Benchmark Dose Modeling – Continuous Models

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Disclaimer

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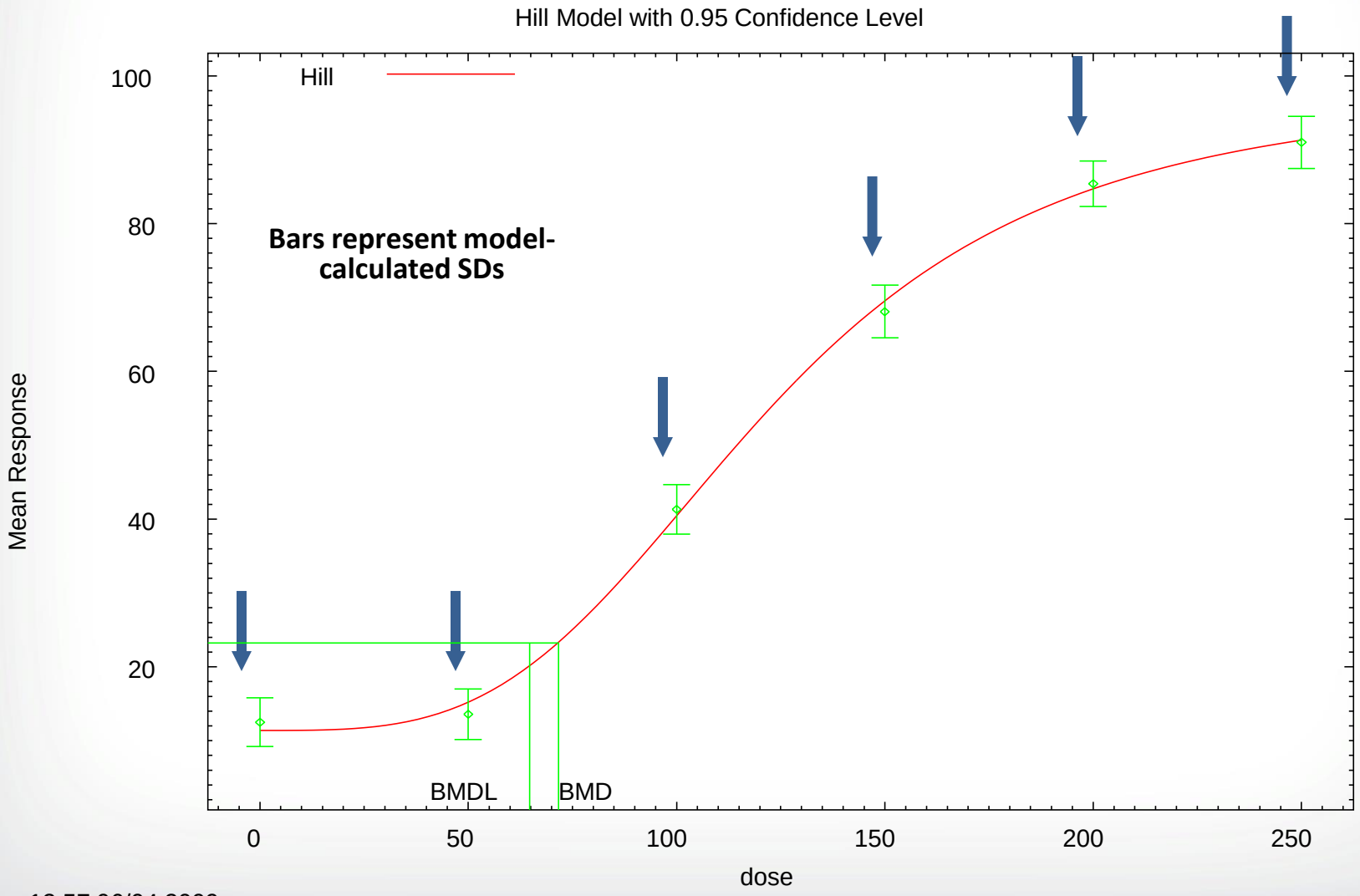
Continuous Data

Description	• Response is measured on a continuous spectrum • Response is a numerical value with a measure of variability (i.e., standard error or standard deviation) • Response can either increase or decrease with dose
Example Endpoints	• Body weight • Organ weight • Enzyme Activity

Model Inputs	• Dose
	• Number of Subjects
	• Mean response (per dose group) **OR** individual animal responses
	• A measure of variability in response
	  ○ Standard deviation (SD) needed for modeling purposes
	  ○ Variability reported as standard error must be converted to SD
	  ○ SD automatically calculated when inputing individual responses

Example of Continuous Data



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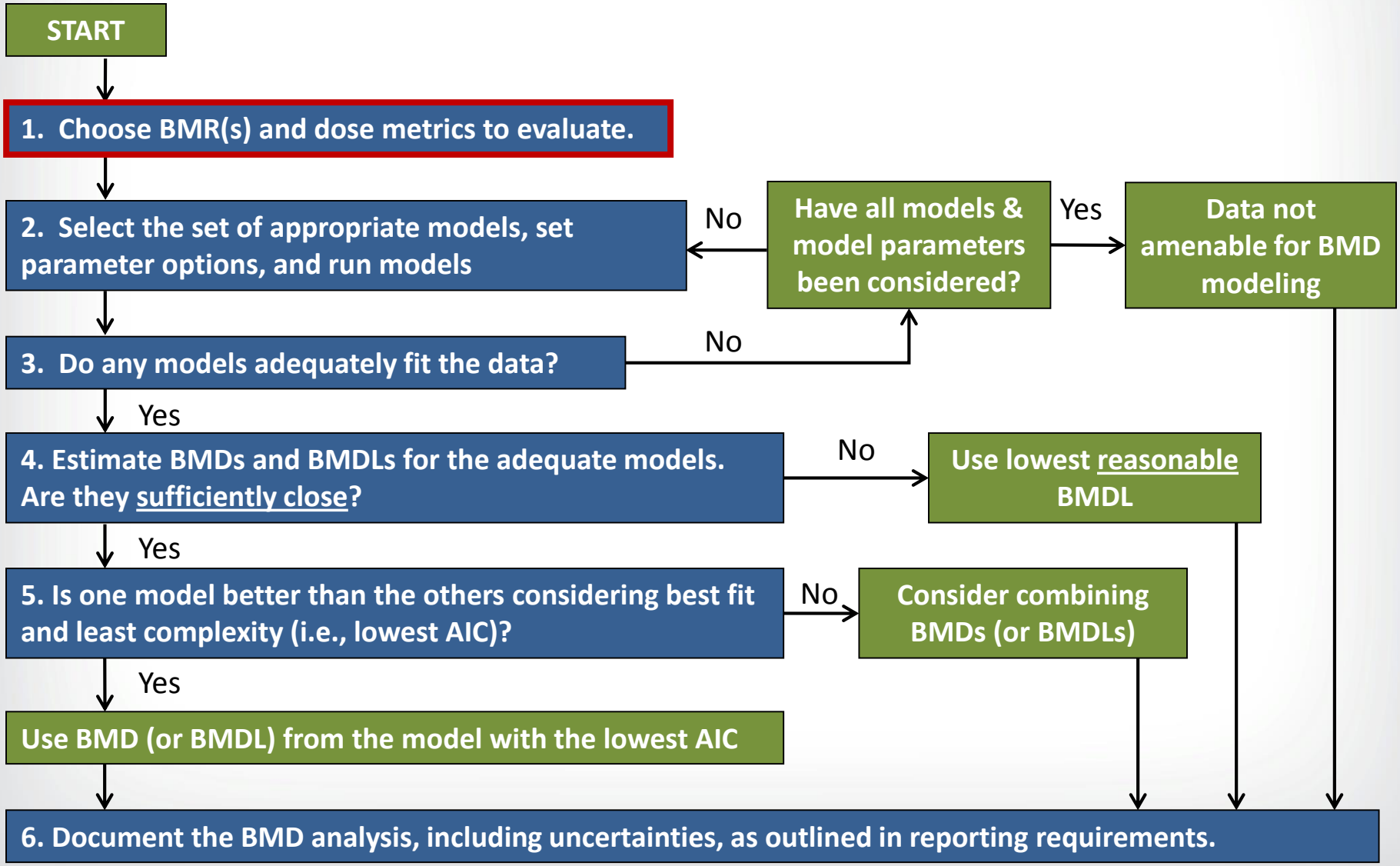
BMD Analysis – Six Steps



Select a Benchmark Response

- **BMR should be near the low end of the range of increases risks that can be detected by a bioassay**
  - Continuous endpoints also have measurement detection limits
- **BMRs that are too low can impart high model dependence in BMD/BMDL estimates due to different model shapes in the extreme low dose areas**
- **Continuous models have multiple types of BMRs to choose from**

Continuous BMR Types

BMR Type	BMR Calculation
Standard Deviation:	$BMR = mean_0 \pm (BMRF \times SD_0)$
Relative Deviation:	$BMR = mean_0 \pm (BMRF \times mean_0)$
Absolute Deviation:	$BMR = mean_0 \pm BMRF$
Point:	$BMR = BMRF$
Extra (Hill only):	$BMR_{up} = mean_0 + BMRF \times (mean_{max} - mean_0)$ $BMR_{down} = mean_0 - BMRF \times (mean_0 - mean_{min})$

Where:

$mean_0$	=	*Modeled mean response at control dose*
SD_0	=	*Modeled standard deviation at control dose*
$BMRF$	=	*BMR factor (user input used to define BMR)*
$mean_{max}$	=	*Maximum mean response in dataset*
$mean_{min}$	=	*Minimum mean response in dataset*

Why Use SD as the BMD for Continuous Data?

- **Preferred approach is to select a BMR that corresponds to a level change that represents a minimal biologically significant response (i.e., 10% decrease in body weight)**

- **In the absence of a biological consideration, a BMR of a change in the mean equal to one control standard deviation (1.0 SD) from the control mean is recommended.**

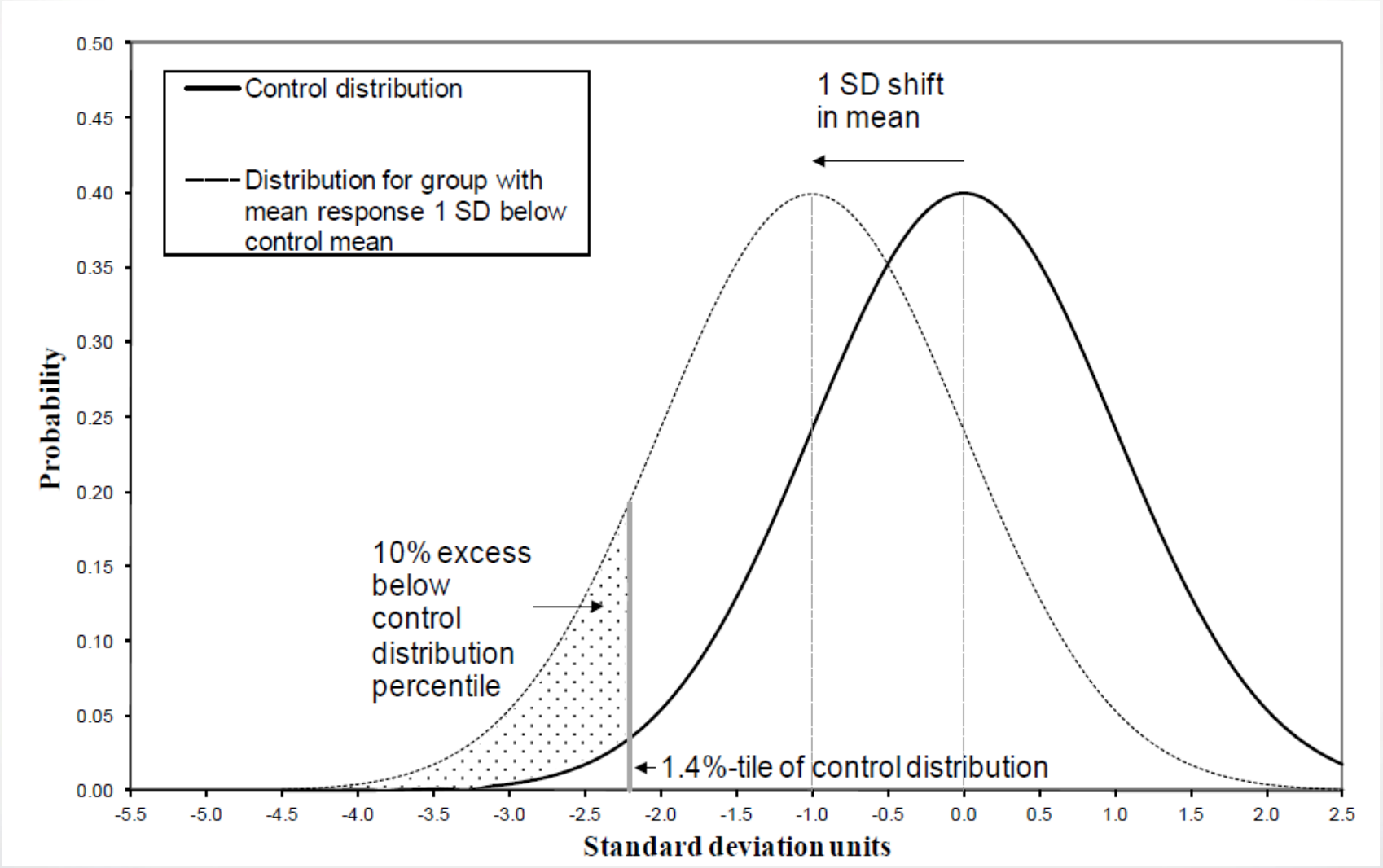
- **In some situations, use of different BMRs is supported**
  - For more severe effects, a BMR of 0.5 SD can be used
  - Results for a 1 SD BMR should always be shown for comparison when using different BMRs.

Why Use SD as the BMR for Continuous Data?

- **For a continuous endpoint in a normally distributed population, if**
  - 1.4% of the animals in the control group are assumed to have an "abnormal response," a change in the mean response by one standard deviation will result in 10% of the animals reaching the abnormal response level (Crump, 1995)
  - This response in 10% of the animals is comparable to the 10% BMR used in dichotomous data modeling

- **NOTE: This assumes a simple shift in a normal distribution. Some toxicity responses may not behave this way**

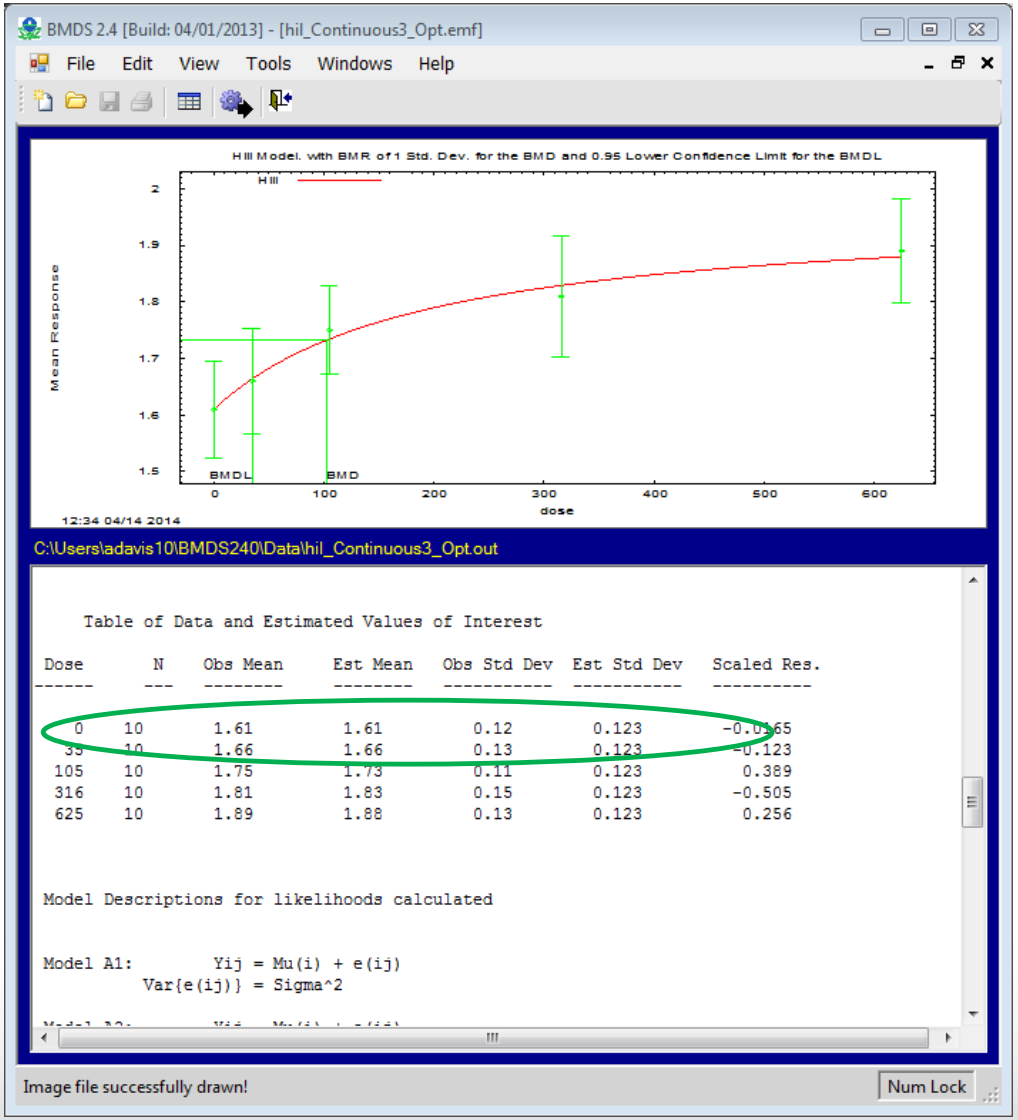
Why Use SD as the BMD for Continuous Data?



Double-checking Control Group SD

- **If using the control group's SD as the BMR, it is vitally important to make sure that the model-estimated SD approximates the reported SD**
- **The *model-estimated* SD is used for determination of the BMD**
- **If the model-estimated SD does not approximate the reported SD, then the BMD could be misspecified**

Double-checking Control Group SD



Using Relative Deviation as the BMR Type

- **If using Relative Deviation (RD), the response associated with the BMR is based on some percentage (i.e., 10%) of the *model-estimated* control mean**

- **An example of this is the assumption that a 10% decrease in body weight is an adverse response. Thus, when modeling body weight, the standard BMR would be 10% RD.**

- **As when using RD as the basis for the BMR, the user must check that the model-estimated control mean approximates the observed control means; if not, the BMD could be misspecified**

The Hybrid Approach for Calculating a BMD

- **The "hybrid approach" is an alternative method for selecting a BMR in order to calculate a BMD for continuous data**
- **Using the hybrid approach, risk is expressed in the same manner as with dichotomous models – as added or extra risk.**
- **Two parameters must be selected by the user:**
  - 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:**

  $0.10 = [P(d) - P(0)] / [1 - P(0)]$

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

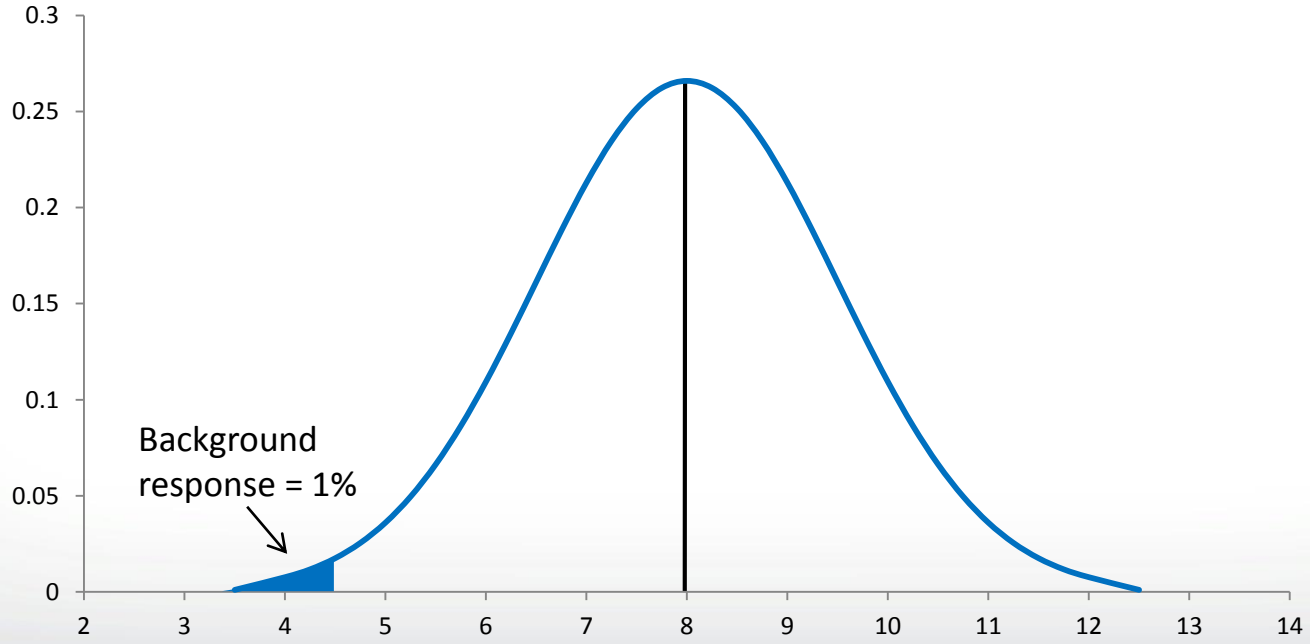
  $P(d) = (0.10 \times [1 - P(0)]) + P(0) = (0.1 \times 0.99) + 0.01 = 0.109$

- **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

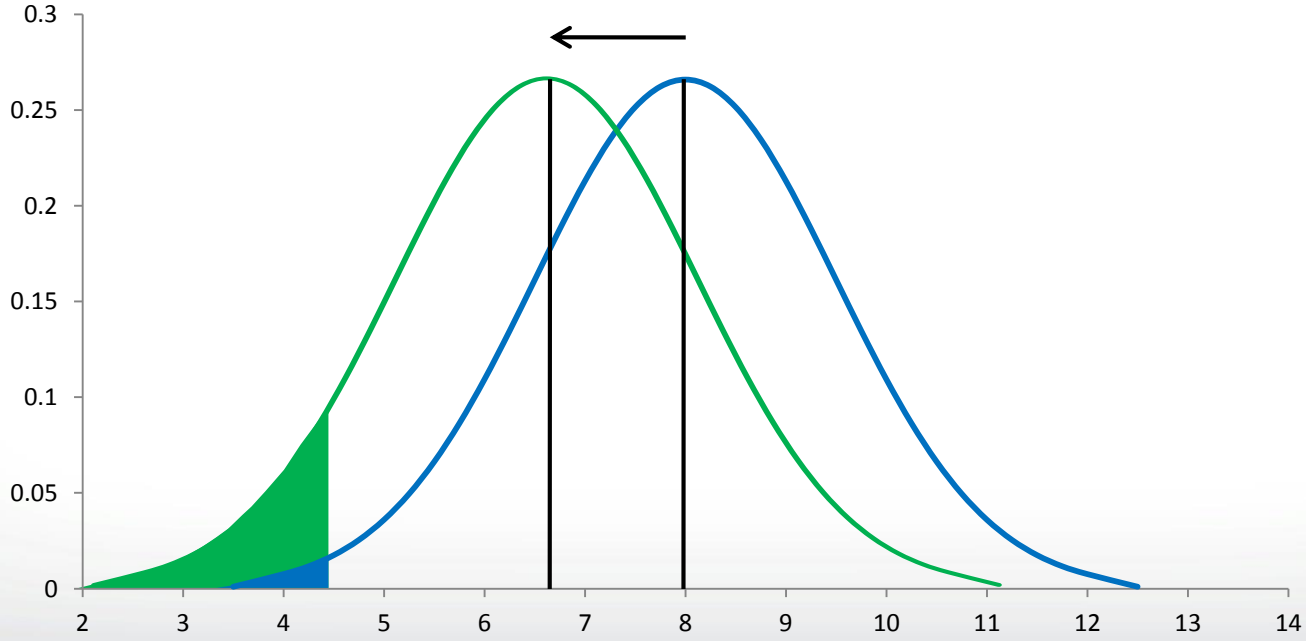
- **Next, the background rate of adverse response in the control group must be selected, in this example, we've chosen 1%**

- **The model will calculate the cut-off values in the control group distribution that correspond to this background rate**

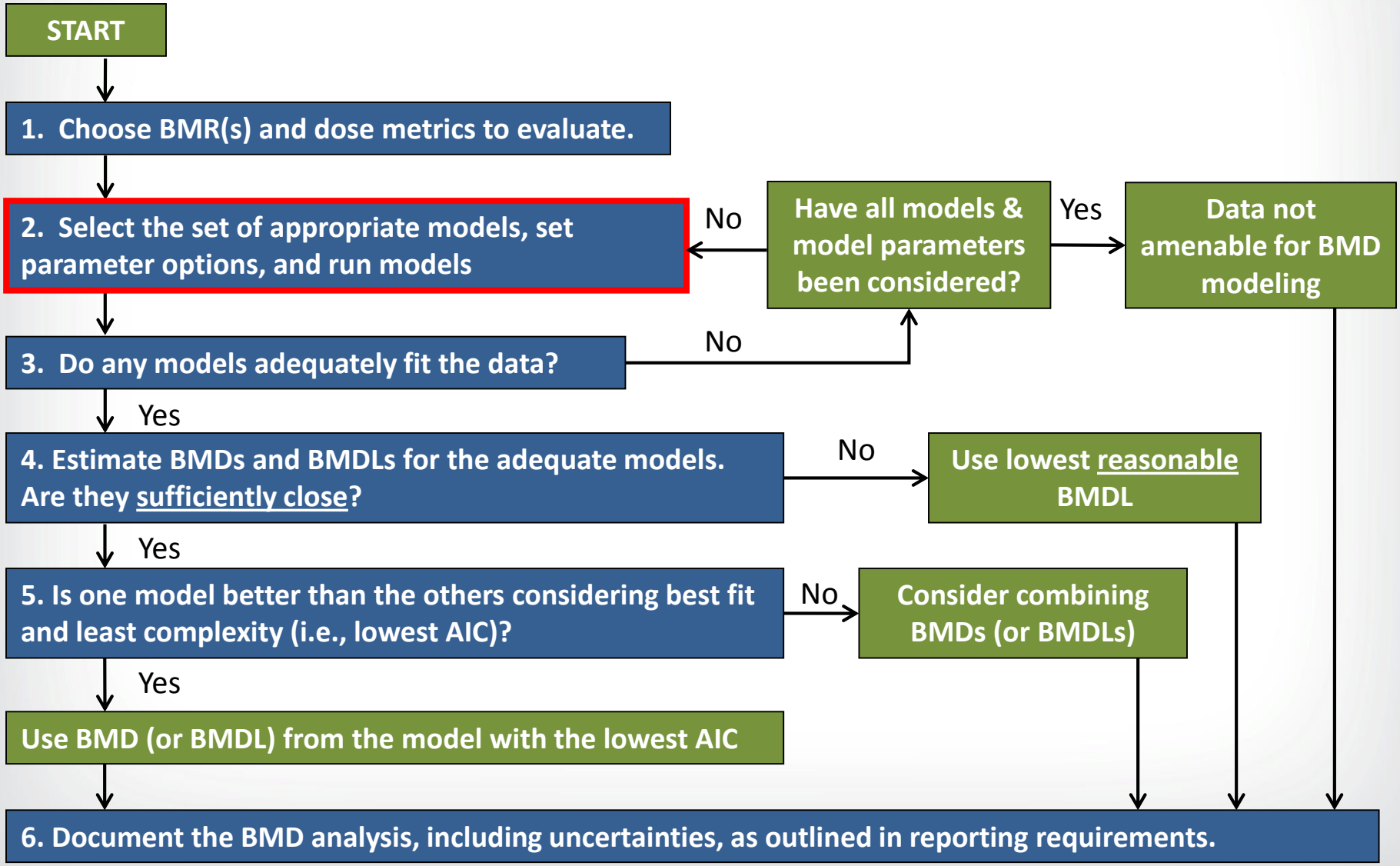


The Hybrid Approach – Selecting the Background Rate

- **Given our selection of 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**



BMD Analysis – Six Steps



Selection of a Specific Model

Biological Interpretation	Can use the Hill or Exponential models for receptor-mediated responses
Policy Decision	U.S. EPA's OPP program uses the exponential models for modeling acetylcholinesterase inhibition data
Otherwise	However, in the absence of biological or policy-driven considerations, criteria for final model selection are usually based on whether various models ***mathematically*** describe the data

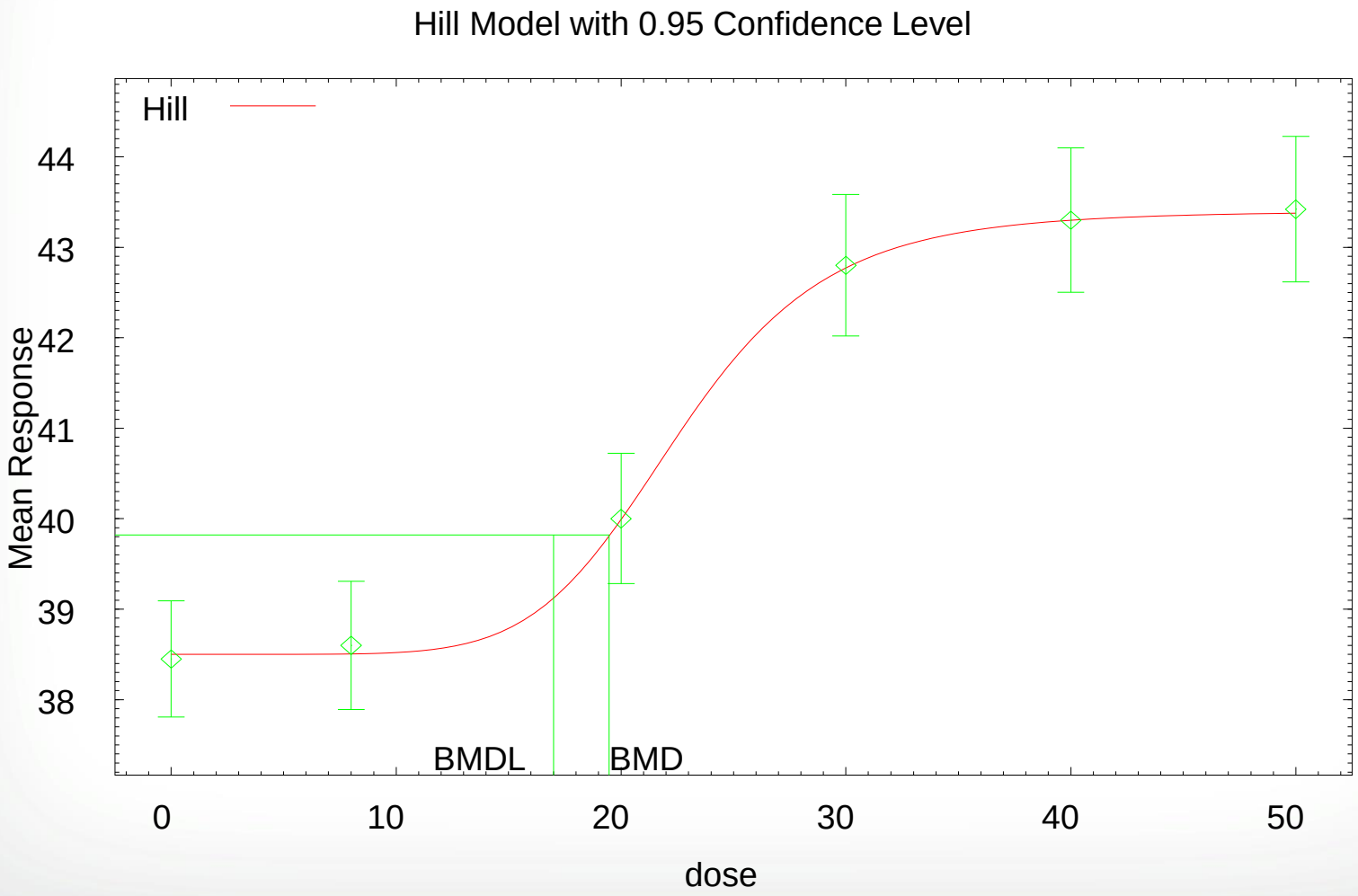
Continuous Model Forms

Model Name	Functional Form	# of Parameters	Model Fits
Polynomial[a]	$\beta_0 + \beta_1 X + \beta_2 X^2 + \ldots + \beta_n X^n$	1 + n	All purpose, can fit non-symmetrical S-shaped datasets with plateaus
Power	$\gamma + \beta X^{\Phi}$	3	L-shaped
Hill	$\gamma + \frac{(v \times X^n)}{(k^n + X^n)}$	4	Symmetrical, sigmoidal, S-shape with plateau
Exponential[b] Model 2 Model 3 Model 4 Model 5	$a \times \exp\{\pm 1 \times b \times X\}$ $a \times \exp\{\pm 1 \times (b \times X)^d\}$ $a \times [c - (c-1) \times \exp\{\pm 1 \times b \times X\}]$ $a \times [c - (c-1) \times \exp\{\pm 1 \times (b \times X)^d\}]$	 2 3 3 4	All purpose (Models 2 & 3) Symmetrical and asymmetrical S-shape with plateau (Models 4 & 5)

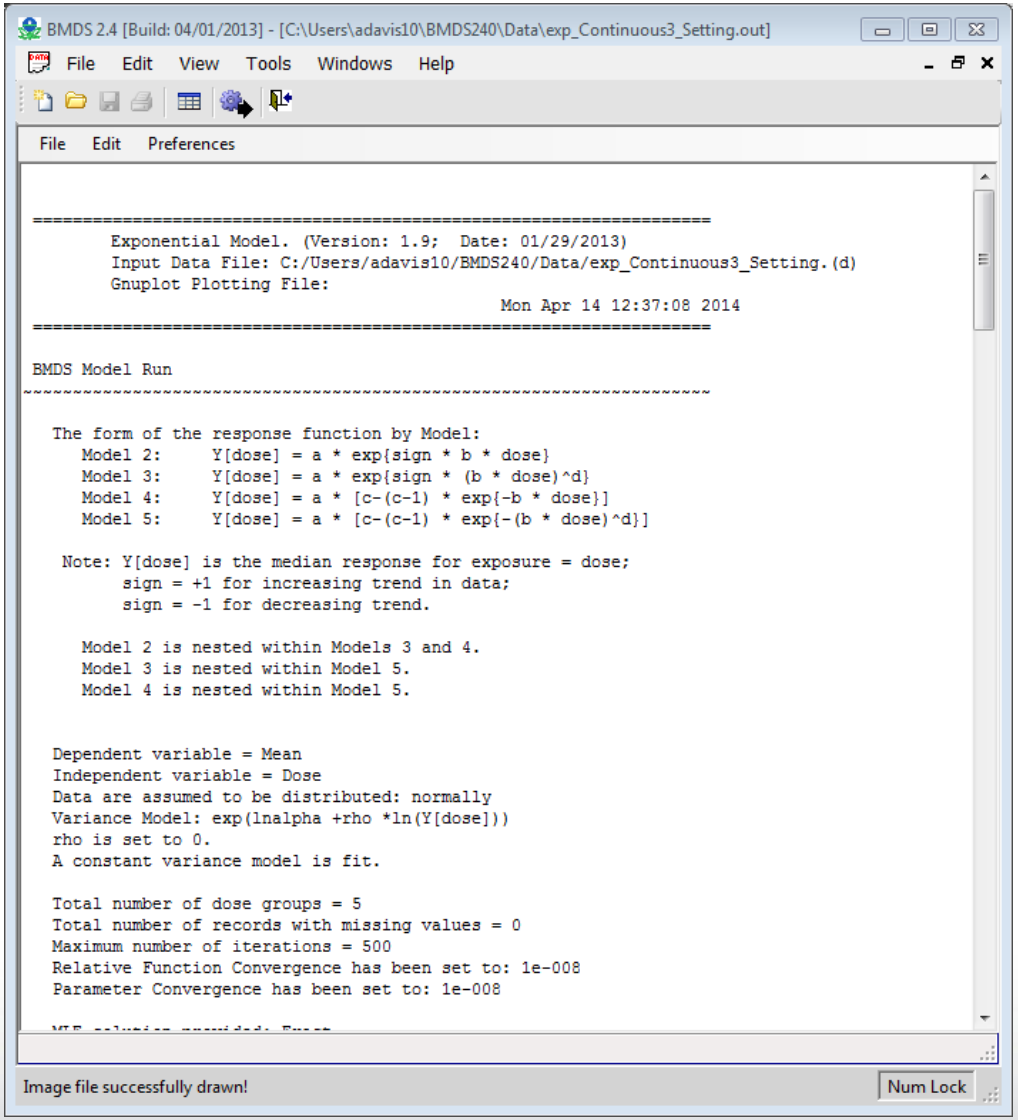
[a] The stand-alone Linear model in BMDS is equal to a first-order polynomial model

[b] Nested family of 4 related models described by Slob (2002) and included in the PROAST software of RIVM

Hill and Exponential Models – Data with Plateaus

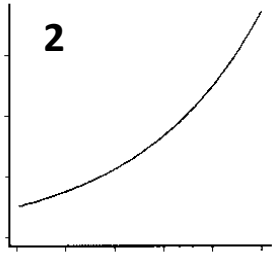


Exponential Models are "Nested"



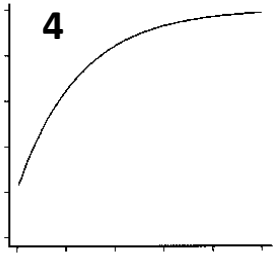
Exponential Models are "Nested"

$a \times \exp\{\pm 1 \times b \times X\}$



$c = 0$

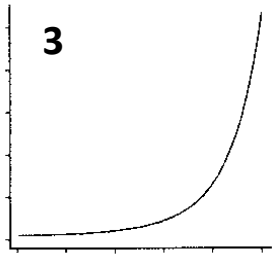
$a \times [c - (c - 1) \times \exp\{-1 \times b \times X\}]$



$d = 1$

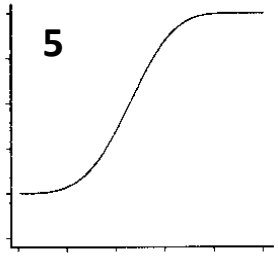
$d = 1$

$a \times \exp\{\pm 1 \times (b \times X)^d\}$



$c = 0$

$a \times [c - (c - 1) \times \exp\{-1 \times (b \times X)^d\}]$



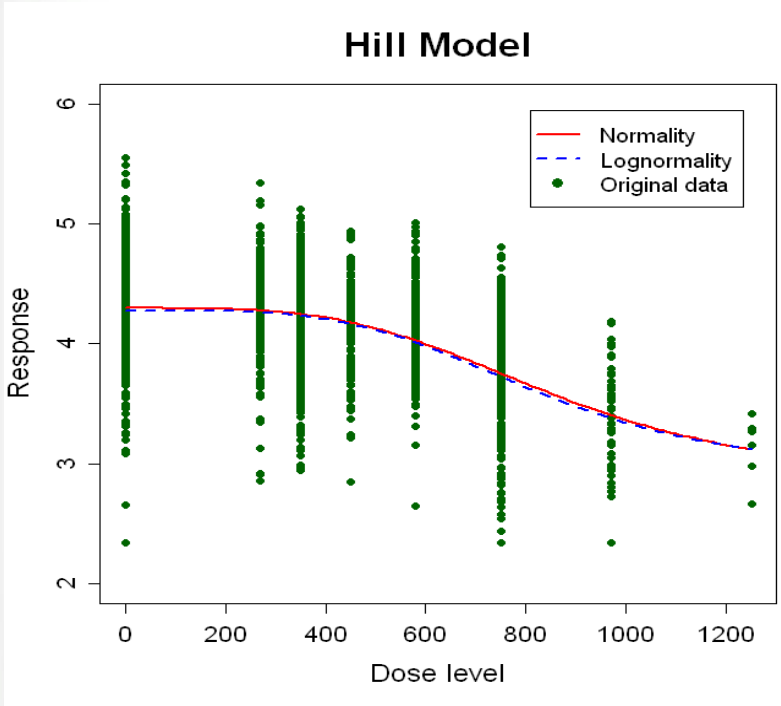
Exponential Models – Log-normality

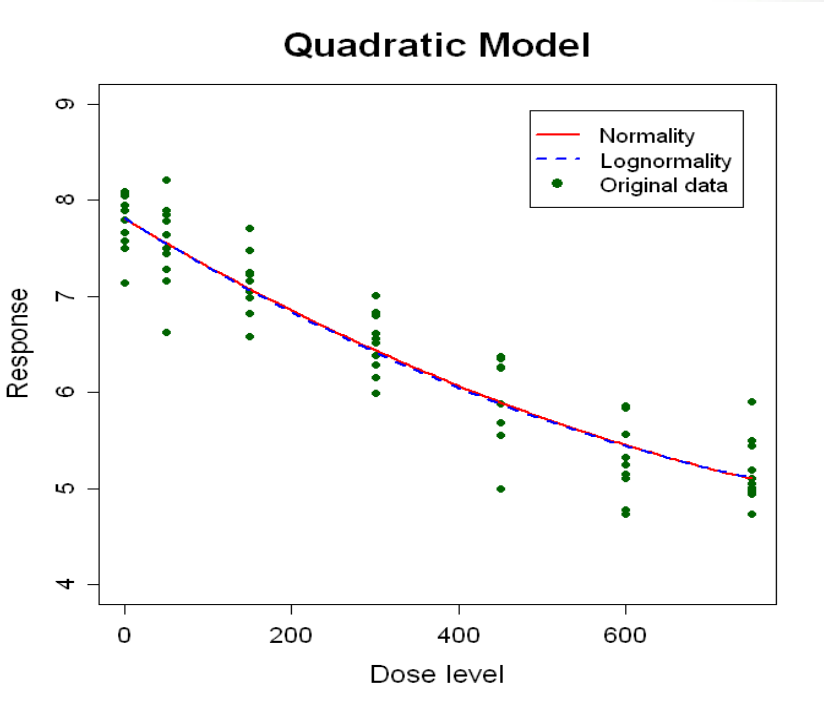
- **Data can be assumed to be lognormally distributed when using the Exponential models**
  - This reflects the distribution of the data per se, not how the modeling is done
  - Many biological parameters are lognormally distributed; a lognormal distribution is also useful to consider whenever responses are constrained to be positive
  - Eventually, lognormal distribution option will be added to other continuous models
  - Modeling gives an approximate maximum likelihood estimate for summary data (observed means and SD)

Consideration of Standard Deviation and Log-normality

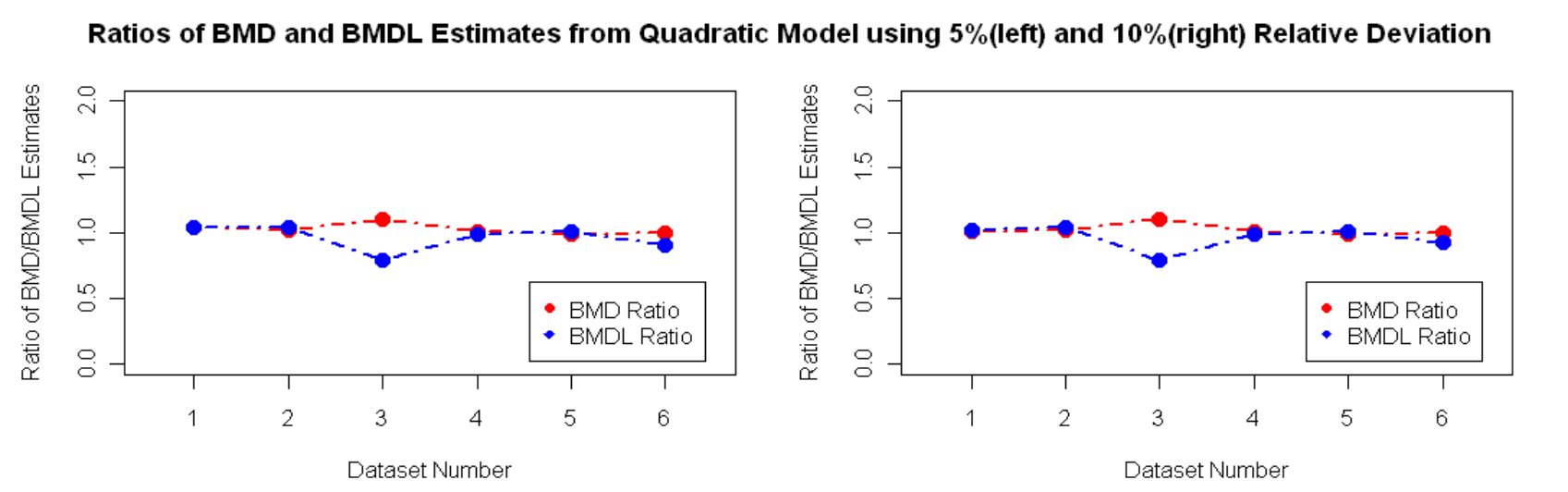
- **The SD is homogenous on a log-scale when within dose-group variance is proportional to the mean response**
-
- **However, an extra parameter is needed to model the within dose-group variance if normality is assumed**
- **Sometimes, the extra parameter can have significant impact on the BMD estimation if the "Hybrid" approach is used (Shao et al., 2013)**

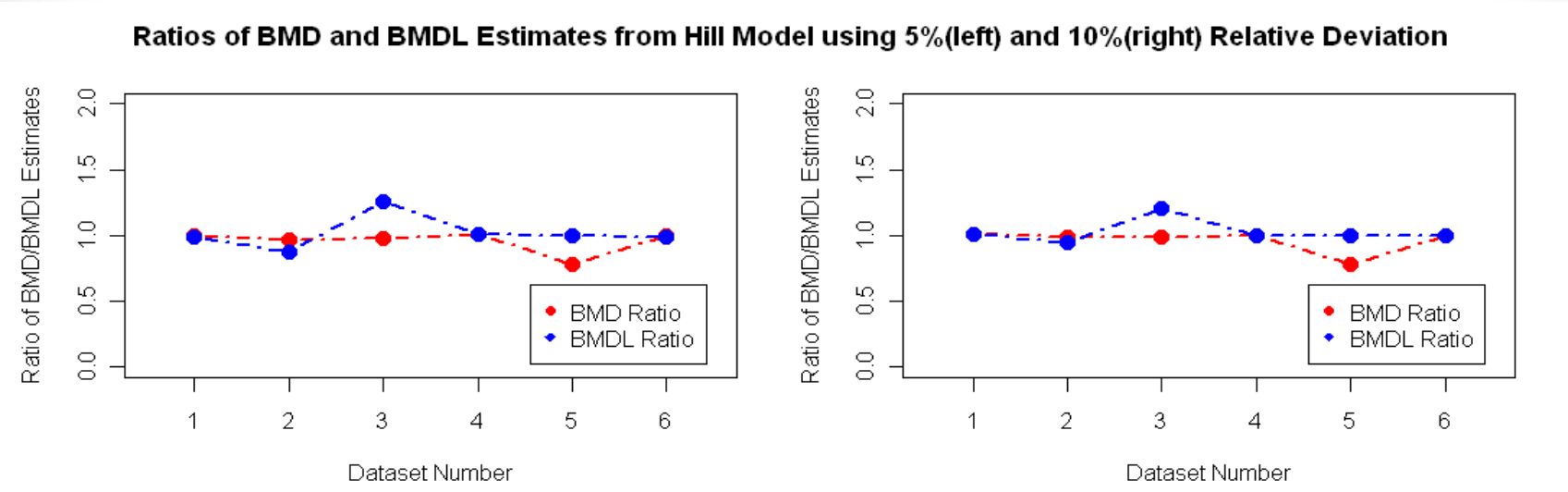
Exponential Models – Log-normality





Normality vs. Log-normality – Difference in BMDs and BMDLs





Restricting Parameters in Continuous Models

- **Model parameters (i.e., slope, background response, etc.) can be bounded to prevent biologically implausible results**
  - Bounding model parameters restricts the shape the dose-response curve can assume
- **These restrictions can impact statistical calculations such as the goodness-of-fit p-value and AIC**
  - Currently, a parameter estimate that "hits a bound" impacts a model's degrees of freedom (DF) (in BMDS, DF is increased by 1)
  - When a parameter hits a bound, that parameter is not counted towards the AIC penalization (EPA's Statistical Working Group may modify this approach in the future)

Restricting Continuous Models – EPA Recommendations

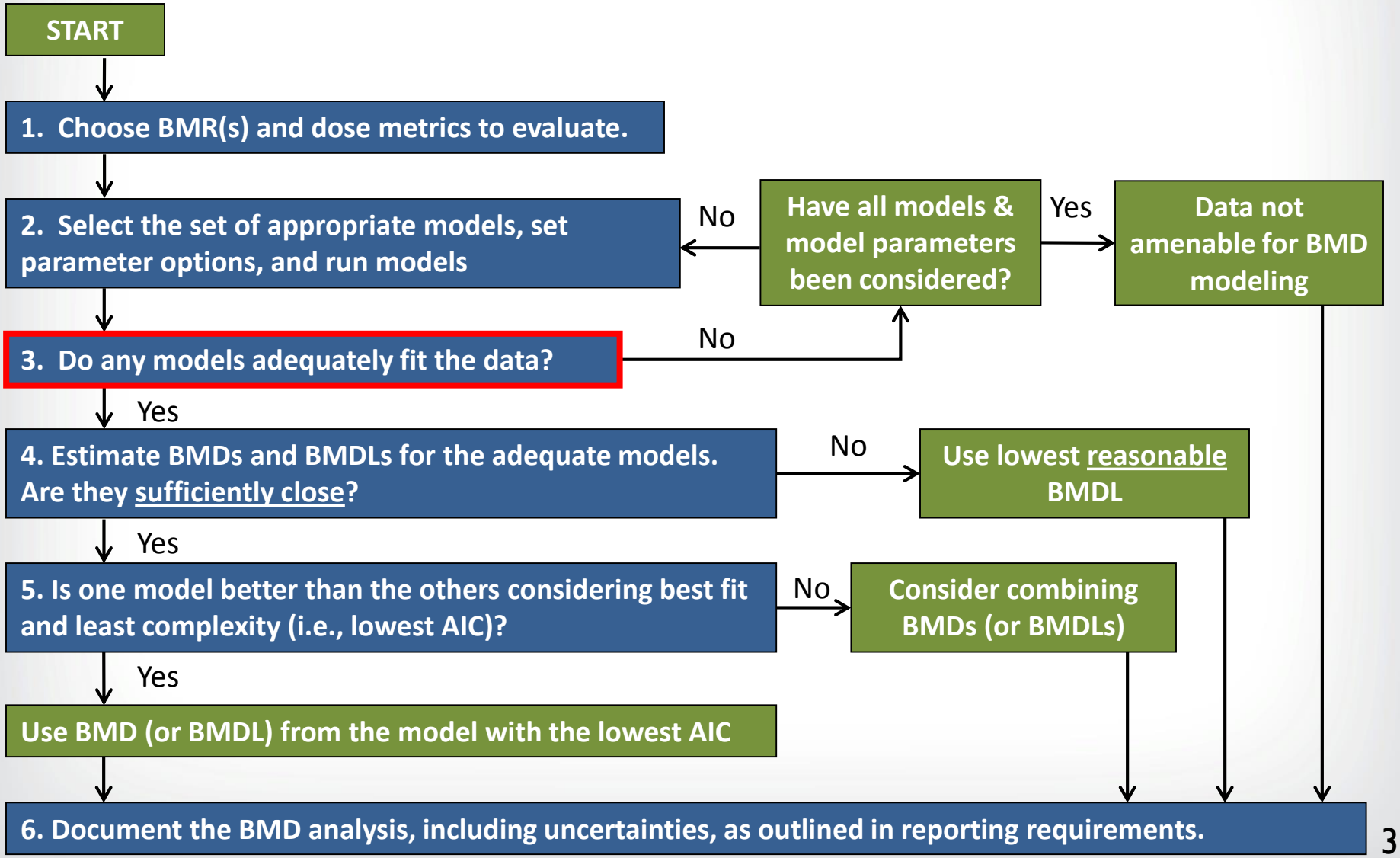
- **User-specified Parameter Restrictions**
  - **Polynomial coefficients** – restrict to positive or negative
  - **Power and slope terms** – restrict to be 1 or greater
  - **Background** - do not set to zero unless biologically justifiable

- **Other Modeling Options**
  - **Threshold parameter** - currently not recommended as the parameter can be misconstrued to have more biological meaning than appropriate
  - **Multivariate Modeling** – currently not available in any continuous models in BMDS, other software packages (i.e., PROAST) can consider covariates for all data types

Exponential Model Restrictions

- **The Exponential Models have built-in restrictions that cannot be changed**
  - **Background Response (a term)** > 0
  - **Slope (b term)** > 0
  - **Asymptote (Models 4 and 5 only, c term)** > 1 (increasing response) **OR** > 0 and < 1 (decreasing response)
  - **Power (Models 3 and 5 only, d term)** >1

BMD Analysis – Six Steps

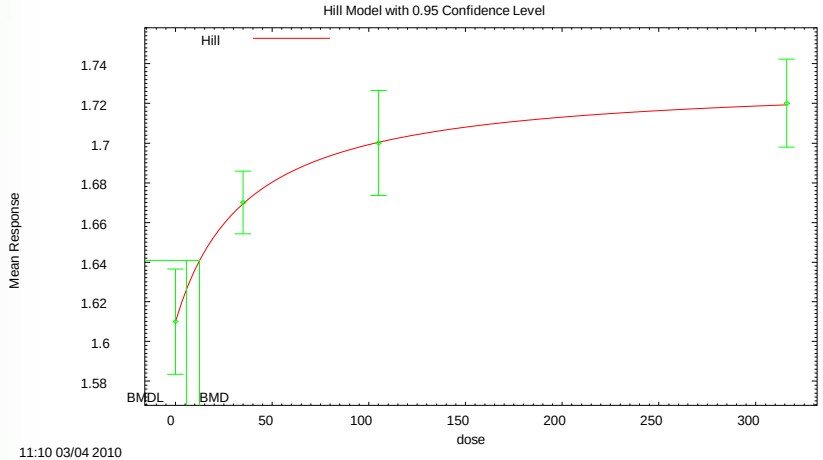


Dose the Model Fit the Data?

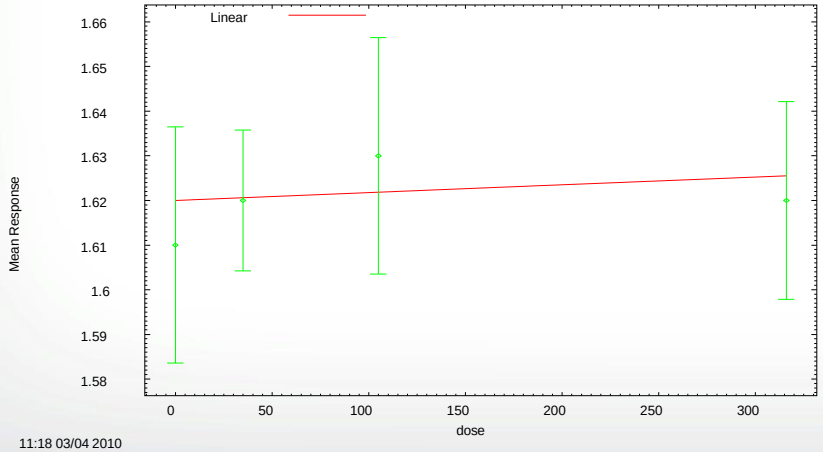
- **For continuous data:**
  - ***Tests of interest (response/variance modeling)***
  - Global measurement: goodness-of-fit p value ($p > 0.1$)
  - Local measurement: Scaled residuals (absolute value < 2.0)
  - Visual inspection of model fitting.

Tests of Interest – Differences in Responses/Variances

- **Test 1 – Do responses and/or variances differ among dose levels?**



The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels. It seems appropriate to model the data



The p-value for Test 1 is greater than .05. There may not be a difference between responses and/or variances among the dose levels. Modeling the data with a dose/response curve may not be appropriate

Tests of Interest – Variance

- **In the current version BMDS, the distribution of continuous measures is assumed to be normal, with either a constant (homogenous) variance or a variance that changes as a power function of the mean value**
  - $\text{Var}(i) = \alpha[\text{mean}(i)]^{\rho}$
  - ρ(rho) = 0, constant variance
  - ρ(rho) $\neq$ 0, modeled variance
- **Test 2 – Are variances homogenous?**
- **Test 3 – Are variances adequately modeled?**
- **Always assume constant variance unless data clearly indicate otherwise**

Tests of Interest - Variance

Continuous data modeled with assumed constant variance

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```
                    Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

   Test     -2*log(Likelihood Ratio)  Test df        p-value

   Test 1                 27.022           8        0.0007008
   Test 2                1.06375           4              0.9
   Test 3                1.06375           4              0.9
   Test 4               0.489269           2            0.783

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here


The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data
```

Variance has been modeled appropriately in this case.

Tests of Interest - Variance

Continuous data modeled with assumed constant variance

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```
                    Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
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                     Tests of Interest

   Test     -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              22.9676           8         0.003406
   Test 2              8.86135           4          0.06466
   Test 3              8.86135           4          0.06466
   Test 4             0.234903           2           0.8892

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  Consider running a
non-homogeneous variance model

The p-value for Test 3 is less than .1.  You may want to consider a
different variance model

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data
```

Variance not modeled appropriately. Use the power variance model.

Tests of Interest - Variance

Continuous data with variance modeled as power function of mean

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                     Tests of Interest

   Test     -2*log(Likelihood Ratio)  Test df        p-value

   Test 1               22.9676           8         0.003406
   Test 2               8.86135           4         0.06466
   Test 3              0.197512           3           0.978
   Test 4              0.134688           1          0.7136

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data
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Variance has been modeled appropriately in this case.

Tests of Interest - Variance

Continuous data with variance modeled as power function of mean

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 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

   Test     -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              71.8879           8          <.0001
   Test 2              41.0241           4          <.0001
   Test 3              11.9065           3         0.00771
   Test 4               2.7823           1         0.09531

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is less than .1.  You may want to consider a
different variance model

The p-value for Test 4 is less than .1.  You may want to try a different
model
```

Variance not modeled appropriately. Can't model this data with BMDS

Does the Model Fit the Data?

- **For continuous data:**
  - Tests of interest (response/variance modeling)
  - ***Global measurement: goodness-of-fit p value (p > 0.1)***
  - Local measurement: Scaled residuals (absolute value < 2.0)
  - Visual inspection of model fitting.

Global Goodness-of-Fit (Test 4)

- **BMDS provides a *p*-value to measure global goodness-of-fit**
  - Measures how model-predicted dose-group response means differ from the actual response means
  - Small values indicate poor fit
  - Recommended cut-off value is $p = 0.10$
  - For models selected *a priori* due to biological or policy preferences (e.g., Exponential models for acetylcholinesterase data), a cut-off value of $p = 0.05$ can alternatively be used

Global Goodness-of-Fit (Test 4)

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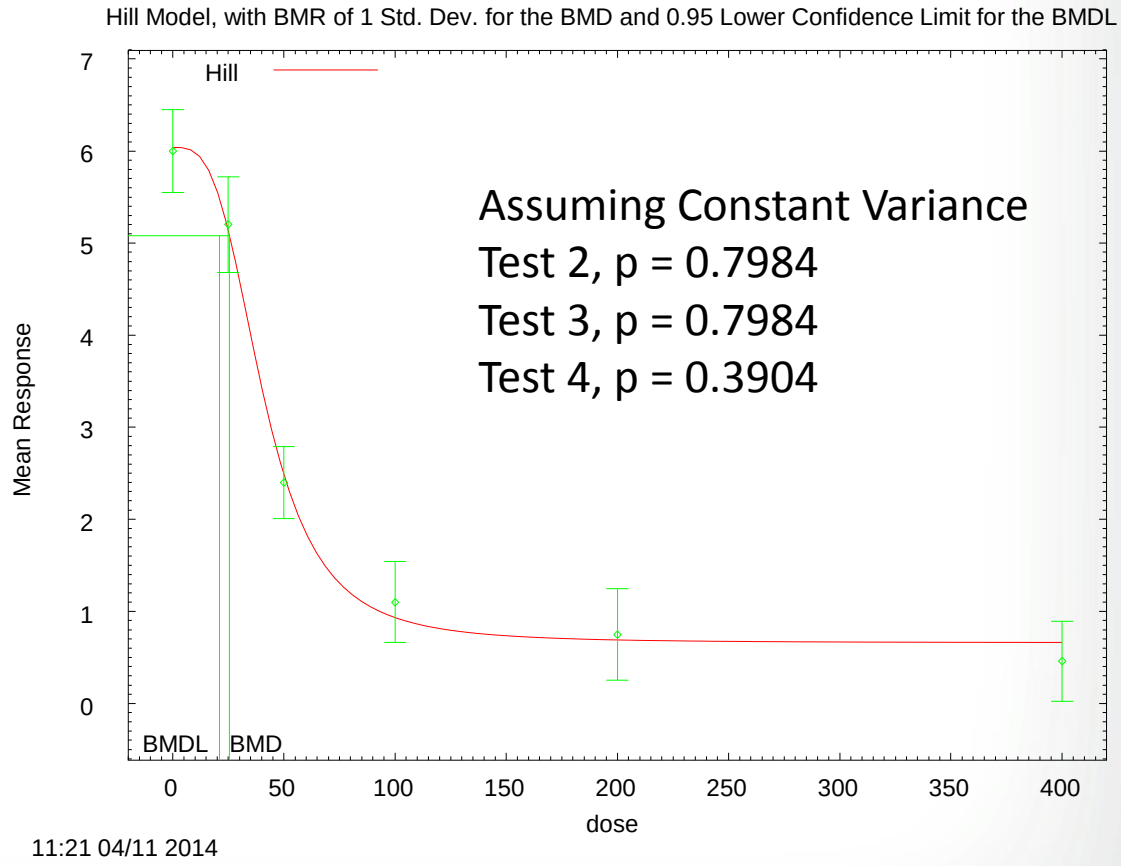
Modeling Recommendations – Poor Global Goodness-of-Fit

- **Consider dropping high dose group(s) that negatively impact low dose fit**
- **Don't drop doses solely to improve fit**
- **To model a high dose "plateau" consider using a Hill or other models that contain an asymptote term**
- **Use PBPK models if available to calculate internal dose metrics that may facilitate better model fitting**

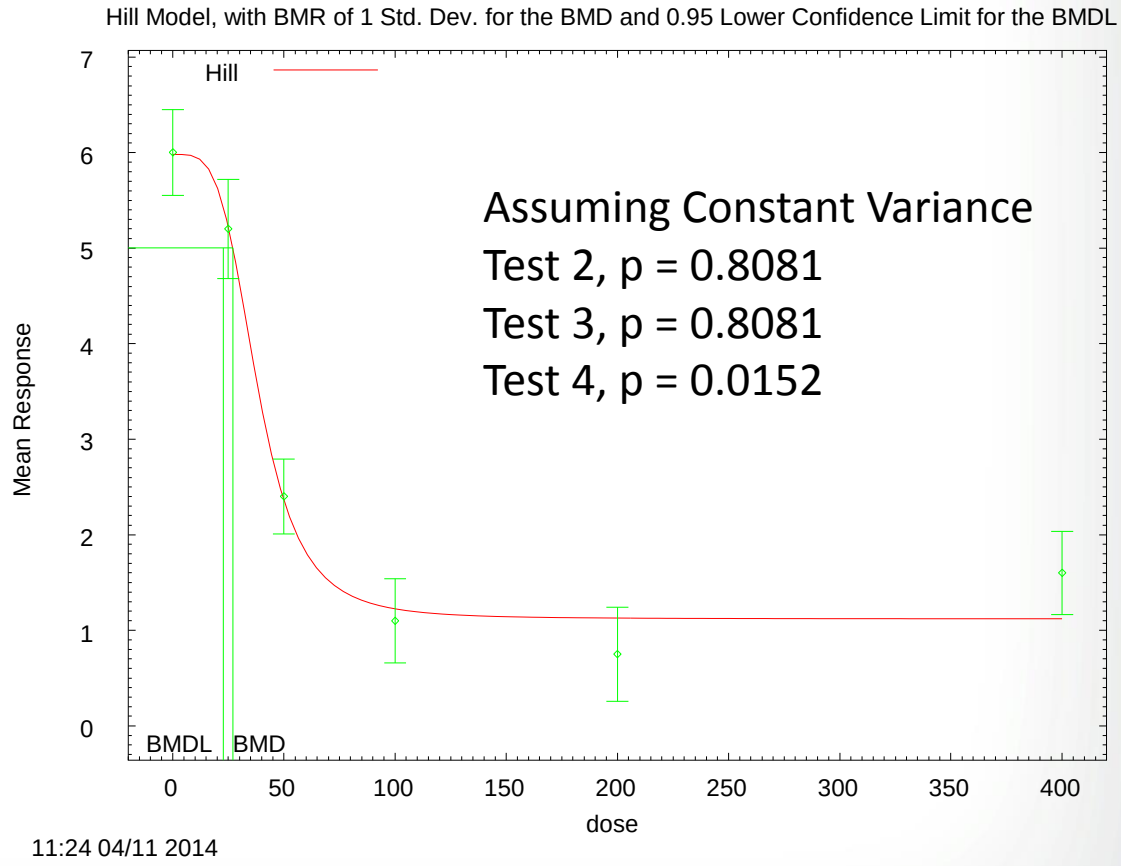
Example 1: When Not to Drop the High Dose

Dose (mg/m^3)	N	Mean	SD
0	20	6.0	0.96
25	20	5.2	1.11
50	19	2.4	0.81
100	20	1.1	0.94
200	20	0.75	1.05
400	20	0.46	0.93



Example 1: When to Drop the High Dose

Dose (mg/m^3)	N	Mean	SD
0	20	6.0	0.96
25	20	5.2	1.11
50	19	2.4	0.81
100	20	1.1	0.94
200	20	0.75	1.05
400	20	1.6	0.93



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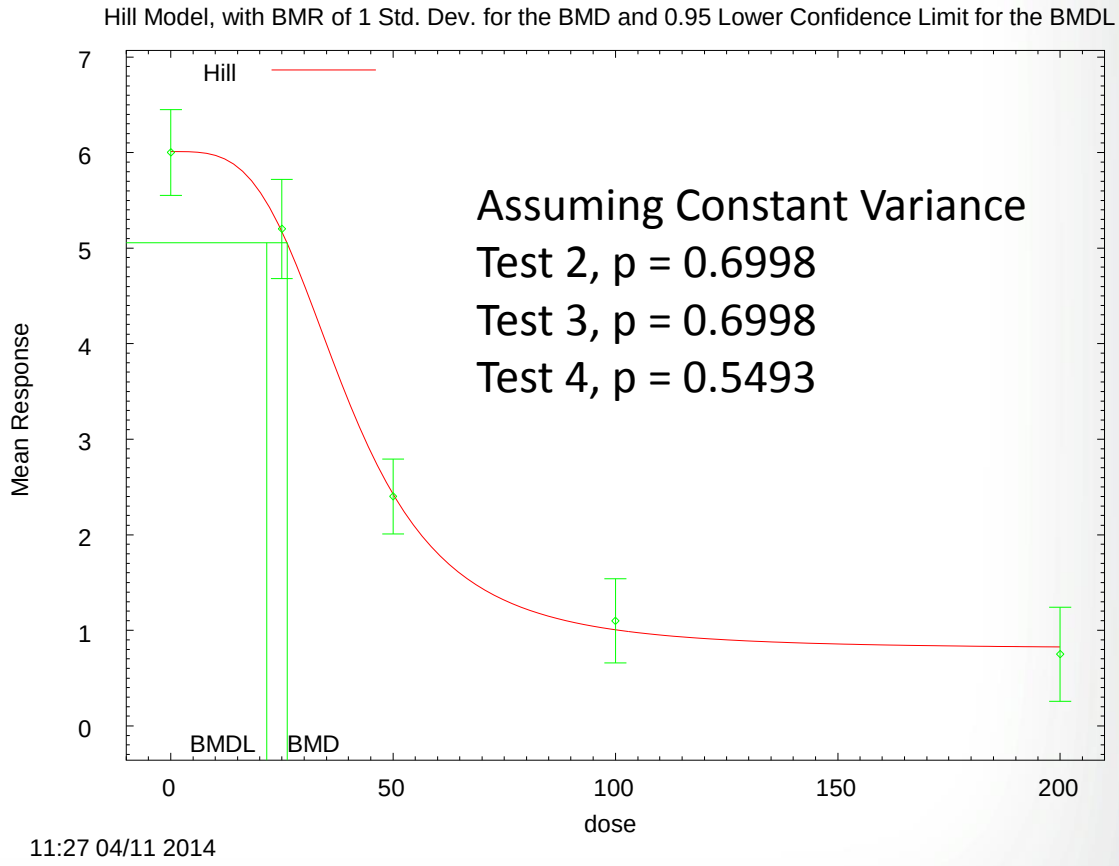
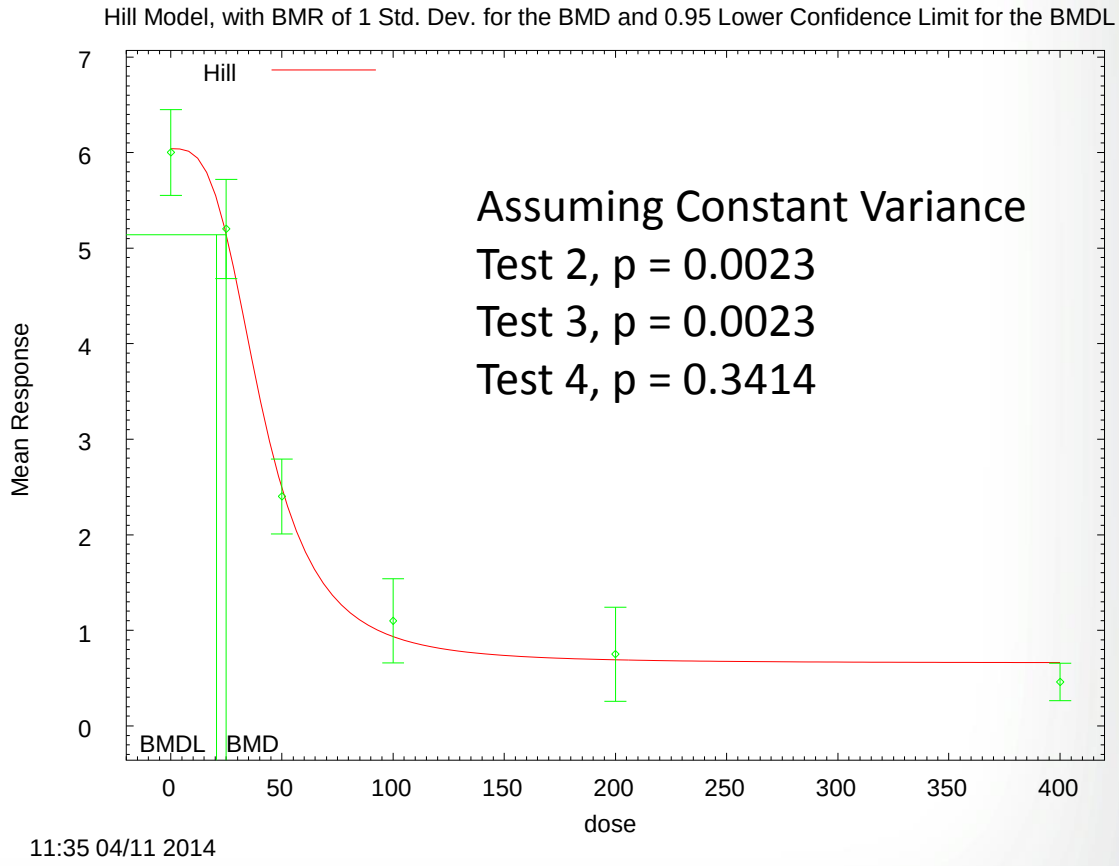


Example 1: When to Drop the High Dose

Dose (mg/m^3)	N	Mean	SD
0	20	6.0	0.96
25	20	5.2	1.11
50	19	2.4	0.81
100	20	1.1	0.94
200	20	0.75	1.05
400	20	0.46	0.42



Example 1: When to Drop the High Dose

Dose (mg/m^3)	N	Mean	SD
0	20	6.0	0.96
25	20	5.2	1.11
50	19	2.4	0.81
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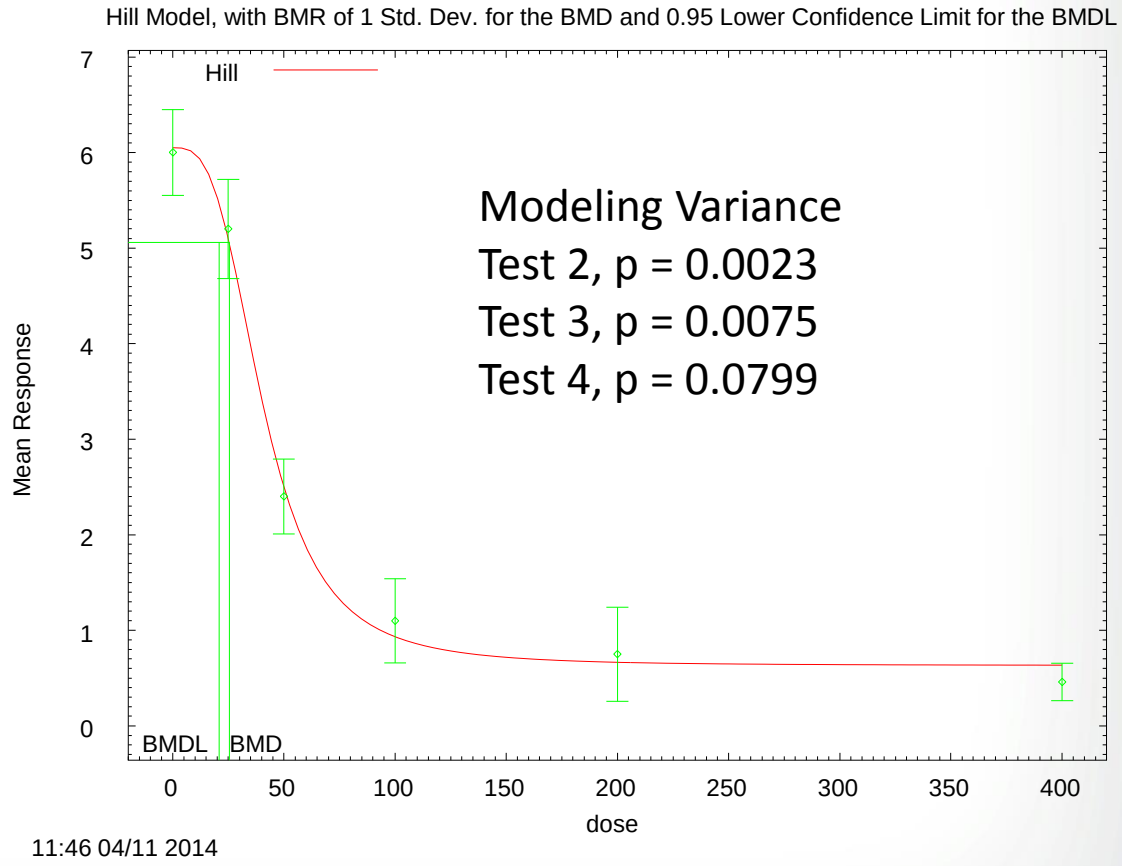
200	20	0.75	1.05
400	20	0.46	0.42



Example 1: When to Drop the High Dose

Dose (mg/m^3)	N	Mean	SD
0	20	6.0	0.96
25	20	5.2	1.11
50	19	2.4	0.81
100	20	1.1	0.94
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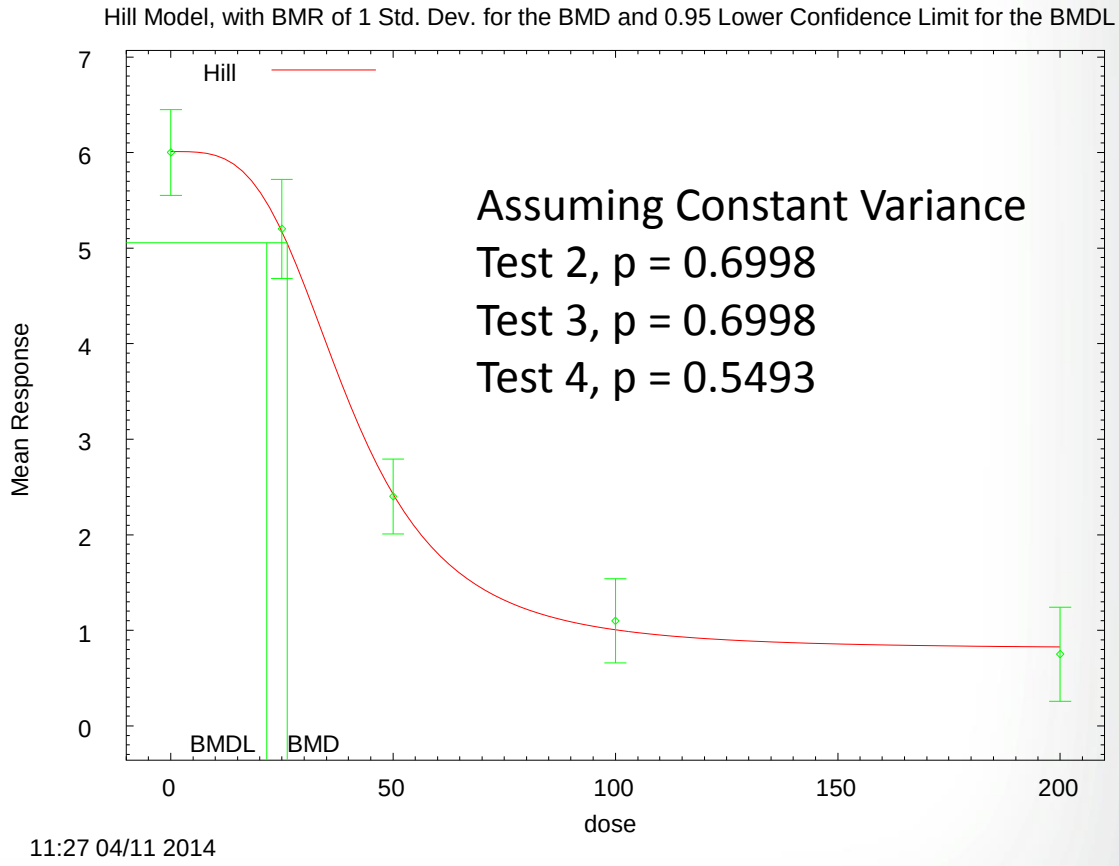


Further Recommendations – Poor Global Goodness-of-Fit

- **Log-transformation of doses**
  - Consult a statistician to determine if log-transformation is appropriate, special care often needs to be taken with the control dose (i.e., $\log_{10}(0)$ is undefined)
  - Both $\log_{10}$ and $\log_e$ transformations are available in BMDS
- **PBPK modeling can be very useful for BMD modeling**
  - For highly supralinear curves, use of internal dose metrics may be helpful, especially in cases of metabolic saturation (e.g., dose-response shape will be linearized)
  - If one particular dose metric fits the response data more closely, this may be an indication that this dose metric is the metric of interest (i.e., C_{max} vs. AUC)

PBPK Models and BMD Modeling

- **Care must be taken when performing BMD analyses with PBPK model-derived estimates of internal dose**
- **Most important question: Is the relationship between external and internal dose metrics linear across all doses?**
- **If yes, then it does not matter when BMD modeling occurs**
  - Can model external doses and then convert BMDs and BMDLs to internal doses (often advantageous if PBPK model is constantly updated or changed)
- **If no, then BMD analysis must be conducted using the internal dose metrics of interest**

Does the Model Fit the Data?

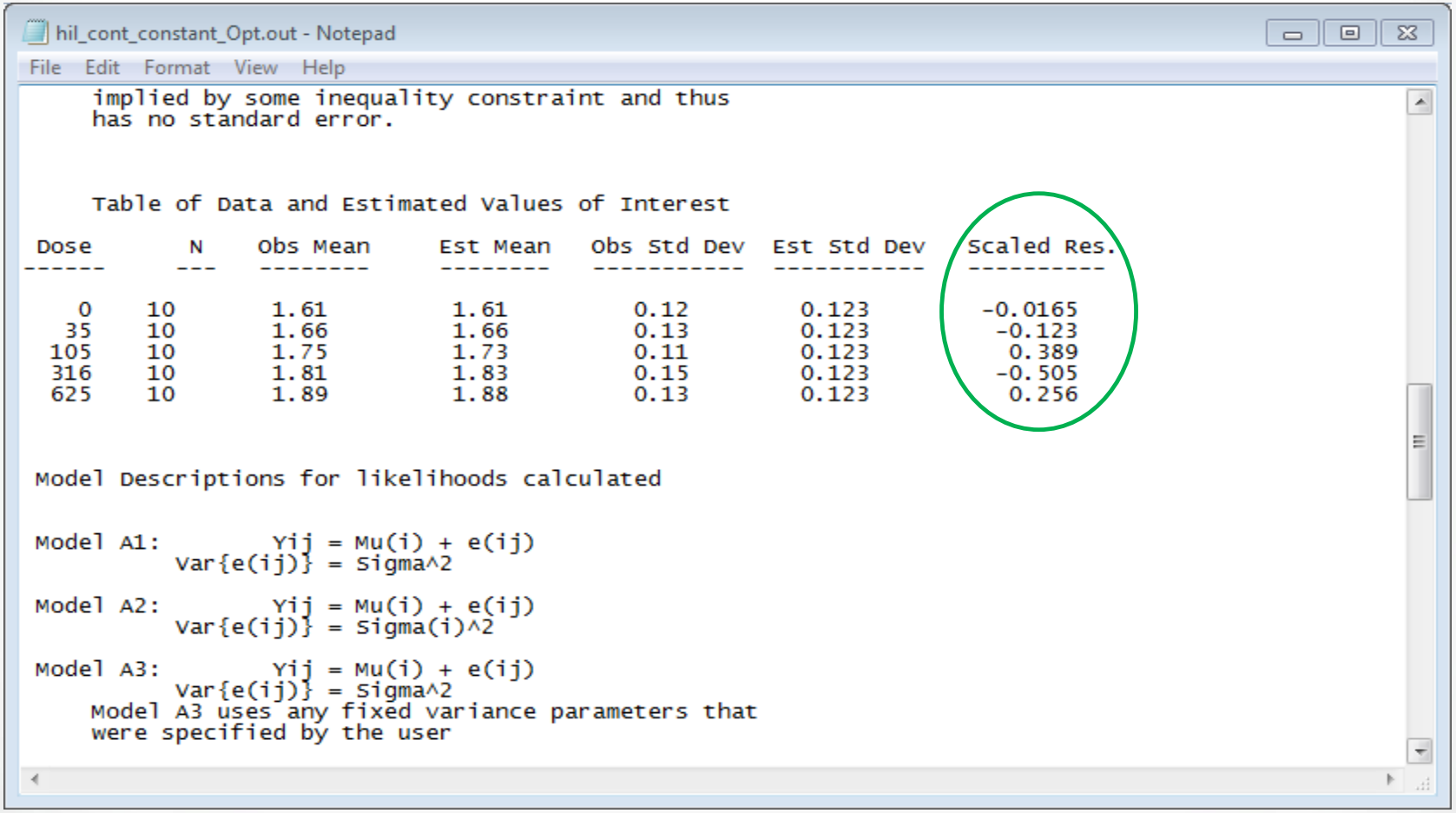
- **For continuous data:**
  - Tests of interest (response/variance modeling)
  - Global measurement: goodness-of-fit p value ($p > 0.1$)
  - ***Local measurement: Scaled residuals (absolute value < 2.0)***
  - Visual inspection of model fitting.

Scaled Residuals

- **Global goodness-of-fit *p*-values are not enough to assess local fit**
  - Models with large *p*-values may consistently "miss the data" (e.g., always on one side of the dose-group means)
  - Models may "fit" the wrong (e.g. high-dose) region of the dose-response curve.

- **Scaled Residuals – measure of how closely the model fits the data at each point; 0 = exact fit**
  - $\frac{Obs\ Mean - Est\ Mean}{\frac{Est\ SD}{\sqrt{n}}}$
  - Absolute values near the BMR should be lowest
  - Question scaled residuals with absolute value > 2

Scaled Residuals



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```
     implied by some inequality constraint and thus
     has no standard error.


     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

    0     10       1.61         1.61         0.12        0.123        -0.0165
   35     10       1.66         1.66         0.13        0.123         -0.123
  105     10       1.75         1.73         0.11        0.123          0.389
  316     10       1.81         1.83         0.15        0.123         -0.505
  625     10       1.89         1.88         0.13        0.123          0.256


 Model Descriptions for likelihoods calculated


 Model A1:         Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

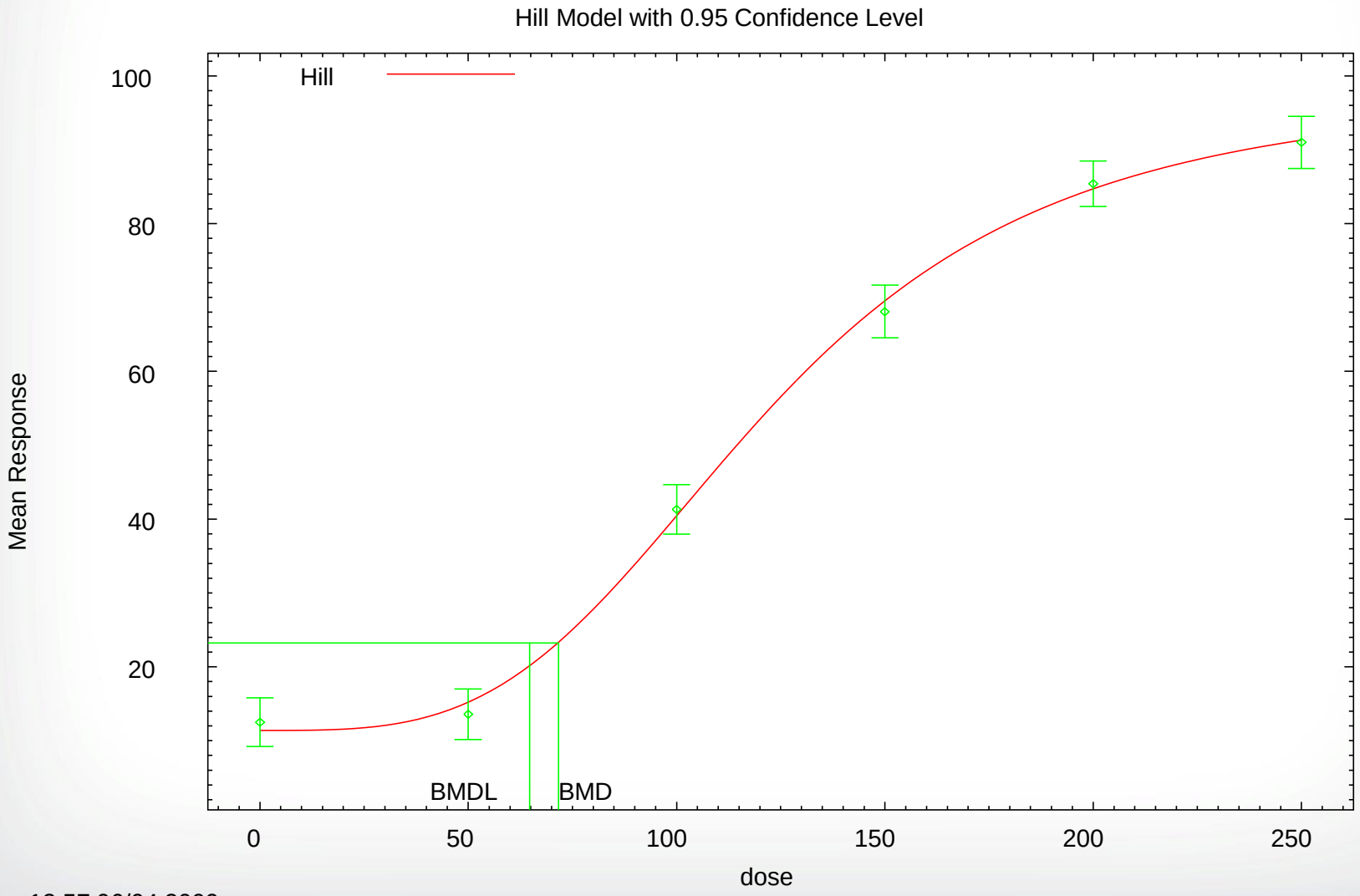
 Model A2:         Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

 Model A3:         Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2
     Model A3 uses any fixed variance parameters that
     were specified by the user
```

Does the Model Fit the Data?

- **For continuous data:**
  - Tests of interest (response/variance modeling)
  - Global measurement: goodness-of-fit p value ($p > 0.1$)
  - Local measurement: Scaled residuals (absolute value < 2.0)
  - ***Visual inspection of model fitting.***

Visual Inspection of Model Fit



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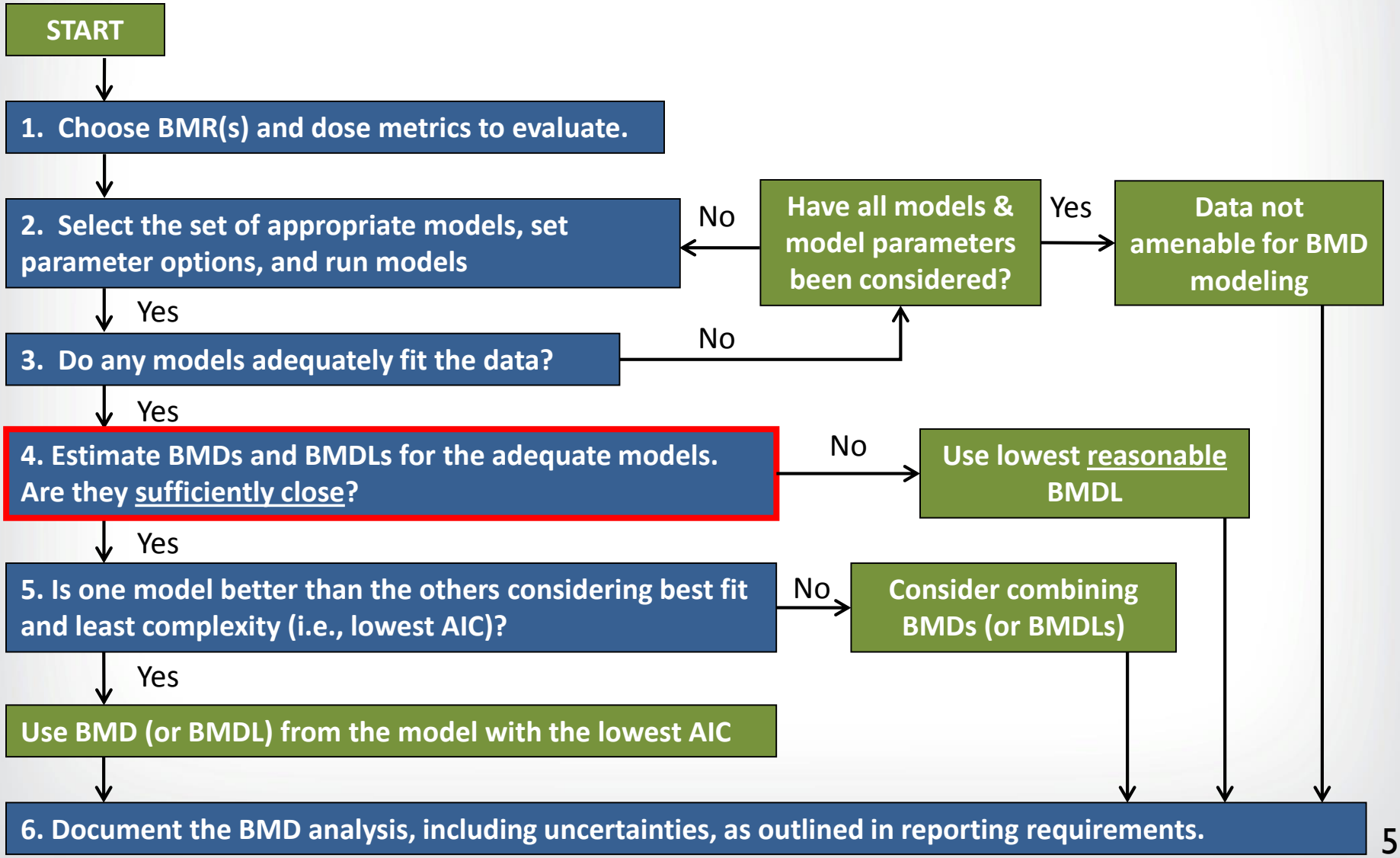
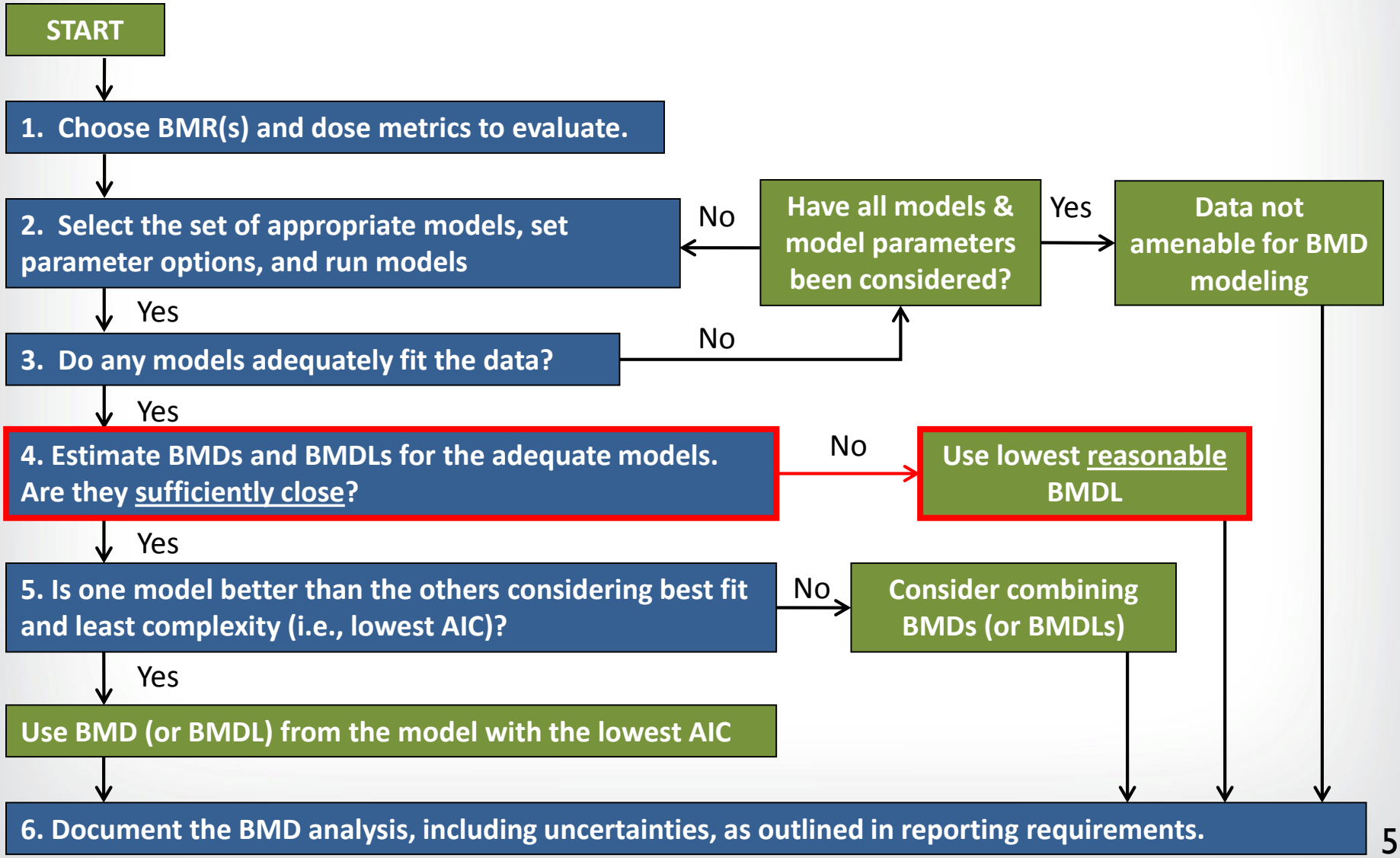
BMD Analysis – Six Steps



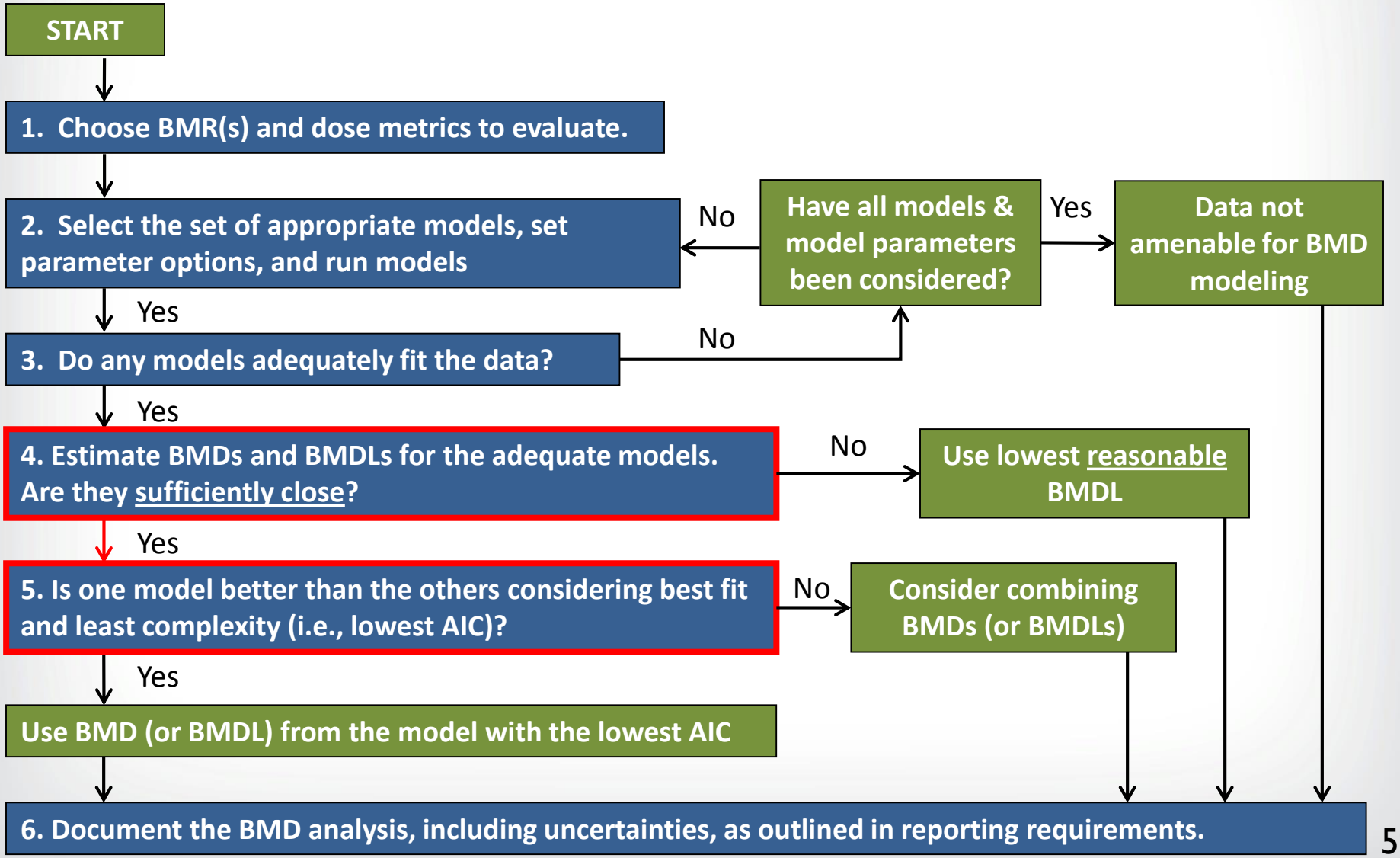
Are BMDL Estimates "Sufficiently Close"?

- **Often, more than one model or modeling options will result in an acceptable fit to the data.**
- **Consider using the lowest BMDL if BMDL estimates from acceptable models are not sufficiently close, indicating model dependence**
- **What is "sufficiently close" can vary based on the needs of the assessment, but generally should not be more than 3-fold.**

BMD Analysis – Six Steps



BMD Analysis – Six Steps



Comparing Model Fit Across Models

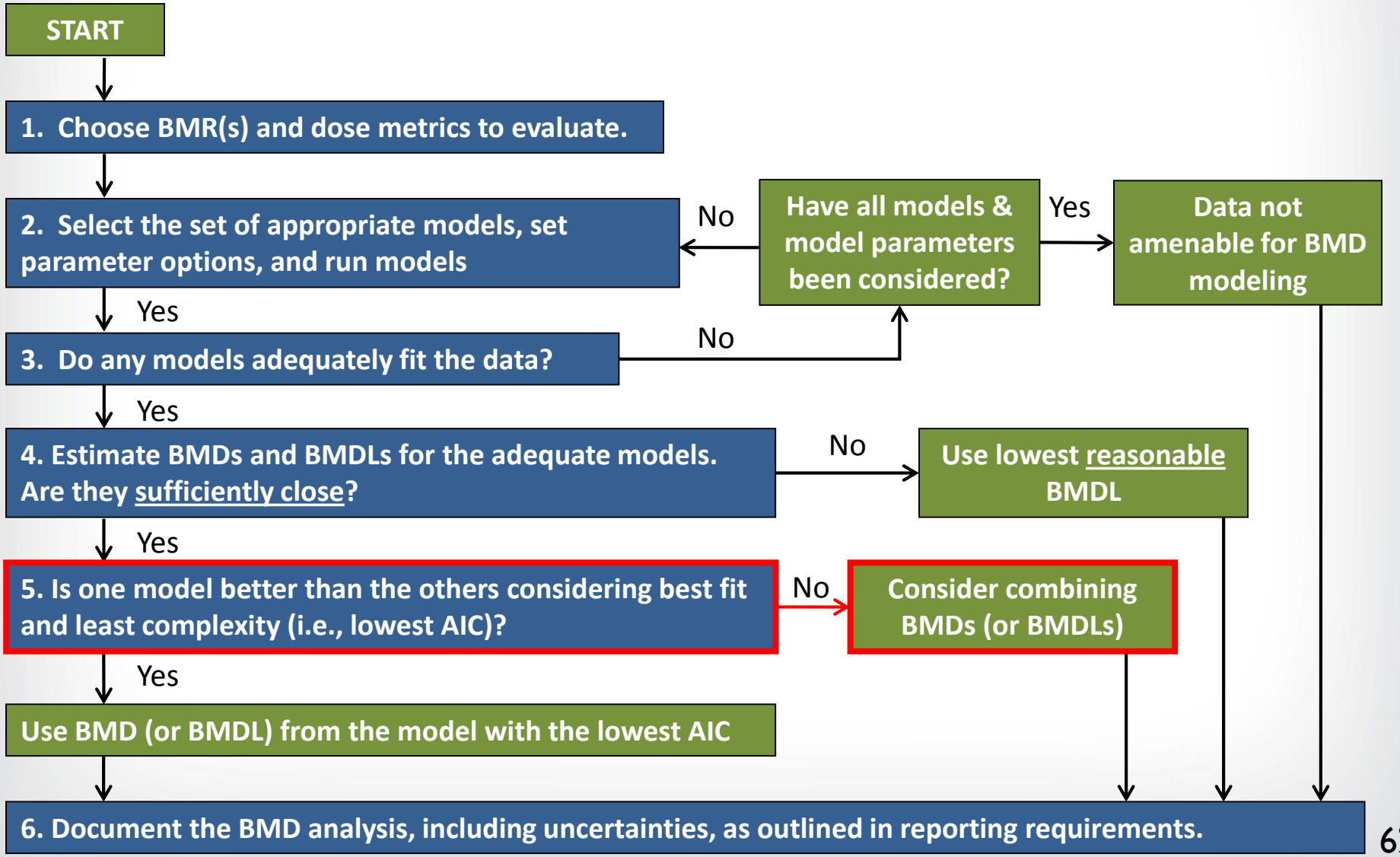
- **Within a family of models (e.g., 2nd degree vs. 1st degree multistage), addition of parameters will generally improve fit**
  - Likelihood ratio tests can determine whether the improvement in fit afforded by extra parameters is justified
  - However, these tests cannot be used to compare models from different families (e.g., multistage vs. log-probit)

- **When comparing models from different families, Akaike's Information Criterion (AIC) is used to identify the best fitting model (the lower the AIC, the better)**

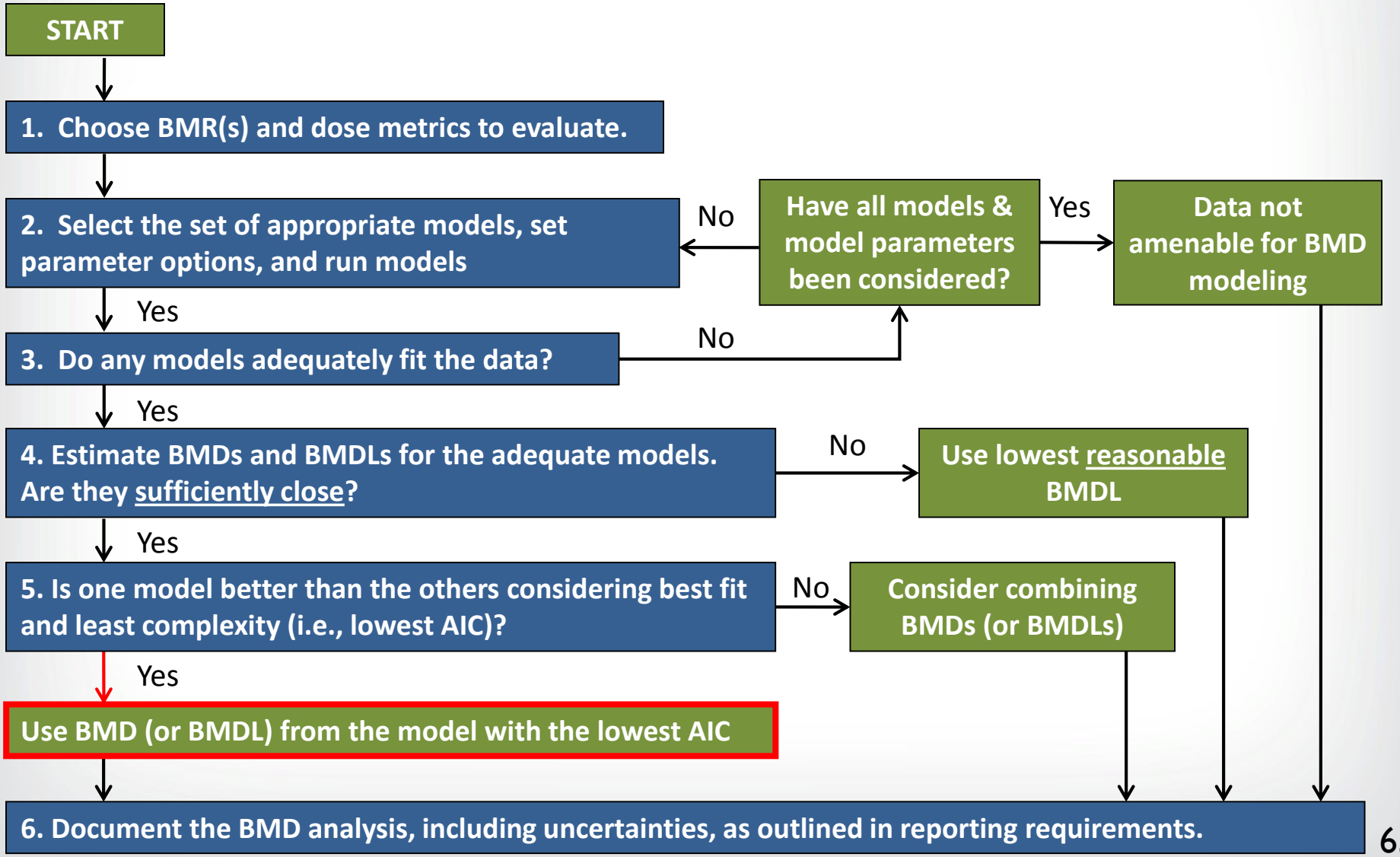
Akaike's Information Criterion (AIC)

- **AIC = -2 x LL + 2 x p**
  - LL = log-likelihood at the maximum likelihood estimates for parameters
  - p = number of model degrees of freedom (dependent on total number of model parameters, number of model parameters that hit a bound, and the number of dose groups in your dataset)
- **Only the DIFFERENCE in AIC is important, not actual value**
- **As a matter of policy, any difference in AIC is considered important. This prevents "model shopping"**

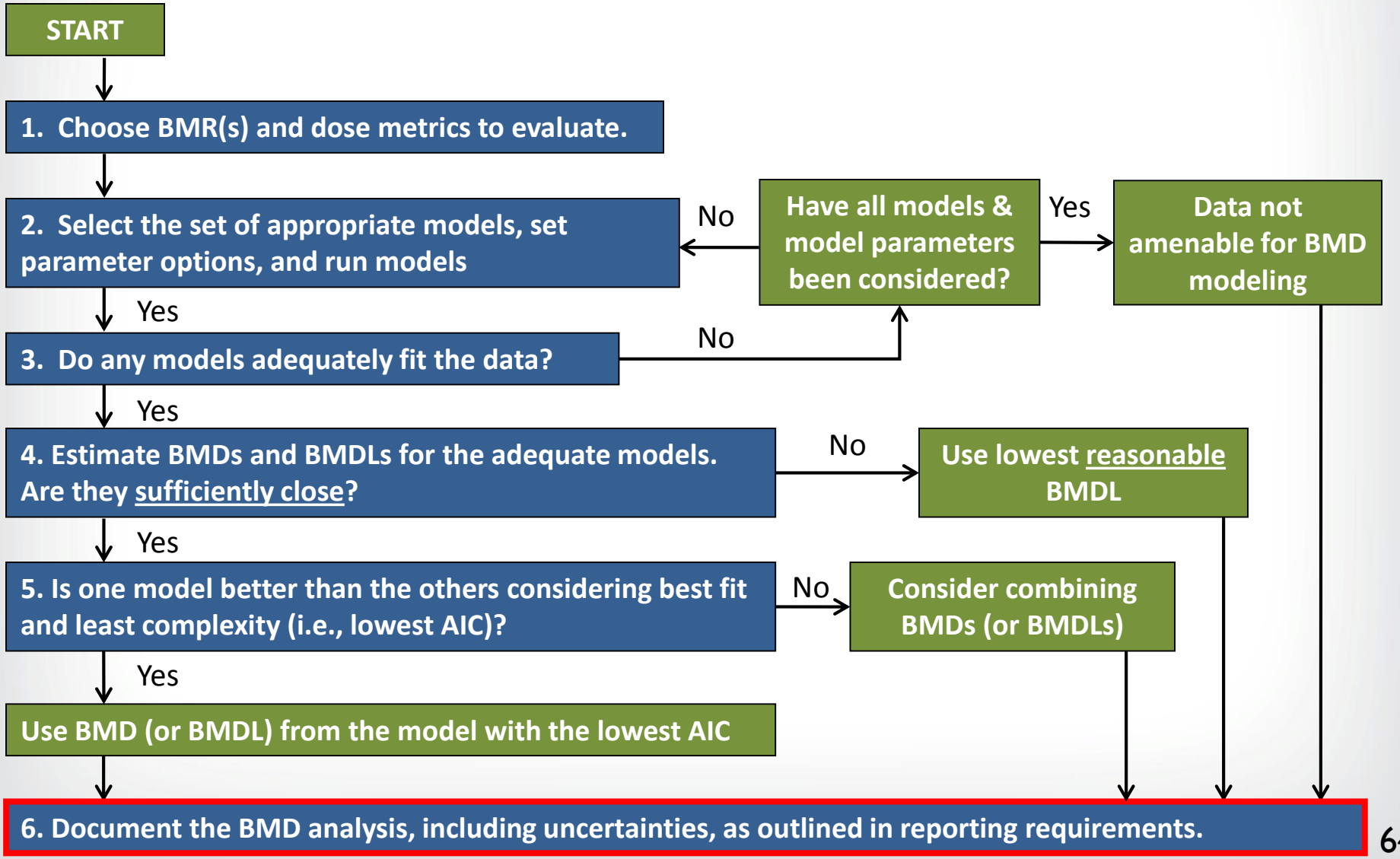
BMD Analysis – Six Steps



BMD Analysis – Six Steps

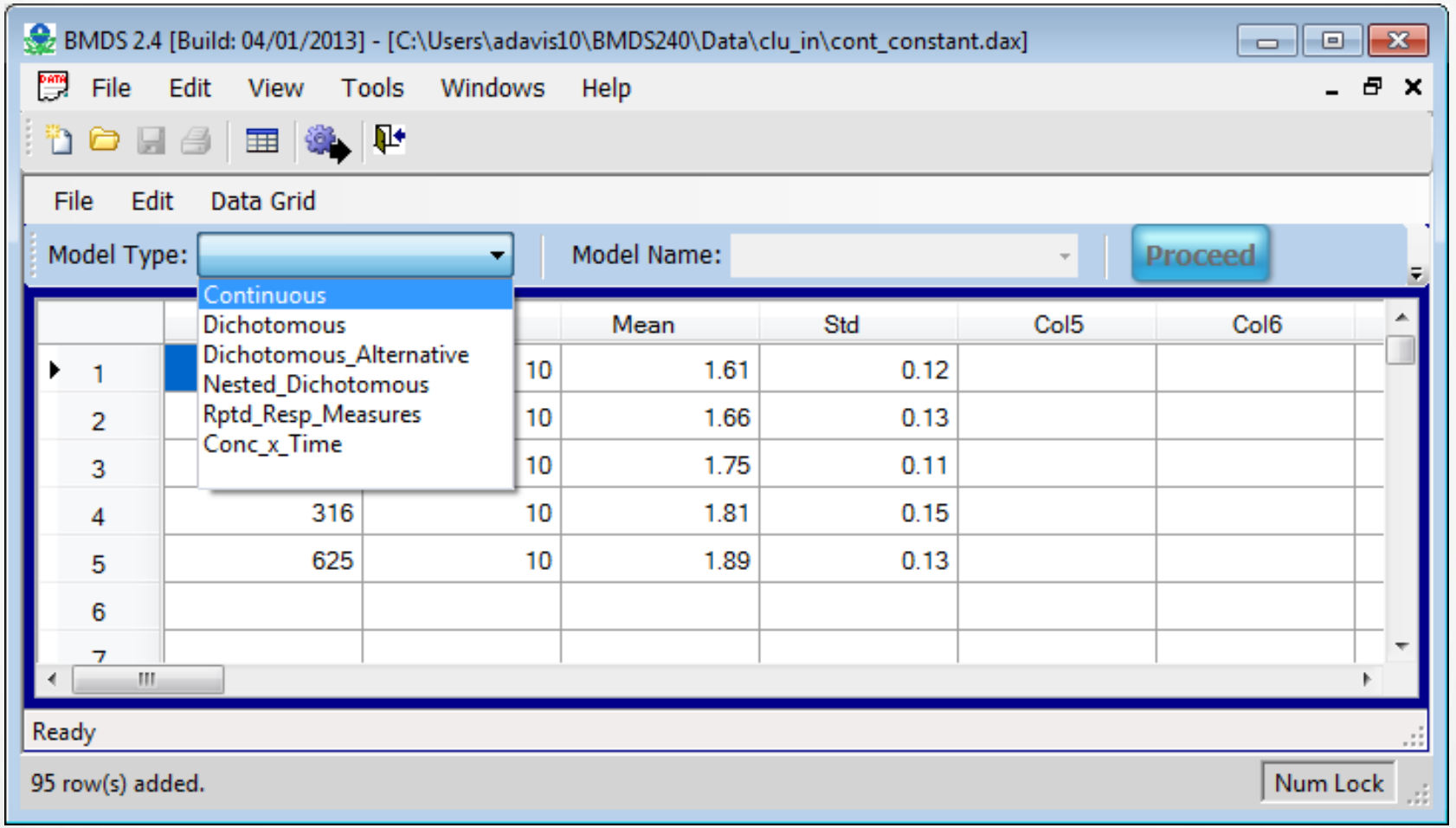


BMD Analysis – Six Steps

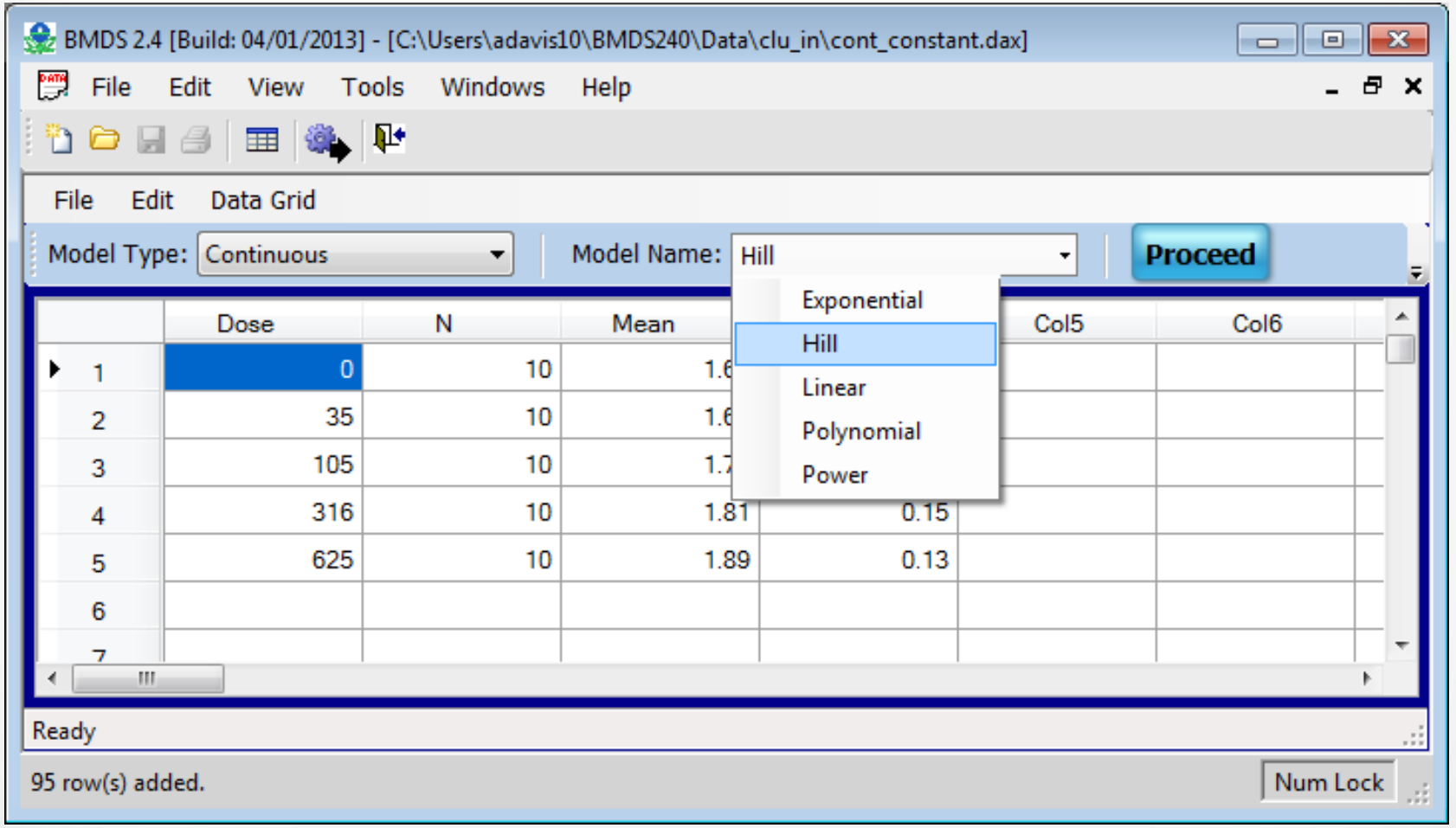


Continuous Data – Running an Individual Model in BMDS

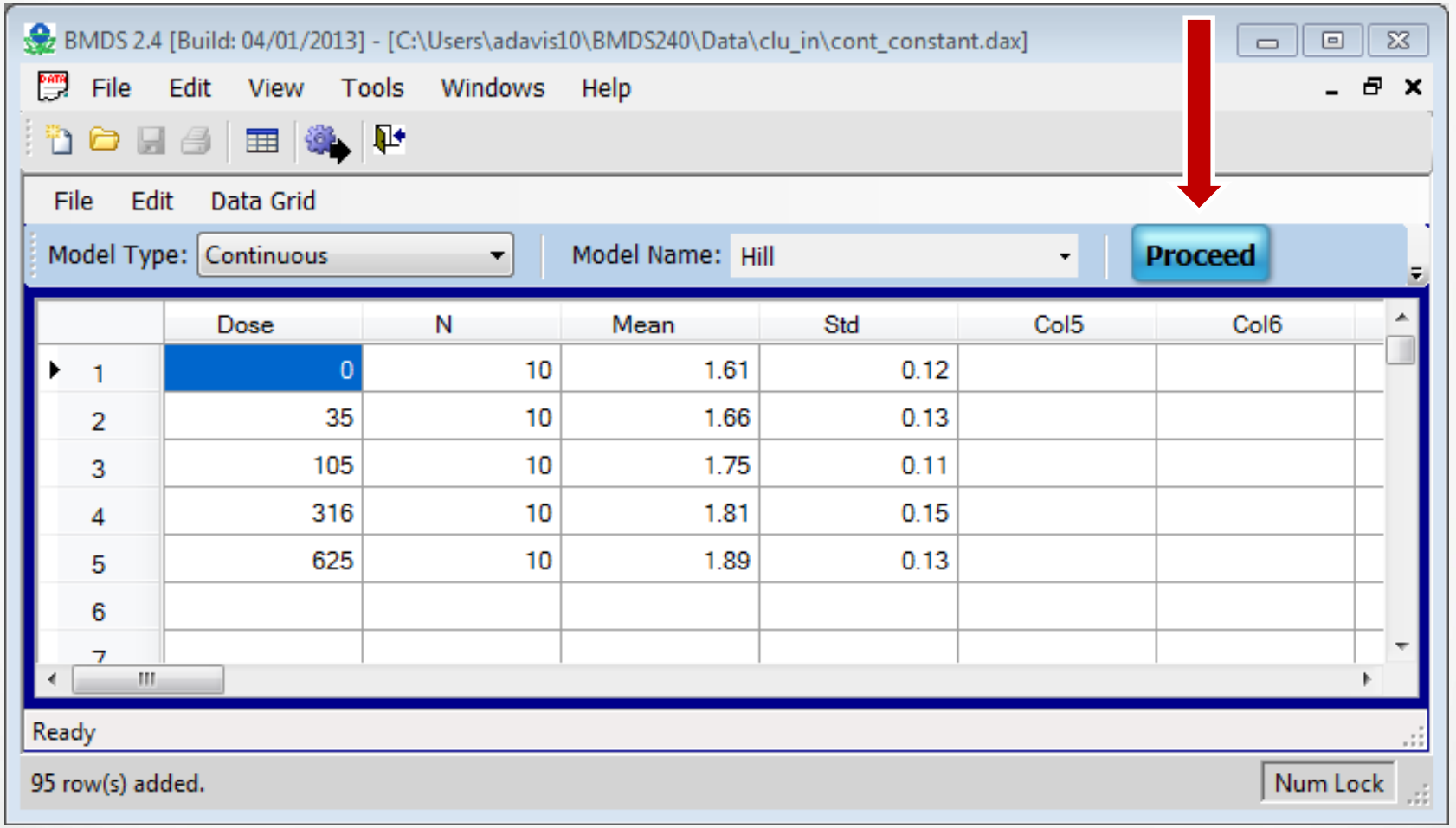
Running an Individual Model – Select a Model Type



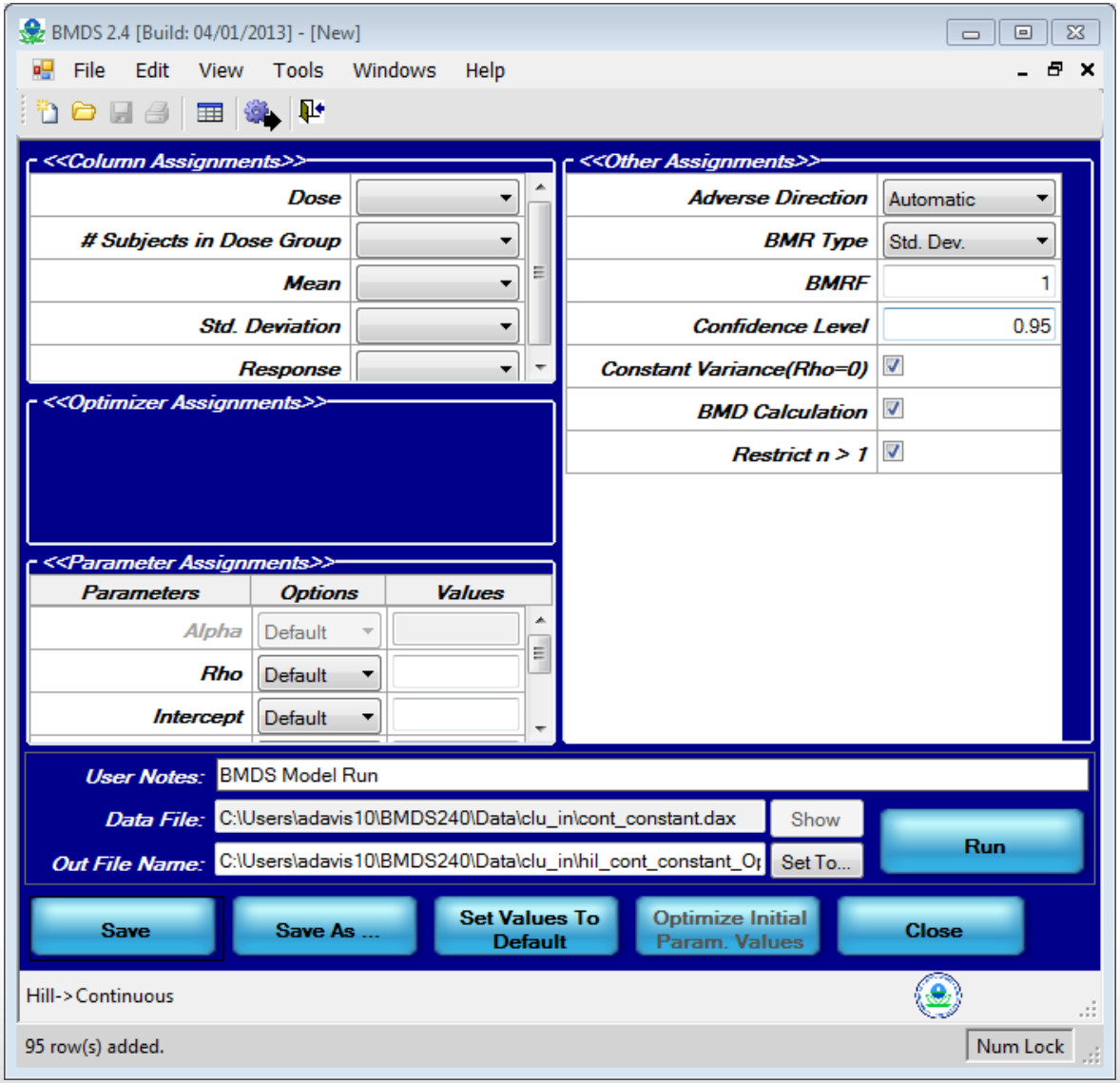
Running an Individual Model – Select a Model



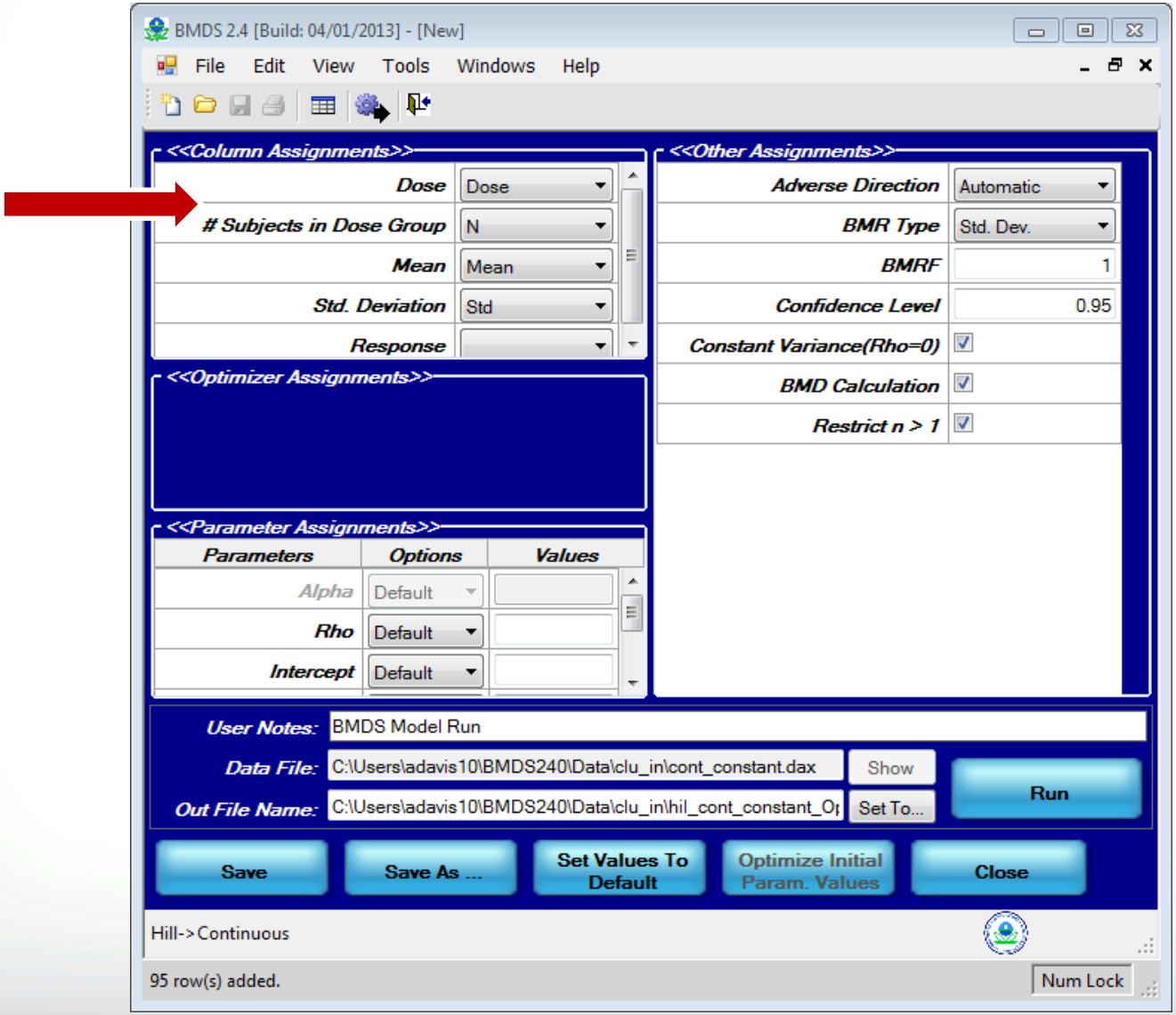
Running an Individual Model – Proceed to Option Screen



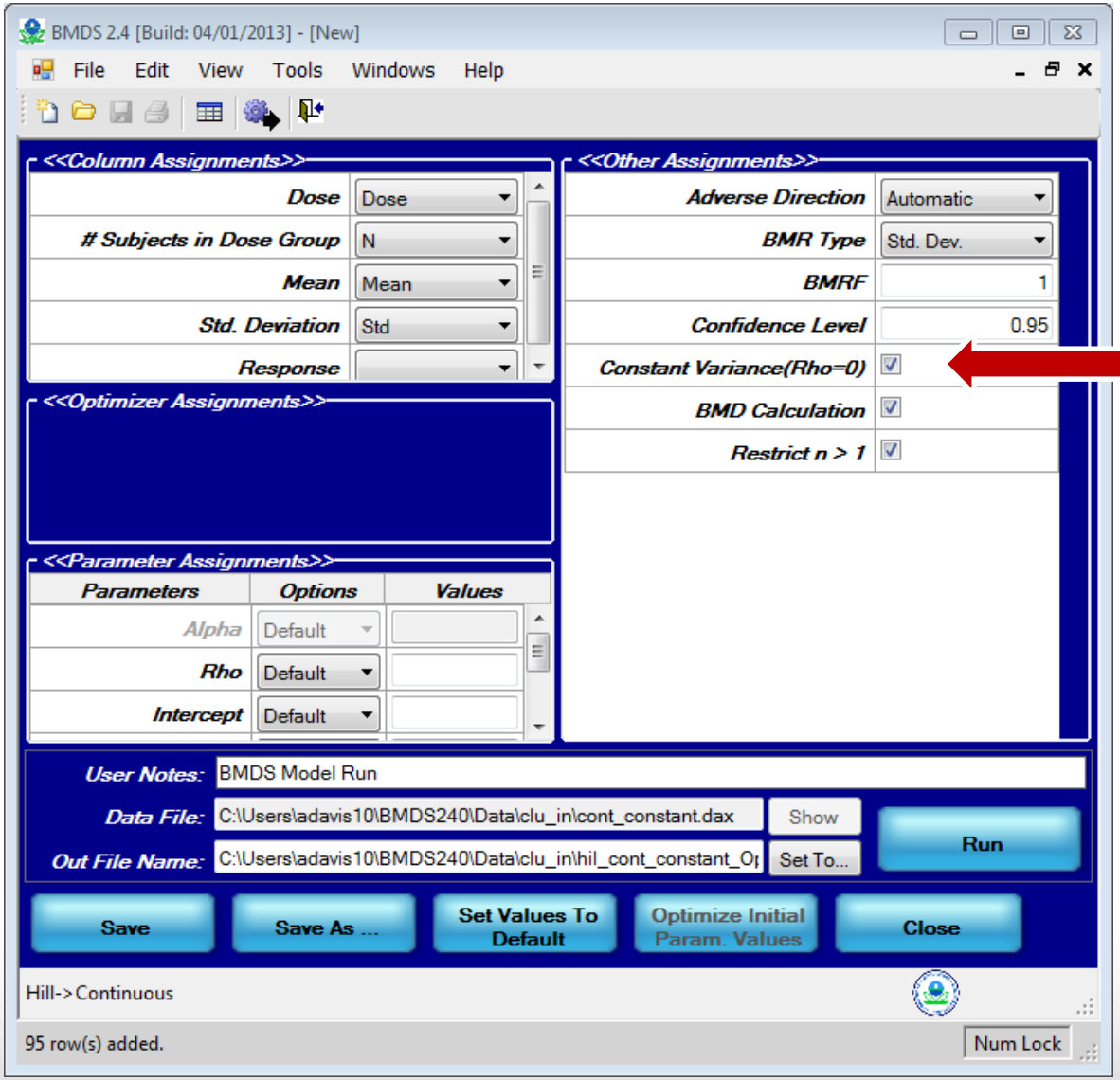
Model Option Screen



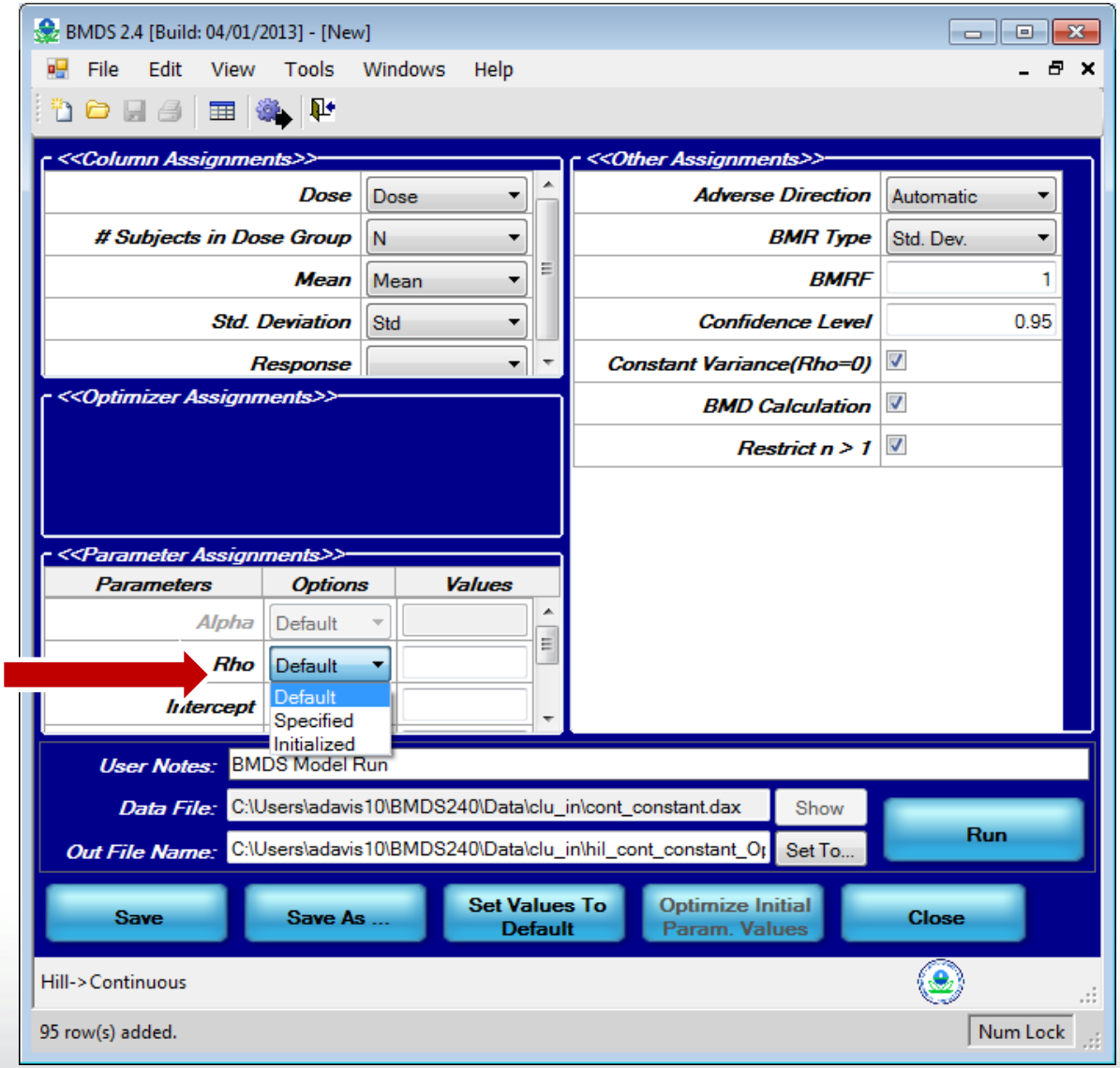
Selecting Column Assignments



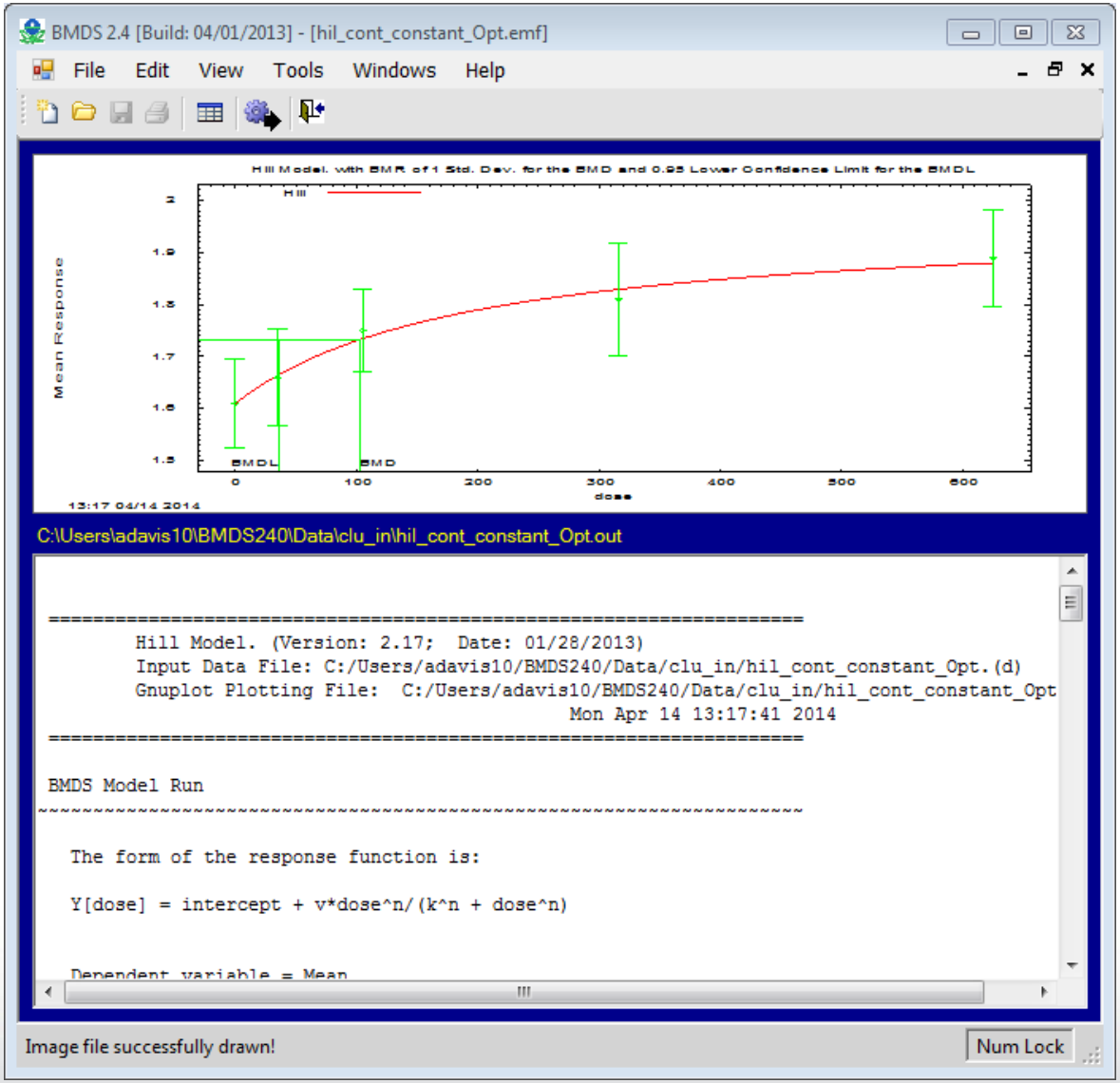
Selecting Model Options



Specifying Model Parameters



Dichotomous Model Plot and Output Files



Dichotomous Model Parameter Estimates

BMDS 2.4 [Build: 04/01/2013] - [hil_cont_constant_Opt.emf]

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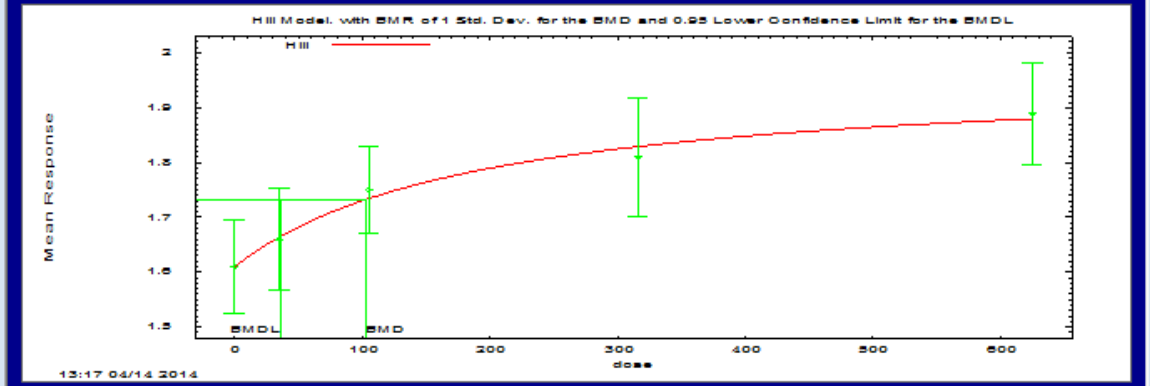

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Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
alpha	0.0150506	0.00301011	0.00915085	0.0209503
intercept	1.61064	0.036591	1.53892	1.68236
v	0.352636	0.0963974	0.1637	0.541571
n	1	NA		
k	192.959	178.848	-157.577	543.496

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

Table of Data and Estimated Values of Interest

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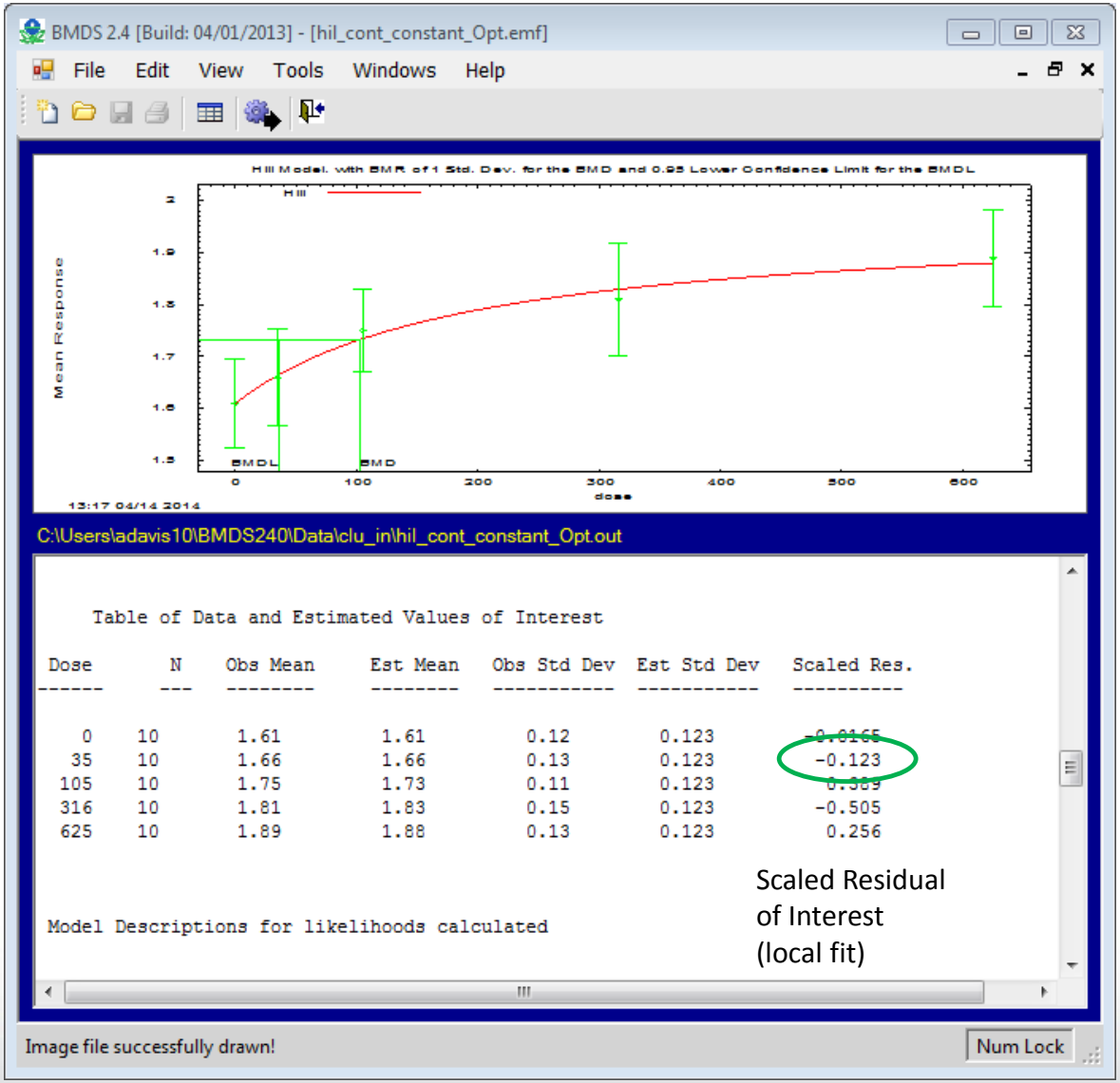
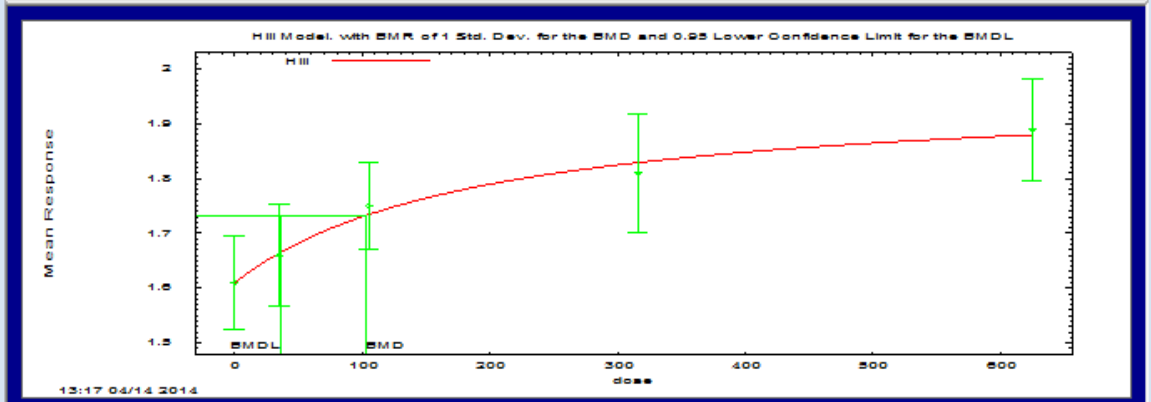
Dichotomous Model Fit Statistics



Dichotomous Model Fit Statistics

BMDS 2.4 [Build: 04/01/2013] - [hil_cont_constant_Opt.emf]

File Edit View Tools Windows Help



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```
                    Explanation of Tests

Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

  Test     -2*log(Likelihood Ratio)  Test df        p-value

  Test 1               27.022          8        0.0007008
  Test 2             1.06375           4              0.9
  Test 3             1.06375           4              0.9
  Test 4            0.489269           2            0.783
```

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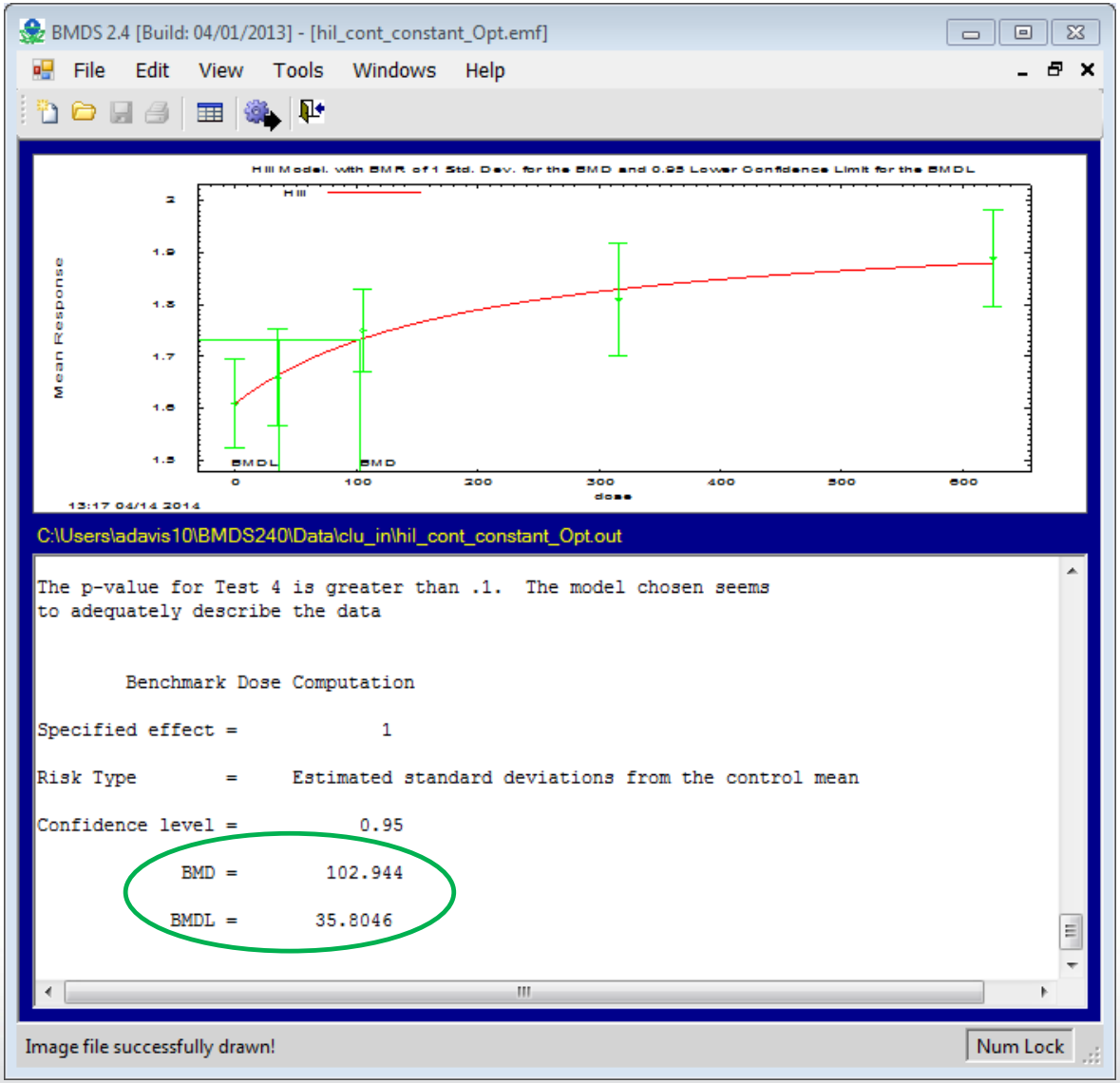
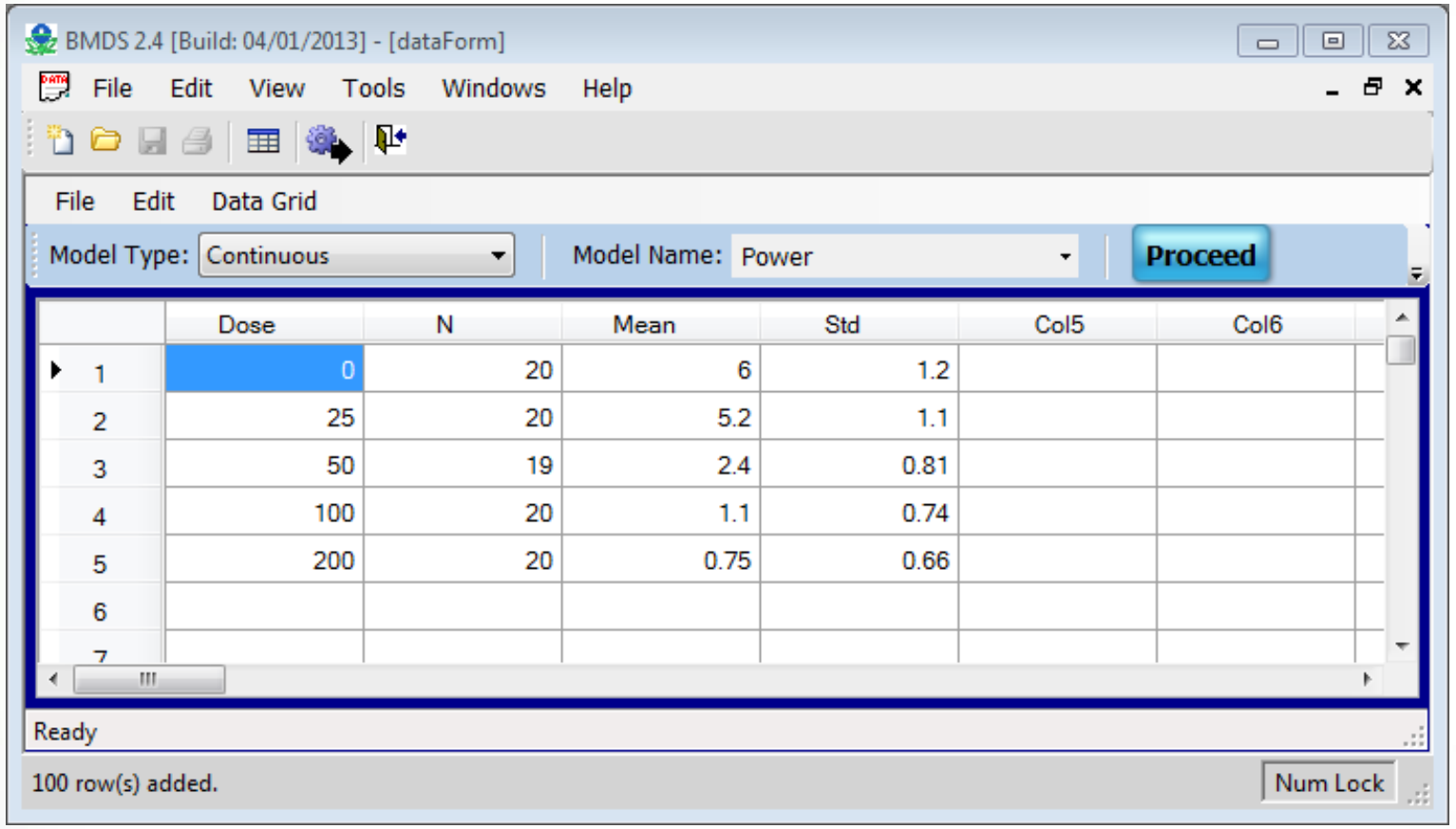
BMD and BMDL Estimates



Opening Output and Plot Files after Analysis

Continuous Data – Exercise #1

Continuous Exercise #1



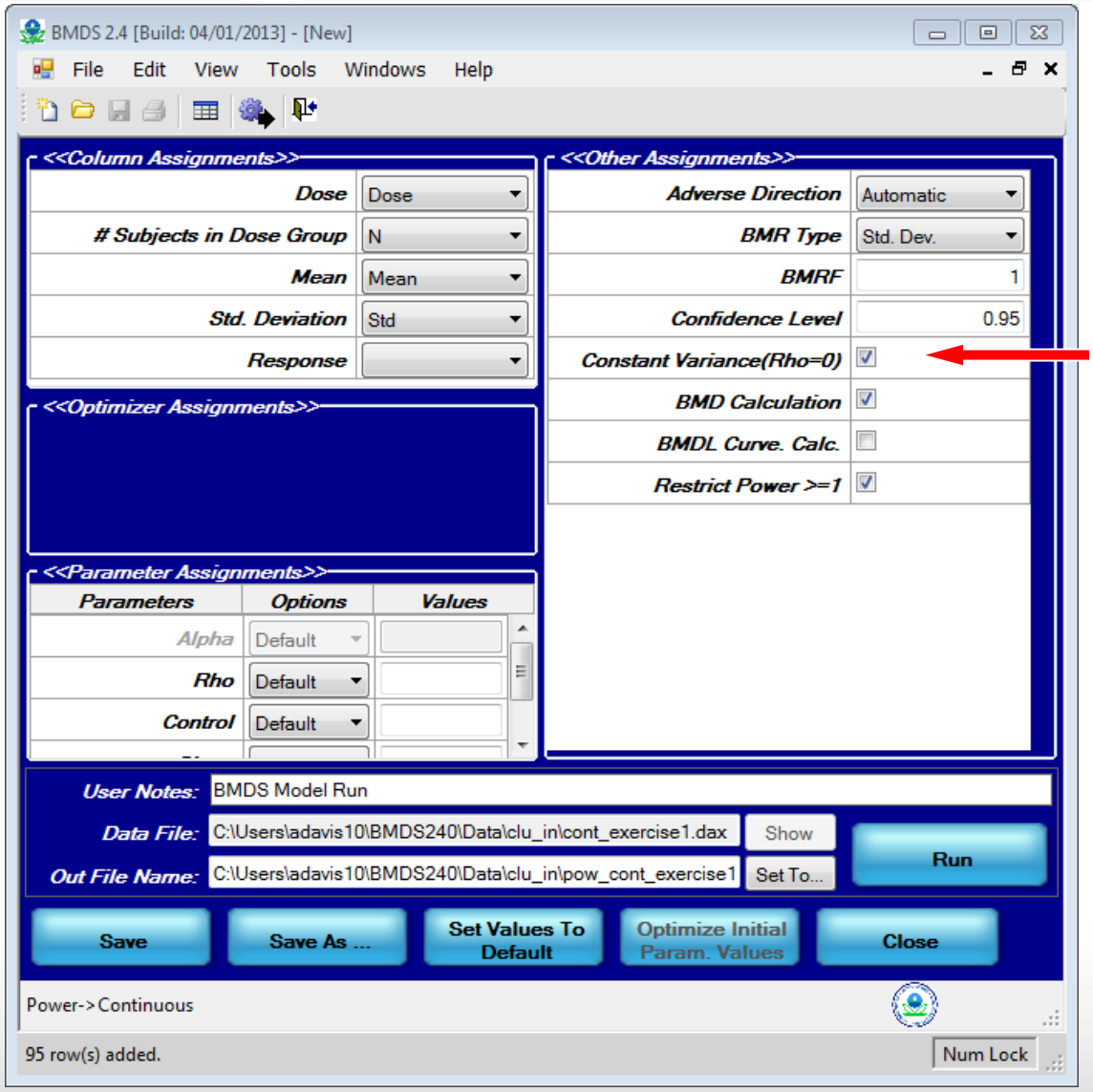
	Dose	N	Mean	Std	Col5	Col6
1	0	20	6	1.2		
2	25	20	5.2	1.1		
3	50	19	2.4	0.81		
4	100	20	1.1	0.74		
5	200	20	0.75	0.66		
6						
7						

Manually enter these data and save as Exercise_1.dax

Continuous Exercise #1

- **Run the Power model against the Exercise #1 data using the Individual Model Run option**
  - Accept all default settings, especially running the model assuming constant variance

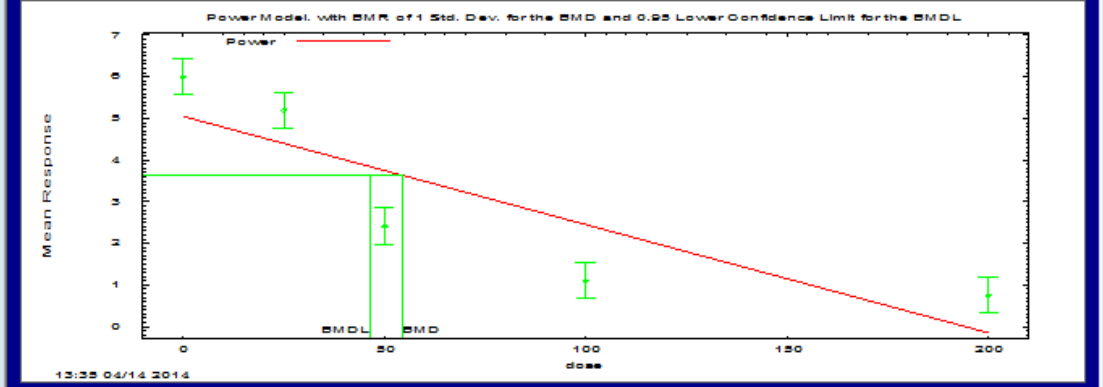
Continuous Exercise #1



Continuous Exercise #1

BMDS 2.4 [Build: 04/01/2013] - [pow_cont_exercise1_Opt.emf]

File Edit View Tools Windows Help



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```
                Explanation of Tests

Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                   Tests of Interest

  Test    -2*log(Likelihood Ratio)  Test df        p-value

  Test 1             198.095          8          <.0001
  Test 2             10.6363          4         0.03097
  Test 3             10.6363          4         0.03097
  Test 4             89.1652          3          <.0001
```

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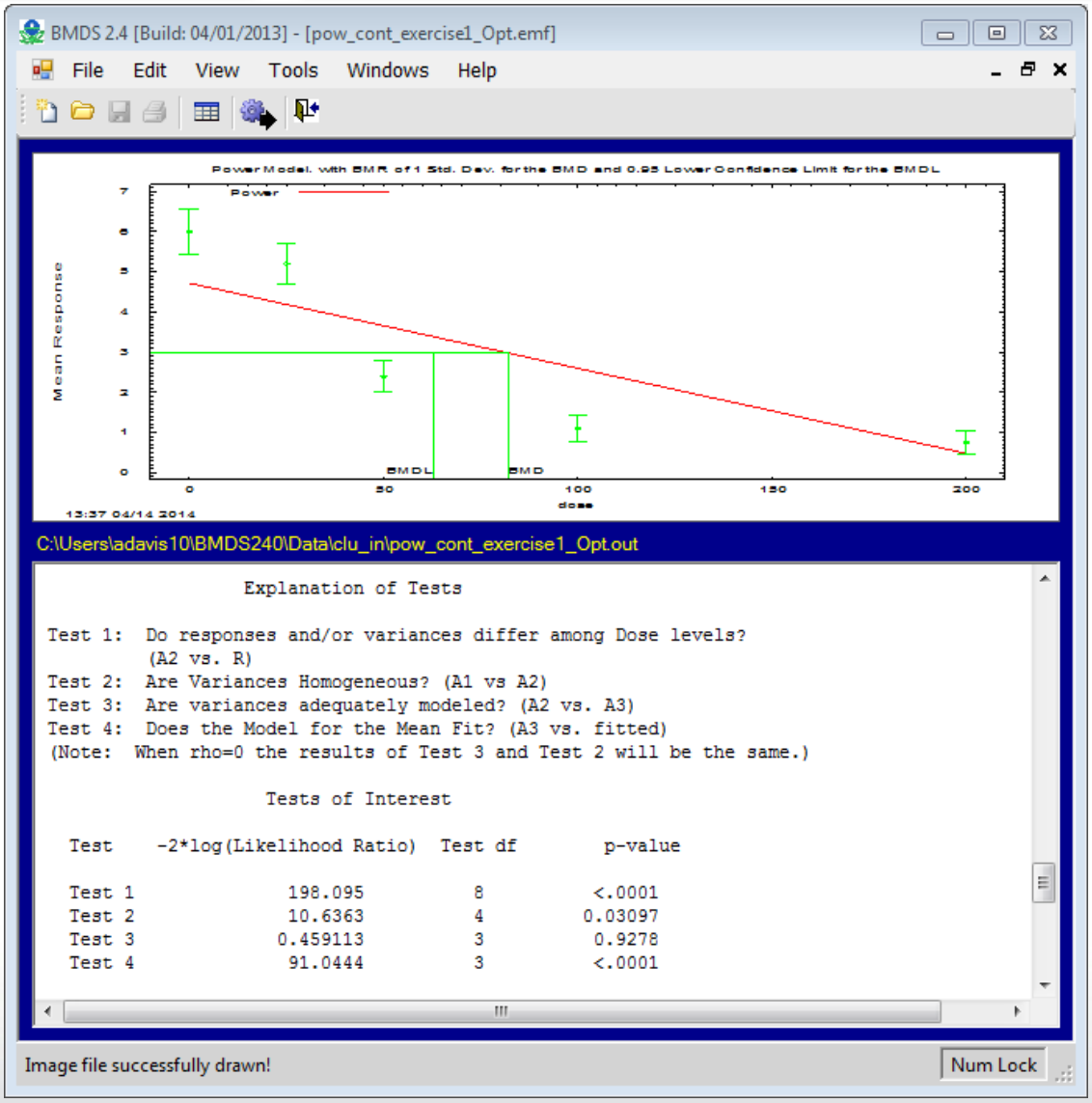
Continuous Exercise #1

- **Re-run the Power model against the Exercise #1 data using the Individual Model Run option**
  - Deselect the option to run with constant variance

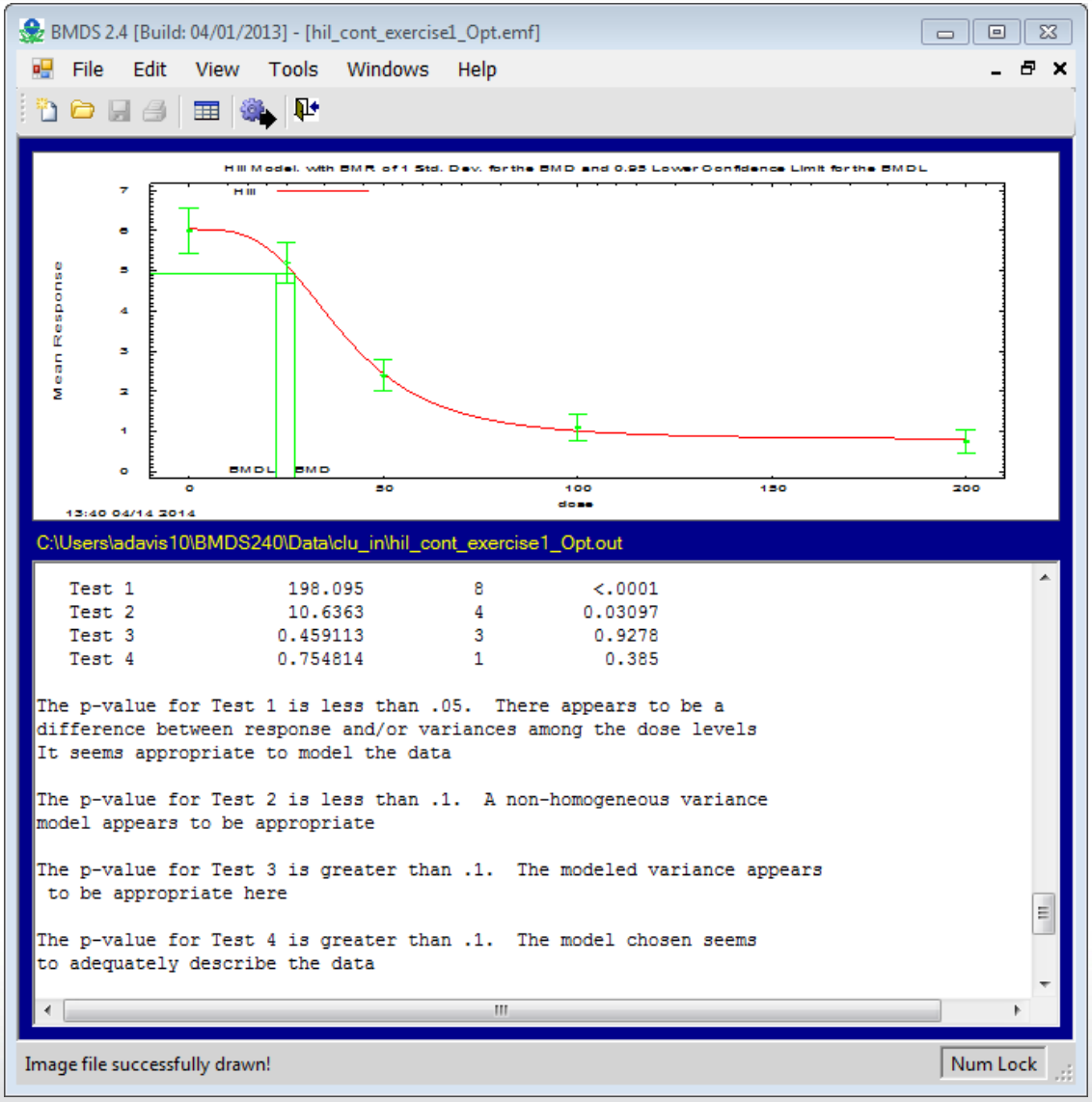
Continuous Exercise #1



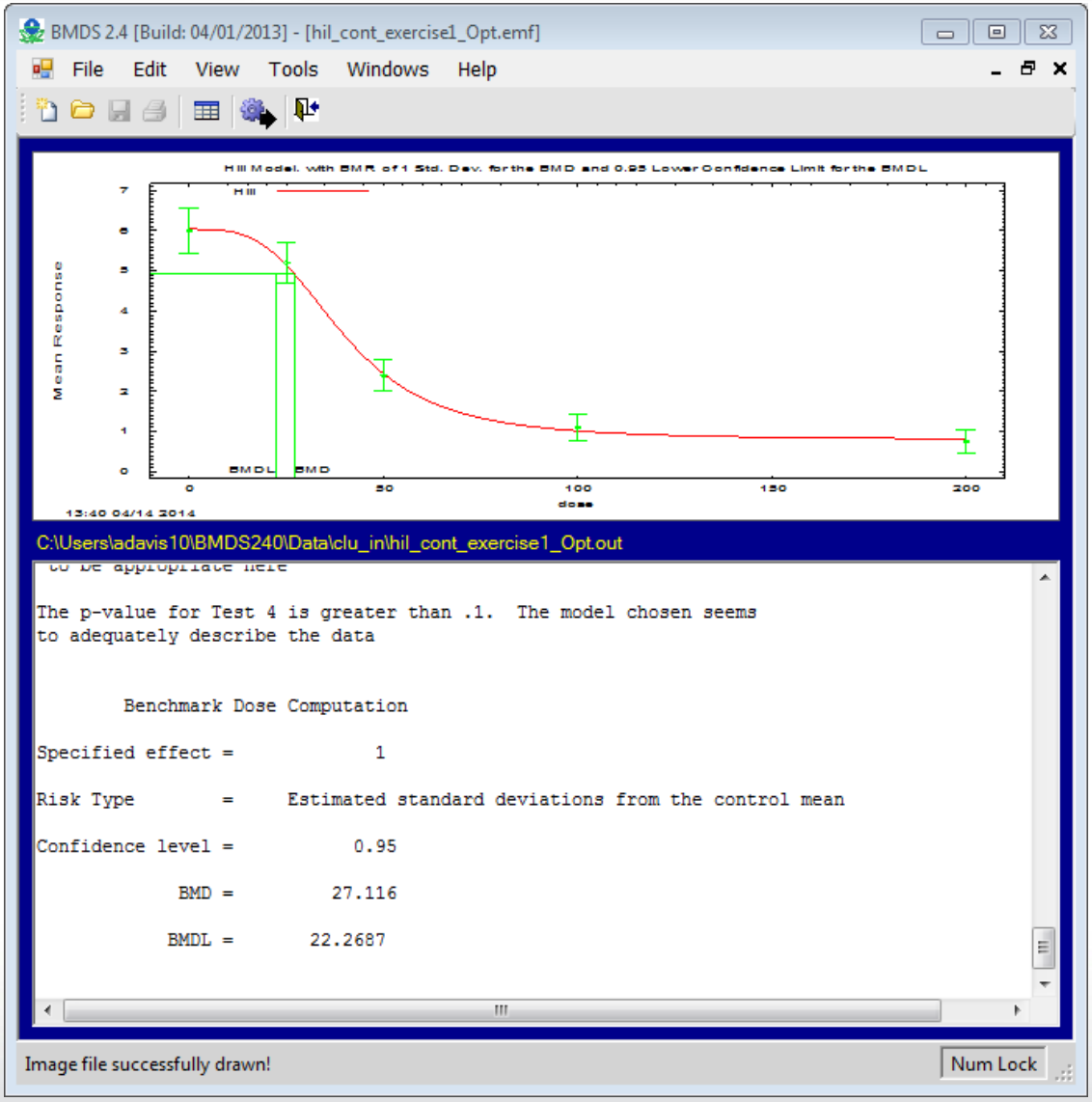
Continuous Exercise #1

- **Run the Hill model against the Exercise #1 data using the Individual Model Run option**
  - Run with non-constant variance

Continuous Exercise #1



Continuous Exercise #1



Continuous Data – Batch Processing using the BMDS Wizard

The BMDS Wizard

- A Microsoft Excel-based tool that allows users to run modeling sessions
- The Wizard acts as a "shell" around BMDS and stores all inputs, outputs, and decisions made in the modeling process
- The BMDS Wizard streamlines data entry and option file creation, and implements logic to compare and analyze modeling results
- Currently, templates for dichotomous, dichotomous cancer, and continuous models are provided

BMDS Wizard Installation

- **When installing BMDS 2.5, preformatted BMDS Wizard templates will automatically be stored in the "Wizard" folder in the BMDS250 directory**
  - To avoid possible problems running the Wizard, EPA recommends that the file path of the Wizard subdirectory not contain any non-alphanumeric characters
  - EPA users will need to locate their BMDS 250 and Wizard folders in the Users folder (C:\Users\name\BMDS250)
  - Non-EPA users can locate their folders in other directories, but the Wizard folder must be in the same directory as the BMDS executable

BMDS Wizard Macros

- **Macros must be enabled in Excel in order for BMDS Wizard to run and to view output files and figures from the "Results" tab of the BMDS Wizard**

Excel 2003

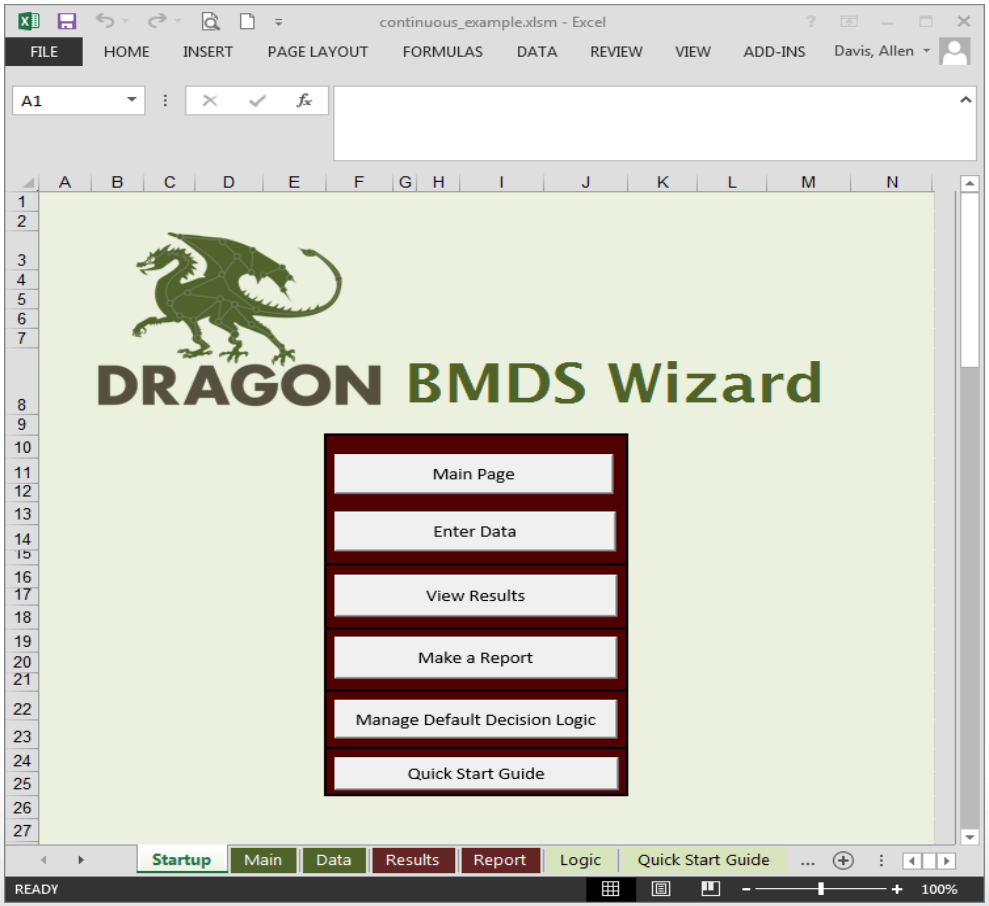
- Open Excel
- Select the "Tools" Menu
- Select Options
- Go to "Security" tab and click "Macro Security"
- Change security level to "Medium" or "Low"

- **Excel 2007**
- Open Excel
- Press the "Office" button and select "Excel Options"
- Go to the "Trust Center" tab and click "Trust Center Settings"
- Change "Macro Settings" to "Disable all macros with notification" or "Enable all macros"

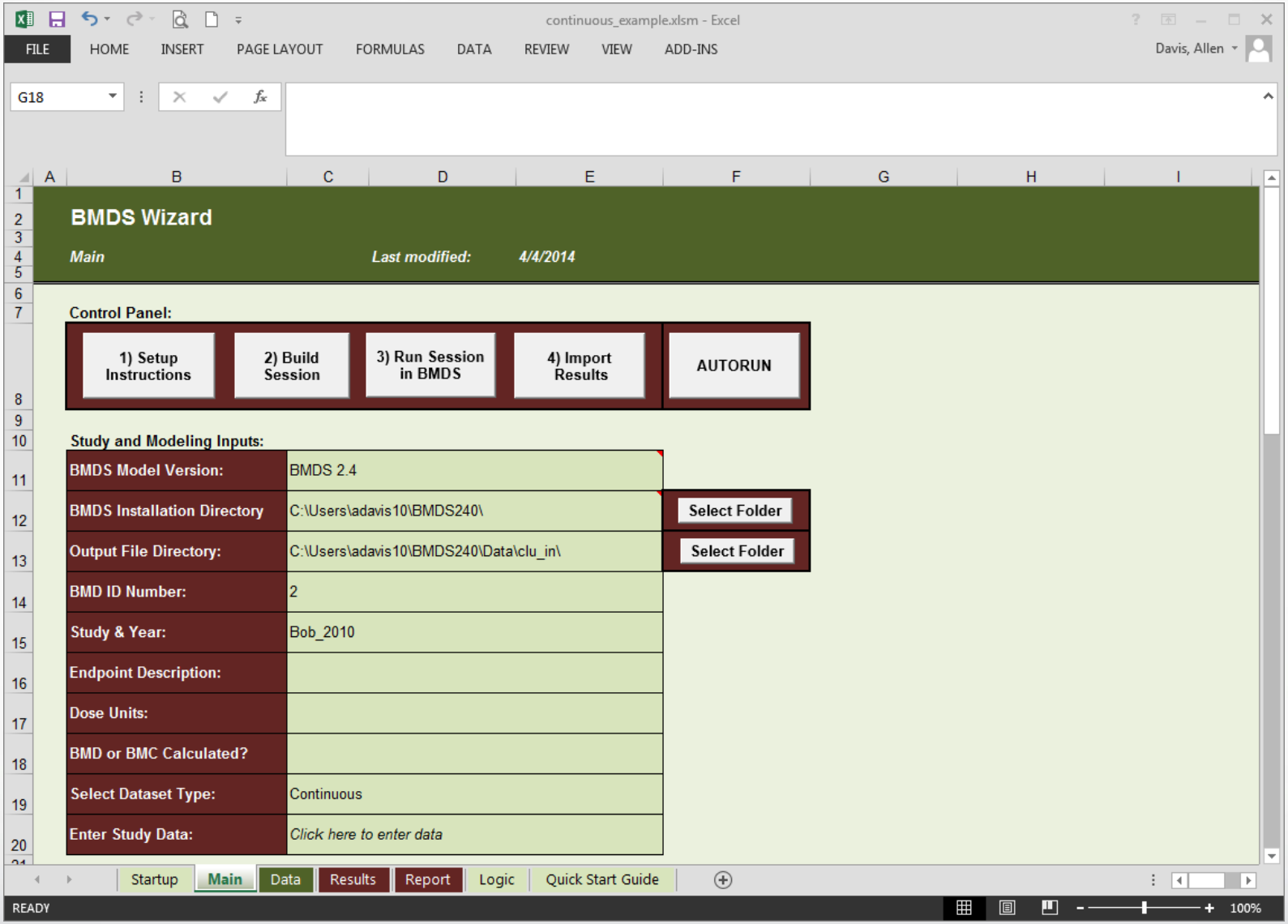
- **Excel 2010/2013**
- Open Excel
- Select "File" on the Ribbon toolbar and click "Options"
- Go to the "Trust Center" tab and click "Trust Center Settings"
- Change "Macro Settings" to "Disable all macros with notification" or "Enable all macros"

Starting a BMDS Wizard Session

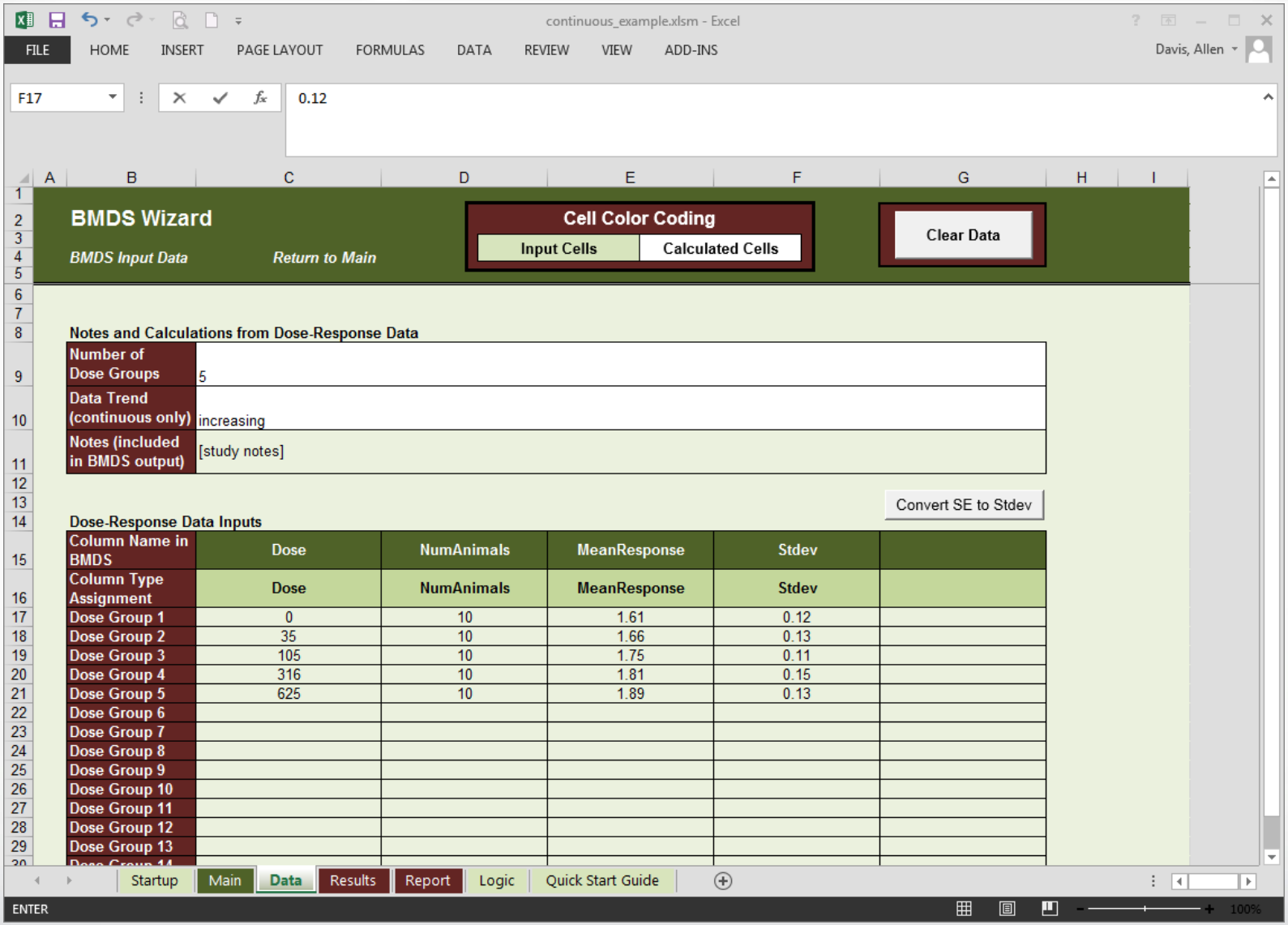
- **Open template file and "Save As" (Excel Macro-Enabled Workbook [*.xlsm]) to new BMDS Wizard file in desired working directory**



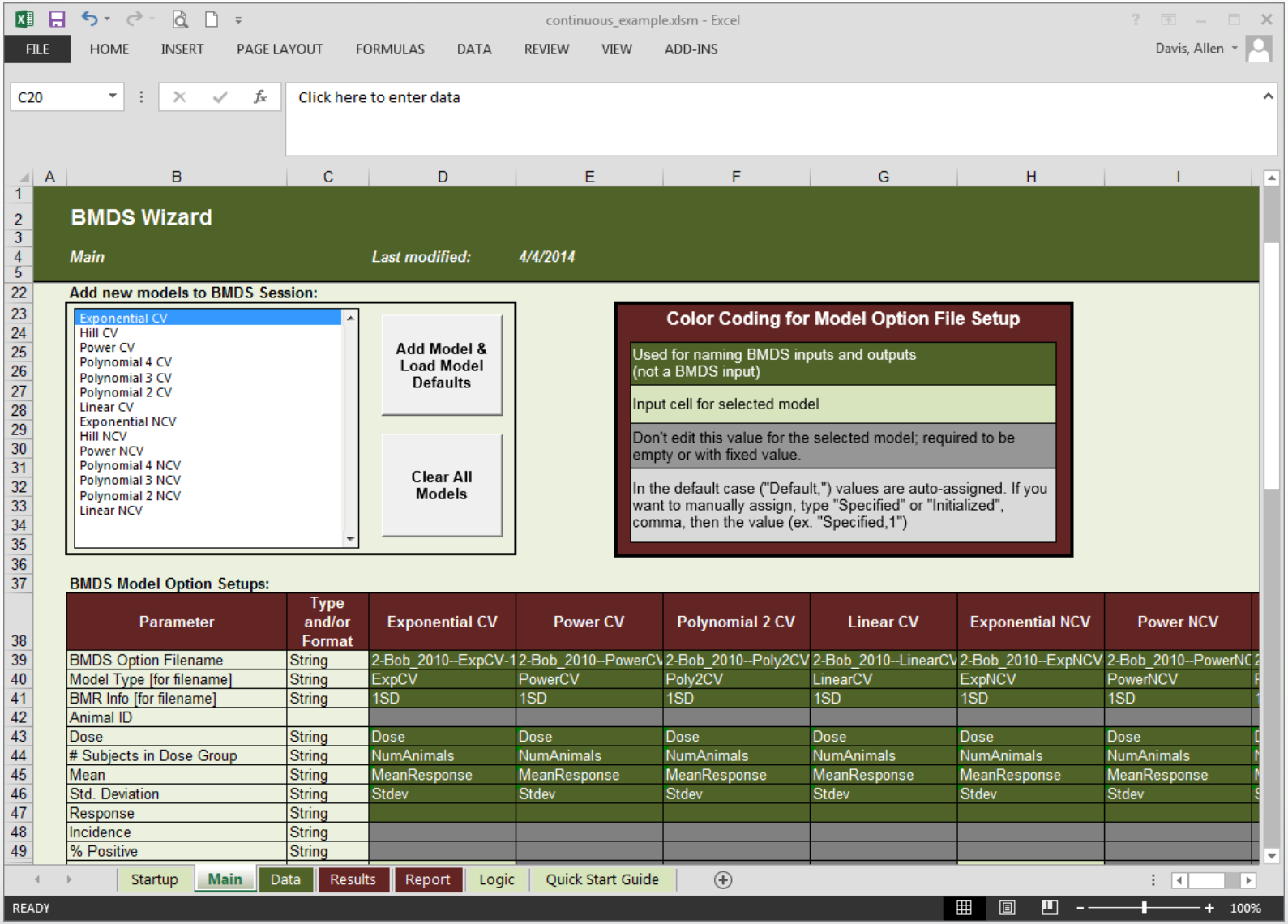
BMDS Wizard – Study and Modeling Inputs



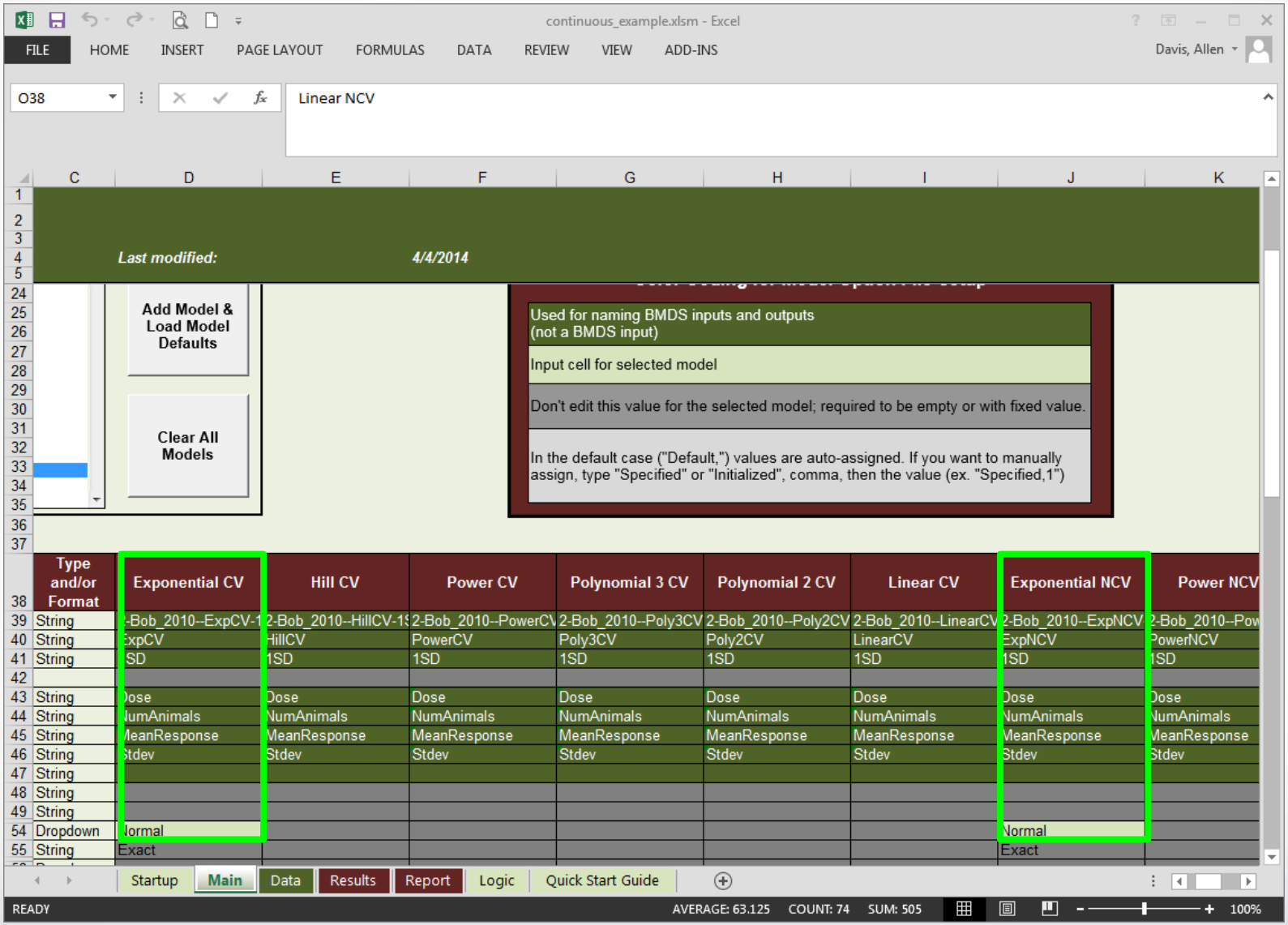
BMDS Wizard – Entering Data



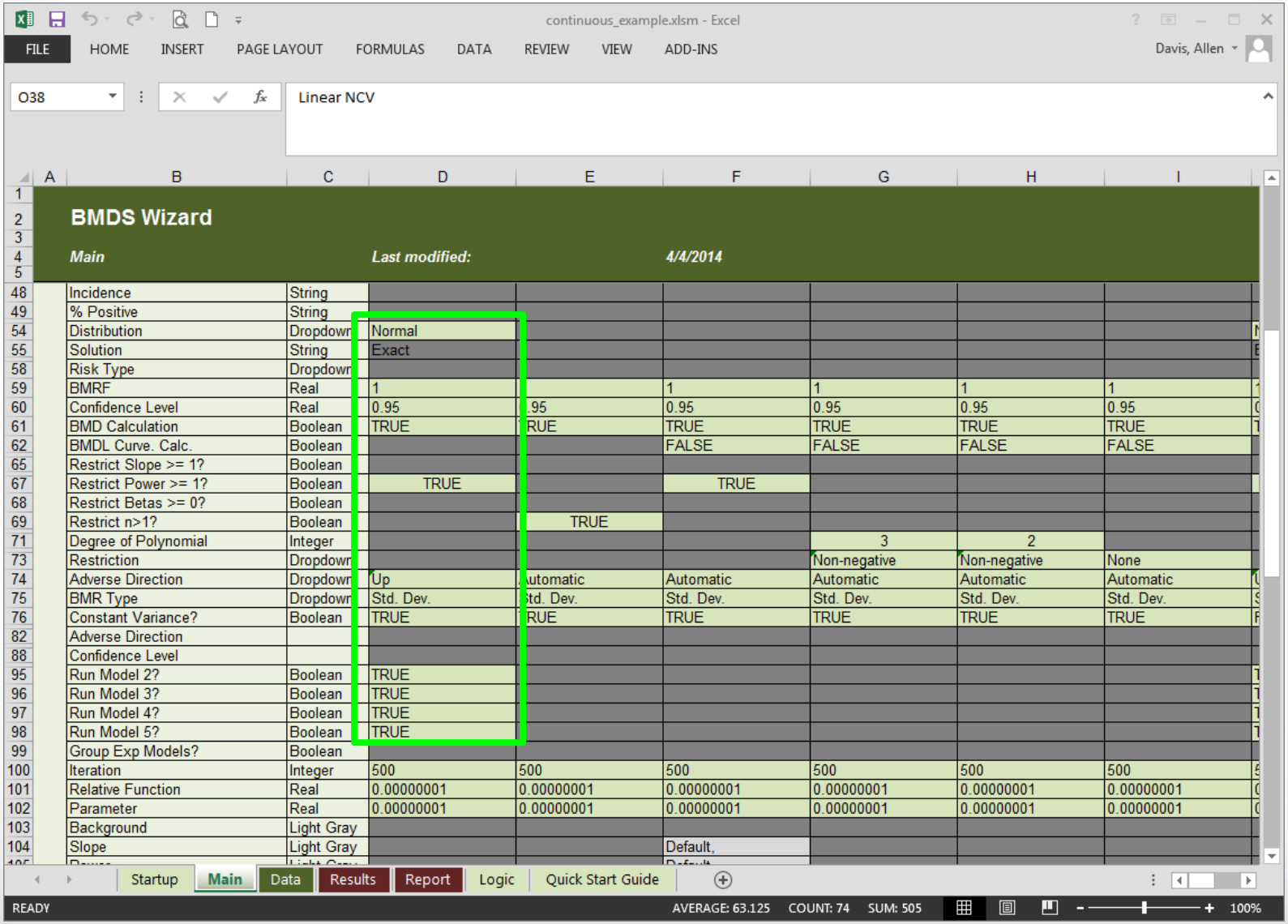
BMDS Wizard – Model Parameters



BMDS Wizard – Model Parameters



BMDS Wizard – Model Parameters



continuous_example.xlsm - Excel

FILE HOME INSERT PAGE LAYOUT FORMULAS DATA REVIEW VIEW ADD-INS

Davis, Allen

O38 | Linear NCV

BMDS Wizard

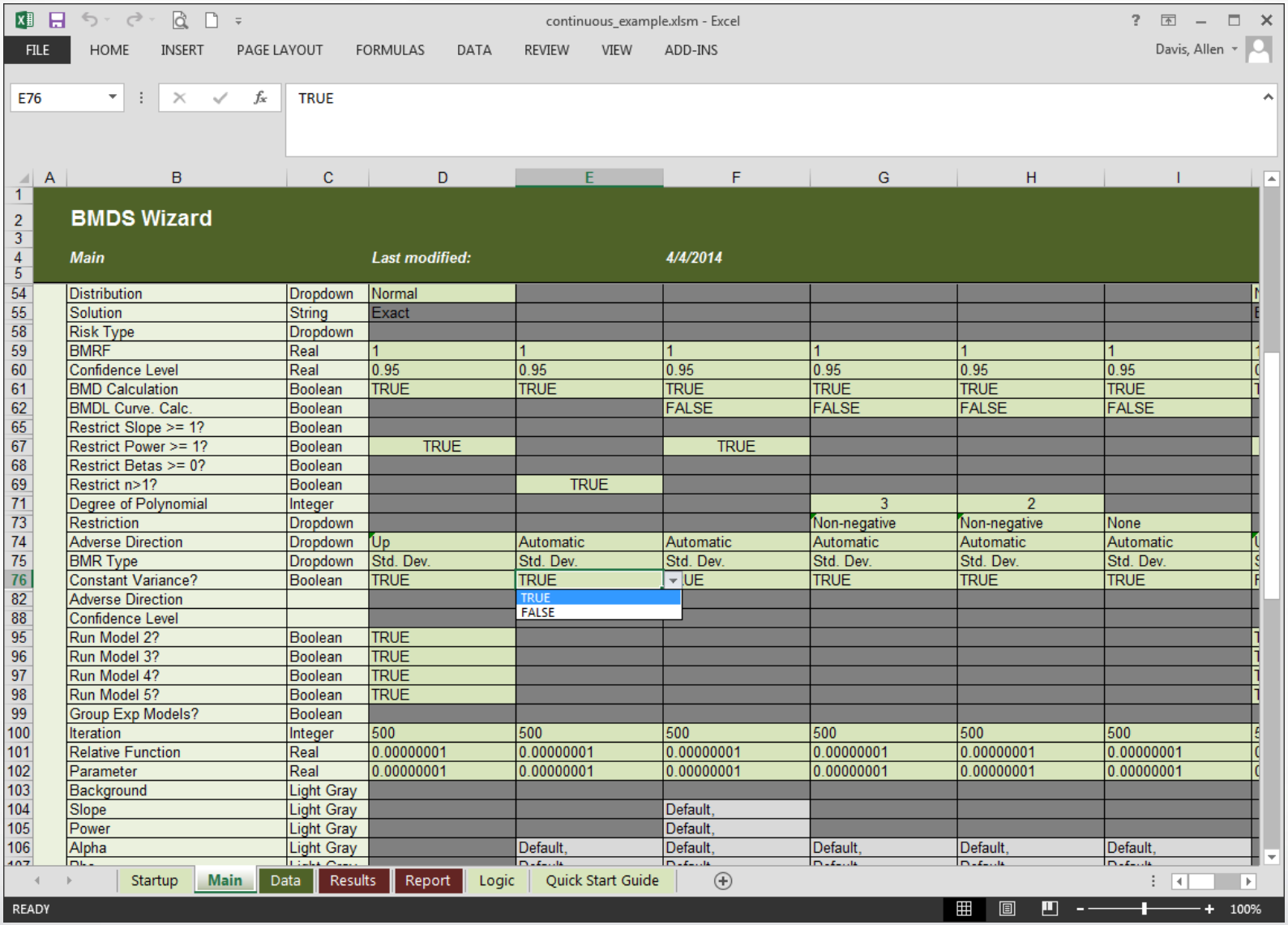
Main *Last modified:* *4/4/2014*

48	Incidence	String						
49	% Positive	String						
54	Distribution	Dropdowr	Normal					
55	Solution	String	Exact					
58	Risk Type	Dropdowr						
59	BMRF	Real	1		1	1	1	1
60	Confidence Level	Real	0.95	.95	0.95	0.95	0.95	0.95
61	BMD Calculation	Boolean	TRUE	RUE	TRUE	TRUE	TRUE	TRUE
62	BMDL Curve. Calc.	Boolean			FALSE	FALSE	FALSE	FALSE
65	Restrict Slope >= 1?	Boolean						
67	Restrict Power >= 1?	Boolean	TRUE		TRUE			
68	Restrict Betas >= 0?	Boolean						
69	Restrict n>1?	Boolean		TRUE				
71	Degree of Polynomial	Integer				3	2	
73	Restriction	Dropdowr				Non-negative	Non-negative	None
74	Adverse Direction	Dropdowr	Up	utomatic	Automatic	Automatic	Automatic	Automatic
75	BMR Type	Dropdowr	Std. Dev.	td. Dev.	Std. Dev.	Std. Dev.	Std. Dev.	Std. Dev.
76	Constant Variance?	Boolean	TRUE	RUE	TRUE	TRUE	TRUE	TRUE
82	Adverse Direction							
88	Confidence Level							
95	Run Model 2?	Boolean	TRUE					
96	Run Model 3?	Boolean	TRUE					
97	Run Model 4?	Boolean	TRUE					
98	Run Model 5?	Boolean	TRUE					
99	Group Exp Models?	Boolean						
100	Iteration	Integer	500	500	500	500	500	500
101	Relative Function	Real	0.00000001	0.00000001	0.00000001	0.00000001	0.00000001	0.00000001
102	Parameter	Real	0.00000001	0.00000001	0.00000001	0.00000001	0.00000001	0.00000001
103	Background	Light Gray						
104	Slope	Light Gray			Default,			

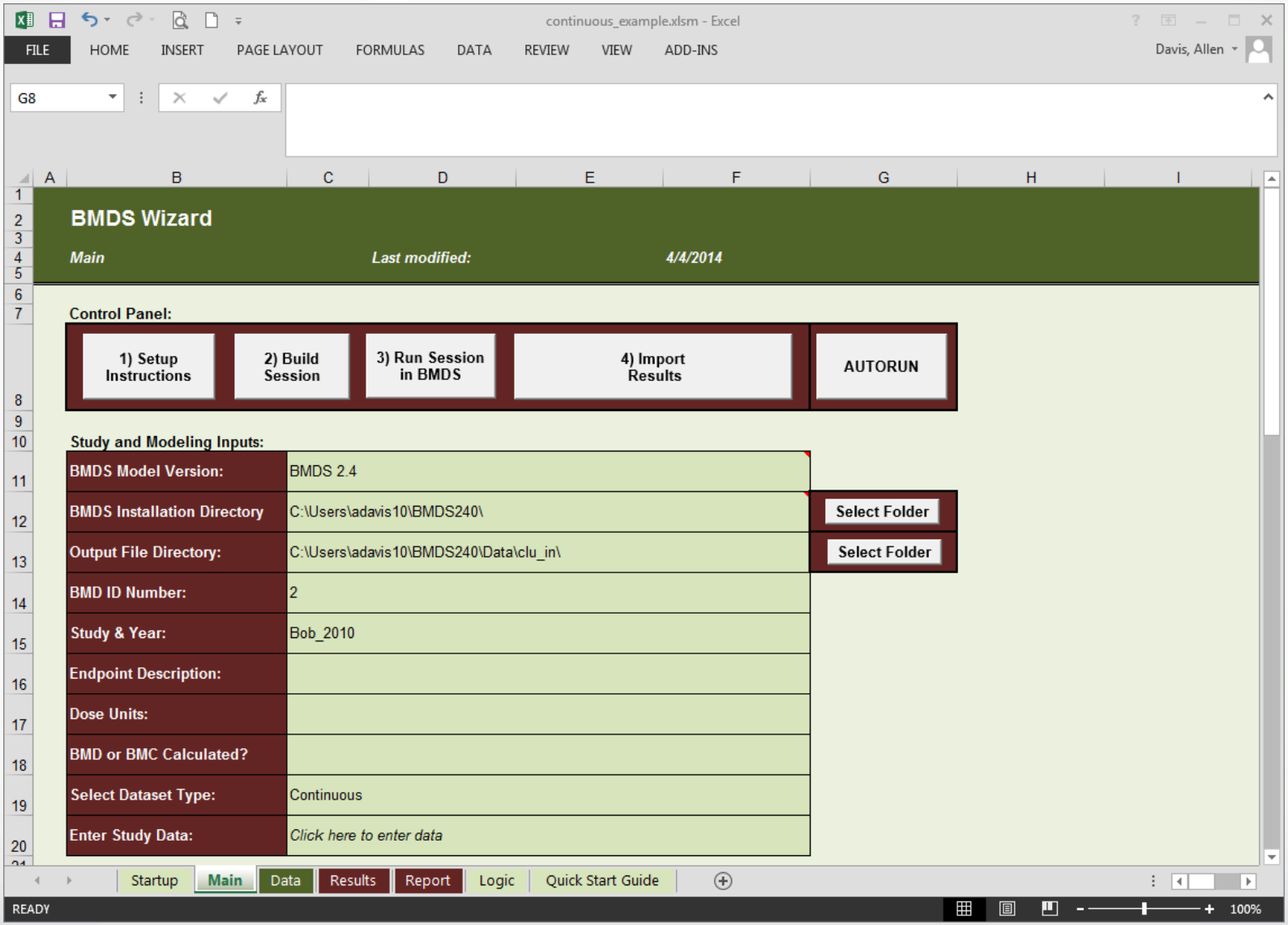
Startup | Main | Data | Results | Report | Logic | Quick Start Guide

READY AVERAGE: 63.125 COUNT: 74 SUM: 505 100%

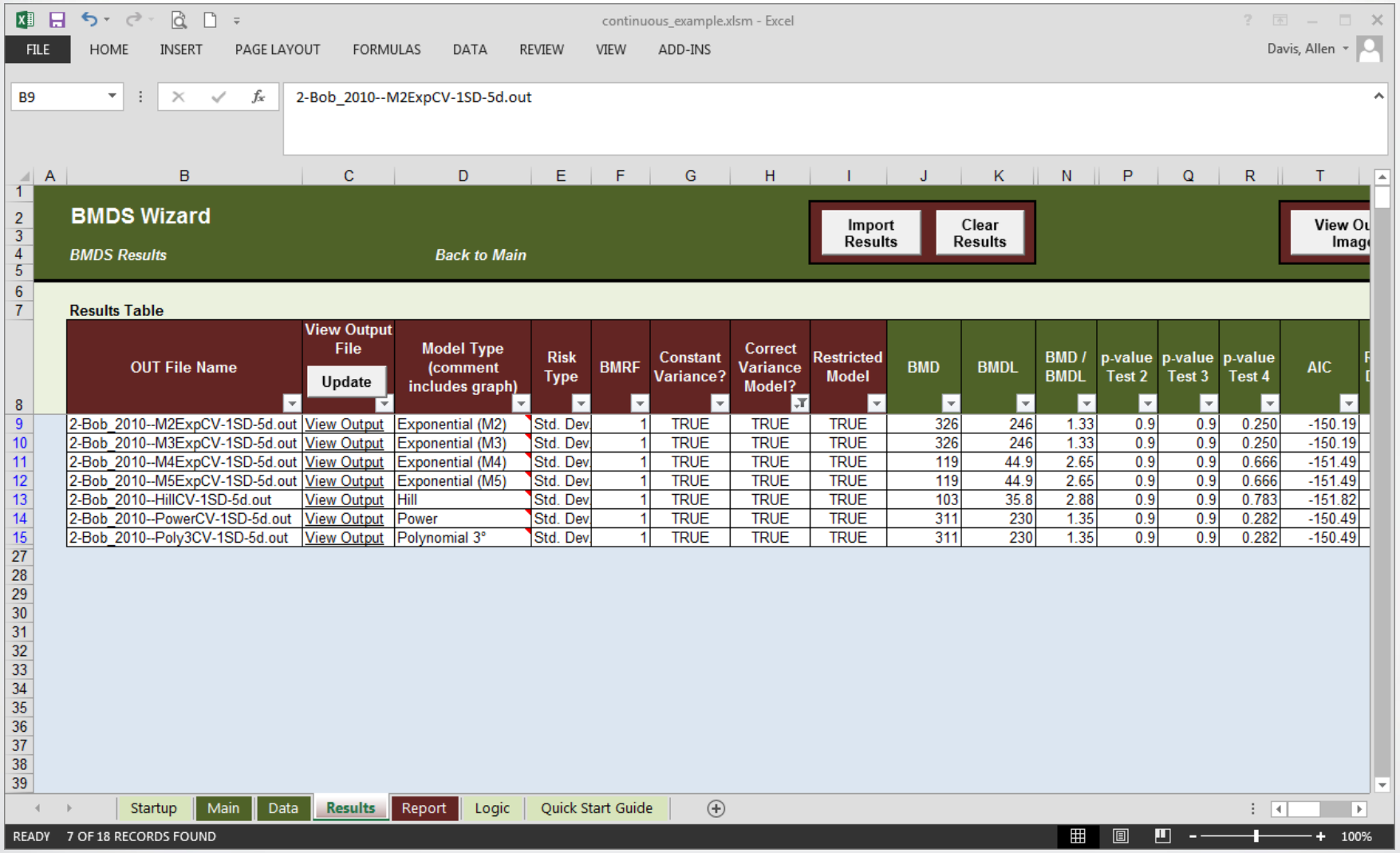
BMDS Wizard – Model Parameters



BMDS Wizard – AutoRunning BMDS

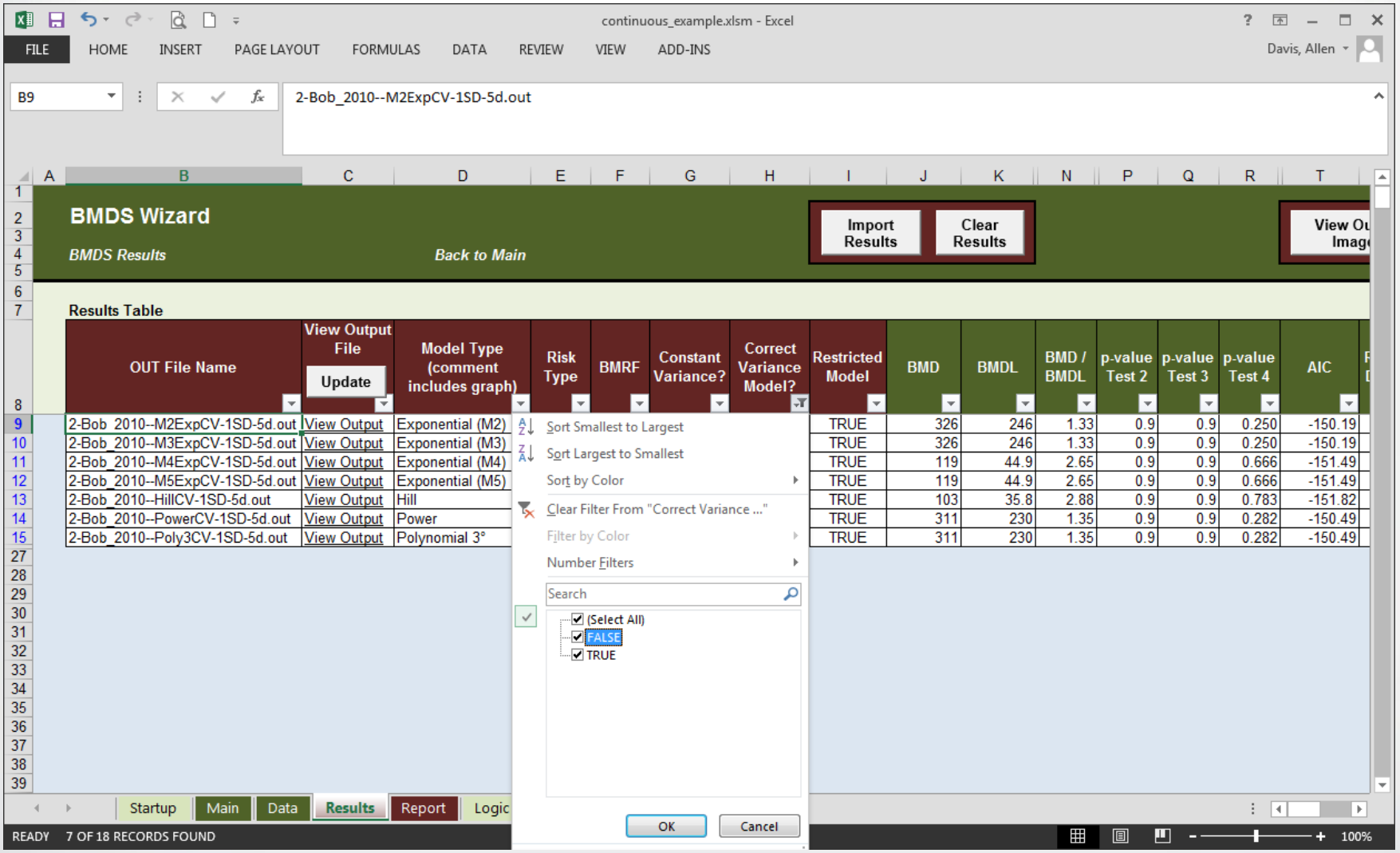


BMDS Wizard – Results

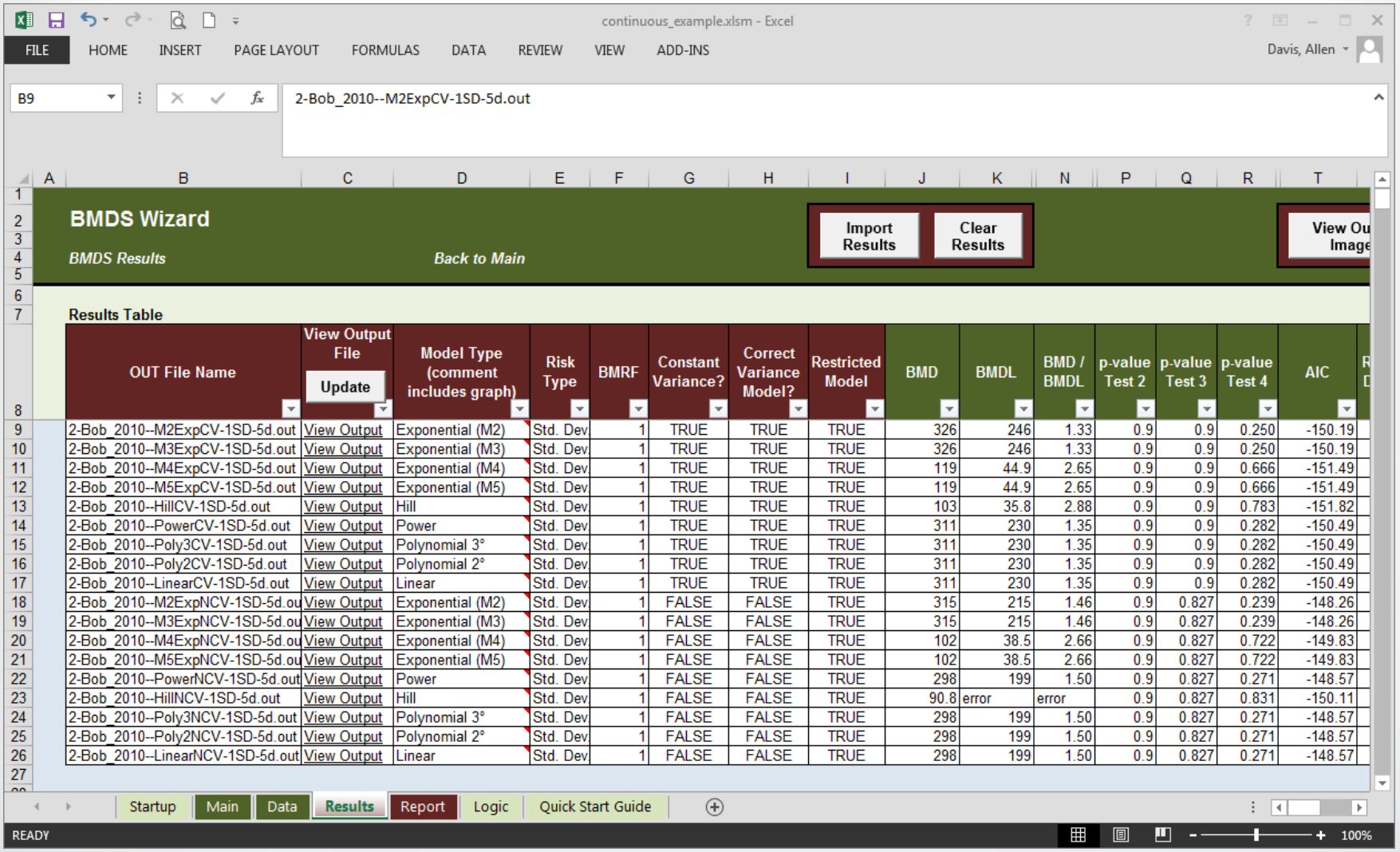


OUT File Name	View Output File (Update)	Model Type (comment includes graph)	Risk Type	BMRF	Constant Variance?	Correct Variance Model?	Restricted Model	BMD	BMDL	BMD / BMDL	p-value Test 2	p-value Test 3	p-value Test 4	AIC
2-Bob_2010--M2ExpCV-1SD-5d.out	View Output	Exponential (M2)	Std. Dev	1	TRUE	TRUE	TRUE	326	246	1.33	0.9	0.9	0.250	-150.19
2-Bob_2010--M3ExpCV-1SD-5d.out	View Output	Exponential (M3)	Std. Dev	1	TRUE	TRUE	TRUE	326	246	1.33	0.9	0.9	0.250	-150.19
2-Bob_2010--M4ExpCV-1SD-5d.out	View Output	Exponential (M4)	Std. Dev	1	TRUE	TRUE	TRUE	119	44.9	2.65	0.9	0.9	0.666	-151.49
2-Bob_2010--M5ExpCV-1SD-5d.out	View Output	Exponential (M5)	Std. Dev	1	TRUE	TRUE	TRUE	119	44.9	2.65	0.9	0.9	0.666	-151.49
2-Bob_2010--HillCV-1SD-5d.out	View Output	Hill	Std. Dev	1	TRUE	TRUE	TRUE	103	35.8	2.88	0.9	0.9	0.783	-151.82
2-Bob_2010--PowerCV-1SD-5d.out	View Output	Power	Std. Dev	1	TRUE	TRUE	TRUE	311	230	1.35	0.9	0.9	0.282	-150.49
2-Bob_2010--Poly3CV-1SD-5d.out	View Output	Polynomial 3°	Std. Dev	1	TRUE	TRUE	TRUE	311	230	1.35	0.9	0.9	0.282	-150.49

BMDS Wizard – Results

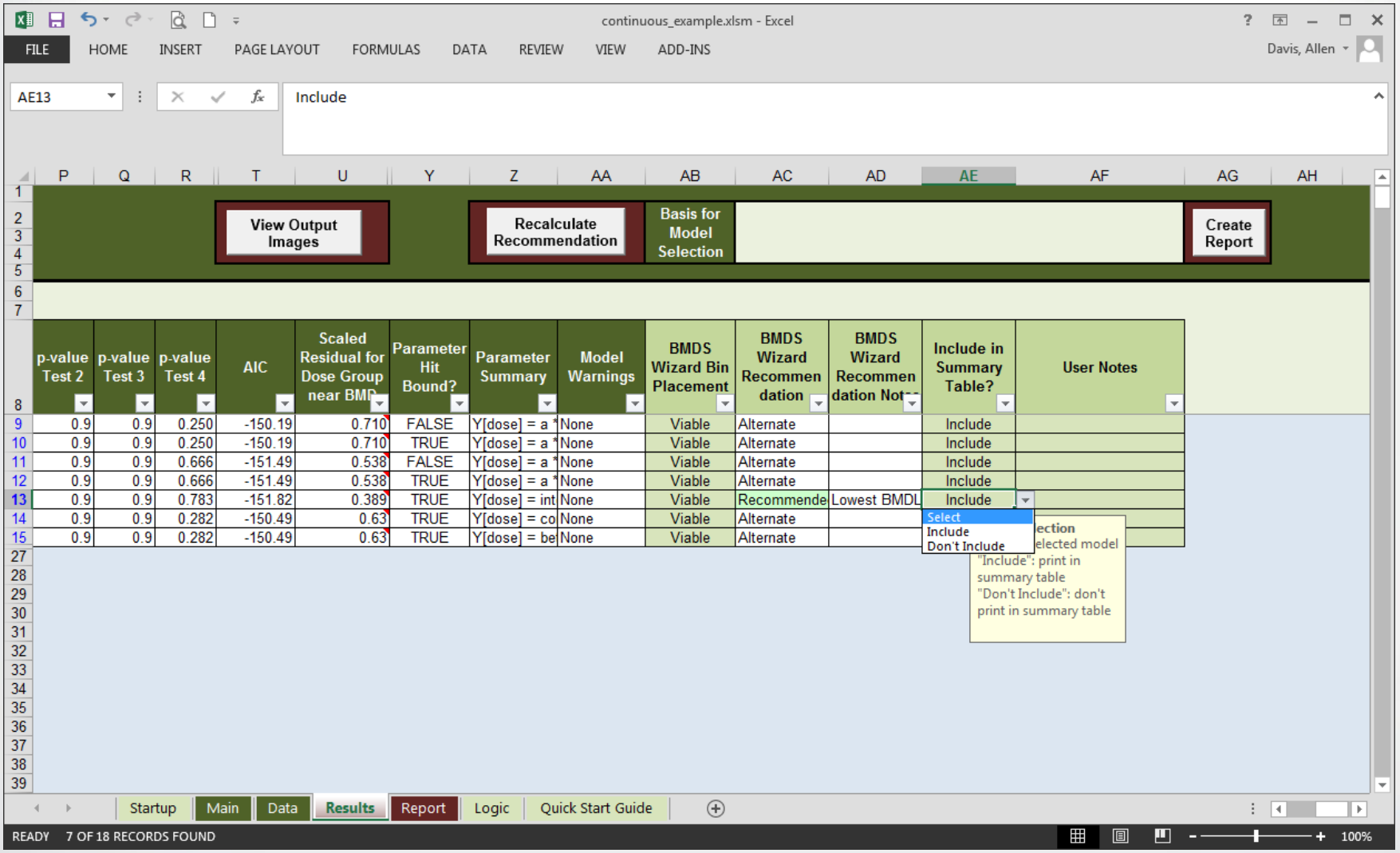


BMDS Wizard – Results

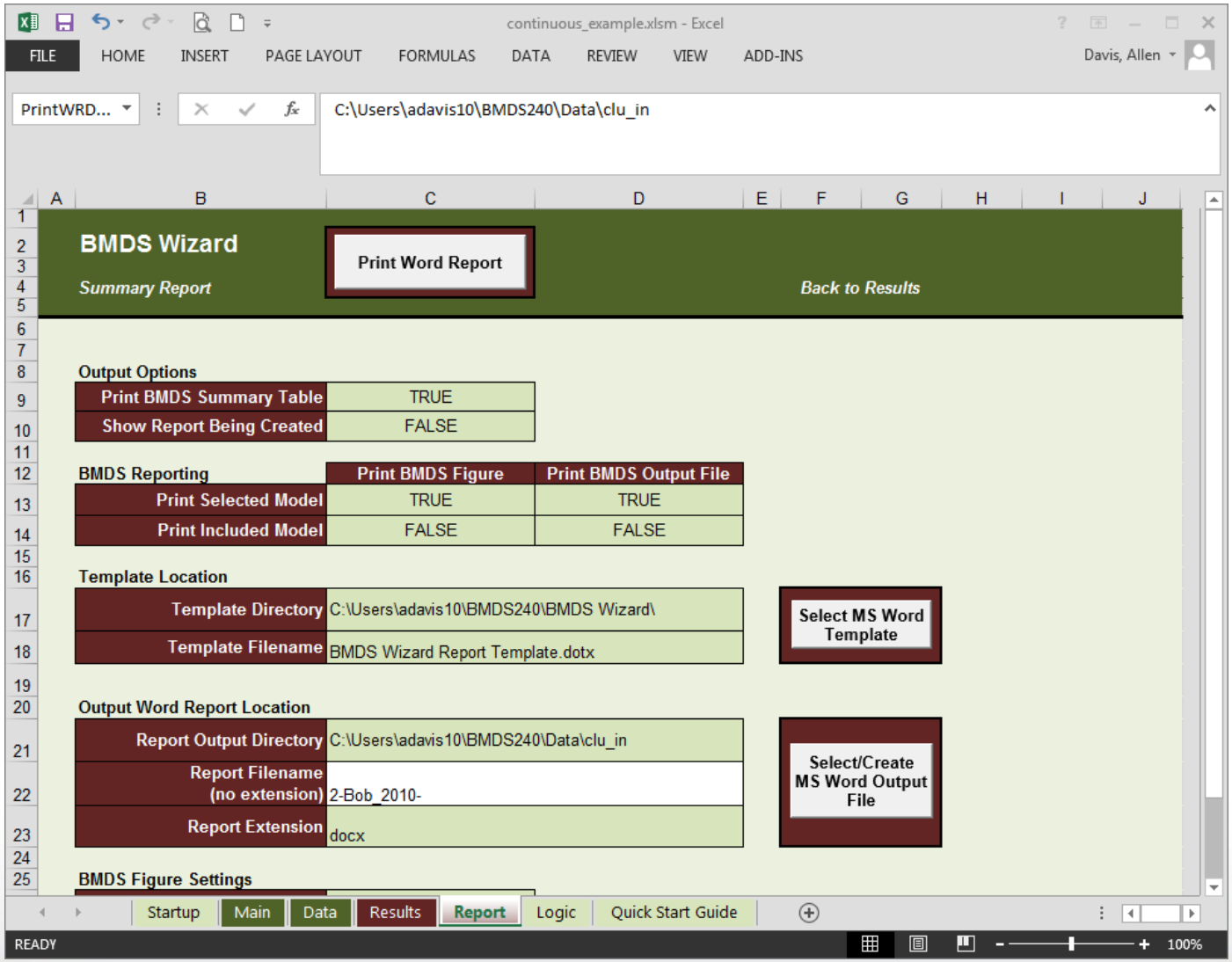


OUT File Name	View Output File (Update)	Model Type (comment includes graph)	Risk Type	BMRF	Constant Variance?	Correct Variance Model?	Restricted Model	BMD	BMDL	BMD / BMDL	p-value Test 2	p-value Test 3	p-value Test 4	AIC
2-Bob_2010--M2ExpCV-1SD-5d.out	View Output	Exponential (M2)	Std. Dev	1	TRUE	TRUE	TRUE	326	246	1.33	0.9	0.9	0.250	-150.19
2-Bob_2010--M3ExpCV-1SD-5d.out	View Output	Exponential (M3)	Std. Dev	1	TRUE	TRUE	TRUE	326	246	1.33	0.9	0.9	0.250	-150.19
2-Bob_2010--M4ExpCV-1SD-5d.out	View Output	Exponential (M4)	Std. Dev	1	TRUE	TRUE	TRUE	119	44.9	2.65	0.9	0.9	0.666	-151.49
2-Bob_2010--M5ExpCV-1SD-5d.out	View Output	Exponential (M5)	Std. Dev	1	TRUE	TRUE	TRUE	119	44.9	2.65	0.9	0.9	0.666	-151.49
2-Bob_2010--HillCV-1SD-5d.out	View Output	Hill	Std. Dev	1	TRUE	TRUE	TRUE	103	35.8	2.88	0.9	0.9	0.783	-151.82
2-Bob_2010--PowerCV-1SD-5d.out	View Output	Power	Std. Dev	1	TRUE	TRUE	TRUE	311	230	1.35	0.9	0.9	0.282	-150.49
2-Bob_2010--Poly3CV-1SD-5d.out	View Output	Polynomial 3°	Std. Dev	1	TRUE	TRUE	TRUE	311	230	1.35	0.9	0.9	0.282	-150.49
2-Bob_2010--Poly2CV-1SD-5d.out	View Output	Polynomial 2°	Std. Dev	1	TRUE	TRUE	TRUE	311	230	1.35	0.9	0.9	0.282	-150.49
2-Bob_2010--LinearCV-1SD-5d.out	View Output	Linear	Std. Dev	1	TRUE	TRUE	TRUE	311	230	1.35	0.9	0.9	0.282	-150.49
2-Bob_2010--M2ExpNCV-1SD-5d.ou	View Output	Exponential (M2)	Std. Dev	1	FALSE	FALSE	TRUE	315	215	1.46	0.9	0.827	0.239	-148.26
2-Bob_2010--M3ExpNCV-1SD-5d.ou	View Output	Exponential (M3)	Std. Dev	1	FALSE	FALSE	TRUE	315	215	1.46	0.9	0.827	0.239	-148.26
2-Bob_2010--M4ExpNCV-1SD-5d.ou	View Output	Exponential (M4)	Std. Dev	1	FALSE	FALSE	TRUE	102	38.5	2.66	0.9	0.827	0.722	-149.83
2-Bob_2010--M5ExpNCV-1SD-5d.ou	View Output	Exponential (M5)	Std. Dev	1	FALSE	FALSE	TRUE	102	38.5	2.66	0.9	0.827	0.722	-149.83
2-Bob_2010--PowerNCV-1SD-5d.out	View Output	Power	Std. Dev	1	FALSE	FALSE	TRUE	298	199	1.50	0.9	0.827	0.271	-148.57
2-Bob_2010--HillNCV-1SD-5d.out	View Output	Hill	Std. Dev	1	FALSE	FALSE	TRUE	90.8	error	error	0.9	0.827	0.831	-150.11
2-Bob_2010--Poly3NCV-1SD-5d.out	View Output	Polynomial 3°	Std. Dev	1	FALSE	FALSE	TRUE	298	199	1.50	0.9	0.827	0.271	-148.57
2-Bob_2010--Poly2NCV-1SD-5d.out	View Output	Polynomial 2°	Std. Dev	1	FALSE	FALSE	TRUE	298	199	1.50	0.9	0.827	0.271	-148.57
2-Bob_2010--LinearNCV-1SD-5d.out	View Output	Linear	Std. Dev	1	FALSE	FALSE	TRUE	298	199	1.50	0.9	0.827	0.271	-148.57

BMDS Wizard – Results



BMDS Wizard – Automatic Report Generation



BMDS Wizard – EPA Format Report in Microsoft Word

1.1. BMDS Summary of (Exercise_4)

Table 1. Model predictions for (Exercise_4)

Model[a]	Goodness of fit		BMD_{1SD} ()	$BMDL_{1SD}$ ()	Basis for model selection
	p-value	AIC			
Exponential (M2) Exponential (M3)[b]	0.250	-150.19	326	246	
Exponential (M4) Exponential (M5)[c]	0.666	-151.49	119	44.9	
Hill	**0.783**	**-151.82**	**103**	**35.8**	
Power[d] Polynomial 4°[e] Linear	0.282	-150.49	311	230	

[a] Constant variance case presented (BMDS Test 2 *p*-value = 0.9), selected model in bold; scaled residuals for selected model for doses 0, 35, 105, 316, and 625 were -0.0165, -0.123, 0.389, -0.505, and 0.256, respectively.
[b] For the Exponential (M3) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M2) model.
[c] For the Exponential (M5) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M4) model.
[d] For the Power model, the power parameter estimate was 1. The models in this row reduced to the Linear model.
[e] For the Polynomial 4° model, the b4, b3, and b2 coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Linear model.

Data from Exercise_4

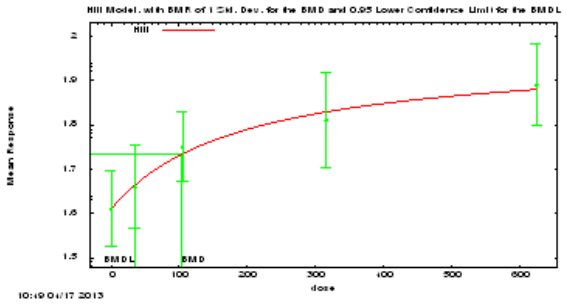


Figure 1. Plot of mean response by dose, with fitted curve for selected model; dose shown in .

Hill Model. (Version: 2.17; Date: 01/28/2013)
The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)
A constant variance model is fit

Benchmark Dose Computation.
BMR = 1 Estimated standard deviations from the control mean
BMD = 102.944
BMDL at the 95% confidence level = 35.8046

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.0150506	0.01656
rho	n/a	0
intercept	1.61064	1.61
v	0.352636	0.28
n	1	0.74024
k	192.959	105

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.61	1.61	0.12	0.123	-0.0165
35	10	1.66	1.66	0.13	0.123	-0.123
105	10	1.75	1.73	0.11	0.123	0.389
316	10	1.81	1.83	0.15	0.123	-0.505
625	10	1.89	1.88	0.13	0.123	0.256

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	80.153141	6	-148.306282
A2	80.685014	10	-141.370028
A3	80.153141	6	-148.306282
fitted	79.908507	4	-151.817014
R	67.174032	2	-130.348065

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	27.022	8	0.0007008
Test 2	1.06375	4	0.9
Test 3	1.06375	4	0.9
Test 4	0.489269	2	0.783

Continuous Data – Exercise #2

Continuous Exercise #2

- Open the default Wizard Template named "BMDS Wizard-continuous StDev.xlsm"
- Save as "Exercise_2.xlsm" (i.e., as a Macro Enabled Excel workbook)
- Select BMDS Installation Directory
- Select Output file directory (usually same directory as where you saved the Wizard template)
- Fill in Study & Year as "Exercise_2"
- Can fill out remaining Study and Modeling Inputs, but its not necessary for this exercise

Continuous Exercise #2

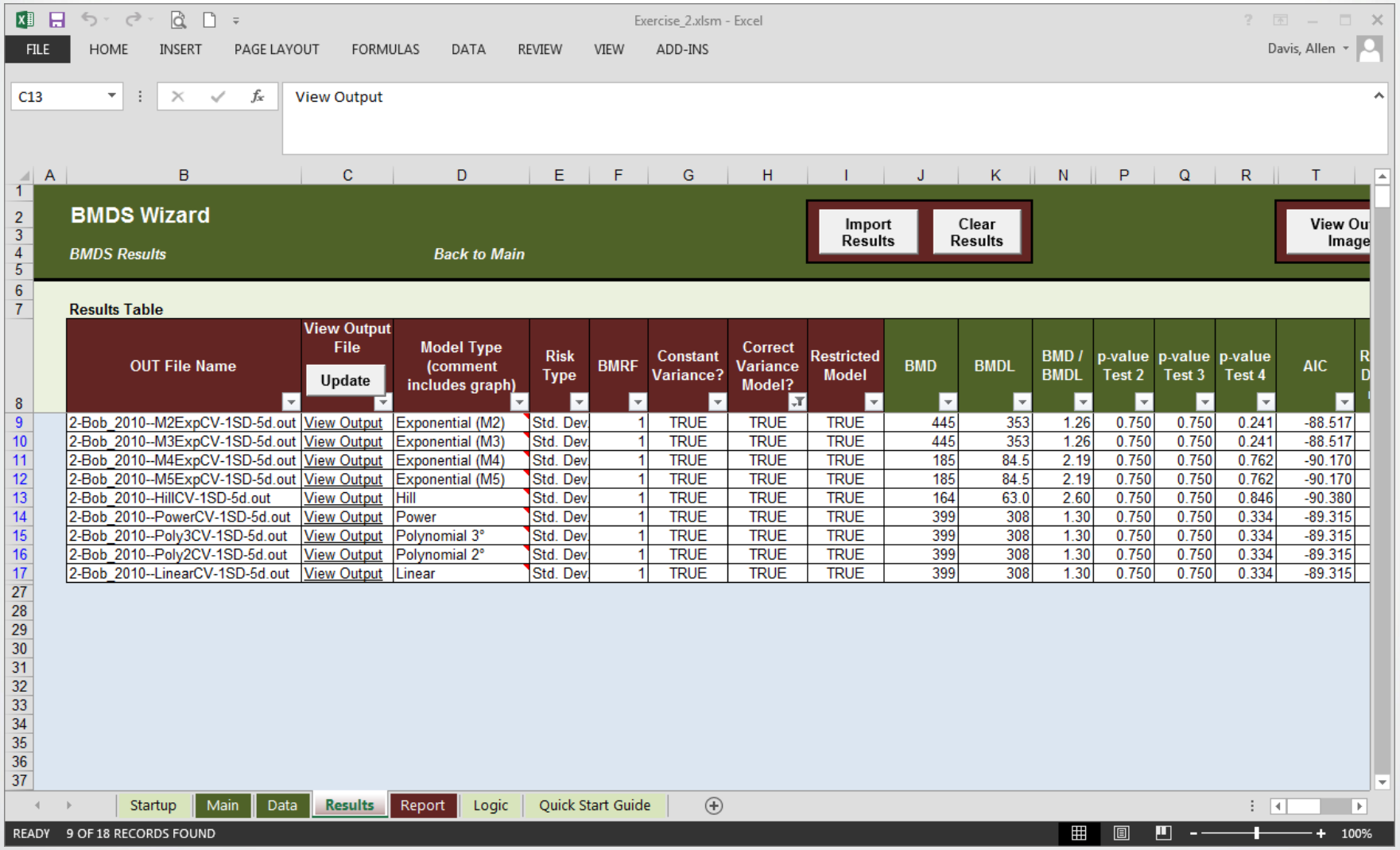
- **On Data worksheet tab, enter the following dose-response data:**

Dose-Response Data Inputs

Column Name in BMDS	Dose	NumAnimals	MeanResponse	Stdev
Column Type Assignment	Dose	NumAnimals	MeanResponse	Stdev
Dose Group 1	0	10	1.61	0.21
Dose Group 2	50	10	1.74	0.26
Dose Group 3	200	10	1.89	0.19
Dose Group 4	600	10	2.1	0.24
Dose Group 5	1000	10	2.24	0.28

- **On Main worksheet tab, click "AUTORUN"**
- **Results will automatically import to Results worksheet tab**
- **Which model would you pick, and why?**

Continuous Exercise #2



OUT File Name	View Output File (Update)	Model Type (comment includes graph)	Risk Type	BMRF	Constant Variance?	Correct Variance Model?	Restricted Model	BMD	BMDL	BMD / BMDL	p-value Test 2	p-value Test 3	p-value Test 4	AIC
2-Bob_2010--M2ExpCV-1SD-5d.out	View Output	Exponential (M2)	Std. Dev	1	TRUE	TRUE	TRUE	445	353	1.26	0.750	0.750	0.241	-88.517
2-Bob_2010--M3ExpCV-1SD-5d.out	View Output	Exponential (M3)	Std. Dev	1	TRUE	TRUE	TRUE	445	353	1.26	0.750	0.750	0.241	-88.517
2-Bob_2010--M4ExpCV-1SD-5d.out	View Output	Exponential (M4)	Std. Dev	1	TRUE	TRUE	TRUE	185	84.5	2.19	0.750	0.750	0.762	-90.170
2-Bob_2010--M5ExpCV-1SD-5d.out	View Output	Exponential (M5)	Std. Dev	1	TRUE	TRUE	TRUE	185	84.5	2.19	0.750	0.750	0.762	-90.170
2-Bob_2010--HillCV-1SD-5d.out	View Output	Hill	Std. Dev	1	TRUE	TRUE	TRUE	164	63.0	2.60	0.750	0.750	0.846	-90.380
2-Bob_2010--PowerCV-1SD-5d.out	View Output	Power	Std. Dev	1	TRUE	TRUE	TRUE	399	308	1.30	0.750	0.750	0.334	-89.315
2-Bob_2010--Poly3CV-1SD-5d.out	View Output	Polynomial 3°	Std. Dev	1	TRUE	TRUE	TRUE	399	308	1.30	0.750	0.750	0.334	-89.315
2-Bob_2010--Poly2CV-1SD-5d.out	View Output	Polynomial 2°	Std. Dev	1	TRUE	TRUE	TRUE	399	308	1.30	0.750	0.750	0.334	-89.315
2-Bob_2010--LinearCV-1SD-5d.out	View Output	Linear	Std. Dev	1	TRUE	TRUE	TRUE	399	308	1.30	0.750	0.750	0.334	-89.315

References

- Crump (1995). Calculation of benchmark doses from continuous data. Risk Anal. 15: 79-89

- Shao, K; Gift, JS; Setzer, RW (2013). Is the assumption of normality or log-normality for continuous response data critical for benchmark dose estimation? Toxicol Appl Pharmacol. 272(3): 767-79