UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

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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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 1 4 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 χ^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

                         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 6.9198135 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

ADULT 1 D - MAIN

Continuous Exponential Model (Decreasing)
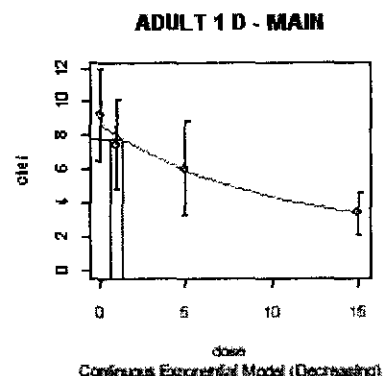
DDVP: Acute, Brain, Adult

```
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

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
```


ADULT 1 D - MAIN
Continuous Exponential Model (Decreasing)
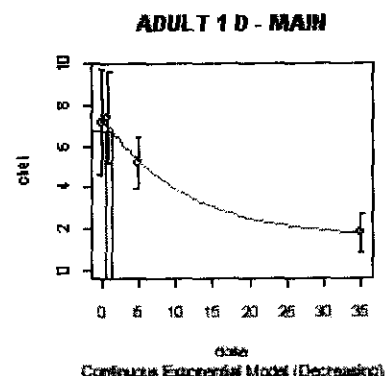
DDVP: Acute, Brain, Adult

```
4    35 5 1.77 1.769368 0.74 0.5147315  0.002747467
```

BMD Computation

$$BMD = 1.455: \quad BMDL = 0.7623$$

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

                       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
```



**ADULT 1 D - MAIN**

Continuous Exponential Model (Decreasing)

| | 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**

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
```

ADULT 1 D - MAIN

Continuous Exponential Model (Decreasing)

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

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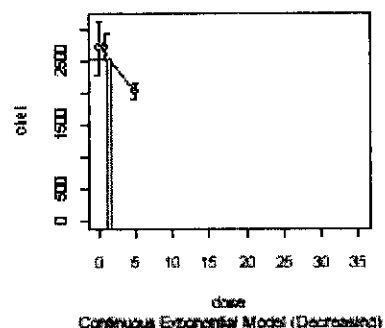  dose n chei Expected  sd   Exp.SD   X2 Resid.
1    0 5 2705 2790.461 343 242.2597 -0.7888111
2    1 5 2719 2618.549 170 227.7068  0.9864189
3    5 5 2015 2030.486  94 177.7275 -0.1948314
```

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

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
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

PND8 1 PND - MAIN
Continuous Exponential Model (Decreasing)

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: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

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
```


PND8 1 PND - MAIN

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
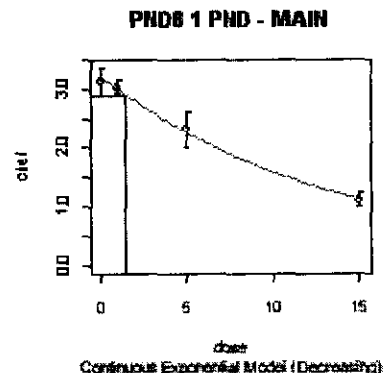
                    BMD = 1.495:   BMDL = 1.403


-------------------------------------------------------------------
                        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

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

PND8 1 PND - MAIN

Continuous Exponential Model (Decreasing)

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

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
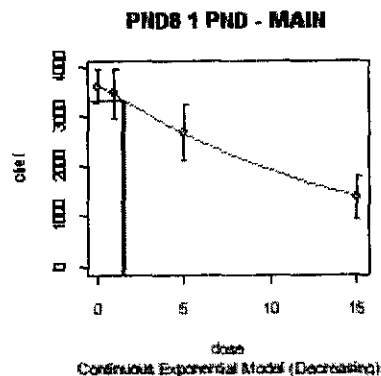433.6720  573.9343  848.7482
```

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
```


MDAdconc 7 D - WHOLE

Continuous Exponential Model (Decreasing)

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:
```
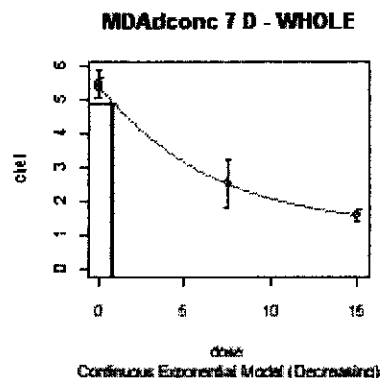    lower       est.      upper
0.5119114  0.6821960  1.0227101
```

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

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

MDAdconc 7 D - WHOLE
Continuous Exponential Model (Decreasing)

DDVP: Repeated, Brain, Adult, Concurrent controls
4 15.0 5 1.51 1.510537 0.26 0.2624115 -0.004578106

```
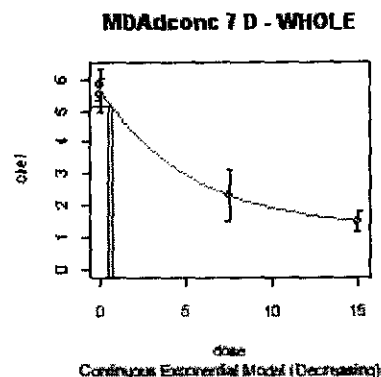--------------------------------------------------------------------
                           BMD Computation

                   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: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

MDAdhist 7 D - WHOLE

Continuous Exponential Model (Decreasing)

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
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

MDAdhist 7 D - WHOLE

Continuous Exponential Model (Decreasing)

 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

DDVP: Repeated, Brain, Adult, Historical controls

4 15.0 5 1.51 1.509570 0.26 0.2200316 0.004374445

```
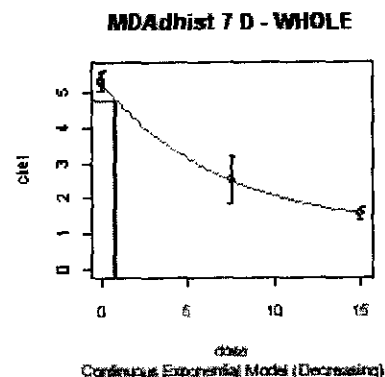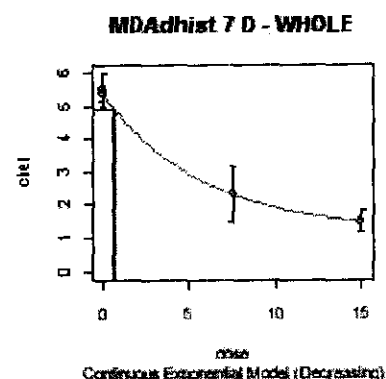--------------------------------------------------------------------
                          BMD Computation

                  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: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

MDAdconc 7 D - WHOLE

Continuous Exponential Model (Decreasing)

	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

DDVP: Repeated, RBC, Adult, Concurrent controls

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

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

MDAdconc 7 D - WHOLE

Continuous Exponential Model (Decreasing)

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

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: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

MDAdhist 7 D - WHOLE

Continuous Exponential Model (Decreasing)

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: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

MDAdhist 7 D - WHOLE

dose

Continuous Exponential Model (Decreasing)

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: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

MDPupconc 7 D - WHOLE

Continuous Exponential Model (Decreasing)

 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: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

MDPupconc 7 D - WHOLE

Continuous Exponential Model (Decreasing)

	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

MDPuphist 7 D - WHOLE

Continuous Exponential Model (Decreasing)

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

MDPuphist 7 D - WHOLE

Continuous Exponential Model (Decreasing)

  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

DDVP: Repeated, Brain, Pup, Historical controls

4 15.0   5 1.58 1.580839 0.21 0.2660983 -0.00704853

```
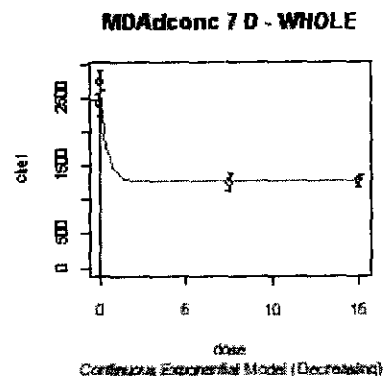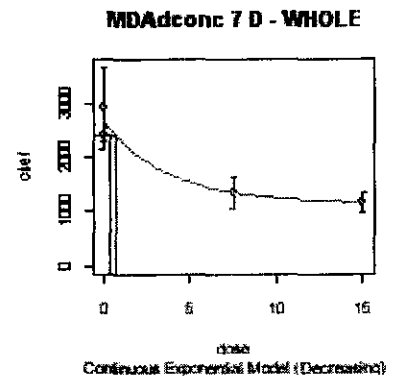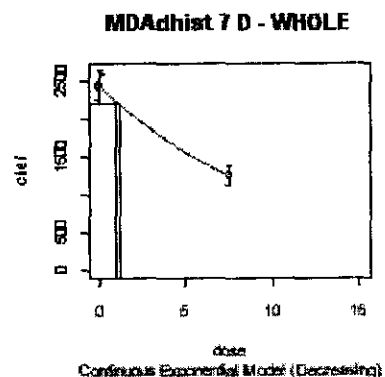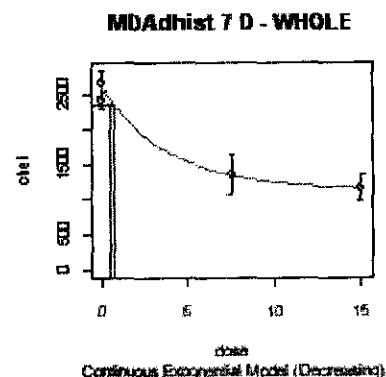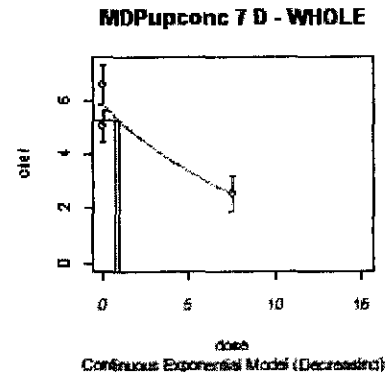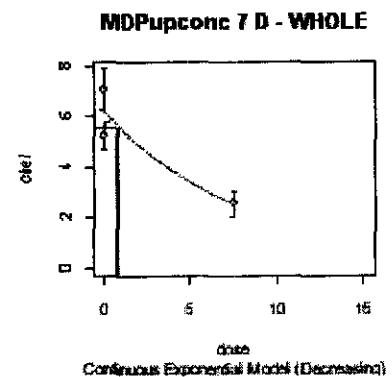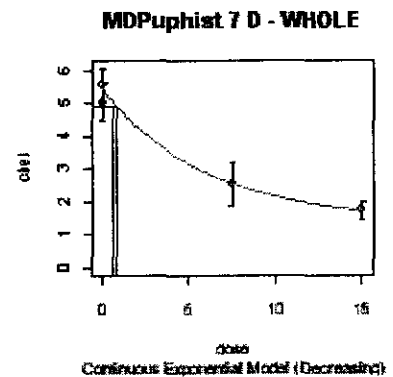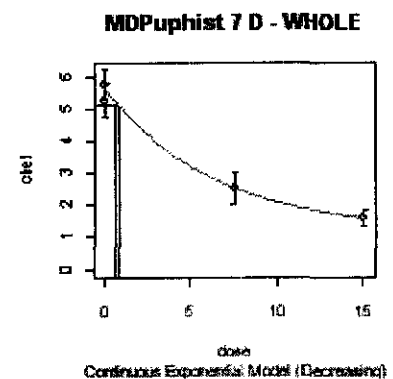----------------------------------------------------------------
                        BMD Computation

             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

MDPupconc 7 D - WHOLE

Continuous Exponential Model (Decreasing)

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

DDVP: Repeated, RBC, Pup, Concurrent controls

4 15.0 5 1208 1208.834 145 144.7334 -0.01289216

```
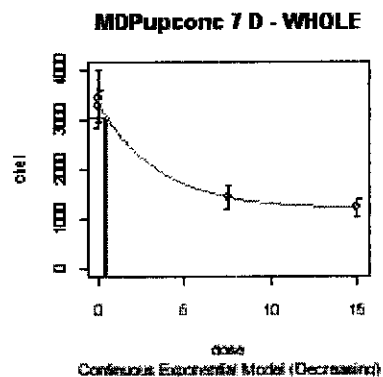---------------------------------------------------------------------
                          BMD Computation

                   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
```
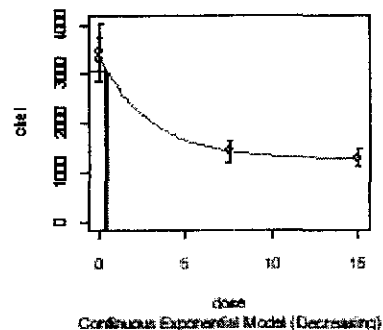


MDPupconc 7 D - WHOLE

Continuous Exponential Model (Decreasing)

```
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

MDPuphist 7 D - WHOLE

Continuous Exponential Model (Decreasing)
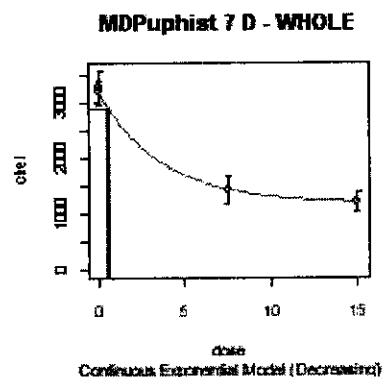
4 15.0 5 1208 1206.804 145 139.2642 0.01920492

```
-------------------------------------------------------------------
                         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

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

MDPuphist 7 D - WHOLE

Coefficients:
```
           lower          est.         upper
A 3063.9309484  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
```
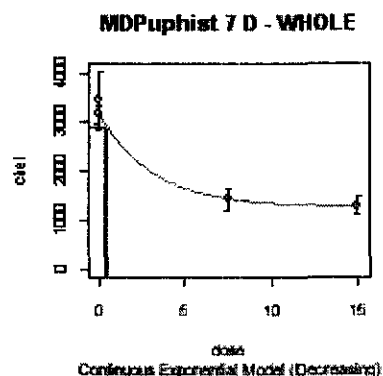
4 15.0   5 1280 1274.714 146 161.4604 0.0732030

```
------------------------------------------------------------
                    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

R128680

Chemical: Dichlorvos

PC Code:
084001
HED File Code: 13000 Tox Reviews
Memo Date: 6/9/2006
File ID: DPD328793
Accession #:   412-06-0192

HED Records Reference Center
7/12/2006