     Expected   Observed    Residual
--------------------------------------------------------------------------
   0.0000     8.0000       0.028         8        0.225          0      -0.4249
   0.0000     8.0000       0.028         8        0.225          0      -0.4249
   0.0000     8.0000       0.028         8        0.225          1       1.4597
   0.0000     8.0000       0.028         8        0.225          0      -0.4249
   0.0000     8.0000       0.028         8        0.225          0      -0.4249

   0.0000     8.0000       0.028         8        0.225          0      -0.4249
   0.0000     8.0000       0.028         8        0.225          0      -0.4249
   0.0000     8.0000       0.028         8        0.225          1       1.4597
   0.0000     8.0000       0.028         8        0.225          0      -0.4249
   0.0000     8.0000       0.028         8        0.225          0      -0.4249
   0.0000     8.0000       0.028         8        0.225          0      -0.4249
   0.0000     8.0000       0.028         8        0.225          0      -0.4249
   0.0000     8.0000       0.028         8        0.225          0      -0.4249
   0.0000     8.0000       0.028         8        0.225          0      -0.4249
   0.0000     8.0000       0.028         8        0.225          2       3.3443
   0.0000     8.0000       0.028         8        0.225          1       1.4597
   0.0000     8.0000       0.028         8        0.225          0      -0.4249
   0.0000     8.0000       0.028         8        0.225          0      -0.4249
```

0.0000	8.0000	0.028	8	0.225	0	-0.4249
0.0000	8.0000	0.028	8	0.225	0	-0.4249
0.0000	8.0000	0.028	8	0.225	0	-0.4249
0.0000	8.0000	0.028	8	0.225	0	-0.4249
0.0000	8.0000	0.028	8	0.225	0	-0.4249
0.1000	8.0000	0.028	8	0.225	0	-0.3040
0.1000	8.0000	0.028	8	0.225	0	-0.3040
0.1000	8.0000	0.028	8	0.225	0	-0.3040
0.1000	8.0000	0.028	8	0.225	0	-0.3040
0.1000	8.0000	0.028	8	0.225	0	-0.3040
0.1000	8.0000	0.028	8	0.225	2	2.3929
0.1000	8.0000	0.028	8	0.225	0	-0.3040
0.1000	8.0000	0.028	8	0.225	0	-0.3040
0.1000	8.0000	0.028	8	0.225	0	-0.3040
0.1000	8.0000	0.028	8	0.225	0	-0.3040
0.1000	8.0000	0.028	8	0.225	0	-0.3040
0.1000	8.0000	0.028	8	0.225	0	-0.3040
0.1000	8.0000	0.028	8	0.225	0	-0.3040
0.1000	8.0000	0.028	8	0.225	0	-0.3040
0.1000	8.0000	0.028	8	0.225	0	-0.3040
0.1000	8.0000	0.028	8	0.225	0	-0.3040
0.1000	8.0000	0.028	8	0.225	1	1.0445
0.1000	8.0000	0.028	8	0.225	0	-0.3040
0.1000	8.0000	0.028	8	0.225	0	-0.3040
0.1000	8.0000	0.028	8	0.225	0	-0.3040
0.1000	8.0000	0.028	8	0.225	0	-0.3040
0.1000	8.0000	0.028	8	0.225	0	-0.3040
0.1000	8.0000	0.028	8	0.225	0	-0.3040
0.5000	8.0000	0.028	8	0.225	5	5.3175
0.5000	8.0000	0.028	8	0.225	0	-0.2511
0.5000	8.0000	0.028	8	0.225	0	-0.2511
0.5000	8.0000	0.028	8	0.225	0	-0.2511
0.5000	8.0000	0.028	8	0.225	0	-0.2511
0.5000	8.0000	0.028	8	0.225	0	-0.2511
0.5000	8.0000	0.028	8	0.225	0	-0.2511
0.5000	8.0000	0.028	8	0.225	0	-0.2511
0.5000	8.0000	0.028	8	0.225	0	-0.2511
0.5000	8.0000	0.028	8	0.225	2	1.9763
0.5000	8.0000	0.028	8	0.225	3	3.0901
0.5000	8.0000	0.028	8	0.225	0	-0.2511
0.5000	8.0000	0.028	8	0.225	0	-0.2511
0.5000	8.0000	0.028	8	0.225	0	-0.2511
0.5000	8.0000	0.028	8	0.225	0	-0.2511
0.5000	8.0000	0.028	8	0.225	0	-0.2511
0.5000	8.0000	0.028	8	0.225	0	-0.2511
0.5000	8.0000	0.028	8	0.225	0	-0.2511
0.5000	8.0000	0.028	8	0.225	0	-0.2511
0.5000	8.0000	0.028	8	0.225	0	-0.2511

```
    0.5000    8.0000      0.028         8       0.225        0      -0.2511
    0.5000    8.0000      0.028         8       0.225        0      -0.2511
    0.5000    8.0000      0.028         8       0.225        0      -0.2511

    3.0000    7.0000      0.106         7       0.740        5       2.7850
    3.0000    8.0000      0.106         8       0.846        0      -0.4888
    3.0000    8.0000      0.106         8       0.846        1       0.0892
    3.0000    8.0000      0.106         8       0.846        0      -0.4888
    3.0000    8.0000      0.106         8       0.846        0      -0.4888
    3.0000    8.0000      0.106         8       0.846        0      -0.4888
    3.0000    8.0000      0.106         8       0.846        0      -0.4888
    3.0000    8.0000      0.106         8       0.846        0      -0.4888
    3.0000    8.0000      0.106         8       0.846        0      -0.4888
    3.0000    8.0000      0.106         8       0.846        0      -0.4888
    3.0000    8.0000      0.106         8       0.846        0      -0.4888
    3.0000    8.0000      0.106         8       0.846        1       0.0892
    3.0000    8.0000      0.106         8       0.846        0      -0.4888
    3.0000    8.0000      0.106         8       0.846        0      -0.4888
    3.0000    8.0000      0.106         8       0.846        0      -0.4888
    3.0000    8.0000      0.106         8       0.846        3       1.2451
    3.0000    8.0000      0.106         8       0.846        6       2.9790
    3.0000    8.0000      0.106         8       0.846        2       0.6671
    3.0000    8.0000      0.106         8       0.846        0      -0.4888
    3.0000    8.0000      0.106         8       0.846        0      -0.4888
    3.0000    8.0000      0.106         8       0.846        0      -0.4888


 Combine litters with adjacent levels of the litter-specific covariate
 within dose groups until the expected count exceeds 3.0, to help improve
 the fit of the X^2 statistic to chi-squared.


                                  Grouped Data


                     Mean                                     chi-squared
      Dose    Lit.-Spec. Cov.     Expected  Observed       Residual
```

```
   -------------------------------------------------------------
    0.0000          8.0000           5.186         5      -0.0730

    0.1000          8.0000           5.186         3      -0.6146

    0.5000          8.0000           5.186        10       1.1180

    3.0000          7.7500           3.277         6       0.8093
    3.0000          8.0000          14.377        12      -0.3332

  Chi-square =        2.40    DF = 0     P-value = NA
```

```
To calculate the BMD and BMDL, the litter specific covariate is fixed
 at the mean litter specific covariate of all the data: 7.988889

   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        3.06927

            BMDL =        1.3914
```

PND 5-11 : NCTR

```
 ====================================================================
        NCTR Model. $Revision: 1.9 $ $Date: 2000/03/01 15:36:12 $
        Input Data File: C:\HOME\BMD_WORKGROUP\DIMETH_DNT_POST.(d)
        Gnuplot Plotting File:  C:\HOME\BMD_WORKGROUP\DIMETH_DNT_POST.plt
                                          Wed Sep 01 14:57:31 2004
 ====================================================================

 BMDS MODEL RUN
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 The probability function is:


 Prob. = 1 - exp[-(alpha + th1*Rij) - (beta + th2*Rij)*Dose^rho],

          where Rij is the centralized litter specific covariate.

 Restrict Power rho >= 1.



 Total number of observations = 90
 Total number of records with missing values = 0
 Total number of parameters in model = 9
 Total number of specified parameters = 2


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

****  We are sorry but Relative Function and Parameter Convergence    ****
****  are currently unavailable in this model.  Please keep checking  ****
****  the web sight for model updates which will eventually           ****
****  incorporate these convergence criterion.  Default values used.  ****
```

```
 User specifies the following paramters:
          theta1 =          0
          theta2 =          0



                  Default Initial Parameter Values
                          alpha =    0.0242335
                           beta =    0.0300182
                            rho =            1
                           phi1 =    0.0358708
                           phi2 =     0.203091
```

```
                                       phi3 =      0.416614
                                       phi4 =      0.425916

Warning: Maximum iteration may be not large enough. Iterations reach the
maxmimum.
Warning: Maximum iteration may be not large enough. Iterations reach the
maxmimum.

                                      Parameter Estimates

       Variable           Estimate             Std. Err.
          alpha           0.0242335            0.0122798
           beta           0.0300182            0.0452706
            rho                   1              1.35543
           phi1           0.0358708            0.0878711
           phi2            0.203091             0.282404
           phi3            0.416614              0.43522
           phi4            0.425916             0.214552



                                    Analysis of Deviance Table

       Model      Log(likelihood)     Deviance  Test DF     P-value
     Full model      -60.6438
   Fitted model      -105.337          89.3861    85         0.2963
  Reduced model       -142.88          164.472    89         <.0001

           AIC:          220.674


                                 Goodness  of  Fit



     Dose   Litter_Size   Est._Prob.    Expected    Observed
  -----------------------------------------------------------
```

```
    0.0000          8        0.024         16.430       18

    3.0000          7        0.108          0.756        5
    3.0000          8        0.108         17.280       13


To calculate the BMD and BMDL, the litter specific covariate is fixed at the
overall mean of the litter specific covariates: 7.988889

   Benchmark Dose Computation

Specified effect =           0.1
```

```
Risk Type        =      Extra risk

Confidence level =      0.950000

             BMD =       3.50989

            BMDL =        1.5505
```

PND 5-11 : RaiVR

```
 ====================================================================
        RaiVR Model. $Revision: 1.8 $ $Date: 1999/11/22 18:51:37 $
        Input Data File: C:\HOME\BMD_WORKGROUP\DIMETH_DNT_POST.(d)
        Gnuplot Plotting File:  C:\HOME\BMD_WORKGROUP\DIMETH_DNT_POST.plt
                                          Wed Sep 01 15:07:30 2004
 ====================================================================

 BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

 The probability function is:


 Prob. = [1-exp(-Alpha-Beta*Dose^Rho)]*exp(-(Th1+Th2*Dose)*Rij),

           where Rij is the litter specific covariate.

 Restrict Power rho >= 1.



 Total number of observations = 90
 Total number of records with missing values = 0
 Total number of parameters in model = 9
 Total number of specified parameters = 2


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

****  We are sorry but Relative Function and Parameter Convergence    ****
****  are currently unavailable in this model.  Please keep checking  ****
****  the web sight for model updates which will eventually           ****
****  incorporate these convergence criterion.  Default values used.  ****
```

```
 User specifies the following parameters:
          theta1 =           0
          theta2 =           0



                  Default Initial Parameter Values
                          alpha =    0.0242335
                           beta =    0.0300182
                            rho =            1
                           phi1 =    0.0358708
                           phi2 =     0.203091
```

```
                           phi3 =      0.416614
                           phi4 =      0.425916



                          Parameter Estimates

       Variable           Estimate             Std. Err.
          alpha           0.0242335           0.0122798
           beta           0.0300182           0.0452706
            rho                   1             1.35543
           phi1           0.0358708           0.0878711
           phi2            0.203091            0.282404
           phi3            0.416614             0.43522
           phi4            0.425916            0.214552



                        Analysis of Deviance Table

       Model      Log(likelihood)     Deviance  Test DF     P-value
     Full model       -60.6438
   Fitted model       -105.337          89.3861    85          0.2963
  Reduced model        -142.88          164.472    89          <.0001


                     Goodness  of  Fit



     Dose   Litter_Size   Est._Prob.   Expected    Observed
  -----------------------------------------------------------
   0.0000         8         0.024         16.430       18

   3.0000         7         0.108          0.756        5
   3.0000         8         0.108         17.280       13
```

```
To calculate the BMD and BMDL, the litter specific covariate is fixed at the
mean of litter specific covariate: 7.988889

   Benchmark Dose Computation

Specified effect =           0.1

Risk Type        =      Extra risk

Confidence level =      0.950000

             BMD =       3.50989
```

```
            BMDL =        1.5505


BMDL curve computation failed for BMR = 0.100000 .
The BMDL curve appearing in the graph may not accurate.
BMDL curve computation failed for BMR = 0.200000 .
The BMDL curve appearing in the graph may not accurate.
BMDL curve computation failed for BMR = 0.300000 .
The BMDL curve appearing in the graph may not accurate.
```