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HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

June 9, 2006

MEMORANDUM

SUBJECT: **Benchmark dose analysis of cholinesterase inhibition data in neonatal and adult rats (MRID no. 46688914) following exposure to *DDVP***
PC Code: 084001. DP Barcode DP 328793. TXR No. 0054223

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6/9/06

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The purpose of the current memo is to provide BMD estimates calculated by the Health Effects Division for the acute and repeated dosing studies in adult and juvenile rats in DDVP (MRID nos. 45805703, 45842301, 46433201, 46153304). The results of this memo are intended to inform the FQPA 10X factor for dichlorvos (also called DDVP) in the single chemical aggregate and cumulative risk assessments.

JUN 14 2006

Summary

This memo describes a benchmark dose analysis for red blood cell (RBC) and brain cholinesterase (ChE) inhibition data in adult and juvenile rats exposed orally to DDVP (MRID nos. 45805703, 45842301, 464433201, 46153304). This analysis was developed using the exponential model provided in EPA's OPCum Risk software. The estimated dose to result in 10% inhibition (BMD_{10}) and the lower 95% confidence limit on the BMD_{10} ($BMDL_{10}$) were calculated. For acute exposures, the calculated $BMDs_{10}$ range from approximately 1.3 mg/kg to 2.0 mg/kg for each compartment, sex and age group (young adult and postnatal day 8 [PND8] rats). Regarding repeated exposures, the Agency has used both concurrent and historical controls to estimate RBC and brain BMD_{10}. For most groups, the calculated the $BMDs_{10}$ ranged from approximately 0.5 mg/kg to 1.2 mg/kg when using the historical or concurrent controls. Overall, for the repeated exposure, the BMDs are similar between compartments, sexes and age groups.

Background

The Agency's draft BMD technical guidance indicates that the BMD approach is a preferable alternative to the NOAEL/LOAEL approach (USEPA, 2000). The Office of Pesticide Programs is increasing its use of BMD techniques in its hazard assessments and risk characterizations. BMDs are preferred over the NOAEL/LOAEL as NOAELs/LOAELs are highly dependent on dose selection in that they are limited to the doses included in a study. Moreover, the NOAEL/LOAEL approach does not account for the uncertainty in the estimate of the dose-response. Benchmark dose 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 that is estimated based on the experimental observations is used to estimate the magnitude of the response for any dose within the experimental dose range. Various mathematical models can be used to model this dose-response curve. Once a BMD model has been selected, the dose associated with a specified response (i.e. benchmark response, BMR) is determined. For cholinesterase data, the BMR is typically expressed as a certain percent change in the control group response (i.e., background). The dose resulting in the specified BMR and estimated based on the modeled dose-response curve is termed the "benchmark dose." Generally, the dose resulting in a BMR of X% change in background is referred to as the BMD_X. The corresponding 95% lower confidence limit on the BMD_X is referred to as the $BMDL_X$. In the case of ChE inhibition for DDVP, EPA has used a BMR of 10% for ChE inhibition. This BMR was selected based on both statistical and toxicological considerations. The reader is referred to the Revised Organophosphate (OP) Cumulative Assessment which provides a detailed power analysis of over 1000 measurements of brain ChE inhibition which indicates that 10% is a level that can be reliably measured in the majority of rat toxicity studies. In the case of the ChE inhibiting pesticides, it is important to consider the degree to which the response level for inhibition of ChE is protective for other toxicities which may result from pesticide exposure. The Agency believes that at a BMR of 10% for brain ChE inhibition is, indeed, protective of other toxicities whereas higher BMR values may not be.

Methods

Selected Model

The BMD analysis of ChE data from the DDVP oral gavage acute and repeated comparative sensitivity toxicity studies was performed using EPA's OPCumRisk program. The exponential function used for modeling the effect of DDVP on ChE activity was:

$$y = B + (A - B)\, e^{-m \times dose}$$

Where **y** is ChE activity, **dose** is the dose in mg/kg, **m** is the dose scale factor, **A** is background ChE activity, and **B** is the limiting high-dose ChE activity. Both y (ChE activity) and dose were extracted from the above referenced toxicity study. The equation for the exponential model reflects the observation that

ChE activity decreases to a limiting value (B) as dose increases. The model has three parameters to be estimated: m (dose scale factor), A (background), and B (limiting high-dose ChE activity).

The OPCumRisk program utilizes the same dose-response model (i.e., decreasing exponential model) as utilized in the Preliminary OP Cumulative Risk Assessment (CRA; USEPA, 2001). The OPCumRisk program can be obtained at www.epa.gov/pesticides/cumulative/EPA_approach_methods.htm. These dose-response models and the respective computer code are publicly available for download, review, and use. This method has been previously evaluated by the FIFRA SAP (www.epa.gov/scipoly/sap/2001/index.htm). For the revised OP CRA (USEPA, 2002), the exponential model was expanded to include a "low dose shoulder." The low dose shoulder corresponds to the portion of the dose-response curve where the slope at the low end of the dose-response curve is more flat compared to the slope at higher doses. This low dose shoulder is not modeled in the OPCumRisk program. For DDVP brain and RBC ChE data in the comparative ChE study, there is little evidence that a low dose shoulder exists and as such, the current BMD analysis is considered adequate and supportable. It is important to note that the exponential model is also being used by EPA in its cumulative risk assessment for the OP common mechanism group (of which DDVP is a member; USEPA, 2002).

The calculated BMD values represent the dose at which a 10% reduction in background ChE activity levels is expected (i.e. BMD_{10} values were calculated). For each ChE dataset, parameters were initially estimated including all dose groups. The OPCumRisk program utilizes a decision algorithm for selecting from among various options for the exponential model. Generally the model is fitted until an adequate p-value for the $\chi 2$ goodness-of-fit (GoF) statistic is obtained. The decision algorithm is provided below.

1. If the p-value for the GoF statistic is greater than 0.05, then the model's fit was considered adequate and the initial parameter estimates were used.

2. Otherwise (that is, if the p-value was less than 0.05, or no estimates resulted because the model did not converge), the horizontal asymptote was set to zero and the model was refit to the data.

3. If the p-value was still less than 0.05, or there was no model fit at all, then the highest dose was dropped and the model was refit with the horizontal asymptote set to zero until either the p-value exceeded 0.05, or there are only three doses remaining.

Although the user can specify options that are not consistent with the default decision algorithm utilized by OPCumRisk, all BMD values provided in these analyses are based on the default decision algorithm. The decision algorithm and technical details of the "basic" exponential model used in this BMD analysis can be obtained at www.epa.gov/scipoly/sap/2001/september/rpfappendix1.pdf.

Results

BMD values (both BMD_{10} and $BMDL_{10}$) were calculated for the brain and RBC ChE data from the oral gavage acute comparative sensitivity toxicity study. These BMD values and the goodness of fit information from the OPCumRisk model runs are provided in Tables 1 and 2 for acute and repeated exposures, respectively. Details of this analysis can be found below in Appendix 1 and 2.

Based on statistical and/or visual fit, the exponential model adequately fit the RBC and brain ChE data from the acute exposures to adult and PND8 rats. Moreover, for acute exposures, all of calculated the BMD_{10} range from approximately 1.3 mg/kg to 2.0 mg/kg. The BMDs are similar between compartments, sexes and age groups. It is also notable that there is a narrow margin between the BMD_{10} and $BMDL_{10}$ indicating quality data and quality model fit.

Table 1. BMD Summary of OPP's Analysis of ChE Data from the DDVP Oral Acute Gavage Comparative Sensitivity Toxicity Study (MRID no. 45805703, 45842301) Based on the Exponential Model

Brain	Male	Adult	1.46	0.76	0.53
		Neonate	1.50	1.40	0.46
	Female	Adult	1.29	0.65	0.51
		Neonate	2.02	1.80	0.95
RBC	Male	Adult	1.66	1.31	0.20
		Neonate	1.63	1.41	0.95
	Female	Adult	1.55	1.26	0.65
		Neonate	1.47	0.83	0.15

Based on statistical and/or visual fit, the exponential model adequately fit most of the sex-age-compartment scenarios for the RBC and brain ChE data from the repeated exposures to DDVP (Table 2). As described in the Data Evaluation Record (DER), the ChE activity measurements in some control groups are unusually high for the laboratory which conducted the repeated exposure study. The registrant, AMVAC, provided historical control values for brain and RBC ChE activity. BMD estimates were developed using both the concurrent and pooled historical control values. For most groups, the calculated the $BMDs_{10}$ ranged from approximately 0.5 mg/kg to 1.2 mg/kg when using the historical or concurrent controls. For the female brain ChE from juvenile rats, when using the concurrent controls, the statistical fit was not adequate ($p < 0.05$); however, when using the historical controls, the fit was improved. For the female adult RBC ChE data, when using the concurrent controls, the BMDs were substantially lower than values calculated for the other groups; when the historical control values were considered, the BMD for this group increased to be consistent with the remaining groups. Overall, for the repeated exposure, the BMDs are similar between compartments, sexes and age groups. It is also notable that the BMD_{10} and $BMDL_{10}$ are close together in magnitude indicating quality data for most treatment groups and quality model fit.

Table 2. BMD Summary of OPP's Analysis of ChE Data from the DDVP Oral *Multi-dosing* Gavage Comparative Sensitivity Toxicity Study (MRID no. 46433201, 46153304) Based on the Exponential Model

Brain (concurrent controls)	Male	Adult	0.72	0.55	0.71
		Neonate	0.88	0.75	0.0081
	Female	Adult	0.88	0.71	0.84
		Neonate	0.95	0.80	0.022
Brain (pooled historical controls)	Male	Adult	0.77	0.62	0.63
		Neonate	0.84	0.65	0.37
	Female	Adult	0.92	0.75	0.75
		Neonate	0.85	0.62	0.39
RBC (concurrent controls)	Male	Adult	0.71	0.45	0.11
		Neonate	0.50	0.35	0.41
	Female	Adult	0.09	0.054	0.66
		Neonate	0.57	0.43	0.69
RBC (pooled historical controls)	Male	Adult	0.75	0.50	0.30
		Neonate	0.55	0.38	0.094
	Female	Adult	1.17	1.00	0.90
		Neonate	0.61	0.46	0.50

Conclusions

The BMD analysis described here provides a robust consideration of the brain and RBC ChE data from the acute and repeated exposure studies in young adult and juvenile rats exposed to DDVP orally. This analysis indicates that for acute and repeated exposures that young adult and juvenile rats respond similarly to oral dosing to DDVP.

References

USEPA, 2000. "Benchmark Dose Technical Guidance Document" Draft report. Risk Assessment Forum, *Office of Research and Development*, U.S. Environmental Protection Agency. Washington, DC. EPA/630/R-00/001

USEPA (2001). Preliminary Organophosphorus Pesticide Cumulative Risk Assessment. *Office of* Pesticide Programs, U.S. Environmental Protection Agency. Washington, *DC.http://www.epa.gov/pesticides/cumulative/pra_op/.*

USEPA, 2002. Revised Organophosphorous Pesticide Cumulative Risk Assessment; June 10, 2002. Office of Pesticide Programs, U.S. Environmental Protection Agency. Washington, D.C. Available: http://www.epa.gov/pesticides/cumulative/rra-op/

Appendix 1: Benchmark dose runs for the acute dosing (MRID no. 45805703, 45842301)

DDVP:1-D:BRAIN:F:MAIN
Tue Apr 25 16:46:22 2006
MRID: ADULT Guideline: 81-1
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)^g)

Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

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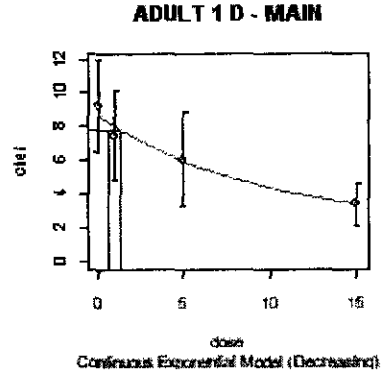
Summary of Model Fitting Results

```
      AIC       BIC    logLik
 85.75863  89.74156 -38.87931

Coefficients:
      Value Std.Error
A 8.7164482 0.9536187
B 2.0810054 2.6396297
m 0.1093959 0.1071854

Correlation:
          A         B         m
A 1.0000000 0.4940059 0.5941367
B 0.4940059 1.0000000 0.9731630
m 0.5941367 0.9731630 1.0000000

Approximate 95% confidence intervals

 Coefficients:
       lower      est.      upper
A 6.91981135 8.7164482 10.9795579
B 0.14322729 2.0810054 30.2357431
m 0.01384314 0.1093959  0.8645054

 Residual standard error:
   lower     est.    upper
2.063742 2.750235 4.122999

Degrees of freedom: 20 total; 17 residual
```



Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 0.4272 with 1 degrees of freedom. P = 0.513

	dose	n	chei	Expected	sd	Exp.SD	X2 Resid.
1	0	5	9.17	8.716448	2.19	2.637271	0.38455377
2	1	5	7.48	8.028853	2.19	2.409555	-0.50933622
3	5	5	6.03	5.920903	2.25	1.741651	0.14006697

DDVP: Acute, Brain, Adult

```
4    15 5 3.36 3.366941 1.00 1.021351 -0.01519591

    ----------------------------------------------------------------
                              BMD Computation

                      BMD = 1.287:  BMDL = 0.6495

    ----------------------------------------------------------------
                              Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background
activity

Potency: 0.1094
se: 0.1072
var=se^2: 0.01149
Per cent. of background at unit dose: 90
Per cent. of background at the highest dose: 19
ED50 (95% CI): 6.336 ( 0.9286 , 43.24 )

ln(Potency) -2.213
se[log(Potency)]: 0.9798
se[log(Potency)]^2: 0.96
```

DDVP: Acute, Brain, Adult

```
                        DDVP:1-D:BRAIN:M:MAIN
                      Tue Apr 25 16:46:28 2006
                    MRID: ADULT   Guideline: 81-1
               Continuous Exponential Model (Decreasing)
               Formula: chei = B + (A-B)*exp(-(m*dose)^g)

Variance Function: power


   The BMD corresponds to a dose that results in a 10% reduction in the
                        response relative to the control
    ------------------------------------------------------------------
                        Summary of Model Fitting Results

      AIC       BIC    logLik
 74.27587  78.25880 -33.13793

Coefficients:
       Value  Std.Error
A 7.50616158 0.77906555
B 1.53331933 0.55183572
m 0.09231263 0.05727478

Correlation:
          A         B         m
A 1.0000000 0.5155696 0.6408690
B 0.5155696 1.0000000 0.8990115
m 0.6408690 0.8990115 1.0000000

Approximate 95% confidence intervals

 Coefficients:
       lower       est.    upper
A 6.02999496 7.50616158 9.343700
B 0.71757370 1.53331933 3.276414
m 0.02493219 0.09231263 0.341792

 Residual standard error:
   lower     est.    upper
1.628137 2.169729 3.252736

Degrees of freedom: 20 total; 17 residual
    ------------------------------------------------------------------
                              Goodness of Fit
 The chi-squared goodness-of-fit values should be taken as general
indications of fit only.  P-values are likely to be inaccurate to some
degree

Pearson Chi-Square Statistic: 0.3867 with 1 degrees of freedom.  P =
0.534

  dose n chei Expected   sd    Exp.SD    X2 Resid.
1    0 5 7.14 7.506162 2.05 2.1838492 -0.374916996
2    1 5 7.42 6.979477 1.81 2.0377088  0.483405815
3    5 5 5.22 5.297988 1.01 1.5652808 -0.111408487
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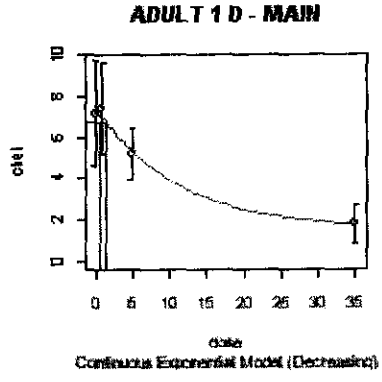

DDVP: Acute, Brain, Adult

4 35 5 1.77 1.769368 0.74 0.5147315 0.002747467

BMD Computation

BMD = 1.455: BMDL = 0.7623

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.09231
se: 0.05727
var=se^2: 0.00328
Per cent. of background at unit dose: 91
Per cent. of background at the highest dose: 4
ED50 (95% CI): 7.509 (2.226 , 25.33)

ln(Potency) -2.383
se[log(Potency)]: 0.6204
se[log(Potency)]^2: 0.385

DDVP: Acute, RBC, Adult

DDVP:1-D:RBC:F:MAIN
Tue Apr 25 16:46:26 2006
MRID: ADULT Guideline: 81-1
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)^g)

Variance Function: power

Highest 1 doses dropped from data set.

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

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Summary of Model Fitting Results

```
      AIC       BIC    logLik
201.74977 203.87392 -97.87489

Coefficients:
         Value    Std.Error
A 2.571638e+03 71.521128484
m 6.799292e-02  0.009431473

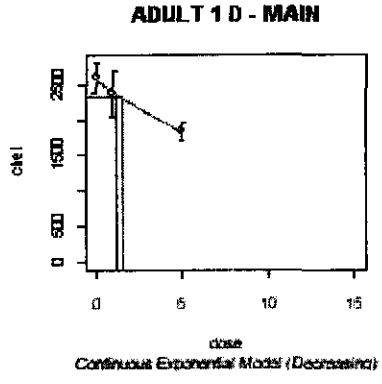
Correlation:
          A         m
A 1.0000000 0.6800864
m 0.6800864 1.0000000

Approximate 95% confidence intervals

 Coefficients:
         lower          est.         upper
A 2.421676e+03 2.571638e+03 2.730886e+03
m 5.038701e-02 6.799292e-02 9.175059e-02

 Residual standard error:
   lower     est.    upper
148.7009 205.1177 330.4533

Degrees of freedom: 15 total; 13 residual
```



Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 0.2042 with 1 degrees of freedom. P = 0.651

	dose	n	chei	Expected	sd	Exp.SD	X2 Resid.
1	0	5	2597	2571.638	179	203.3146	0.27893149
2	1	5	2373	2402.597	264	189.8396	-0.34861343
3	5	5	1835	1830.480	101	144.2978	0.07003547

DDVP: Acute, RBC, Adult

BMD Computation

BMD = 1.55: BMDL = 1.262

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.06799
se: 0.009431
var=se^2: 8.895e-05
Per cent. of background at unit dose: 93
Per cent. of background at the highest dose: 71
ED50 (95% CI): 10.19 (7.768 , 13.38)

ln(Potency) -2.688
se[log(Potency)]: 0.1387
se[log(Potency)]^2: 0.01924

DDVP: Acute, RBC, Adult

```
                        DDVP:1-D:RBC:M:MAIN
                      Tue Apr 25 16:46:32 2006
                    MRID: ADULT   Guideline: 81-1
                Continuous Exponential Model (Decreasing)
                Formula: chei = B + (A-B)*exp(-(m*dose)^g)

Variance Function: power

Highest 1 doses dropped from data set.


   The BMD corresponds to a dose that results in a 10% reduction in the
                        response relative to the control
    ------------------------------------------------------------------
                        Summary of Model Fitting Results

      AIC       BIC    logLik
 207.4049  209.5290 -100.7024

Coefficients:
         Value   Std.Error
A 2.790461e+03 85.30415667
m 6.358638e-02  0.01043262

Correlation:
           A         m
A 1.0000000 0.6773461
m 0.6773461 1.0000000

Approximate 95% confidence intervals

 Coefficients:
         lower         est.        upper
A 2.612126e+03 2.790461e+03 2.980971e+03
m 4.460953e-02 6.358638e-02 9.063597e-02

 Residual standard error:
   lower     est.    upper
171.6033 236.7092 381.3486

Degrees of freedom: 15 total; 13 residual
    ------------------------------------------------------------------
                              Goodness of Fit
 The chi-squared goodness-of-fit values should be taken as general
indications of fit only.  P-values are likely to be inaccurate to some
degree

Pearson Chi-Square Statistic: 1.633 with 1 degrees of freedom.  P =
0.201

  dose n chei Expected  sd   Exp.SD  X2 Resid.
1    0 5 2705 2790.461 343 242.2597 -0.7888111
2    1 5 2719 2618.549 170 227.7068  0.9864189
3    5 5 2015 2030.486  94 177.7275 -0.1948314
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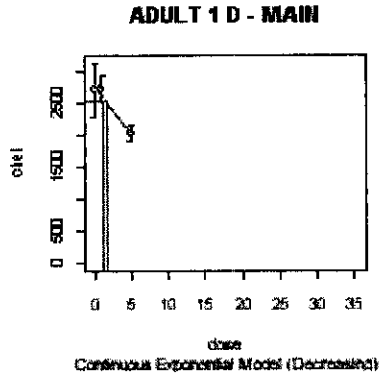

DDVP: Acute, RBC, Adult

BMD Computation

BMD = 1.657: BMDL = 1.305

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.06359
se: 0.01043
var=se^2: 0.0001088
Per cent. of background at unit dose: 94
Per cent. of background at the highest dose: 73
ED50 (95% CI): 10.9 (7.903 , 15.04)

ln(Potency) -2.755
se[log(Potency)]: 0.1641
se[log(Potency)]^2: 0.02692

DDVP: Acute, Brain, Pup

DDVP:1-PND:BRAIN:F:MAIN
Tue Apr 25 16:46:45 2006
MRID: PND8 Guideline: 81-1
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)^g)

Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

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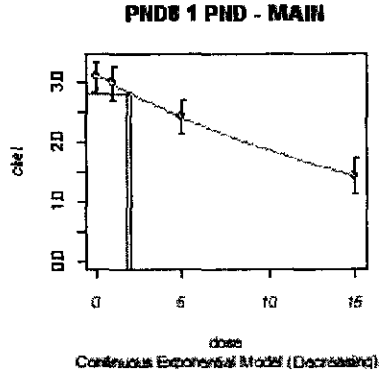
Summary of Model Fitting Results

```
      AIC       BIC    logLik
4.4493049 7.4365018 0.7753475

Coefficients:
       Value   Std.Error
A 3.11393414 0.096228698
m 0.05220586 0.003914497

Correlation:
          A         m
A 1.0000000 0.6615286
m 0.6615286 1.0000000
```

Approximate 95% confidence intervals

```
 Coefficients:
       lower       est.      upper
A 2.91818820 3.11393414 3.32281030
m 0.04459687 0.05220586 0.06111309

 Residual standard error:
    lower      est.     upper
0.2410419 0.3190020 0.4717480

Degrees of freedom: 20 total; 18 residual
```



Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 0.1003 with 2 degrees of freedom. P = 0.951

	dose	n	chei	Expected	sd	Exp.SD	X2 Resid.
1	0	5	3.08	3.113934	0.21	0.3220624	-0.2356035
2	1	5	2.98	2.955539	0.23	0.3058005	0.1788627
3	5	5	2.41	2.398534	0.23	0.2485596	0.1031516
4	15	5	1.42	1.423045	0.24	0.1480511	-0.0459906

DDVP: Acute, Brain, Pup

BMD Computation

BMD = 2.018: BMDL = 1.797

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.05221
se: 0.003914
var=se^2: 1.532e-05
Per cent. of background at unit dose: 95
Per cent. of background at the highest dose: 46
ED50 (95% CI): 13.28 (11.46 , 15.38)

ln(Potency) -2.953
se[log(Potency)]: 0.07498
se[log(Potency)]^2: 0.005622

DDVP: Acute, Brain, Pup

DDVP:1-PND:BRAIN:M:MAIN
Tue Apr 25 16:46:52 2006
MRID: PND8 Guideline: 81-1
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)^g)

Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

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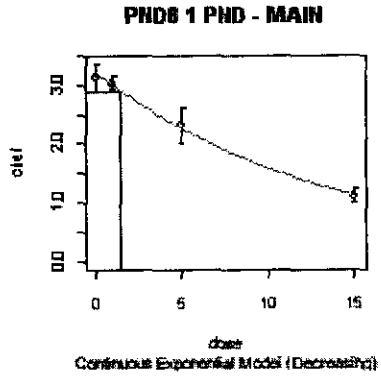
Summary of Model Fitting Results

```
       AIC        BIC     logLik
-11.513330  -8.526133   8.756665

Coefficients:
       Value   Std.Error
A 3.22799583 0.070577502
m 0.07048969 0.002815596

Correlation:
          A         m
A 1.0000000 0.6557125
m 0.6557125 1.0000000

Approximate 95% confidence intervals

 Coefficients:
       lower       est.      upper
A 3.08307201 3.22799583 3.37973197
m 0.06481574 0.07048969 0.07666033

 Residual standard error:
    lower      est.     upper
0.1743612 0.2307548 0.3412458

Degrees of freedom: 20 total; 18 residual
```



Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 1.551 with 2 degrees of freedom. P = 0.46

	dose	n	chei	Expected	sd	Exp.SD	X2 Resid.
1	0	5	3.14	3.227996	0.20	0.23552098	-0.8354443
2	1	5	3.04	3.008290	0.10	0.21999032	0.3223142
3	5	5	2.33	2.269167	0.24	0.16745554	0.8123092
4	15	5	1.11	1.121331	0.09	0.08465241	-0.2992973

DDVP: Acute, Brain, Pup

BMD Computation

BMD = 1.495: BMDL = 1.403

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.07049
se: 0.002816
var=se^2: 7.928e-06
Per cent. of background at unit dose: 93
Per cent. of background at the highest dose: 35
ED50 (95% CI): 9.833 (9.093 , 10.63)

ln(Potency) -2.652
se[log(Potency)]: 0.03994
se[log(Potency)]^2: 0.001595

DDVP: Acute, RBC, Pup

DDVP:1-PND:RBC:F:MAIN
Tue Apr 25 16:46:50 2006
MRID: PND8 Guideline: 81-1
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)^g)

Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

---

Summary of Model Fitting Results

AIC	BIC	logLik
311.3597	315.3426	-151.6799

Coefficients:

	Value	Std.Error
A	3565.7686985	253.06695411
B	1304.7155991	653.72006213
m	0.1170090	0.08519761

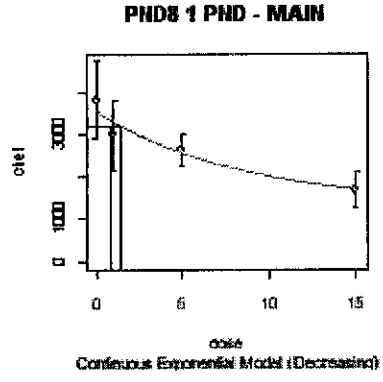
Correlation:

	A	B	m
A	1.0000000	0.4552855	0.5739303
B	0.4552855	1.0000000	0.9594333
m	0.5739303	0.9594333	1.0000000

Approximate 95% confidence intervals

Coefficients:

	lower	est.	upper
A	3069.8953381	3565.7686985	4141.7393788
B	453.3342457	1304.7155991	3755.0280190
m	0.0251796	0.1170090	0.5437383



Residual standard error:

lower	est.	upper
553.7944	738.0112	1106.3850

Degrees of freedom: 20 total; 17 residual

Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 2.127 with 1 degrees of freedom. P = 0.145

	dose	n	chei	Expected	sd	Exp.SD	X2 Resid.
1	0	5	3830	3565.769	733	696.0392	0.84885899
2	1	5	2991	3316.097	662	639.2002	-1.13726262
3	5	5	2636	2564.305	315	480.8800	0.33337969

DDVP: Acute, RBC, Pup

```
4    15 5 1689 1695.615 349 331.6280 -0.04460369

    ------------------------------------------------------------------
                              BMD Computation

                        BMD = 1.467:  BMDL = 0.8317

    ------------------------------------------------------------------
                              Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background
activity

Potency: 0.117
se: 0.0852
var=se^2: 0.007259
Per cent. of background at unit dose: 89
Per cent. of background at the highest dose: 17
ED50 (95% CI): 5.924 ( 1.422 , 24.68 )

ln(Potency) -2.146
se[log(Potency)]: 0.7281
se[log(Potency)]^2: 0.5302
```

DDVP: Acute, RBC, Pup

DDVP:1-PND:RBC:M:MAIN
Tue Apr 25 16:46:56 2006
MRID: PND8 Guideline: 81-1
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)^g)

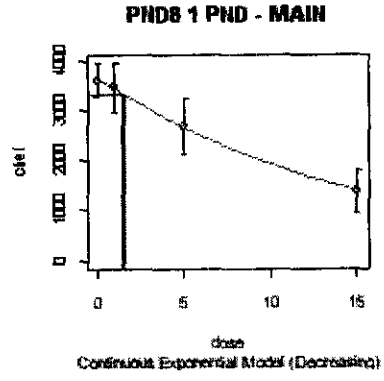
Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

---

Summary of Model Fitting Results

```
      AIC       BIC    logLik
 301.8481  304.8353 -147.9240

Coefficients:
         Value    Std.Error
A 3.677296e+03 1.737759e+02
m 6.483032e-02 6.020933e-03

Correlation:
          A         m
A 1.0000000 0.6594638
m 0.6594638 1.0000000

Approximate 95% confidence intervals

 Coefficients:
         lower         est.         upper
A 3.329745e+03 3.677296e+03 4.061124e+03
m 5.333839e-02 6.483032e-02 7.879824e-02

 Residual standard error:
   lower     est.    upper
433.6720 573.9343 848.7482

Degrees of freedom: 20 total; 18 residual
```



Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 0.09684 with 2 degrees of freedom. P = 0.953

	dose	n	chei	Expected	sd	Exp.SD	X2 Resid.
1	0	5	3620	3677.296	276	580.9977	-0.22051497
2	1	5	3473	3446.460	411	545.1029	0.10887159
3	5	5	2693	2659.202	442	422.3719	0.17892749
4	15	5	1384	1390.583	359	223.2216	-0.06594177

DDVP: Acute, RBC, Pup

BMD Computation

BMD = 1.625: BMDL = 1.41

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.06483
se: 0.006021
var=se^2: 3.625e-05
Per cent. of background at unit dose: 94
Per cent. of background at the highest dose: 38
ED50 (95% CI): 10.69 (8.912 , 12.83)

ln(Potency) -2.736
se[log(Potency)]: 0.09287
se[log(Potency)]^2: 0.008625

Appendix 2: Benchmark dose runs for the repeated dosing (MRID no. 46433201, 46153304)

DDVP: Repeated, Brain, Adult, Concurrent controls

DDVP:7-D:BRAIN:F:WHOLE
Mon Apr 24 21:43:34 2006
MRID: MDAdconc Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)^g)

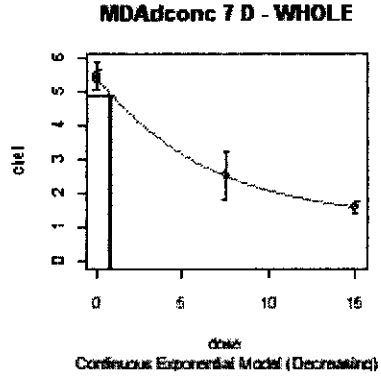
Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

---

Summary of Model Fitting Results

```
     AIC      BIC   logLik
25.51746 29.50039 -8.75873

Coefficients:
      Value  Std.Error
A 5.4680592 0.21623032
B 1.1331342 0.27076016
m 0.1529701 0.03053395

Correlation:
          A         B         m
A 1.0000000 0.1901865 0.3377826
B 0.1901865 1.0000000 0.9369459
m 0.3377826 0.9369459 1.0000000

Approximate 95% confidence intervals

 Coefficients:
      lower      est.     upper
A 5.0303656 5.4680592 5.9438367
B 0.6844438 1.1331342 1.8759659
m 0.1003945 0.1529701 0.2330789

 Residual standard error:
    lower      est.     upper
0.5119114 0.6821960 1.0227101

Degrees of freedom: 20 total; 17 residual
```



Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 0.03915 with 1 degrees of freedom. P = 0.843

	dose	n	chei	Expected	sd	Exp.SD	X2 Resid.
1	0.0	5	5.51	5.468059	0.34	0.6770768	0.138510867
2	0.1	5	5.36	5.402252	0.25	0.6689085	-0.141243990
3	7.5	5	2.51	2.509476	0.56	0.3104510	0.003776490

DDVP: Repeated, Brain, Adult, Concurrent controls

4 15.0 5 1.57 1.570124 0.15 0.1945313 -0.001419862

BMD Computation

BMD = 0.8814: BMDL = 0.713

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.153
se: 0.03053
var=se^2: 0.0009323
Per cent. of background at unit dose: 86
Per cent. of background at the highest dose: 10
ED50 (95% CI): 4.531 (3.064 , 6.701)

ln(Potency) -1.878
se[log(Potency)]: 0.1996
se[log(Potency)]^2: 0.03984

DDVP: Repeated, Brain, Adult, Concurrent controls

DDVP:7-D:BRAIN:M:WHOLE
Mon Apr 24 21:43:40 2006
MRID: MDAdconc Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)^g)

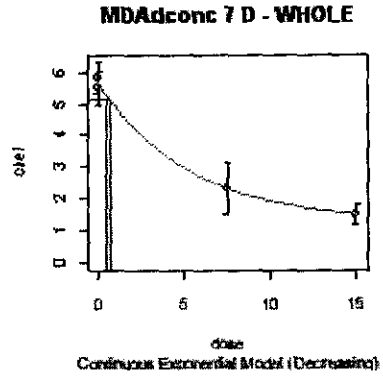
Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

---

Summary of Model Fitting Results

```
      AIC       BIC    logLik
 38.65735  42.64027 -15.32867

Coefficients:
      Value  Std.Error
A 5.7226764 0.31678214
B 1.2589525 0.25158074
m 0.1917306 0.04343782

Correlation:
          A         B         m
A 1.0000000 0.1403111 0.3067966
B 0.1403111 1.0000000 0.8887349
m 0.3067966 0.8887349 1.0000000

Approximate 95% confidence intervals

 Coefficients:
      lower      est.     upper
A 5.0918770 5.7226764 6.4316216
B 0.8258587 1.2589525 1.9191677
m 0.1188781 0.1917306 0.3092295

 Residual standard error:
    lower      est.     upper
0.7591362 1.0116588 1.5166222

Degrees of freedom: 20 total; 17 residual
```



Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 0.1429 with 1 degrees of freedom. P = 0.705

```
  dose n chei Expected   sd    Exp.SD    X2 Resid.
1  0.0 5 5.84 5.722676 0.40 0.9917110  0.264536182
2  0.1 5 5.52 5.637908 0.42 0.9768860 -0.269889484
3  7.5 5 2.32 2.318672 0.68 0.4003437  0.007418733
```

DDVP: Repeated, Brain, Adult, *Concurrent controls*

4 15.0 5 1.51 1.510537 0.26 0.2624115 -0.004578106

BMD Computation

BMD = 0.7156: BMDL = 0.551

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.1917
se: 0.04344
var=se^2: 0.001887
Per cent. of background at unit dose: 83
Per cent. of background at the highest dose: 5.6
ED50 (95% CI): 3.615 (2.319 , 5.636)

ln(Potency) -1.652
se[log(Potency)]: 0.2266
se[log(Potency)]^2: 0.05133

DDVP: Repeated, Brain, Adult, Historical controls

DDVP:7-D:BRAIN:F:WHOLE
Mon Apr 24 21:43:45 2006
MRID: MDAdhist Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)^g)

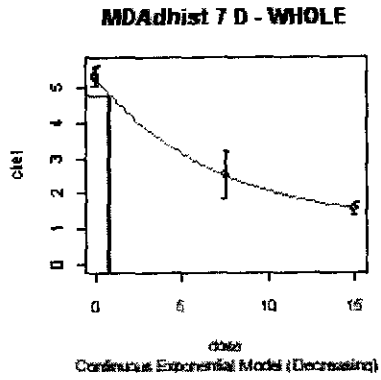
Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

---

Summary of Model Fitting Results

```
      AIC       BIC    logLik
 64.04178  70.79730 -28.02089

Coefficients:
      Value  Std.Error
A 5.3368308 0.11905590
B 1.0997356 0.28281397
m 0.1465709 0.02915622

Correlation:
          A         B         m
A 1.0000000 0.1150917 0.2036726
B 0.1150917 1.0000000 0.9481542
m 0.2036726 0.9481542 1.0000000
```




```
Approximate 95% confidence intervals

 Coefficients:
       lower      est.     upper
A 5.10097136 5.3368308 5.5835960
B 0.65311837 1.0997356 1.8517598
m 0.09794975 0.1465709 0.2193271

 Residual standard error:
    lower      est.     upper
0.5322331 0.6528354 0.8446040

Degrees of freedom: 40 total; 37 residual
```

Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 0.104 with 1 degrees of freedom. P = 0.747

	dose	n	chei	Expected	sd	Exp.SD	X2 Resid.
1	0.0	25	5.32	5.336831	0.60	0.6499687	-0.129474129
2	0.1	5	5.36	5.275180	0.25	0.6424933	0.295197982
3	7.5	5	2.51	2.511155	0.56	0.3062988	-0.008433535

DDVP: Repeated, Brain, Adult, Historical controls

4 15.0 5 1.57 1.569894 0.15 0.1909515 0.001242926

BMD Computation

BMD = 0.9185: BMDL = 0.7518

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.1466
se: 0.02916
var=se^2: 0.0008501
Per cent. of background at unit dose: 86
Per cent. of background at the highest dose: 11
ED50 (95% CI): 4.729 (3.202 , 6.984)

ln(Potency) -1.92
se[log(Potency)]: 0.1989
se[log(Potency)]^2: 0.03957

DDVP: Repeated, Brain, Adult, Historical controls

DDVP:7-D:BRAIN:M:WHOLE
Mon Apr 24 21:43:52 2006
MRID: MDAdhist Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)^g)

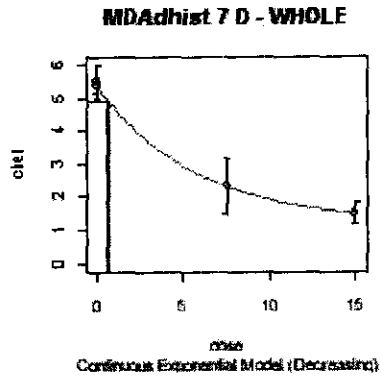
Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

---

Summary of Model Fitting Results

```
      AIC       BIC    logLik
 78.62698  85.38250 -35.31349

Coefficients:
      Value  Std.Error
A 5.4406635 0.14572755
B 1.2233684 0.23205212
m 0.1793503 0.03602974

Correlation:
            A          B         m
A 1.00000000 0.08852252 0.1851917
B 0.08852252 1.00000000 0.9107214
m 0.18519170 0.91072141 1.0000000

Approximate 95% confidence intervals

 Coefficients:
      lower      est.     upper
A 5.1532609 5.4406635 5.7440950
B 0.8329963 1.2233684 1.7966830
m 0.1193784 0.1793503 0.2694501

 Residual standard error:
    lower      est.     upper
0.6580918 0.8072133 1.0443300

Degrees of freedom: 40 total; 37 residual
```



Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 0.2307 with 1 degrees of freedom. P = 0.631

	dose	n	chei	Expected	sd	Exp.SD	X2 Resid.
1	0.0	25	5.41	5.440664	0.61	0.7954922	-0.192733152
2	0.1	5	5.52	5.365700	0.42	0.7846436	0.439720961
3	7.5	5	2.32	2.322001	0.68	0.3407920	-0.013132451

4 15.0 5 1.51 1.509570 0.26 0.2200316 0.004374445

BMD Computation

BMD = 0.7701: BMDL = 0.6168

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.1794
se: 0.03603
var=se^2: 0.001298
Per cent. of background at unit dose: 84
Per cent. of background at the highest dose: 6.8
ED50 (95% CI): 3.865 (2.607 , 5.73)

ln(Potency) -1.718
se[log(Potency)]: 0.2009
se[log(Potency)]^2: 0.04036

DDVP: Repeated, RBC, Adult, Concurrent controls

DDVP:7-D:RBC:F:WHOLE
Mon Apr 24 21:43:38 2006
MRID: MDAdconc Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)^g)

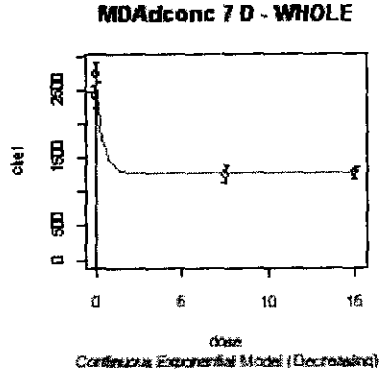
Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

---

Summary of Model Fitting Results

```
      AIC       BIC    logLik
 252.1003  256.0833 -122.0502

Coefficients:
        Value  Std.Error
A 2727.000013 79.6172246
B 1258.499990 25.9812588
m    2.397083  0.8174793

Correlation:
              A             B          m
A 1.000000e+00 1.765012e-06 0.66321810
B 1.765012e-06 1.000000e+00 0.05862781
m 6.632181e-01 5.862781e-02 1.00000000

Approximate 95% confidence intervals

 Coefficients:
        lower        est.       upper
A 2564.091283 2727.000013 2900.259098
B 1204.860966 1258.499990 1314.526963
m    1.167355    2.397083    4.922246

 Residual standard error:
   lower     est.    upper
133.5911 178.0295 266.8919

Degrees of freedom: 20 total; 17 residual
```



Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 0.1959 with 1 degrees of freedom. P = 0.658

	dose	n	chei	Expected	sd	Exp.SD	X2 Resid.
1	0.0	5	2727	2727.0	150	178.02953	-1.663420e-07
2	0.1	5	2414	2414.0	158	157.59563	2.423883e-07
3	7.5	5	1247	1258.5	109	82.15994	-3.129848e-01

4 15.0 5 1270 1258.5 70 82.15994 3.129847e-01

BMD Computation

BMD = 0.0857: BMDL = 0.05385

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 2.397
se: 0.8175
var=se^2: 0.6683
Per cent. of background at unit dose: 9.1
Per cent. of background at the highest dose: 2.4e-14
ED50 (95% CI): 0.2892 (0.1482 , 0.5642)

ln(Potency) 0.8743
se[log(Potency)]: 0.341
se[log(Potency)]^2: 0.1163

DDVP: Repeated, RBC, Adult, Concurrent controls

DDVP:7-D:RBC:M:WHOLE
Mon Apr 24 21:43:43 2006
MRID: MDAdconc Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)^g)

Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

---

Summary of Model Fitting Results

AIC	BIC	logLik
290.6427	294.6256	-141.3214

Coefficients:

	Value	Std.Error
A	2681.7192647	145.3811253
B	1135.7992785	123.8320471
m	0.2702996	0.1094602

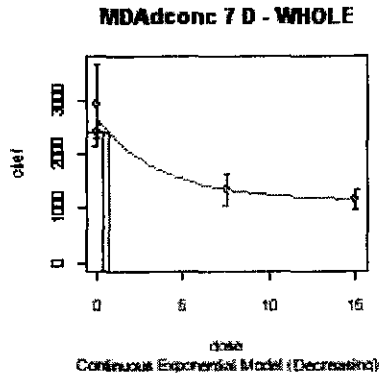
Correlation:

	A	B	m
A	1.0000000	0.0618944	0.1785788
B	0.0618944	1.0000000	0.8143054
m	0.1785788	0.8143054	1.0000000

Approximate 95% confidence intervals

Coefficients:

	lower	est.	upper
A	2391.8831196	2681.7192647	3006.6762692
B	902.4076927	1135.7992785	1429.5534174
m	0.1150242	0.2702996	0.6351871



Residual standard error:

lower	est.	upper
368.1789	490.6517	735.5575

Degrees of freedom: 20 total; 17 residual

Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 2.552 with 1 degrees of freedom. P = 0.110

	dose	n	chei	Expected	sd	Exp.SD	X2 Resid.
1	0.0	5	2908	2681.719	610	453.8838	1.11477671
2	0.1	5	2413	2640.493	111	445.6730	-1.14139604
3	7.5	5	1346	1339.393	236	220.5037	0.06699746

DDVP: Repeated, RBC, Adult, Concurrent controls

```
4 15.0 5 1159 1162.612 155 200.3797 -0.04030813

-----------------------------------------------------------------
                        BMD Computation

                BMD = 0.7048:  BMDL = 0.4481

-----------------------------------------------------------------
                        Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background
activity

Potency: 0.2703
se: 0.1095
var=se^2: 0.01198
Per cent. of background at unit dose: 76
Per cent. of background at the highest dose: 1.7
ED50 (95% CI): 2.564 ( 1.16 , 5.671 )

ln(Potency) -1.308
se[log(Potency)]: 0.405
se[log(Potency)]^2: 0.164
```

DDVP: Repeated, RBC, Adult, Historical controls

DDVP:7-D:RBC:F:WHOLE
Mon Apr 24 21:43:50 2006
MRID: MDAdhist Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)^g)

Variance Function: power

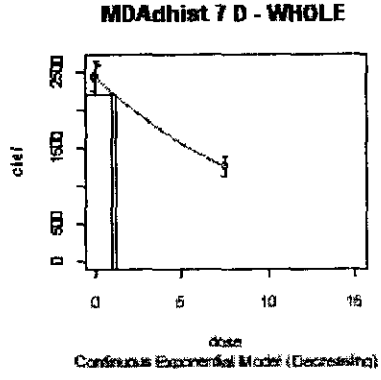
Highest 1 doses dropped from data set.

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

---

Summary of Model Fitting Results

```
      AIC       BIC    logLik
 432.6351  436.8387 -213.3175

Coefficients:
         Value    Std.Error
A 2.453625e+03 68.975570904
m 9.025628e-02  0.009178156

Correlation:
          A         m
A 1.0000000 0.4137541
m 0.4137541 1.0000000

Approximate 95% confidence intervals

 Coefficients:
         lower          est.        upper
A 2.316326e+03 2.453625e+03 2599.0618980
m 7.328462e-02 9.025628e-02    0.1111583

 Residual standard error:
   lower     est.    upper
273.4370 344.5616 466.0030

Degrees of freedom: 30 total; 28 residual
```



Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 0.01654 with 1 degrees of freedom. P = 0.898

	dose	n	chei	Expected	sd	Exp.SD	X2 Resid.
1	0.0	20	2458	2453.625	399	343.9574	0.056889167
2	0.1	5	2414	2431.579	158	340.8656	-0.115315893
3	7.5	5	1247	1246.880	109	174.7398	0.001538003

BMD Computation

BMD = 1.167: BMDL = 1

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.09026
se: 0.009178
var=se^2: 8.424e-05
Per cent. of background at unit dose: 91
Per cent. of background at the highest dose: 51
ED50 (95% CI): 7.68 (6.292 , 9.374)

ln(Potency) -2.405
se[log(Potency)]: 0.1017
se[log(Potency)]^2: 0.01034

DDVP: Repeated, RBC, Adult, Historical controls

DDVP:7-D:RBC:M:WHOLE
Mon Apr 24 21:43:56 2006
MRID: MDAdhist Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)^g)

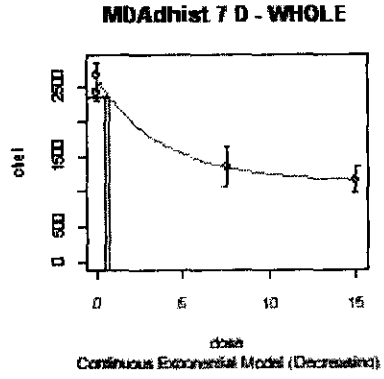
Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

---

Summary of Model Fitting Results

```
      AIC       BIC    logLik
 506.1301  512.3515 -249.0650

Coefficients:
         Value   Std.Error
A 2610.5056190  77.5940879
B 1131.7044406 110.4118748
m    0.2605430   0.0942001

Correlation:
             A          B         m
A 1.00000000 0.04048633 0.1151000
B 0.04048633 1.00000000 0.8225566
m 0.11509996 0.82255665 1.0000000

Approximate 95% confidence intervals

 Coefficients:
         lower         est.         upper
A 2457.1412313 2610.5056190 2773.4423646
B  927.7403439 1131.7044406 1380.5101278
m    0.1247496    0.2605430    0.5441513

 Residual standard error:
   lower     est.    upper
314.8342 391.4927 517.8247

Degrees of freedom: 35 total; 32 residual
```



Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 1.095 with 1 degrees of freedom. P = 0.295

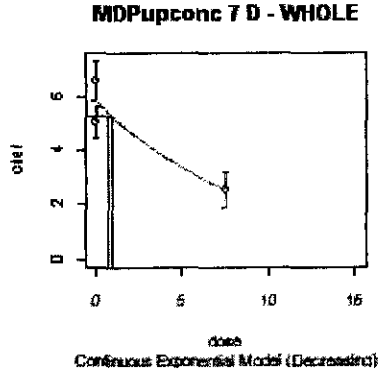
	dose	n	chei	Expected	sd	Exp.SD	X2 Resid.
1	0.0	20	2650	2610.506	411	385.8967	0.45769820
2	0.1	5	2413	2572.474	111	379.8508	-0.93877615
3	7.5	5	1346	1341.244	236	195.8061	0.05430863

DDVP: Repeated, RBC, Adult, Historical controls

```
4 15.0  5 1159 1161.395 155 173.2784 -0.03091094

-----------------------------------------------------------------
                        BMD Computation

                BMD = 0.7455:  BMDL = 0.4982

-----------------------------------------------------------------
                        Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background
activity

Potency: 0.2605
se: 0.0942
var=se^2: 0.008874
Per cent. of background at unit dose: 77
Per cent. of background at the highest dose: 2
ED50 (95% CI): 2.66 ( 1.31 , 5.404 )

ln(Potency) -1.345
se[log(Potency)]: 0.3616
se[log(Potency)]^2: 0.1307
```

DDVP: Repeated, Brain, Pup, Concurrent controls

```
                        DDVP:7-D:BRAIN:F:WHOLE
                       Mon Apr 24 21:43:59 2006
                MRID: MDPupconc   Guideline: NONGUIDELINE
                Continuous Exponential Model (Decreasing)
                Formula: chei = B + (A-B)*exp(-(m*dose)^g)

Variance Function: power

Highest 1 doses dropped from data set.


   The BMD corresponds to a dose that results in a 10% reduction in the
                        response relative to the control
    ------------------------------------------------------------------
                        Summary of Model Fitting Results

      AIC       BIC    logLik
 39.29316  41.41732 -16.64658

Coefficients:
      Value  Std.Error
A 5.8381055 0.33369886
m 0.1111981 0.01312090

Correlation:
          A         m
A 1.0000000 0.5883474
m 0.5883474 1.0000000

Approximate 95% confidence intervals

 Coefficients:
       lower      est.     upper
A 5.15992657 5.8381055 6.6054187
m 0.08617663 0.1111981 0.1434846

 Residual standard error:
    lower      est.     upper
0.8565106 1.1814689 1.9033966

Degrees of freedom: 15 total; 13 residual
    ------------------------------------------------------------------
                              Goodness of Fit
 The chi-squared goodness-of-fit values should be taken as general
indications of fit only.  P-values are likely to be inaccurate to some
degree

Pearson Chi-Square Statistic: 5.215 with 1 degrees of freedom.  P =
0.0224

  dose n chei Expected   sd    Exp.SD   X2 Resid.
1  0.0 5 6.59 5.838105 0.59 1.0482540  1.60389304
2  0.1 5 5.02 5.773546 0.46 1.0365378 -1.62558583
3  7.5 5 2.54 2.535575 0.54 0.4511931  0.02192763
```



BMD Computation

BMD = 0.9475: BMDL = 0.7935

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.1112
se: 0.01312
var=se^2: 0.0001722
Per cent. of background at unit dose: 89
Per cent. of background at the highest dose: 43
ED50 (95% CI): 6.233 (4.946 , 7.855)

ln(Potency) -2.196
se[log(Potency)]: 0.118
se[log(Potency)]^2: 0.01392

DDVP: Repeated, Brain, Pup, Concurrent controls

DDVP:7-D:BRAIN:M:WHOLE
Mon Apr 24 21:44:06 2006
MRID: MDPupconc Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)^g)

Variance Function: power

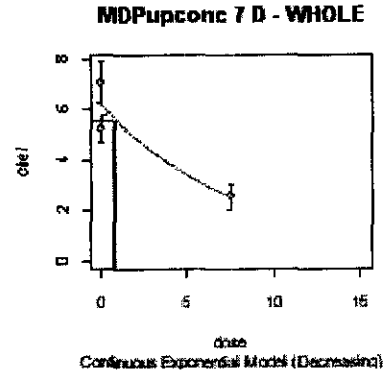
Highest 1 doses dropped from data set.

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

---

Summary of Model Fitting Results

```
      AIC       BIC    logLik
 38.62180  40.74595 -16.31090

Coefficients:
      Value  Std.Error
A 6.2176817 0.33406064
m 0.1201434 0.01231365

Correlation:
          A        m
A 1.000000 0.589248
m 0.589248 1.000000

Approximate 95% confidence intervals

 Coefficients:
       lower      est.     upper
A 5.53629700 6.2176817 6.9829285
m 0.09628064 0.1201434 0.1499205

 Residual standard error:
    lower      est.     upper
0.8659536 1.1944947 1.9243816

Degrees of freedom: 15 total; 13 residual
```



Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 7.004 with 1 degrees of freedom. P = 0.00813

	dose	n	chei	Expected	sd	Exp.SD	X2 Resid.
1	0.0	5	7.09	6.217682	0.64	1.0494073	1.85872816
2	0.1	5	5.27	6.143427	0.44	1.0367170	-1.88387271
3	7.5	5	2.53	2.525203	0.41	0.4213597	0.02545729

BMD Computation

BMD = 0.877: BMDL = 0.7504

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.1201
se: 0.01231
var=se^2: 0.0001516
Per cent. of background at unit dose: 89
Per cent. of background at the highest dose: 41
ED50 (95% CI): 5.769 (4.719 , 7.053)

ln(Potency) -2.119
se[log(Potency)]: 0.1025
se[log(Potency)]^2: 0.0105

DDVP:7-D:BRAIN:F:WHOLE
Mon Apr 24 21:44:12 2006
MRID: MDPuphist Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)^g)

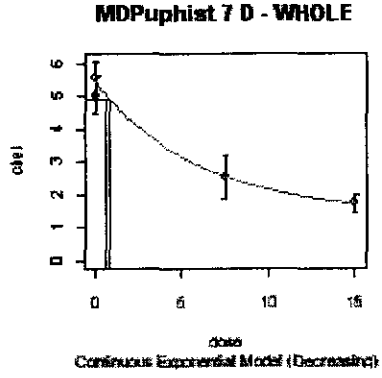
Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

---

Summary of Model Fitting Results

```
      AIC       BIC    logLik
 91.73904  98.07312 -41.86952

Coefficients:
      Value  Std.Error
A 5.4535860 0.20843990
B 1.3874190 0.37759636
m 0.1686908 0.05235096

Correlation:
          A         B         m
A 1.0000000 0.0969725 0.1952096
B 0.0969725 1.0000000 0.9213612
m 0.1952096 0.9213612 1.0000000
```



Approximate 95% confidence intervals

```
 Coefficients:
       lower      est.     upper
A 5.04558081 5.4535860 5.8945841
B 0.79750815 1.3874190 2.4136825
m 0.08971903 0.1686908 0.3171746

 Residual standard error:
   lower     est.    upper
0.867120 1.075062 1.415080

Degrees of freedom: 36 total; 33 residual
```

Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 0.7522 with 1 degrees of freedom. P = 0.386

	dose	n	chei	Expected	sd	Exp.SD	X2 Resid.
1	0.0	21	5.54	5.453586	1.18	1.0587084	0.374039299
2	0.1	5	5.02	5.385569	0.46	1.0451764	-0.782104088
3	7.5	5	2.54	2.534843	0.54	0.4881430	0.023622823

4 15.0 5 1.71 1.711208 0.22 0.3342521 -0.008084159

BMD Computation

BMD = 0.8537: BMDL = 0.6228

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.1687
se: 0.05235
var=se^2: 0.002741
Per cent. of background at unit dose: 84
Per cent. of background at the highest dose: 8
ED50 (95% CI): 4.109 (2.237 , 7.549)

ln(Potency) -1.78
se[log(Potency)]: 0.3103
se[log(Potency)]^2: 0.09631

DDVP:7-D:BRAIN:M:WHOLE
Mon Apr 24 21:44:18 2006
MRID: MDPuphist Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)^g)

Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

---

Summary of Model Fitting Results

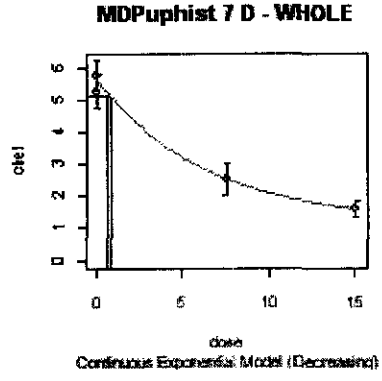
AIC	BIC	logLik
90.63050	97.28474	-41.31525

Coefficients:

	Value	Std.Error
A	5.6883165	0.17732604
B	1.1782553	0.33427136
m	0.1610776	0.03905932

Correlation:

	A	B	m
A	1.0000000	0.1065217	0.2028358
B	0.1065217	1.0000000	0.9324765
m	0.2028358	0.9324765	1.0000000



Approximate 95% confidence intervals

Coefficients:

	lower	est.	upper
A	5.33981535	5.6883165	6.059562
B	0.66276419	1.1782553	2.094690
m	0.09850411	0.1610776	0.263400

Residual standard error:

lower	est.	upper
0.7834716	0.9634302	1.2514578

Degrees of freedom: 39 total; 36 residual

Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 0.8159 with 1 degrees of freedom. P = 0.366

	dose	n	chei	Expected	sd	Exp.SD	X2 Resid.
1	0.0	24	5.76	5.688316	1.05	0.9517421	0.36898250
2	0.1	5	5.27	5.616251	0.44	0.9394402	-0.82415231
3	7.5	5	2.53	2.525726	0.41	0.4194838	0.02278489

4 15.0 5 1.58 1.580839 0.21 0.2660983 -0.00704853

BMD Computation

BMD = 0.837: BMDL = 0.6514

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.1611
se: 0.03906
var=se^2: 0.001526
Per cent. of background at unit dose: 85
Per cent. of background at the highest dose: 8.9
ED50 (95% CI): 4.303 (2.675 , 6.921)

ln(Potency) -1.826
se[log(Potency)]: 0.2425
se[log(Potency)]^2: 0.0588

DDVP:7-D:RBC:F:WHOLE
Mon Apr 24 21:44:03 2006
MRID: MDPupconc Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)^g)

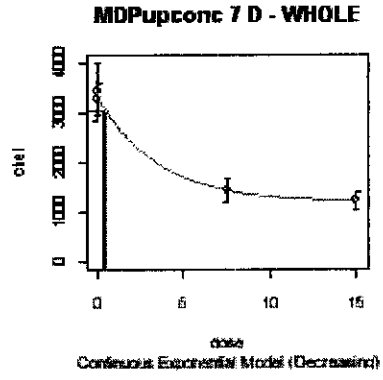
Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

---

Summary of Model Fitting Results

```
      AIC       BIC    logLik
 282.2902  286.2732 -137.1451

Coefficients:
         Value    Std.Error
A 3367.8252655 128.82707749
B 1182.3605015  84.42210176
m    0.2942281   0.06693016

Correlation:
           A          B         m
A 1.00000000 0.05726548 0.1789545
B 0.05726548 1.00000000 0.7844004
m 0.17895453 0.78440045 1.0000000

Approximate 95% confidence intervals

 Coefficients:
         lower          est.        upper
A 3106.7025997 3367.8252655 3650.8956538
B 1017.0123351 1182.3605015 1374.5913469
m    0.1820754    0.2942281    0.4754635

 Residual standard error:
   lower     est.    upper
305.9931 407.7801 611.3211

Degrees of freedom: 20 total; 17 residual
```



Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 0.1602 with 1 degrees of freedom. P = 0.689

	dose	n	chei	Expected	sd	Exp.SD	X2 Resid.
1	0.0	5	3418	3367.825	470	401.9922	0.27909526
2	0.1	5	3254	3304.460	257	394.2670	-0.28617896
3	7.5	5	1424	1422.897	201	169.0092	0.01459009

4 15.0 5 1208 1208.834 145 144.7334 -0.01289216

BMD Computation

BMD = 0.5688: BMDL = 0.427

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.2942
se: 0.06693
var=se^2: 0.00448
Per cent. of background at unit dose: 75
Per cent. of background at the highest dose: 1.2
ED50 (95% CI): 2.356 (1.508 , 3.679)

ln(Potency) -1.223
se[log(Potency)]: 0.2275
se[log(Potency)]^2: 0.05175

DDVP:7-D:RBC:M:WHOLE
Mon Apr 24 21:44:10 2006
MRID: MDPupconc Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
*Formula: chei = B + (A-B)*exp(-(m*dose)^g)*

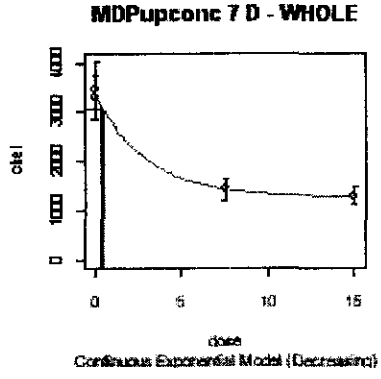
Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

---

Summary of Model Fitting Results

```
      AIC       BIC    logLik
 284.3103  288.2933 -138.1552

Coefficients:
         Value   Std.Error
A 3405.8244474 134.5531824
B 1265.5873297  82.6795659
m    0.3447276   0.0992573

Correlation:
           A          B         m
A 1.00000000 0.05821642 0.1595949
B 0.05821642 1.00000000 0.7517474
m 0.15959491 0.75174742 1.0000000

Approximate 95% confidence intervals

 Coefficients:
         lower         est.        upper
A 3133.4511572 3405.8244474 3701.8736162
B 1102.6365176 1265.5873297 1452.6194839
m    0.1877810    0.3447276    0.6328497

 Residual standard error:
   lower     est.    upper
317.7069 423.3904 634.7231

Degrees of freedom: 20 total; 17 residual
```



Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 0.6739 with 1 degrees of freedom. P = 0.412

	dose	n	chei	Expected	sd	Exp.SD	X2 Resid.
1	0.0	5	3299	3405.824	353	418.5584	-0.57068917
2	0.1	5	3441	3333.302	484	410.1457	0.58715849

```
3  7.5 5 1423 1426.879 186 177.3018 -0.04892138
4 15.0 5 1280 1277.743 146 155.8875  0.03238133
```

BMD Computation

BMD = 0.5028: BMDL = 0.3509

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.3447
se: 0.09926
var=se^2: 0.009852
Per cent. of background at unit dose: 71
Per cent. of background at the highest dose: 0.57
ED50 (95% CI): 2.011 (1.144 , 3.535)

ln(Potency) -1.065
se[log(Potency)]: 0.2879
se[log(Potency)]^2: 0.0829

DDVP:7-D:RBC:F:WHOLE
Mon Apr 24 21:44:16 2006
MRID: MDPuphist Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)^g)

Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

---

Summary of Model Fitting Results

AIC	BIC	logLik
471.1821	477.1681	-231.5910

Coefficients:

	Value	Std.Error
A	3212.0118304	78.13348301
B	1175.9601007	84.40054910
m	0.2793221	0.06360987

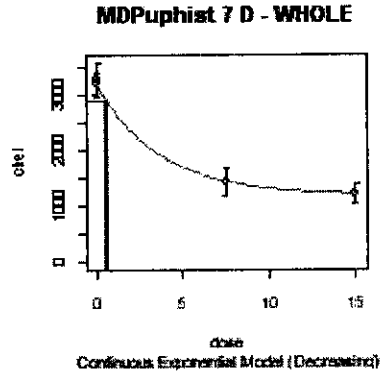
Correlation:

	A	B	m
A	1.00000000	0.03961674	0.1212268
B	0.03961674	1.00000000	0.7972136
m	0.12122680	0.79721362	1.0000000

Approximate 95% confidence intervals

Coefficients:

	lower	est.	upper
A	3056.3407841	3212.0118304	3375.6117944
B	1015.6286087	1175.9601007	1361.6022102
m	0.1754370	0.2793221	0.4447228



Residual standard error:

lower	est.	upper
301.6668	377.5026	504.5976

Degrees of freedom: 33 total; 30 residual

Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 0.4548 with 1 degrees of freedom. P = 0.5

	dose	n	chei	Expected	sd	Exp.SD	X2 Resid.
1	0.0	18	3185	3212.012	377	372.5099	-0.30764682
2	0.1	5	3254	3155.927	257	366.1959	0.59885197
3	7.5	5	1424	1426.559	201	166.5420	-0.03435202

4 15.0 5 1208 1206.804 145 139.2642 0.01920492

BMD Computation

BMD = 0.6147: BMDL = 0.4647

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.2793
se: 0.06361
var=se^2: 0.004046
Per cent. of background at unit dose: 76
Per cent. of background at the highest dose: 1.5
ED50 (95% CI): 2.482 (1.588 , 3.878)

ln(Potency) -1.275
se[log(Potency)]: 0.2277
se[log(Potency)]^2: 0.05186

DDVP:7-D:RBC:M:WHOLE
Mon Apr 24 21:44:21 2006
MRID: MDPuphist Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)^g)

Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

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Summary of Model Fitting Results

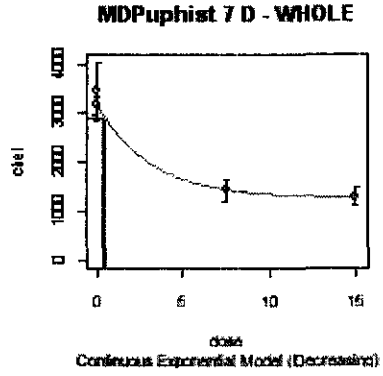
AIC	BIC	logLik
508.6161	514.8375	-250.3081

Coefficients:

	Value	Std.Error
A	3229.7438903	83.54133448
B	1259.4597968	88.49275967
m	0.3240709	0.09828153

Correlation:

	A	B	m
A	1.00000000	0.03616319	0.1024154
B	0.03616319	1.00000000	0.7630263
m	0.10241540	0.76302628	1.0000000



Approximate 95% confidence intervals

Coefficients:

	lower	est.	upper
A	3063.9809484	3229.7438903	3404.4746923
B	1091.5109432	1259.4597968	1453.2506428
m	0.1747259	0.3240709	0.6010671

Residual standard error:

lower	est.	upper
355.8975	442.5545	585.3637

Degrees of freedom: 35 total; 32 residual

Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 2.812 with 1 degrees of freedom. P = 0.0936

	dose	n	chei	Expected	sd	Exp.SD	X2 Resid.
1	0.0	20	3162	3229.744	385	415.0112	-0.7300042
2	0.1	5	3441	3166.916	484	407.7138	1.5031865
3	7.5	5	1423	1432.825	186	187.6611	-0.1170705

DDVP: Repeated, RBC, Pup, Historical controls

```
4 15.0  5 1280 1274.714 146 161.4604  0.0732030

-----------------------------------------------------------------
                          BMD Computation

                  BMD = 0.5525;  BMDL = 0.3825

-----------------------------------------------------------------
                          Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background
activity

Potency: 0.3241
se: 0.09828
var=se^2: 0.009659
Per cent. of background at unit dose: 72
Per cent. of background at the highest dose: 0.77
ED50 (95% CI): 2.139 ( 1.18 , 3.876 )

ln(Potency) -1.127
se[log(Potency)]: 0.3033
se[log(Potency)]^2: 0.09197
```

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R128680

Chemical: Dichlorvos

PC Code:
084001

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