United States
Environmental Protection Agency

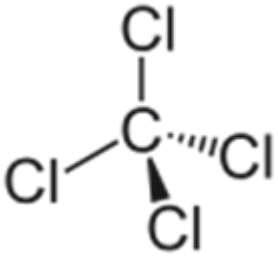
Office of Chemical Safety and
Pollution Prevention

Final Risk Evaluation for Carbon Tetrachloride

Supplemental File:

Benchmark Dose Modeling and Source Code for PBPK Model for Derivation of the IRIS Reference Concentration (POD for Chronic Inhalation Exposures) and Inhalation Unit Risk

CASRN: 56-23-5



October 2020

BENCHMARK DOSE MODELING FOR DERIVING THE REFERENCE CONCENTRATION

MALE RAT:

Incidence data for fatty changes of the liver
Male F344 rats exposed to carbon tetrachloride vapor for 104 weeks (6 hours/day, 5 days/week)
Exposure concentrations modeled: ***0, 5, 25, 125 ppm***
BMR = 10%

Model	V_{max} = 0.4				V_{max} = 0.65			
	AIC	χ^2 *p*-value[a]	BMC_{10}	$BMCL_{10}$	AIC	χ^2 *p*-value[a]	BMC_{10}	$BMCL_{10}$
MCA (µmol/L)								
Gamma[b]	144.336	0.0007	0.0793248	0.0551873	144.772	0.0005	0.0689847	0.051179
Logistic[c]	155.104	0.0000	0.170834	0.137191	156.51	0.0000	0.157857	0.126743
Log-Logistic[c]	**137.403**	**0.4355**	**0.136715**	**0.0790319**	**137.463**	**0.4087**	**0.123076**	**0.0707077**
Multistage 1-degree[d,e]	142.388	0.0074	0.0714015	0.0550523	142.778	0.0031	0.0665234	0.0511645
Probit[c]	169.521	0.0000	0.22329	0.17626	171.234	0.0000	0.21463	0.168317
Log-probit[c]	138.408	0.1761	0.124953	0.0755939	138.529	0.1581	0.112257	0.0803264
Quantal-linear	142.388	0.0074	0.0714017	0.0550523	142.778	0.0031	0.0665234	0.0511645
Weibull[b]	142.388	0.0074	0.0714016	0.0550523	142.778	0.0031	0.0665235	0.0511645
MRAMKL (µmol/hr-kg liver)								
Gamma[b]	137.468	0.4177	3.98707	2.6343	137.338	0.4760	5.31098	3.35649
Logistic[c]	**136.747**	**0.3444**	**3.25675**	**2.58557**	**136.513**	**0.3671**	**4.60057**	**3.65284**
Log-Logistic[c]	136.933	0.8012	4.56744	3.08461	136.996	0.7246	6.20422	4.00273
Multistage 2-degree[e,f]	137.073	0.2702	3.55184	2.02617	138.991	0.0944	4.99656	2.5022
Probit[c]	138.891	0.0826	2.97807	2.41619	138.712	0.0728	4.23817	3.44383
Log-probit[c]	136.871	0.9538	4.27176	3.06539	136.872	0.9470	5.73628	3.97844
Quantal-linear	151.674	0.0008	1.01942	0.831472	148.898	0.0025	1.45532	1.18412
Weibull[b]	138.997	0.1316	3.34831	2.18252	138.601	0.1751	4.4781	2.81908

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria; *p* value from the χ^2 test.
[b]Power restricted to ≥1.
[c]Slope restricted to ≥1.
[d]Used smallest degree polynomial available with an adequate fit; the 2- and 3-degree polynomials provided the same fit as the 1-degree.
[e]Betas restricted to >0.
[f]Used smallest degree polynomial available with an adequate fit; the 3-degree polynomial provided the same fit as the 2-degree.

FEMALE RAT:

Incidence data for fatty changes of the liver
Female F344 rats exposed to carbon tetrachloride vapor for 104 weeks (6 hours/day, 5 days/week)
Exposure concentrations modeled: ***0, 5, 25, 125 ppm***
BMR = 10%

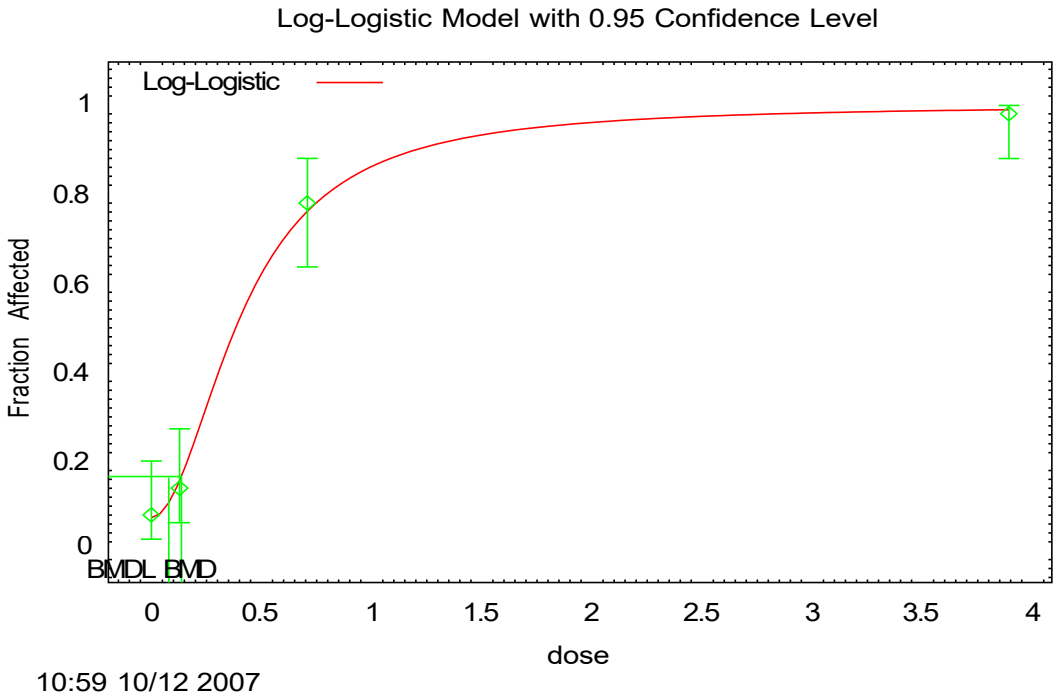
None of the models in BMDS provided an adequate fit of the female rat data.

Incidence data for fatty changes of the liver
Female F344 rats exposed to carbon tetrachloride vapor for 104 weeks (6 hours/day, 5 days/week)
Exposure concentrations modeled: ***0, 5, 25 ppm*** (high dose dropped)
BMR = 10%

Model	V_{max} = 0.4				V_{max} = 0.65			
	AIC	χ^2 *p*-value[a]	BMC_{10}	$BMCL_{10}$	AIC	χ^2 *p*-value[a]	BMC_{10}	$BMCL_{10}$
MCA (µmol/L)								
Gamma[b]	92.9928	NA	0.187771	0.107455	92.9928	NA	0.170979	0.0971536
Logistic[c]	93.4185	0.1121	0.106984	0.0803379	93.3172	0.1201	0.0979754	0.0734707
Log-Logistic[c]	92.9928	NA	0.182663	0.111838	92.9928	NA	0.166144	0.101213
Multistage[d,e]	**2nd degree 92.4089**	**0.2442**	**0.123631**	**0.0851972**	**2nd degree 92.3049**	**0.2617**	**0.113721**	**0.0775873**
	3rd degree 94.9928	NA	0.213915	0.090506	3rd degree 92.9928	NA	0.195194	0.08177
Probit[c]	93.6833	0.0968	0.100288	0.0779817	93.5689	0.1043	0.0919928	0.0714911
Log-probit[c]	92.9928	NA	0.174053	0.112578	92.9928	NA	0.158234	0.101889
Quantal-linear	111.424	0.0000	0.0363563	0.0277405	111.025	0.0001	0.0332712	0.0253689
Weibull[b]	92.9928	NA	0.213201	0.102923	92.9928	NA	0.194228	0.0930656
MRAMKL (µmol/hr-kg liver)								
Gamma[b]	92.9928	NA	4.85516	3.42634	92.9928	NA	6.52318	4.43018
Logistic[c]	99.7262	0.0020	2.45785	1.90371	97.8675	0.0064	3.34536	2.58247
Log-Logistic[c]	92.9928	NA	4.84705	3.48106	92.9928	NA	6.48806	4.51798
Multistage[d,e]	2nd degree 100.7	0.0039	2.43344	1.99357	2nd degree 98.1134	0.0124	3.42266	2.75565
	3rd degree 92.2866	**0.2650**	**3.76974**	**2.82488**	**3rd degree 91.5964**	**0.4421**	**5.42354**	**3.74923**
Probit[c]	100.988	0.0013	2.16088	1.70134	98.8142	0.0044	2.98448	2.34695
Log-probit[c]	92.9928	NA	4.69168	3.49658	92.9928	NA	6.26103	4.54001
Quantal-linear	127.034	0.0000	0.817323	0.634088	123.548	0.0000	1.12472	0.870515
Weibull[b]	92.9928	NA	5.3798	3.29131	92.9928	NA	7.27174	4.24944

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria; *p* value from the χ^2 test.
[b]Power restricted to ≥1.
[c]Slope restricted to ≥1.
[d]Used smallest degree polynomial available with an adequate fit.
[e]Betas restricted to >0.

Male Rat
Dose metric: MCA
Vmax = 0.4 mg/hour/kg $BW^{0.07}$

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      Logistic Model. (Version: 2.9; Date: 02/20/2007)
      Input Data File: G:\CARBON TET\BMD\BMD MODELING 10-2007\RFC RAT LIVER\MALE RAT\MCA-
VMAX=0.4\RAT-FATTYLIVER-MCA-4.(d)
      Gnuplot Plotting File: G:\CARBON TET\BMD\BMD MODELING 10-2007\RFC RAT LIVER\MALE RAT\MCA-
VMAX=0.4\RAT-FATTYLIVER-MCA-4.plt
                          Fri Oct 12 10:59:34 2007
 =====================================================================

 BMDS MODEL RUN
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   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]

   Dependent variable = FattyLiver
   Independent variable = umol/L
   Slope parameter is not restricted

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

   User has chosen the log transformed model

                 Default Initial Parameter Values
                    background =         0.08
                     intercept =      1.42536
                         slope =      1.89476
```

Asymptotic Correlation Matrix of Parameter Estimates

	background	intercept	slope
background	1	-0.077	0.34
intercept	-0.077	1	0.54
slope	0.34	0.54	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval	
			Lower Conf. Limit	Upper Conf. Limit
background	0.073606	*	*	*
intercept	1.74202	*	*	*
slope	1.97967	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-65.434	4			
Fitted model	-65.7017	3	0.535433	1	0.4643
Reduced model	-138.619	1	146.371	3	<.0001

AIC: 137.403

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0736	3.680	4	50	0.173
0.1280	0.1559	7.796	7	50	-0.310
0.7080	0.7614	38.068	39	50	0.309
3.8920	0.9891	49.456	49	50	-0.621

Chi^2 = 0.61 d.f. = 1 P-value = 0.4355

Benchmark Dose Computation

Specified effect = 0.1

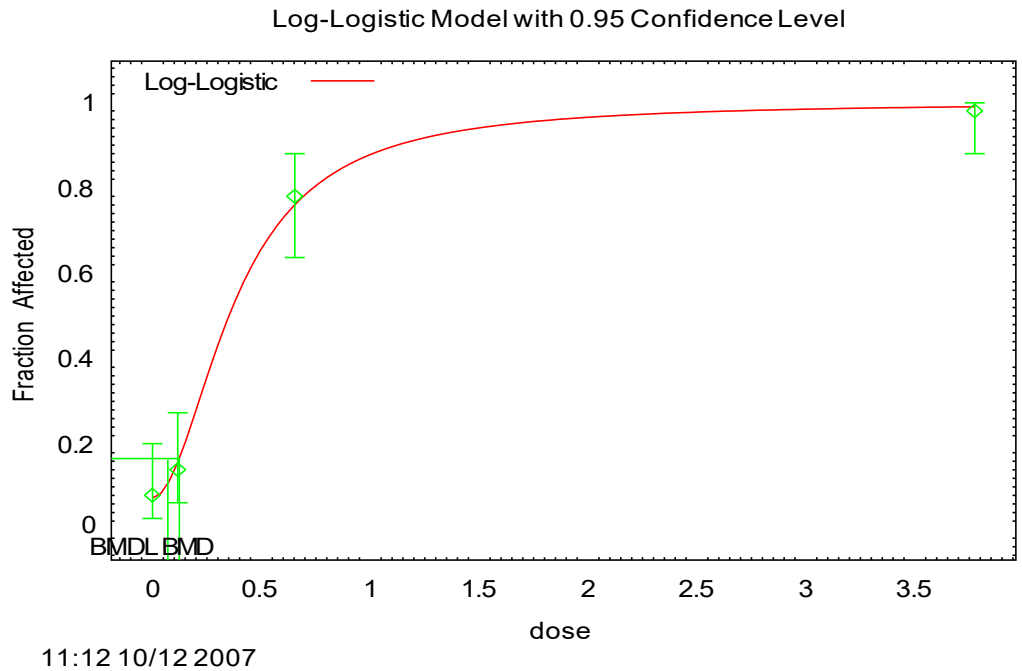
Risk Type = Extra risk

Confidence level = 0.95

BMD = 0.136715

BMDL = 0.0790319

Male Rat
Dose metric: MCA
Vmax = 0.65 mg/hour/kg $BW^{0.07}$

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=====================================================================
      Logistic Model. (Version: 2.9; Date: 02/20/2007)
      Input Data File: G:\CARBON TET\BMD\BMD MODELING 10-2007\RFC RAT LIVER\MALE RAT\MCA-
VMAX=0.65\RAT-FATTYLIVER-MCA-65.(d)
      Gnuplot Plotting File: G:\CARBON TET\BMD\BMD MODELING 10-2007\RFC RAT LIVER\MALE RAT\MCA-
VMAX=0.65\RAT-FATTYLIVER-MCA-65.plt
                        Fri Oct 12 11:12:25 2007
 =====================================================================

 BMDS MODEL RUN
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   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]

   Dependent variable = FattyLiver
   Independent variable = umol/L
   Slope parameter is restricted as slope >= 1

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

   User has chosen the log transformed model


                 Default Initial Parameter Values
                    background =         0.08
                     intercept =      1.54201
                         slope =      1.85672


           Asymptotic Correlation Matrix of Parameter Estimates

             background     intercept        slope
```

background	1	-0.05	0.33
intercept	-0.05	1	0.6
slope	0.33	0.6	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
background	0.0733292	*	*	*
intercept	1.88323	*	*	*
slope	1.94775	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-65.434	4			
Fitted model	-65.7316	3	0.595159	1	0.4404
Reduced model	-138.619	1	146.371	3	<.0001

AIC: 137.463

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0733	3.666	4	50	0.181
0.1160	0.1568	7.841	7	50	-0.327
0.6530	0.7603	38.017	39	50	0.326
3.7750	0.9895	49.476	49	50	-0.661

Chi^2 = 0.68 d.f. = 1 P-value = 0.4087

Benchmark Dose Computation

Specified effect = 0.1

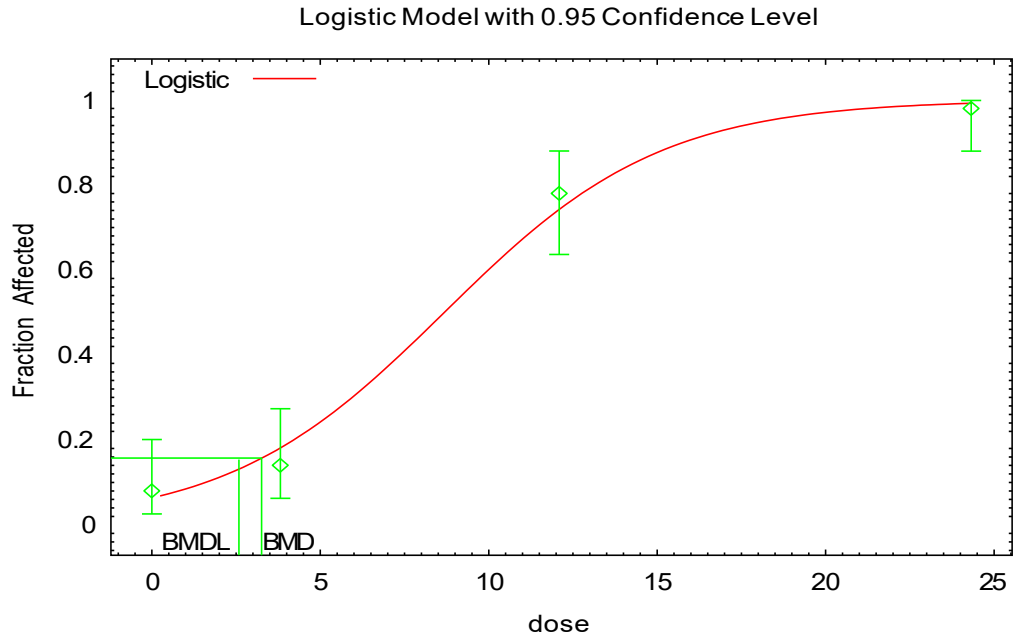
Risk Type = Extra risk

Confidence level = 0.95

BMD = 0.123076

BMDL = 0.0707077

Male Rat
Dose metric: MRAMKL
Vmax = 0.4 mg/hour/kg $BW^{0.07}$

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=================================================================
      Logistic Model. (Version: 2.9; Date: 02/20/2007)
      Input Data File: G:\CARBON TET\BMD\BMD MODELING 10-2007\RFC RAT LIVER\MALE RAT\MRAMKL-
VMAX=0.4\FATTY_LIVER_MRAMKL-4.(d)
      Gnuplot Plotting File: G:\CARBON TET\BMD\BMD MODELING 10-2007\RFC RAT LIVER\MALE
RAT\MRAMKL-VMAX=0.4\FATTY_LIVER_MRAMKL-4.plt
                          Fri Oct 12 11:17:49 2007
 =================================================================

 BMDS MODEL RUN
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   The form of the probability function is:

   P[response] = 1/[1+EXP(-intercept-slope*dose)]

   Dependent variable = FattyLiver
   Independent variable = umol/hr-kgL
   Slope parameter is not restricted

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


                  Default Initial Parameter Values
                     background =            0   Specified
                      intercept =     -2.35241
                          slope =     0.249767


           Asymptotic Correlation Matrix of Parameter Estimates

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

	intercept	slope
intercept	1	-0.82
slope	-0.82	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
intercept	-2.68587	0.383165	-3.43685	-1.93488
slope	0.309634	0.0415113	0.228273	0.390994

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-65.434	4			
Fitted model	-66.3737	2	1.87944	2	0.3907
Reduced model	-138.619	1	146.371	3	<.0001

AIC: 136.747

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0638	3.191	4	50	0.468
3.8130	0.1816	9.082	7	50	-0.764
12.0920	0.7424	37.118	39	50	0.609
24.3200	0.9922	49.609	49	50	-0.979

Chi^2 = 2.13 d.f. = 2 P-value = 0.3444

Benchmark Dose Computation

Specified effect = 0.1

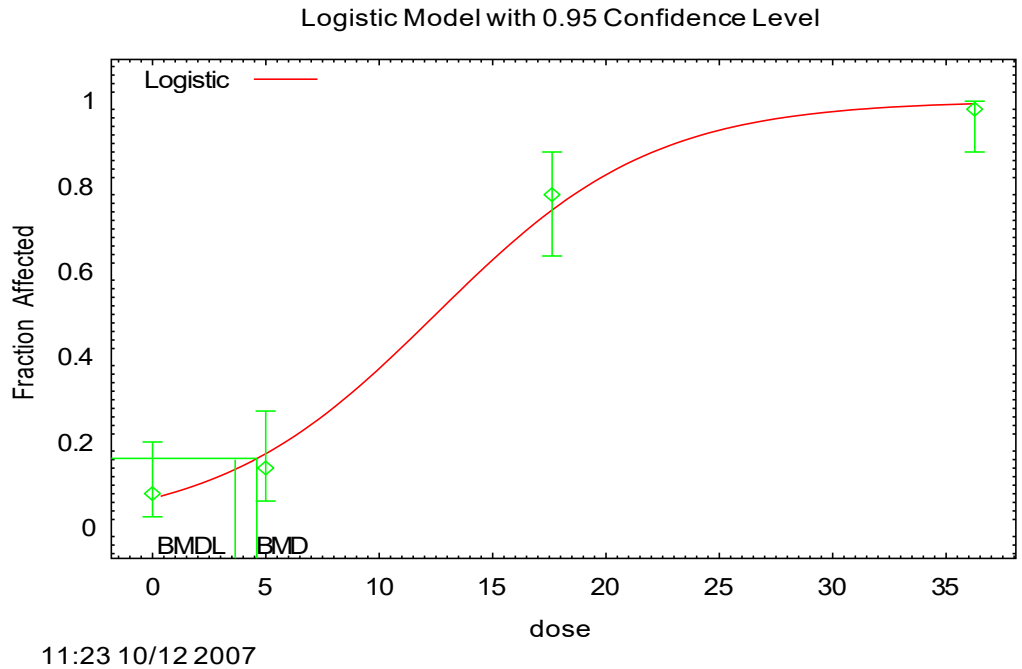
Risk Type = Extra risk

Confidence level = 0.95

BMD = 3.25675

BMDL = 2.58557

Male Rat
Dose metric: MRAMKL
Vmax = 0.65 mg/hour/kg $BW^{0.07}$

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==========================================================================
      Logistic Model. (Version: 2.9; Date: 02/20/2007)
      Input Data File: G:\CARBON TET\BMD\BMD MODELING 10-2007\RFC RAT LIVER\MALE RAT\MRAMKL-
VMAX=0.65\MRAT_FATTY_LIVER_MRAMKL-65.(d)
      Gnuplot Plotting File: G:\CARBON TET\BMD\BMD MODELING 10-2007\RFC RAT LIVER\MALE
RAT\MRAMKL-VMAX=0.65\MRAT_FATTY_LIVER_MRAMKL-65.plt
                           Fri Oct 12 11:23:29 2007
 ==========================================================================

 BMDS MODEL RUN
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   The form of the probability function is:

   P[response] = 1/[1+EXP(-intercept-slope*dose)]


   Dependent variable = FattyLiver
   Independent variable = umol/hr-kgL
   Slope parameter is not restricted

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


                  Default Initial Parameter Values
                     background =            0   Specified
                      intercept =     -2.28912
                          slope =     0.166325


            Asymptotic Correlation Matrix of Parameter Estimates

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

	intercept	slope
intercept	1	-0.8
slope	-0.8	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
intercept	-2.59592	0.370821	-3.32272	-1.86913
slope	0.207777	0.0278282	0.153235	0.26232

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-65.434	4			
Fitted model	-66.2567	2	1.64536	2	0.4393
Reduced model	-138.619	1	146.371	3	<.0001

AIC: 136.513

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0694	3.470	4	50	0.295
4.9910	0.1738	8.690	7	50	-0.631
17.6260	0.7439	37.195	39	50	0.585
36.2660	0.9929	49.645	49	50	-1.085

Chi^2 = 2.00 d.f. = 2 P-value = 0.3671

Benchmark Dose Computation

Specified effect = 0.1

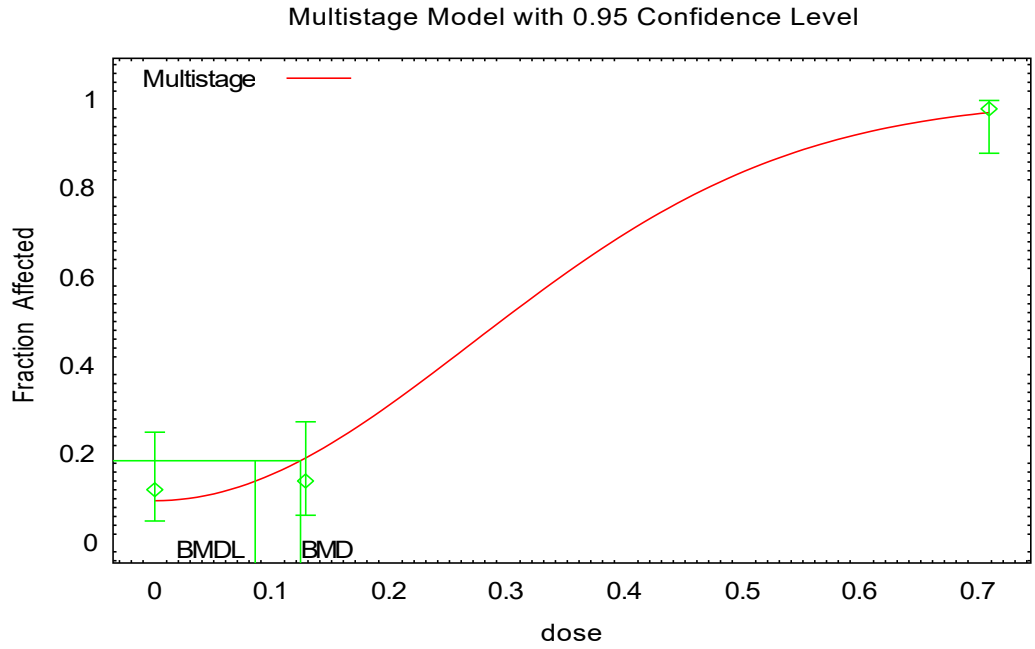
Risk Type = Extra risk

Confidence level = 0.95

BMD = 4.60057

BMDL = 3.65284

Female Rat
Dose metric: MCA
Vmax = 0.4 mg/hour/kg $BW^{0.07}$



11:42 10/12 2007

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=================================================================
      Multistage Model. (Version: 2.8; Date: 02/20/2007)
      Input Data File: G:\CARBON TET\BMD\BMD MODELING 10-2007\RFC RAT LIVER\FEMALE RAT\MCA-
VMAX=0.4\FRAT-FATTYLIVER-MCA-4.(d)
      Gnuplot Plotting File: G:\CARBON TET\BMD\BMD MODELING 10-2007\RFC RAT LIVER\FEMALE
RAT\MCA-VMAX=0.4\FRAT-FATTYLIVER-MCA-4.plt
                        Fri Oct 12 11:42:22 2007
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 BMDS MODEL RUN
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   The form of the probability function is:

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

   The parameter betas are restricted to be positive

   Dependent variable = FattyLiver
   Independent variable = umol/L

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


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


                  Default Initial Parameter Values
                     Background =    0.0746099
                        Beta(1) =            0
                        Beta(2) =      7.64624


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Beta(1)
```

have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	Background	Beta(2)
Background	1	-0.21
Beta(2)	-0.21	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.0951491	*	*	*
Beta(1)	0	*	*	*
Beta(2)	6.89319	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-43.4964	3			
Fitted model	-44.2044	2	1.41613	1	0.234
Reduced model	-101.707	1	116.422	2	<.0001

AIC: 92.4089

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0951	4.757	6	50	0.599
0.1280	0.1918	9.589	7	50	-0.930
0.7080	0.9714	48.571	49	50	0.364

Chi^2 = 1.36 d.f. = 1 P-value = 0.2442

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

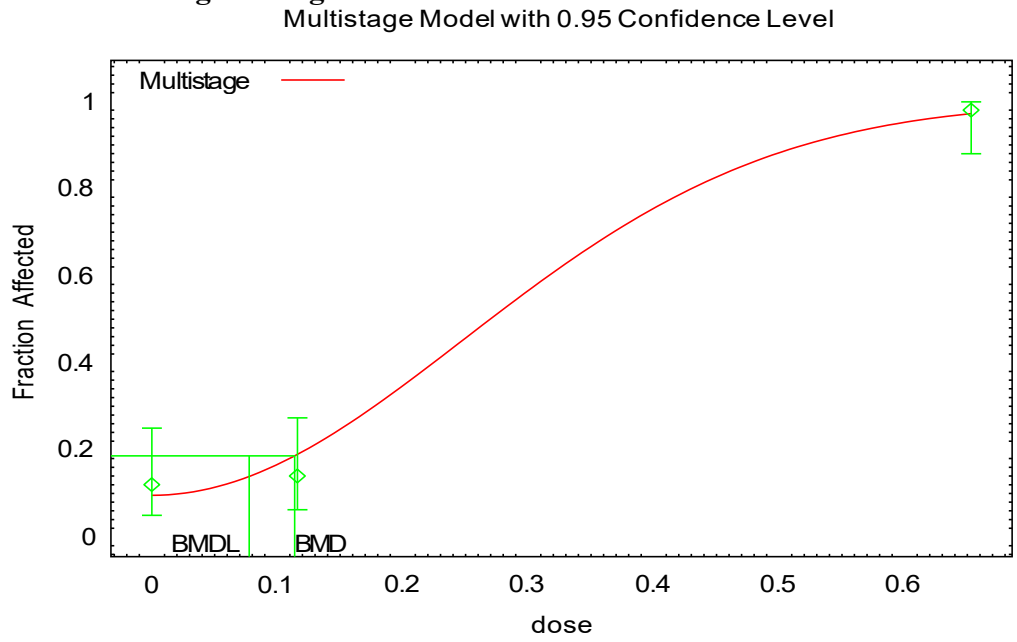
BMD = 0.123631

BMDL = 0.0851972

BMDU = 0.148857

Taken together, (0.0851972, 0.148857) is a 90 % two-sided confidence
interval for the BMD

Female Rat
Dose metric: MCA
Vmax = 0.65 mg/hour/kg $BW^{0.07}$




```
=====================================================================
      Multistage Model. (Version: 2.8; Date: 02/20/2007)
      Input Data File: G:\CARBON TET\BMD\BMD MODELING 10-2007\RFC RAT LIVER\FEMALE RAT\MCA-
VMAX=0.65\FRAT-FATTYLIVER-MCA-65.(d)
      Gnuplot Plotting File: G:\CARBON TET\BMD\BMD MODELING 10-2007\RFC RAT LIVER\FEMALE
RAT\MCA-VMAX=0.65\FRAT-FATTYLIVER-MCA-65.plt
                        Fri Oct 12 11:47:23 2007
 =====================================================================

 BMDS MODEL RUN
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   The form of the probability function is:

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

   The parameter betas are restricted to be positive


   Dependent variable = FattyLiver
   Independent variable = umol/L

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


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


                  Default Initial Parameter Values
                     Background =    0.0765787
                        Beta(1) =            0
                        Beta(2) =      8.98383


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Beta(1)
```

have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	Background	Beta(2)
Background	1	-0.21
Beta(2)	-0.21	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.095736	*	*	*
Beta(1)	0	*	*	*
Beta(2)	8.14699	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-43.4964	3			
Fitted model	-44.1525	2	1.31215	1	0.252
Reduced model	-101.707	1	116.422	2	<.0001

AIC: 92.3049

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0957	4.787	6	50	0.583
0.1160	0.1896	9.481	7	50	-0.895
0.6530	0.9720	48.599	49	50	0.344

Chi^2 = 1.26 d.f. = 1 P-value = 0.2617

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

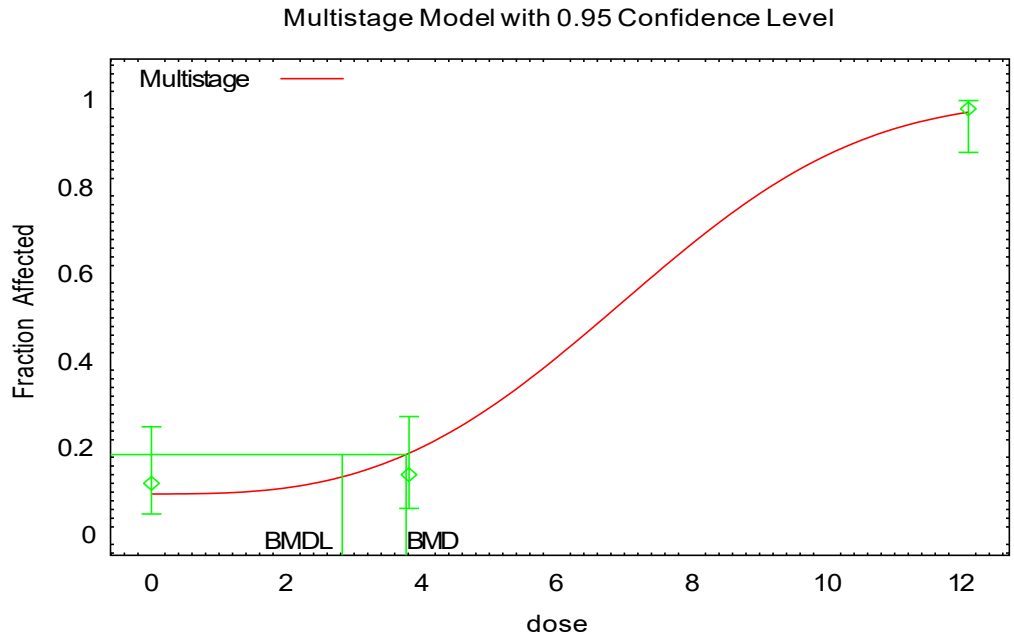
BMD = 0.113721

BMDL = 0.0775873

BMDU = 0.137047

Taken together, (0.0775873, 0.137047) is a 90 % two-sided confidence
interval for the BMD

Female Rat
Dose metric: MRAMKL
Vmax = 0.4 mg/hour/kg $BW^{0.07}$




```
=================================================================
      Multistage Model. (Version: 2.8; Date: 02/20/2007)
      Input Data File: G:\CARBON TET\BMD\BMD MODELING 10-2007\RFC RAT LIVER\FEMALE RAT\MRAMKL-
VMAX=0.4\FRAT_FATTY_LIVER_MRAMKL-4.(d)
      Gnuplot Plotting File: G:\CARBON TET\BMD\BMD MODELING 10-2007\RFC RAT LIVER\FEMALE
RAT\MRAMKL-VMAX=0.4\FRAT_FATTY_LIVER_MRAMKL-4.plt
                        Fri Oct 12 11:52:42 2007
 =================================================================

 BMDS MODEL RUN
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Observation # < parameter # for Multistage model.
   The form of the probability function is:

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

   The parameter betas are restricted to be positive


   Dependent variable = FattyLiver
   Independent variable = umol/hr-kgL

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


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


                  Default Initial Parameter Values
                     Background =    0.0769299
                        Beta(1) =            0
                        Beta(2) =            0
                        Beta(3) =   0.00216647
```

Asymptotic Correlation Matrix of Parameter Estimates

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

	Background	Beta(3)
Background	1	-0.21
Beta(3)	-0.21	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.0958436	*	*	*
Beta(1)	0	*	*	*
Beta(2)	0	*	*	*
Beta(3)	0.00196673	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-43.4964	3			
Fitted model	-44.1433	2	1.29386	1	0.2553
Reduced model	-101.707	1	116.422	2	<.0001

AIC: 92.2866

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0958	4.792	6	50	0.580
3.8130	0.1892	9.462	7	50	-0.889
12.0920	0.9721	48.603	49	50	0.340

Chi^2 = 1.24 d.f. = 1 P-value = 0.2650

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

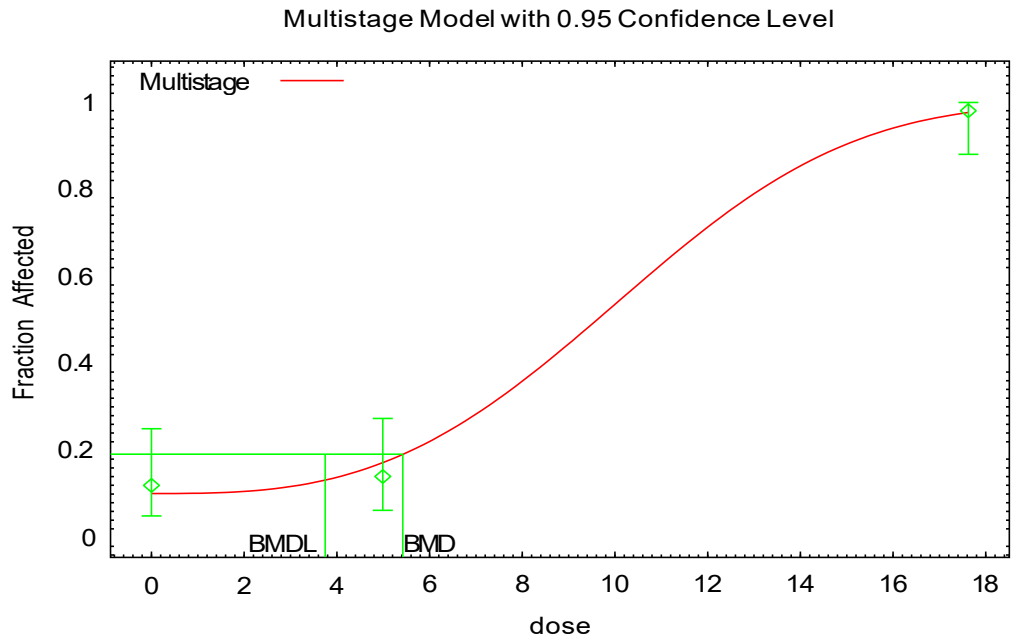
BMD = 3.76974

BMDL = 2.82488

BMDU = 4.26949

Taken together, (2.82488, 4.26949) is a 90 % two-sided confidence interval for the BMD

Female Rat
Dose metric: MRAMKL
Vmax = 0.65 mg/hour/kg $BW^{0.07}$




```
=====================================================================
      Multistage Model. (Version: 2.8; Date: 02/20/2007)
      Input Data File: G:\CARBON TET\BMD\BMD MODELING 10-2007\RFC RAT LIVER\FEMALE RAT\MRAMKL-
VMAX=0.65\FRAT_FATTY_LIVER_MRAMKL-65.(d)
      Gnuplot Plotting File: G:\CARBON TET\BMD\BMD MODELING 10-2007\RFC RAT LIVER\FEMALE
RAT\MRAMKL-VMAX=0.65\FRAT_FATTY_LIVER_MRAMKL-65.plt
                          Fri Oct 12 11:57:06 2007
 =====================================================================

 BMDS MODEL RUN
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Observation # < parameter # for Multistage model.
   The form of the probability function is:

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

   The parameter betas are restricted to be positive


   Dependent variable = FattyLiver
   Independent variable = umol/hr-kgL

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

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


                  Default Initial Parameter Values
                     Background =            0
                        Beta(1) =            0
                        Beta(2) =            0
                        Beta(3) =  0.000714264


           Asymptotic Correlation Matrix of Parameter Estimates
```

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

	Background	Beta(3)
Background	1	-0.19
Beta(3)	-0.19	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.101433	*	*	*
Beta(1)	0	*	*	*
Beta(2)	0	*	*	*
Beta(3)	0.000660435	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-43.4964	3			
Fitted model	-43.7982	2	0.603632	1	0.4372
Reduced model	-101.707	1	116.422	2	<.0001

AIC: 91.5964

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.1014	5.072	6	50	0.435
4.9910	0.1723	8.613	7	50	-0.604
17.6260	0.9759	48.793	49	50	0.191

Chi^2 = 0.59 d.f. = 1 P-value = 0.4421

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 5.42354

BMDL = 3.74923

BMDU = 6.17189

Taken together, (3.74923, 6.17189) is a 90 % two-sided confidence
interval for the BMD

CANCER ASSESSMENT: BMD MODELING OUTPUTS FOR LOW-DOSE LINEAR EXTRAPOLATION APPROACH

Benchmark Dose Analysis

Liver tumors (adenoma or carcinoma)
Female F344 rats exposed to carbon tetrachloride vapor for 104 weeks (6 hours/day, 5 days/week)
Exposure concentrations modeled: ***0, 5, 25, 125 ppm***
Multistage; MCA: 2-stage model MRAMKL: 4-stage model

BMR (extra risk)	V_{max} = 0.4					V_{max} = 0.65				
	AIC	χ^2 *p*-value[a]	BMC	BMCL	BMR/ BMCL	AIC	χ^2 *p*-value[a]	BMC	BMCL	BMR/ BMCL
MCA (µmol/L)										
0.05	61.6602	0.9842	0.609955	0.387377	0.129	61.5904	0.9916	0.588686	0.354766	0.141
MRAMKL (µmol/hr-kg liver)										
0.05	63.3399	0.6503	9.8151	8.40334	0.00595	62.8343	0.7440	14.582	12.2867	0.00407

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria; *p*-value from the χ^2 test.

Liver tumors (adenoma or carcinoma)
Female F344 rats exposed to carbon tetrachloride vapor for 104 weeks (6 hours/day, 5 days/week)
Exposure concentrations modeled: ***0, 5, 25 ppm***
Multistage; 2-stage model

BMR (extra risk)	V_{max} = 0.4					V_{max} = 0.65				
	AIC	χ^2 *p*-value[a]	BMC	BMCL	BMR/ BMCL	AIC	χ^2 *p*-value[a]	BMC	BMCL	BMR/ BMCL
MCA (µmol/L)										
0.05	24.8957	0.9507	0.655398	0.345984	0.144	24.8889	0.9523	0.604144	0.317726	0.157
MRAMKL (µmol/hr-kg liver)										
0.05	25.2825	0.8571	11.5604	6.92352	0.00722	25.1734	0.8831	16.6986	9.76339	0.00512

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria; *p*-value from the χ^2 test.

Note: 3-stage model did not provide a sufficiently improved model fit.

Liver tumors (adenoma or carcinoma)
Female BDF1 mouse exposed to carbon tetrachloride vapor for 104 weeks (6 hours/day, 5 days/week)
Exposure concentrations modeled: ***0, 5, 25 ppm***
Multistage; MCA: 2-stage model MRAMKL: 2-stage model

BMR (extra risk)	Fisher					Thrall				
	AIC	χ^2 *p*-value[a]	BMC	BMCL	BMR/ BMCL	AIC	χ^2 *p*-value[a]	BMC	BMCL	BMR/ BMCL
MCA (µmol/L)										
0.1	117.307	NA	0.10186	0.0467576	2.14	117.307	NA	0.194624	0.0885305	1.13
MRAMKL (µmol/hr-kg liver)										
0.1	115.912	0.4437	9.70893	6.3204	0.0158	117.341	0.1654	10.4557	7.59255	0.0132

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria; *p*-value from the χ^2 test.

Note: 3-stage model did not provide a sufficiently improved model fit.

Liver tumors (adenoma or carcinoma)
Female BDF1 mouse exposed to carbon tetrachloride vapor for 104 weeks (6 hours/day, 5 days/week)
Exposure concentrations modeled: ***0, 5 ppm***
Multistage; 2-stage model

BMR (extra risk)	Fisher					Thrall				
	AIC	χ^2 *p*-value[a]	BMC	BMCL	BMR/ BMCL	AIC	χ^2 *p*-value[a]	BMC	BMCL	BMR/ BMCL
MCA (µmol/L)										
0.1	80.6149	NA	0.101967	0.044224	2.26	80.6149	NA	0.195666	0.0848621	1.18
MRAMKL (µmol/hr-kg liver)										
0.1	80.6149	NA	11.6352	5.04631	0.0198	80.6149	NA	14.1982	6.15788	0.0162

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria; *p*-value from the χ^2 test.

Liver tumors (adenoma or carcinoma)
Male BDF1 mouse exposed to carbon tetrachloride vapor for 104 weeks (6 hours/day, 5 days/week)
Exposure concentrations modeled: ***0, 5, 25 ppm***
Note: models could not fit data with all 4 dose groups; highest dose group dropped
BMR = 0.1
Multistage; 3-stage model

BMR (extra risk)	Fisher					Thrall				
	AIC	χ^2 *p*-value[a]	BMC	BMCL	BMR/ BMCL	AIC	χ^2 *p*-value[a]	BMC	BMCL	BMR/ BMCL
MCA (µmol/L)										
0.1	151.192	0.3562	0.191106	0.063650	1.57	151.158	0.3660	0.388392	0.122027	0.819
MRAMKL (µmol/hr-kg liver)										
0.1	152.089	0.1864	13.3804	7.30705	0.0137	152.924	0.1086	14.185	8.82145	0.0113

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria; *p*-value from the χ^2 test.

Pheochromocytomas
Female BDF1 mouse exposed to carbon tetrachloride vapor for 104 weeks (6 hours/day, 5 days/week)
Exposure concentrations modeled: ***0, 5, 25, 125 ppm***
Multistage; 2-stage model
BMR = 10%

BMR (extra risk)	Fisher					Thrall				
	AIC	χ^2 *p*-value[a]	BMC	BMCL	BMR/ BMCL	AIC	χ^2 *p*-value[a]	BMC	BMCL	BMR/ BMCL
	MCA (µmol/L)									
0.1	71.4077	0.7947	1.42662	1.13753	0.0879	71.3358	0.8039	2.94801	2.34113	0.0427

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria; *p*-value from the χ^2 test.

Note: 3-stage model did not provide a sufficiently improved model fit.

Pheochromocytomas
Male BDF1 mouse exposed to carbon tetrachloride vapor for 104 weeks (6 hours/day, 5 days/week)
Exposure concentrations modeled: ***0, 5, 25, 125 ppm***
Cancer Multistage
BMR = 10%
Cancer Multistage (restricted mode) model did not provide an adequate fit of the male pheochromocytoma data (1, 2, and 3 stage models provided the same outputs); therefore other models in BMDS were used (see table below).

BMR (extra risk)	Fisher					Thrall				
	AIC	χ^2 *p*-value[a]	BMC	BMCL	BMR/ BMCL	AIC	χ^2 *p*-value[a]	BMC	BMCL	BMR/ BMCL
	MCA (µmol/L)									
1st, 2nd & 3rd 0.1	139.129	0.0513	0.292123	0.230102	0.435	139.077	0.0488	0.600117	0.472644	0.212

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria; *p*-value from the χ^2 test.

Pheochromocytomas
Male BDF1 mouse exposed to carbon tetrachloride vapor for 104 weeks (6 hours/day, 5 days/week)
Exposure concentrations modeled: ***0, 5, 25, 125 ppm***
Models other than Multistage
BMR = 0.1

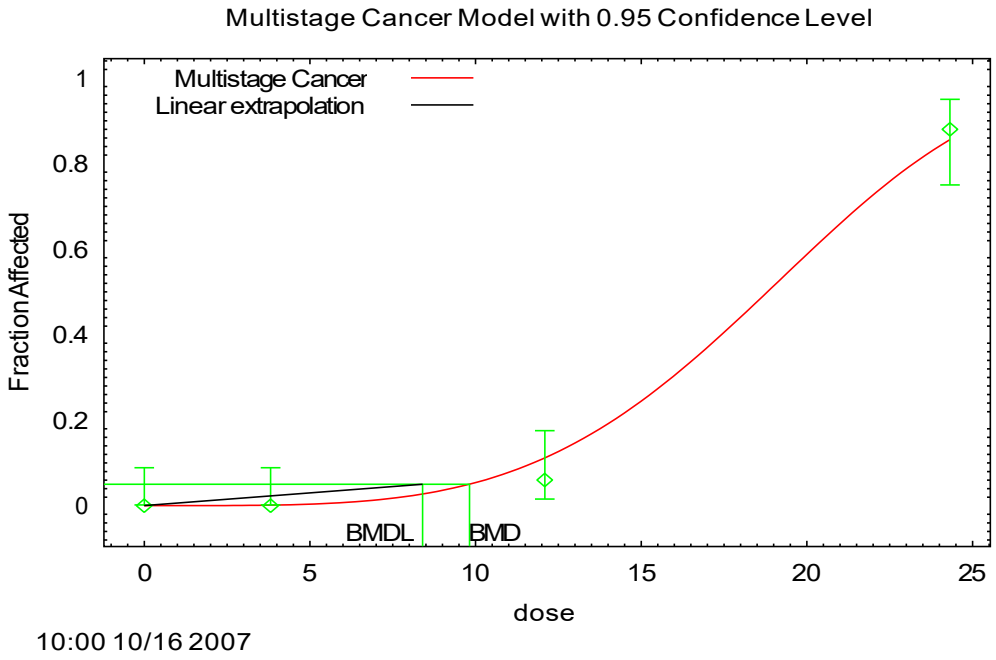
	Fisher					Thrall				
Model	**AIC**	**χ^2 *p*-value[a]**	**BMC**	**BMCL**	**BMR/ BMCL**	**AIC**	**χ^2 *p*-value[a]**	**BMC**	**BMCL**	**BMR/ BMCL**
MCA (µmol/L)										
Gamma[b]	139.129	0.0513	0.292124	0.230102	0.435	139.077	0.0488	0.600118	0.472644	0.212
Gamma -- unrestricted	140.755	0.0401	0.238028	0.10463	0.956	140.587	0.0428	0.473653	0.204957	0.488
Logistic[c]	161.228	0.0000	0.929566	0.75614	0.132	161.353	0.0000	1.9184	1.56019	0.064
Logistic -- unrestricted	161.228	0.0000	0.929566	0.75614	0.132	161.353	0.0000	1.9184	1.56019	0.064
Log-logistic[c]	138.661	0.0978	0.24731	0.147398	0.678	138.467	0.1050	0.492945	0.297393	0.336
Log-logistic – unrestricted	138.661	0.0978	0.247311	0.130943	0.764	138.467	0.1050	0.492945	0.257935	0.388
Probit[c]	159.808	0.0000	0.851235	0.702221	0.142	159.949	0.0000	1.75643	1.44878	0.069
Probit – unrestricted	159.808	0.0000	0.851235	0.702221	0.142	159.949	0.0000	1.75643	1.44878	0.069
Log-probit[c]	141.637	0.0044	0.423924	0.340228	0.294	141.988	0.0035	0.867906	0.696011	0.144
Log-probit – unrestricted	**137.136**	**0.1533**	**0.264859**	**0.150882**	**0.663**	**136.945**	**0.1648**	**0.527758**	**0.297349**	**0.336**
Quantal-linear	139.129	0.0513	0.292124	0.230102	0.435	139.077	0.0488	0.60012	0.472644	0.212
Weibull[b]	139.129	0.0513	0.292124	0.230102	0.435	139.077	0.0488	0.60012	0.472644	0.212
Weibull -- unrestricted	140.513	0.0497	0.226525	0.10562	0.947	140.316	0.0535	0.45102	0.207636	0.482

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria; *p*-value from the χ^2 test.
[b]Power restricted to ≥1.
[c]Slope restricted to ≥1.

Female F344 rat -- hepatocellular adenomas or carcinomas (0, 5, 25, 125 ppm dose groups)

Dose metric: MRAMKL

Vmax = 0.4 mg/hour/kg $BW^{0.07}$




```
=====================================================================
      Multistage Cancer Model. (Version: 1.5; Date: 02/20/2007)
      Input Data File: G:\CARBON TET\BMD\BMD MODELING 10-2007\TUMORS FEMALE RAT LIVER\MRAMKL-
VMAX=0.4\FRAT_LIVER_ADCAR_MRAMKL-4.(d)
     Gnuplot Plotting File: G:\CARBON TET\BMD\BMD MODELING 10-2007\TUMORS FEMALE RAT
LIVER\MRAMKL-VMAX=0.4\FRAT_LIVER_ADCAR_MRAMKL-4.plt
                          Tue Oct 16 10:00:27 2007
 =====================================================================

 BMDS MODEL RUN
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Observation # < parameter # for Multistage Cancer model.
   The form of the probability function is:

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

   The parameter betas are restricted to be positive


   Dependent variable = IncLiverTumor
   Independent variable = umol/hr-kgL

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


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

                 Default Initial Parameter Values
                    Background =           0
                       Beta(1) =           0
                       Beta(2) =           0
                       Beta(3) =           0
                       Beta(4) = 6.11699e-006


           Asymptotic Correlation Matrix of Parameter Estimates
```

(*** The model parameter(s) -Background -Beta(1) -Beta(2) -Beta(3)
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	Beta(4)
Beta(4)	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0	*	*	*
Beta(1)	0	*	*	*
Beta(2)	0	*	*	*
Beta(3)	0	*	*	*
Beta(4)	5.52689e-006	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-29.6946	4			
Fitted model	-30.67	1	1.95065	3	0.5827
Reduced model	-109.05	1	158.71	3	<.0001

AIC: 63.3399

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0	50	0.000
3.8130	0.0012	0.058	0	50	-0.242
12.0920	0.1114	5.572	3	50	-1.156
24.3200	0.8554	42.768	44	50	0.495

Chi^2 = 1.64 d.f. = 3 P-value = 0.6503

Benchmark Dose Computation

Specified effect = 0.05

Risk Type = Extra risk

Confidence level = 0.95

BMD = 9.8151

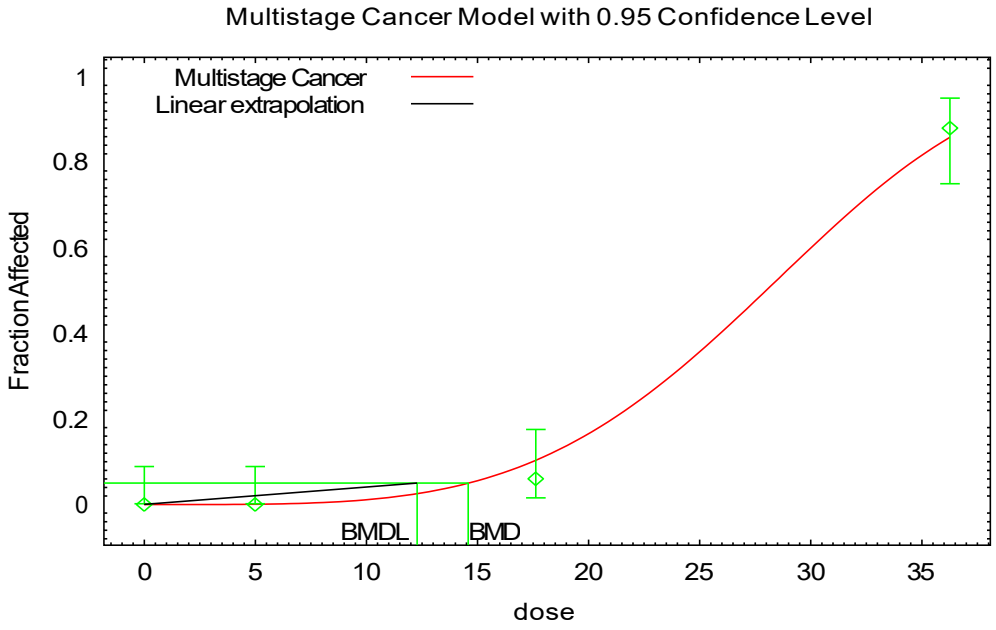
BMDL = 8.40334

BMDU = 10.5331

Taken together, (8.40334, 10.5331) is a 90 % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor = 0.00595002

Dose metric: MRAMKL
Vmax = 0.65 mg/hour/kg $BW^{0.07}$




```
=================================================================
      Multistage Cancer Model. (Version: 1.5; Date: 02/20/2007)
      Input Data File: G:\CARBON TET\BMD\BMD MODELING 10-2007\TUMORS FEMALE RAT LIVER\MRAMKL-
VMAX=0.65\FRAT_LIVER_ADCAR_MRAMKL-65.(d)
      Gnuplot Plotting File: G:\CARBON TET\BMD\BMD MODELING 10-2007\TUMORS FEMALE RAT
LIVER\MRAMKL-VMAX=0.65\FRAT_LIVER_ADCAR_MRAMKL-65.plt
                        Tue Oct 16 10:05:09 2007
 =================================================================

 BMDS MODEL RUN
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Observation # < parameter # for Multistage Cancer model.
   The form of the probability function is:

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

   The parameter betas are restricted to be positive

   Dependent variable = IncLiverTumor
   Independent variable = umol/hr-kgL

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


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


                  Default Initial Parameter Values
                     Background =            0
                        Beta(1) =            0
                        Beta(2) =            0
                        Beta(3) =            0
                        Beta(4) = 1.23526e-006
```

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -Background -Beta(1) -Beta(2) -Beta(3)
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	Beta(4)
Beta(4)	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0	*	*	*
Beta(1)	0	*	*	*
Beta(2)	0	*	*	*
Beta(3)	0	*	*	*
Beta(4)	1.13446e-006	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-29.6946	4			
Fitted model	-30.4171	1	1.44504	3	0.695
Reduced model	-109.05	1	158.71	3	<.0001

AIC: 62.8343

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0	50	0.000
4.9910	0.0007	0.035	0	50	-0.188
17.6260	0.1037	5.186	3	50	-1.014
36.2660	0.8595	42.974	44	50	0.418

Chi^2 = 1.24 d.f. = 3 P-value = 0.7440

Benchmark Dose Computation

Specified effect = 0.05

Risk Type = Extra risk

Confidence level = 0.95

BMD = 14.582

BMDL = 12.2867

BMDU = 15.6526

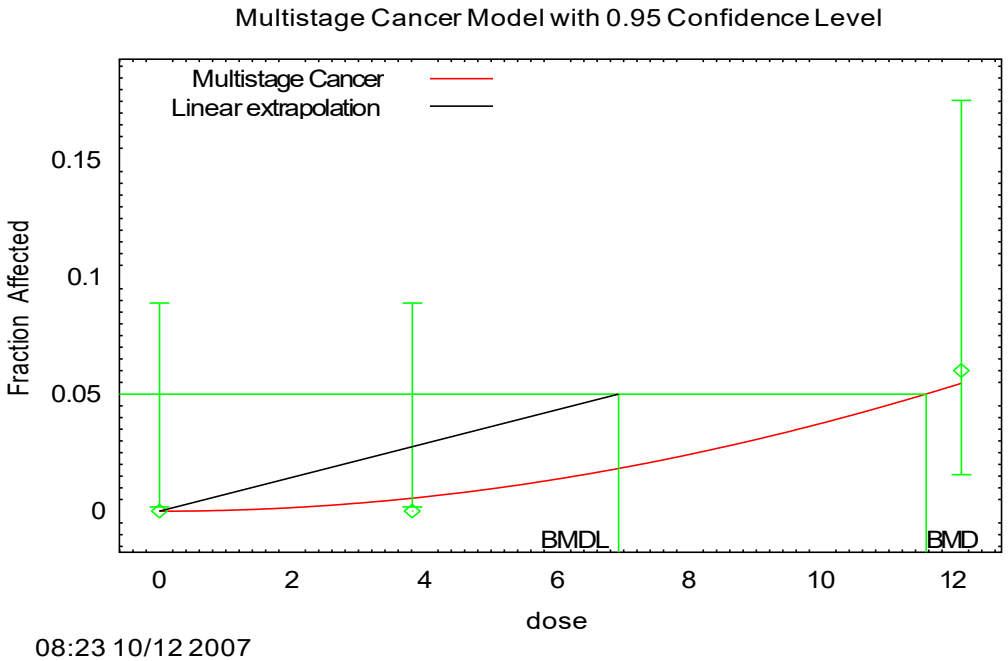
Taken together, (12.2867, 15.6526) is a 90 % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor = 0.00406945

Female F344 rat -- hepatocellular adenomas or carcinomas (0, 5, 25 ppm dose groups)

Dose metric: MRAMKL

Vmax = 0.4 mg/hour/kg $BW^{0.07}$



08:23 10/12 2007

```
 ======================================================================
      Multistage Cancer Model. (Version: 1.5; Date: 02/20/2007)
      Input Data File: G:\CARBON TET\BMD\BMD MODELING 10-2007\TUMORS FEMALE RAT LIVER\MRAMKL-
VMAX=0.4\FRAT_LIVER_ADCAR_MRAMKL-4.(d)
      Gnuplot Plotting File: G:\CARBON TET\BMD\BMD MODELING 10-2007\TUMORS FEMALE RAT
LIVER\MRAMKL-VMAX=0.4\FRAT_LIVER_ADCAR_MRAMKL-4.plt
                           Fri Oct 12 08:23:17 2007
 ======================================================================

 BMDS MODEL RUN
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   The form of the probability function is:

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

   The parameter betas are restricted to be positive


   Dependent variable = IncLiverTumor
   Independent variable = umol/hr-kgL

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


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

                 Default Initial Parameter Values
                    Background =            0
                       Beta(1) =            0
                       Beta(2) =   0.00044169


            Asymptotic Correlation Matrix of Parameter Estimates

            ( *** The model parameter(s)  -Background    -Beta(1)
                  have been estimated at a boundary point, or have been specified by the user,
```

and do not appear in the correlation matrix)

	Beta(2)
Beta(2)	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0	*	*	*
Beta(1)	0	*	*	*
Beta(2)	0.000383811	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-11.3484	3			
Fitted model	-11.6412	1	0.585705	2	0.7461
Reduced model	-14.7059	1	6.71498	2	0.03482

AIC: 25.2825

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0	50	0.000
3.8130	0.0056	0.278	0	50	-0.529
12.0920	0.0546	2.729	3	50	0.169

Chi^2 = 0.31 d.f. = 2 P-value = 0.8571

Benchmark Dose Computation

Specified effect = 0.05

Risk Type = Extra risk

Confidence level = 0.95

BMD = 11.5604

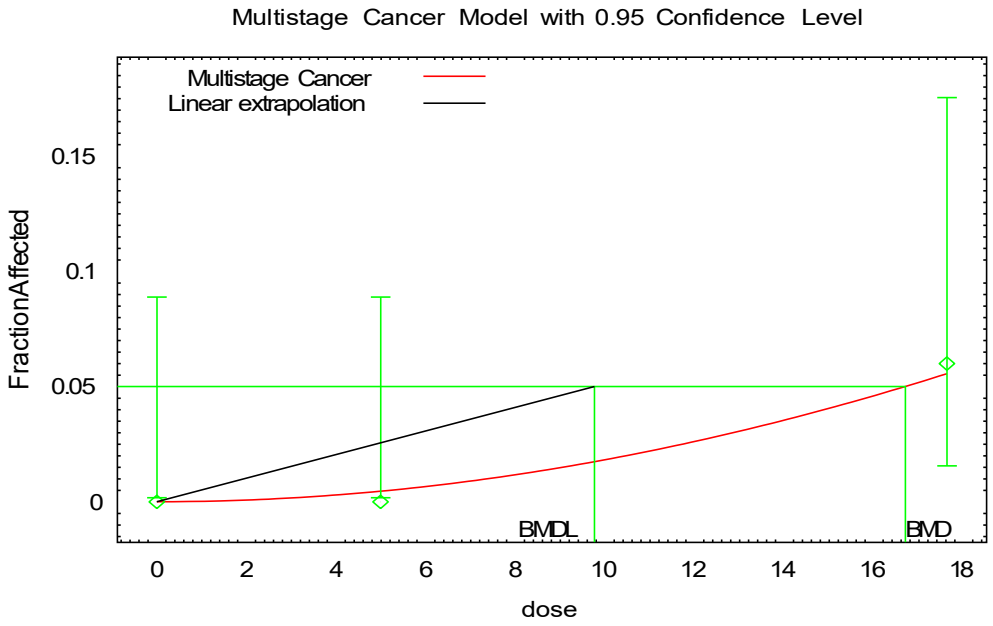
BMDL = 6.92352

BMDU = 30.5183

Taken together, (6.92352, 30.5183) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.00722176

Dose metric: MRAMKL
Vmax = 0.65 mg/hour/kg $BW^{0.07}$




```
 ======================================================================
      Multistage Cancer Model. (Version: 1.5; Date: 02/20/2007)
      Input Data File: G:\CARBON TET\BMD\BMD MODELING 10-2007\TUMORS FEMALE RAT LIVER\MRAMKL-
VMAX=0.65\FRAT_LIVER_ADCAR_MRAMKL-65.(d)
      Gnuplot Plotting File: G:\CARBON TET\BMD\BMD MODELING 10-2007\TUMORS FEMALE RAT
LIVER\MRAMKL-VMAX=0.65\FRAT_LIVER_ADCAR_MRAMKL-65.plt
                           Fri Oct 12 08:35:44 2007
 ======================================================================

 BMDS MODEL RUN
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   The form of the probability function is:

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

   The parameter betas are restricted to be positive


   Dependent variable = IncLiverTumor
   Independent variable = umol/hr-kgL

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


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

                  Default Initial Parameter Values
                     Background =            0
                        Beta(1) =            0
                        Beta(2) =  0.000206402


           Asymptotic Correlation Matrix of Parameter Estimates

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

                Beta(2)
```

Beta(2) 1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0	*	*	*
Beta(1)	0	*	*	*
Beta(2)	0.000183949	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-11.3484	3			
Fitted model	-11.5867	1	0.476667	2	0.7879
Reduced model	-14.7059	1	6.71498	2	0.03482

AIC: 25.1734

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0	50	0.000
4.9910	0.0046	0.229	0	50	-0.479
17.6260	0.0555	2.777	3	50	0.137

Chi^2 = 0.25 d.f. = 2 P-value = 0.8831

Benchmark Dose Computation

Specified effect = 0.05

Risk Type = Extra risk

Confidence level = 0.95

BMD = 16.6986

BMDL = 9.76339

BMDU = 43.9237

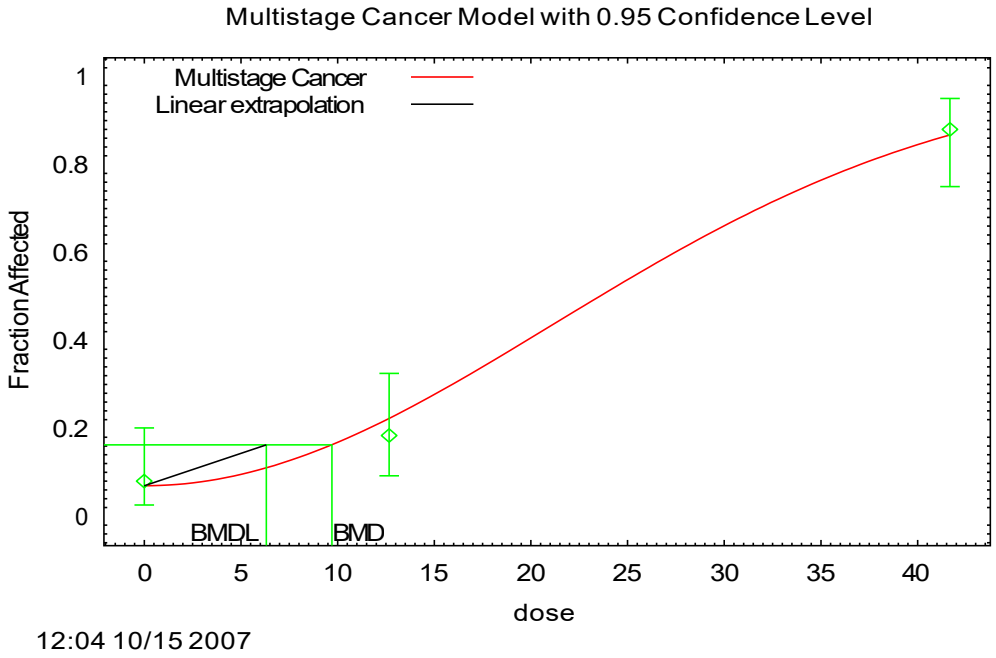
Taken together, (9.76339, 43.9237) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.00512117

Female BDF1 mouse – hepatocellular adenomas or carcinomas (0, 5, 25 ppm dose groups)

Dose metric: MRAMKL

Fisher model

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=================================================================
      Multistage Cancer Model. (Version: 1.5; Date: 02/20/2007)
      Input Data File: G:\CARBON TET\BMD\BMD MODELING 10-2007\TUMORS FEMALE MOUSE LIVER\MRAMKL-
FISHER\FMOUSE_LIVER_ADCAR_MRAMKL-FISHER.(d)
      Gnuplot Plotting File: G:\CARBON TET\BMD\BMD MODELING 10-2007\TUMORS FEMALE MOUSE
LIVER\MRAMKL-FISHER\FMOUSE_LIVER_ADCAR_MRAMKL-FISHER.plt
                          Fri Oct 12 08:54:44 2007
 =================================================================

 BMDS MODEL RUN
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   The form of the probability function is:

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

   The parameter betas are restricted to be positive


   Dependent variable = IncLiverTumor
   Independent variable = umol/hr-kgL

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


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

 Default Initial Parameter Values Background =
      0.0482072
                        Beta(1) =            0
                        Beta(2) =   0.00119035


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Beta(1)
                 have been estimated at a boundary point, or have been specified by the user,
```

and do not appear in the correlation matrix)

	Background	Beta(2)
Background	1	-0.38
Beta(2)	-0.38	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.0693295	*	*	*
Beta(1)	0	*	*	*
Beta(2)	0.00111772	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-55.6537	3			
Fitted model	-55.9559	2	0.604318	1	0.4369
Reduced model	-99.1295	1	86.9516	2	<.0001

AIC: 115.912

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0693	3.466	4	50	0.297
12.6660	0.2221	10.883	9	49	-0.647
41.6750	0.8664	43.321	44	50	0.282

Chi^2 = 0.59 d.f. = 1 P-value = 0.4437

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 9.70893

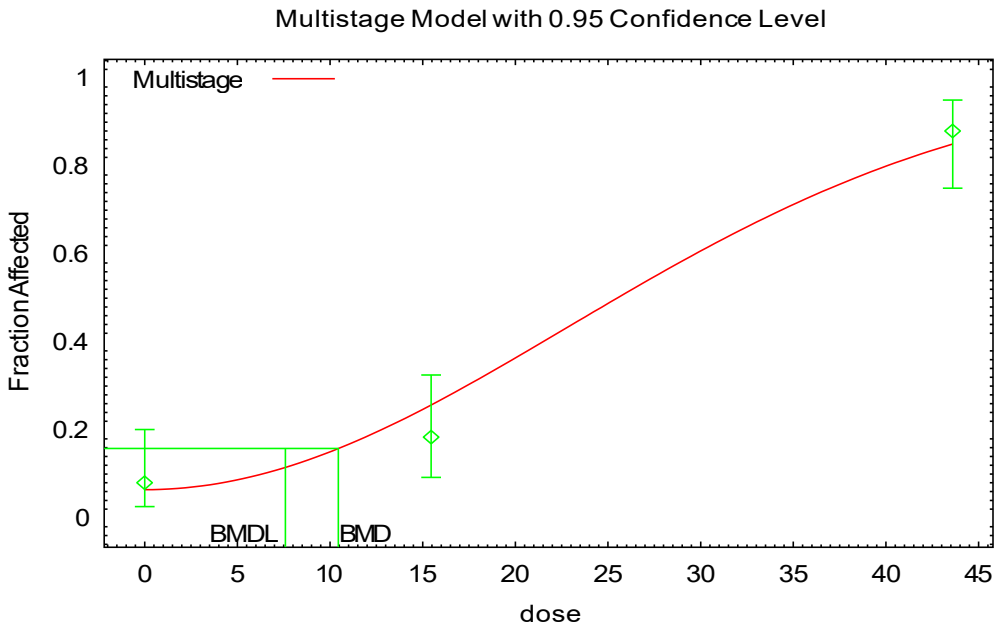
BMDL = 6.3204

BMDU = 11.2942

Taken together, (6.3204 , 11.2942) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.0158218

Dose metric: MRAMKL
Thrall model



12:10 10/15 2007

```
 ================================================================
              Multistage Model. (Version: 2.8; Date: 02/20/2007)
             Input Data File: G:\CARBON TET\BMD\BMD MODELING 10-2007\TUMORS FEMALE
MOUSE LIVER\MRAMKL-THRALL\FMOUSE_LIVER_ADCAR_MRAMKL-THRALL.(d)
             Gnuplot Plotting File: G:\CARBON TET\BMD\BMD MODELING 10-2007\TUMORS
FEMALE MOUSE LIVER\MRAMKL-THRALL\FMOUSE_LIVER_ADCAR_MRAMKL-THRALL.plt
                                                    Fri Oct 12 09:01:03 2007
 ================================================================

 BMDS MODEL RUN
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   The form of the probability function is:

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

   The parameter betas are restricted to be positive


   Dependent variable = IncLiverTumor
   Independent variable = umol/hr-kgL

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


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


                 Default Initial Parameter Values
                    Background =    0.0162478
                       Beta(1) =            0
                       Beta(2) =   0.00110173
```

user,

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -Beta(1)
have been estimated at a boundary point, or have been specified by the

and do not appear in the correlation matrix)

	Background	Beta(2)
Background	1	-0.4
Beta(2)	-0.4	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.0643165	*	*	*
Beta(1)	0	*	*	*
Beta(2)	0.000963757	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-55.6537	3			
Fitted model	-56.6705	2	2.03362	1	0.1539
Reduced model	-99.1295	1	86.9516	2	<.0001

AIC: 117.341

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0643	3.216	4	50	0.452
15.4560	0.2567	12.580	9	49	-1.171
43.5990	0.8502	42.510	44	50	0.590

Chi^2 = 1.92 d.f. = 1 P-value = 0.1654

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 10.4557

BMDL = 7.59255

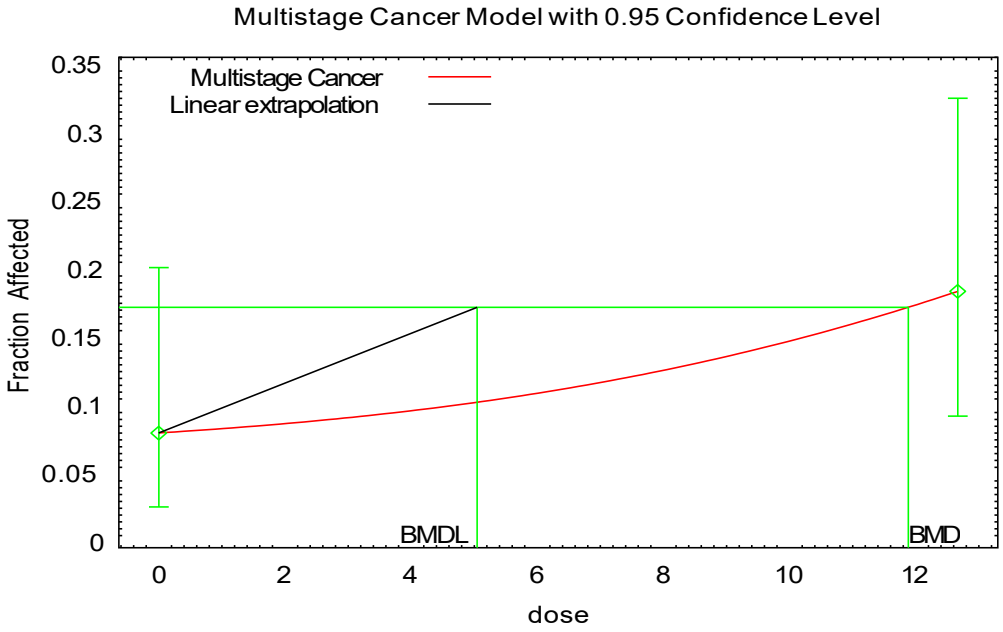
BMDU = 12.107

Taken together, (7.59255, 12.107) is a 90 % two-sided confidence interval for the BMD

Female BDF1 mouse – hepatocellular adenomas or carcinomas (0, 5 ppm dose groups)

Dose metric: MRAMKL

Fisher model




```
======================================================================
      Multistage Cancer Model. (Version: 1.5; Date: 02/20/2007)
      Input Data File: G:\CARBON TET\BMD\BMD MODELING 10-2007\TUMORS FEMALE MOUSE LIVER\MRAMKL-
FISHER\FMOUSE_LIVER_ADCAR_MRAMKL-FISHER.(d)
      Gnuplot Plotting File: G:\CARBON TET\BMD\BMD MODELING 10-2007\TUMORS FEMALE MOUSE
LIVER\MRAMKL-FISHER\FMOUSE_LIVER_ADCAR_MRAMKL-FISHER.plt
                          Fri Oct 12 09:15:17 2007
 ======================================================================

 BMDS MODEL RUN
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Observation # < parameter # for Multistage Cancer model.
   The form of the probability function is:

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

   The parameter betas are restricted to be positive

   Dependent variable = IncLiverTumor
   Independent variable = umol/hr-kgL

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

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


                  Default Initial Parameter Values
                     Background =      0.24898
                        Beta(1) =    0.0160225
                        Beta(2) =     0.001265
```

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Beta(1)	Beta(2)
Background	1	-2.2e-008	8.3e-009
Beta(1)	-6e-009	1	-1
Beta(2)	-3.2e-009	-1	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.08	*	*	*
Beta(1)	0.00471969	*	*	*
Beta(2)	0.000372627	*	*	*

* - Indicates that this value is not calculated.

Error in computing chi-square; returning 2

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-37.3075	2			
Fitted model	-37.3075	3	2.84217e-014	-1	NA
Reduced model	-38.4987	1	2.38238	1	0.1227

AIC: 80.6149

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0800	4.000	4	50	-0.000
12.6660	0.1837	9.000	9	49	0.000

Chi^2 = 0.00 d.f. = -1 P-value = NA

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

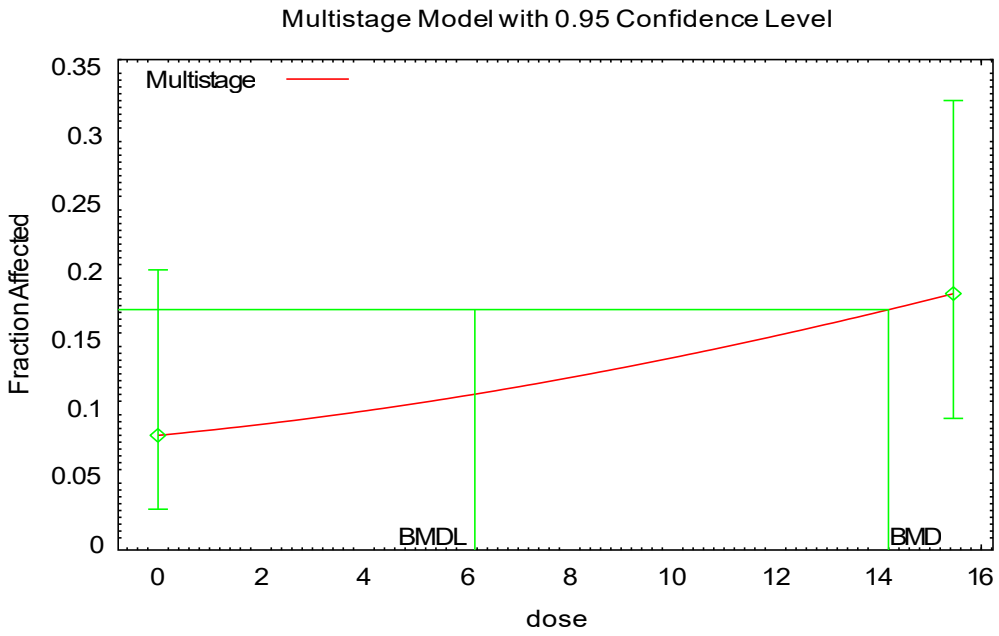
BMD = 11.6352

BMDL = 5.04631

BMDU did not converge for BMR = 0.100000
BMDU calculation failed
BMDU = 3.56605e+007

Multistage Cancer Slope Factor = 0.0198165

Dose metric: MRAMKL
Thrall model



12:50 10/15 2007

```
 ======================================================================
      Multistage Model. (Version: 2.8; Date: 02/20/2007)
      Input Data File: G:\CARBON TET\BMD\BMD MODELING 10-2007\TUMORS FEMALE MOUSE LIVER\MRAMKL-
THRALL\FMOUSE_LIVER_ADCAR_MRAMKL-THRALL.(d)
      Gnuplot Plotting File: G:\CARBON TET\BMD\BMD MODELING 10-2007\TUMORS FEMALE MOUSE
LIVER\MRAMKL-THRALL\FMOUSE_LIVER_ADCAR_MRAMKL-THRALL.plt
                          Fri Oct 12 09:17:46 2007
 ======================================================================

 BMDS MODEL RUN
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Observation # < parameter # for Multistage model.
   The form of the probability function is:

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

   The parameter betas are restricted to be positive

   Dependent variable = IncLiverTumor
   Independent variable = umol/hr-kgL

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

 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008
 Default Initial Parameter Values Background =
      0.24898
                        Beta(1) =    0.0131302
                        Beta(2) =  0.000849523


           Asymptotic Correlation Matrix of Parameter Estimates

             Background      Beta(1)      Beta(2)
```

```
Background            1      NA             NA

   Beta(1)       NA             NA             NA

   Beta(2)       NA             NA             NA


NA - This parameter's variance has been estimated as zero or less.
THE MODEL HAS PROBABLY NOT CONVERGED!!!
```

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.08	*	*	*
Beta(1)	0.00386773	*	*	*
Beta(2)	0.000250241	*	*	*

```
* - Indicates that this value is not calculated.

At least some variance estimates are negative.
THIS USUALLY MEANS THE MODEL HAS NOT CONVERGED!
Try again from another starting point.

Error in computing chi-square; returning 2
```

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-37.3075	2			
Fitted model	-37.3075	3	2.84217e-014	-1	NA
Reduced model	-38.4987	1	2.38238	1	0.1227

AIC: 80.6149

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0800	4.000	4	50	-0.000
15.4560	0.1837	9.000	9	49	0.000

Chi^2 = 0.00 d.f. = -1 P-value = NA

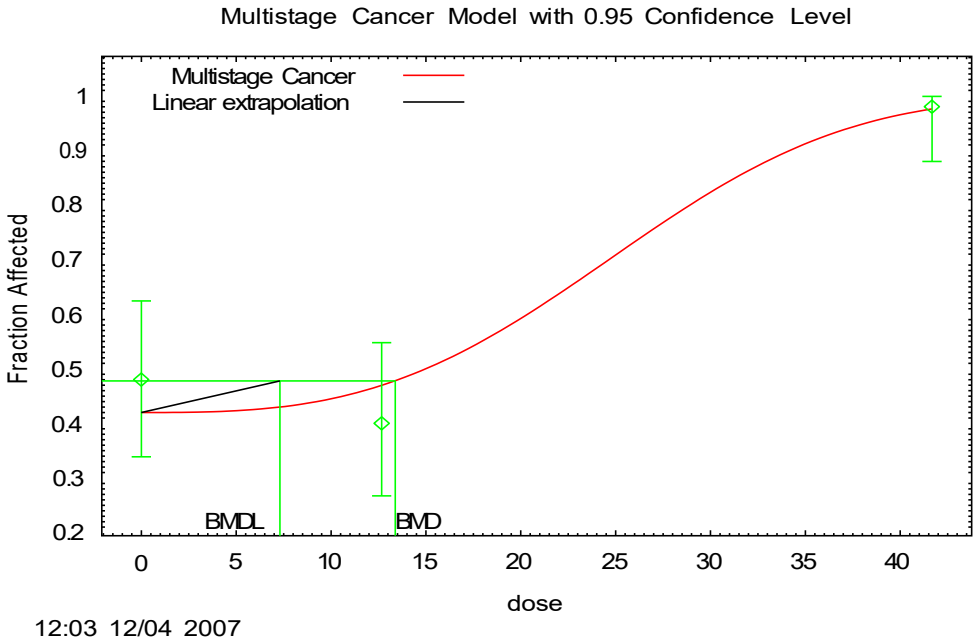
Benchmark Dose Computation

```
Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =         14.1982

            BMDL =         6.15788

            BMDU =    2.64632e+014

Taken together, (6.15788, 2.64632e+014) is a 90     % two-sided confidence
interval for the BMD
```

Male BDF1 mouse – hepatocellular adenomas or carcinomas (0, 5, 25 ppm)

Dose metric: MRAMKL

Fisher model




```
 ======================================================================
      Multistage Cancer Model. (Version: 1.5; Date: 02/20/2007)
      Input Data File: G:\CARBON TET\BMD\BMD MODELING 10-2007\TUMORS MALE MOUSE LIVER\MRAMKL-
FISHER\MMOUSE_LIVER_ADCAR_MRAMKL-FISHER.(d)
      Gnuplot Plotting File: G:\CARBON TET\BMD\BMD MODELING 10-2007\TUMORS MALE MOUSE
LIVER\MRAMKL-FISHER\MMOUSE_LIVER_ADCAR_MRAMKL-FISHER.plt
                        Tue Dec 04 12:03:25 2007
 ======================================================================

 BMDS MODEL RUN
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Observation # < parameter # for Multistage Cancer model.
   The form of the probability function is:

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

   The parameter betas are restricted to be positive


   Dependent variable = IncLiverTumor
   Independent variable = umol/hr-kgL

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

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


                  Default Initial Parameter Values
                     Background =     0.352068
                        Beta(1) =            0
                        Beta(2) =            0
                        Beta(3) = 4.77425e-005


            Asymptotic Correlation Matrix of Parameter Estimates
```

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

	Background	Beta(3)
Background	1	-0.22
Beta(3)	-0.22	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.41973	*	*	*
Beta(1)	0	*	*	*
Beta(2)	0	*	*	*
Beta(3)	4.39818e-005	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-73.1699	3			
Fitted model	-74.0443	2	1.74874	1	0.186
Reduced model	-99.6096	1	52.8795	2	<.0001

AIC: 152.089

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.4197	20.987	24	50	0.864
12.6660	0.4693	23.467	20	50	-0.982
41.6750	0.9760	48.798	49	50	0.187

Chi^2 = 1.75 d.f. = 1 P-value = 0.1864

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 13.3804

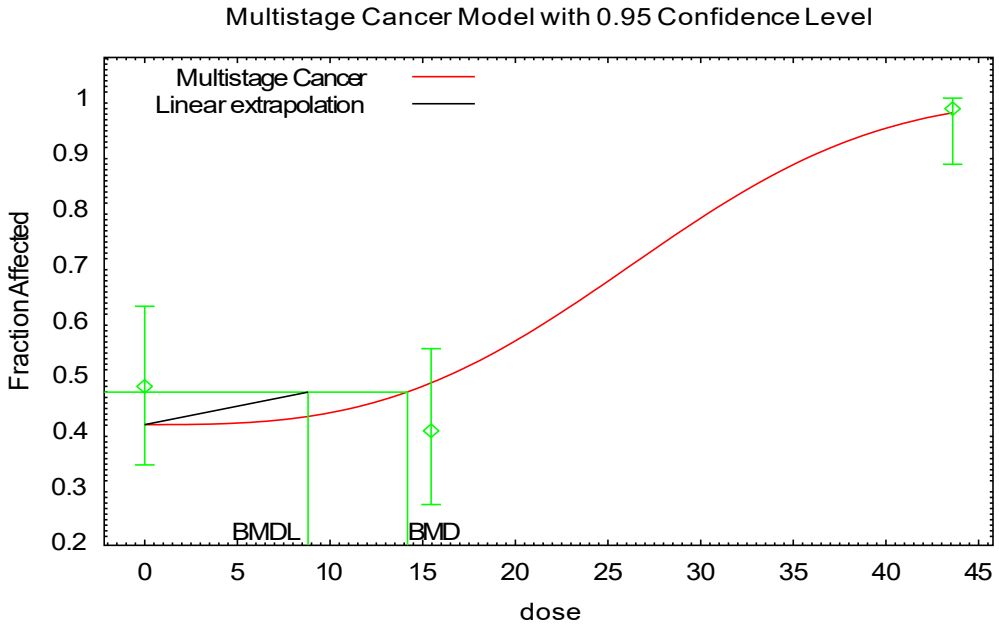
BMDL = 7.30705

BMDU = 15.6428

Taken together, (7.30705, 15.6428) is a 90 % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor = 0.0136854

Dose metric: MRAMKL
Thrall model




```
=================================================================
      Multistage Cancer Model. (Version: 1.5; Date: 02/20/2007)
      Input Data File: G:\CARBON TET\BMD\BMD MODELING 10-2007\TUMORS MALE MOUSE LIVER\MRAMKL-
THRALL\MMOUSE_LIVER_ADCAR_MRAMKL-THRALL.(d)
      Gnuplot Plotting File: G:\CARBON TET\BMD\BMD MODELING 10-2007\TUMORS MALE MOUSE
LIVER\MRAMKL-THRALL\MMOUSE_LIVER_ADCAR_MRAMKL-THRALL.plt
                        Tue Dec 04 12:19:57 2007
 =================================================================

 BMDS MODEL RUN
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Observation # < parameter # for Multistage Cancer model.
   The form of the probability function is:

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

   The parameter betas are restricted to be positive


   Dependent variable = IncLiverTumor
   Independent variable = umol/hr-kgL

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


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008
 Default Initial Parameter Values Background =
      0.317881
                       Beta(1) =            0
                       Beta(2) =            0
                       Beta(3) = 4.21166e-005


            Asymptotic Correlation Matrix of Parameter Estimates

            ( *** The model parameter(s)  -Beta(1)    -Beta(2)
                  have been estimated at a boundary point, or have been specified by the user,
```

and do not appear in the correlation matrix)

	Background	Beta(3)
Background	1	-0.26
Beta(3)	-0.26	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.410703	*	*	*
Beta(1)	0	*	*	*
Beta(2)	0	*	*	*
Beta(3)	3.69143e-005	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-73.1699	3			
Fitted model	-74.462	2	2.58426	1	0.1079
Reduced model	-99.6096	1	52.8795	2	<.0001
AIC:	152.924				

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.4107	20.535	24	50	0.996
15.4560	0.4858	24.289	20	50	-1.214
43.5990	0.9724	48.618	49	50	0.330

Chi^2 = 2.57 d.f. = 1 P-value = 0.1086

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 14.185

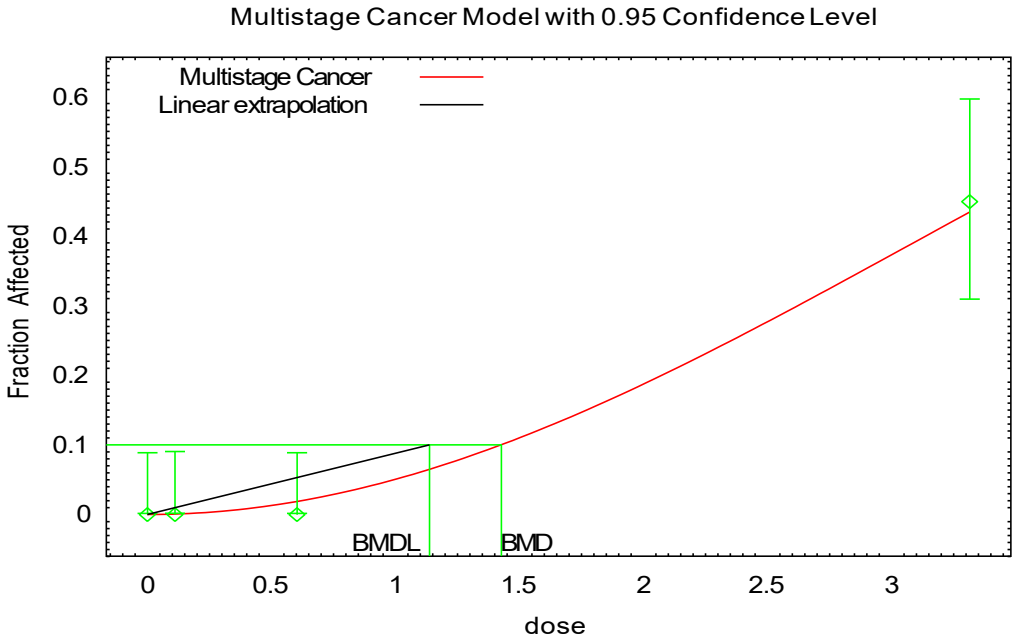
BMDL = 8.82145

BMDU = 16.5171

Taken together, (8.82145, 16.5171) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.011336

BDF1 mouse (female) – pheochromocytomas
Dose metric: MCA
Fisher model



09:49 10/12 2007

```
 ======================================================================
      Multistage Cancer Model. (Version: 1.5; Date: 02/20/2007)
      Input Data File: G:\CARBON TET\BMD\BMD MODELING 10-2007\TUMORS FEMALE
PHEOCHROMOCYTOMAS\FISHER\FMOUSE_PHEOCHROMOCYTOMA_MCA-FISHER.(d)
      Gnuplot Plotting File: G:\CARBON TET\BMD\BMD MODELING 10-2007\TUMORS FEMALE
PHEOCHROMOCYTOMAS\FISHER\FMOUSE_PHEOCHROMOCYTOMA_MCA-FISHER.plt
                          Fri Oct 12 09:49:11 2007
 ======================================================================

 BMDS MODEL RUN
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   The form of the probability function is:

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

   The parameter betas are restricted to be positive

   Dependent variable = Pheochrom
   Independent variable = umol/L

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


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


                  Default Initial Parameter Values
                     Background =            0
                        Beta(1) =            0
                        Beta(2) =    0.0548062
```

Asymptotic Correlation Matrix of Parameter Estimates

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

	Beta(2)
Beta(2)	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0	*	*	*
Beta(1)	0	*	*	*
Beta(2)	0.0517683	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-33.7087	4			
Fitted model	-34.7039	1	1.99041	3	0.5744
Reduced model	-69.0688	1	70.7202	3	<.0001

AIC: 71.4077

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0	50	0.000
0.1110	0.0006	0.031	0	49	-0.177
0.6030	0.0186	0.932	0	50	-0.975
3.3150	0.4338	21.259	22	49	0.214

Chi^2 = 1.03 d.f. = 3 P-value = 0.7947

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 1.42662

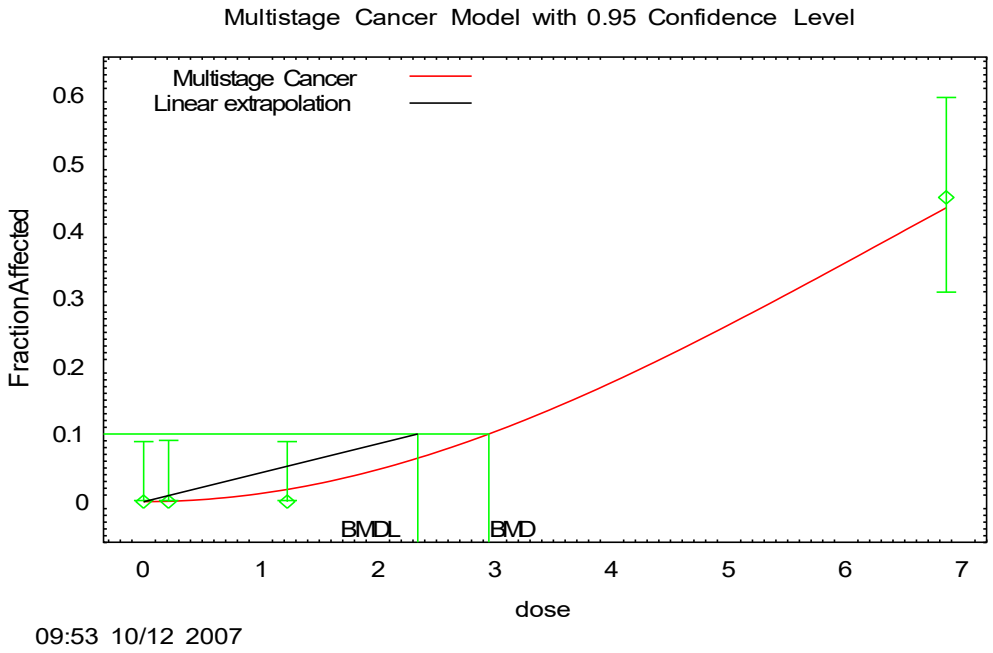
BMDL = 1.13753

BMDU = 1.72224

Taken together, (1.13753, 1.72224) is a 90 % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor = 0.08791

Dose metric: MCA
Thrall model




```
 ======================================================================
      Multistage Cancer Model. (Version: 1.5; Date: 02/20/2007)
      Input Data File: G:\CARBON TET\BMD\BMD MODELING 10-2007\TUMORS FEMALE
PHEOCHROMOCYTOMAS\THRALL\FMOUSE_PHEOCHROMOCYTOMA-MCA-THRALL.(d)
      Gnuplot Plotting File: G:\CARBON TET\BMD\BMD MODELING 10-2007\TUMORS FEMALE
PHEOCHROMOCYTOMAS\THRALL\FMOUSE_PHEOCHROMOCYTOMA-MCA-THRALL.plt
                          Fri Oct 12 09:53:23 2007
 ======================================================================

 BMDS MODEL RUN
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   The form of the probability function is:

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

   The parameter betas are restricted to be positive

   Dependent variable = Pheochrom
   Independent variable = umol/L

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


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


                  Default Initial Parameter Values
                     Background =            0
                        Beta(1) =            0
                        Beta(2) =    0.0128084


           Asymptotic Correlation Matrix of Parameter Estimates
```

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

Beta(2)

	Beta(2)
Beta(2)	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0	*	*	*
Beta(1)	0	*	*	*
Beta(2)	0.0121232	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-33.7087	4			
Fitted model	-34.6679	1	1.91847	3	0.5895
Reduced model	-69.0688	1	70.7202	3	<.0001

AIC: 71.3358

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0	50	0.000
0.2130	0.0005	0.027	0	49	-0.164
1.2260	0.0181	0.903	0	50	-0.959
6.8560	0.4344	21.285	22	49	0.206

Chi^2 = 0.99 d.f. = 3 P-value = 0.8039

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 2.94801

BMDL = 2.34113

BMDU = 3.55893

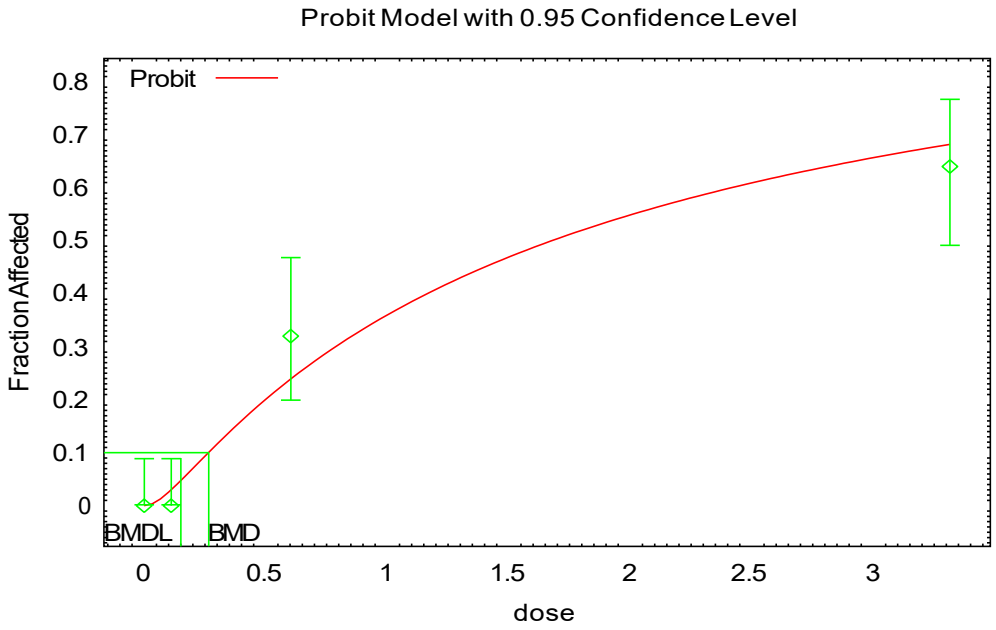
Taken together, (2.34113, 3.55893) is a 90 % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor = 0.0427144

BDF1 mouse (male) – pheochromocytomas

Dose metric: MCA

Fisher model



12:55 11/30 2007

```
================================================================
      Probit Model. (Version: 2.8; Date: 02/20/2007)
      Input Data File: G:\CARBON TET\BMD\BMD MODELING 10-2007\TUMORS MALE
PHEOCHROMOCYTOMAS\FISHER\MMOUSE_PHEOCHROMOCYTOMA_MCA-FISHER.(d)
      Gnuplot Plotting File: G:\CARBON TET\BMD\BMD MODELING 10-2007\TUMORS MALE
PHEOCHROMOCYTOMAS\FISHER\MMOUSE_PHEOCHROMOCYTOMA_MCA-FISHER.plt
                          Fri Nov 30 12:55:04 2007
 ================================================================
 BMDS MODEL RUN
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   The form of the probability function is:

   P[response] = Background
               + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)),

   where CumNorm(.) is the cumulative normal distribution function

   Dependent variable = Pheochrom
   Independent variable = umol/L
   Slope parameter is not restricted

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

   User has chosen the log transformed model

                 Default Initial (and Specified) Parameter Values
                    background =            0
                     intercept =    -0.416734
                         slope =     0.792244


          Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -background
```

have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	intercept	slope
intercept	1	-0.092
slope	-0.092	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
background	0	NA		
intercept	-0.358995	0.125298	-0.604574	-0.113416
slope	0.694404	0.110458	0.47791	0.910899

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

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-64.0144	4			
Fitted model	-66.5682	2	5.10756	2	0.07779
Reduced model	-110.216	1	92.4032	3	<.0001

AIC: 137.136

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0	50	0.000
0.1110	0.0297	1.484	0	50	-1.237
0.6030	0.2388	11.939	16	50	1.347
3.3150	0.6820	34.099	32	50	-0.637

Chi^2 = 3.75 d.f. = 2 P-value = 0.1533

Benchmark Dose Computation

Specified effect = 0.1

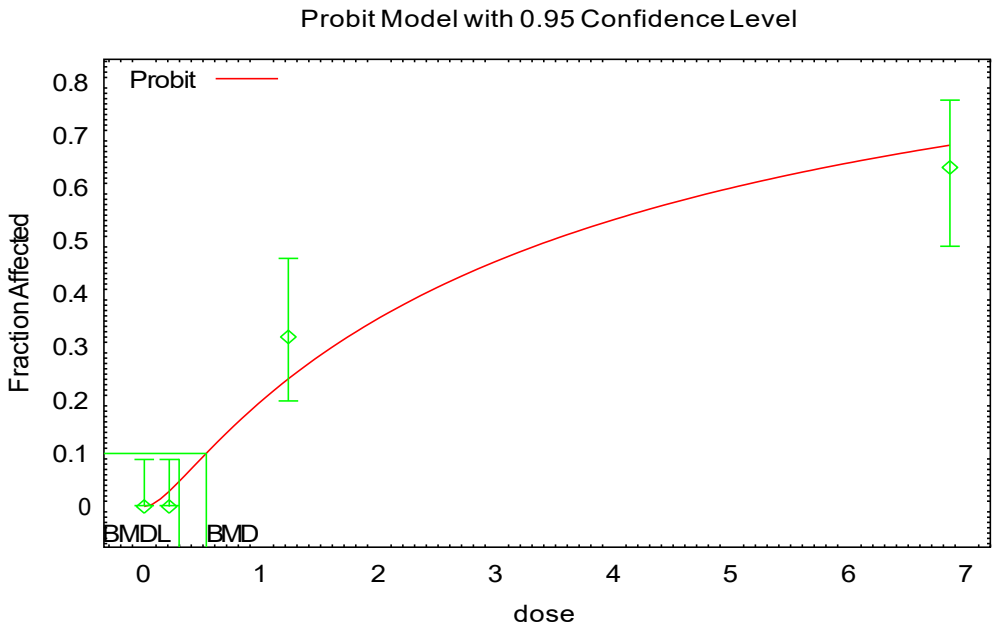
Risk Type = Extra risk

Confidence level = 0.95

BMD = 0.264859

BMDL = 0.150882

Dose metric: MCA
Thrall model




```
=====================================================================
      Probit Model. (Version: 2.8; Date: 02/20/2007)
      Input Data File: G:\CARBON TET\BMD\BMD MODELING 10-2007\TUMORS MALE
PHEOCHROMOCYTOMAS\THRALL\MMOUSE_PHEOCHROMOCYTOMA_MCA-THRALL.(d)
      Gnuplot Plotting File: G:\CARBON TET\BMD\BMD MODELING 10-2007\TUMORS MALE
PHEOCHROMOCYTOMAS\THRALL\MMOUSE_PHEOCHROMOCYTOMA_MCA-THRALL.plt
                          Fri Nov 30 13:15:12 2007
 =====================================================================
 BMDS MODEL RUN
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   The form of the probability function is:

   P[response] = Background
               + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)),

   where CumNorm(.) is the cumulative normal distribution function

   Dependent variable = Pheochrom
   Independent variable = umol/L
   Slope parameter is not restricted

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

   User has chosen the log transformed model

                 Default Initial (and Specified) Parameter Values
                    background =            0
                     intercept =    -0.965049
                         slope =     0.776315


           Asymptotic Correlation Matrix of Parameter Estimates

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

	intercept	slope
intercept	1	-0.58
slope	-0.58	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
background	0	NA		
intercept	-0.844448	0.153761	-1.14581	-0.543082
slope	0.683918	0.109119	0.470048	0.897787

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

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-64.0144	4			
Fitted model	-66.4723	2	4.91585	2	0.08561
Reduced model	-110.216	1	92.4032	3	<.0001

AIC: 136.945

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0	50	0.000
0.2130	0.0286	1.429	0	50	-1.213
1.2260	0.2404	12.019	16	50	1.318
6.8560	0.6816	34.080	32	50	-0.631

Chi^2 = 3.61 d.f. = 2 P-value = 0.1648

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 0.527758

BMDL = 0.297349

SOURCE CODE FOR PHYSIOLOGICALLY BASED PHARMACOKINETIC MODELS

```
% ----------------------------------------------------------------------
%
% File: HUMINH.M
%
% Programmed by Gary Diamond
% Syracuse Research Corporation, 02/2005
%
%This run time file implements CCL4.CSL for inhalation exposure
%(human parameters)
% ----------------------------------------------------------------------
%Prepare time history variables
prepare @clear @all

%Set communication interval
CINT=1.;

%Set simulation stop (hr)
TSTOP=17250.;

%Integration error check
!!SET WESITG=.F.

%Air Exposure Parameters
AIRC=2.27; %ppm
AIRON=0.; %hr
AIROFF=1000000.; %17520.; %hr
CIOFF=0.; %ppm
APER1=24.; %hr
AWID1=24.; %hr
APER2=168.; %hr
AWID2=168.; %hr

%Oral Exposure Parameters
RGIL=0.0;
FGIL=1.0;

%Human Parameters
BW=70.;
VLC=0.04;
VFC=0.30; %Revised from 0.1 (03/2007)
VSC=0.62;
VRC=0.05;
```

```
QCC=15.;
QPC=15.;
QSF=0.74;
QLC=0.25;
QFC=0.06;
QSC=0.18;
QRC=0.51;

PBLD=2.64;
PL=3.14;
PF=79.42;
PS=1.0;
PR=3.14;

%Chemical Parameters
MW=153.8;
VMAXC=1.49;
KMX = 0.25;
VMAXSF=0.7;
A1=0.065;
A2=0.095;
A3=0.84;
K1=0.25;
K2=0.03;
K3=0.025;
K4=0.;
K5=0.0004;

!! START /NC

%Output
HUM1=[_time _day _air _ca _ramkb _mcl _cf _af, _cl];

HUM2=rot90(fliplr(HUM1));
out=fopen('HUMAN.out','w');
fprintf(out,"%f,%f,%f,%e,%e,%e,%e,%e\n",HUM2);
fclose(out);
```

```
% ----------------------------------------------------------------------
%
% File: HUMOR.M
%
% Programmed by Gary Diamond
% Syracuse Research Corporation, 10/2007
%
%This run time file implements CCL4.CSL for "oral" exposure (RGIL)
%(human parameters)
% ----------------------------------------------------------------------
%Prepare time history variables
prepare @clear @all

%Set communication interval
CINT=24.;

%Set simulation stop (hr)
TSTOP=5000.;

%Integration error check
!!SET  WESITG=.F.

%Air Exposure Parameters
AIRC=0.;      %ppm
AIRON=0.; %hr
AIROFF=1000000.; %17520.; %hr
CIOFF=0.; %ppm
APER1=24.; %hr
AWID1=24.; %hr
APER2=168.; %hr
AWID2=168.; %hr

%Oral Exposure Parameters
RGILC=10.0;
FGIL=1.0;

%Human Parameters
BW=70.;
VLC=0.04;
VFC=0.30; %Revised from 0.1
VSC=0.62;
VRC=0.05;

QCC=15.;
QPC=15.;
QSF=0.74;
```

```
QLC=0.25;
QFC=0.06;
QSC=0.18;
QRC=0.51;

PBLD=2.64;
PL=3.14;
PF=79.42;
PS=1.0;
PR=3.14;

%Chemical Parameters
MW=153.8;
VMAXC=0.40;
KMX = 0.25;
VMAXSF=0.7;
A1=0.065;
A2=0.095;
A3=0.84;
K1=0.25;
K2=0.03;
K3=0.025;
K4=0.;
K5=0.0004;

!! START /NC

%Output
HUM1=[_time _rgil _mca _mramkl];

HUM2=rot90(fliplr(HUM1));
out=fopen('HUMAN.out','w');
fprintf(out,"%e,%e,%e,%e\n",HUM2);
fclose(out);
```

```
% ----------------------------------------------------------------------
%
% File: MOUINH_JF.M
%
% Programmed by Gary Diamond
% Syracuse Research Corporation, 10/2007
%
%This run time file implements CCL4.CSL for inhlation exposure
%(mouse parameters, Fisher et al. 2004)
% ----------------------------------------------------------------------
%Prepare time history variables
prepare @clear @all

%Set communication interval
CINT=24.;

%Set simulation stop (hr)
TSTOP=17520.;

%Integration error check
!!SET  WESITG=.F.

%Air Exposure Parameters:
AIRC=125.; %ppm
AIRON=0.; %hr
AIROFF=17520; %hr
CIOFF=0.; %ppm
APER1=24.; %hr
AWID1=6.; %hr
APER2=168.; %hr
AWID2=120.; %hr

%Mouse Parameters:
BW=0.036;
VLC=0.04;
VFC=0.04;
VSC=0.69;
VRC=0.14;

QCC=30.;
QPC=30.;
QSF=0.75;
QLC=0.24;
QFC=0.05;
QSC=0.17;
QRC=0.54;
```

```
PBLD=3.8;
PL=4.8;
PF=91.4;
PS=2.5;
PR=4.8;

%Chemical Parameters:
MW=153.8;
VMAXC=1.;
KMX = 0.3;
VMAXSF=0.75;

%From Thrall et al 2000
A1=0.065;
A2=0.095;
A3=0.84;
K1=0.25;
K2=0.03;
K3=0.025;
K4=0.;
K5=0.00042;

!! START /NC
%Output
%MOU=[AIR MCA MRAMKB MCL MRAMKL]
MOU1=[_time _day _air _mramkl _mca _mramkb _mcl _mramkl]; %output matrix

%formating of output for printed comma-dilimited file:
MOU2=rot90(fliplr(MOU1));
out=fopen('MOU.out','w');
%fprintf(out,"%f,%f,%f,%f,%f,%f,%f\n",MOU2);
%fprintf(out,"%f,%f,%f,%e,%e,%e,%e,%e\n",MOU2);
fprintf(out,"%e\n",MOU);
fclose(out);
```

```
% ----------------------------------------------------------------------
%
% File: MOUINH_KT.M
%
% Programmed by Gary Diamond
% Syracuse Research Corporation, 3/2007
%
%This run time file implements CCL4.CSL for inhlation exposure
%(mouse parameters, Thrall et al. 2000)
% ----------------------------------------------------------------------
%Prepare time history variables
prepare @clear @all

%Set communication interval
CINT=24.;

%Set simulation stop (hr)
TSTOP=17520.;

%Integration error check
!!SET  WESITG=.F.

%Air Exposure Parameters:
AIRC=2.5; %ppm
AIRON=0.; %hr
AIROFF=17520; %hr
CIOFF=0.; %ppm
APER1=24.; %hr
AWID1=6.; %hr
APER2=168.; %hr
AWID2=120.; %hr

%Mouse Parameters:
BW=0.036;
VLC=0.04;
VFC=0.04;
VSC=0.78;
VRC=0.05;

QCC=28.;
QPC=28.;
QSF=0.74;
QLC=0.24;
QFC=0.05;
QSC=0.19;
QRC=0.52;
```

```
PBLD=7.83;
PL=2.08;
PF=23.0;
PS=0.61;
PR=2.08;

%Chemical Parameters:
MW=153.8;
VMAXC=0.79;
KMX = 0.46;
VMAXSF=0.7;
A1=0.065;
A2=0.095;
A3=0.84;
K1=0.25;
K2=0.03;
K3=0.025;
K4=0.;
K5=0.00042;

!! START /NC

%Output
%MOU=[AIR MCA MRAMKB MCL MRAMKL]
MOU1=[_time _day _air _mramkl _mca _mcl]; %output matrix

%formating of output for printed comma-dilimited file:
MOU2=rot90(fliplr(MOU1));
out=fopen('MOU.out','w');
fprintf(out,"%f,%f,%e,%e,%e,%e\n",MOU2);
fprintf(out,"%e\n",MOU);
fclose(out);
```

```
% ----------------------------------------------------------------------
%
% File: RATINH.M
%
% Programmed by Gary Diamond
% Syracuse Research Corporation, 02/2005
%
%This run time file implements CCL4.CSL for inhalation exposure
%(rat parameters)
% ----------------------------------------------------------------------
%Prepare time history variables
prepare @clear @all

%Set communication interval
CINT=1.;

%Set simulation stop (hr)
TSTOP=17250.;

%Integration error check
!!SET WESITG=.F.

%Air Exposure Parameters:
AIRC=4.;      %ppm
AIRON=0.; %hr
AIROFF=17520; %hr
CIOFF=0.; %ppm
APER1=24.; %hr
AWID1=6.; %6.; %hr
APER2=168.; %hr
AWID2=120.; %120.; %hr

%Rat Parameters:
BW=0.452;
VLC=0.04;
VFC=0.08;
VSC=0.74;
VRC=0.05;

QCC=15.;
QPC=15.;
QSF=0.74;
QLC=0.25;
QFC=0.04;
QSC=0.20;
QRC=0.51;
```

```
PBLD=4.52;
PL=3.14;
PF=79.42;
PS=1.0;
PR=3.14;

%Chemical Parameters:
MW=153.8;
VMAXC=0.4;
KMX = 0.25;
VMAXSF=0.7;
A1=0.065;
A2=0.095;
A3=0.84;
K1=0.25;
K2=0.03;
K3=0.025;
K4=0.;
K5=0.00042;


!! START /NC

%Output
RAT1=[_time _day _air _mca _mramkl _mcl]; %output matrix

%formating of output for printed comma-dilimited file:
%RAT2=rot90(fliplr(RAT1));
%out=fopen('RAT.out','w');
%fprintf(out,"%f,%f,%f,%e,%e,%e\n",RAT2);
%fclose(out);
```

```
PROGRAM: CCL4R

      !This program simulates the pharmacokinetics of carbon tetrachloride
      !The program is based on ITRICCL4.ACSL,  developed by KD THRALL  9/98; ACSL code provided to
GDiamond, 04/2004
      !The above code was translated with minor modifications, by GDiamond, 05/2004

INITIAL
      VARIABLE  TIME = 0.0 !Set independent variable to be TIME
  ALGORITHM  IALG = 2 !Numerical integration algorithm - Gear for stiff systems
      CINTERVAL  CINT=100. !Communication interval
      NSTP = 1000 !Set initital integration cycle length at CINT/1000
      MERROR AL=0.0001 !Set error tolerance for Gear

  !*****BODY AND TISSUE MASSES*****
      CONSTANT  BW = 0.2 !Body weight (kg)
  CONSTANT  VLC = 0.04 !Liver fraction of body weight
      CONSTANT  VFC = 0.08 !Adipose fraction of body weight
      CONSTANT  VSC = 0.74 !Slowly-perfused fraction of body weight
  CONSTANT  VRC = 0.05 !Rapdily-perfused fraction of body weight

      VL=VLC*BW !Liver (kg
   VF=VFC*BW !Adipose (kg)
   VS=VSC*BW !Slowly-perfused (kg)
   VR=VRC*BW !Rapidly-perfused (kg)

      !*****BLOOD FLOWS*****
      CONSTANT  QCC=14 !Cardiac output (L/hr-BW^SF)
      CONSTANT  QPC=14 !Alveolar ventilation (L/hr-BW^SF)
      CONSTANT  QLC = 0.25 !Liver fraction of cardiac output
  CONSTANT  QFC = 0.09      !Adipose fraction of cardiac output
  CONSTANT  QSC = 0.15      !Slowly-perfused fraction of cardiac output
  CONSTANT  QRC = 0.51      !Rapidly-perfused fraction of cardiac output

      CONSTANT  QSF = 0.74 !QC and QP scaling factor (SF)
      QC=QCC*BW**QSF!Cardiac output (L/hr)
      QP=QPC*BW**QSF !Alveolar ventilation (L/hr)

      QL = QLC*QC !Liver (L/hr)
  QF = QFC*QC !Adipose (L/hr)
  QS = QSC*QC !Slowly-perfused (L/hr)
  QR = QRC*QC !Rapidly-perfused (L/hr)

      !*****PARTITION COEFFICIENTS*****
      CONSTANT  PBLD = 4.52 !Blood:air partition coefficient
```

```
CONSTANT PL = 3.14 !Liver:blood partition coefficient
CONSTANT PF = 79.42 !Adipose:blood partition coefficient
   CONSTANT PS = 1.0       !Slowly-perfused:blood partition coefficient
CONSTANT PR = 3.14 !Rapidly-perfused:blood partition coefficient

   !*****METABOLISM and EXCRETION*****
   CONSTANT MW=153.8 !Molecular weight of CCl4
   CONSTANT VMAXC = 0.40 !VMAX for metabolism in liver (mg/hr-BW^SF)
   CONSTANT KMX = 0.25 !KM for metabolism in liver (mg/L)
   CONSTANT VMAXSF=0.7 !Scaling factor for VMAXC (SF)
   CONSTANT A1=0.085 !Fraction of metabolism rate to M1 pool
   CONSTANT A2=0.095 !Fraction of metabolism rate to M2 pool
   CONSTANT A3=0.84 !Fraction of metabolism rate to M3 pool
   CONSTANT K1=0.123    !Rate constant for conversion of M1 to exhaled metabolite (CO2) (hr-1)
   CONSTANT K2=0.03 !Rate constant for conversion of M2 to urinary metabolite (hr-1)
   CONSTANT K3=0.0252 !Rate constant for conversion of M3 to fecal metabolite (hr-1)
   CONSTANT K4=0. !Rate constant for conversion of M2 to M1 (hr-1)
   CONSTANT K5=0.00042 !Rate constant for conversion of M3 to M1 (hr-1)

   VMAX = 1000*VMAXC*BW**VMAXSF/MW!Maximum rate of metabolism in liver (umol/hr)
   KM = 1000*KMX/MW !Michaelis constant for metabolism in liver (umol/L)

   !*****EXPOSURE - AIR*****
   CONSTANT AIRC = 1. !Air exposure concentration (ppm)
   AIR = AIRC; !Air exposure concentration (ppm)
AIRCM = AIR/24.45 !Air exposure (umol/L)
   mgAIR = AIR*MW/24.45 !Air exposure (mg/m3)
   ugAIR=AIR*MW/24.45 !Air exposure concentration (ug/L)

   CONSTANT TSTOP = 700. !Length of simulaion (hr)
   CONSTANT AIRON=0. !Time air exposure starts (hr)
   CONSTANT AIROFF=700. !Time air exposure stops (hr)
   CONSTANT CIOFF=0. !Concentration in inhaled air when exposure is off (ppm)
   CONSTANT APER1=24. !Pulse period 1 for air exposure (e.g., hours in a day)
   CONSTANT AWID1=24. !Pulse width 1 for air exposure (e.g., 6 hours each day)
   CONSTANT APER2=168. !Pulse period 2 for air exposure (e.g., hours in a day)
   CONSTANT AWID2=168. !Pulse width 2 for air exposure (e.g., 6 hours each day)
!*****EXPOSURE - ORAL ******GD 08/2007
   CONSTANT RGILC=0. !Rate of uptake from GI to liver (umol/hr)
RGIL=RGILC !Rate of uptake from GI to liver (umol/hr)
                                    !Use for simuulating constant rate of uptake from GI-tract
   MGRGIL=RGIL*MW/1000    !Rate of uptake from GI to liver (mg/hr)
   MGRGILKGD=RGIL*24*MW/(1000*BW)!Rate of uptake to liver (mg/kg-day)
   CONSTANT GILF=1.      !Absorption fraction
   !CONSTANT POINTS = 96.
   !CINT = TSTOP/POINTS !Sets communication for 96 times in the simulation
```

```
END      !of INITIAL  section of program

DYNAMIC

DERIVATIVE

    DAY=TIME/24
    YEAR=DAY/365

    !*****CONCENTRATION IN INHALED AIR (umol/L)*****
    CION = AIRCM*PULSE(AIRON,APER1,AWID1)*PULSE(AIRON,APER2,AWID2)
    CI = RSW(TIME.LE.AIROFF,CION,CIOFF)
    RAI = QP*(CA/PBLD-CI)!Rate inhaled (umol/hr)
    CP = CI*24.45 !Concentration in chamber (ppm)

    !*****AMOUNT TAKEN  IN BY ONE ANIMAL (umol)*****
    RIN = QP*CI
    AIN = INTEG(RIN,0.0)

    !*****LIVER*****
    !Use for simulation of constant rate of uptake from GI-tract (GD 08/2007)
    RAL = QL*(CA-CVL)+RGIL-RAM      !Rate of change in amount (umol/hr)

    !Use for simulation of inhalation exposure
    !RAL = QL*(CA-CVL)-RAM !Rate of change in amount (umol/hr)
    AL = INTEG(RAL,  0.0) !Amount (umol)
    CVL = CL/PL !Concentration in venous blood (umol/L)
    CL = AL/VL !Concentration (umol/L)
    AUCCL = INTEG(CL,0.) !AUC concentration (umol/L x hr)

    !Average concentration in liver (umol/L) - MCL(GD 05/2004)
    IF (TIME .GT. 0.) THEN
    MCL = AUCCL/TIME
    ELSE
    MCL= 0.
    END IF

    ugCL = CL*MW/1000      !Concentration (ug/g)
    MugCL = MCL*MW/1000      !Average concentration (ug/g)
    AUCugCL = AUCCL*MW/1000 !AUC concentration (ug/g xhr)

    !*****METABOLIZED*****
    RAM = (VMAX*CVL)/(KM+CVL)      !Rate, total (umol/hr)
    RAMKB= RAM/BW !Rate, total (umol/hr x kq body)
    RAMKL=RAM/VL  !Rate, total (umol/hr x kg liver)
    AUCRAM=INTEG(RAM,0.0)  !AUC rate (umol/hr x hr)
```

```
    !Average rate of metabolism (umol/hr) - MRAM (GD 05/2004)
    IF (TIME .GT. 0.) THEN
    MRAM = AUCRAM/TIME
    ELSE
    MRAM= 0.
    END IF

    MRAMKB=MRAM/BW !Average rate, total (umol/hr x kg body) (GD 05/2004)
    MRAMKL=MRAM/VL !Average rate, total (umol/hr x kg liver) (GD 05/2004

    RAXA = RAM*A1-K1*AXA+K4*AXU+K5*AXF !Rate to air pool (umol/hr)
    RAXF = RAM*A3-K3*AXF-K5*AXF !Rate to feces pool (umol/hr)
    RAXU = RAM*A2-K2*AXU-K4*AXU !Rate to urine pool(umol/hr)
    AM = INTEG(RAM,0.) !Amount total (umol)
    AMK = AM/BW !Amount total (umol/kg bw)
    AMKL=AM/VL !Amount total (umol/kg liver)
    AXA = INTEG(RAXA,0.) !Amount in air pool (umol)
    AXF = INTEG(RAXF,0.) !Amount in feces pool (umol)
    AXU = INTEG(RAXU,0.) !Amount in urine pool (umol)

    RA = AXA*k1 !Rate to air (umol/hr)
    RU = AXU*k2 !Rate to urine (umol/hr)
    RF = AXF*k3 !Rate to feces (umol/hr)
    ugRA = RA*MW !Rate to air (ug/hr)
    ugRU = RU*MW !Rate to urine (ug/hr)
    ugRF = RF*MW !Rate to feces (ug/hr)
    CAX = RA/((3/2)*QP) !Concentration of metabolite in exhaled air (umol/L)
    CAXM = CAX*24.45 !Concentration of metabolite in exhaled air (ppm)

    !*****FAT*****
RAF = QF*(CA-CVF) !Rate of change in amount (umol/hr)
AF = INTEG(RAF, 0.0) !Amount (umol)
CVF = CF/PF !Concentration in venous blood (umol/L)
CF = AF/VF !Concentration (umol/L)
    AUCCF = INTEG(CF, 0.) !AUC concentration (umol/L x hr)

    !Average concentration in fat (umol/L) - MCF (GD 03/2007)
    IF (TIME .GT. 0.) THEN
    MCF = AUCCF/TIME
    ELSE
    MCF=0.
    END IF

ugCF = CF*MW/1000    !Concentration(ug/g)
    MugCF = MCF*MW/1000     !Average concentration (ug/g)
    AUCugCF = AUCCF*MW/1000    !AUC concentration (ug/g x hr)
```

```
    !*****SLOWLY PERFUSED TISSUES*****
RAS = QS*(CA-CVS) !Rate of change in amount (umol/hr)
AS = INTEG(RAS, 0.0) !Amount (umol)
CVS = CS/PS !Concentration in venous blood (umol/L)
CS = AS/VS !Concentration in umol/L
ugCS = CS*MW/1000 !Concentration in ug/g

!*****RICHLY PERFUSED TISSUES*****
RAR = QR*(CA-CVR) !Rate of change in amount (umol/hr)
AR = INTEG(RAR,0.0) !Amount (umol)
CVR = CR/PR !Concentration in venous blood (umol/L)
CR = AR/VR !Concentration in umol/L
ugCR = CR*MW/1000 !Concentration in ug/g

!*****MIXED VENOUS BLOOD*****
CV = (QF*CVF+QL*CVL+QS*CVS+QR*CVR)/QC     !Concentration (umol/L)
    AUCCV=INTEG(CV,0.)  !AUC concentration (umol/L x hr)


    !Average concentration in venous blood (umol/L) - MCV (GD 05/2004)
    IF (TIME .GT. 0.) THEN
    MCV = AUCCV/TIME
    ELSE
    MCV=0.
    END IF

ugCV = CV*MW/1000 !Concentration (ug/g)
    MugCV = MCV*MW/1000     !Average concentration (ug/g)
    AUCugCV = AUCCV*MW/1000 !AUC concentration (ug/g x hr)

!*****ARTERIAL BLOOD*****
CA = (QC*CV+QP*CI)/(QC+(QP/PBLD)) !Concentration(umol/L)
    AUCCA=INTEG(CA,0.)  !AUC concentration (umol/L x hr)


    !Average concentration in atrerial blood (umol/L) - MCA (GD 05/2004)
    IF (TIME .GT. 0.) THEN
    MCA = AUCCA/TIME
    ELSE
    MCA=0.
    END IF

    ugCA=CA*MW/1000 !Concentration (ug/g)
    MugCA=MCA*MW/1000 !Average concentration (ug/g)
    AUCugCA=AUCCA*MW/1000     !AUC concentration (ug/g x hr)
```

```
  !*****AMOUNT EXHALED*****
  CX=CA/PBLD !Concentration in alveolar air (umol/L)
  CXPPM = (0.7*CX+0.3*CI)*24.45 !Concentration in exhaled air (ppm)
                                          !Total ventilation is 0.7 of alveolar ventilation
  RAX= QP*CX !Rae of change in amount (umol/hr)
  AX=INTEG(RAX,0.) !Amount (umol)

      !*****NET AMOUNT ABOSORBED*****
      DOSEX = AIN-AX !Net amount absorbed(umol)
      BODY=AL+AF+AS+AR !Amount in body (umol)
      MASSB = BODY+AM+AX !Mass balance (umol)

END !of DERIVATIVE section of program

TERMT(TIME .GE. TSTOP) !Termination condition

END     !of DYNAMIC section of program

TERMINAL

END !of TEMINAL section of program

END     !of program
```