



# Benchmark Dose Modeling – Modeling Time

*Allen Davis, MSPH*

*Jeff Gift, Ph.D.*

*Jay Zhao, Ph.D.*

*National Center for Environmental Assessment, U.S. EPA*





## Disclaimer

**The views expressed in this presentation are those of the author(s) and do not necessarily reflect the views or policies of the US EPA.**



# 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  $\times$  time (C  $\times$  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 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  $\times$  time ( $C \times t$ ) data**
  - $C \times t$  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

- **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 reasons:**
  - 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**

- **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:  $A(t) = A_0 + A_1t$
  - 2<sup>nd</sup> degree polynomial:  $A(t) = A_0 + A_1t + A_2t^2$
- 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

- **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

BMDS 2.2 [Build: 12/08/2011]

File Edit View Tools Windows Help

C:\BMDS220\Data\TETacForeGrip.dax

File Edit Data Grid

Model Type: [dropdown] Model Name: [dropdown] Proceed Trend Test

	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			

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- **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:**

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

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

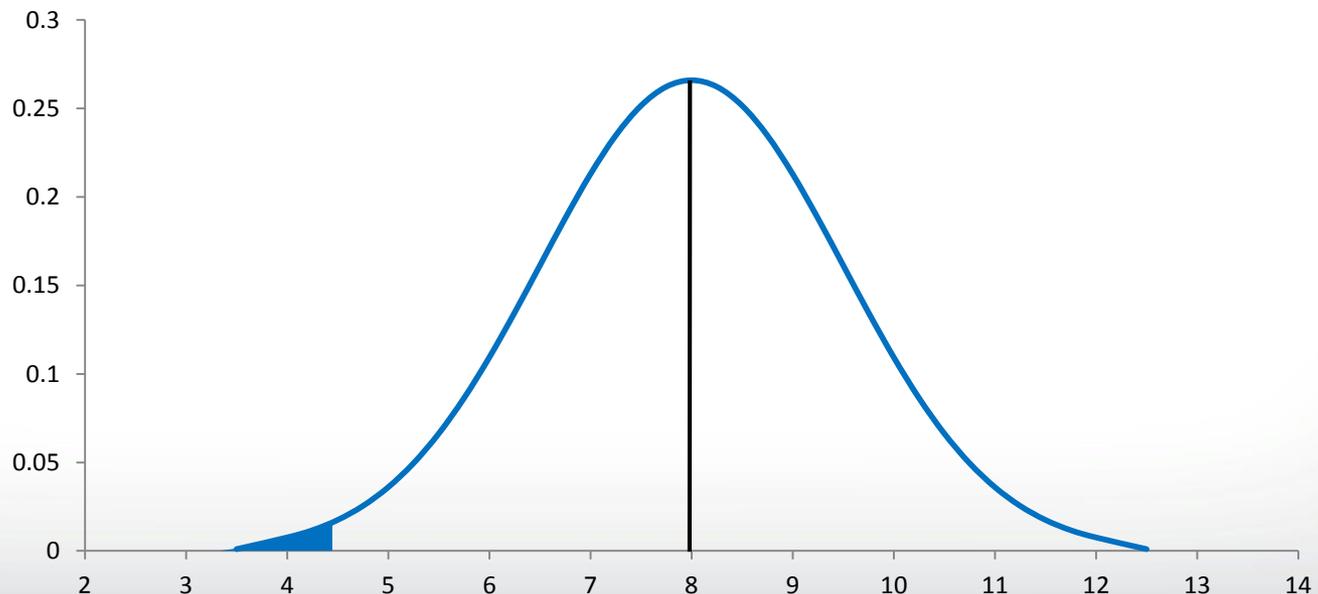
$$P(BMD_{\gamma}, t) = (0.10 * [1 - P(0, t)]) + P(0, t) = (0.1 * 0.99) + 0.01 = 0.109$$

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



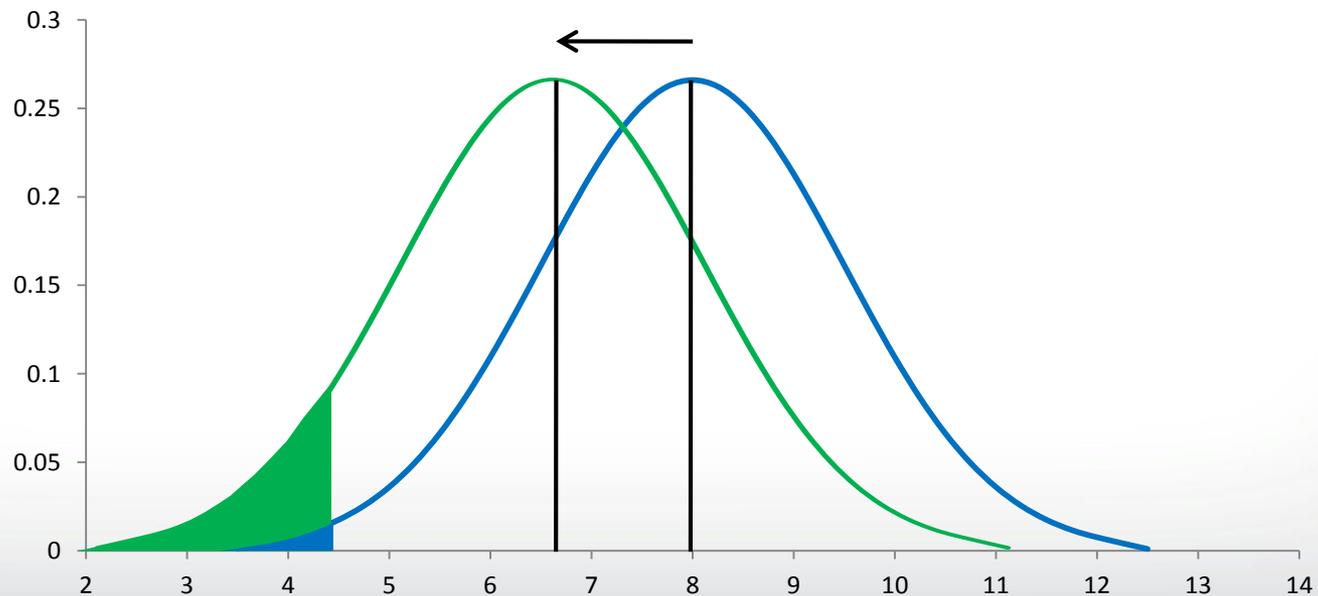
# The Hybrid Approach – Selecting the Background Rate

- **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



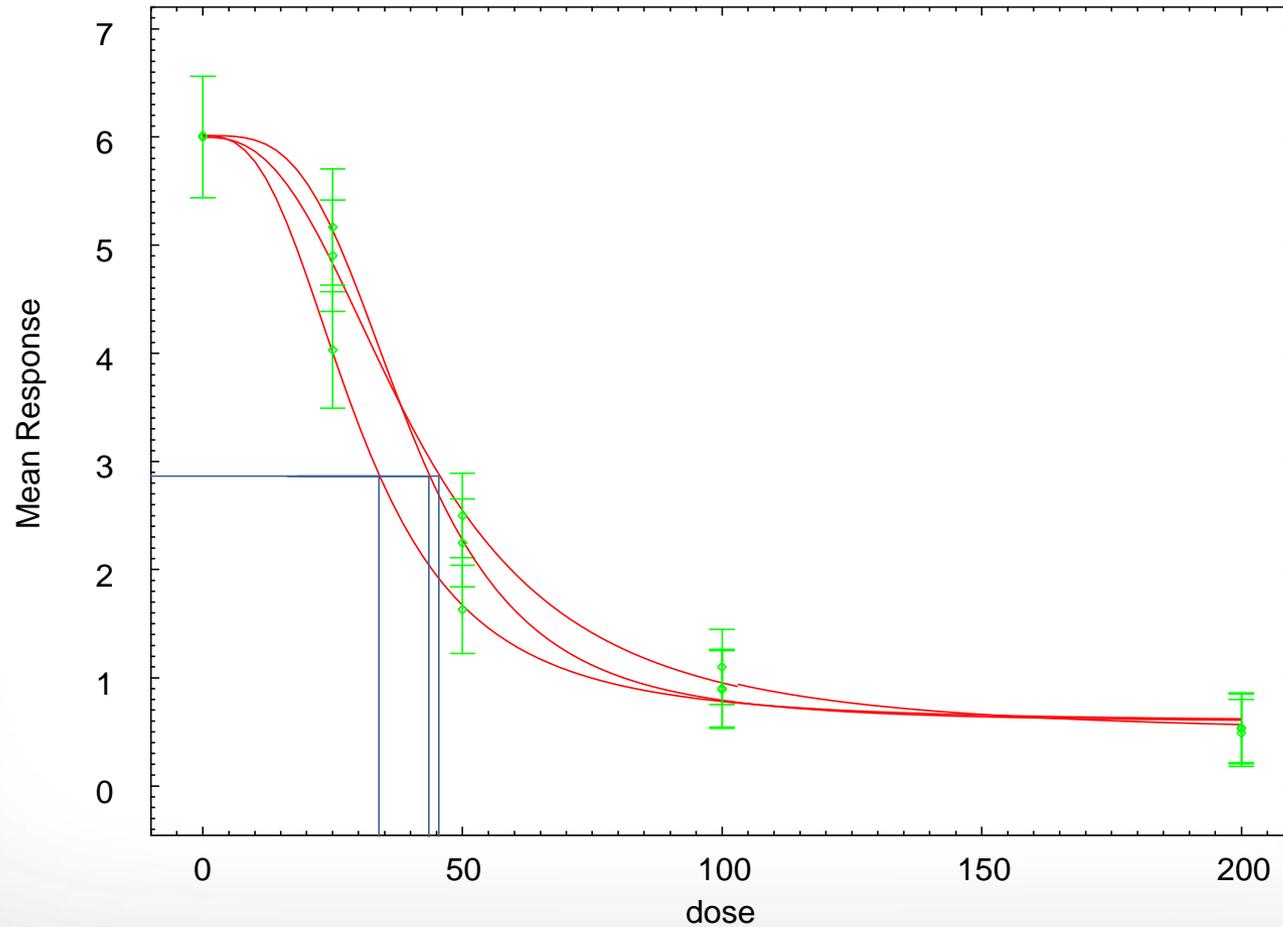


## Toxicodiffusion Model – Calculating the BMD

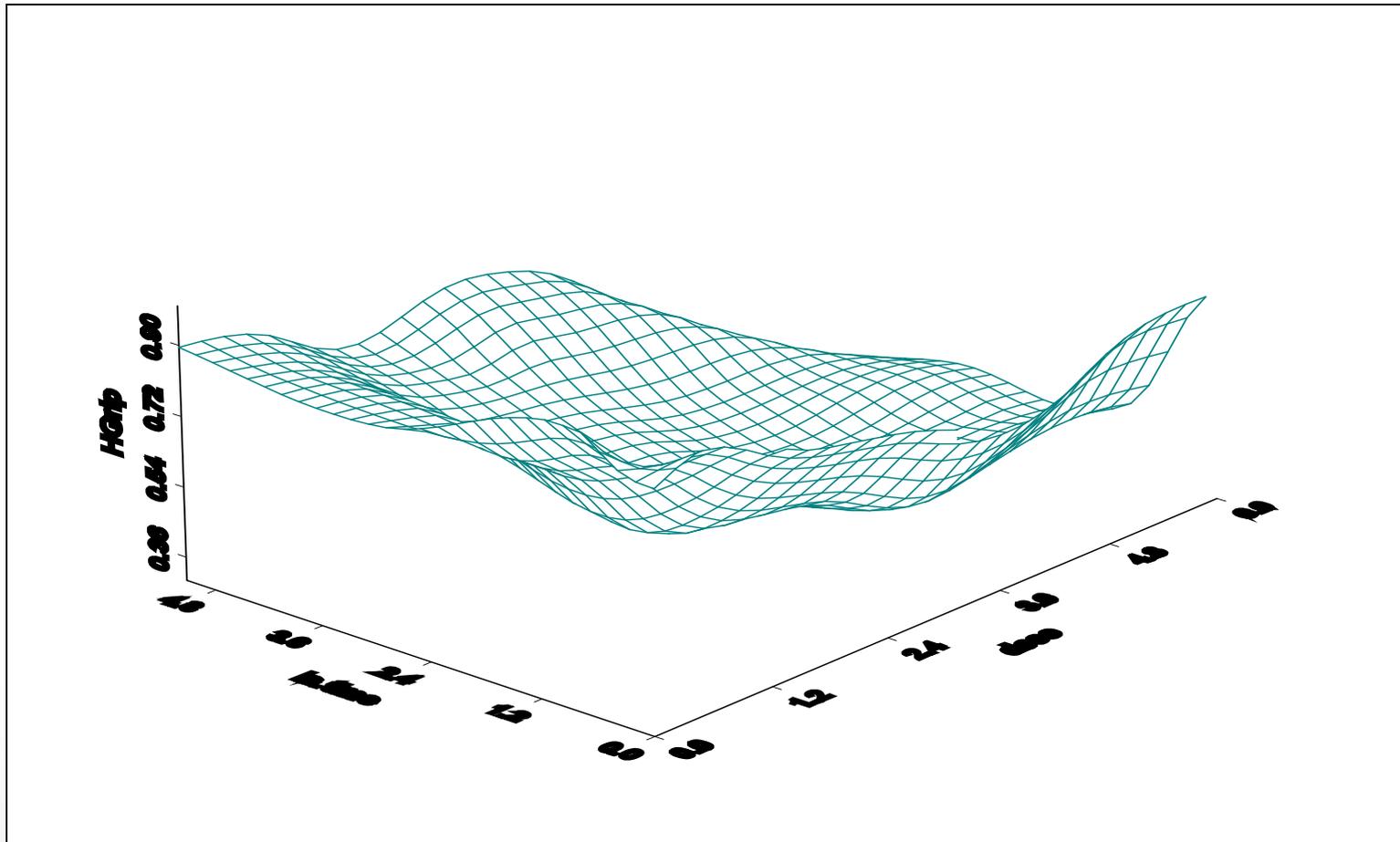
- In order to profile the **BMD** (i.e.,  $BMD_{\gamma}(t)$ ) with respect to time, a sequence of points  $\{t\}$  is chosen and the corresponding  $\{BMD_{\gamma}(t)\}$  values are calculated
- Given that response rates may vary over time, there may be multiple values of  $\{BMD_{\gamma}(t)\}$  that 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

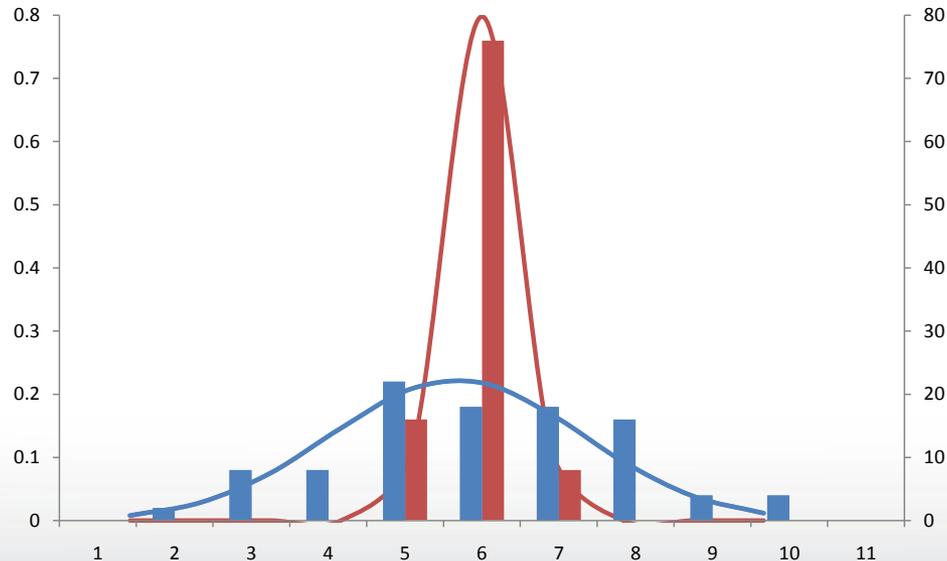




## Toxicodiffusion Model – Calculating the BMDL

- **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 5<sup>th</sup> percentile of a sampled set of BMDs would be reported as the 95% lower bound on the BMD, i.e., 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

BMDS 2.4 [Build: 04/01/2013] - [C:\Users\adavis10\BMDS240\Data\TETacForeGrip.dax]

File Edit View Tools Windows Help

File Edit Data Grid

Model Type: [ ] Model Name: [ ] [Proceed] [Trend Test]

	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			
185	840	6	0	1.225			

Ready

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# Select Model Type

BMDS 2.4 [Build: 04/01/2013] - [C:\Users\adavis10\BMDS240\Data\TETacForeGrip.dax]

File Edit View Tools Windows Help

File Edit Data Grid

Model Type:  Model Name:  **Proceed** **Trend Test**

- Continuous
- Dichotomous
- Dichotomous\_Alternative
- Nested\_Dichotomous
- Rptd\_Resp\_Measures**
- Conc\_x\_Time

			time	fore.grip	Col5	Col6	Col7
167			6	24	.555		
168			6	168	.75		
169			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		
185	840		6	0	1.225		

Ready

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# Toxicodiffusion Model Automatically Selected

BMDS 2.4 [Build: 04/01/2013] - [C:\Users\adavis10\BMDS240\Data\TETacForeGrip.dax]

File Edit View Tools Windows Help

File Edit Data Grid

Model Type: Rptd\_Resp\_Measures Model Name: ToxicoDiffusion\_beta Proceed Trend Test

	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			
185	840	6	0	1.225			

Ready

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# Toxicodiffusion Model – Column Assignments

BMDS 2.4 [Build: 04/01/2013] - [New]

File Edit View Tools Windows Help

<<Column Assignments>>

Animal ID	ID
Dose	dose
Time	time
Response	fore.grip

<<Other Assignments>>

Exposure Time	0
Background Degree	0
BMR Risk Type	Extra
BMR Risk Level	0.05
Adverse Direction	Lowertail
Adverse Definition	Background Rate
Adverse Level	0.05
Low Cut-off	-9999
High Cut-off	-9999

<<Plotting Assignments>>

Chart Title (optional)	
Time Axis Scale	Natural
# of Time Points	100

<<Parameter Assignments>>

Parameters	Options	Values
A0	Default	-9999
B0	Default	-9999
C0	Default	-9999

<< Study Description >>

Chemical Name	
Exposure Type	
Species Name	
Gender	

Study Name: ToxicoDiffusion Bootstrap BMDS MODEL RUN

Data File: C:\Users\adavis10\BMDS240\Data\TETacForeGrip.dax Show

Out File Name: C:\Users\adavis10\BMDS240\Data\txd\_TETacForeGrip\_Setting.out Set To... Run

Save Save As ... Set Values To Default Optimize Initial Param. Values Close

ToxicoDiffusion\_beta->Rptd\_Resp\_Measures

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# Toxicodiffusion Model – Plotting Assignments

BMDS 2.4 [Build: 04/01/2013] - [New]

File Edit View Tools Windows Help

<<Column Assignments>>

Animal ID	ID
Dose	dose
Time	time
Response	fore.grip

<<Plotting Assignments>>

Chart Title (optional)	
Time Axis Scale	Natural
# of Time Points	Natural

<<Parameter Assignments>>

Parameters	Options	Values
A0	Default	-9999
B0	Default	-9999
C0	Default	-9999

<<Other Assignments>>

Exposure Time	0
Background Degree	0
BMR Risk Type	Extra
BMR Risk Level	0.05
Adverse Direction	Lowertail
Adverse Definition	Background Rate
Adverse Level	0.05
Low Cut-off	-9999
High Cut-off	-9999

<< Study Description >>

Chemical Name	
Exposure Type	
Species Name	
Gender	

Study Name: ToxicoDiffusion Bootstrap BMDS MODEL RUN

Data File: C:\Users\adavis10\BMDS240\Data\TETacForeGrip.dax Show

Out File Name: C:\Users\adavis10\BMDS240\Data\txd\_TETacForeGrip\_Setting.out Set To... Run

Save Save As ... Set Values To Default Optimize Initial Param. Values Close

ToxicoDiffusion\_beta->Rptd\_Resp\_Measures

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# Toxicodiffusion Model – Other Assignments

BMDS 2.4 [Build: 04/01/2013] - [New]

File Edit View Tools Windows Help

<<Column Assignments>>

Animal ID	ID
Dose	dose
Time	time
Response	fore.grip

<<Plotting Assignments>>

Chart Title (optional)	
Time Axis Scale	Natural
# of Time Points	100

<<Parameter Assignments>>

Parameters	Options	Values
A0	Default	-9999
B0	Default	-9999
C0	Default	-9999

<<Other Assignments>>

Exposure Time	0
Background Degree	0
BMR Risk Type	Extra
BMR Risk Level	0.05
Adverse Direction	Lowertail
Adverse Definition	Background Rate
Adverse Level	0.05
Low Cut-off	-9999
High Cut-off	-9999

<< Study Description >>

Chemical Name	
Exposure Type	
Species Name	
Gender	

Study Name: ToxicoDiffusion Bootstrap BMDS MODEL RUN

Data File: C:\Users\adavis10\BMDS240\Data\TETacForeGrip.dax Show

Out File Name: C:\Users\adavis10\BMDS240\Data\txd\_TETacForeGrip\_Setting.out Set To... Run

Save Save As ... Set Values To Default Optimize Initial Param. Values Close

ToxicoDiffusion\_beta->Rptd\_Resp\_Measures

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# Toxicodiffusion Model – Other Assignments

BMDS 2.4 [Build: 04/01/2013] - [New]

File Edit View Tools Windows Help

File Edit View Tools Windows Help

<<Column Assignments>>

Animal ID	ID
Dose	dose
Time	time
Response	fore.grip

<<Plotting Assignments>>

Chart Title (optional)	
Time Axis Scale	Natural
# of Time Points	100

<<Parameter Assignments>>

Parameters	Options	Values
A0	Default	-9999
B0	Default	-9999
C0	Default	-9999

<<Other Assignments>>

Exposure Time	0
Background Degree	0
BMR Risk Type	Extra
BMR Risk Level	Extra
Adverse Direction	Lowertail
Adverse Definition	Background Rate
Adverse Level	0.05
Low Cut-off	-9999
High Cut-off	-9999

<< Study Description >>

Chemical Name	
Exposure Type	
Species Name	
Gender	

Study Name: ToxicoDiffusion Bootstrap BMDS MODEL RUN

Data File: C:\Users\adavis10\BMDS240\Data\TETacForeGrip.dax Show

Out File Name: C:\Users\adavis10\BMDS240\Data\txd\_TETacForeGrip\_Setting.out Set To... Run

Save Save As ... Set Values To Default Optimize Initial Param. Values Close

ToxicoDiffusion\_beta->Rptd\_Resp\_Measures

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# Toxicodiffusion Model – Other Assignments

BMDS 2.4 [Build: 04/01/2013] - [New]

File Edit View Tools Windows Help

Column Assignments

Animal ID	ID
Dose	dose
Time	time
Response	fore.grip

Plotting Assignments

Chart Title (optional)	
Time Axis Scale	Natural
# of Time Points	100

Parameter Assignments

Parameters	Options	Values
A0	Default	-9999
B0	Default	-9999
C0	Default	-9999

Other Assignments

Exposure Time	0
Background Degree	0
BMR Risk Type	Extra
BMR Risk Level	0.05
Adverse Direction	Lowertail
Adverse Definition	Background Rate
Adverse Level	0.05
Low Cut-off	-9999
High Cut-off	-9999

Study Description

Chemical Name	
Exposure Type	
Species Name	
Gender	

Study Name: ToxicoDiffusion Bootstrap BMDS MODEL RUN

Data File: C:\Users\adavis10\BMDS240\Data\TETacForeGrip.dax Show

Out File Name: C:\Users\adavis10\BMDS240\Data\txd\_TETacForeGrip\_Setting.out Set To...

Run

Save Save As ... Set Values To Default Optimize Initial Param. Values Close

ToxicoDiffusion\_beta->Rptd\_Resp\_Measures

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# Toxicodiffusion Model – Other Assignments

BMDS 2.4 [Build: 04/01/2013] - [New]

File Edit View Tools Windows Help

<<Column Assignments>>

Animal ID	ID
Dose	dose
Time	time
Response	fore.grip

<<Plotting Assignments>>

Chart Title (optional)	
Time Axis Scale	Natural
# of Time Points	100

<<Parameter Assignments>>

Parameters	Options	Values
A0	Default	-9999
B0	Default	-9999
C0	Default	-9999

<<Other Assignments>>

Exposure Time	0
Background Degree	0
BMR Risk Type	Extra
BMR Risk Level	0.05
Adverse Direction	Lowertail
Adverse Definition	Background Rate
Adverse Level	Background Rate Cut Point
Low Cut-off	-9999
High Cut-off	-9999

<< Study Description >>

Chemical Name	
Exposure Type	
Species Name	
Gender	

Study Name: ToxicoDiffusion Bootstrap BMDS MODEL RUN

Data File: C:\Users\adavis10\BMDS240\Data\TETacForeGrip.dax Show

Out File Name: C:\Users\adavis10\BMDS240\Data\txd\_TETacForeGrip\_Setting.out Set To... Run

Save Save As ... Set Values To Default Optimize Initial Param. Values Close

ToxicoDiffusion\_beta->Rptd\_Resp\_Measures

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# Toxicodiffusion Model – Other Assignments

BMDS 2.4 [Build: 04/01/2013] - [New]

File Edit View Tools Windows Help

File Edit View Tools Windows Help

**<<Column Assignments>>**

<b>Animal ID</b>	ID
<b>Dose</b>	dose
<b>Time</b>	time
<b>Response</b>	fore.grip

**<<Plotting Assignments>>**

<b>Chart Title (optional)</b>	
<b>Time Axis Scale</b>	Natural
<b># of Time Points</b>	100

**<<Parameter Assignments>>**

Parameters	Options	Values
A0	Default	-9999
B0	Default	-9999
C0	Default	-9999

**<<Other Assignments>>**

<b>Adverse Definition</b>	Background Rate
<b>Adverse Level</b>	0.05
<b>Low Cut-off</b>	-9999
<b>High Cut-off</b>	-9999
<b>Use Two Sided CI?</b>	<input type="checkbox"/>
<b>Confidence Level</b>	0.05
<b>Bootstrap Iterations</b>	100
<b>Save Bootstrap Result?</b>	<input type="checkbox"/>

**<< Study Description >>**

<b>Chemical Name</b>	
<b>Exposure Type</b>	
<b>Species Name</b>	
<b>Gender</b>	

**Study Name:** ToxicoDiffusion Bootstrap BMDS MODEL RUN

**Data File:** C:\Users\adavis10\BMDS240\Data\TETacForeGrip.dax

**Out File Name:** C:\Users\adavis10\BMDS240\Data\txd\_TETacForeGrip\_Setting.out

ToxicoDiffusion\_beta->Rptd\_Resp\_Measures

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BMDS 2.4 [Build: 04/01/2013] - [C:/Users/adavis10/BMDS240/Data/TETacForeGrip.out]

File Edit View Tools Windows Help

File Edit Preferences

Analysis of Toxicodiffusion Bootstrap BMDS MODEL RUN  
STUDY DESCRIPTION  
Dose Levels: 0 0.75 1.5 3 6  
Test Times: 0 2 24 168  
Exposure Time: 0  
Sample Size: 198

DOSE-RESPONSE MODELING  
A+B\*dose\*time\*exp(-K\*time)/(1+C\*dose\*time\*exp(-K\*time))

AIC	BIC	logLik
-99.76988	-80.04027	55.88494

Random effects:  
Formula: A ~ 1 | ID  
A Residual  
StdDev: 0.08384292 0.16723250

Fixed effects:

	Value	Std.Error	DF	t-value	p-value
A	1.02558328	0.021766397	145	47.117732	8.499645e-90
B.dose	-0.01373109	0.006012917	145	-2.283599	2.384794e-02
C.dose	0.02673254	0.017756512	145	1.505507	1.343692e-01
K	0.01991699	0.002467258	145	8.072523	2.409297e-13

Correlation:

	A	B.dose	C.dose	K
A	1.0000000	-0.4672524	0.3598873	0.0548682
B.dose	-0.4672524	1.0000000	-0.9504070	-0.5524777
C.dose	0.3598873	-0.9504070	1.0000000	0.4633031
K	0.0548682	-0.5524777	0.4633031	1.0000000

Standardized Within-Group Residuals:

Min	Q1	Med	Q3	Max
-2.66913962	-0.50714699	-0.03634028	0.72698913	2.44610785

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# Toxicodiffusion Model – Results

BMDS 2.4 [Build: 04/01/2013] - [C:/Users/adavis10/BMDS240/Data/TETacForeGrip.out]

File Edit View Tools Windows Help

File Edit Preferences

Correlation:

	A	B.dose	C.dose	K
A	1.0000000	-0.4672524	0.3598873	0.0548682
B.dose	-0.4672524	1.0000000	-0.9504070	-0.5524777
C.dose	0.3598873	-0.9504070	1.0000000	0.4633031
K	0.0548682	-0.5524777	0.4633031	1.0000000

Standardized Within-Group Residuals:

Min	Q1	Med	Q3	Max
-2.66913962	-0.50714699	-0.03634028	0.72698913	2.44610785

Initial Values: 1.018812 -0.03783458 0.0835662 0.01713397

Possible Initial Values

	A0	B0	C0	K0
1	1.018812	-0.037834581	0.08356620	0.01713397
2	1.018812	-0.021291539	0.06687200	0.02608923
3	1.018812	-0.003587980	0.01375968	0.01725628
4	1.018812	-0.006326717	-0.06284446	0.02118212
5	1.018812	-0.013809128	0.04031584	0.01921920
6	1.018812	-0.017260204	0.02533835	0.02041540

**BENCHMARK DOSE ESTIMATION**

Risk Type: extra  
Spontaneous Risk Level: 5 %  
Area of Adverse Effects: Lowertail  
BMR Level: 5 %

**BOOTSTRAP ESTIMATION OF BMDL**

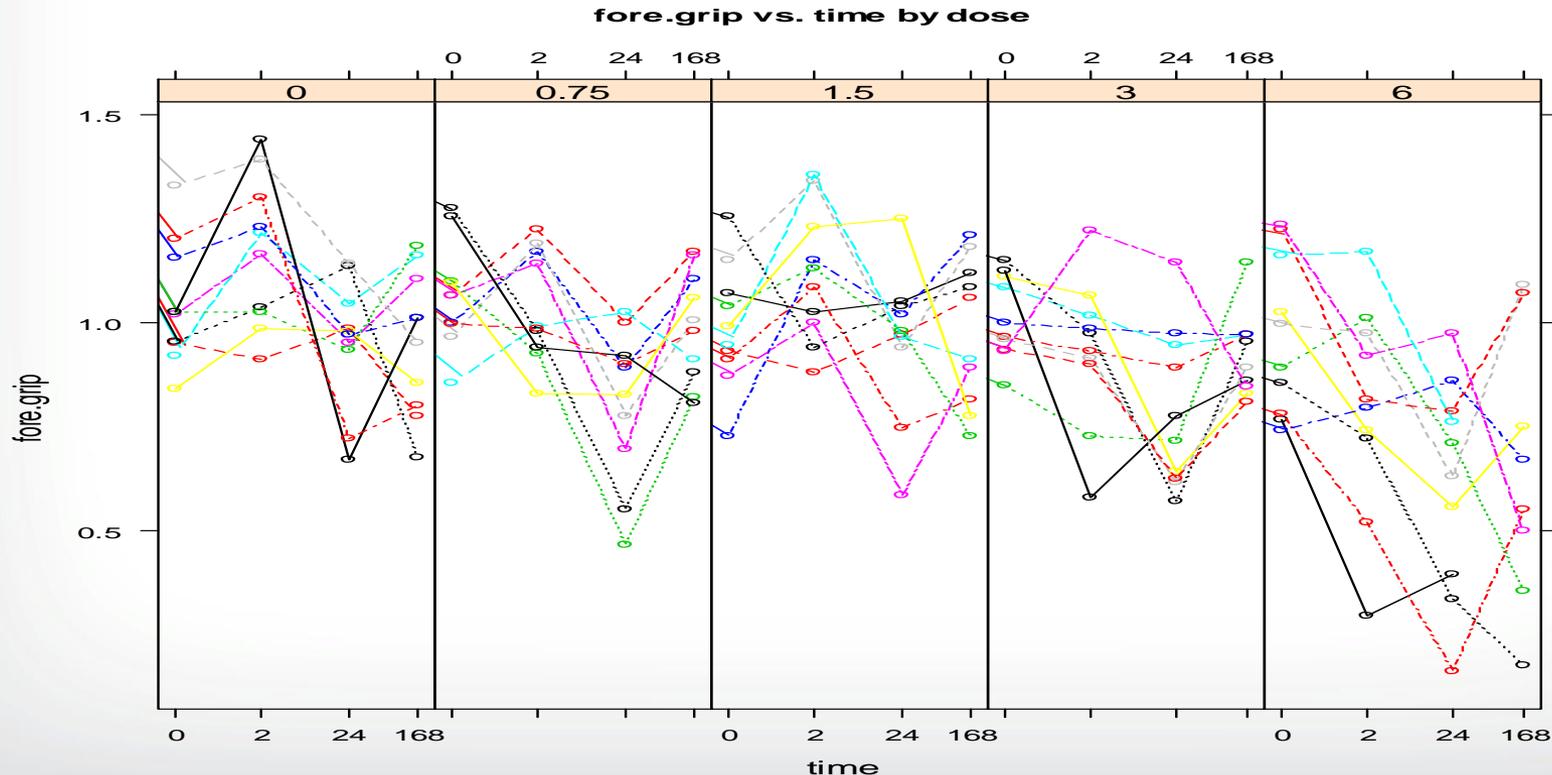
Bootstrap Replications: 100  
Minimum BMD: 0.259562  
At Test Time: 50.4  
Conf. Level: 95 %  
BMDL: 0.178158

Image file successfully drawn! Num Lock



# Toxicodiffusion Model – Plots and Assessing Fit

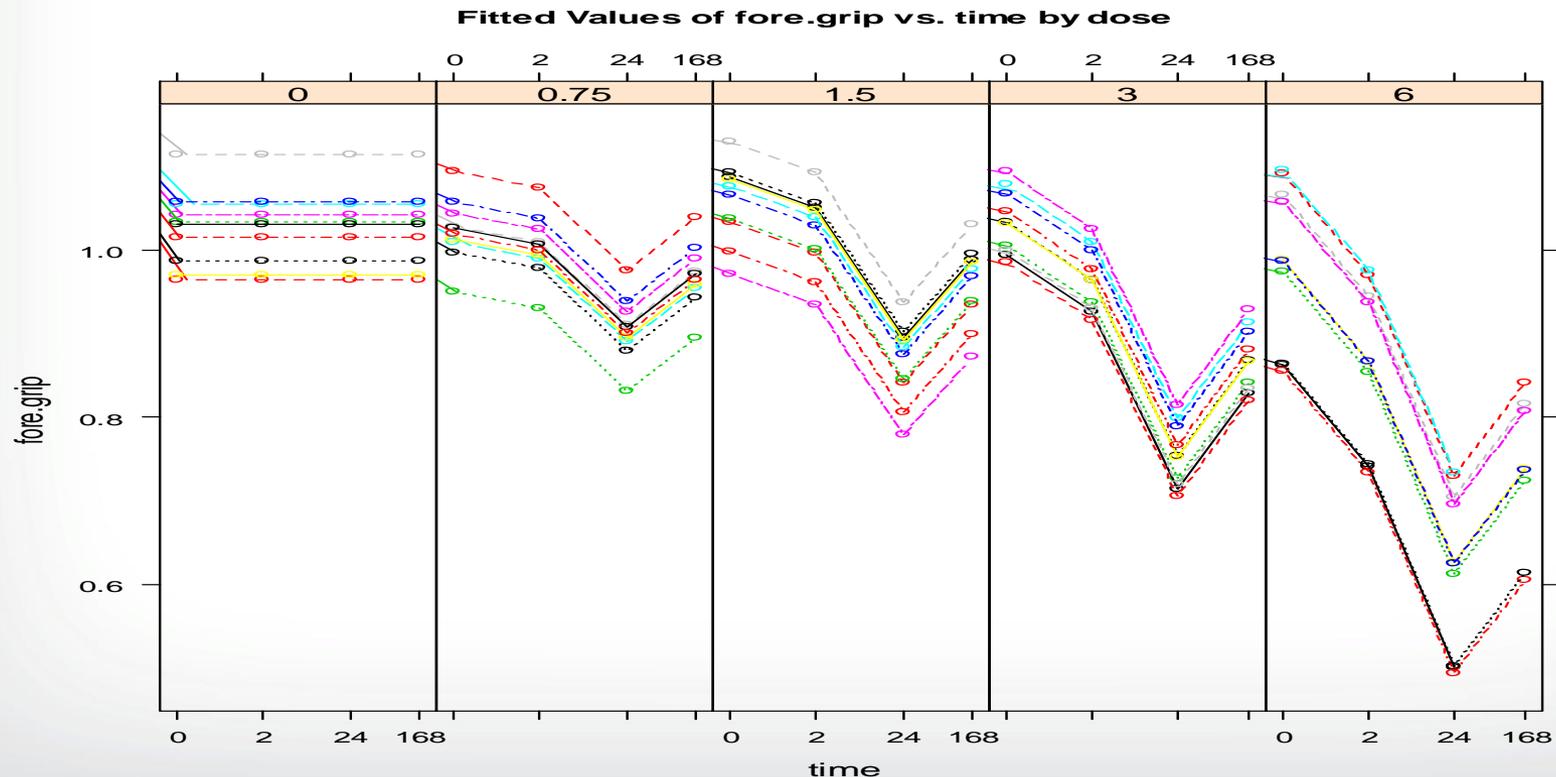
- **Observed trajectory** – displays each subject's responses by connecting the observed responses across time
  - Useful for determining the trajectory of the control group and how exposure changes the trajectory over time





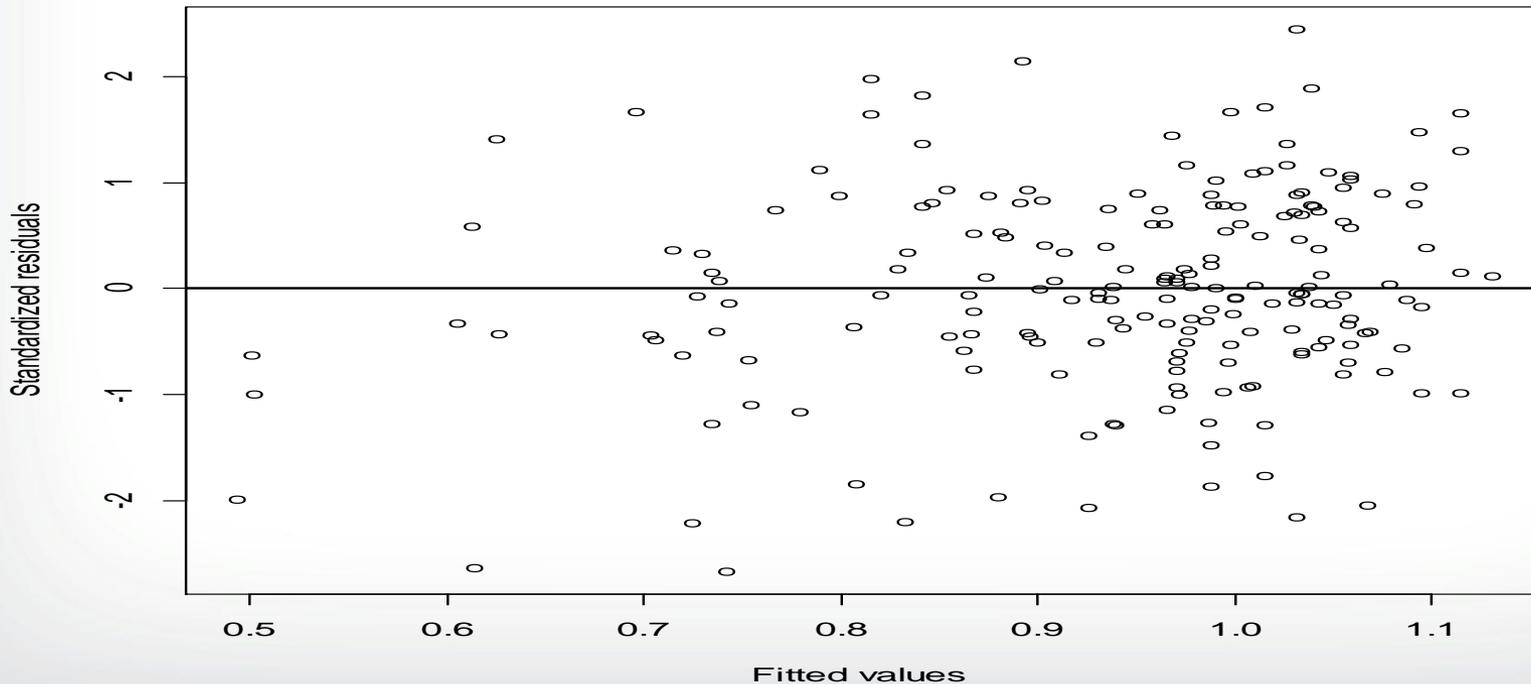
# Toxicodiffusion Model – Plots and Assessing Fit

- **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



- **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

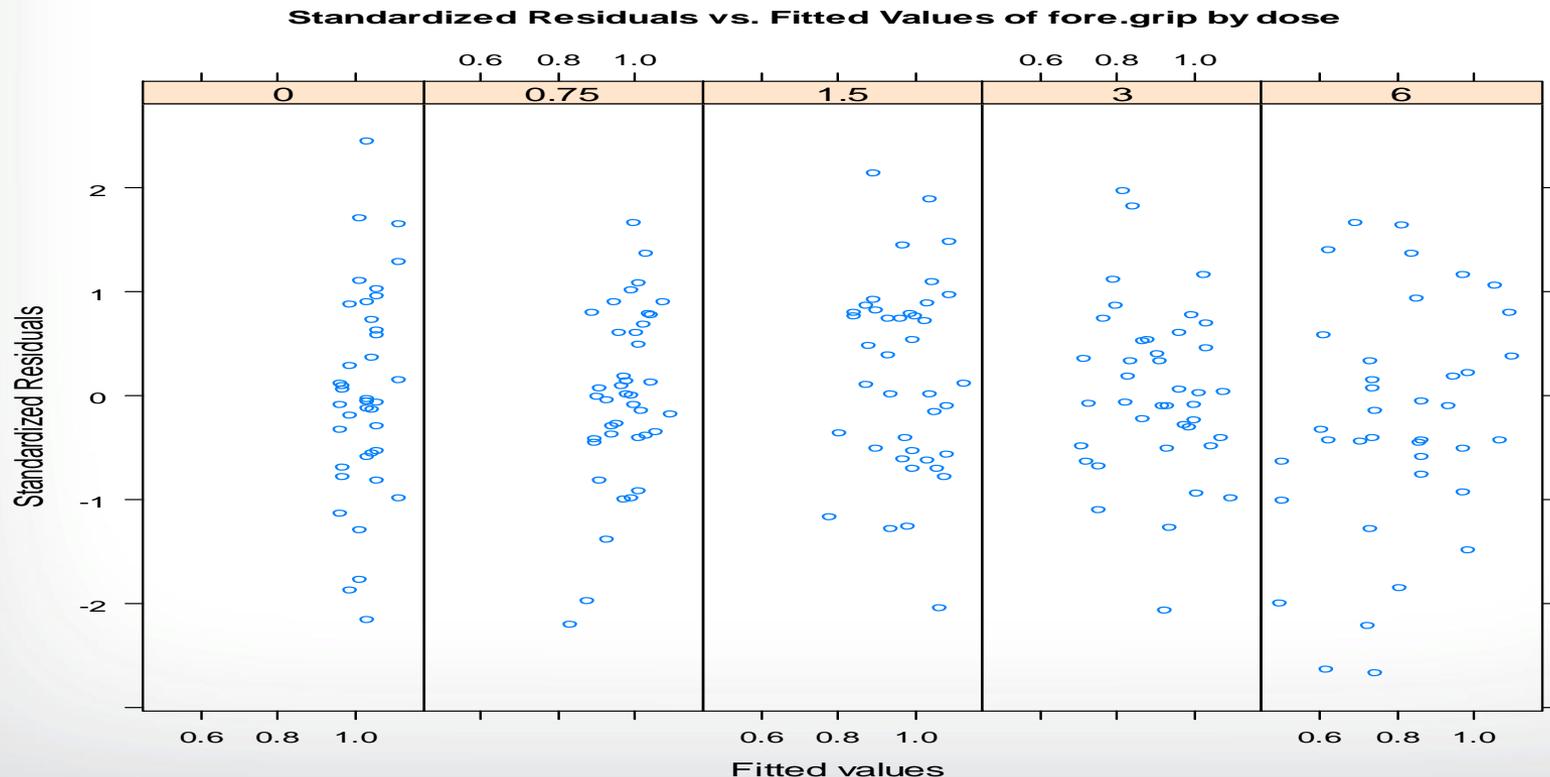
Standardized Residuals vs. Fitted values of fore.grip





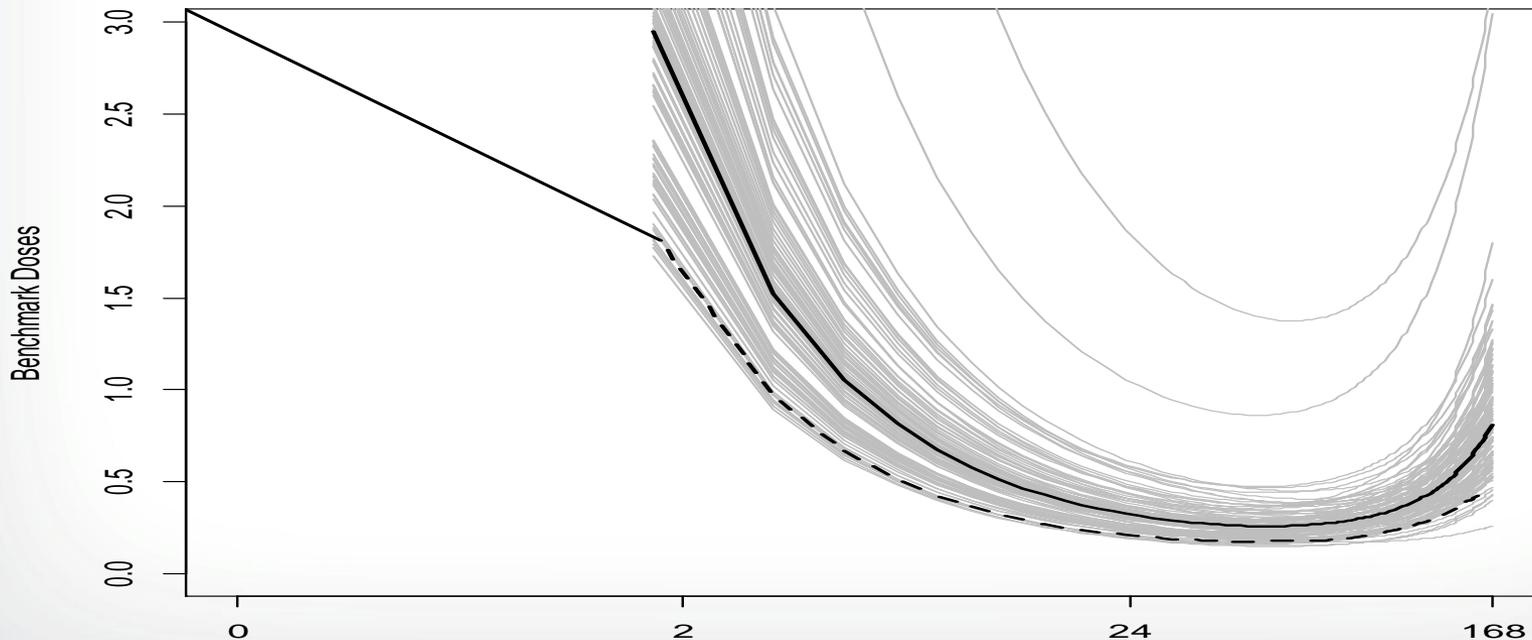
# Toxicodiffusion Model – Plots and Assessing Fit

- **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



- **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)

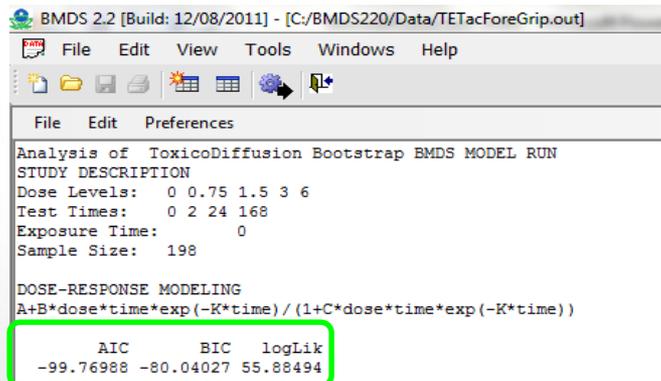
**BMD Time-Profile Based on fore.grip  
( extra Risk at 5 % BMR Level)**



Dashed lines(s) is 95 % Confidence Band(s)

- 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.,  $A(t) = A_0 + A_1t$ ) may be more appropriate
- The **AIC** and **BIC** values to assess whether the addition of an extra parameter improves model fit.

$$A(t) = A_0$$



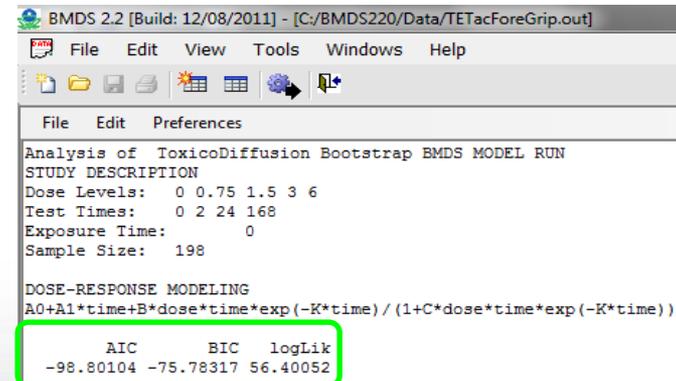
```

BMDS 2.2 [Build: 12/08/2011] - [C:/BMDS220/Data/TETacForeGrip.out]
File Edit View Tools Windows Help
File Edit Preferences
Analysis of ToxicoDiffusion Bootstrap BMDs MODEL RUN
STUDY DESCRIPTION
Dose Levels: 0 0.75 1.5 3 6
Test Times: 0 2 24 168
Exposure Time: 0
Sample Size: 198

DOSE-RESPONSE MODELING
A+B*dose*time*exp(-K*time)/(1+C*dose*time*exp(-K*time))

AIC      BIC      logLik
-99.76988 -80.04027 55.88494
    
```

$$A(t) = A_0 + A_1t$$



```

BMDS 2.2 [Build: 12/08/2011] - [C:/BMDS220/Data/TETacForeGrip.out]
File Edit View Tools Windows Help
File Edit Preferences
Analysis of ToxicoDiffusion Bootstrap BMDs MODEL RUN
STUDY DESCRIPTION
Dose Levels: 0 0.75 1.5 3 6
Test Times: 0 2 24 168
Exposure Time: 0
Sample Size: 198

DOSE-RESPONSE MODELING
A0+A1*time+B*dose*time*exp(-K*time)/(1+C*dose*time*exp(-K*time))

AIC      BIC      logLik
-98.80104 -75.78317 56.40052
    
```



# *Toxicodiffusion Modeling Exercise*



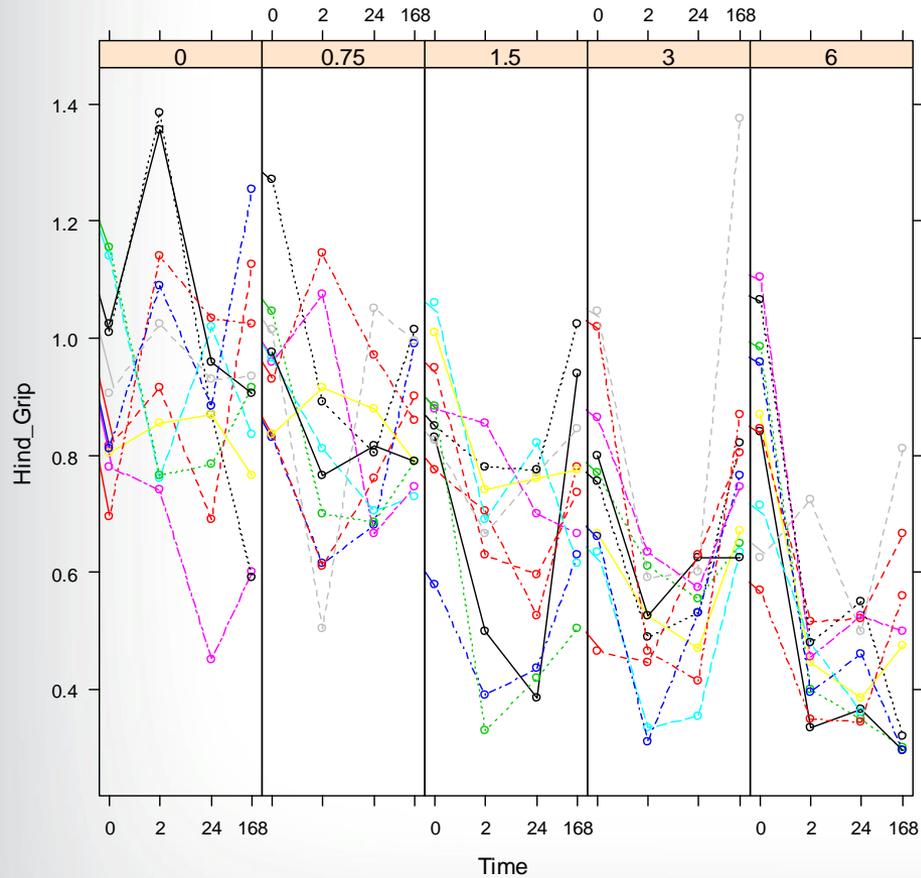
# Toxicodiffusion Modeling Exercise

- **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

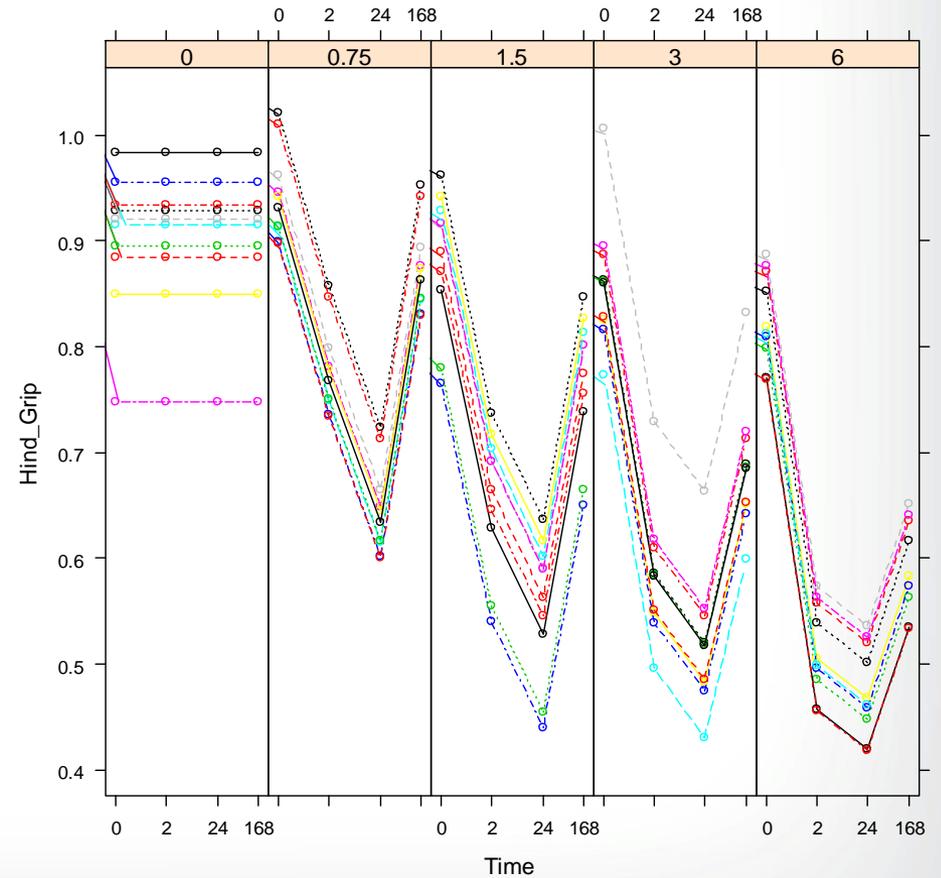


# Toxicodiffusion Modeling Exercise – Results

Hind\_Grip vs. Time by Dose



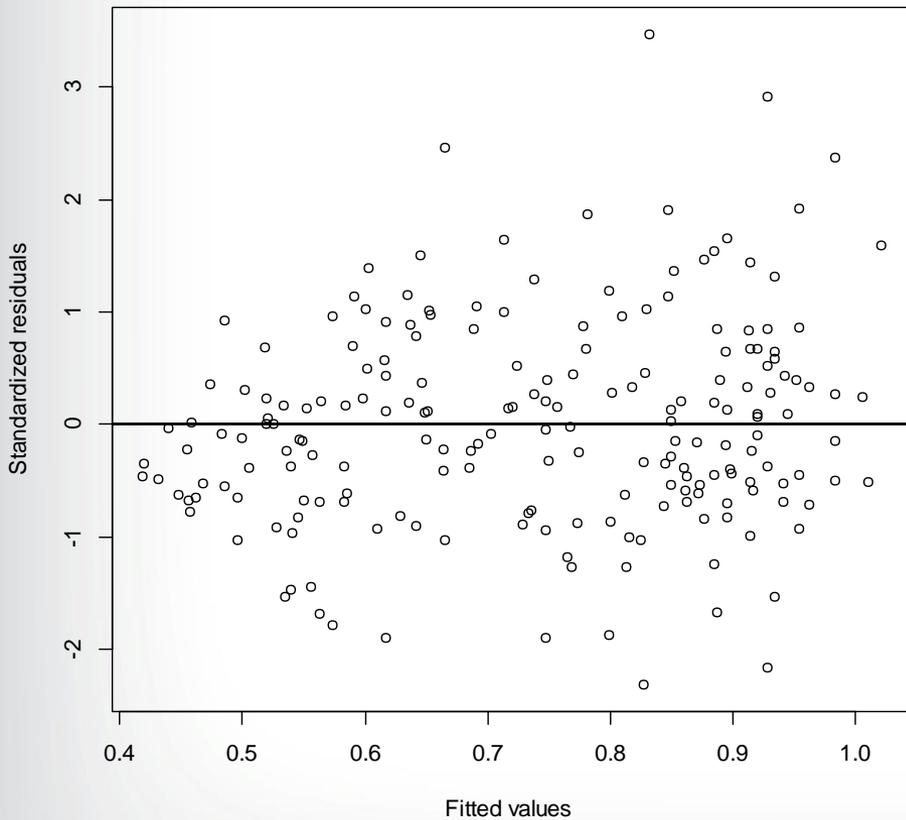
Fitted Values of Hind\_Grip vs. Time by Dose



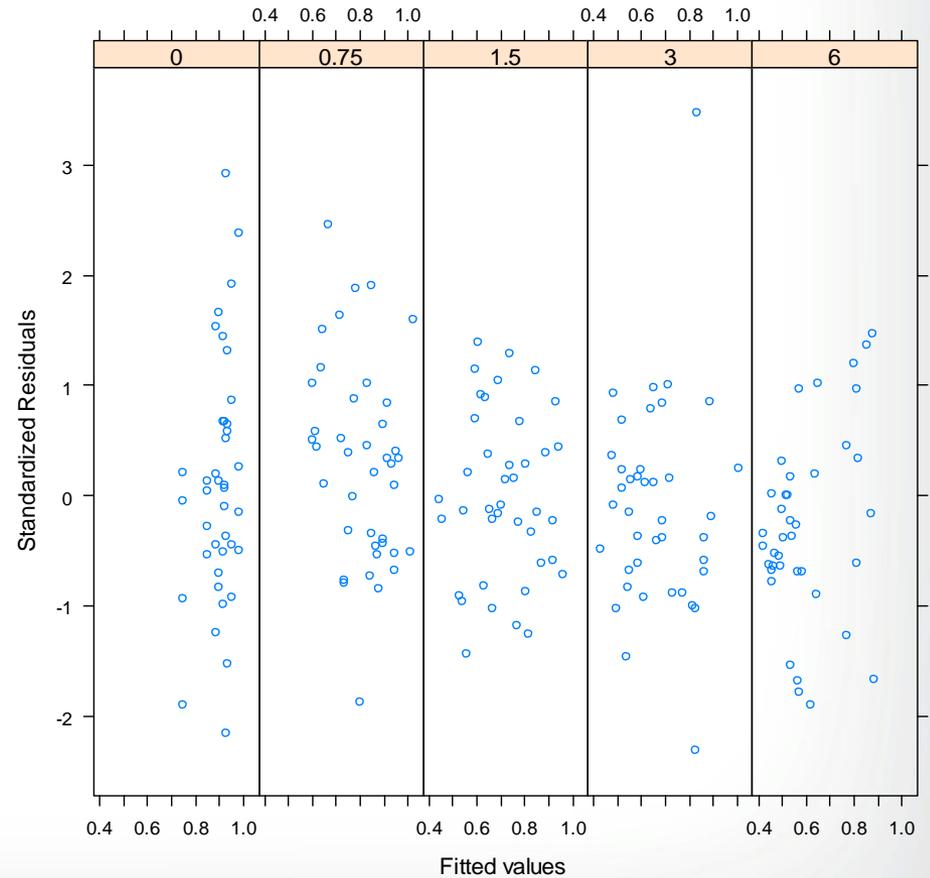


# Toxicodiffusion Modeling Exercise – Results

Standardized Residuals vs. Fitted values of Hind\_Grip



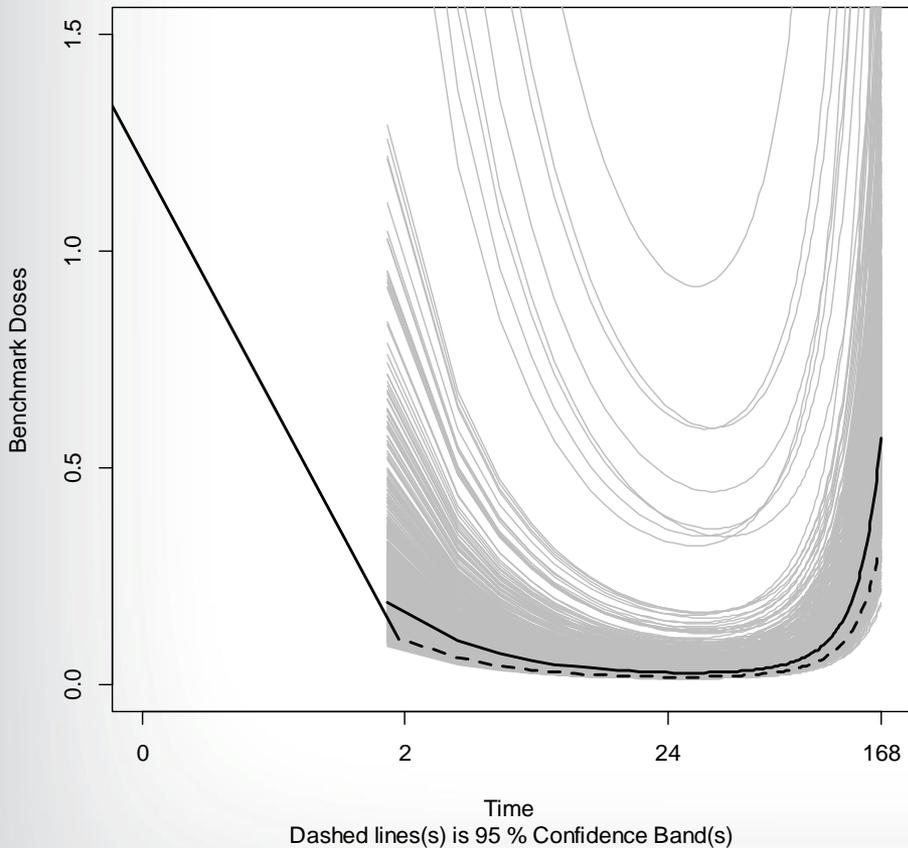
Standardized Residuals vs. Fitted Values of Hind\_Grip by Dose





# Toxicodiffusion Modeling Exercise – Results

BMD Time-Profile Based on Hind\_Grip  
(extra Risk at 5 % BMR Level)



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	



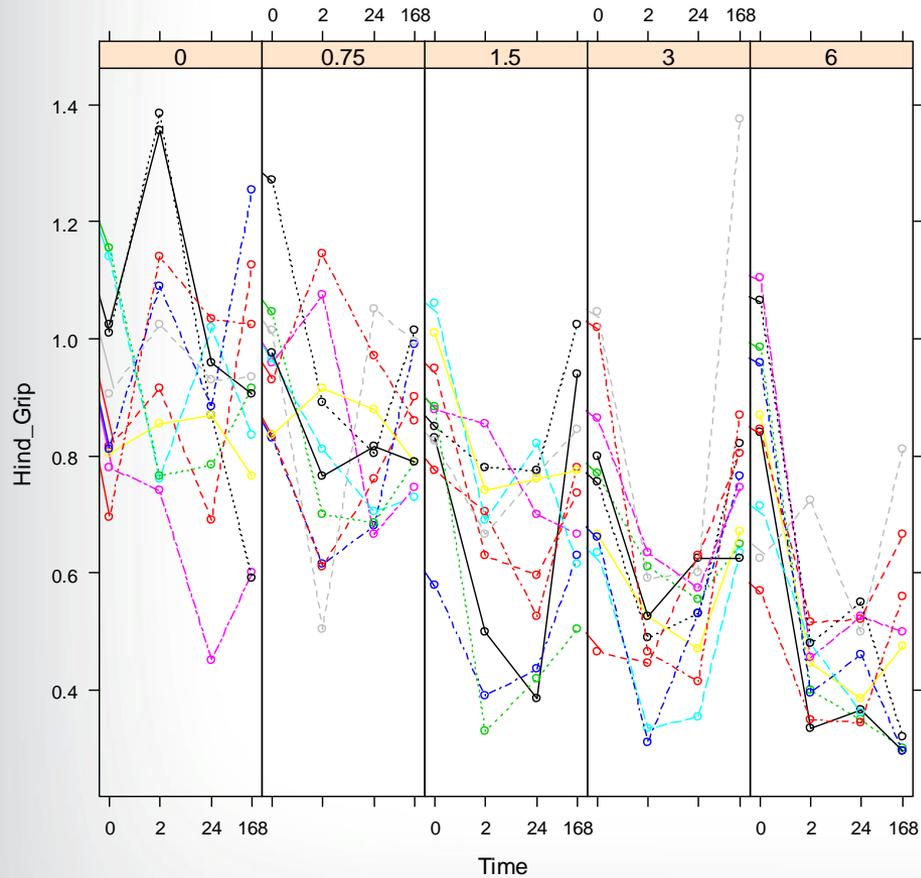
# Toxicodiffusion Modeling Exercise – Results

- **Open hind\_grip\_AI.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

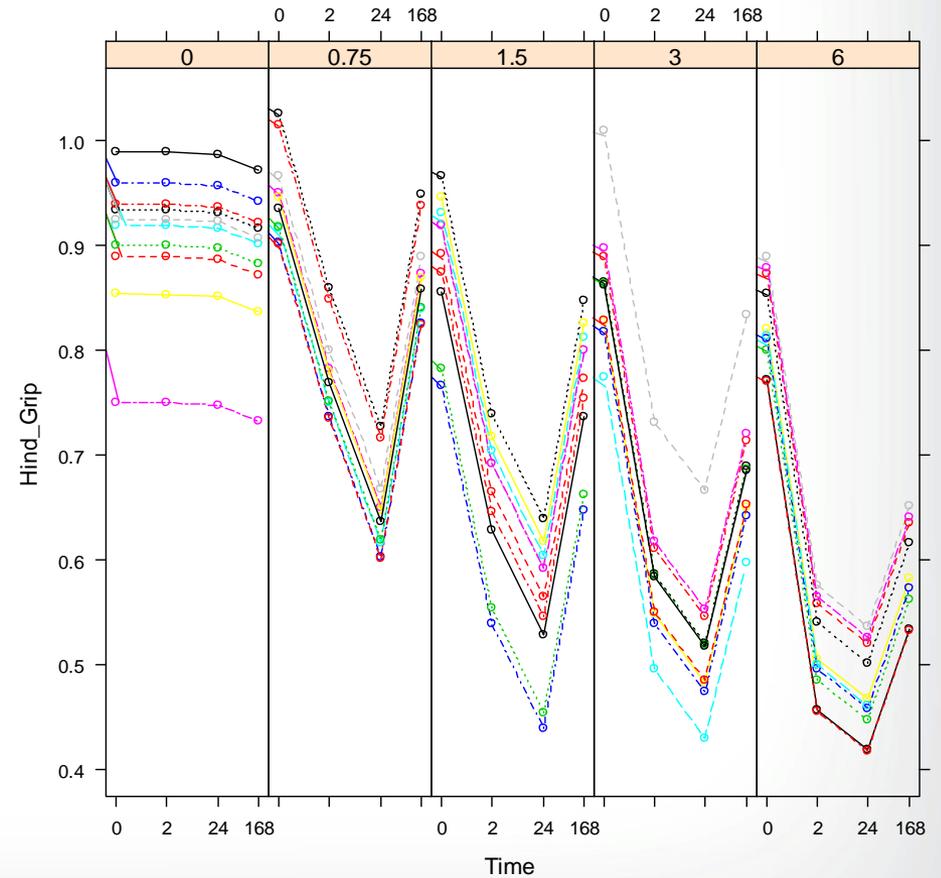


# Toxicodiffusion Modeling Exercise – Results

Hind\_Grip vs. Time by Dose



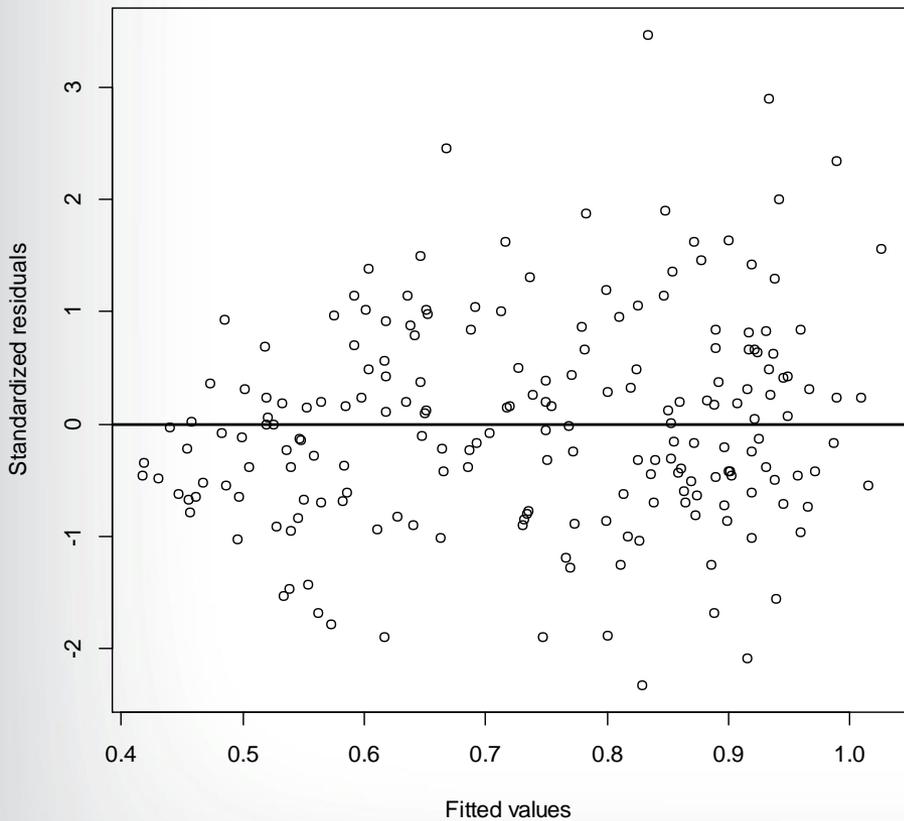
Fitted Values of Hind\_Grip vs. Time by Dose



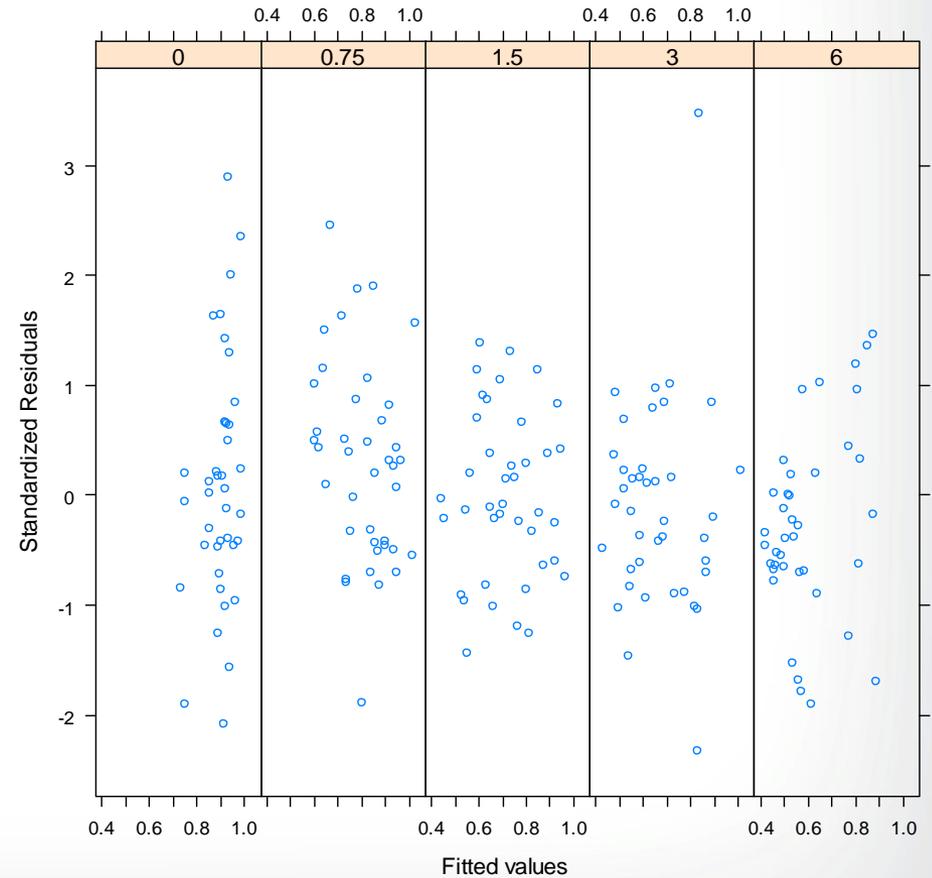


# Toxicodiffusion Modeling Exercise – Results

Standardized Residuals vs. Fitted values of Hind\_Grip



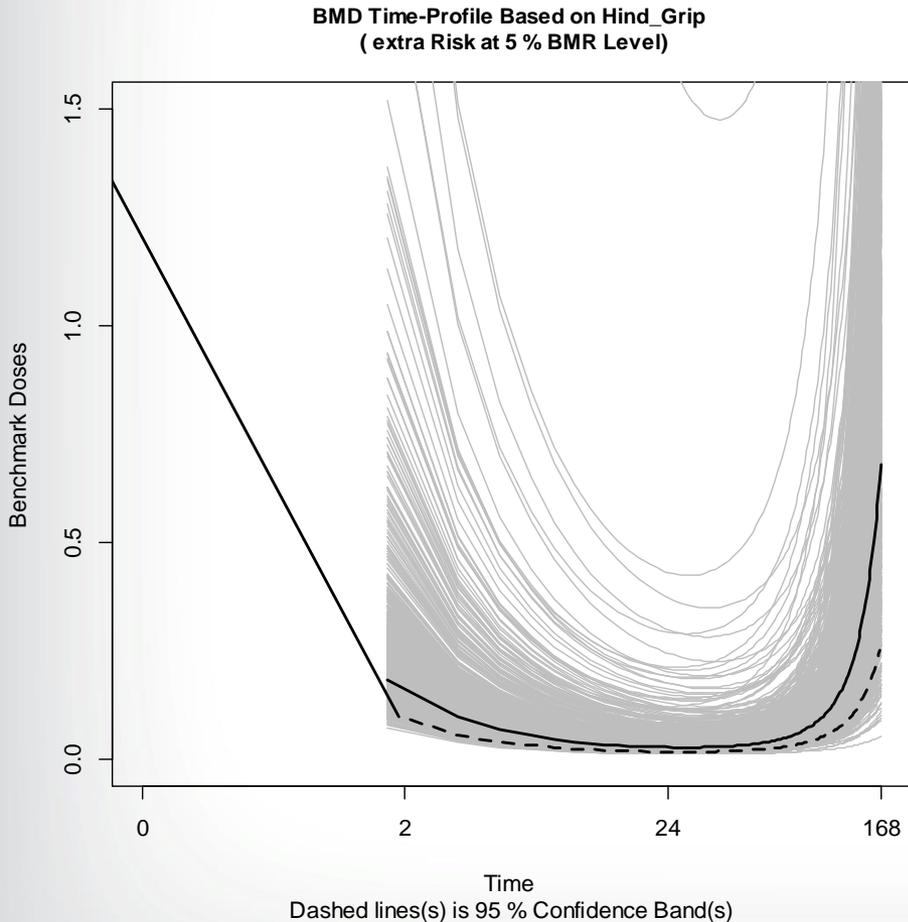
Standardized Residuals vs. Fitted Values of Hind\_Grip by Dose





# 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 $\times$ Time ( $C \times T$ ) 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
<i>Local irritants</i>		
NH <sub>3</sub>	2.0	(1.6, 2.4)
HCl	1.0	(0.7, 1.3)
ClF <sub>5</sub>	2.0	(1.4, 2.6)
NO <sub>2</sub>	3.5	(2.7, 4.3)
Cl <sub>2</sub>	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 <sub>2</sub>	2.2	(2.0, 2.4)
Dibutylhexamethylenediamine	1.0	(0.6, 1.4)
<i>Systemic action</i>		
HCN	2.7	(1.8, 3.7)
H <sub>2</sub> S	2.2	(1.6, 2.7)
Methyl t-butyl ether	2.0	(1.0, 2.9)
CH <sub>2</sub> ClBr	1.6	(1.4, 1.8)
C <sub>2</sub> H <sub>4</sub> Br <sub>2</sub>	1.2	(1.1, 1.2)
C <sub>2</sub> Cl <sub>4</sub>	2.0	(1.4, 2.6)
C <sub>2</sub> HCl <sub>3</sub>	0.8	(0.3, 1.4)
CCl <sub>4</sub>	2.8	(1.9, 3.7)
Acrylonitrile	1.1	(1.0, 1.2)

- **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:**

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

- $b_0, b_1 \dots$  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  $f_c(c)$ ,  $f_t(t)$ ,  $f_x(x)$  terms
  - Number of product terms is limited to 2 currently
  - Inclusion of product terms may lead to difficulties in model interpretability

- **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

BMDS 2.4 [Build: 04/01/2013] - [C:\Users\adavis10\BMDS240\Data\clu\_in\tenBerge\_demo.dax]

File Edit View Tools Windows Help

Model Type:  Model Name:  Proceed Trend Test

	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		

Ready

58 row(s) added. Num Lock



# Select "Conc x Time" for Model Type

BMDS 2.4 [Build: 04/01/2013] - [C:\Users\adavis10\BMDS240\Data\clu\_in\tenBerge\_demo.dax]

File Edit View Tools Windows Help

File Edit Data Grid

Model Type: Continuous Model Name:  Proceed Trend Test

Continuous  
Dichotomous  
Dichotomous\_Alternative  
Nested\_Dichotomous  
Rptd\_Resp\_Measures  
Conc\_x\_Time

		BodyWeight	Exposed	Dead	Col6	Col7
1	5	222	10	0		
2	10	217	10	1		
3	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	

Ready

58 row(s) added.

Num Lock



# ten Berge Model is Automatically Selected

BMDS 2.4 [Build: 04/01/2013] - [C:\Users\adavis10\BMDS240\Data\clu\_in\tenBerge\_demo.dax]

File Edit View Tools Windows Help

Model Type: Conc\_x\_Time Model Name: tenBerge Proceed Trend Test

	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		

Ready

58 row(s) added. Num Lock



# Ten Berge Model Option Screen

BMDS 2.4 [Build: 04/01/2013] - [TenBerge Model]

File Edit View Tools Windows Help

File

<< Dataset: C:\Users\sladavis\10\BMDS240\Data\clu\_intenBerge\_demo.dax >>

	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		

<< Column Assignments >>

Description	Column	Transform.	Main Effect
# Subjects			
Incidence			
Explanatory Var1		none	<input type="checkbox"/>
Explanatory Var2		none	<input type="checkbox"/>
Explanatory Var3		none	<input type="checkbox"/>

<< Product Terms >>

1		
2		
3		

Model **Probit** Background Correction **1** Out File

Description	Calculate Dose For Given Response	Calc'd Response For Given Exp. Vars	Ratio of Parameters For Two Exp. Vars
Calculations Desired?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Compute Confidence Interval?	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Std. Deviation for Confidence Interval	1.96	1.96	1.96
% Response of Interest	95		

Ratio for Parameters  And

<< Calculated Dose >>

Find Corr. Value For		
When	=	

<< Calculated Response >>

When		
When	=	

For accurate results, please ensure the dataset structure conforms to this sequence:

- The first columns in the dataset should be the Main Effect columns (e.g. Dose and Time). These columns can be in any order but they must appear first.
- The final columns in the dataset should be the # Subjects and Incidence columns. IN THAT ORDER.
- Other columns (e.g. Age, Litter) can appear in any order following the Main Effect columns but before the # Subjects and Incidence.

Run Save Save As ... Close

58 row(s) added. Num Lock



# Ten Berge Model – Column Assignments

BMDS 2.4 [Build: 04/01/2013] - [TenBerge Model]

File Edit View Tools Windows Help

File

<< Dataset: C:\Users\ladavis10\BMDs2401Data\clu\_intenBerge\_demo.dax >>

	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		

<< Column Assignments >>

Description	Column	Transform.	Main Effect
# Subjects			
Incidence			
Explanatory Var1	Exposure_ppm		
Explanatory Var2	Time_min		
Explanatory Var3	BodyWeight	none	<input type="checkbox"/>
	Exposed	none	<input type="checkbox"/>
	Dead	none	<input type="checkbox"/>

<< Product Terms >>

1		
2		
3		

Model: Probit Background Correction: 1 Out File:

Description	Calculate Dose For Given Response	Calc'd Response For Given Exp. Vars	Ratio of Parameters For Two Exp. Vars
Calculations Desired?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Compute Confidence Interval?	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Std. Deviation for Confidence Interval	1.96	1.96	1.96
% Response of Interest	95		

Ratio for Parameters: And:

<< Calculated Dose >>

Find Corr. Value For		
When	=	

<< Calculated Response >>

When		
When	=	

For accurate results, please ensure the dataset structure conforms to this sequence:

- The first columns in the dataset should be the Main Effect columns (e.g. Dose and Time). These columns can be in any order but they must appear first.
- The final columns in the dataset should be the # Subjects and Incidence columns. IN THAT ORDER.
- Other columns (e.g. Age, Litter) can appear in any order following the Main Effect columns but before the # Subjects and Incidence.

Run Save Save As ... Close

58 row(s) added. Num Lock



# ten Berge Model – Column Assignments

BMDS 2.4 [Build: 04/01/2013] - [TenBerge Model]

File Edit View Tools Windows Help

File

<< Dataset: C:\Users\sladavis\10\BMDS240\Data\clu\_intenBerge\_demo.dax >>

	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		

<< Column Assignments >>

Description	Column	Transform.	Main Effect
# Subjects	Exposed		
Incidence	Dead		
Explanatory Var1	Exposure_ppm	none	<input type="checkbox"/>
Explanatory Var2	Time_min	none	<input type="checkbox"/>
Explanatory Var3	BodyWeight	none	<input type="checkbox"/>

<< Product Terms >>

1		
2		
3		

Model: Probit Background Correction: 1 Out File:

Description	Calculate Dose For Given Response	Calc'd Response For Given Exp. Vars	Ratio of Parameters For Two Exp. Vars
Calculations Desired?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Compute Confidence Interval?	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Std. Deviation for Confidence Interval	1.96	1.96	1.96
% Response of Interest	95		

Ratio for Parameters: And:

<< Calculated Dose >>

Find Corr. Value For		
When	=	

<< Calculated Response >>

When		
When	=	

For accurate results, please ensure the dataset structure conforms to this sequence:

- The first columns in the dataset should be the Main Effect columns (e.g. Dose and Time). These columns can be in any order but they must appear first.
- The final columns in the dataset should be the # Subjects and Incidence columns. IN THAT ORDER.
- Other columns (e.g. Age, Litter) can appear in any order following the Main Effect columns but before the # Subjects and Incidence.

Run Save Save As ... Close

58 row(s) added. Num Lock



# Ten Berge Model – Variable Transformations

BMDS 2.4 [Build: 04/01/2013] - [TenBerge Model]

File Edit View Tools Windows Help

File

<< Dataset: C:\Users\ladavis10\BMDs2401\Data\clu\_intenBerge\_demo.dax >>

	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		

<< Column Assignments >>

Description	Column	Transform.	Main Effect
# Subjects	Exposed		
Incidence	Dead		
Explanatory Var1	Exposure_ppm	none	<input type="checkbox"/>
Explanatory Var2	Time_min	logarithmic	<input type="checkbox"/>
Explanatory Var3	BodyWeight	none	<input type="checkbox"/>

<< Product Terms >>

1		
2		
3		

Model: Probit Background Correction: 1 Out File:

Description	Calculate Dose For Given Response	Calc'd Response For Given Exp. Vars	Ratio of Parameters For Two Exp. Vars
Calculations Desired?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Compute Confidence Interval?	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Std. Deviation for Confidence Interval	1.96	1.96	1.96
% Response of Interest	95		

Ratio for Parameters: And:

<< Calculated Dose >>

Find Corr. Value For		
When	=	

<< Calculated Response >>

When		
When	=	

For accurate results, please ensure the dataset structure conforms to this sequence:

- The first columns in the dataset should be the Main Effect columns (e.g. Dose and Time). These columns can be in any order but they must appear first.
- The final columns in the dataset should be the # Subjects and Incidence columns. IN THAT ORDER.
- Other columns (e.g. Age, Litter) can appear in any order following the Main Effect columns but before the # Subjects and Incidence.

Run Save Save As ... Close

58 row(s) added. Num Lock



# Ten Berge Model – Including Variables as Main Effects

BMDS 2.4 [Build: 04/01/2013] - [TenBerge Model]

File Edit View Tools Windows Help

File

<< Dataset: C:\Users\ladavis10\BMDs2401\Data\clu\_intenBerge\_demo.dax >>

	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		

<< Column Assignments >>

Description	Column	Transform.	Main Effect
# Subjects	Exposed		<input type="checkbox"/>
Incidence	Dead		<input type="checkbox"/>
Explanatory Var1	Exposure_ppm	logarithmic	<input checked="" type="checkbox"/>
Explanatory Var2	Time_min	logarithmic	<input checked="" type="checkbox"/>
Explanatory Var3	BodyWeight	none	<input type="checkbox"/>

<< Product Terms >>

1		
2		
3		

Model: Probit Background Correction: 1 Out File:

Description	Calculate Dose For Given Response	Calc'd Response For Given Exp. Vars	Ratio of Parameters For Two Exp. Vars
Calculations Desired?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Compute Confidence Interval?	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Std. Deviation for Confidence Interval	1.96	1.96	1.96
% Response of Interest	95		

Ratio for Parameters: And:

<< Calculated Dose >>

Find Corr. Value For		
When	=	

<< Calculated Response >>

When		
When	=	

For accurate results, please ensure the dataset structure conforms to this sequence:

- The first columns in the dataset should be the Main Effect columns (e.g. Dose and Time). These columns can be in any order but they must appear first.
- The final columns in the dataset should be the # Subjects and Incidence columns. IN THAT ORDER.
- Other columns (e.g. Age, Litter) can appear in any order following the Main Effect columns but before the # Subjects and Incidence.

Run Save Save As ... Close

58 row(s) added. Num Lock



# Ten Berge Model – Product Terms

BMDS 2.4 [Build: 04/01/2013] - [TenBerge Model]

File Edit View Tools Windows Help

File

<< Dataset: C:\Users\sladavis\10\BMDS2401\Data\clu\_intenBerge\_demo.dax >>

	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		

<< Column Assignments >>

Description	Column	Transform.	Main Effect
# Subjects	Exposed		
Incidence	Dead		
Explanatory Var1	Exposure_ppm	logarithmic	<input checked="" type="checkbox"/>
Explanatory Var2	Time_min	logarithmic	<input checked="" type="checkbox"/>
Explanatory Var3	BodyWeight	none	<input type="checkbox"/>

<< Product Terms >>

1		
2	Exposure_ppm	
3	Time_min	
	BodyWeight	

Model: Probit Background Correction: 1 Out File:

Description	Calculate Dose For Given Response	Calc'd Response For Given Exp. Vars	Ratio of Parameters For Two Exp. Vars
Calculations Desired?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Compute Confidence Interval?	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Std. Deviation for Confidence Interval	1.96	1.96	1.96
% Response of Interest	95		

Ratio for Parameters: And:

<< Calculated Dose >>

Find Corr. Value For		
When	=	
When	=	
When	=	

<< Calculated Response >>

When	=	

For accurate results, please ensure the dataset structure conforms to this sequence:

- The first columns in the dataset should be the Main Effect columns (e.g. Dose and Time). These columns can be in any order but they must appear first.
- The final columns in the dataset should be the # Subjects and Incidence columns. IN THAT ORDER.
- Other columns (e.g. Age, Litter) can appear in any order following the Main Effect columns but before the # Subjects and Incidence.

Run Save Save As ... Close

58 row(s) added. Num Lock



# Ten Berge Model – Select Specific Model

BMDS 2.4 [Build: 04/01/2013] - [TenBerge Model]

File Edit View Tools Windows Help

File

<< Dataset: C:\Users\ladavis\10\BMDS240\Data\clu\_intenBerge\_demo.dax >>

	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		

<< Column Assignments >>

Description	Column	Transform.	Main Effect
# Subjects	Exposed		
Incidence	Dead		
Explanatory Var1	Exposure_ppm	logarithmic	<input checked="" type="checkbox"/>
Explanatory Var2	Time_min	logarithmic	<input checked="" type="checkbox"/>
Explanatory Var3	BodyWeight	none	<input type="checkbox"/>

<< Product Terms >>

1		
2		
3		

Model: Probit (dropdown menu open showing Probit, Logit)

Background Correction: 1

Out File: [ ]

	Calculate Dose For Given Response	Calc'd Response For Given Exp. Vars	Ratio of Parameters For Two Exp. Vars
Calculations Desired?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Compute Confidence Interval?	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Std. Deviation for Confidence Interval	1.96	1.96	1.96
% Response of Interest	95		

Ratio for Parameters: [ ] And [ ]

<< Calculated Dose >>

Find Corr. Value For		
When	=	

<< Calculated Response >>

When		
When	=	

For accurate results, please ensure the dataset structure conforms to this sequence:

- The first columns in the dataset should be the Main Effect columns (e.g. Dose and Time). These columns can be in any order but they must appear first.
- The final columns in the dataset should be the # Subjects and Incidence columns. IN THAT ORDER.
- Other columns (e.g. Age, Litter) can appear in any order following the Main Effect columns but before the # Subjects and Incidence.

Run Save Save As ... Close

58 row(s) added. Num Lock



# 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

BMDS 2.4 [Build: 04/01/2013] - [TenBerge Model]

File Edit View Tools Windows Help

File

<< Dataset: C:\Users\sladavis\10\BMDS2401\Data\clu\_intenBerge\_demo.dax >>

	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		

<< Column Assignments >>

Description	Column	Transform.	Main Effect
# Subjects	Exposed		
Incidence	Dead		
Explanatory Var1	Exposure_ppm	logarithmic	<input checked="" type="checkbox"/>
Explanatory Var2	Time_min	logarithmic	<input checked="" type="checkbox"/>
Explanatory Var3	BodyWeight	none	<input type="checkbox"/>

<< Product Terms >>

1		
2		
3		

Model: Probit Background Correction: 1 Out File:

Description	Calculate Dose For Given Response	Calc'd Response For Given Exp. Vars	Ratio of Parameters For Two Exp. Vars
Calculations Desired?	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Compute Confidence Interval?	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Std. Deviation for Confidence Interval	1.96	1.96	1.96
% Response of Interest	50		

Ratio for Parameters: Exposure\_ppm And Time\_min

<< Calculated Dose >>

Find Corr. Value For	Exposure_ppm		
When	Time_min	=	60
When		=	
When		=	

<< Calculated Response >>

When	Exposure_ppm	=	2000
When	Time_min	=	30
When		=	
When		=	

For accurate results, please ensure the dataset structure conforms to this sequence:

- The first columns in the dataset should be the Main Effect columns (e.g. Dose and Time). These columns can be in any order but they must appear first.
- The final columns in the dataset should be the # Subjects and Incidence columns. IN THAT ORDER.
- Other columns (e.g. Age, Litter) can appear in any order following the Main Effect columns but before the # Subjects and Incidence.

Run Save Save As ... Close

58 row(s) added. Num Lock



# ten Berge Model – Calculations of Interest

BMDS 2.4 [Build: 04/01/2013] - [TenBerge Model]

File Edit View Tools Windows Help

File

<< Dataset: C:\Users\sladavis\10\BMDS2401\Data\clu\_intenBerge\_demo.dax >>

	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		

<< Column Assignments >>

Description	Column	Transform.	Main Effect
# Subjects	Exposed		
Incidence	Dead		
Explanatory Var1	Exposure_ppm	logarithmic	<input checked="" type="checkbox"/>
Explanatory Var2	Time_min	logarithmic	<input checked="" type="checkbox"/>
Explanatory Var3	BodyWeight	none	<input type="checkbox"/>

<< Product Terms >>

1		
2		
3		

Model Probit Background Correction 1 Out File

Description	Calculate Dose For Given Response	Calc'd Response For Given Exp. Vars	Ratio of Parameters For Two Exp. Vars
Calculations Desired?	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Compute Confidence Interval?	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Std. Deviation for Confidence Interval	1.96	1.96	1.96
% Response of Interest	50		

Ratio for Parameters Exposure\_ppm And Time\_min

<< Calculated Dose >>

Find Corr. Value For	Exposure_ppm		
When	Time_min	=	60
When		=	
When		=	

<< Calculated Response >>

When	Exposure_ppm	=	2000
When	Time_min	=	30
When		=	
When		=	

For accurate results, please ensure the dataset structure conforms to this sequence:

1. The first columns in the dataset should be the Main Effect columns (e.g. Dose and Time). These columns can be in any order but they must appear first.
2. The final columns in the dataset should be the # Subjects and Incidence columns. IN THAT ORDER.
3. Other columns (e.g. Age, Litter) can appear in any order following the Main Effect columns but before the # Subjects and Incidence.

Run Save Save As ... Close

58 row(s) added. Num Lock



# ten Berge Model – Results

```
BMDS 2.4 [Build: 04/01/2013] - [C:\Users\adavis10\BMDS240\Data\clu_in\tentenBrg.out]
File Edit View Tools Windows Help
File Edit Preferences
=====
Ten Berge Model. (Version: 1.0; Date: 12/26/2006)
Input Data File: C:\Users\adavis10\BMDS240\Data\clu_in\tentenBrg.(d)
Gnuplot Plotting File: C:\Users\adavis10\BMDS240\Data\clu_in\tentenBrg.plt
Thu Apr 17 14:25:00 2014
=====
Dose-Response Analysis

Method of Maximum Likelihood according to:
D.J. Finney, 1977. Probit Analysis. Cambridge University Press.
=====

Model: P(v1, v2, ...) = Link(B0 + B1*v1 + B2*v2 + ...)

Link is either Logit or Probit
v1, v2, ... are the variables (transformations of the input parameters)

Number of input parameters = 3
Total number of observations = 42
Total number of records with missing values = 0

Exposure_ppm      Time_min      Exposed      Dead
-----
50.00      5.00      10.      0.
50.00      10.00     10.      1.
50.00      20.00     10.      0.
50.00      30.00     10.      2.
50.00      40.00     10.      1.
50.00      50.00     10.      1.
50.00      60.00     10.      2.
300.00     5.00      10.      0.
300.00     10.00     10.      1.
300.00     20.00     10.      1.
300.00     30.00     10.      3.
300.00     40.00     10.      2.
300.00     50.00     10.      2.
300.00     60.00     10.      4.
600.00     5.00      10.      1.
600.00     10.00     10.      1.
600.00     20.00     10.      2.
600.00     30.00     10.      4.

58 row(s) added. Num Lock
```



# ten Berge Model - Results

```
BMDS 2.4 [Build: 04/01/2013] - [C:\Users\adavis10\BMDS240\Data\clu_in\ntenBrg.out]
File Edit View Tools Windows Help
File Edit Preferences
Selection of observations from number 1 through 42

Transformation of input parameters
Exposure_ppm      is transformed logarithmically!
Time_min          is transformed logarithmically!
BodyWeight        is not transformed at all!

Probit link used without background response correction!

Variable 1 = Transformed Exposure_ppm
Variable 2 = Transformed Time_min

Chi-Square        = 30.53
Degrees of Freedom = 39

B0 = 1.024e-001    Student t for B0 = 0.20
B1 = 4.490e-001    Student t for B1 = 8.15
B2 = 4.704e-001    Student t for B2 = 5.35

variance B00 = 2.640e-001
covariance B01 = -2.339e-002
covariance B02 = -3.022e-002
variance B11 = 3.039e-003
covariance B12 = 7.458e-004
variance B22 = 7.739e-003

Probability of correct model (p-value) is 0.832056
The prediction of the model is sufficient. Use for estimation of the
95% confidence limits the Standard Normal Deviate

No correction for variances required!

Estimation of Exposure_ppm
Response = 50.000000 percent
Time_min = 60.000000

Estimated Exposure_ppm 50.000000 percent = 7.486e+002
Deviate Corresponding to Confidence Level of Interest = 1.960000
Lower limit Exposure_ppm 50.000000 percent = 4.726e+002
Upper limit Exposure_ppm 50.000000 percent = 1.175e+003

Probability of correct model (p-value) is 0.832056
The prediction of the model is sufficient. Use for estimation of the
95% confidence limits the Standard Normal Deviate

58 row(s) added. Num Lock
```



# ten Berge Model – Results

```
BMDS 2.4 [Build: 04/01/2013] - [C:\Users\adavis10\BMDS240\Data\clu_in\tenBrg.out]
File Edit View Tools Windows Help
File Edit Preferences
Selection of observations from number 1 through 42

Transformation of input parameters
Exposure_ppm      is transformed logarithmically!
Time_min          is transformed logarithmically!
BodyWeight        is not transformed at all!

Probit link used without background response correction!

Variable 1 = Transformed Exposure_ppm
Variable 2 = Transformed Time_min

Chi-Square      = 30.53
Degrees of Freedom = 39

B0 = 1.024e-001      Student t for B0 = 0.20
B1 = 4.490e-001      Student t for B1 = 8.15
B2 = 4.704e-001      Student t for B2 = 5.35

variance B00 = 2.640e-001
covariance B01 = -2.339e-002
covariance B02 = -3.022e-002
variance B11 = 3.039e-003
covariance B12 = 7.458e-004
variance B22 = 7.739e-003

Probability of correct model (p-value) is 0.832056
The prediction of the model is sufficient. Use for estimation of the
95% confidence limits the Standard Normal Deviate

No correction for variances required!

Estimation of Exposure_ppm
Response = 50.000000 percent
Time_min = 60.000000

Estimated Exposure_ppm 50.000000 percent = 7.486e+002
Deviate Corresponding to Confidence Level of Interest = 1.960000
Lower limit Exposure_ppm 50.000000 percent = 4.726e+002
Upper limit Exposure_ppm 50.000000 percent = 1.175e+003

Probability of correct model (p-value) is 0.832056
The prediction of the model is sufficient. Use for estimation of the
95% confidence limits the Standard Normal Deviate

58 row(s) added. Num Lock
```



# ten Berge Model – Results

```
BMDS 2.4 [Build: 04/01/2013] - [C:\Users\adavis10\BMDS240\Data\clu_in\tentenBrg.out]
File Edit View Tools Windows Help
File Edit Preferences
95% confidence limits the Standard Normal Deviate
No correction for variances required!
Estimation of Exposure_ppm
Response = 50.000000 percent
Time_min = 60.000000
Estimated Exposure_ppm 50.000000 percent = 7.486e+002
Deviate Corresponding to Confidence Level of Interest = 1.960000
Lower limit Exposure_ppm 50.000000 percent = 4.726e+002
Upper limit Exposure_ppm 50.000000 percent = 1.175e+003
Probability of correct model (p-value) is 0.832056
The prediction of the model is sufficient. Use for estimation of the
95% confidence limits the Standard Normal Deviate
No correction for variances required!
Estimation of response
Exposure_ppm = 2000.000000
Time_min = 30.000000
Response = 5.46e+001 percent
Deviate Corresponding to Confidence Level of Interest = 1.960000
LL-response = 4.83e+001 percent
UL-response = 6.08e+001 percent
Probability of correct model (p-value) is 0.832056
The prediction of the model is sufficient. Use for estimation of the
95% confidence limits the Standard Normal Deviate
No correction for variances required!
Estimation of ratio between regression coefficients
Ratio between regression coefficients
Exposure_ppm and Time_min
Deviate Corresponding to Confidence Level of Interest = 1.960000
Ratio = 0.954602
Confidence limits
0.566673 1.342530
58 row(s) added. Num Lock
```

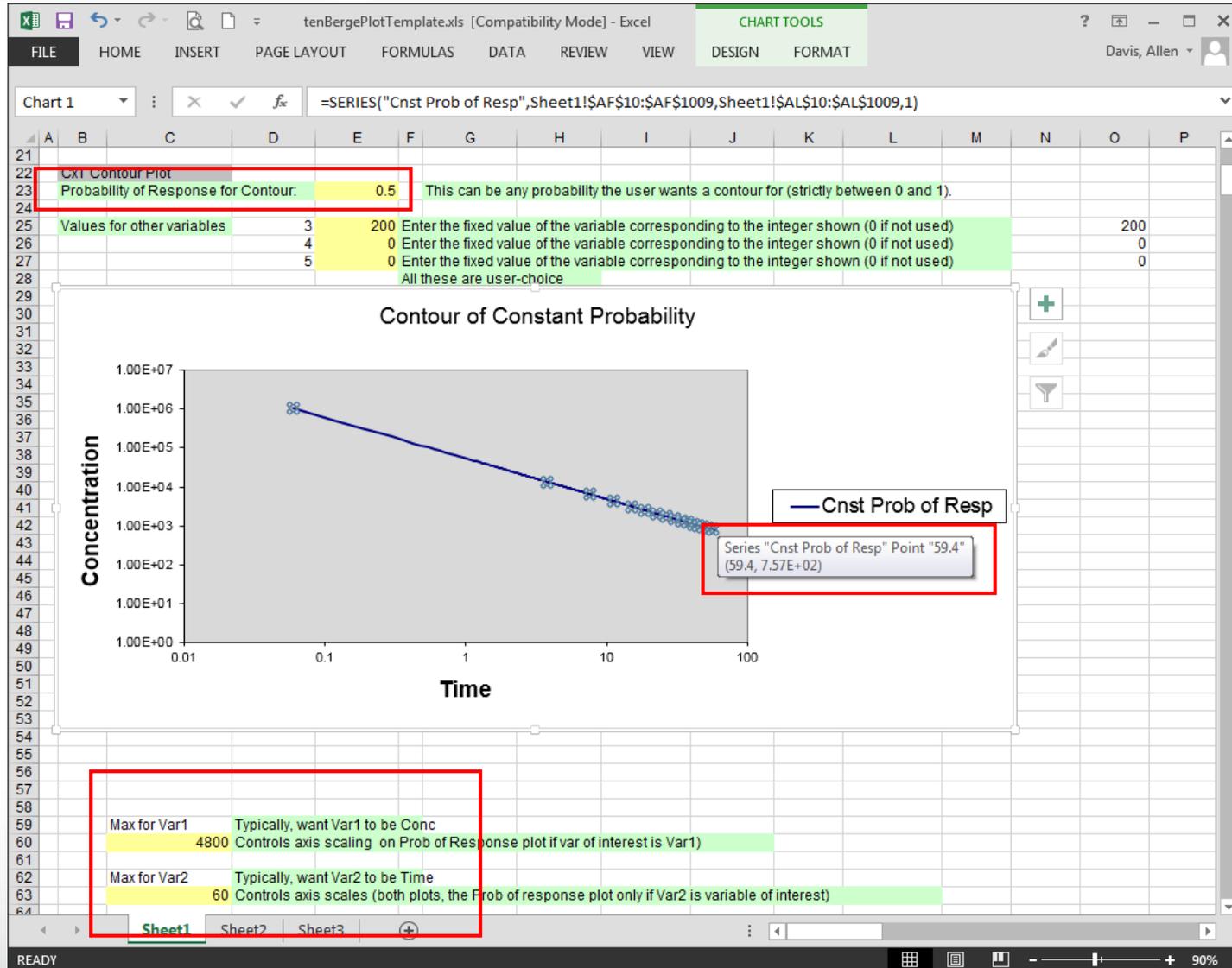


# ten Berge Model – Results

```
BMDS 2.4 [Build: 04/01/2013] - [C:\Users\adavis10\BMDS240\Data\clu_in\tenBrg.out]
File Edit View Tools Windows Help
File Edit Preferences
95% confidence limits the Standard Normal Deviate
No correction for variances required!
Estimation of Exposure_ppm
Response = 50.000000 percent
Time_min = 60.000000
Estimated Exposure_ppm 50.000000 percent = 7.486e+002
Deviate Corresponding to Confidence Level of Interest = 1.960000
Lower limit Exposure_ppm 50.000000 percent = 4.726e+002
Upper limit Exposure_ppm 50.000000 percent = 1.175e+003
Probability of correct model (p-value) is 0.832056
The prediction of the model is sufficient. Use for estimation of the
95% confidence limits the Standard Normal Deviate
No correction for variances required!
Estimation of response
Exposure_ppm = 2000.000000
Time_min = 30.000000
Response = 5.46e+001 percent
Deviate Corresponding to Confidence Level of Interest = 1.960000
LL-response = 4.83e+001 percent
UL-response = 6.08e+001 percent
Probability of correct model (p-value) is 0.832056
The prediction of the model is sufficient. Use for estimation of the
95% confidence limits the Standard Normal Deviate
No correction for variances required!
Estimation of ratio between regression coefficients
Ratio between regression coefficients
Exposure_ppm and Time_min
Deviate Corresponding to Confidence Level of Interest = 1.960000
Ratio = 0.954602
Confidence limits
0.566673 1.342530
58 row(s) added. Num Lock
```

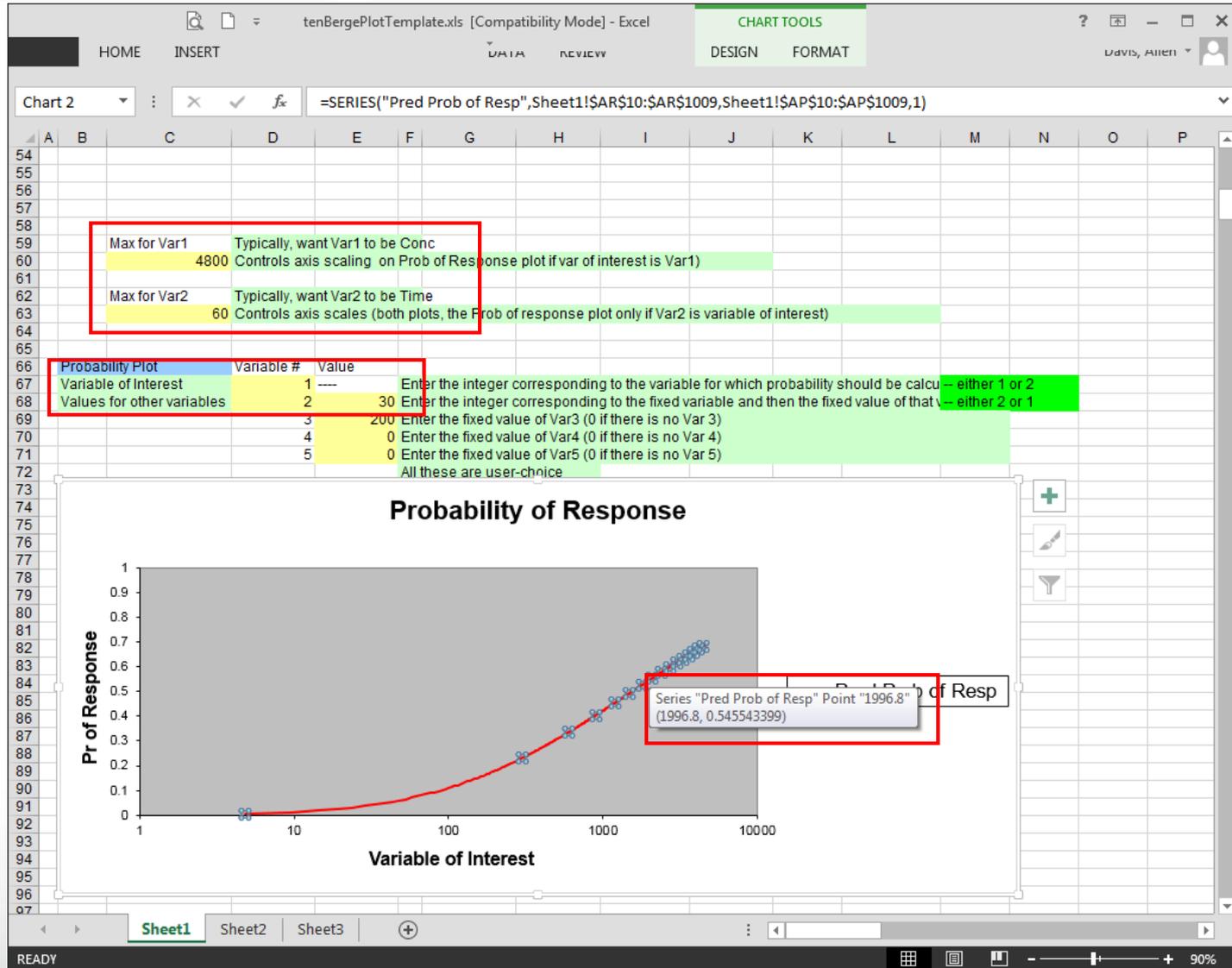


# ten Berge Model – Plots



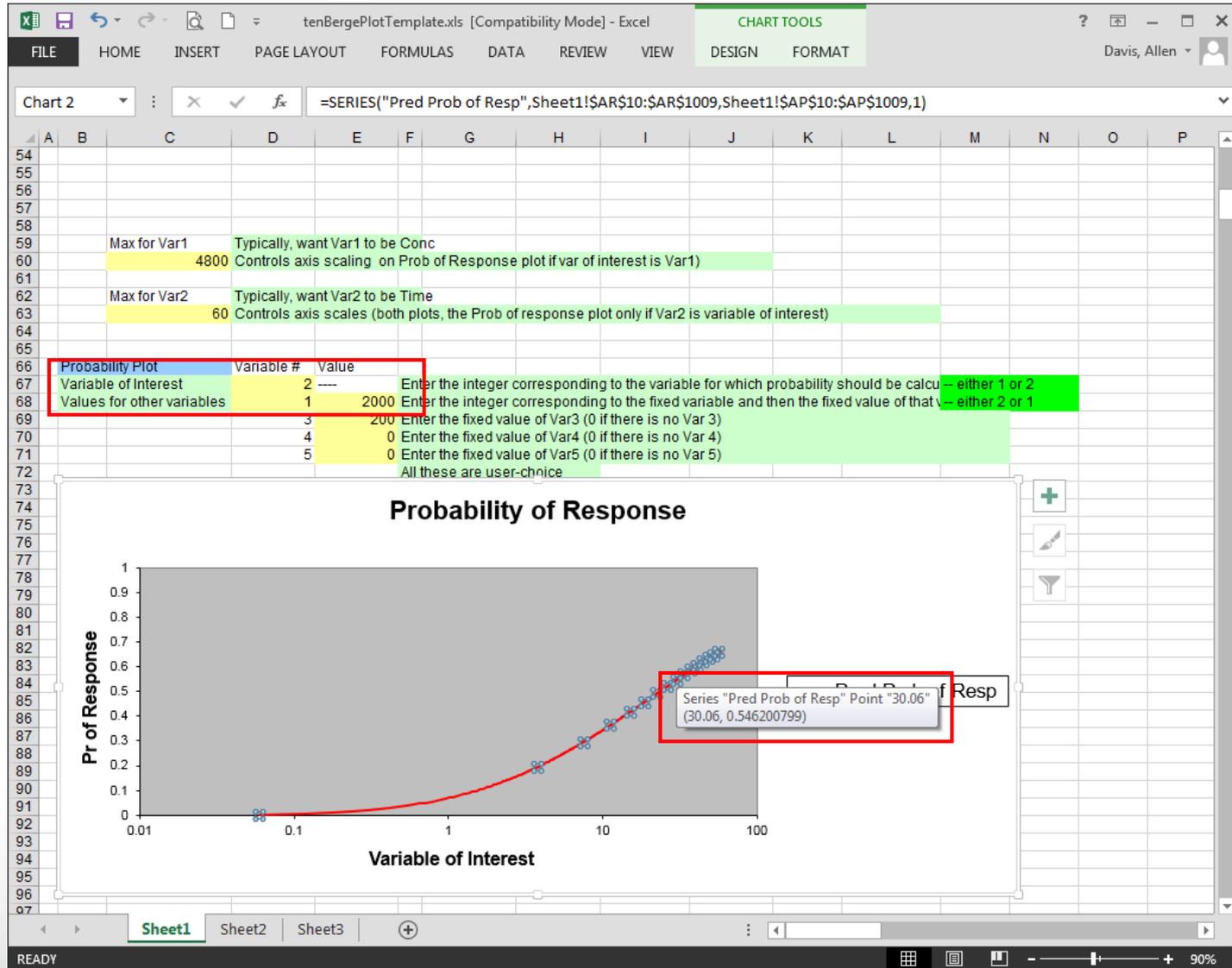


# ten Berge Model – Plots





# 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**

BMDS 2.4 [Build: 04/01/2013] - [TenBerge Model]

File Edit View Tools Windows Help

File

<< Dataset: C:\Users\ladavis\10\BMDS240\Data\clu\_in\tenBerge\_exercise.dax >>

	Exposure_ppm	Time_min	Exposed	Dead	Col5	Col6	Col7
1	100	50	10	1			
2	100	10	10	1			
3	100	60	10	2			

<< Column Assignments >>

Description	Column	Transform.	Main Effect
# Subjects	Exposed		
Incidence	Dead		
Explanatory Var1	Exposure_ppm	logarithmic	<input checked="" type="checkbox"/>
Explanatory Var2	Time_min	logarithmic	<input checked="" type="checkbox"/>
Explanatory Var3		none	<input type="checkbox"/>

<< Product Terms >>

1		
2		
3		

Model Probit Background Correction 1 Out File

Description	Calculate Dose For Given Response	Calc'd Response For Given Exp. Vars	Ratio of Parameters For Two Exp. Vars
Calculations Desired?	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Compute Confidence Interval?	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Std. Deviation for Confidence Interval	1.96	1.96	1.96
% Response of Interest	60		

Ratio for Parameters Exposure\_ppm And Time\_min

<< Calculated Dose >>

Find Corr. Value For	Exposure_ppm		
When	Time_min	=	30
When		=	
When		=	

<< Calculated Response >>

When	Exposure_ppm	=	2000
When	Time_min	=	60
When		=	
When		=	

For accurate results, please ensure the dataset structure conforms to this sequence:

1. The first columns in the dataset should be the Main Effect columns (e.g. Dose and Time). These columns can be in any order but they must appear first.
2. The final columns in the dataset should be the # Subjects and Incidence columns. IN THAT ORDER.
3. Other columns (e.g. Age, Litter) can appear in any order following the Main Effect columns but before the # Subjects and Incidence.

Run Save Save As ... Close

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# 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

```

BMDS 2.4 [Build: 04/01/2013] - [C:\Users\adavis10\BMD5240\Data\clu_in\tenBrg.out]
File Edit View Tools Windows Help

File Edit Preferences

variance B00 = 3.001e-001
covariance B01 = -2.927e-002
covariance B02 = -3.194e-002
variance B11 = 3.993e-003
covariance B12 = 9.625e-004
variance B22 = 7.897e-003

Probability of correct model (p-value) is 0.954560
The prediction of the model is sufficient. Use for estimation of the
95% confidence limits the Standard Normal Deviate

No correction for variances required!

Estimation of Exposure_ppm
Response = 60.000000 percent
Time_min = 30.000000

Estimated Exposure_ppm 60.000000 percent = 1.650e+003
Deviate Corresponding to Confidence Level of Interest = 1.960000
Lower limit Exposure_ppm 60.000000 percent = 1.240e+003
Upper limit Exposure_ppm 60.000000 percent = 2.417e+003

Probability of correct model (p-value) is 0.954560
The prediction of the model is sufficient. Use for estimation of the
95% confidence limits the Standard Normal Deviate

No correction for variances required!

Estimation of response
Exposure_ppm = 2000.000000
Time_min = 60.000000

Response = 7.55e+001 percent
Deviate Corresponding to Confidence Level of Interest = 1.960000
LL-response = 6.69e+001 percent
UL-response = 8.27e+001 percent

Probability of correct model (p-value) is 0.954560
The prediction of the model is sufficient. Use for estimation of the
95% confidence limits the Standard Normal Deviate

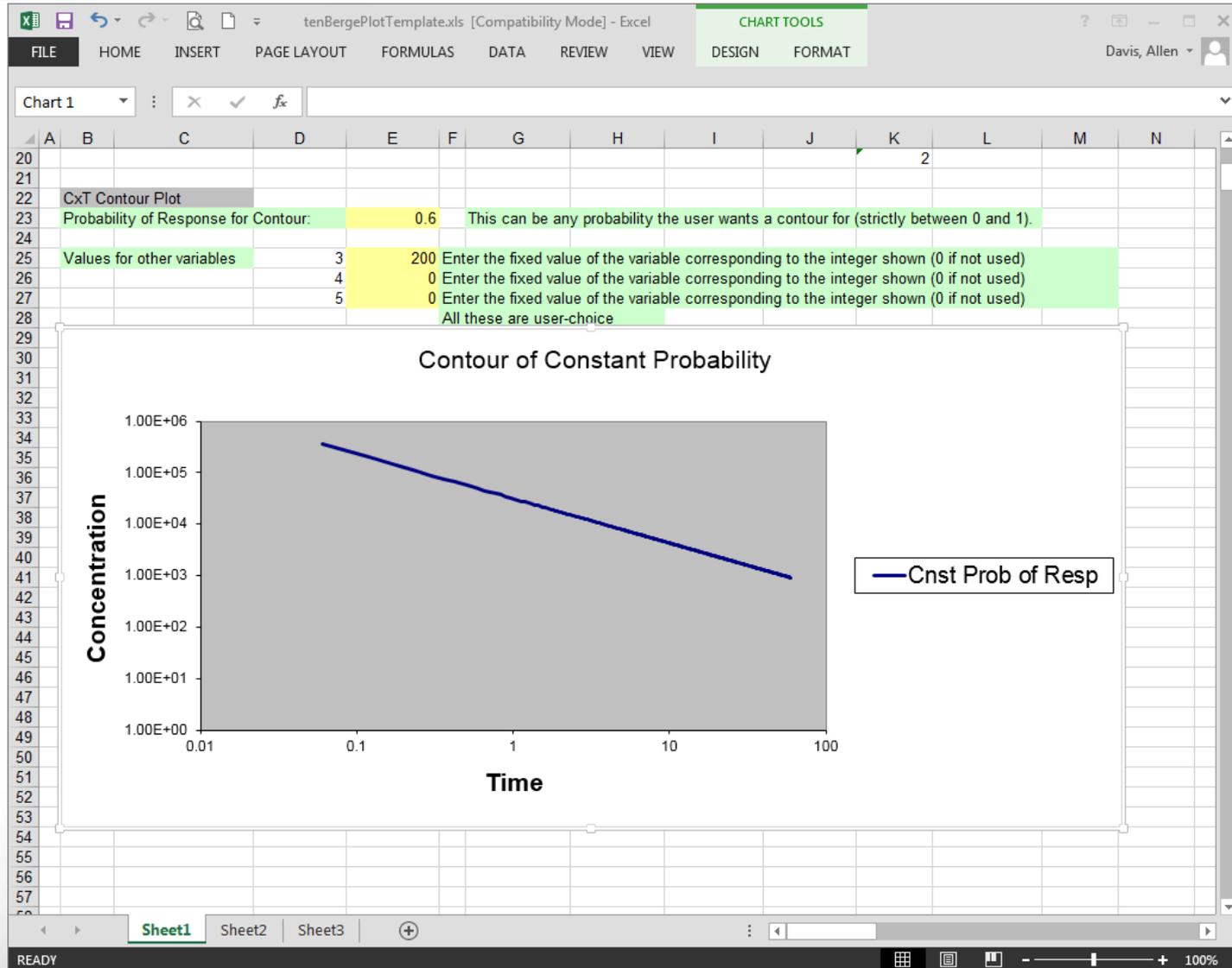
No correction for variances required!

Estimation of ratio between regression coefficients

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```



# 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%

BMDS 2.4 [Build: 04/01/2013] - [C:\Users\adavis10\BMD5240\Data\clu\_in\tenBrg.out]

File Edit View Tools Windows Help

File Edit Preferences

The prediction of the model is sufficient. Use for estimation of the 95% confidence limits the Standard Normal Deviate

No correction for variances required!

Estimation of Exposure\_ppm  
 Response = 60.000000 percent  
 Time\_min = 30.000000

Estimated Exposure\_ppm 60.000000 percent = 1.650e+003  
 Deviate Corresponding to Confidence Level of Interest = 1.960000  
 Lower limit Exposure\_ppm 60.000000 percent = 1.240e+003  
 Upper limit Exposure\_ppm 60.000000 percent = 2.417e+003

Probability of correct model (p-value) is 0.954560  
 The prediction of the model is sufficient. Use for estimation of the 95% confidence limits the Standard Normal Deviate

No correction for variances required!

Estimation of response  
 Exposure\_ppm = 2000.000000  
 Time\_min = 60.000000

Response = 7.55e+001 percent  
 Deviate Corresponding to Confidence Level of Interest = 1.960000  
 LL-response = 6.69e+001 percent  
 UL-response = 8.27e+001 percent

Probability of correct model (p-value) is 0.954560  
 The prediction of the model is sufficient. Use for estimation of the 95% confidence limits the Standard Normal Deviate

No correction for variances required!

Estimation of ratio between regression coefficients  
 Ratio between regression coefficients  
 Exposure\_ppm and Time\_min

Deviates Corresponding to Confidence Level of Interest = 1.960000

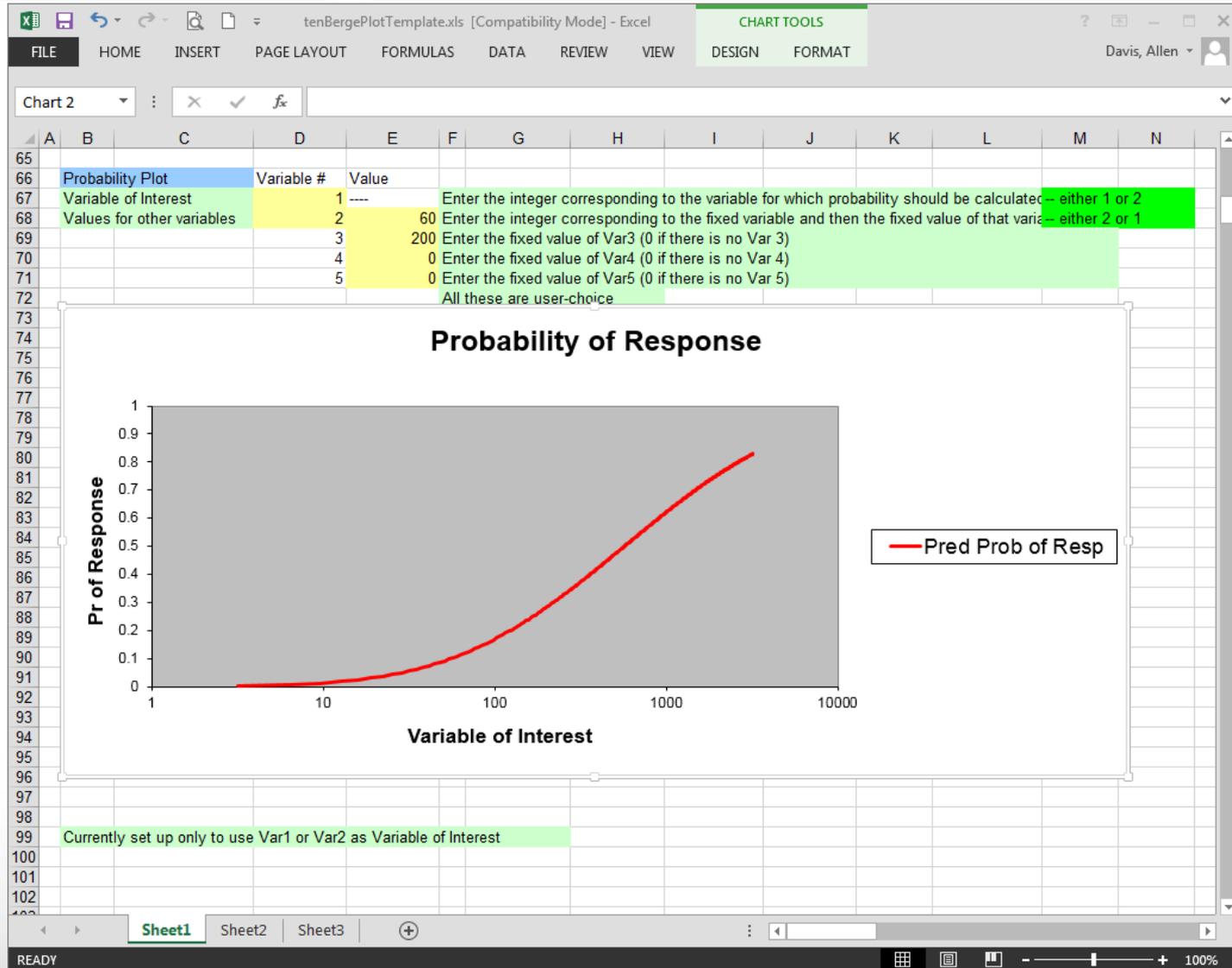
Ratio = 1.154502

Confidence limits  
 0.699105 1.609898

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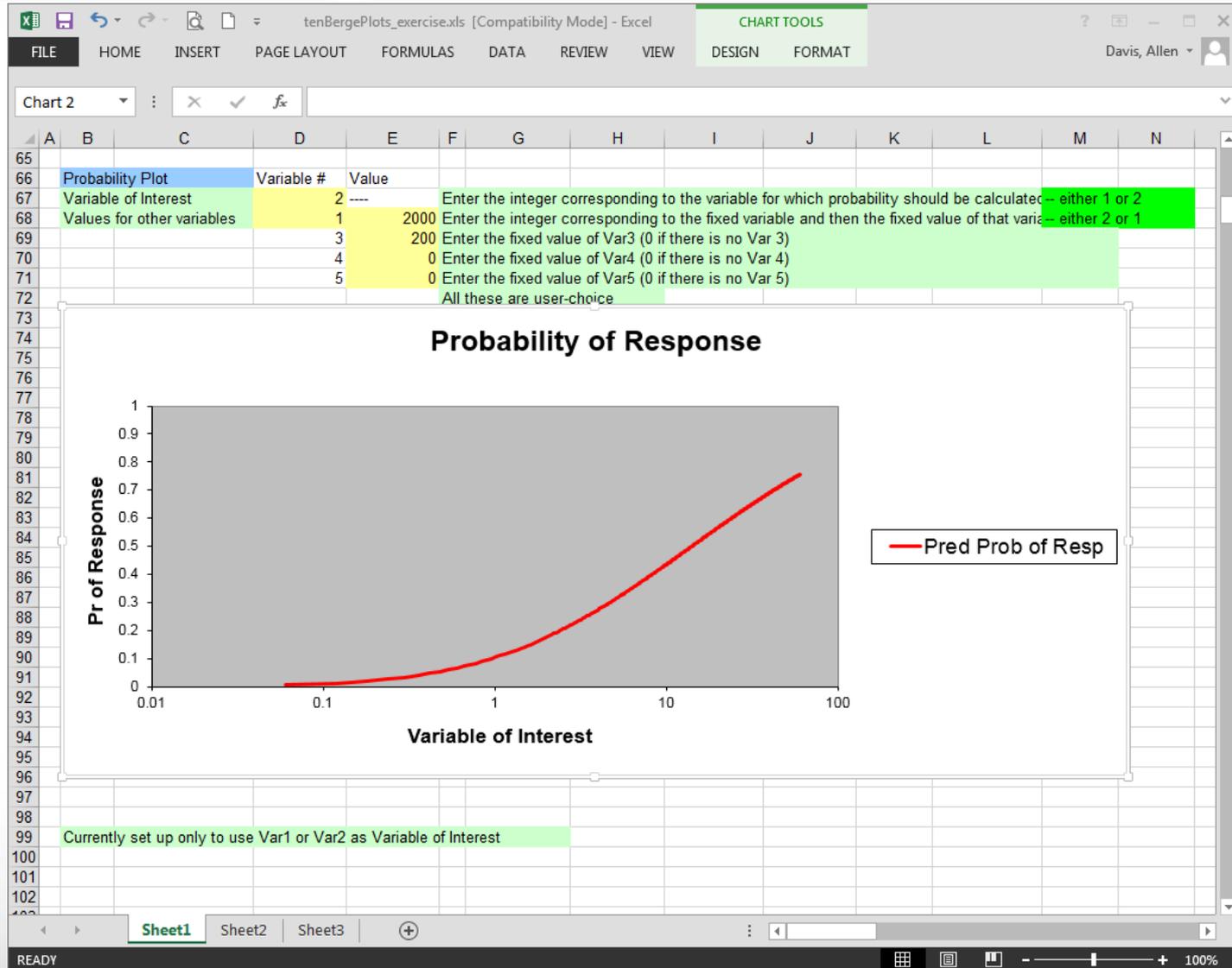


# ten Berge Modeling Results – Response for Given Variables Plot





# 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

```

BMDS 2.4 [Build: 04/01/2013] - [C:\Users\adavis10\BMDS240\Data\clu_in\tenBrg.out]
File Edit View Tools Windows Help

File Edit Preferences

The prediction of the model is sufficient. Use for estimation of the
95% confidence limits the Standard Normal Deviate

No correction for variances required!

Estimation of Exposure_ppm
Response      = 60.000000 percent
Time_min     = 30.000000

Estimated Exposure_ppm 60.000000 percent = 1.650e+003
Deviate Corresponding to Confidence Level of Interest = 1.960000
Lower limit Exposure_ppm 60.000000 percent = 1.240e+003
Upper limit Exposure_ppm 60.000000 percent = 2.417e+003

Probability of correct model (p-value) is 0.954560
The prediction of the model is sufficient. Use for estimation of the
95% confidence limits the Standard Normal Deviate

No correction for variances required!

Estimation of response
Exposure_ppm      = 2000.000000
Time_min         = 60.000000

Response          = 7.55e+001 percent
Deviate Corresponding to Confidence Level of Interest = 1.960000
LL-response       = 6.69e+001 percent
UL-response       = 8.27e+001 percent

Probability of correct model (p-value) is 0.954560
The prediction of the model is sufficient. Use for estimation of the
95% confidence limits the Standard Normal Deviate

No correction for variances required!

Estimation of ratio between regression coefficients
Ratio between regression coefficients
Exposure_ppm and Time_min

Deviate Corresponding to Confidence Level of Interest = 1.960000

Ratio            = 1.154502

Confidence limits
0.699105        1.609898
  
```

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- **Toxicodiffusion Model**

- Zhu, Y., Wessel, M.R., Liu, T., and Moser, V.C. (2005) Analyses of Neurobehavioral Screening Data: Dose-Time-Response Modeling of Continuous Outcomes. *Regulatory Toxicology and Pharmacology* 41, pp 240-255
- Zhu, Y., Jia, Z., Wang, W., Gift, J., Moser, V.C., and B.J. Pierre-Louis (2005), Data Analysis of Neurobehavioral Screening Data: Benchmark Dose Estimation. *Regulatory Toxicology and Pharmacology*, pp 190-201

- **ten Berge Model**

- ten Berge, W.F., Zwart, A., Appelman, L.M. (1986) Concentration-Time Mortality Response Relationship of Irritant and Systemically Acting Vapours and Gases. *Journal of Hazardous Materials*, 13, pp 301-309