Benchmark Dose Modeling – Modeling Time

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Models Covered in This Course

- **Currently there are two models included in BMDS that can incorporate time in the modeling scheme**
  - **The toxicodiffusion model** is used for time-course or repeated response data where a particular effect has been measured at multiple time-points
  - **The ten Berge concentration × time (C × T) model** is primarily used in the context of acute inhalation studies where groups of animals are exposed to multiple concentrations of a chemical for varying durations of exposure.

- **Currently, there is a cancer model that incorporates time that is covered in the Cancer Training Module**
  - This model, the Multistage-Weibull time-to-tumor model, is run outside of BMDS program but is available from the BMDS website: http://epa.gov/ncea/bmds/dwnldu.html#msw

Repeated Response Data – The Toxicodiffusion Model

Repeated Response Data

- **Repeated response measures, or time-course data, can be used to characterize toxicity responses that vary according to dose and time**
- **Neurotoxicity tests, such as functional observational batteries (FOBs), often generate repeated response data**
- **Repeated response data is different from concentration × time (C × t) data**
  - C × t data involves animals exposed to a chemical at a particular dose for a certain duration of time
  - Repeated measure data involves animals exposed to a chemical once and where responses are measured at multiple time points before, during, or following that exposure

Traditional Analysis of Time-Course Data

- **Historically, analysis of FOB or other repeated-response data has been conducted using Analysis of Variance (ANOVA) methods**
  - ANOVA is effective at detecting dose- and time-related changes in responses
  - However, they cannot describe the magnitude or underlying shape of the dose-response curve along the recorded time-course
- **In order to describe the dose-response characteristics, one option would be to model independent time points separately, but this type of analysis is unsatisfactory for 3 reason:**
  - It would be limited to the experimental time points
  - The time trend of the dose-effects would not be fully utilized
  - It might not reflect the magnitude of toxic effects at the most sensitive time point
- **For these reasons Zhu et al. (2005a,b) developed the toxicodiffusion model**

Toxicodiffusion Model Form

- **The equation for the toxicodiffusion model is given as:**

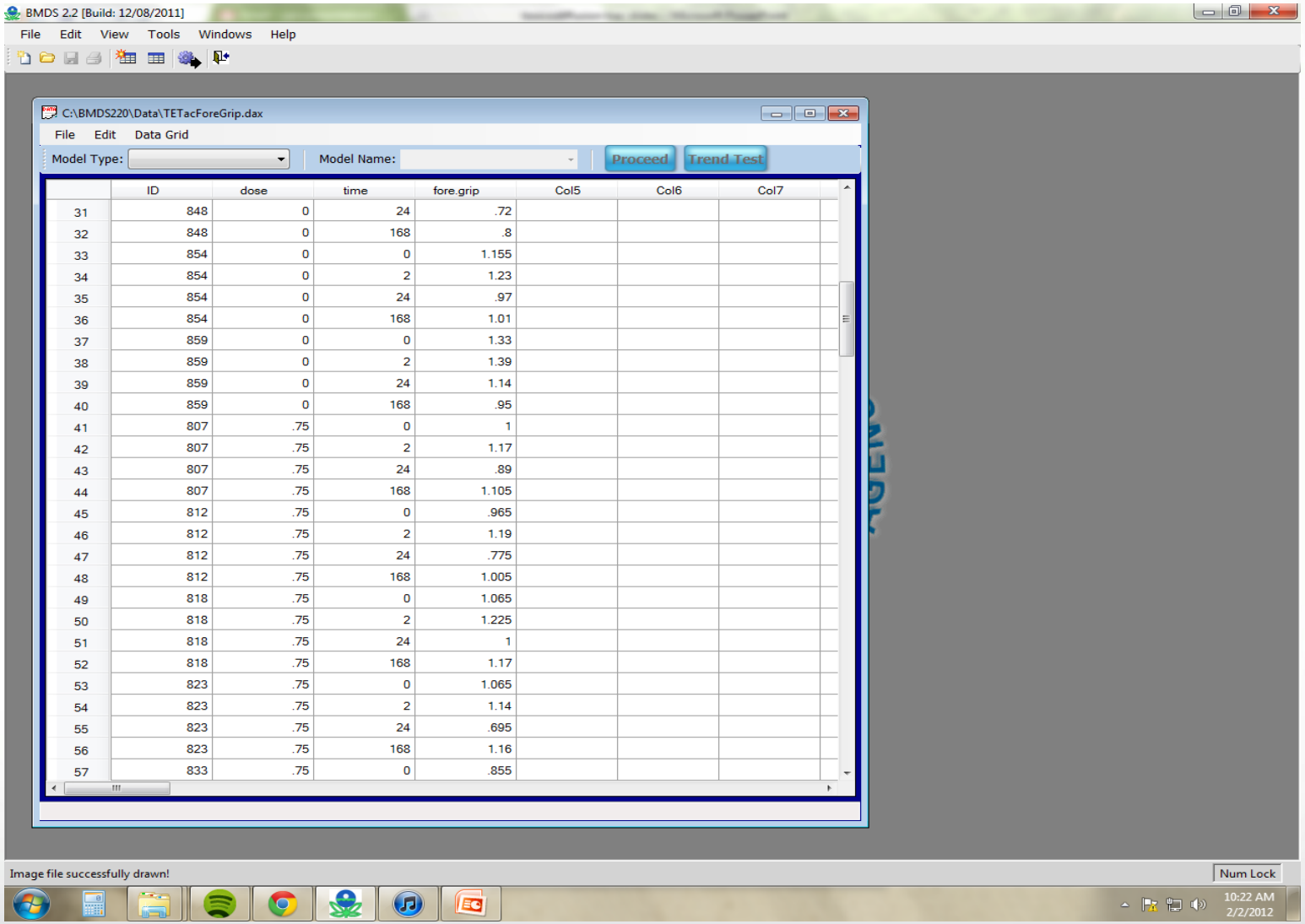
$$\eta(d,t) = A(t) + f(d,t), \text{where } f(d,t) = \frac{(B*t*d*exp(-k*t))}{(1+C*t*d*exp(-k*t))}$$

  - When first order kinetics are applicable, the parameter k can be interpreted as the elimination coefficient
  - $A(t)$ represents the time-course that is predicted in the absence of exposure
    - Constant: $A(t) = A_0$
    - Linear: $A(t) = A_0 + A_1 t$
    - 2nd degree polynomial: $A(t) = A_0 + A_1 t + A_2 t^2$
  - The toxicodiffusion model is particularly well-suited for describing dose-time-response relationships of transient dose effects
    - $f(d,t)$ starts at a value of 0 when $t = 0$, increases with time and reaches peak effect $\left(\frac{Bd}{Cd+k*e}\right)$ at $t = \frac{1}{k}$, and eventually returns to 0 with sufficiently large time

Repeated Response Data

- **For the purposes of modeling repeated response data in BMDS, the data must be structured as follows:**
  - The response variable measured on a continuous scale
  - A single exposure (or exposure interval) and several (4-5) doses
  - The time component is coded between 0 (beginning) and the maximum positive value (last time point for which data is available).
  - The outcome is measured repeatedly over time on each study subject, and the time of observation is given. It is not necessary for each subject to have the same time points
  - Individual animal data and multiple subjects per dose group are required
  - Dose effects are observed at more than one dose level, and differences in dose effect are seen at some time points

Repeated Response Datafile Format



	ID	dose	time	fore.grip	Col5	Col6	Col7
31	848	0	24	.72			
32	848	0	168	.8			
33	854	0	0	1.155			
34	854	0	2	1.23			
35	854	0	24	.97			
36	854	0	168	1.01			
37	859	0	0	1.33			
38	859	0	2	1.39			
39	859	0	24	1.14			
40	859	0	168	.95			
41	807	.75	0	1			
42	807	.75	2	1.17			
43	807	.75	24	.89			
44	807	.75	168	1.105			
45	812	.75	0	.965			
46	812	.75	2	1.19			
47	812	.75	24	.775			
48	812	.75	168	1.005			
49	818	.75	0	1.065			
50	818	.75	2	1.225			
51	818	.75	24	1			
52	818	.75	168	1.17			
53	823	.75	0	1.065			
54	823	.75	2	1.14			
55	823	.75	24	.695			
56	823	.75	168	1.16			
57	833	.75	0	.855			

Toxicodiffusion Model in BMDS

- **Unlike other models in BMDS, the toxicodiffusion model requires that users install the R Statistical software package (version 2.6.2 or higher)**

- **The toxicodiffusion model also is the only model in BMDS currently that uses the "hybrid approach" to calculate a BMD for continuous data based on dichotomized risk, requiring two user-selected parameters:**
  - The benchmark response (BMR) – expressed as either added or extra risk (e.g., 10% extra risk)
  - The background rate (i.e., probability) of an adverse response in the control group

The Hybrid Approach – Selecting the BMR

- **As with dichotomous models, EPA recommends the use of extra risk as this accounts for the presence of background responses**

- **10% extra risk would be expressed as:**

$$0.10 = \left[P\left(BMD_\gamma, t\right) - P(0,t)\right]/(1 - P(0,t)]$$

If $P(0,t) = 0.01$ (i.e., there is a 1% probability of adversity in the control group at time t), then

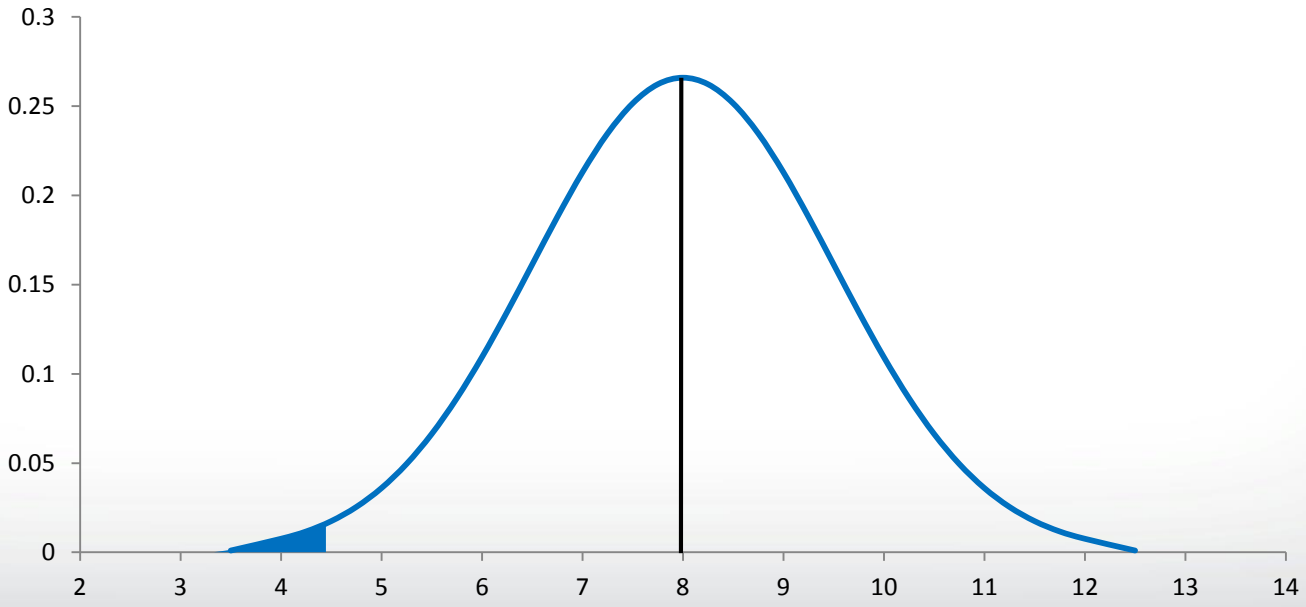
$$P\left(BMD_\gamma, t\right) = (0.10 * [1 - P(0,t)]) + P(0,t) = (0.1 * 0.99) + 0.01 = 0.109$$

- **Therefore, we are interested in the dose that results in 10.9% of subjects exhibiting an adverse response**

The Hybrid Approach – Selecting the Background Rate

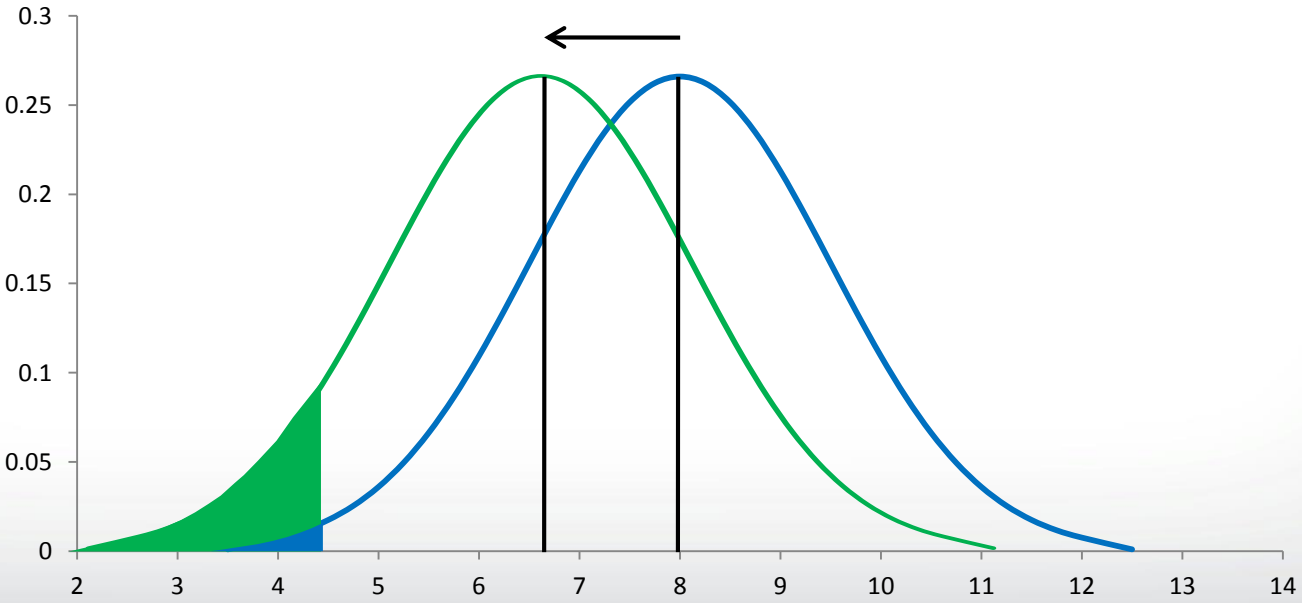
- **Next, the background rate of adverse response in the control group must be selected, in this example, we've chosen 1%**

- **AT EACH TESTING TIME POINT, the model calculates the cut-off values in the control group distribution that correspond to the background rate**



The Hybrid Approach – Selecting the Background Rate

- **Given a BMR of 10% extra risk AND a background rate of 1% for adverse responses in the control group the model will calculate the dose that corresponds to a shift in the mean that results in 10.9% of the animals falling beyond the control group cut-off values**



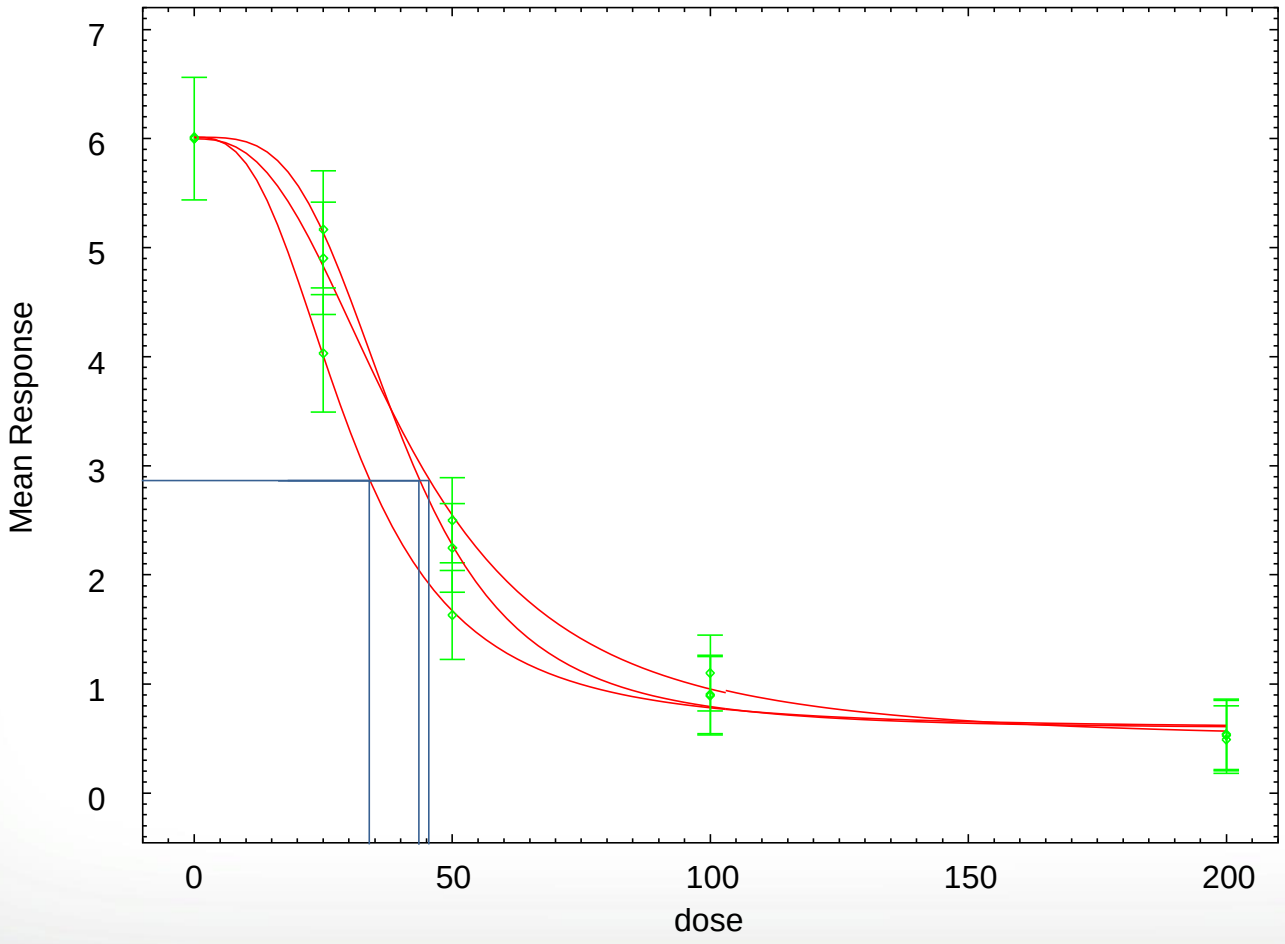
Toxicodiffusion Model – Calculating the BMD

- **In order to profile the BMD (i.e., $BMD_\gamma(t)$) with respect to time, a sequence of points $\{t\}$ is chosen and the corresponding $\{BMD_\gamma(t)\}$ values are calculated**

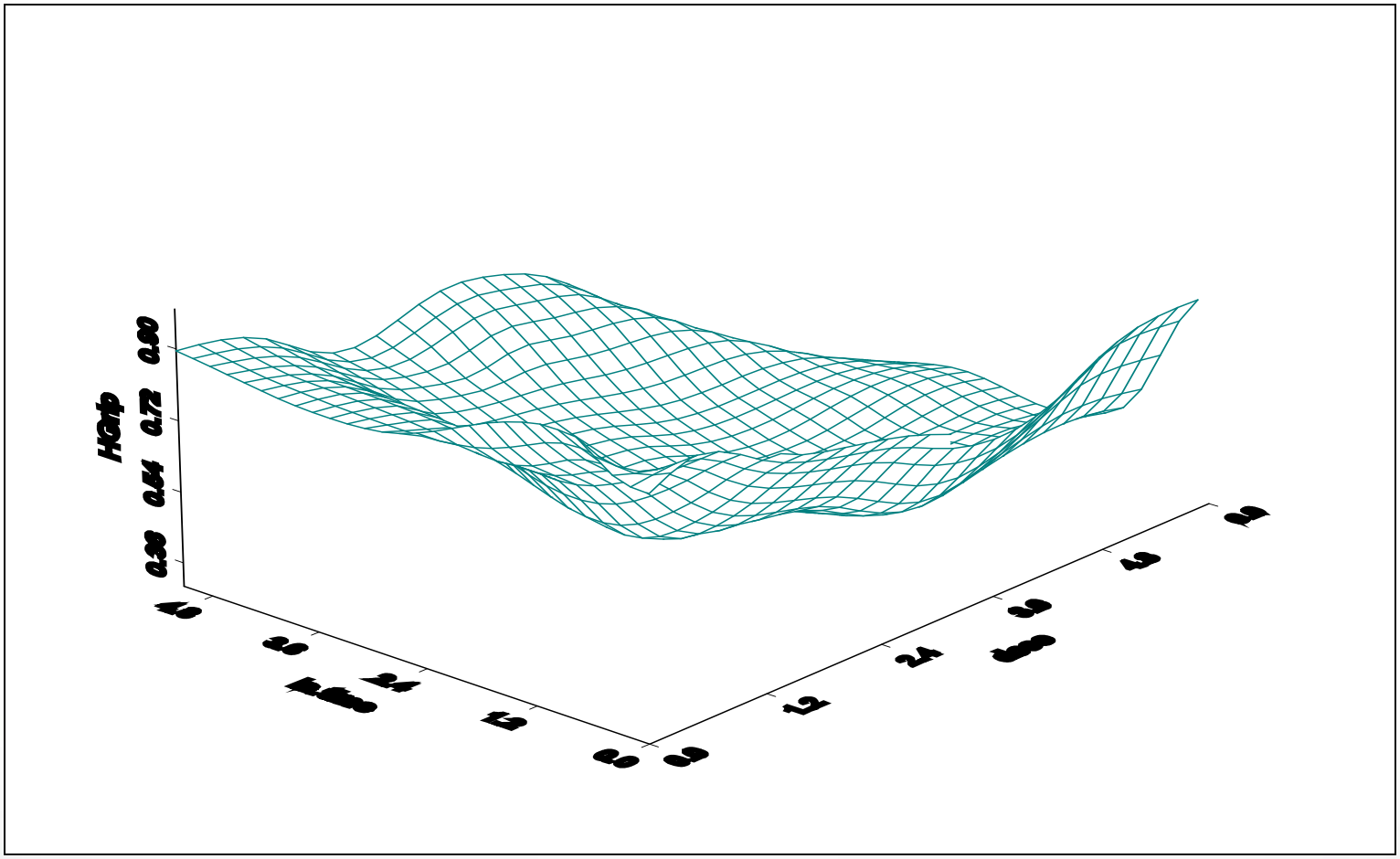
- **Given that response rates may vary over time, there may be multiple values of $\{BMD_\gamma(t)\}$ that yield responses equal to the BMR at multiple time points $\{t\}$**

- **Therefore, the reported BMD is the minimum of these multiple doses, i.e., $BMD_\gamma(t^*) = min_t \{BMD_\gamma(t)\}$**

Toxicodiffusion Model – Calculating the BMD



Toxicodiffusion Model – Calculating the BMD



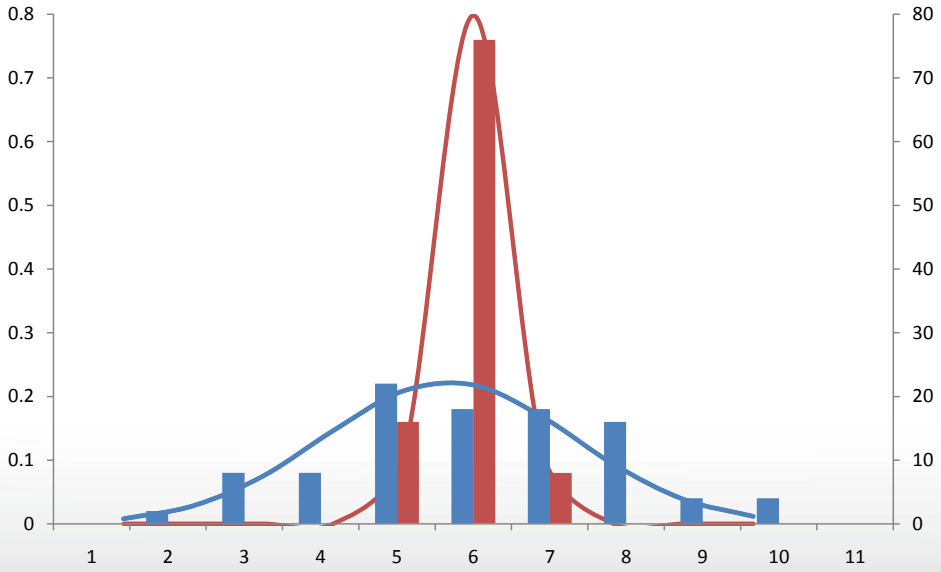
Toxicodiffusion Model – Calculating the BMDL

- **The toxicodiffusion model uses bootstrap resampling of residuals and random effect coefficients to calculate the BMDL**
  - The residuals and random effect coefficients were originally estimated during the original fitting of the model to the data
  - The model repeats the sampling procedure a user-specified number of times, with each re-sampled residual resulting in a new estimate of model parameters, and thus, a new BMD
- **This procedure produces a number of BMDs equal to the number of sampling repeats**
  - The percentiles across this sampling of bootstrapped BMDs can be used to calculate the BMDL
  - The 5th percentile of a sampled set of BMDs would be reported as the 95% lower bound on the BMD, i.e., the BMDL

Toxicodiffusion Model – Calculating the BMDL

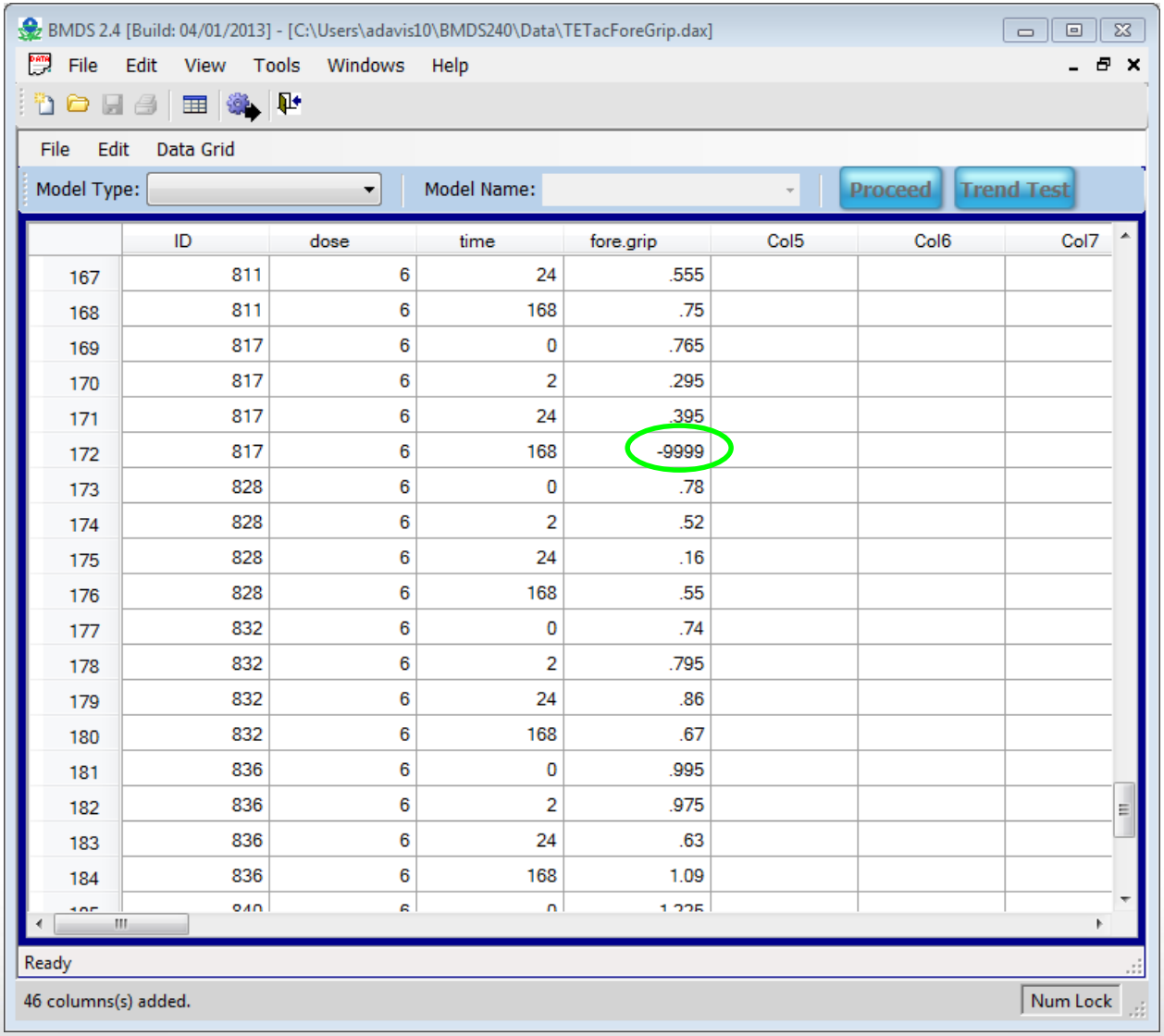
- **Because the BMDL calculation uses *random* re-sampling, the BMDLs calculated from repeated modeling runs will differ slightly for the same dataset.**

- **One way to control this difference is to increase the number of bootstrap iterations, this will decrease the range of calculated BMDLs**



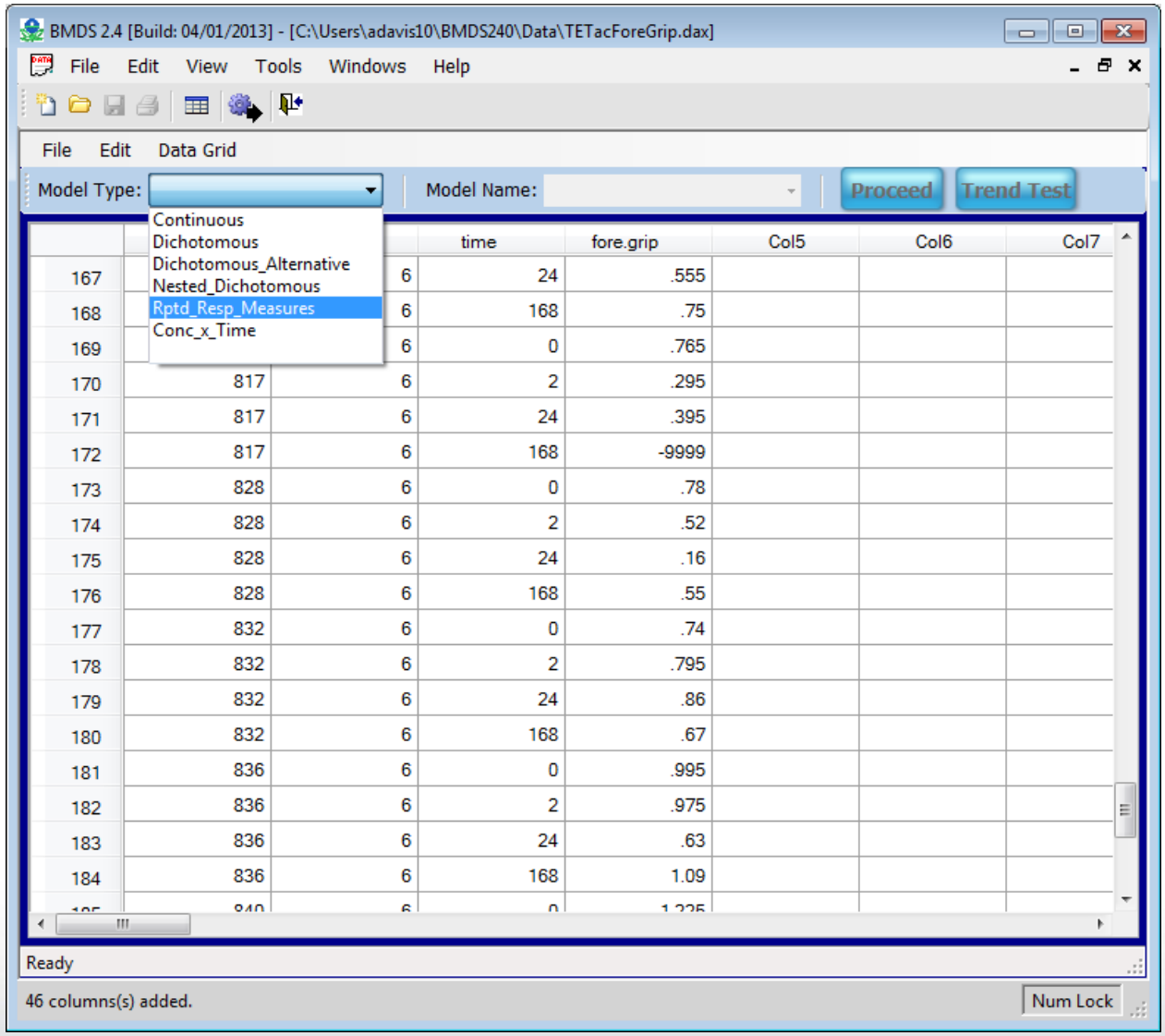
Running The Toxicodiffusion Model in BMDS

Datafile Structure

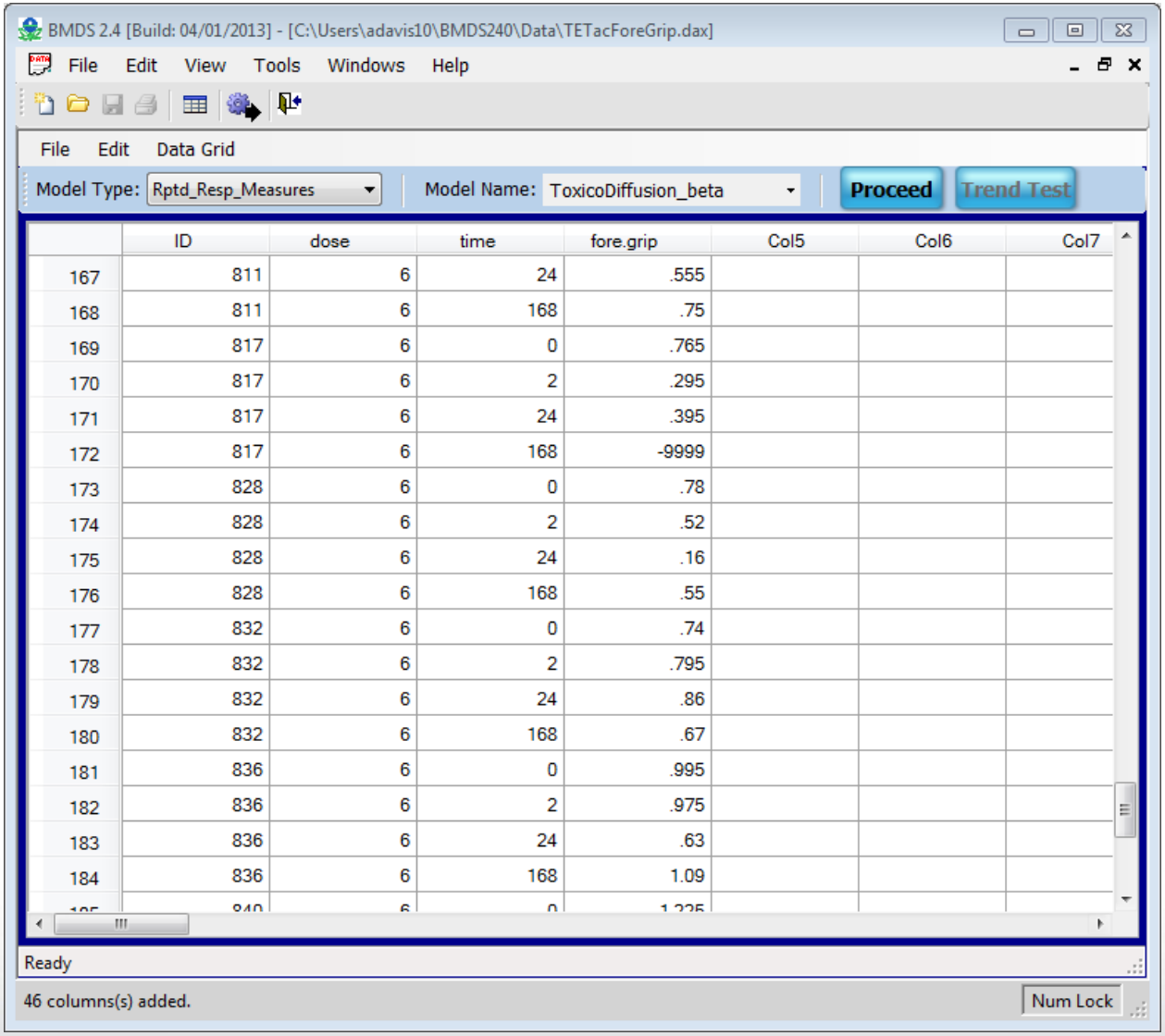


	ID	dose	time	fore.grip	Col5	Col6	Col7
167	811	6	24	.555			
168	811	6	168	.75			
169	817	6	0	.765			
170	817	6	2	.295			
171	817	6	24	.395			
172	817	6	168	-9999			
173	828	6	0	.78			
174	828	6	2	.52			
175	828	6	24	.16			
176	828	6	168	.55			
177	832	6	0	.74			
178	832	6	2	.795			
179	832	6	24	.86			
180	832	6	168	.67			
181	836	6	0	.995			
182	836	6	2	.975			
183	836	6	24	.63			
184	836	6	168	1.09			

Select Model Type



Toxicodiffusion Model Automatically Selected



	ID	dose	time	fore.grip	Col5	Col6	Col7
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172	817	6	168	-9999			
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175	828	6	24	.16			
176	828	6	168	.55			
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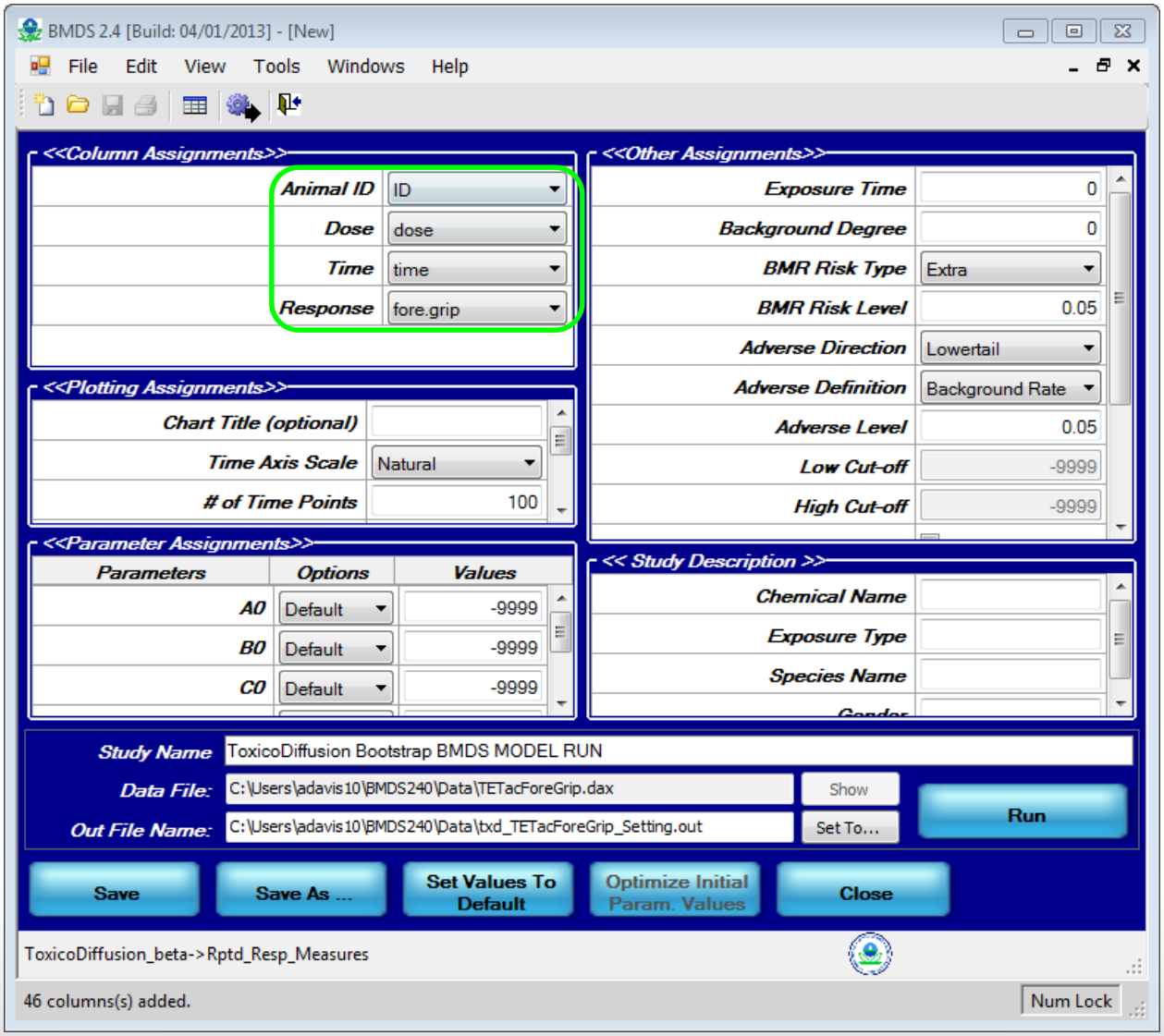
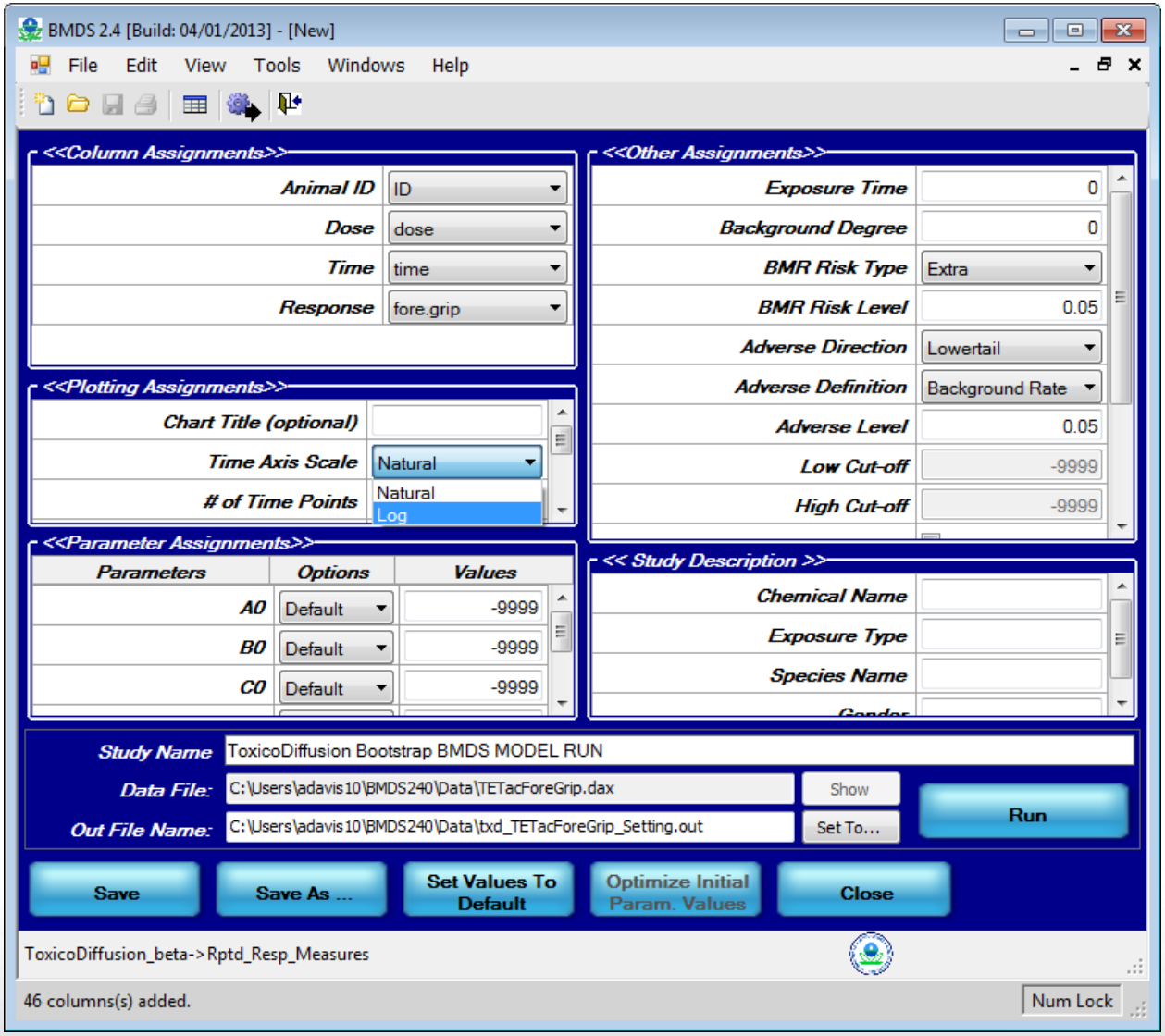
181	836	6	0	.995			
182	836	6	2	.975			
183	836	6	24	.63			
184	836	6	168	1.09			

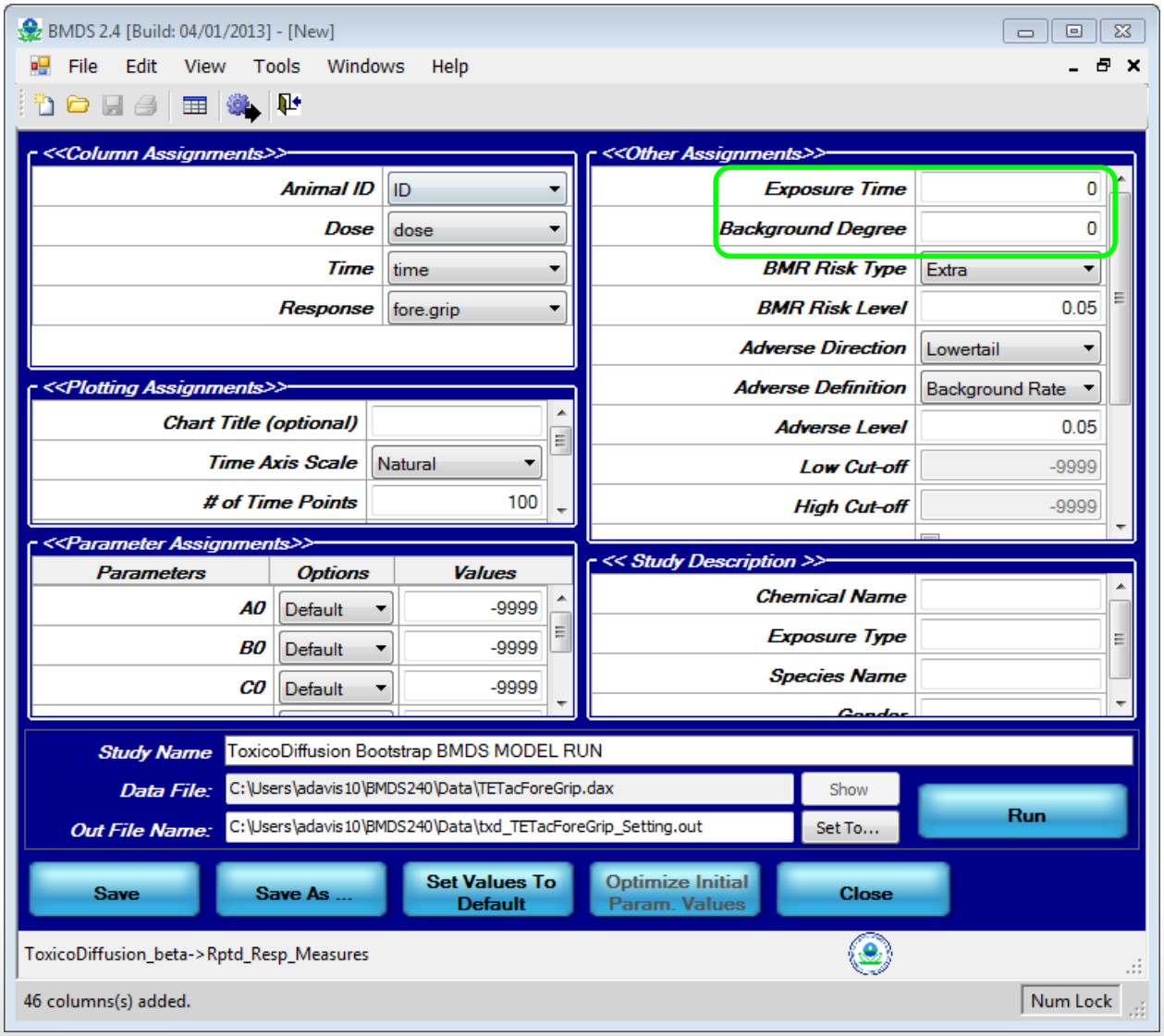
Toxicodiffusion Model – Column Assignments



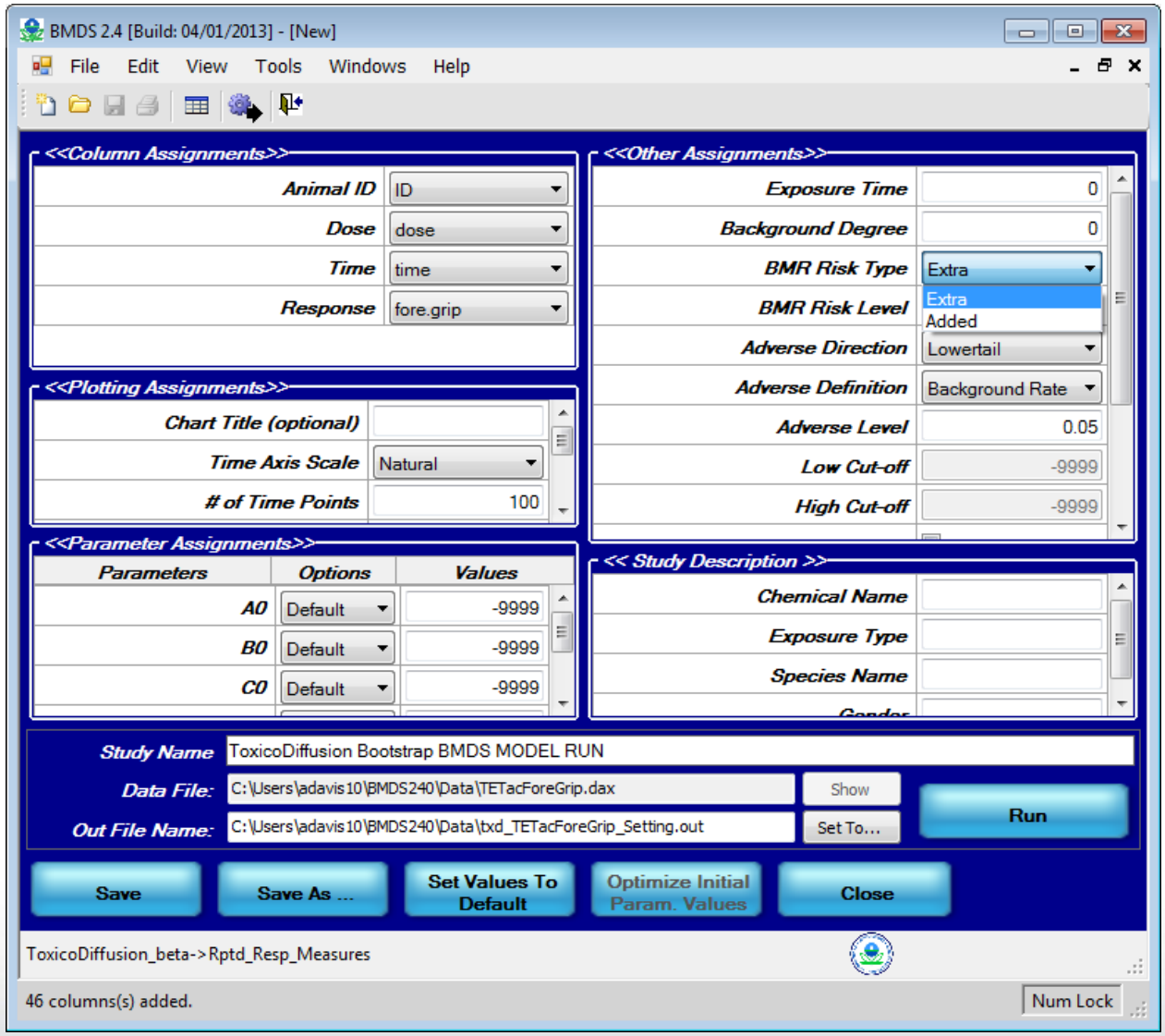
Toxicodiffusion Model – Plotting Assignments



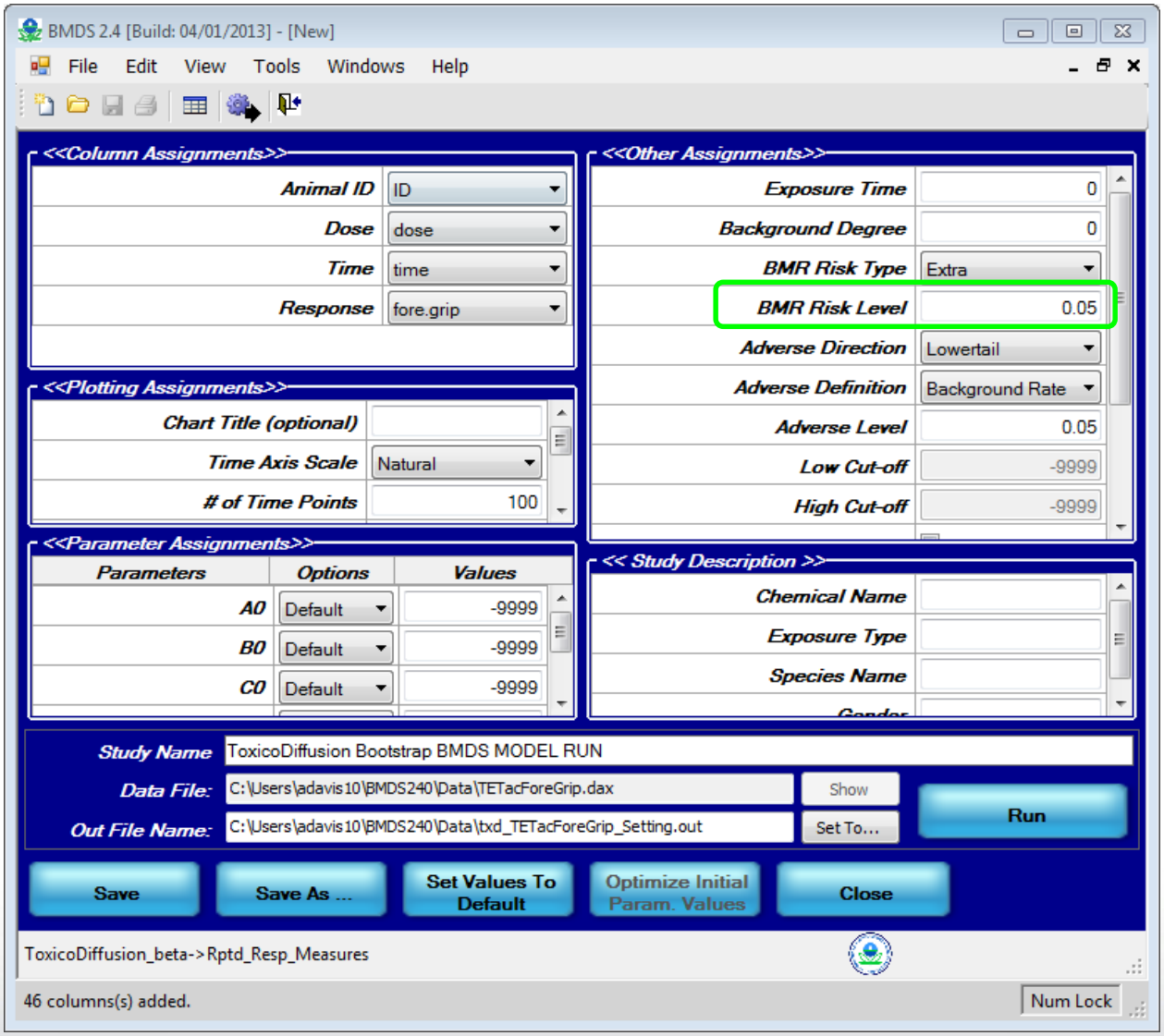
Toxicodiffusion Model – Other Assignments



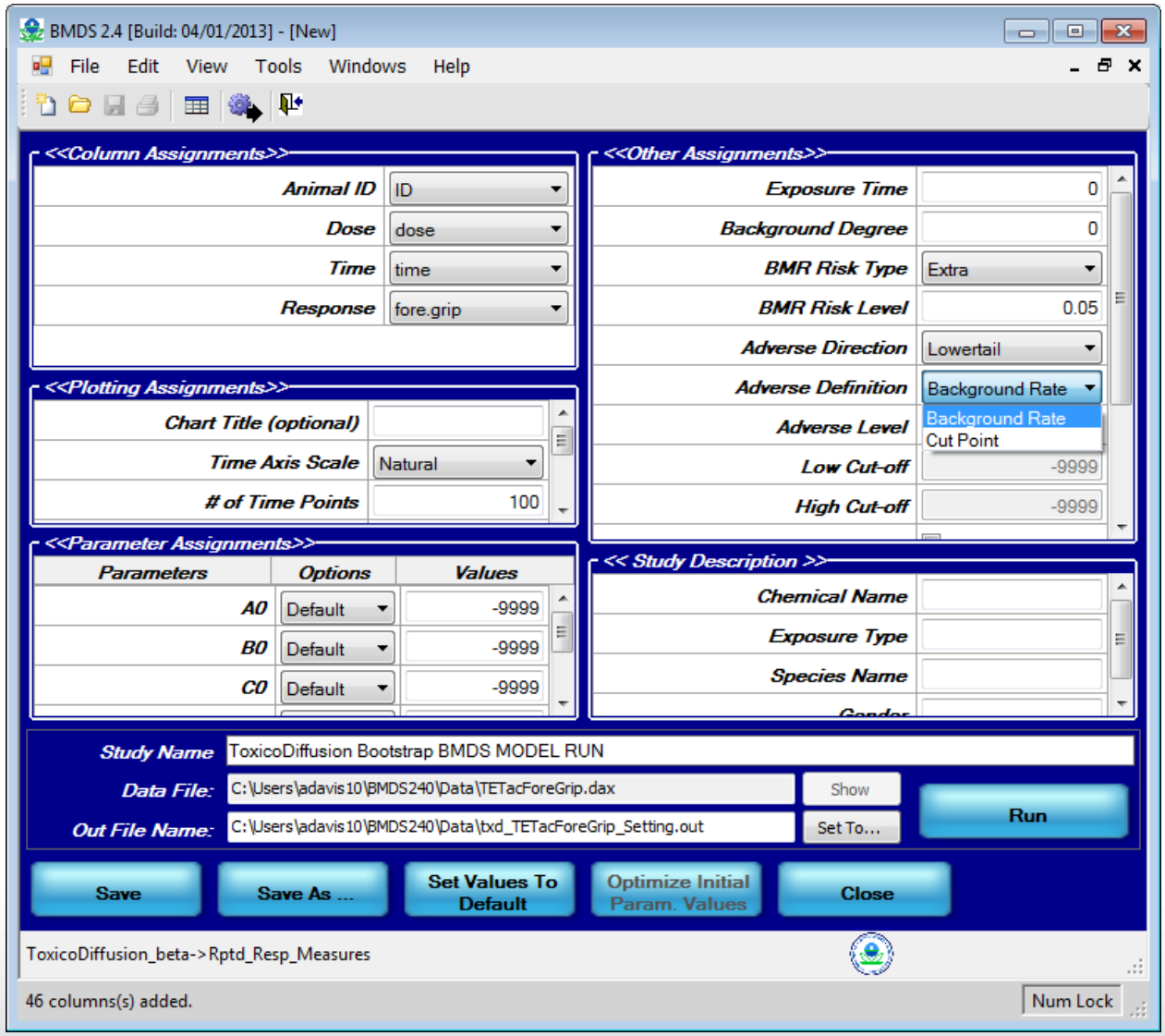
Toxicodiffusion Model – Other Assignments



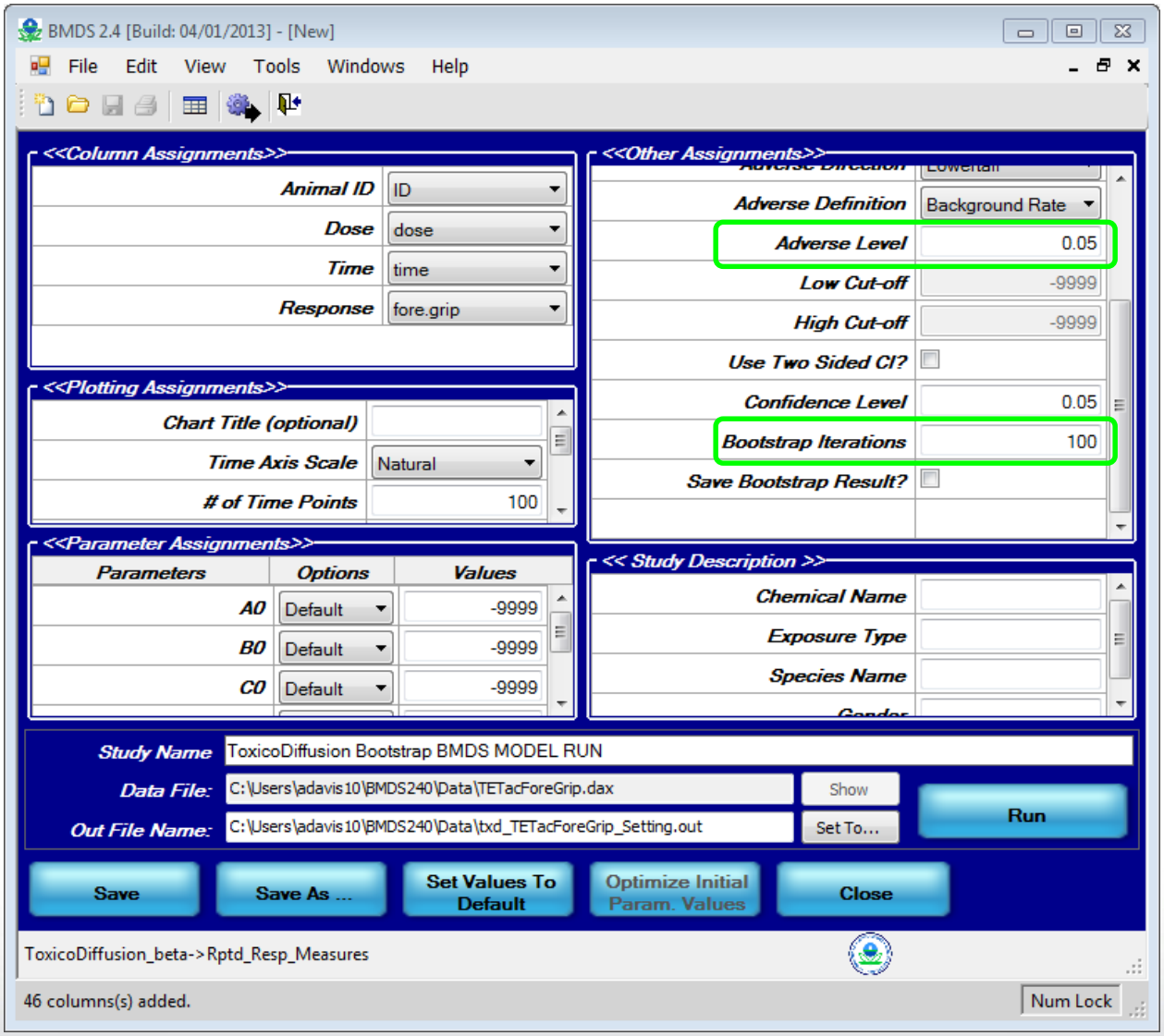
Toxicodiffusion Model – Other Assignments



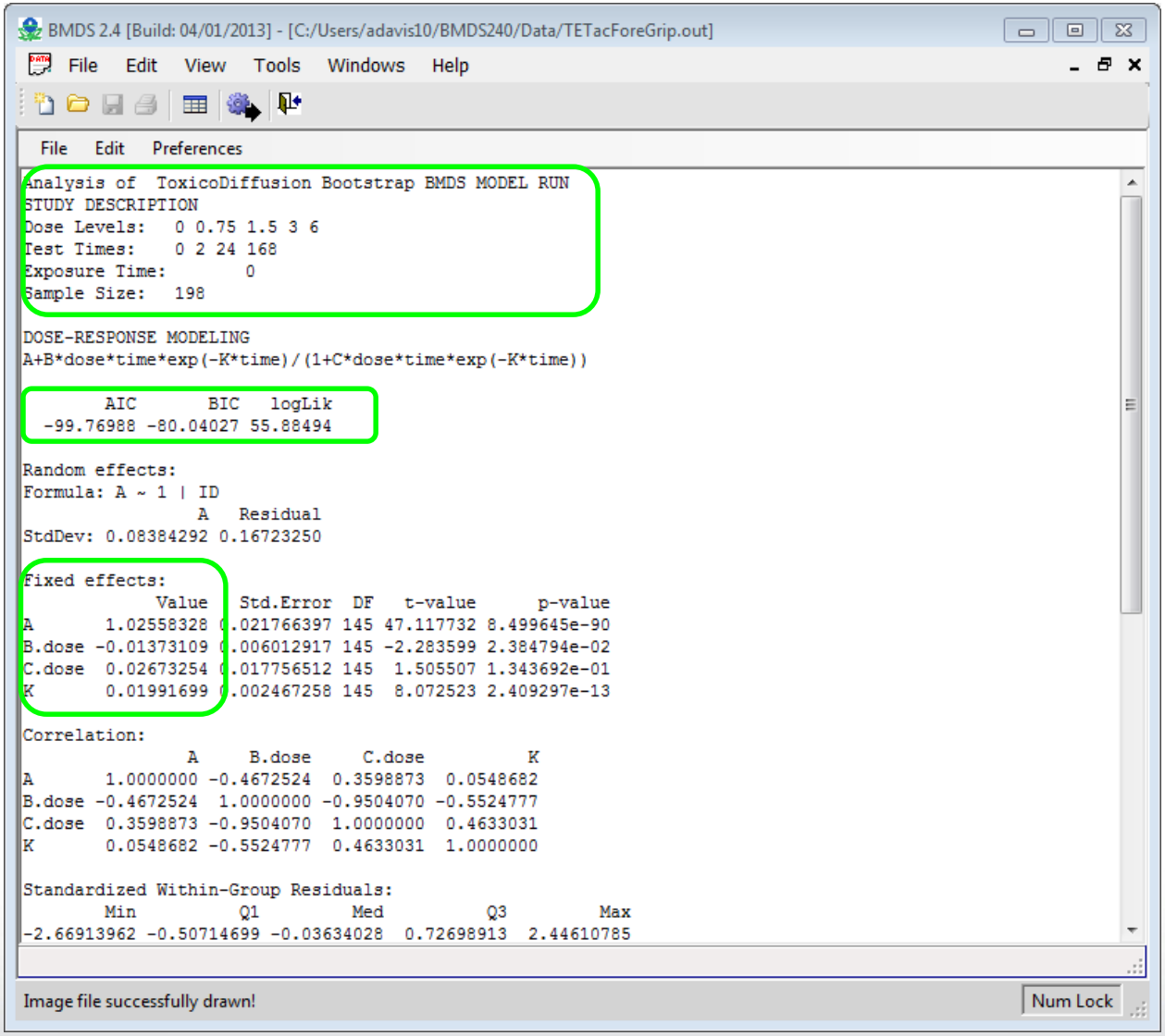
Toxicodiffusion Model – Other Assignments



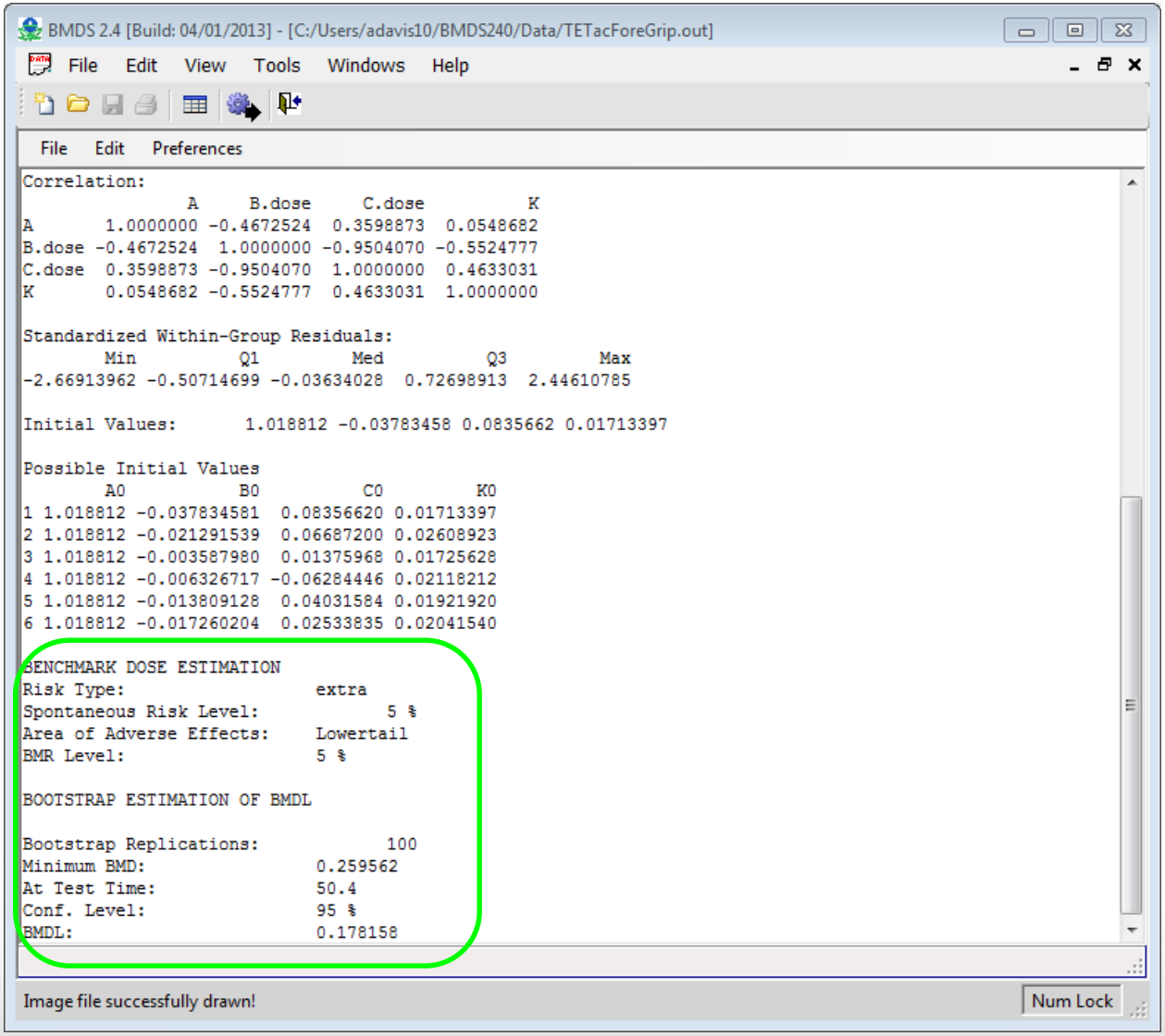
Toxicodiffusion Model – Other Assignments



Toxicodiffusion Model – Results

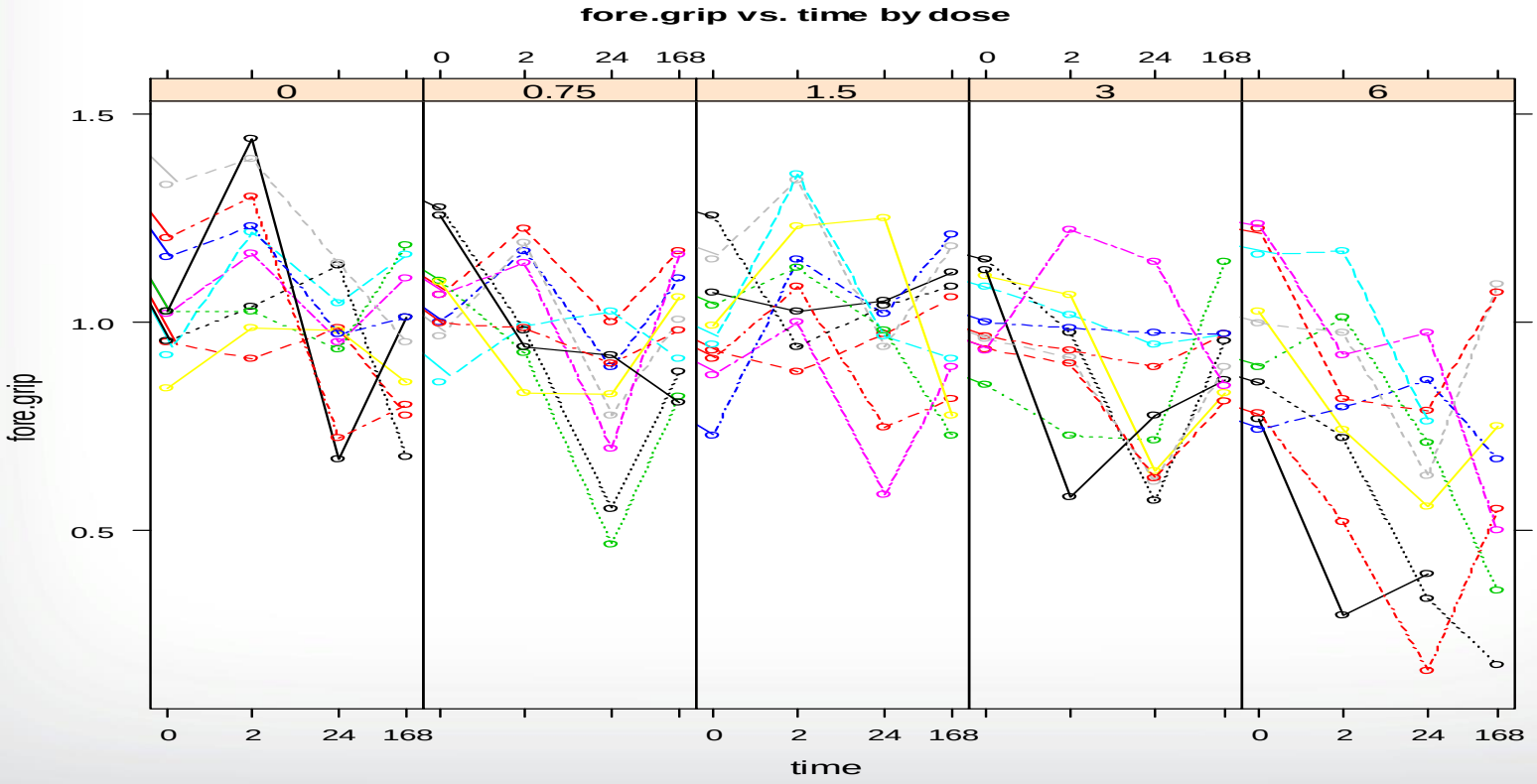


Toxicodiffusion Model – Results



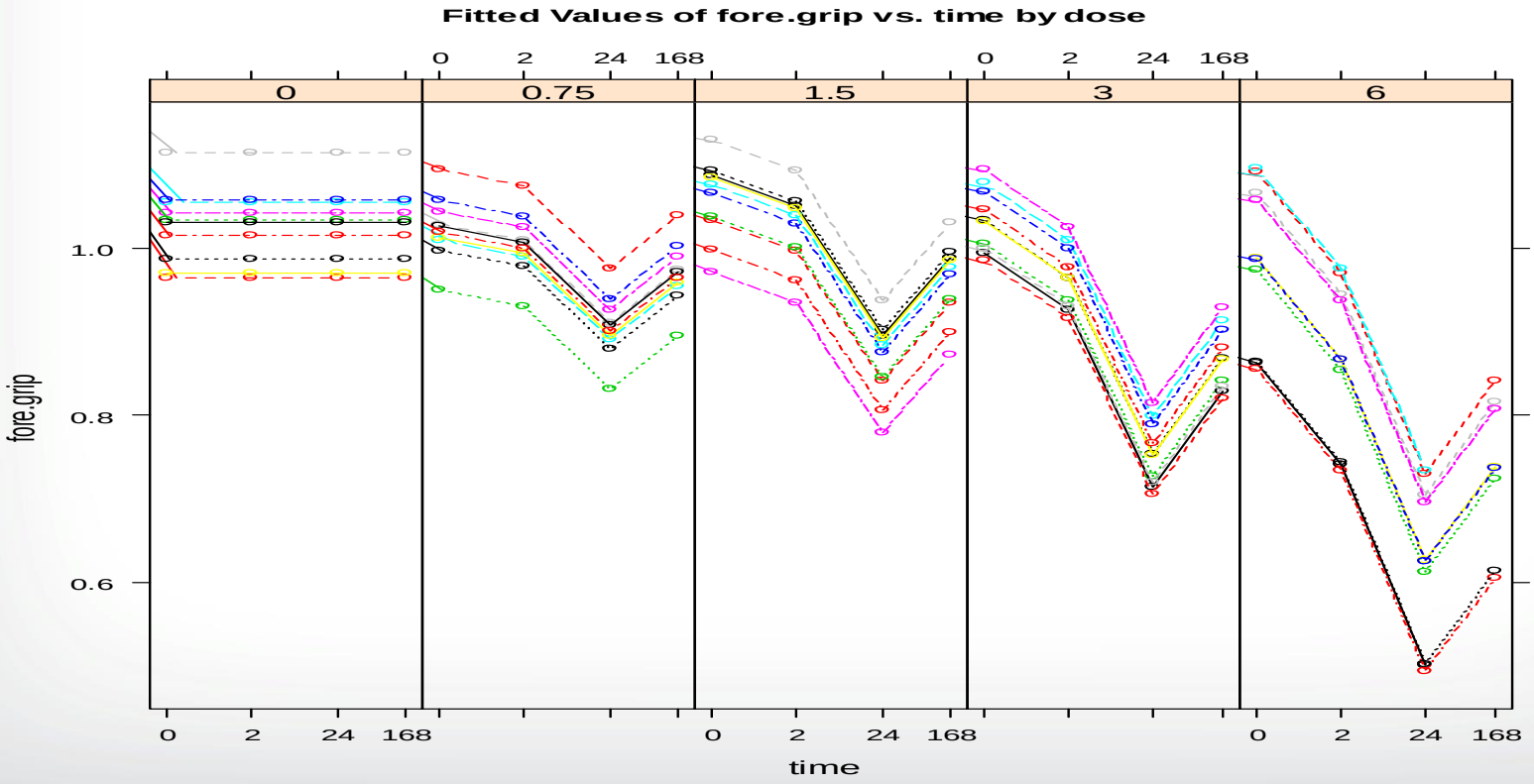
Toxicodiffusion Model – Plots and Assessing Fit

- **Observed trajectory – displays each subject's responses by connecting the observed responses across time**
  - Useful for determining the trajectory of the control group and how exposure changes the trajectory over time



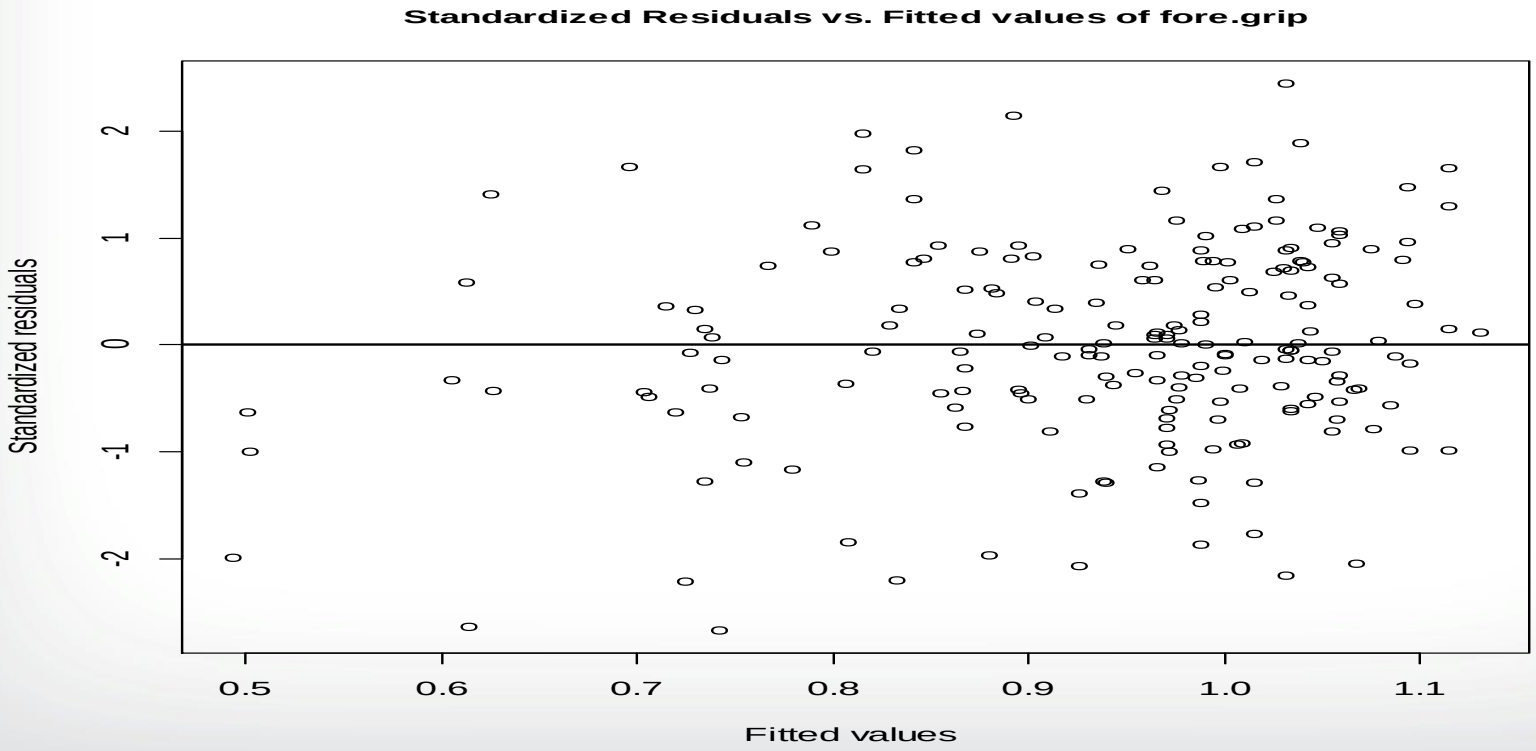
Toxicodiffusion Model – Plots and Assessing Fit

- **Fitted trajectory – displays each subject's fitted responses by connecting the observed responses across time**
  - Useful for determining whether the predicted responses show trajectories resembling the observed trends



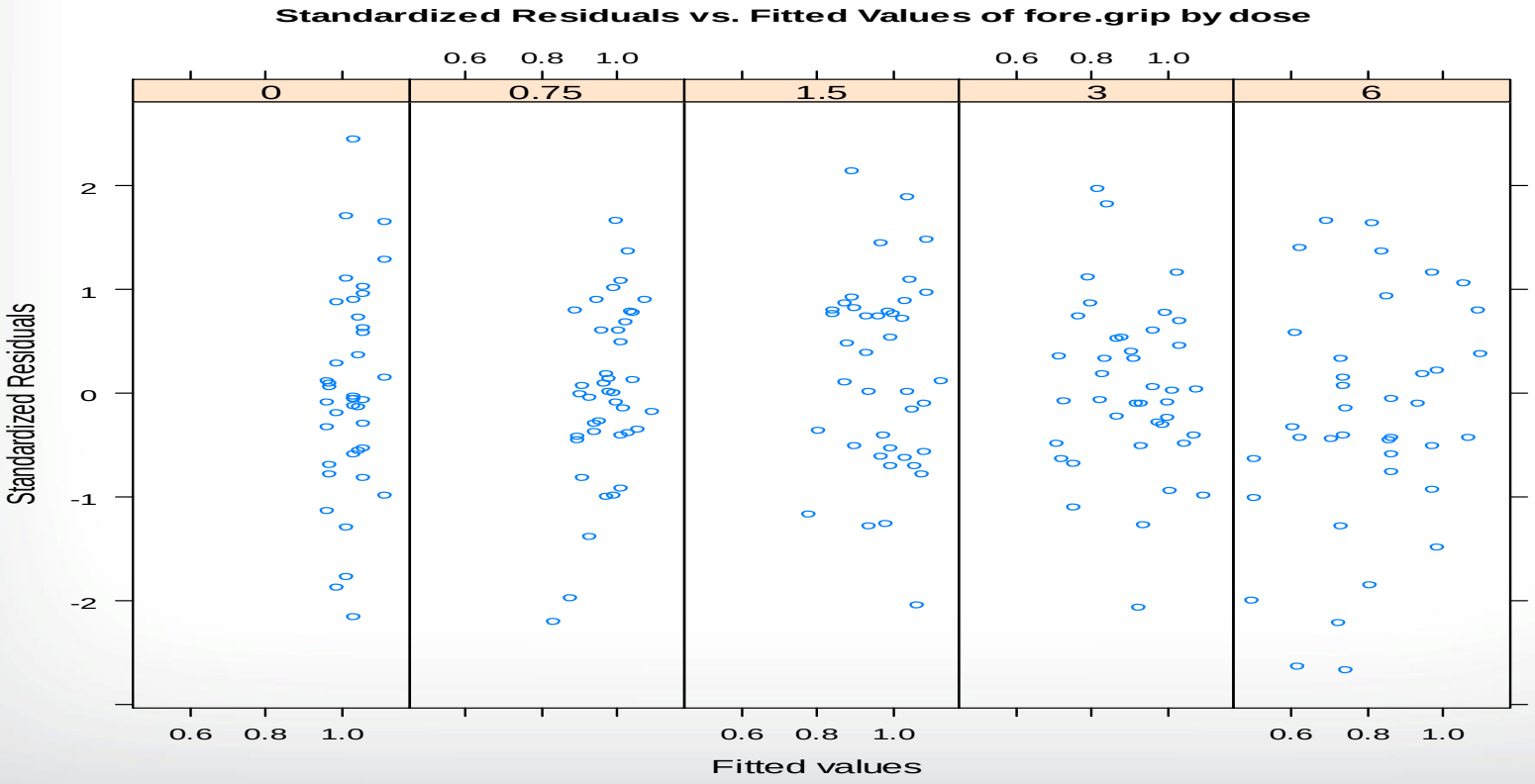
Toxicodiffusion Model – Plots and Assessing Fit

- **Pooled residuals across all dose groups**
  - Allows the user to check for randomness with respect to the level of response
  - The presence of any trend (decreasing, increasing, curved) indicates the inappropriateness of the model



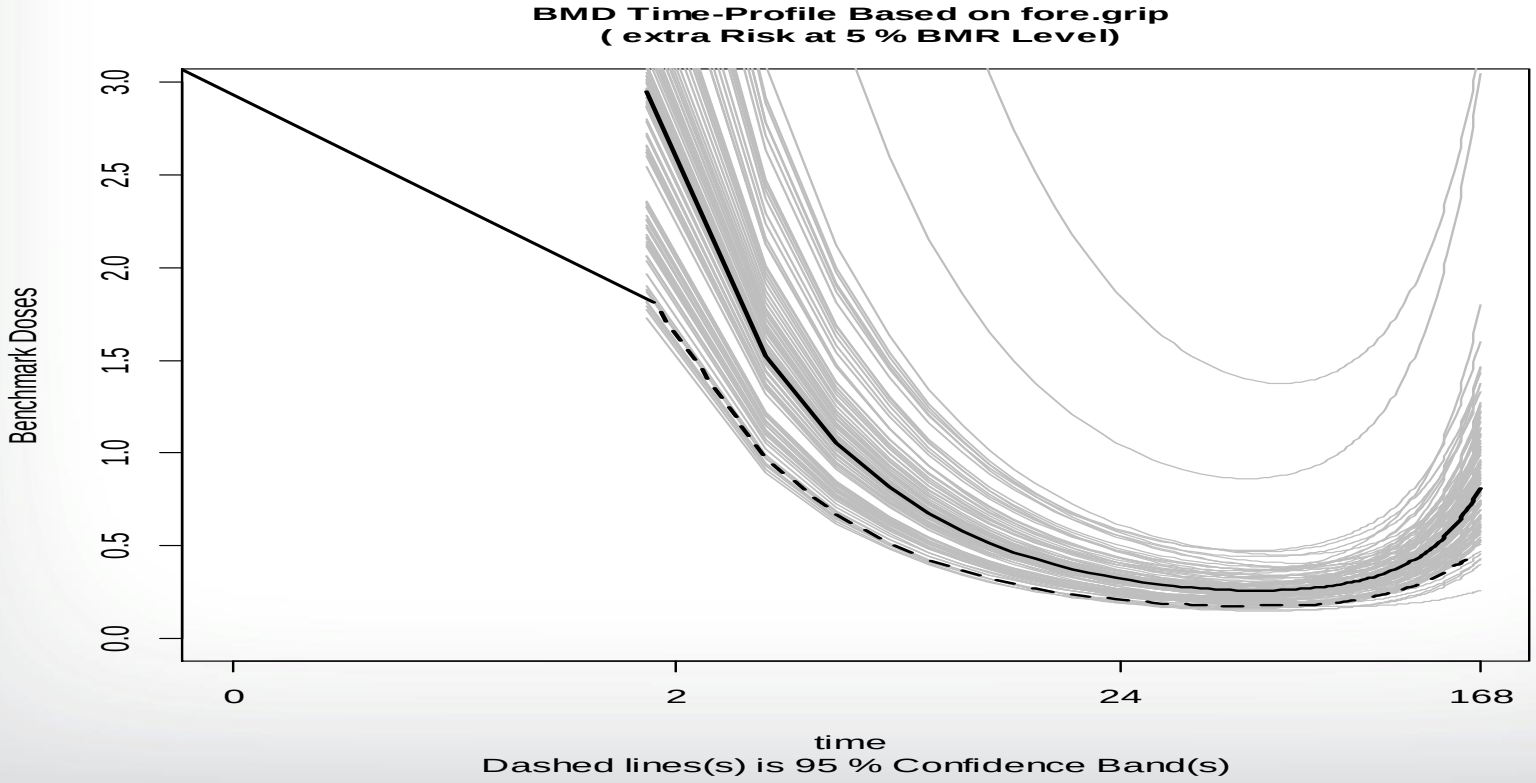
Toxicodiffusion Model – Plots and Assessing Fit

- **Pooled residuals within dose groups**
  - Allows the user to check for randomness with respect to the level of response
  - The presence of any trend (decreasing, increasing, curved) indicates the inappropriateness of the model



Toxicodiffusion Model – Plots and Assessing Fit

- **Bootstrap graph – shows the time-profile of the resampled BMDs**
  - Dark black line – original fit to the data
  - Light grey lines – resampled BMDs
  - Dark dashed black line – chosen percentile of the resampled BMDs (i.e., BMDL)

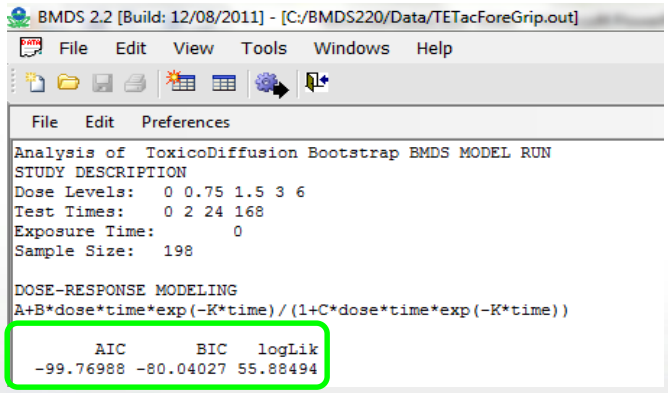


Toxicodiffusion Model – Assessing Fit Across Models

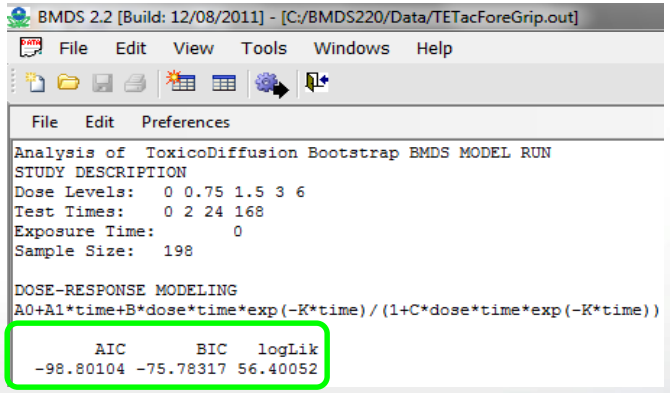
- **In this example, the observed trajectory in the control group appears to decrease over time.**
  - Therefore, a constant background rate (i.e., $A(t) = A_0$) may not be suitable, and the linear background rate (i.e., $A(t) = A_0 + A_1 t$) may be more appropriate

- **The AIC and BIC values to assess whether the addition of an extra parameter improves model fit.**

$A(t) = A_0$



$A(t) = A_0 + A_1 t$



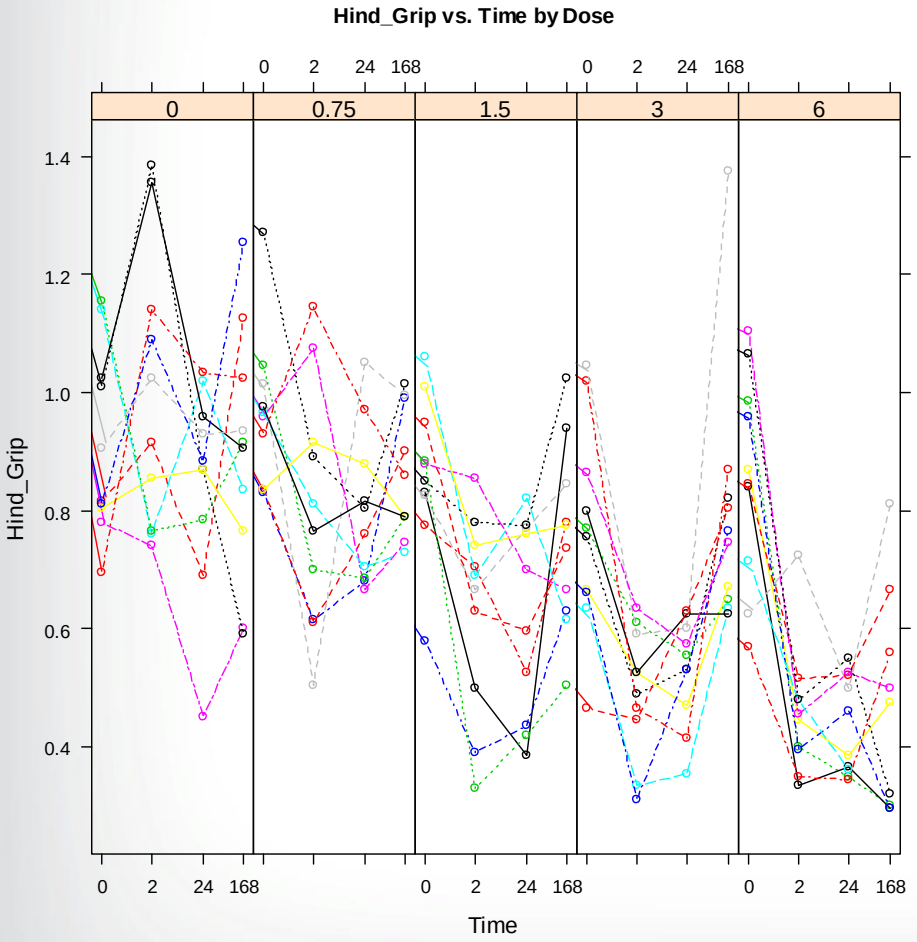
Toxicodiffusion Modeling Exercise

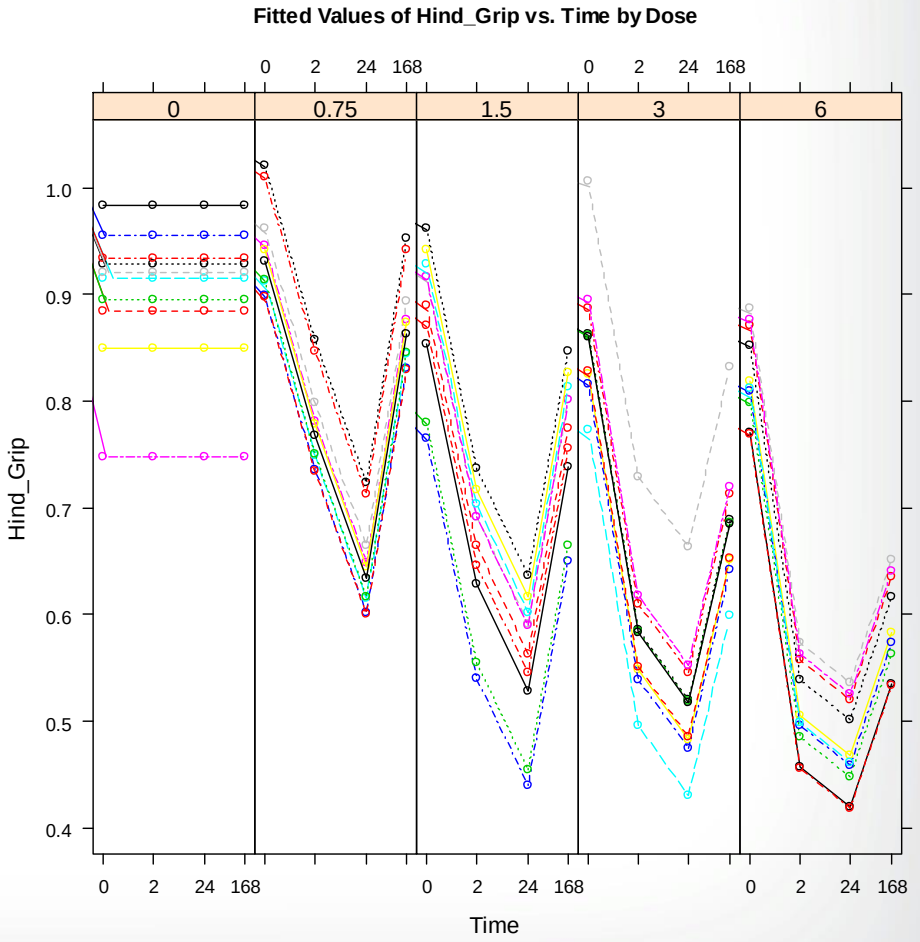
Toxicodiffusion Modeling Exercise

- **Open hind_grip_A0.dax**
  - Model Type: Rptd_Resp_Measures
  - Model Name: Toxicodiffusion_beta

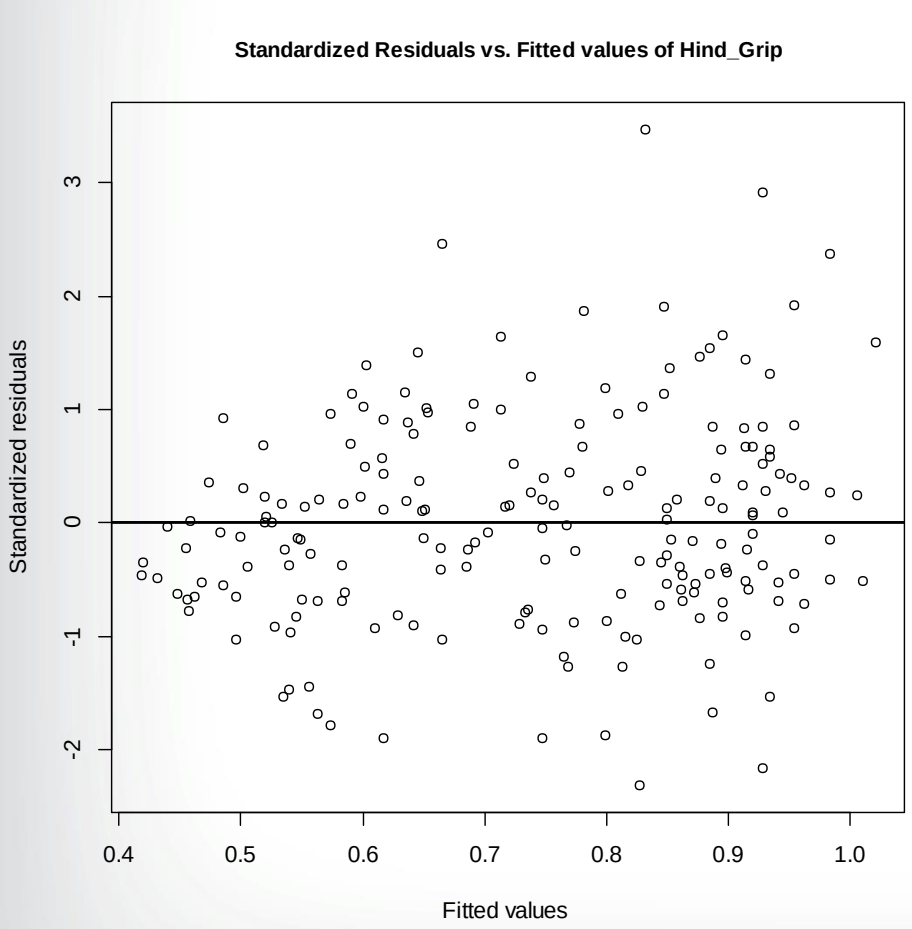
- **Parameterize the option files as follows and run model:**
  - Fill in Column Assignments as appropriate
  - Time Scale Axis = Log
  - Exposure time = 0
  - Background degree = 0
  - BMR = 5% Extra risk
  - Adverse Direction = Lowertail
  - Adverse Definition = Background Rate
  - Adverse Level = 5%
  - Bootstrap Iterations = 1000

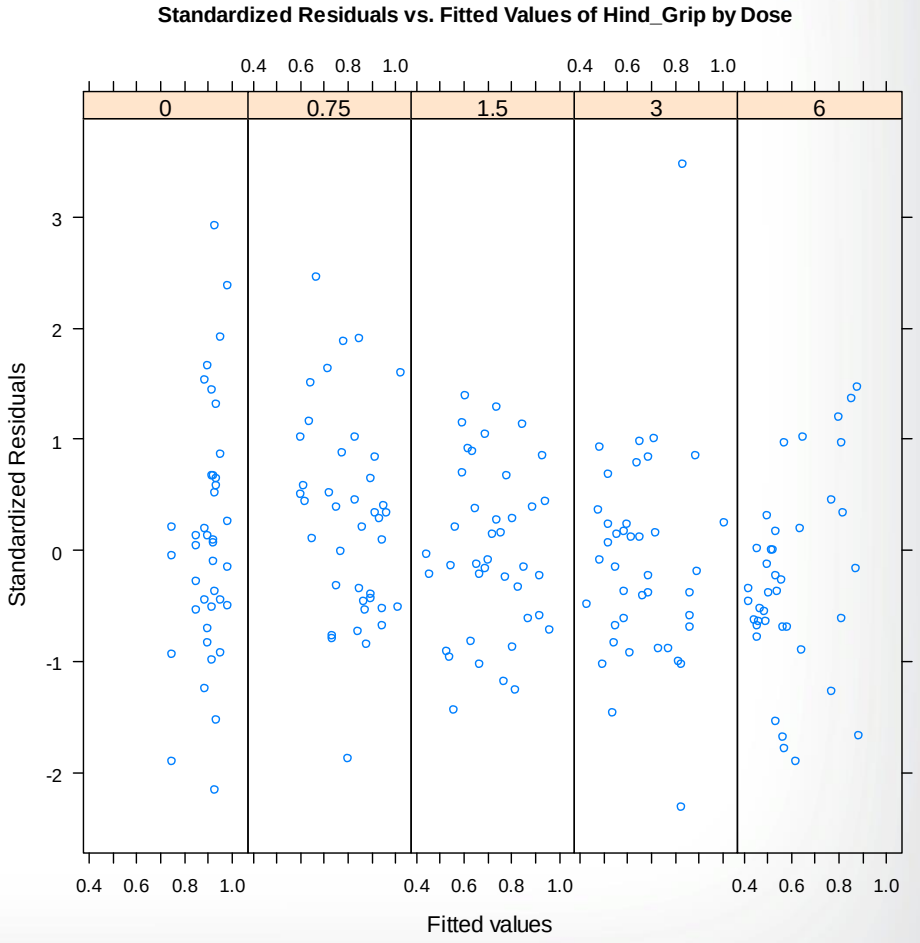
Toxicodiffusion Modeling Exercise – Results



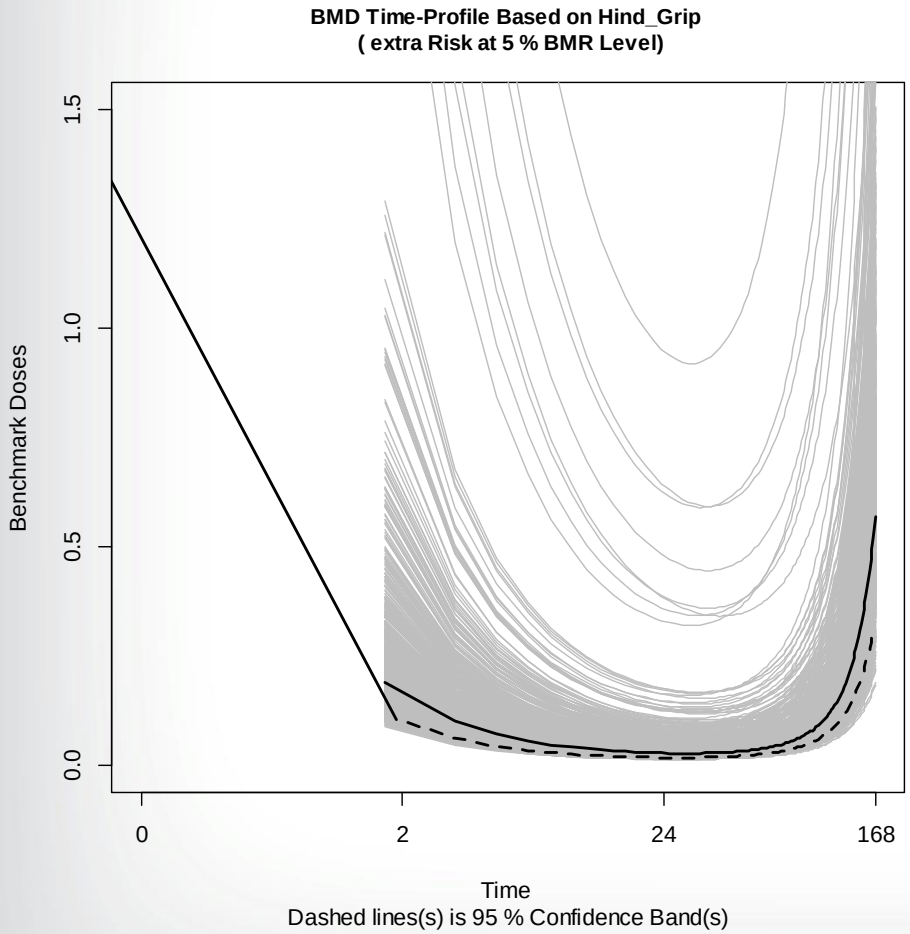


Toxicodiffusion Modeling Exercise – Results





Toxicodiffusion Modeling Exercise – Results



BMDS Summary Table

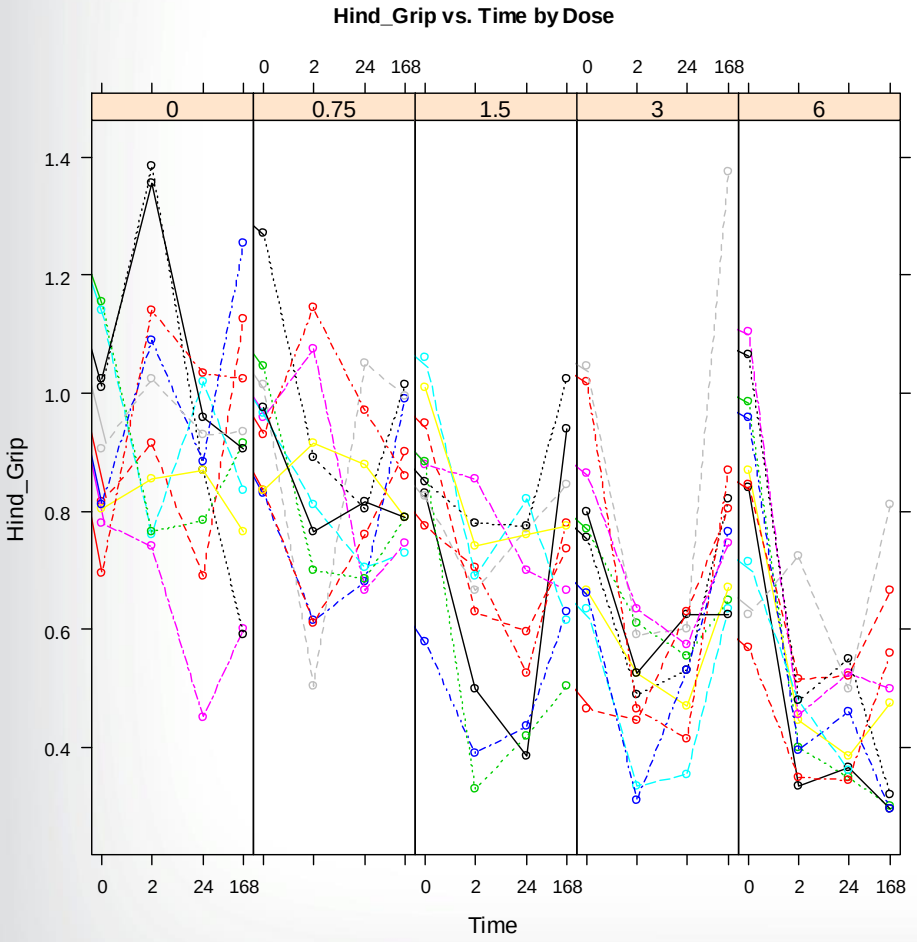
	Toxicodiffusion (A=0)	Toxicodiffusion (A=1)
AIC	-120.495	
BIC	-100.7351	
C.dose	0.5935487	
K	0.0343045	
BMD	0.028027	
Test-time	28.56	
BMDL	0.018353	

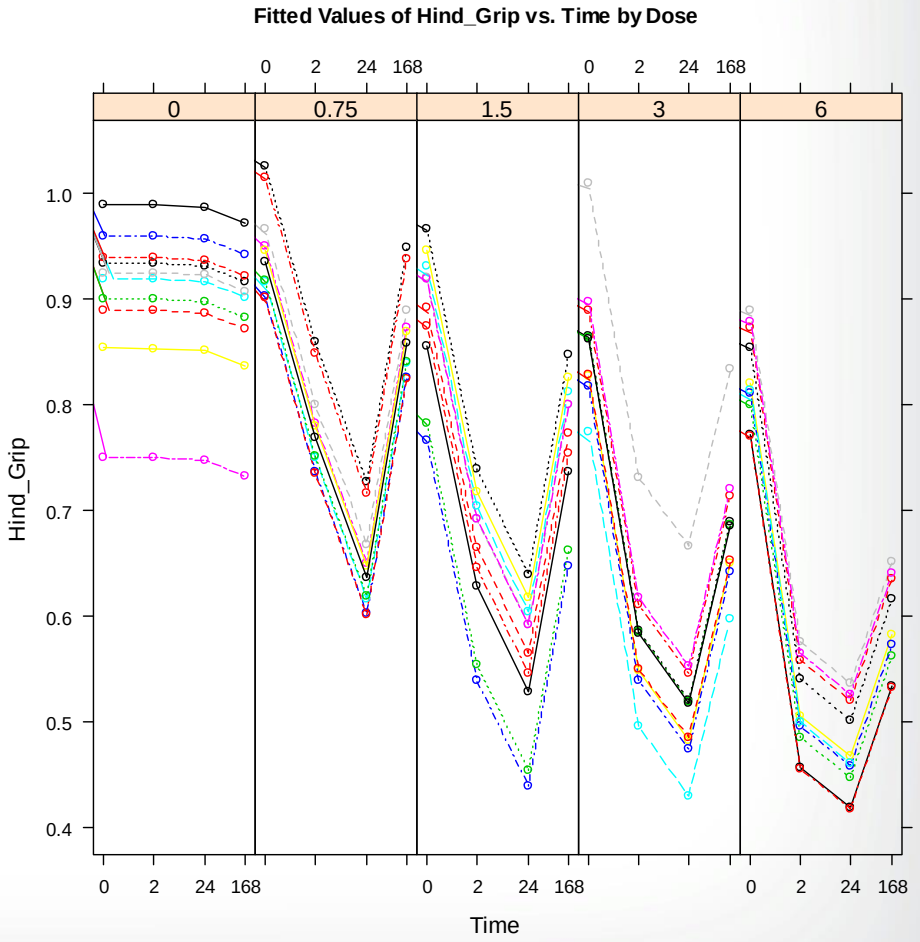
Toxicodiffusion Modeling Exercise – Results

- **Open hind_grip_A1.dax**
  - Model Type: Rptd_Resp_Measures
  - Model Name: Toxicodiffusion_beta

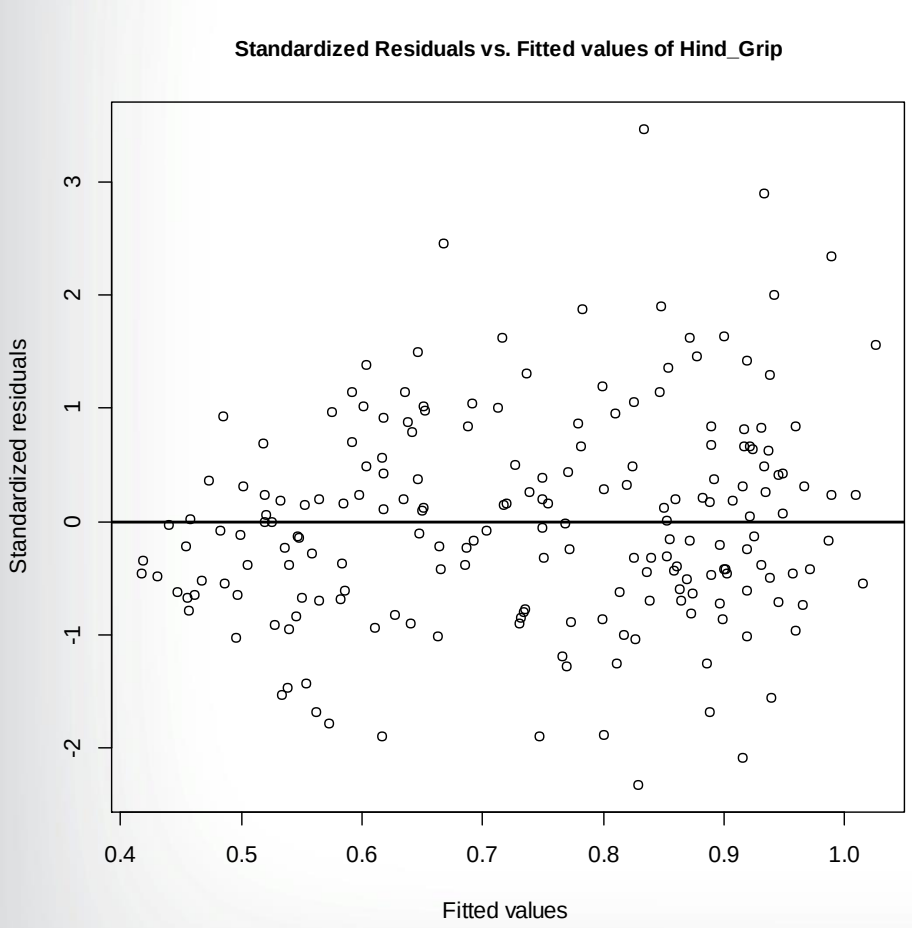
- **Parameterize the option files as follows and run model:**
  - Fill in Column Assignments as appropriate
  - Time Scale Axis = Log
  - Exposure time = 0
  - Background degree = **1 (must change from default)**
  - BMR = 5% Extra risk
  - Adverse Direction = Lowertail
  - Adverse Definition = Background Rate
  - Adverse Level = 5%
  - Bootstrap Iterations = 1000

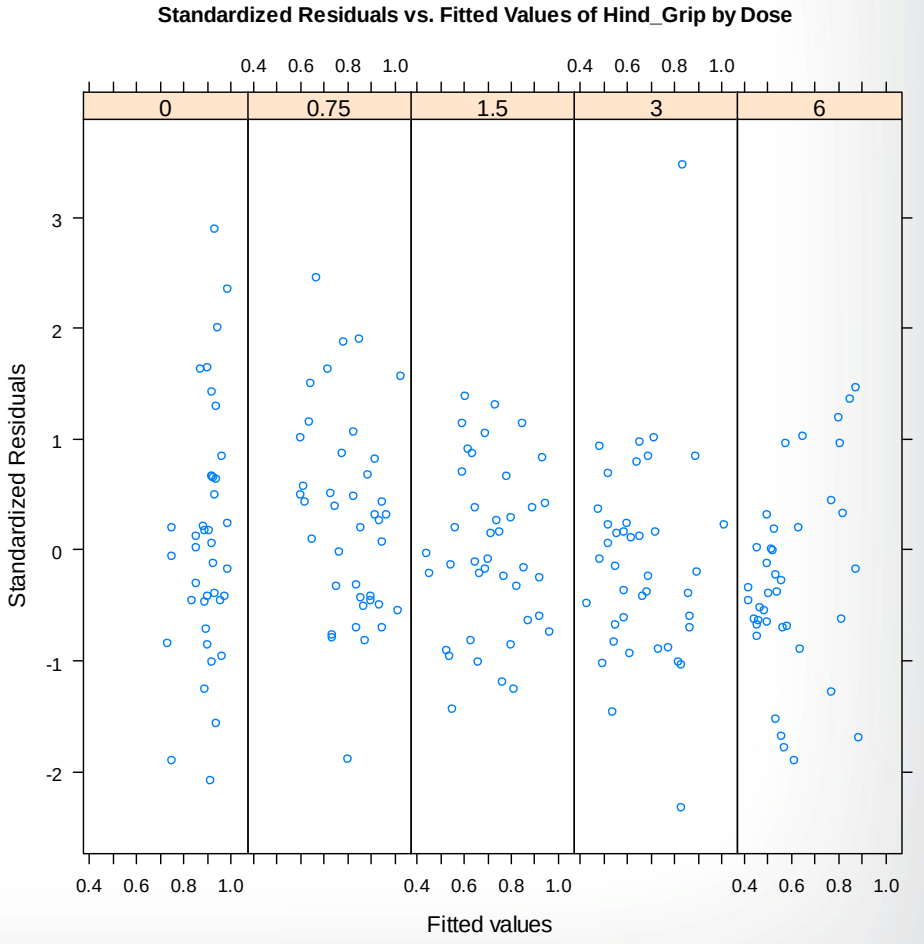
Toxicodiffusion Modeling Exercise – Results



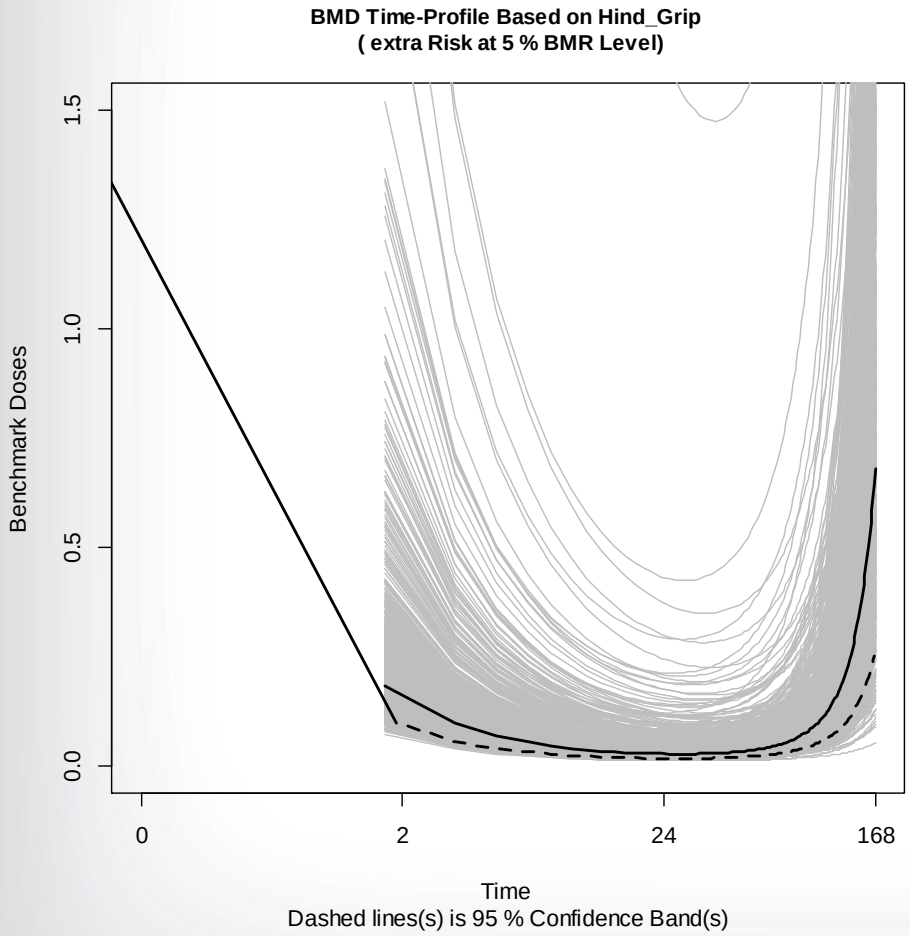


Toxicodiffusion Modeling Exercise – Results





Toxicodiffusion Modeling Exercise – Results



BMDS Summary Table

	Toxicodiffusion (A=0)	Toxicodiffusion (A=1)
AIC	-120.495	-118.6422
BIC	-100.7351	-95.58902
C.dose	0.5935487	0.6153080
K	0.0343045	0.0355523
BMD	0.028027	0.028045
Test-time	28.56	28.56
BMDL	0.018353	0.017513

Concentration × Time (C × T) Data – The ten Berge Model

Concentration × Time (C × T) Modeling – Haber's Law

- **C × T modeling has primarily been done in the context of acute inhalation exposures**

- **In these instances, both exposure concentration and duration of exposure are important for estimating responses**

- **Haber's Law**
  - $C \times t = k$
  - Originally formulated in the early 1900s by Fritz Haber in the context of researching the effects of exposure to chemical warfare agents
  - Assumes equivalency any two combinations of exposure concentration and duration that have equal products ($C_1t_1 = C_2t_2$)

Concentration × Time (C × T) Modeling – Haber's Law

- **Haber himself recognized that the simplified form of his equation was an approximation and only useful under certain conditions**
  - Haber's law does not take into account rates of detoxification, fractional absorption, differences in physiological parameters (e.g., ventilation rate, body weight) of exposed subjects
  - In certain cases, (e.g., when duration of exposure approaches the half-life of the chemical in the body) more sophisticated mathematical models are necessary
  - However, due to its simplicity, Haber's Law extensively used toxicological dose-response research

- **However, multiple, alternative approaches have been recommended to more accurately describe the relationship between concentration, duration, and response**

Concentration × Time (C × T) Modeling – ten Berge Equation

- **ten Berge et al. (1986) investigated the ability of Haber's Law to describe mortality due to acute inhalation exposures**
  - Haber's Law was expressed as $Y = b_0 + b_1 \ln(c) + b_2 \ln(t)$
  - Assuming Haber's Law adequately describes the mortality response, the values of b_1 and b_2 should be roughly equivalent

Concentration × Time (C × T) Modeling – ten Berge Equation

TABLE 1

Regression coefficients of the concentration—time mortality response relationships of several irritant chemicals for different species according to eqn. (1)

Chemical	Species, sex	Regression coefficients		
		b_0	b_1	b_2
Ammonia [2]	male + female rats	−47.9	4.65	2.30
Ammonia [2]	male rats	−76.2	7.17	3.71
Ammonia [2]	female rats	−62.6	5.91	2.76
Ammonia [3, 4]	mouse	−54.5	5.95	2.89
HCl gas [5]	rat	−47.7	4.06	4.90
HCl aerosol [5]	rat	−29.1	2.77	2.68
HCl gas [5]	mouse	−10.5	1.40	1.16
HCl aerosol [5]	mouse	−22.8	2.51	2.21
Chlorine pentafluoride [6]	rat	−29.3	3.92	2.10
Chlorine pentafluoride [6]	mouse	−15.5	2.42	1.57
Chlorine pentafluoride [6]	dog	−20.8	2.79	1.95
Chlorine pentafluoride [6]	monkey	−17.6	2.87	0.696
Nitrogen dioxide [7]	rat	−15.2	3.09	0.885
Nitrogen dioxide [7]	guinea pig	−10.5	2.63	0.537
Nitrogen dioxide [7]	rabbit	−5.43	1.52	0.352
Nitrogen dioxide [7]	dog	−38.7	6.48	1.97
Nitrogen dioxide [7]	mouse	−35.6	6.43	1.76
Chlorine [8]	mouse	−23.2	3.82	1.10
Perfluoroisobutylene [9]	rat	−14.9	2.87	2.36
Crotonaldehyde [10]	rat	−15.6	2.00	1.72
Hydrogen fluoride [11]	rabbits + guinea pigs	−7.35	1.38	0.71
Ethylene imine [12]	rat	−3.85	0.959	0.714
Ethylene imine [12]	guinea pig	−19.5	2.25	2.58
Bromine [8]	mouse	−24.7	3.13	1.44
Dibutylhexamethylenediamine [13]	rat	−11.7	1.33	1.29

TABLE 2

Regression coefficients of the concentration—time mortality response relationship of several systemically acting chemicals for different species according to eqn. (1)

Chemical	Species, sex	Regression coefficients		
		b_0	b_1	b_2
Hydrogen cyanide [14]	goat	−27.3	4.50	2.02
Hydrogen cyanide [14]	monkey	−6.87	1.57	0.835
Hydrogen cyanide [14]	rabbit	−15.6	3.22	0.744
Hydrogen cyanide [14]	rat	−3.27	1.15	0.701
Hydrogen cyanide [14]	cat	−8.26	2.09	0.741
Hydrogen cyanide [14]	dog	−1.30	1.02	0.327
Hydrogen sulphide [15]	cat + rabbit	−42.6	5.13	2.36
Methyl t-butyl ether [16]	mouse	−25.1	3.98	2.02
Methylenechlorobromide [17]	male rats	−45.0	3.56	2.26
Methylenechlorobromide [17]	female rats	−49.1	3.86	2.34
Ethylenedibromide [18]	rat	−32.5	3.12	2.69
Tetrachloroethylene [19]	rat	−39.1	3.34	1.65
Trichloroethylene [20]	rat	−8.36	0.768	0.909
Carbon tetrachloride [21]	rat	−39.4	3.46	1.22
Acrylonitrile [22]	rat	−42.1	3.83	3.74
Acrylonitrile [23]	rat	−165	15.2	11.4

Concentration × Time (C × T) Modeling – ten Berge Equation

- **Given the failure of Haber's Law to adequately describe the mortality responses, ten Berge suggested an mathematical re-formulation of the relationship between concentration and duration**
  - ten Berge's equation: $C^n \times t = k$
  - Formulated by rearranging $Y = b_0 + b_1 \ln(c) + b_2 \ln(t)$ to $Y = b_0 + b_2 \ln(c^n t)$, where $n = b_1/b_2$
  - ten Berge demonstrated that $c^n t$ predicted mortality response quite well

- **The value of n indicates which variable influences responses to a greater degree**
  - $n > 1$, response is concentration-dependent
  - $n < 1$, response is time-dependent

- **ten Berge further extended Haber's Law to situations where concentration varies during the exposure period:** $\int [c(t)]^n dt$

Concentration × Time (C × T) Modeling – ten Berge Equation

TABLE 4

Value of the exponent n for several gases and vapours, of which the probit Y of the mortality response in relation to exposure concentration c and exposure period t can be predicted by eqn. (3).

Gas or vapour	Exponent n	95% confidence limits
Local irritants		
NH_3	2.0	(1.6, 2.4)
HCl	1.0	(0.7, 1.3)
ClF_5	2.0	(1.4, 2.6)
NO_2	3.5	(2.7, 4.3)
Cl_2	3.5	(2.5, 4.4)
Perfluoroisobutylene	1.2	(1.1, 1.4)
Crotonaldehyde	1.2	(1.1, 1.3)
HF	2.0	(1.2, 2.8)
Ethylene imine	1.1	(0.8, 1.3)
Br_2	2.2	(2.0, 2.4)
Dibutylhexamethylenediamine	1.0	(0.6, 1.4)
Systemic action		
HCN	2.7	(1.8, 3.7)
H_2S	2.2	(1.6, 2.7)
Methyl t-butyl ether	2.0	(1.0, 2.9)
CH_2ClBr	1.6	(1.4, 1.8)
$C_2H_4Br_2$	1.2	(1.1, 1.2)
C_2Cl_4	2.0	(1.4, 2.6)
C_2HCl_3	0.8	(0.3, 1.4)
CCl_4	2.8	(1.9, 3.7)
Acrylonitrile	1.1	(1.0, 1.2)

ten Berge Modeling in BMDS

- **The ten Berge model was originally coded in Visual Basic by the study authors, and has been implemented in BMDS in the C language**

- **The general form of the equation is:**

$$z = b_0 + b_1 f_c(\mathrm{c}) + b_2 f_t(t) + b_3 f_x(x) + b_4 r_4(c, t, x) + \cdots$$

  - b_0, b_1 ... are model parameters estimated via maximum likelihood methods
  - $c =$ concentration, $t =$ time, $x =$ some other explanatory variable
  - $f_i(u)$ =some transformation on the explanatory variable: identity, u; logarithmic, $\ln(u)$; or reciprocal, $\frac{1}{u}$
  - $r_j(c, t, x)$ =interactions (products) of the $f_c(\mathrm{c}), f_t(t), f_x(x)$ terms
    - Number of product terms is limited to 2 currently
    - Inclusion of product terms may lead to difficulties in model interpretability

ten Berge Modeling in BMDS

- **For most modeling applications, the model formulation of most interest only incorporates c and t parameters that have been logarithmically transformed:**

$$z = b_0 + b_1 \ln(c) + b_2 \ln(t)$$

- **Rearrangement by log rules leads to the model form**

$$z = b_0 + b_2 \ln(c^n t), \text{ where } n = b_1 / b_2$$

Formatting Data for ten Berge Model

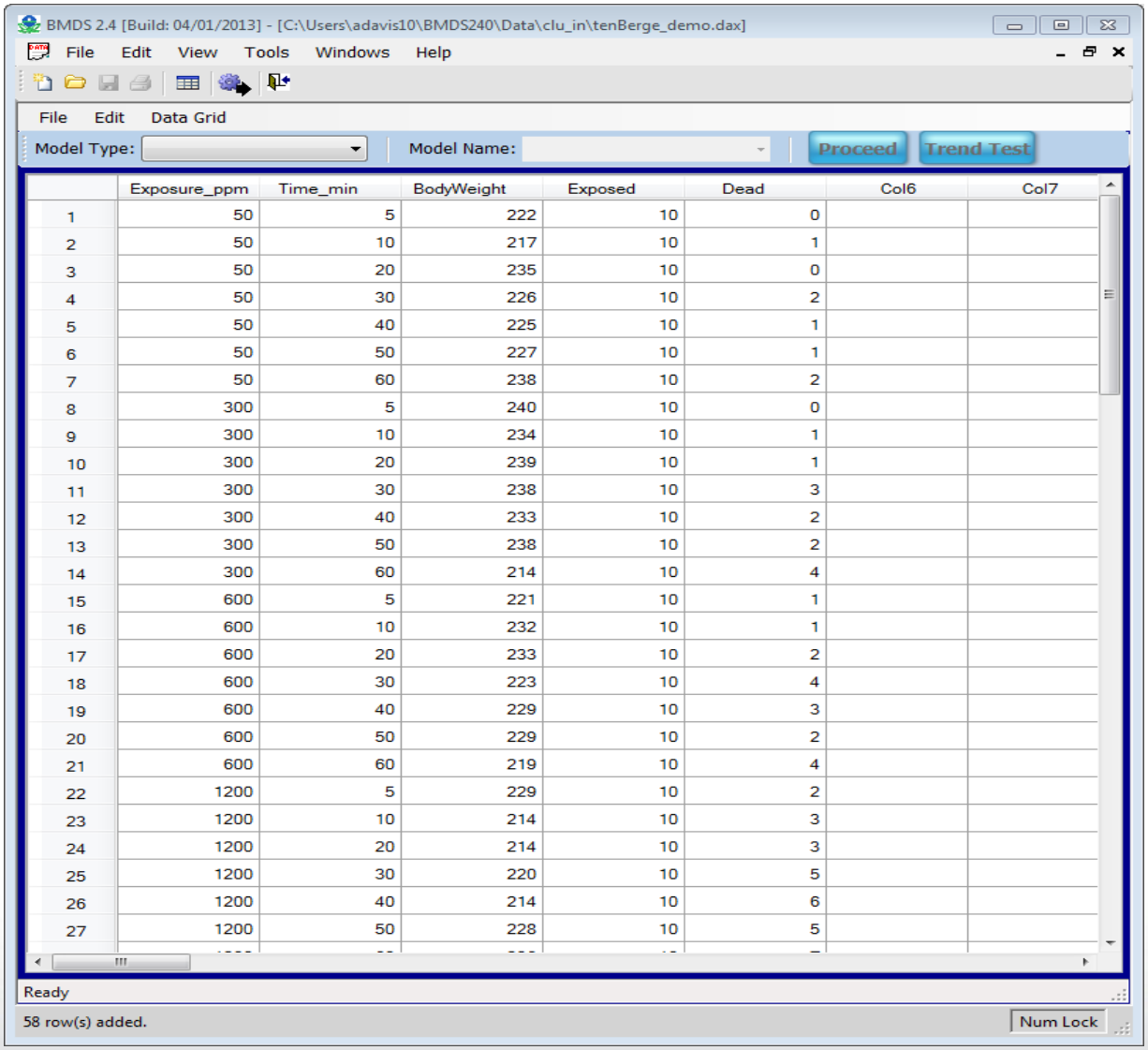
- **Can create datasets within BMDS, or import them from other spreadsheet applications**

- **Data needs to be in the following format:**
  - The first columns must be the main effect columns (i.e., concentration and time), in any order **BUT** they must appear first
  - The final columns in the dataset should # Subjects and Incidence **IN THAT ORDER**
  - Other explanatory variables (e.g., body weight, age) can appear in any order between the main effect columns and the # Subjects/Incidence columns

- **Datasets needs at a minimum:**
  - Total number of exposed subjects
  - Number of affected subjects
  - 2 explanatory variables

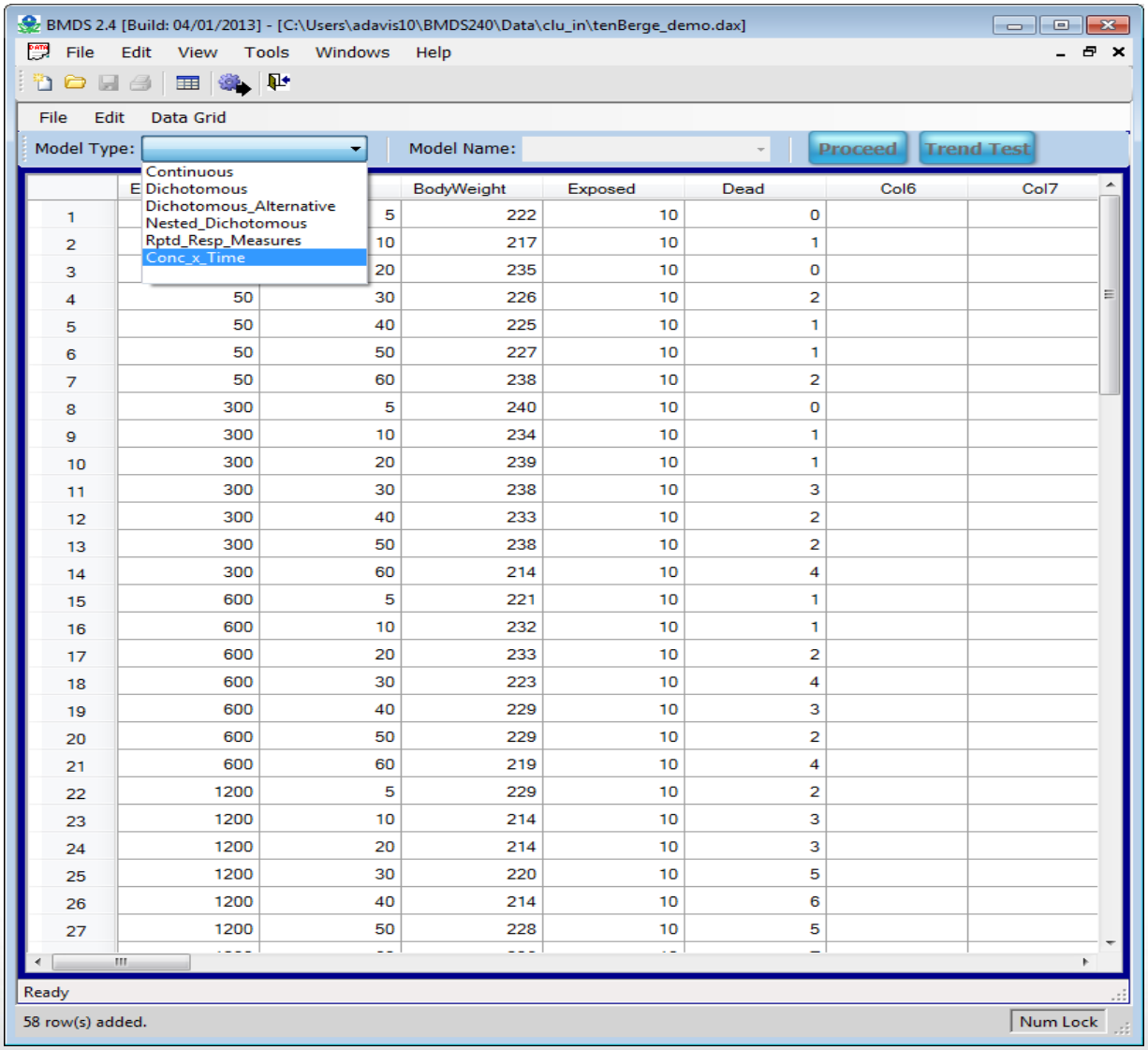
Running The ten Berge Model in BMDS

Dataset Structure

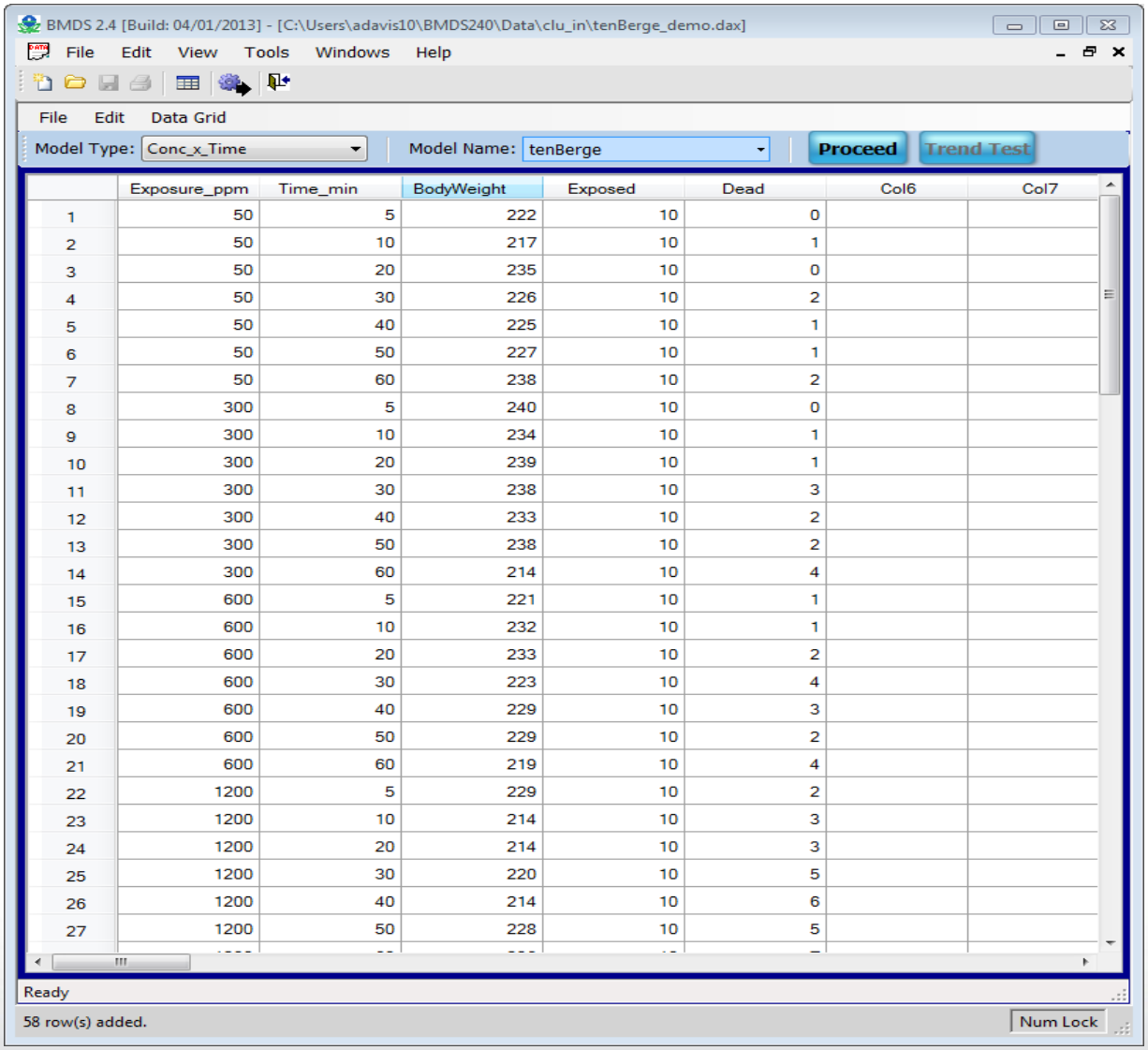


	Exposure_ppm	Time_min	BodyWeight	Exposed	Dead	Col6	Col7
1	50	5	222	10	0		
2	50	10	217	10	1		
3	50	20	235	10	0		
4	50	30	226	10	2		
5	50	40	225	10	1		
6	50	50	227	10	1		
7	50	60	238	10	2		
8	300	5	240	10	0		
9	300	10	234	10	1		
10	300	20	239	10	1		
11	300	30	238	10	3		
12	300	40	233	10	2		
13	300	50	238	10	2		
14	300	60	214	10	4		
15	600	5	221	10	1		
16	600	10	232	10	1		
17	600	20	233	10	2		
18	600	30	223	10	4		
19	600	40	229	10	3		
20	600	50	229	10	2		
21	600	60	219	10	4		
22	1200	5	229	10	2		
23	1200	10	214	10	3		
24	1200	20	214	10	3		
25	1200	30	220	10	5		
26	1200	40	214	10	6		
27	1200	50	228	10	5		

Select "Conc × Time" for Model Type

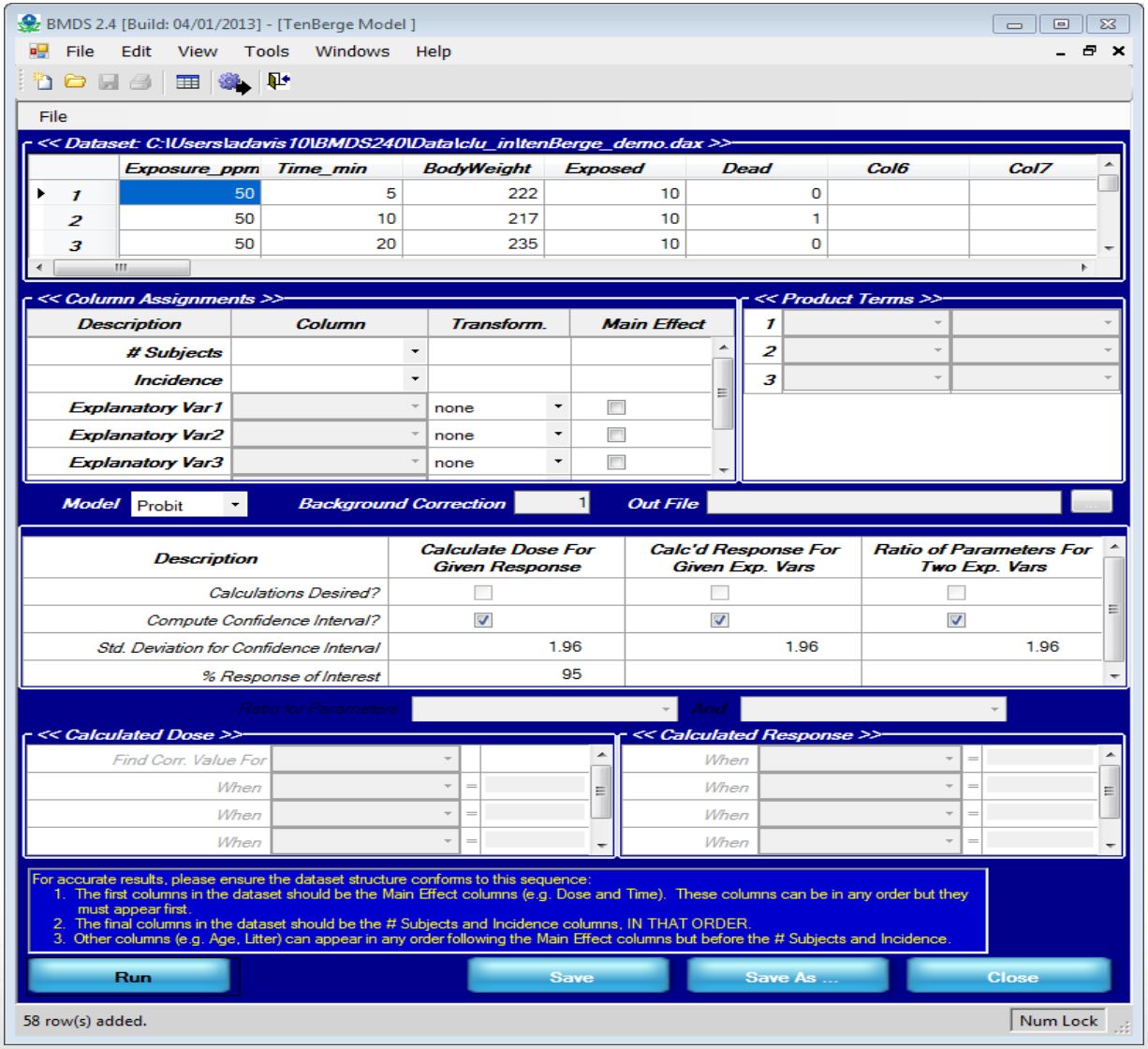


ten Berge Model is Automatically Selected

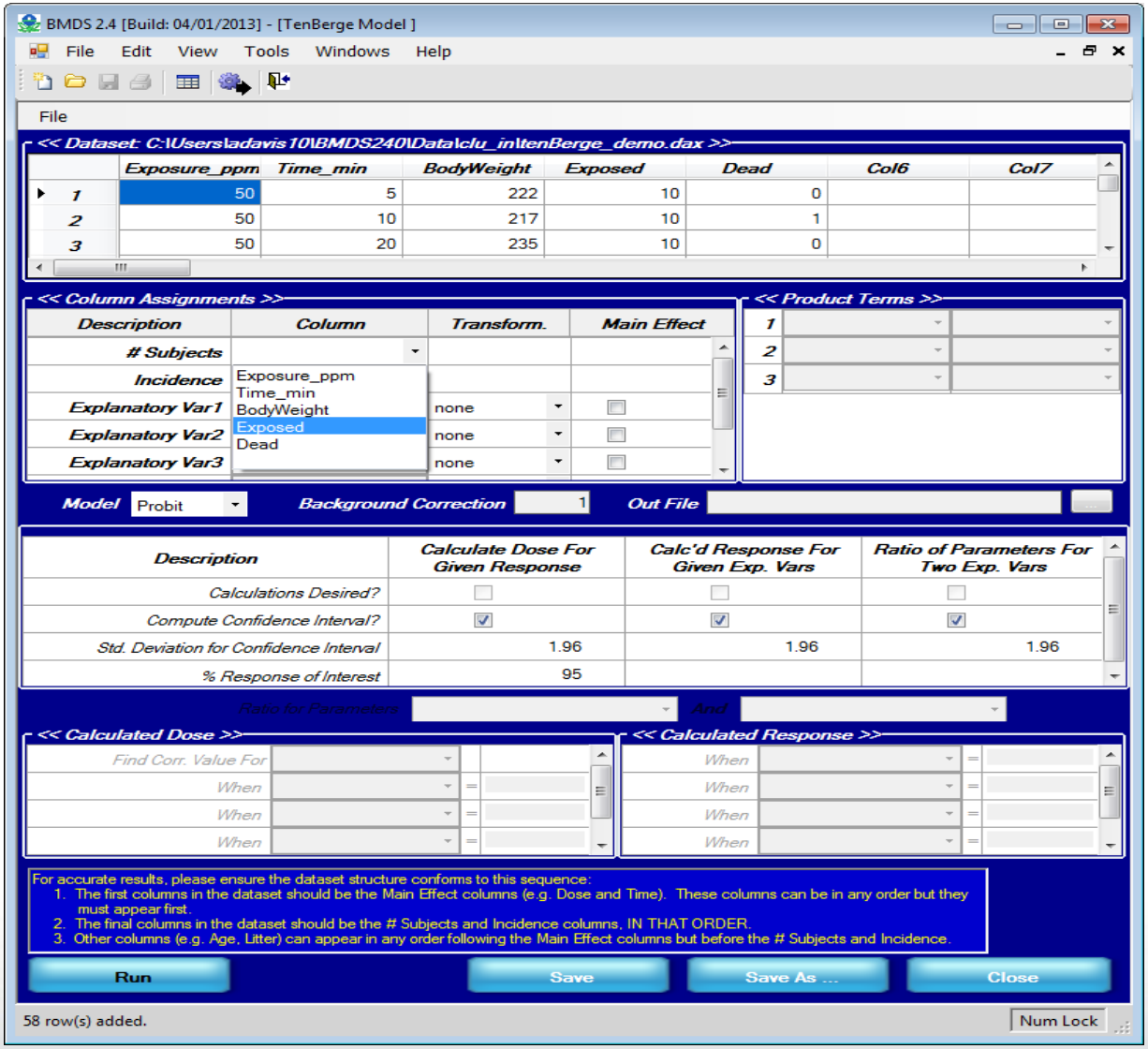


	Exposure_ppm	Time_min	BodyWeight	Exposed	Dead	Col6	Col7
1	50	5	222	10	0		
2	50	10	217	10	1		
3	50	20	235	10	0		
4	50	30	226	10	2		
5	50	40	225	10	1		
6	50	50	227	10	1		
7	50	60	238	10	2		
8	300	5	240	10	0		
9	300	10	234	10	1		
10	300	20	239	10	1		
11	300	30	238	10	3		
12	300	40	233	10	2		
13	300	50	238	10	2		
14	300	60	214	10	4		
15	600	5	221	10	1		
16	600	10	232	10	1		
17	600	20	233	10	2		
18	600	30	223	10	4		
19	600	40	229	10	3		
20	600	50	229	10	2		
21	600	60	219	10	4		
22	1200	5	229	10	2		
23	1200	10	214	10	3		
24	1200	20	214	10	3		
25	1200	30	220	10	5		
26	1200	40	214	10	6		
27	1200	50	228	10	5		

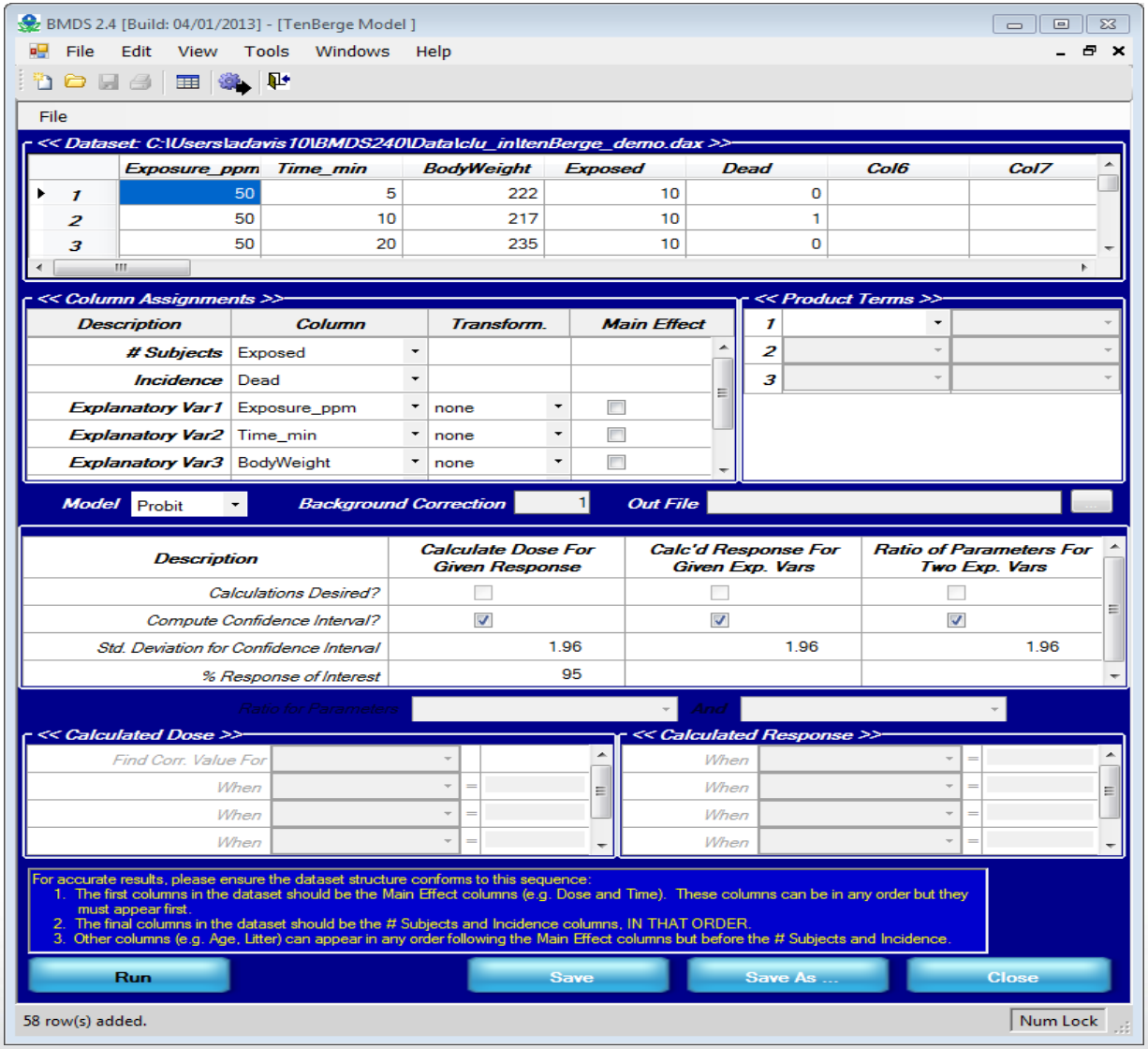
ten Berge Model Option Screen



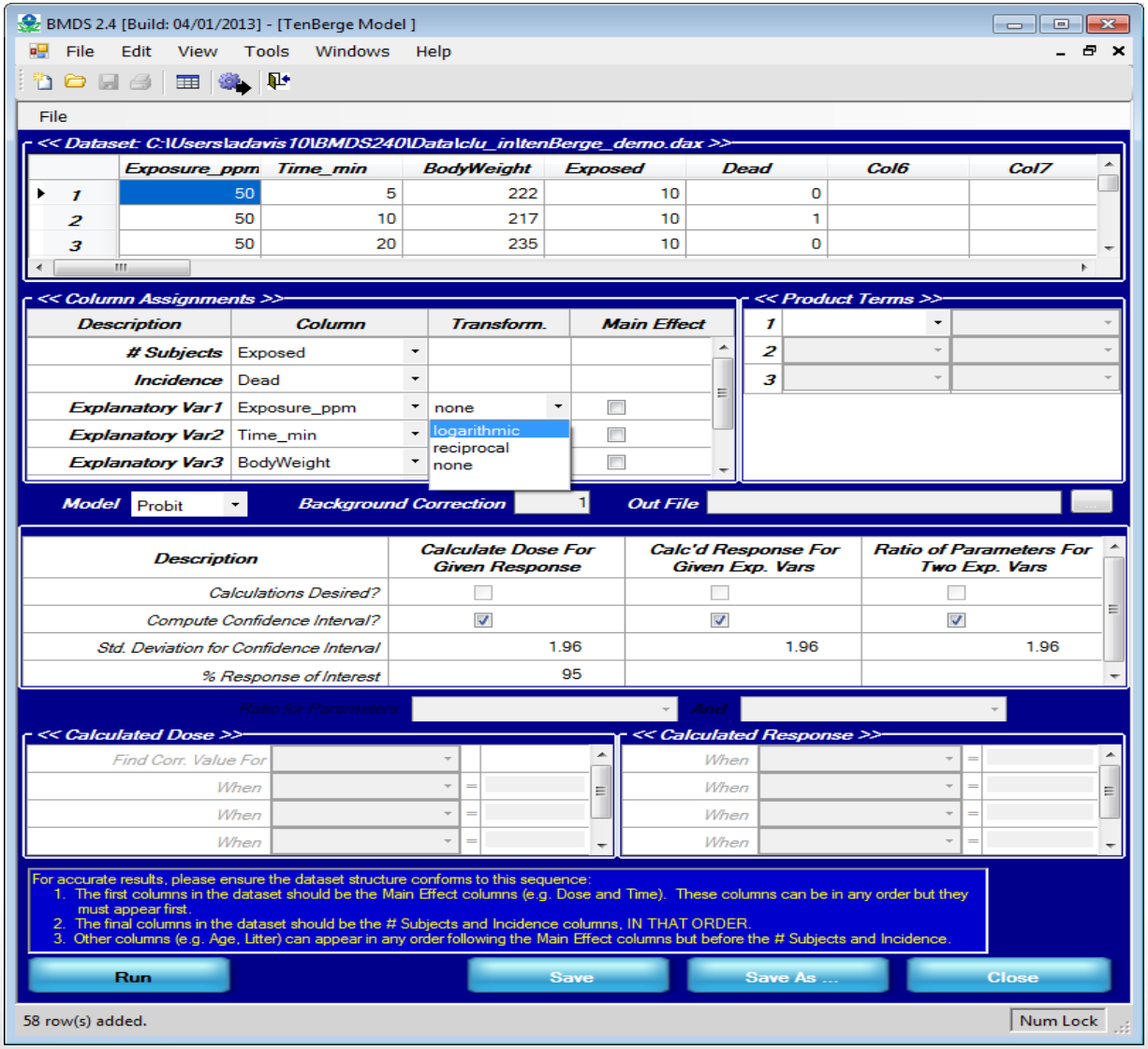
ten Berge Model – Column Assignments



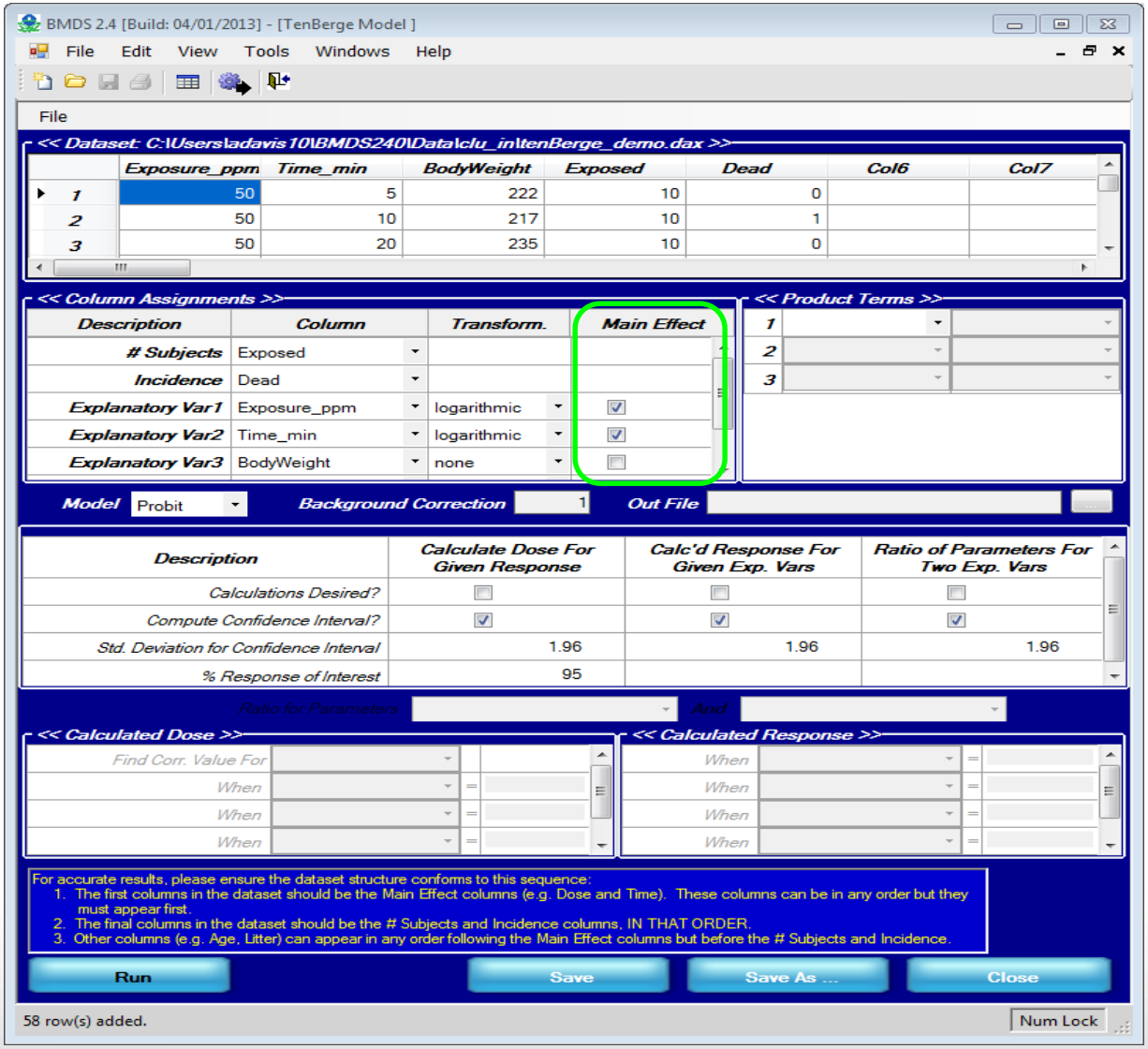
ten Berge Model – Column Assignments



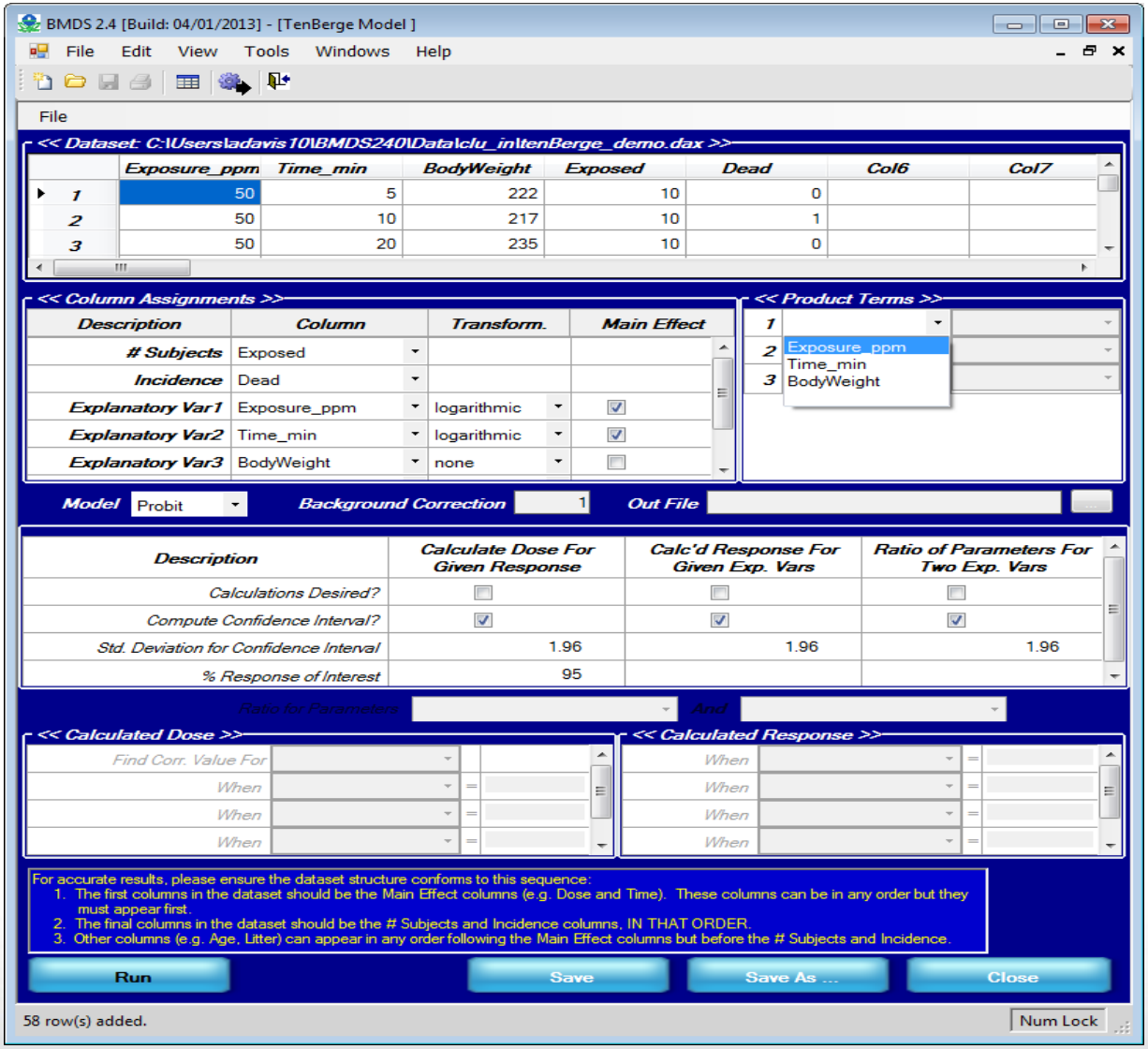
ten Berge Model – Variable Transformations



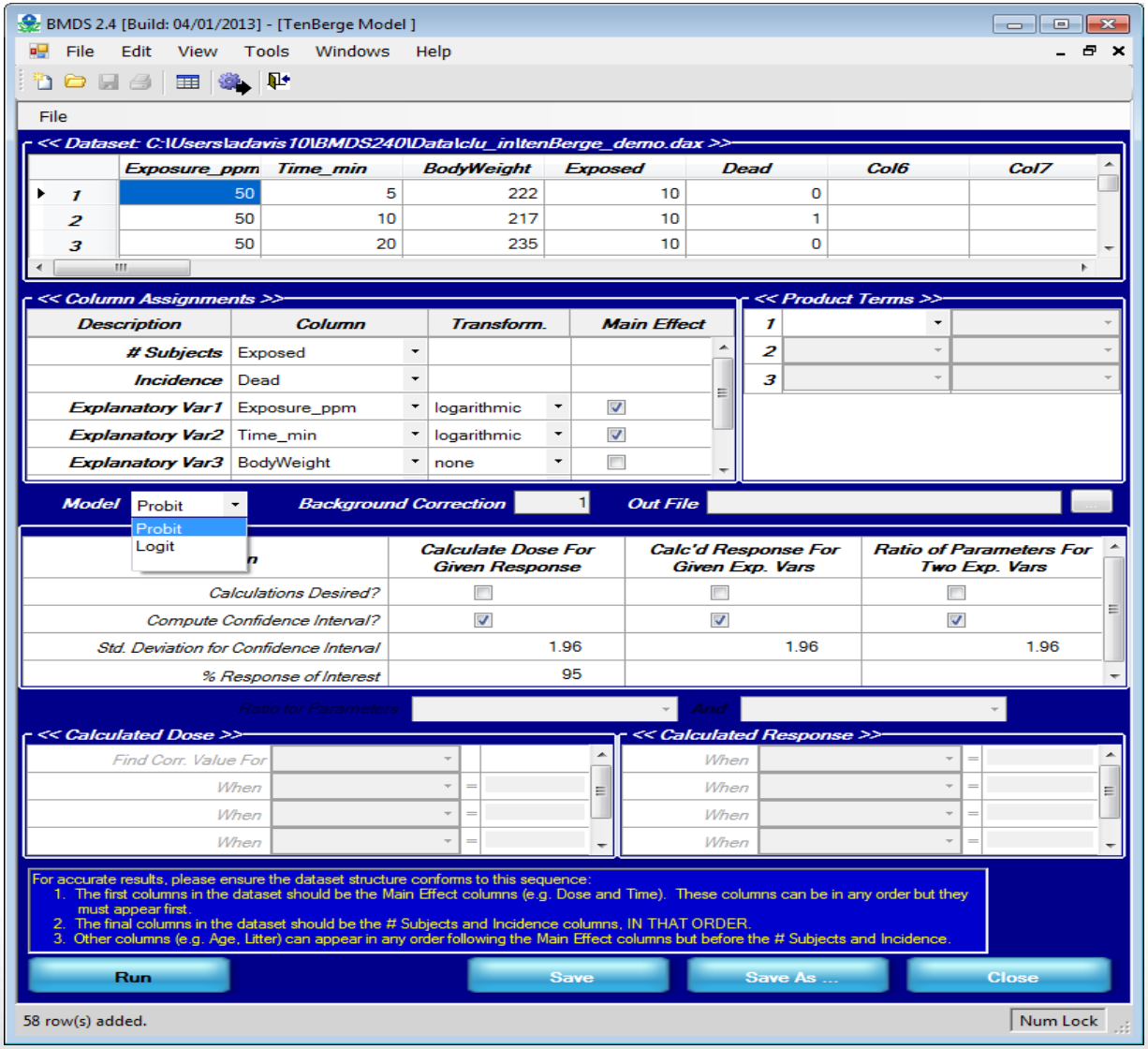
ten Berge Model – Including Variables as Main Effects



ten Berge Model – Product Terms



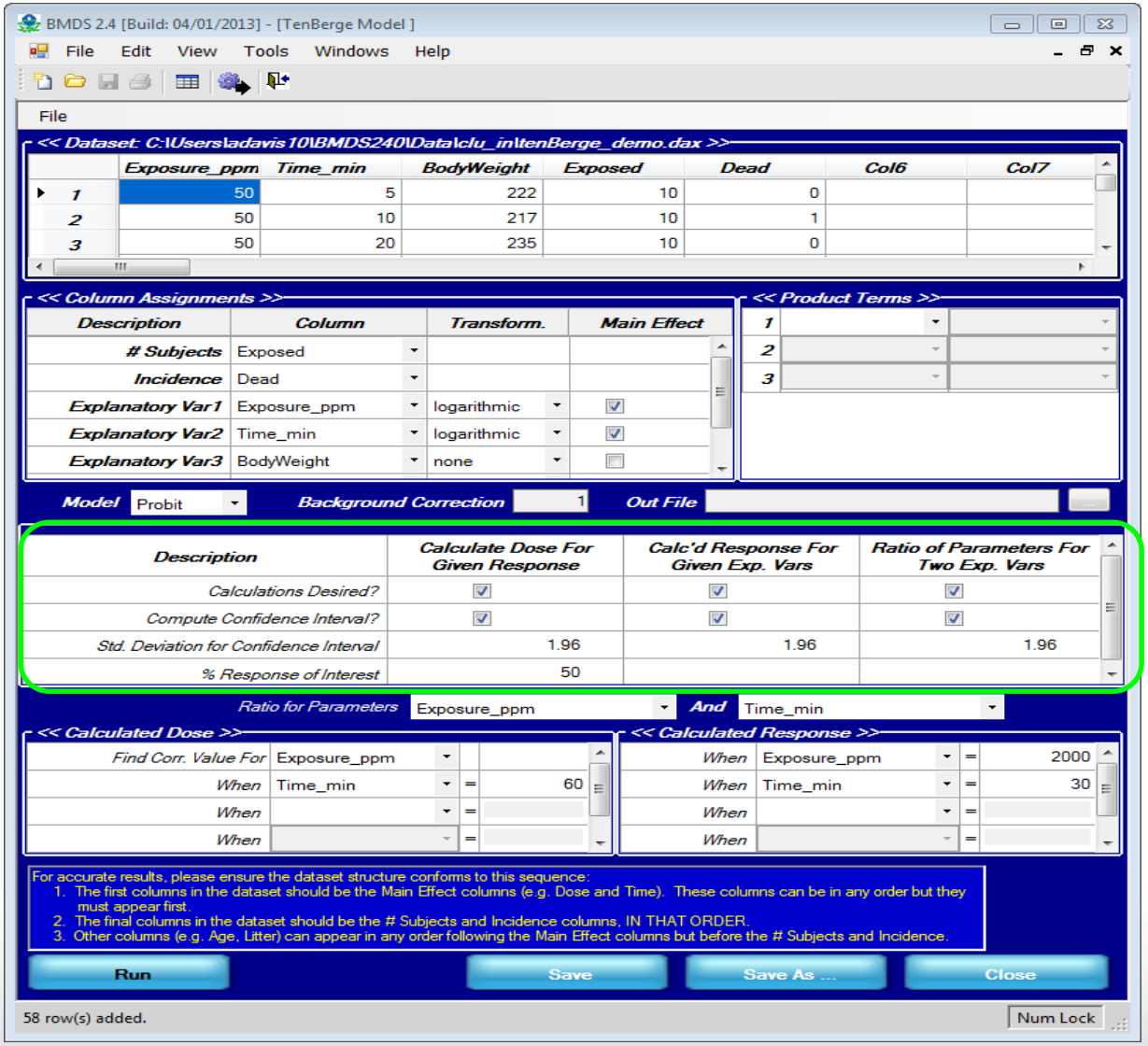
ten Berge Model – Select Specific Model



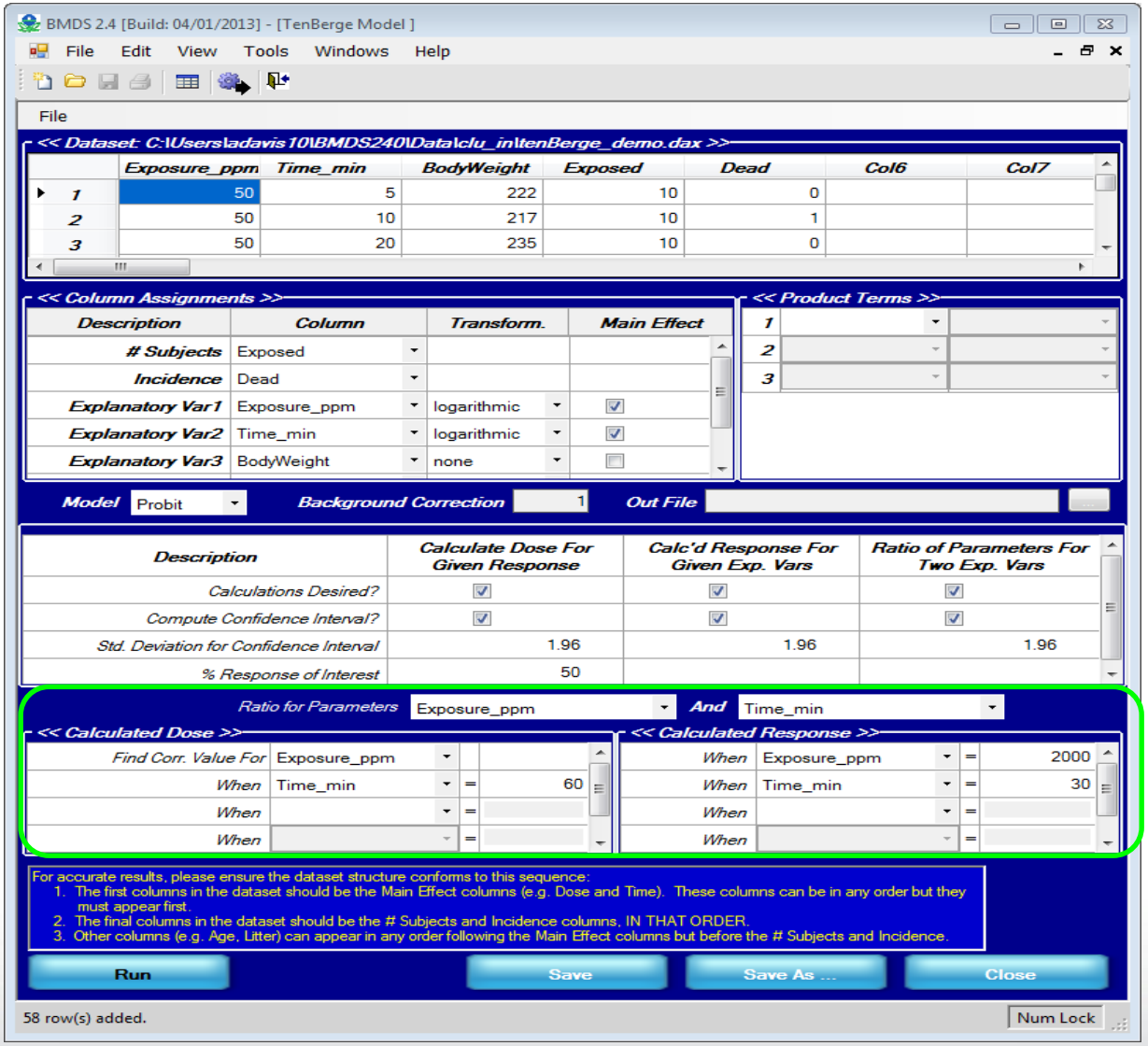
Choose Model Calculations of Interest

- **The ten Berge model is able to perform the following three calculations, providing the user with estimates and confidence intervals:**
  - A value for one explanatory variable, given a percent response and specified values for the other explanatory variables
  - The percent response given specified values for all of the explanatory variables
  - The ratio between the regression coefficients of two explanatory variables (i.e., the value of n, when concentration and time are included as main effects and logarithmically transformed)

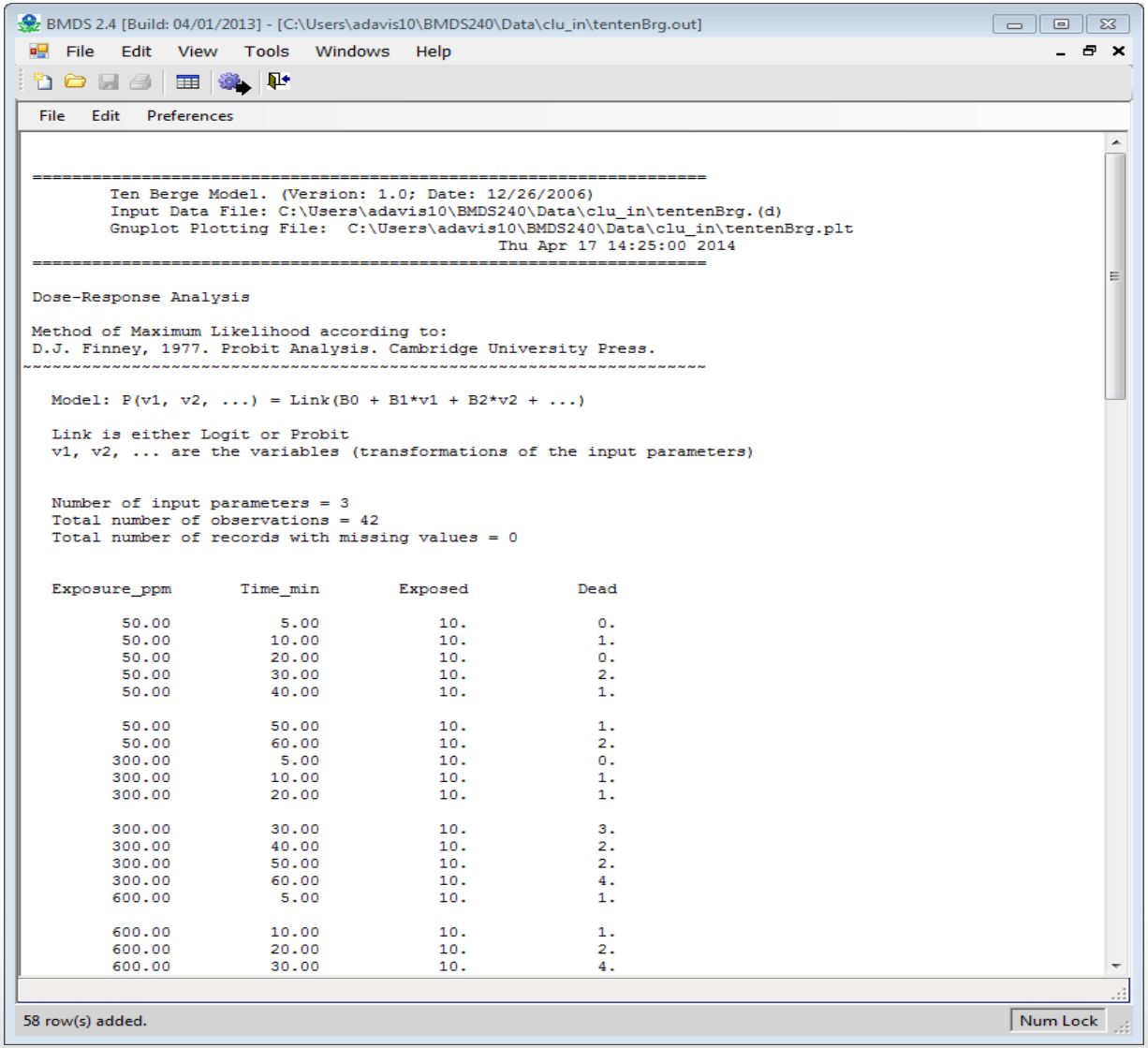
ten Berge Model – Calculations of Interest



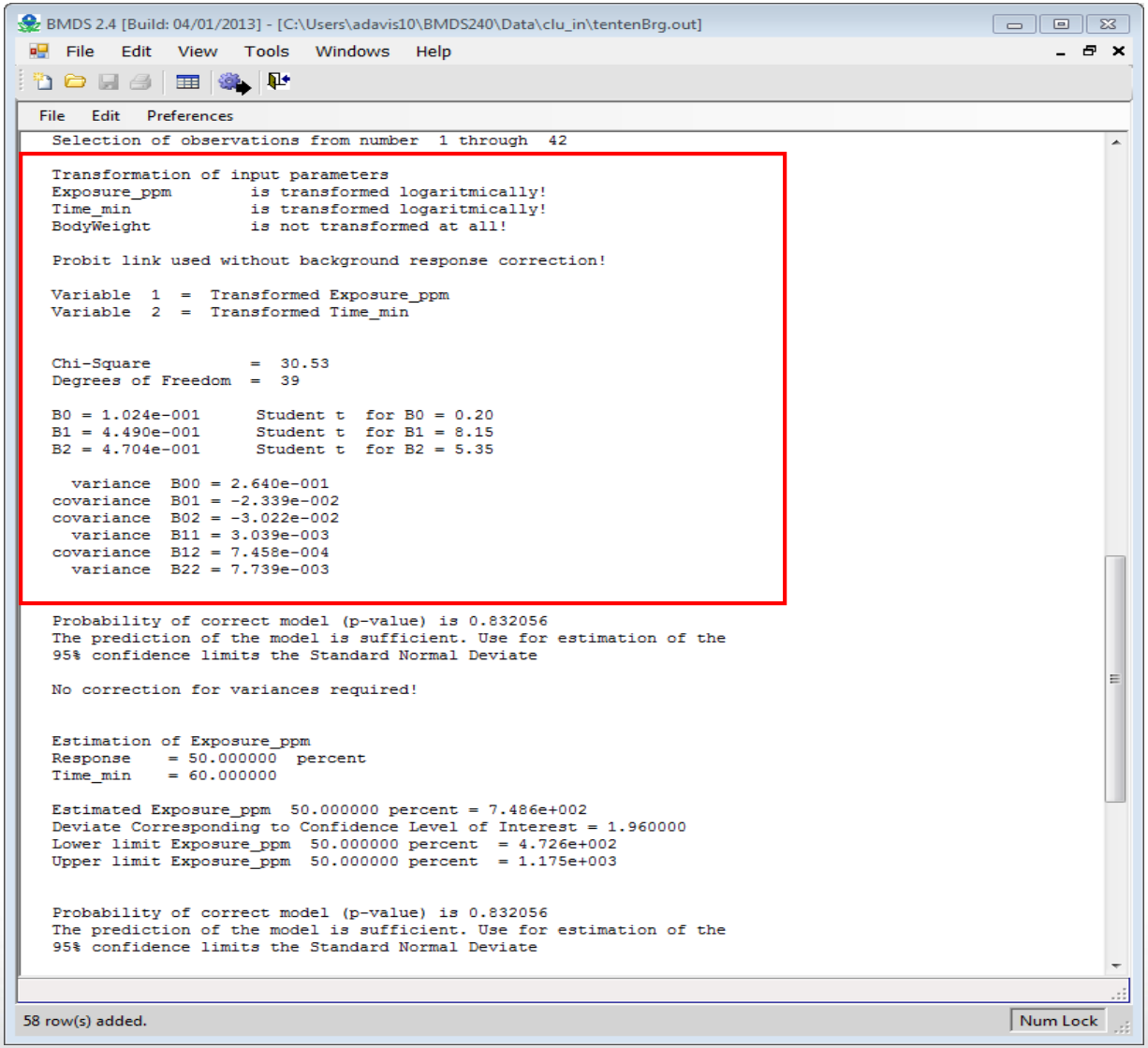
ten Berge Model – Calculations of Interest



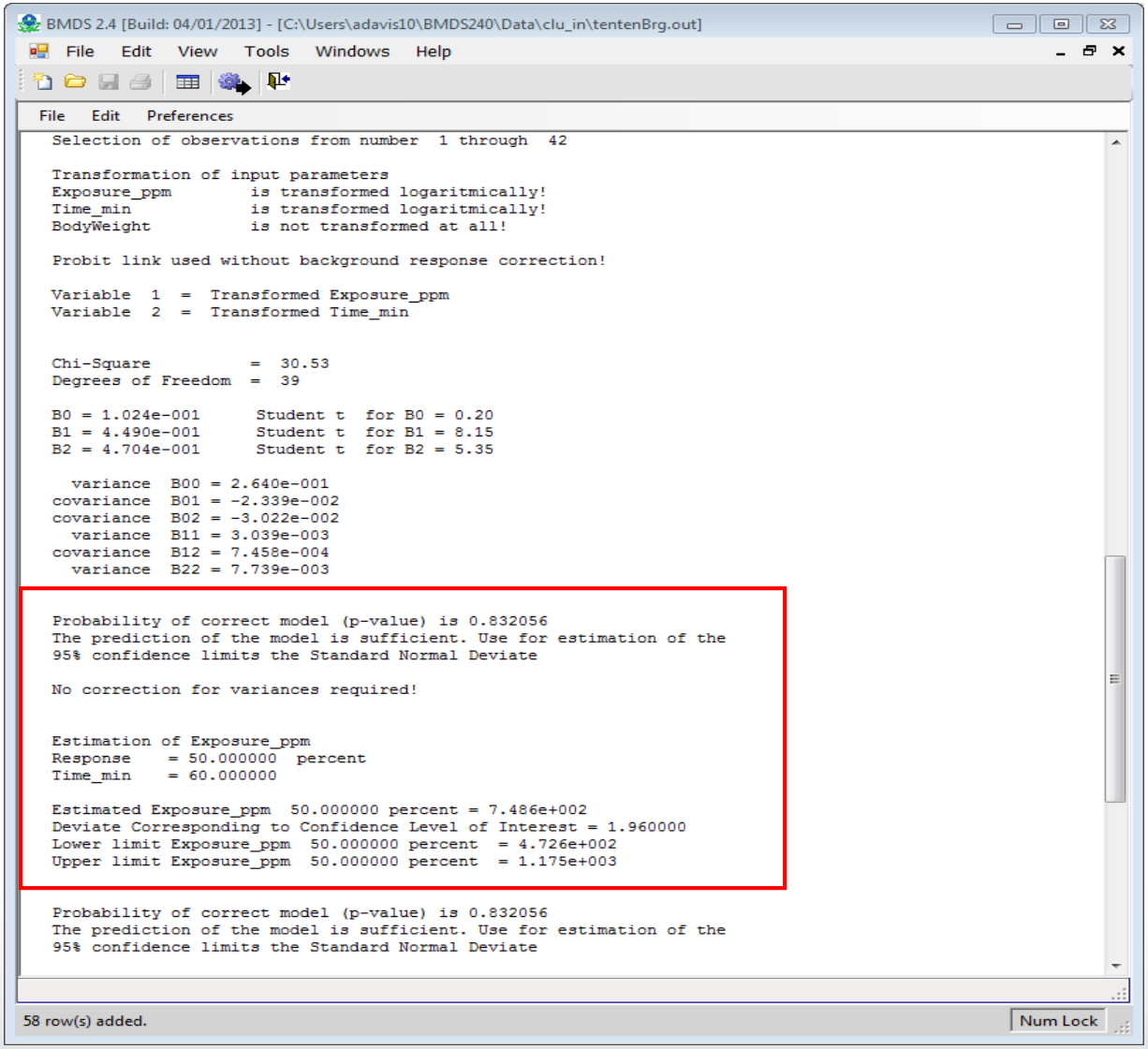
ten Berge Model – Results



ten Berge Model - Results



ten Berge Model – Results



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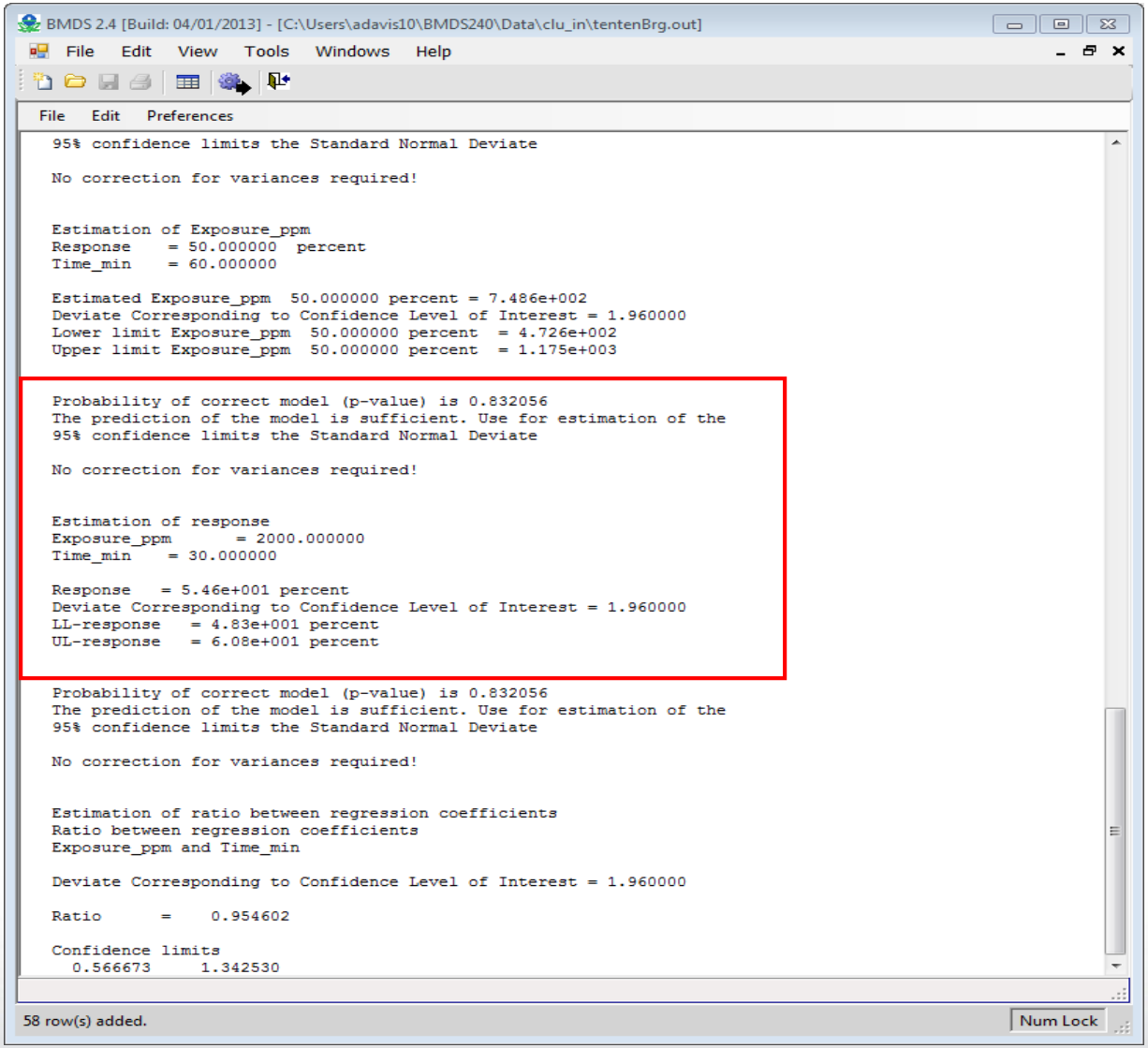
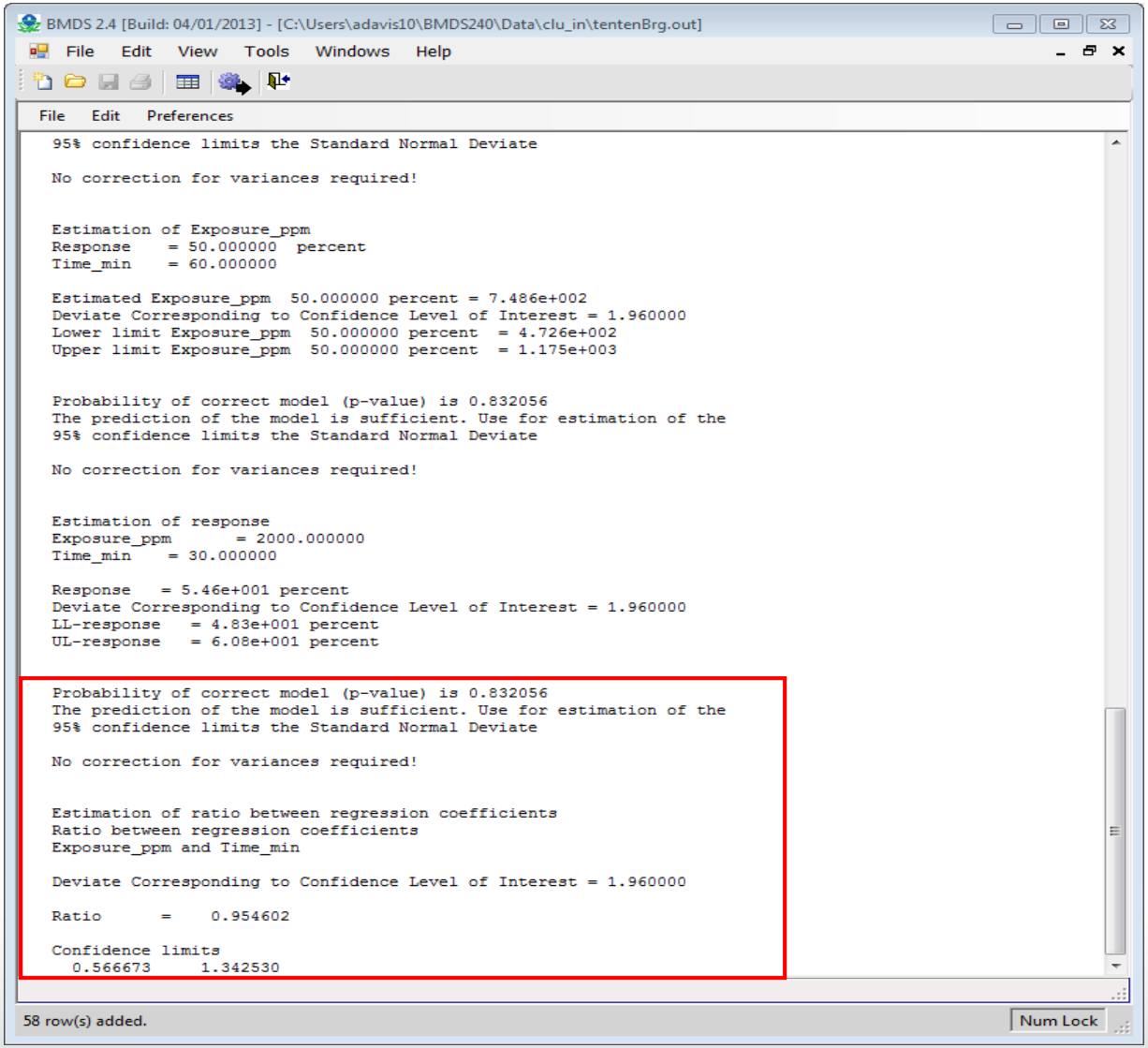
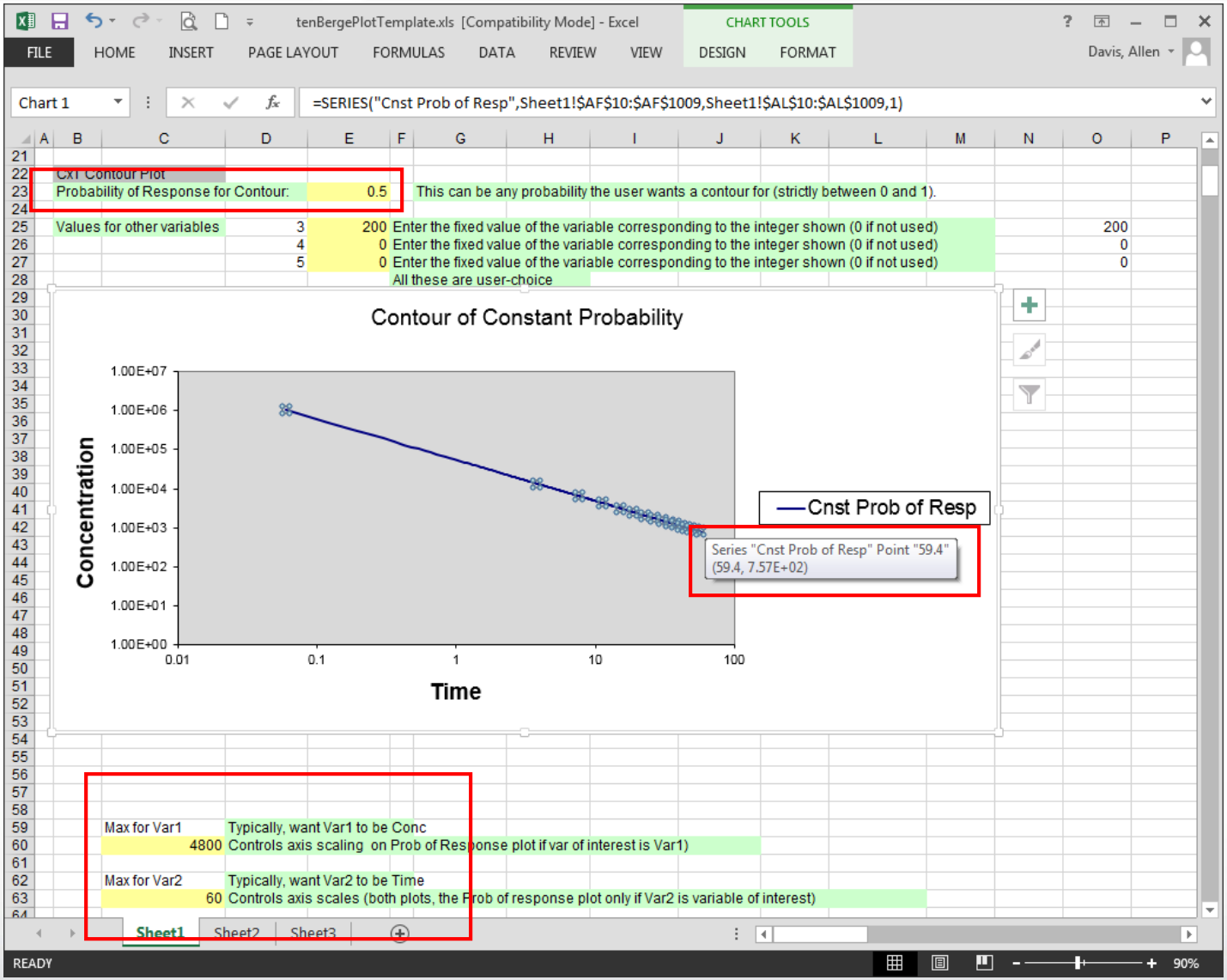


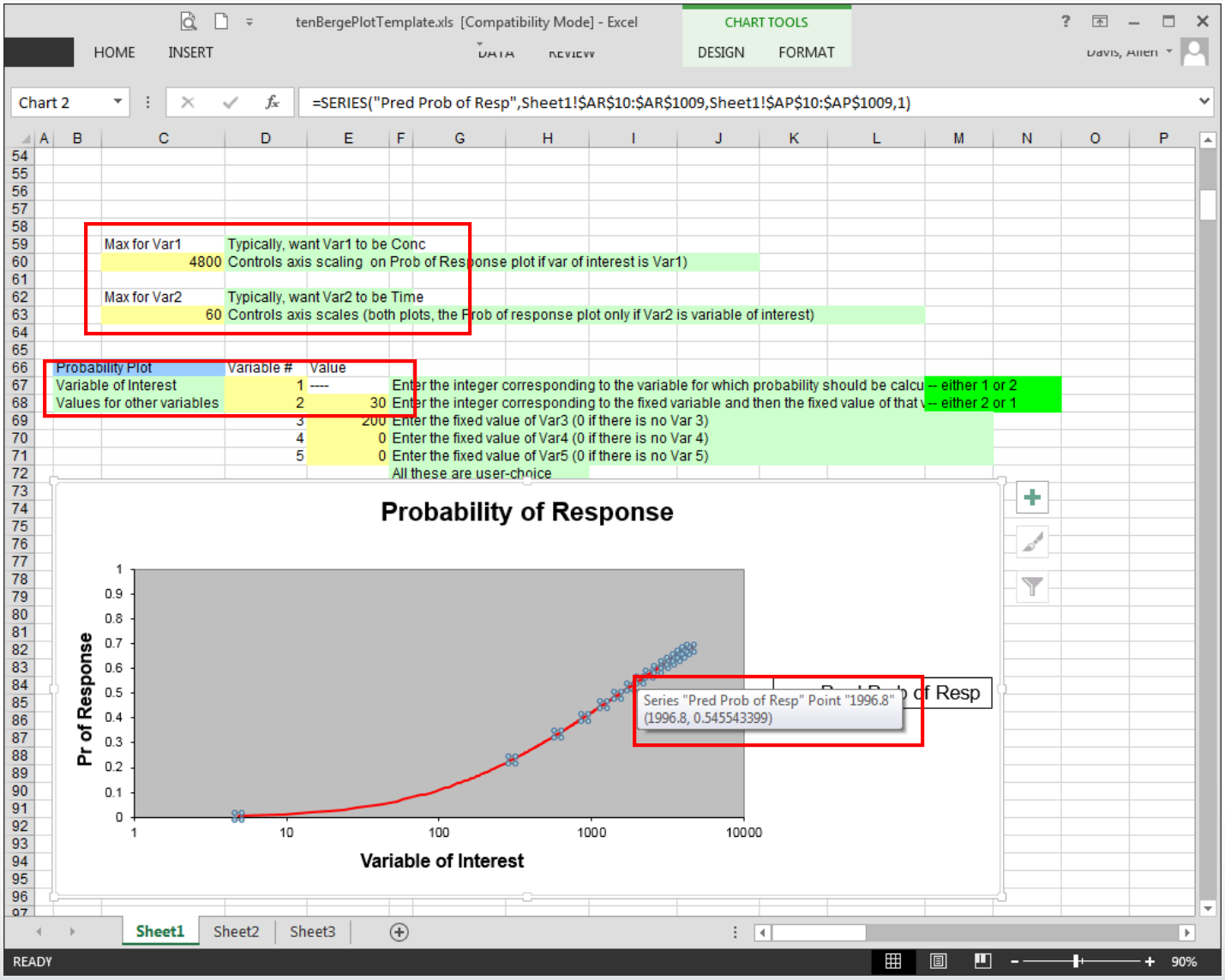
ten Berge Model – Results



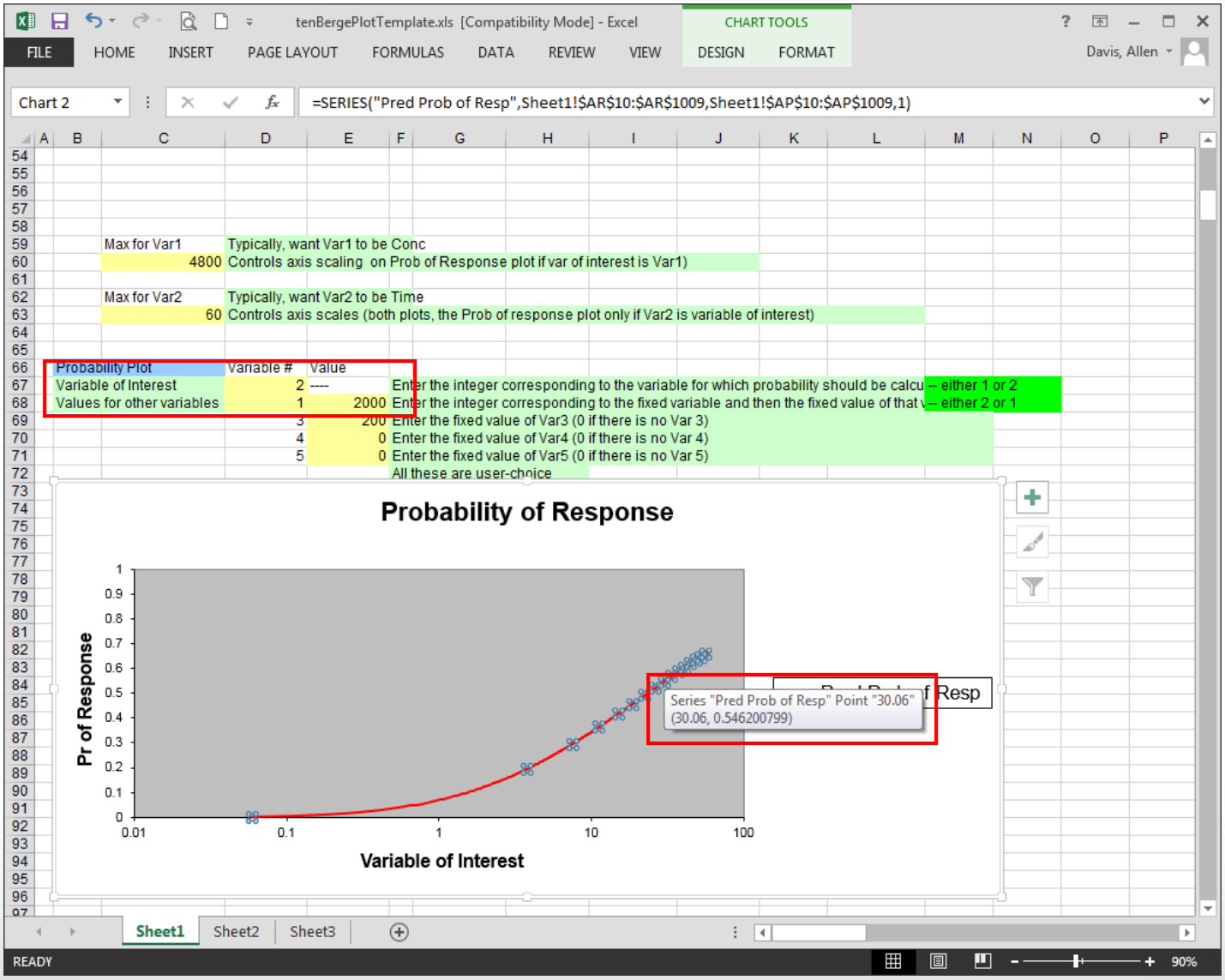
ten Berge Model – Plots



ten Berge Model – Plots



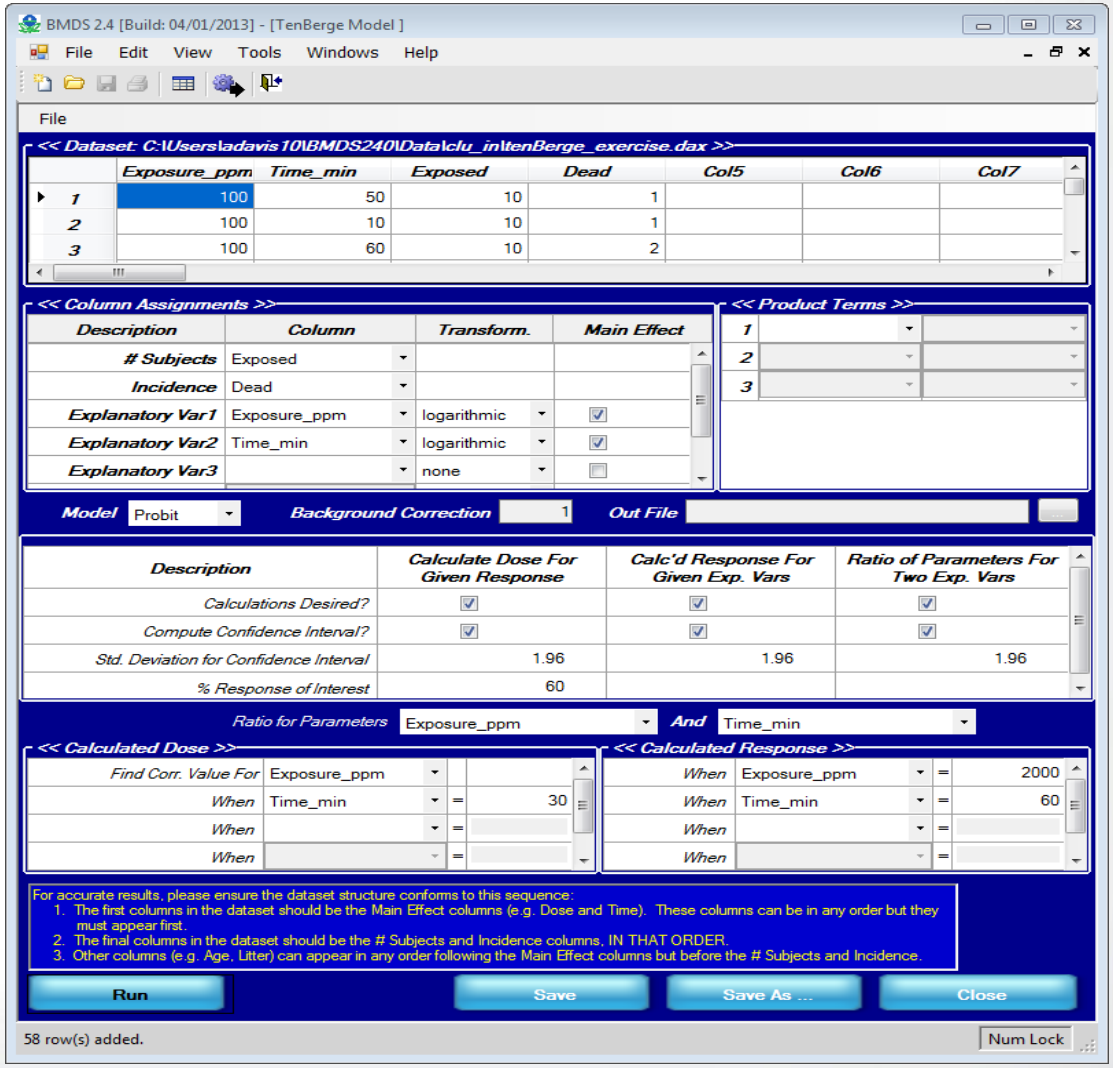
ten Berge Model – Plots



ten Berge Modeling Exercise

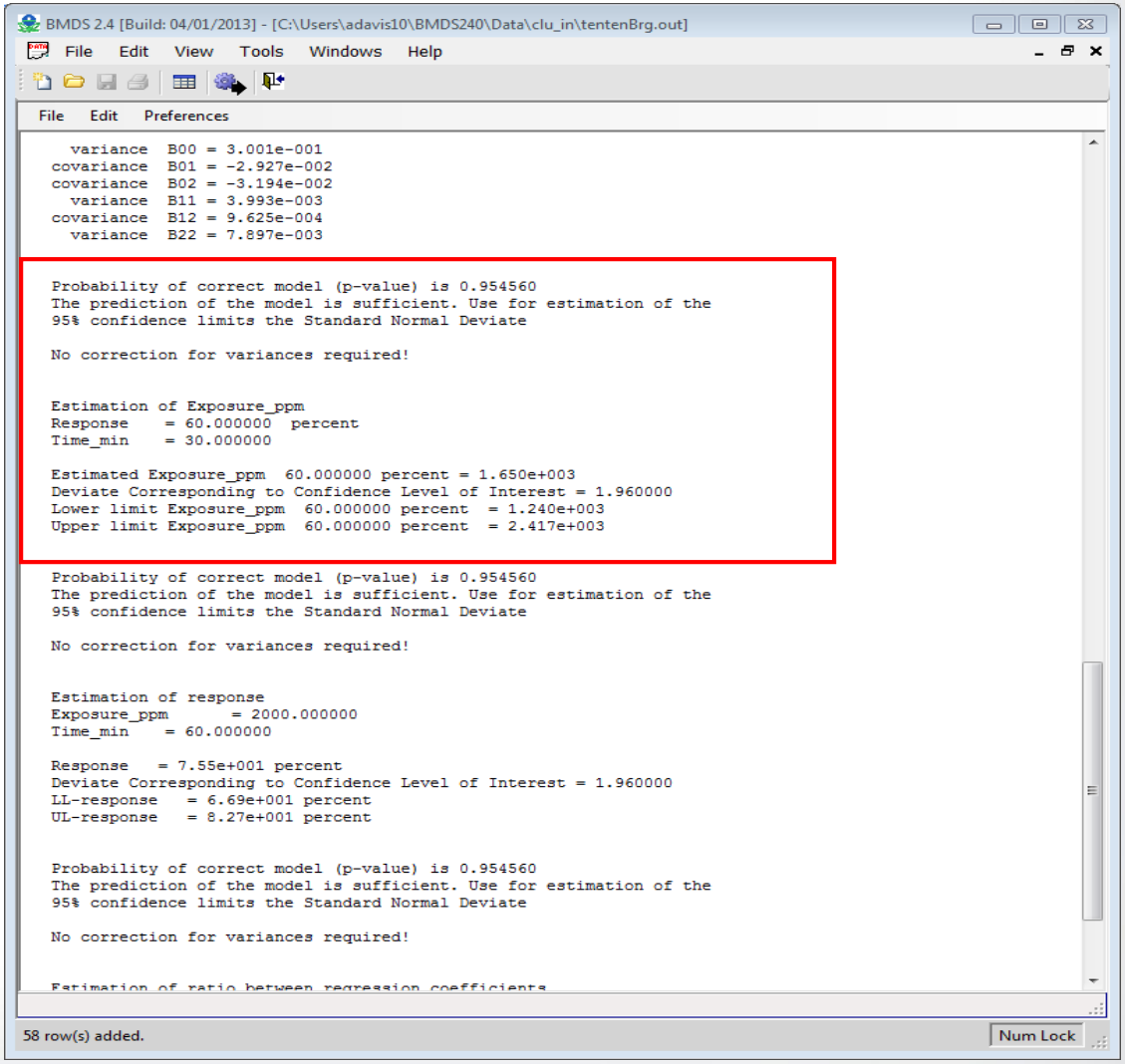
ten Berge Modeling Exercise

- **Open tenBerge_exercise.dax**
- **Open option file (Model Type: Conc_x_Time; Model Name: tenBerge, Proceed)**
- **Parameterize the option file as shown**

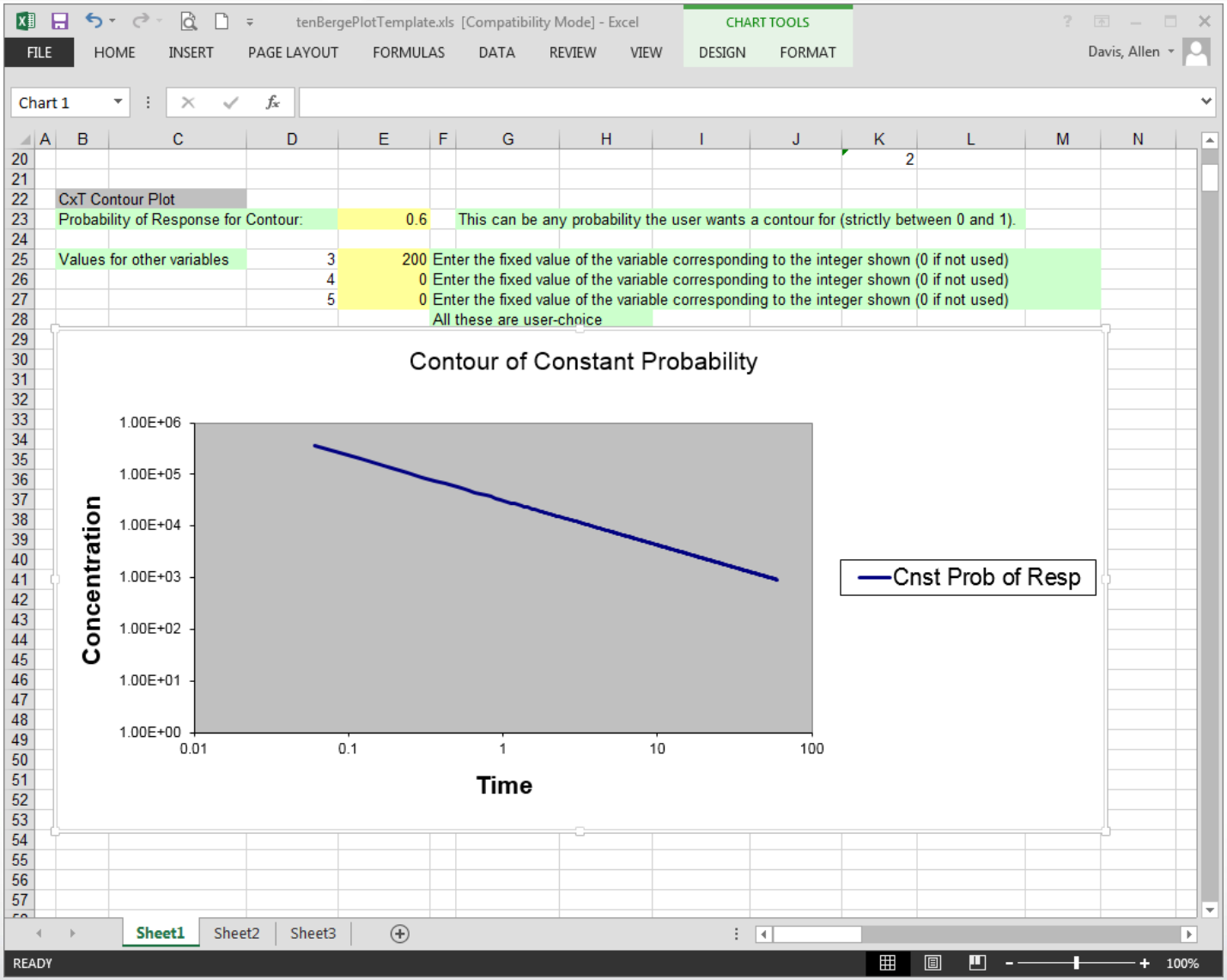


ten Berge Modeling Results – Dose for a Given Response

	Dose for Given Response
Response %	60%
Time	30 minutes
p-value	0.95456
Dose	1650 ppm
Lower CI	1240 ppm
Upper CI	2417 ppm

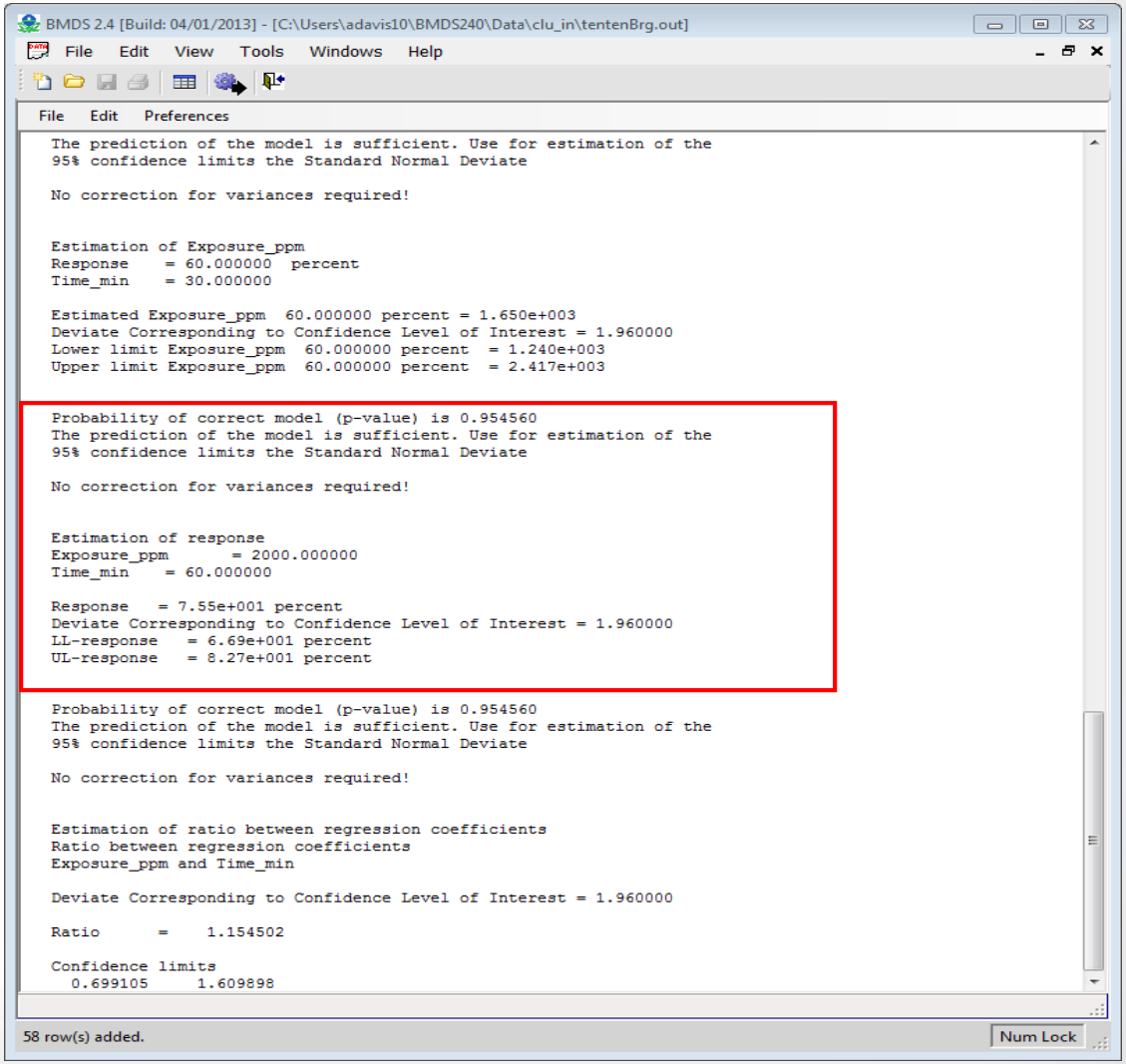


ten Berge Modeling Results – Dose for a Given Response Plot

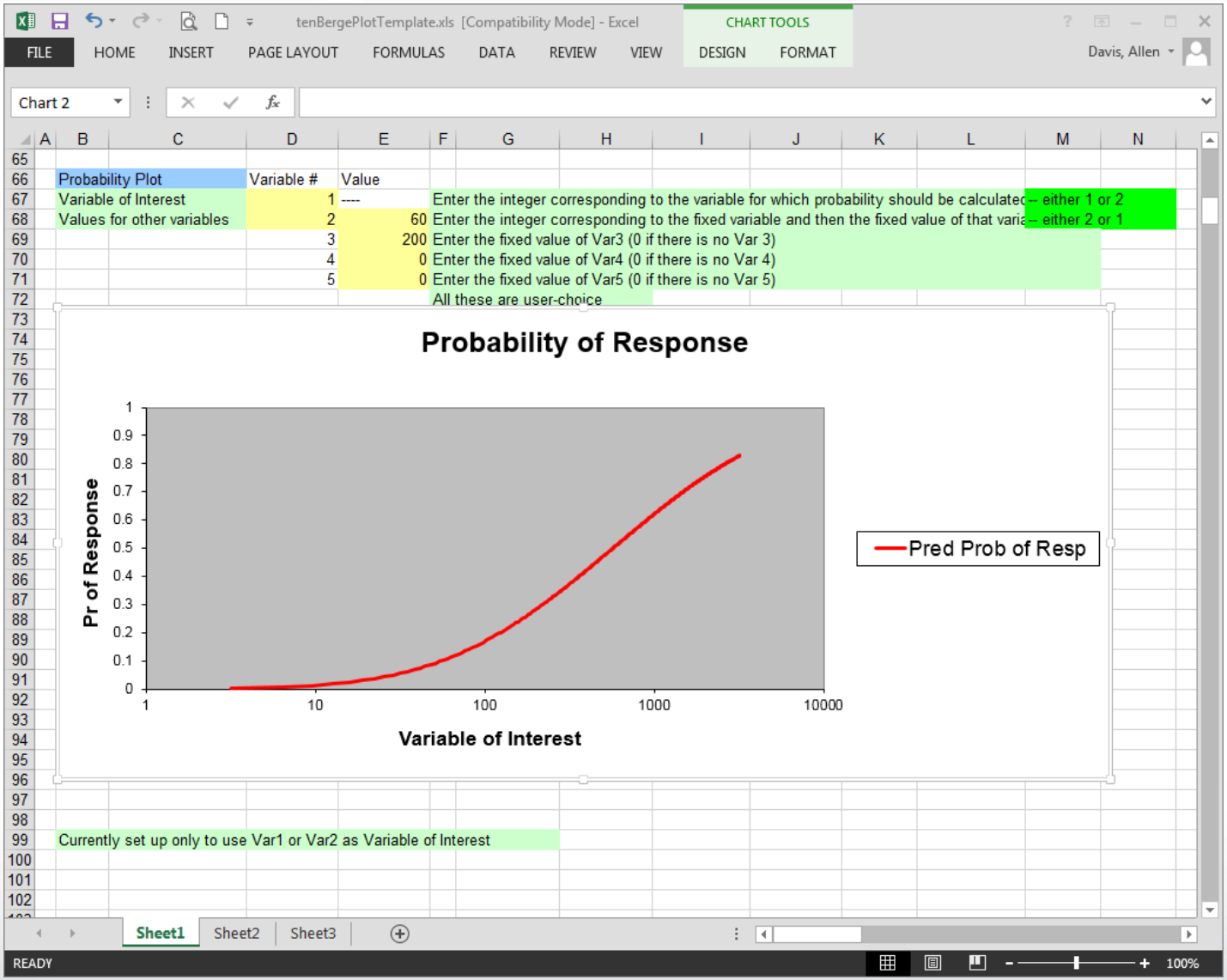


ten Berge Modeling Results – Response for Given Variables

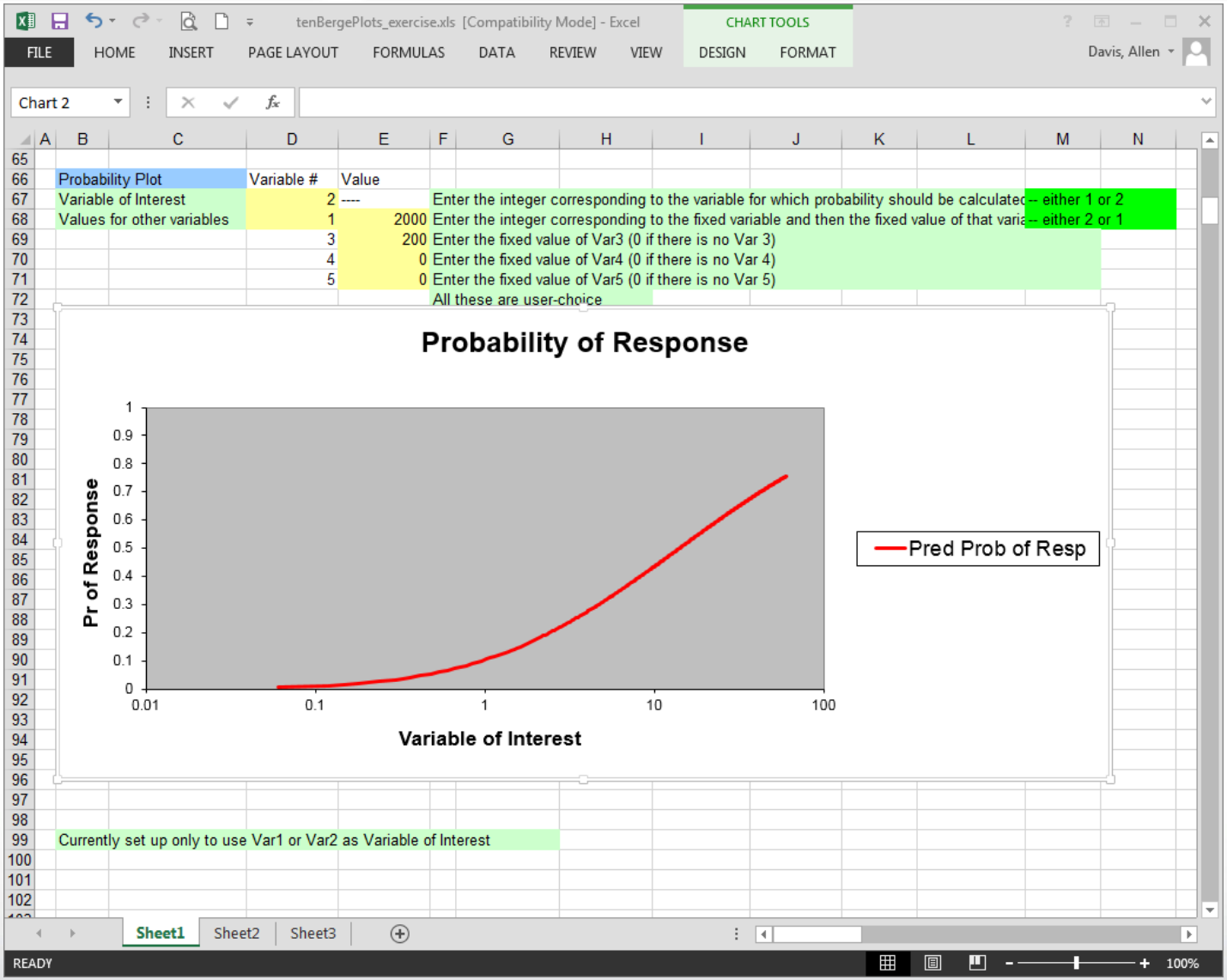
	Response for Given Variables
Exposure	2000
Time	60 minutes
p-value	0.95456
Response	75.5%
Lower CI	66.9%
Upper CI	82.7%



ten Berge Modeling Results – Response for Given Variables Plot

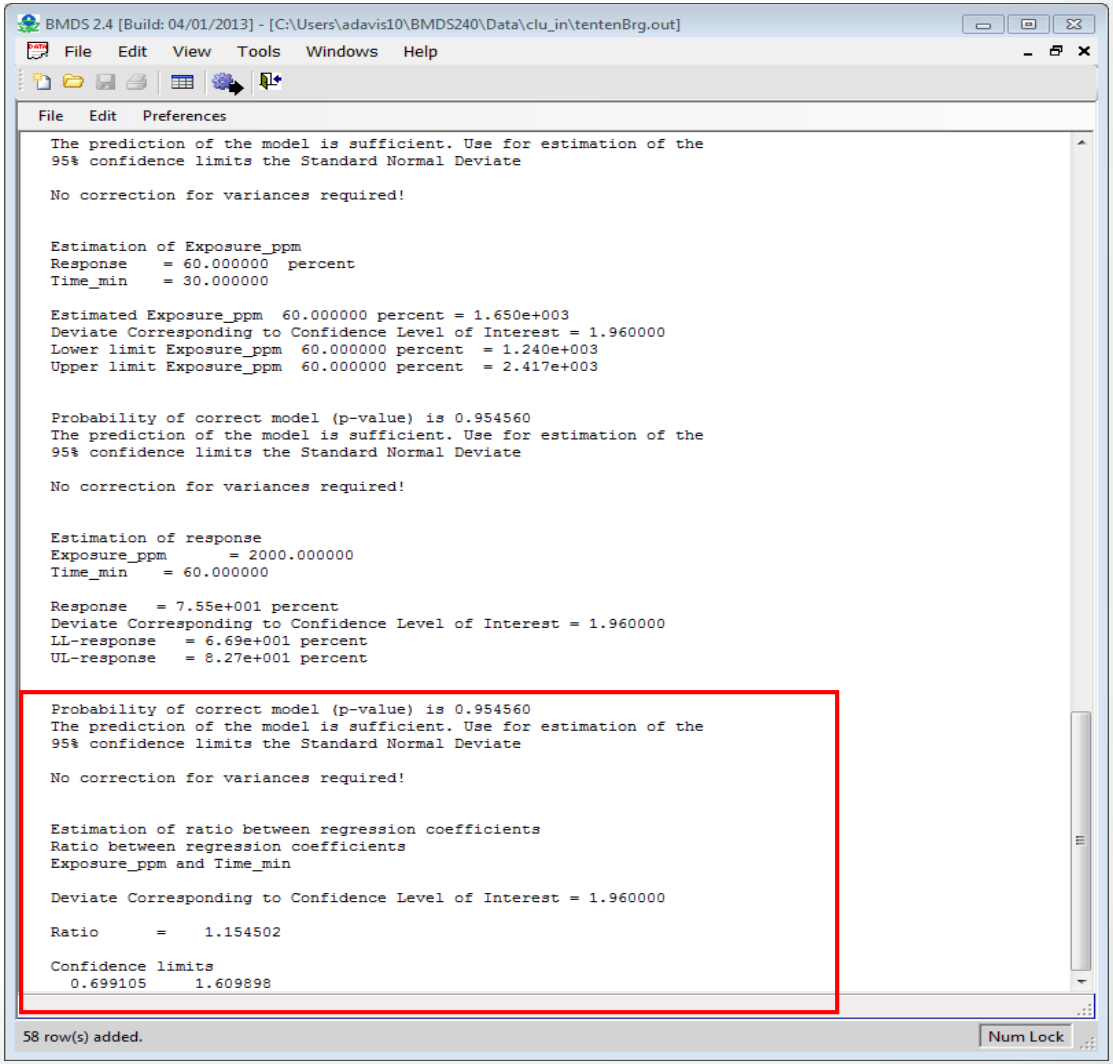


ten Berge Modeling Results – Response for Given Variables Plot



ten Berge Modeling Results – Ratio Between Regression Coefficients

	Ratio Between Regression Coefficients
Ratio	1.154
Lower CI	0.699
Upper CI	1.609



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