



Benchmark Dose Modeling – Continuous Models

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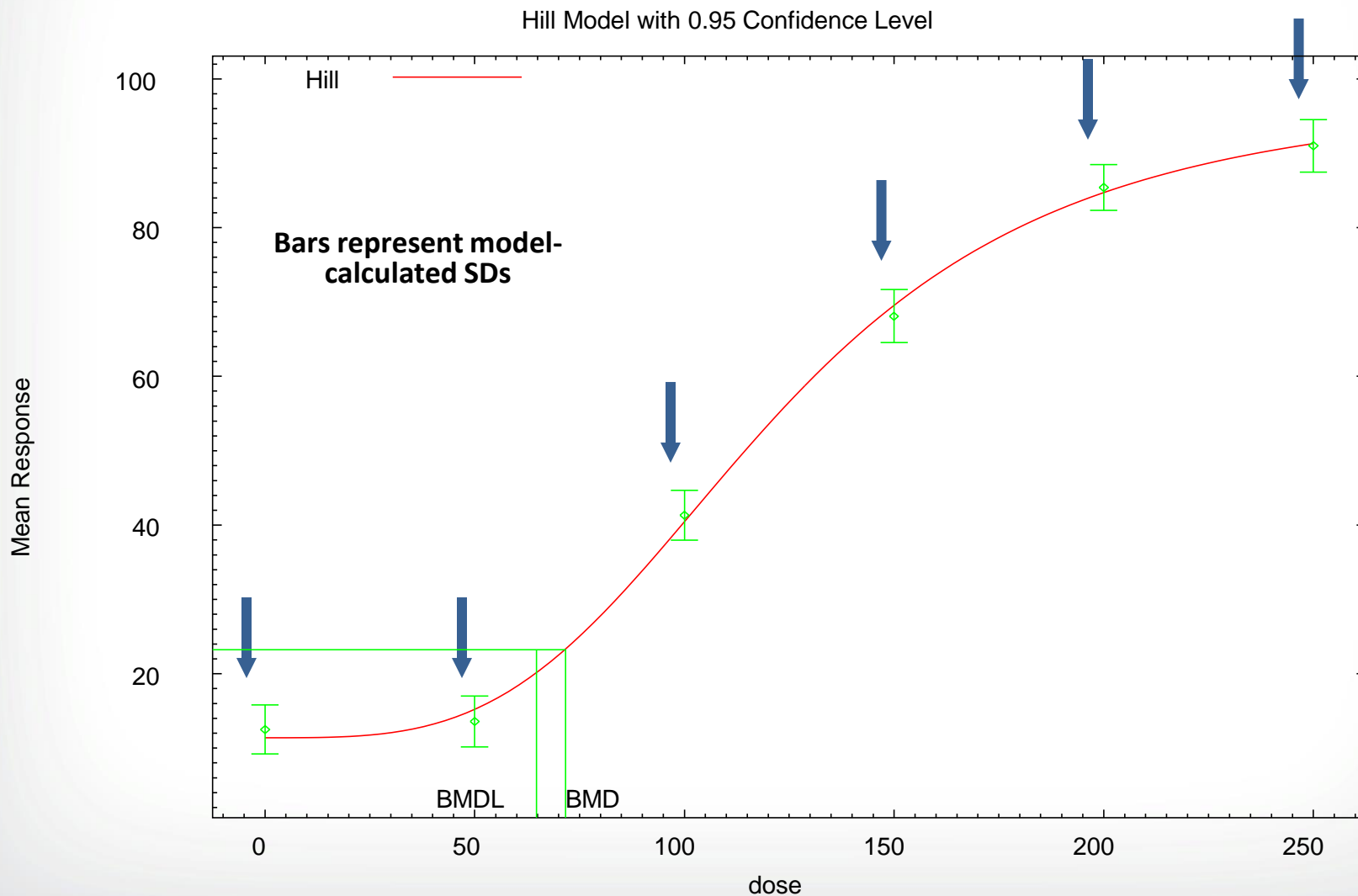
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Description	<ul style="list-style-type: none">• Response is measured on a continuous spectrum• Response is a numerical value with a measure of variability (i.e., standard error or standard deviation)• Response can either increase or decrease with dose
Example Endpoints	<ul style="list-style-type: none">• Body weight• Organ weight• Enzyme Activity
Model Inputs	<ul style="list-style-type: none">• Dose• Number of Subjects• Mean response (per dose group) OR individual animal responses• A measure of variability in response<ul style="list-style-type: none">○ Standard deviation (SD) needed for modeling purposes○ Variability reported as standard error must be converted to SD○ SD automatically calculated when inputting individual responses

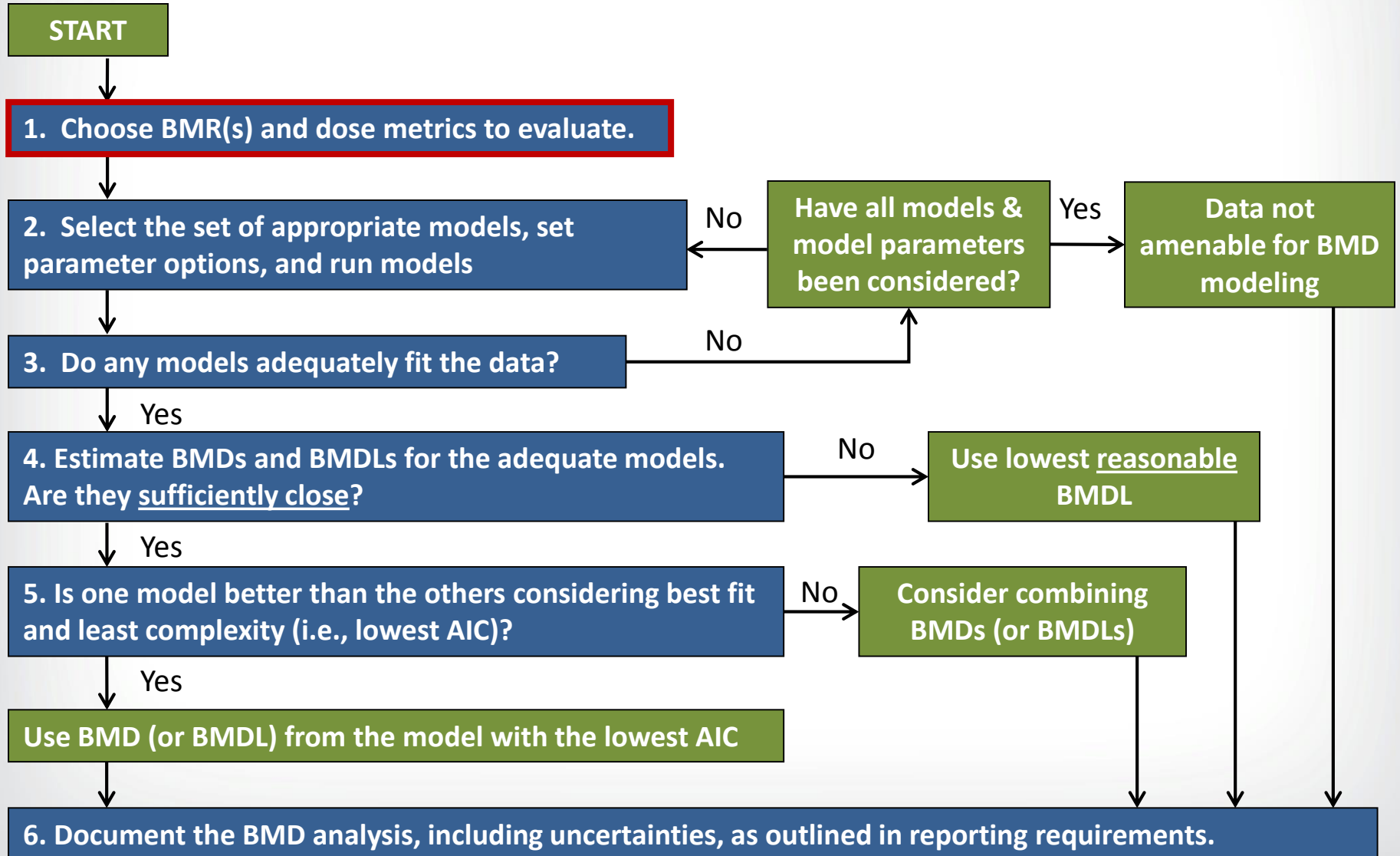


Example of Continuous Data





BMD Analysis – Six Steps



- **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:	$BMR = \text{mean}_0 \pm (BMRF \times SD_0)$
Relative Deviation:	$BMR = \text{mean}_0 \pm (BMRF \times \text{mean}_0)$
Absolute Deviation:	$BMR = \text{mean}_0 \pm BMRF$
Point:	$BMR = BMRF$
Extra (Hill only):	$BMR_{up} = \text{mean}_0 + BMRF \times (\text{mean}_{max} - \text{mean}_0)$ $BMR_{down} = \text{mean}_0 - BMRF \times (\text{mean}_0 - \text{mean}_{min})$

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.

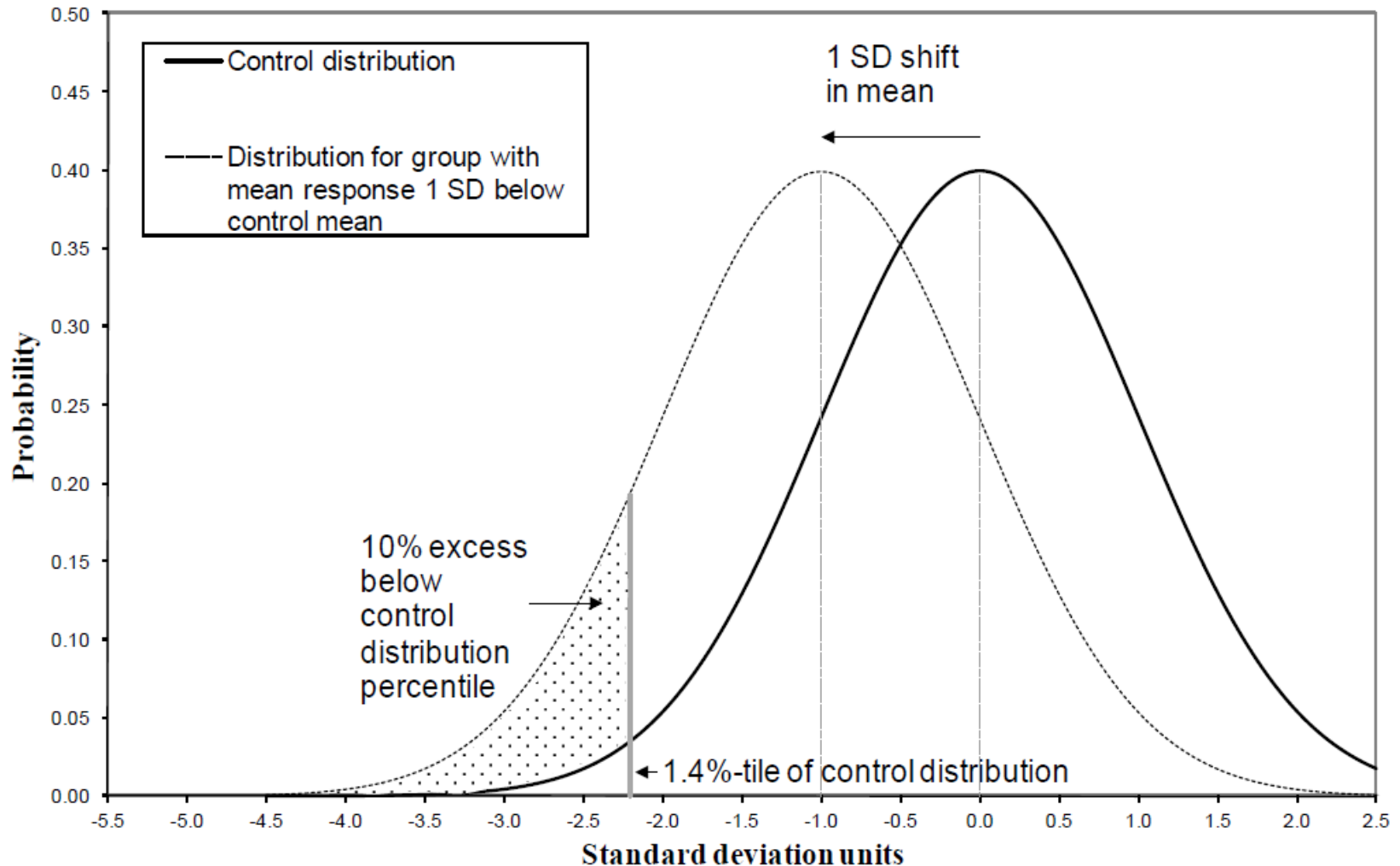


Why Use SD as the BMR for Continuous Data?

- **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?



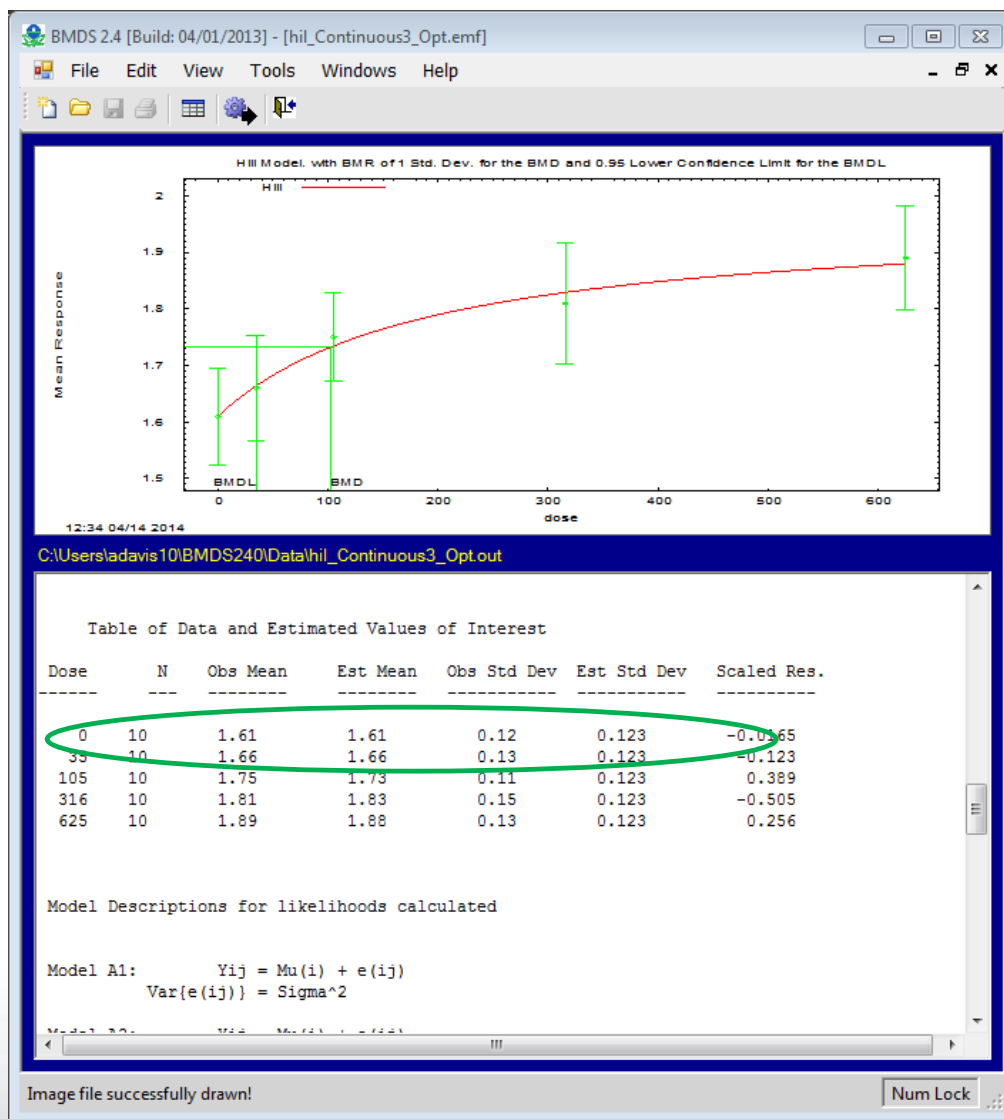


Double-checking Control Group SD

- **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:**

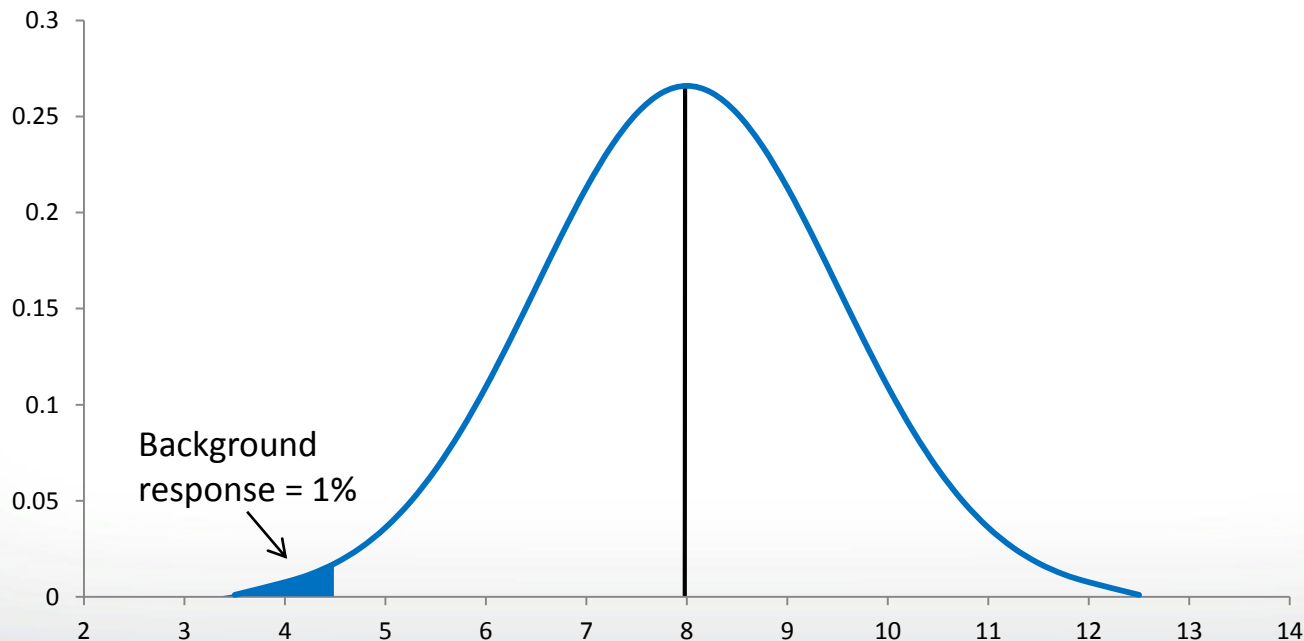
$$0.10 = [P(d) - P(0)] / [1 - P(0)]$$

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

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

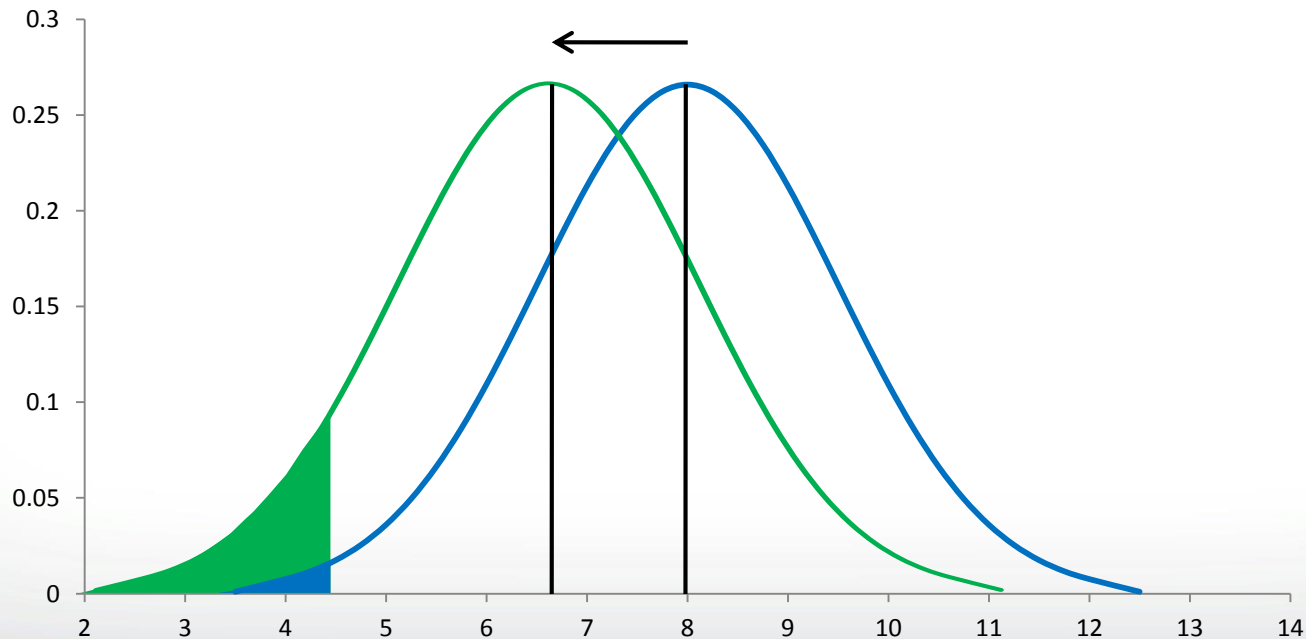
- **Therefore, we are interested in the dose that results in 10.9% of subjects exhibiting an adverse response**

- **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**



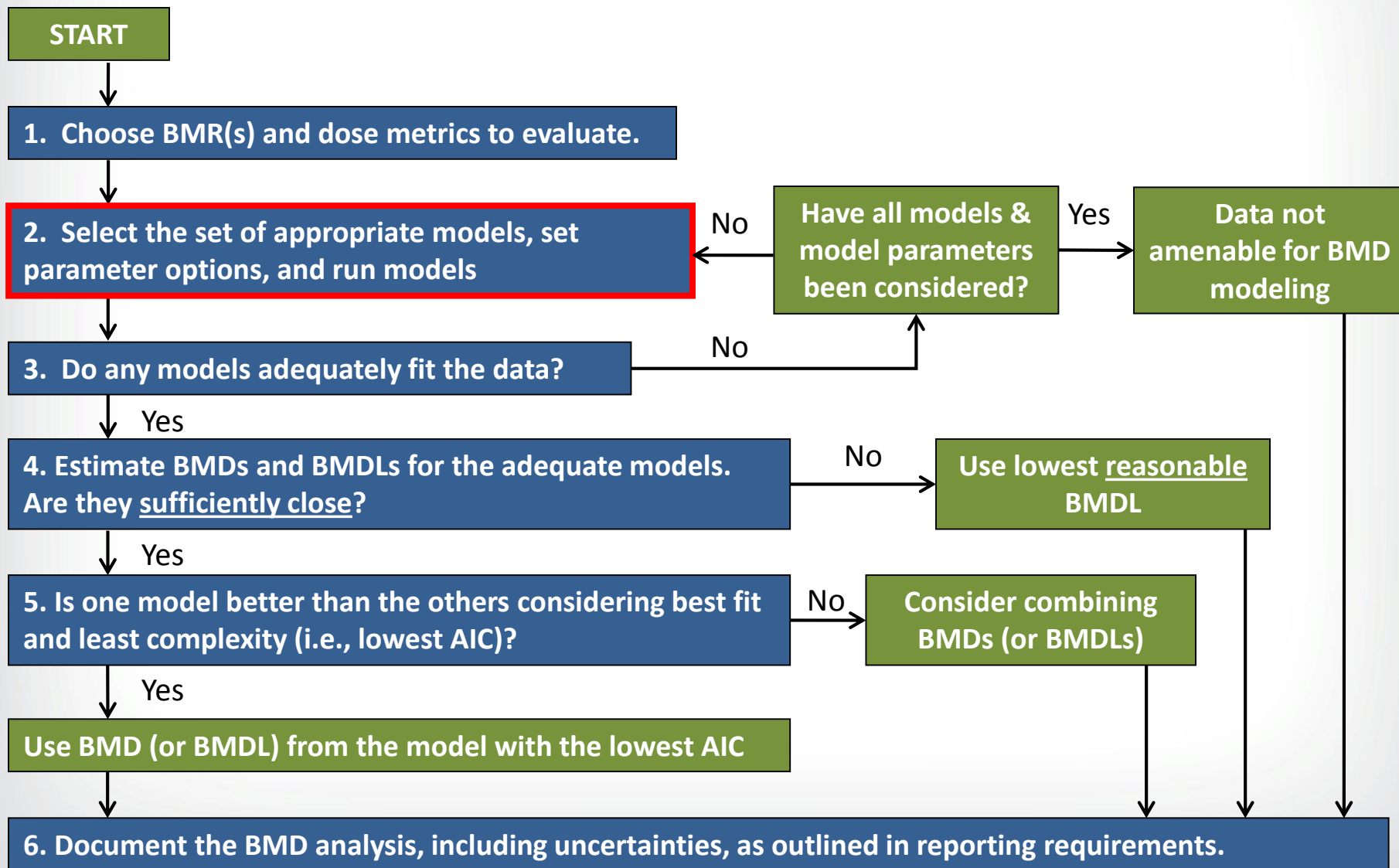
The Hybrid Approach – Selecting the Background Rate

- **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



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 <i>mathematically</i> describe the data



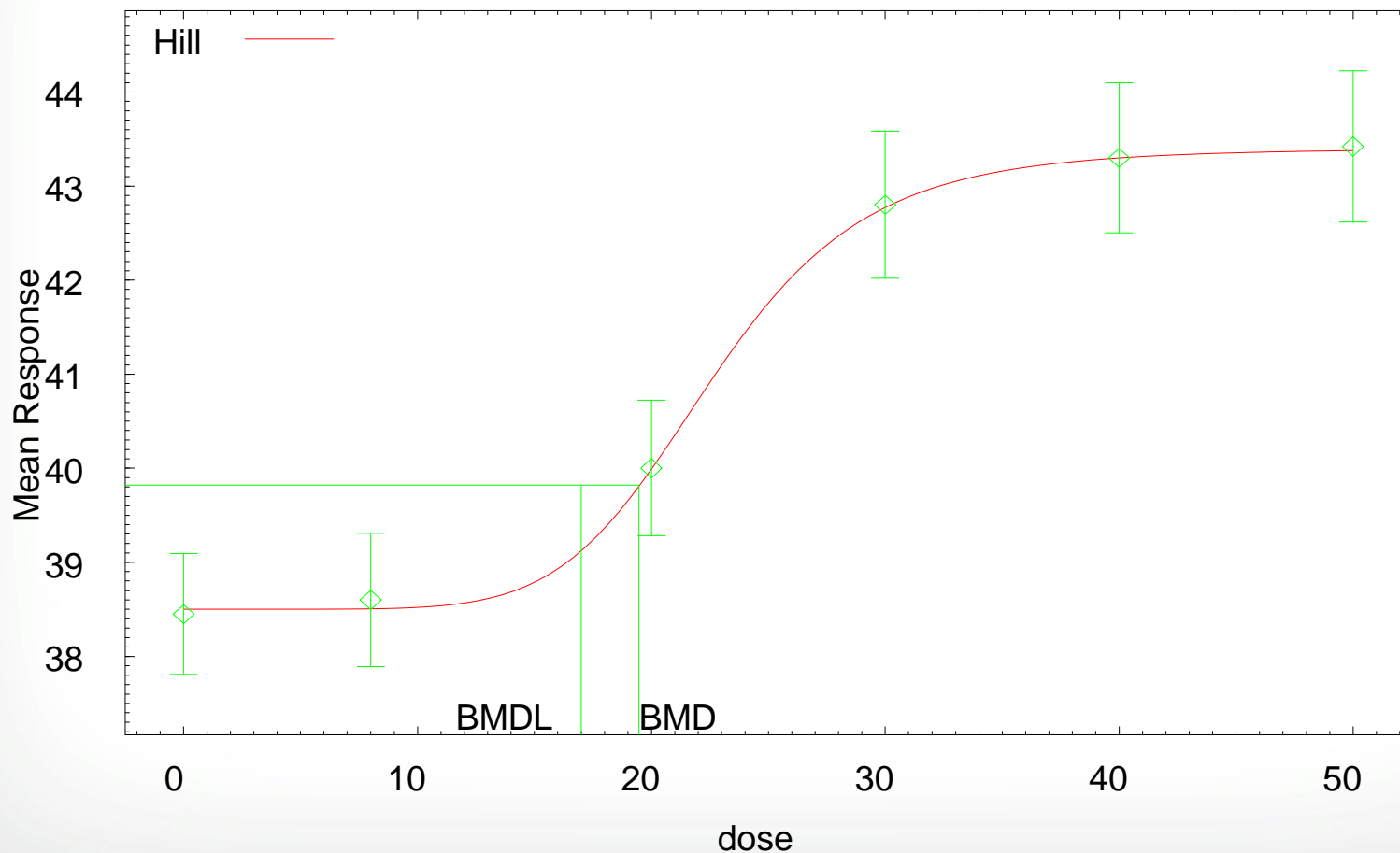
Continuous Model Forms

Model Name	Functional Form	# of Parameters	Model Fits
Polynomial ^a	$\beta_0 + \beta_1 X + \beta_2 X^2 + \dots + \beta_n X^n$	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 $a \times \exp\{\pm 1 \times b \times X\}$ Model 3 $a \times \exp\{\pm 1 \times (b \times X)^d\}$ Model 4 $a \times [c - (c - 1) \times \exp\{\pm 1 \times b \times X\}]$ Model 5 $a \times [c - (c - 1) \times \exp\{\pm 1 \times (b \times X)^d\}]$	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 Model with 0.95 Confidence Level





Exponential Models are “Nested”

```
BMDS 2.4 [Build: 04/01/2013] - [C:\Users\adavis10\BMDS240\Data\exp_Continuous3_Setting.out]
File Edit View Tools Windows Help
File Edit Preferences
=====
Exponential Model. (Version: 1.9; Date: 01/29/2013)
Input Data File: C:/Users/adavis10/BMDS240/Data/exp_Continuous3_Setting.(d)
Gnuplot Plotting File:
=====
Mon Apr 14 12:37:08 2014
=====
BMDS Model Run
=====
The form of the response function by Model:
Model 2:  Y[dose] = a * exp{sign * b * dose}
Model 3:  Y[dose] = a * exp{sign * (b * dose)^d}
Model 4:  Y[dose] = a * [c-(c-1) * exp{-b * dose}]
Model 5:  Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

Note: Y[dose] is the median response for exposure = dose;
      sign = +1 for increasing trend in data;
      sign = -1 for decreasing trend.

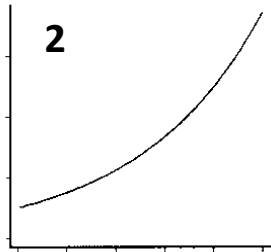
Model 2 is nested within Models 3 and 4.
Model 3 is nested within Model 5.
Model 4 is nested within Model 5.

Dependent variable = Mean
Independent variable = Dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha + rho * ln(Y[dose]))
rho is set to 0.
A constant variance model is fit.

Total number of dose groups = 5
Total number of records with missing values = 0
Maximum number of iterations = 500
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008
MFE values provided: Exact
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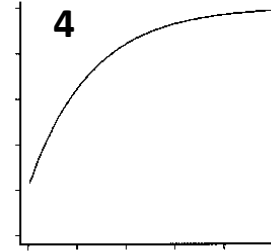
Exponential Models are “Nested”

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



$c = 0$
←

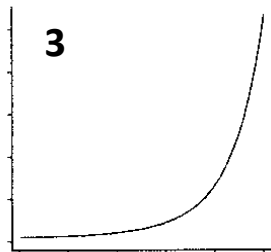
$$a \times [c - (c - 1) \times \exp\{-1 \times b \times X\}]$$



↑
 $d = 1$

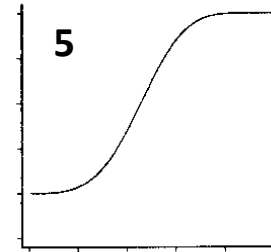
↑
 $d = 1$

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



$c = 0$
←

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

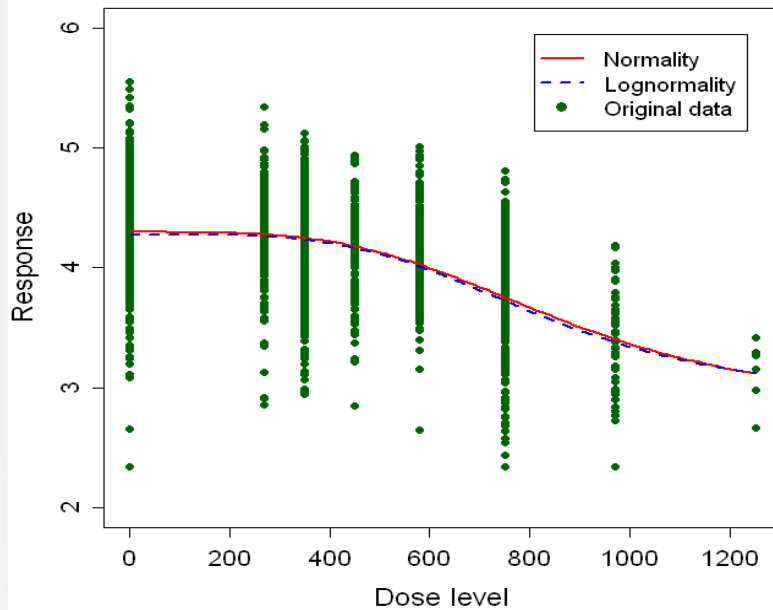


- **Data can be assumed to be lognormally distributed when using the Exponential models**
 - This reflects the distribution of the data per se, not how the modeling is done
 - Many biological parameters are lognormally distributed; a lognormal distribution is also useful to consider whenever responses 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)

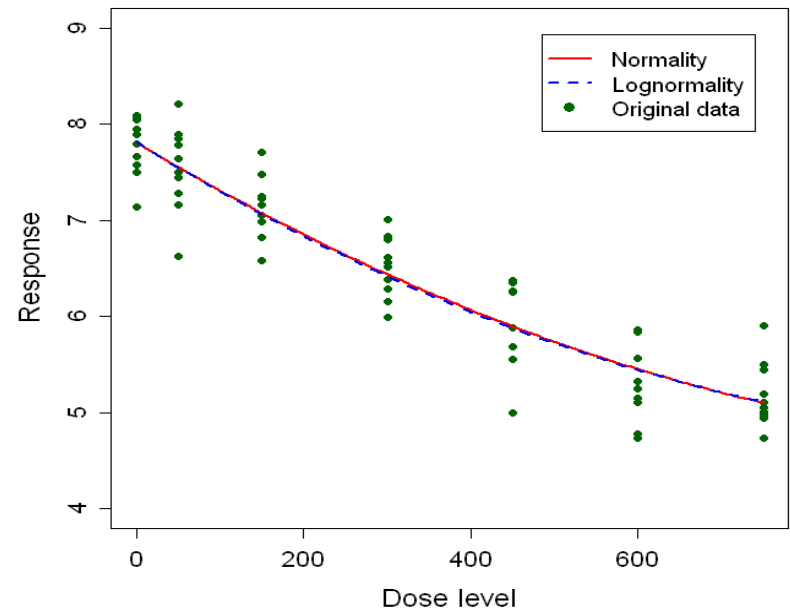
- **The SD is homogenous on a log-scale when within dose-group variance is proportional to the mean response**
-
- **However, an extra parameter is needed to model the within dose-group variance if normality is assumed**
- **Sometimes, the extra parameter can have significant impact on the BMD estimation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

Exponential Models – Log-normality

Hill Model



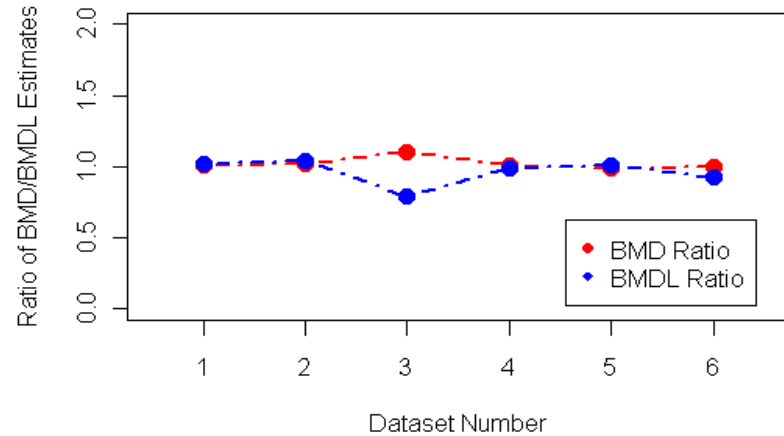
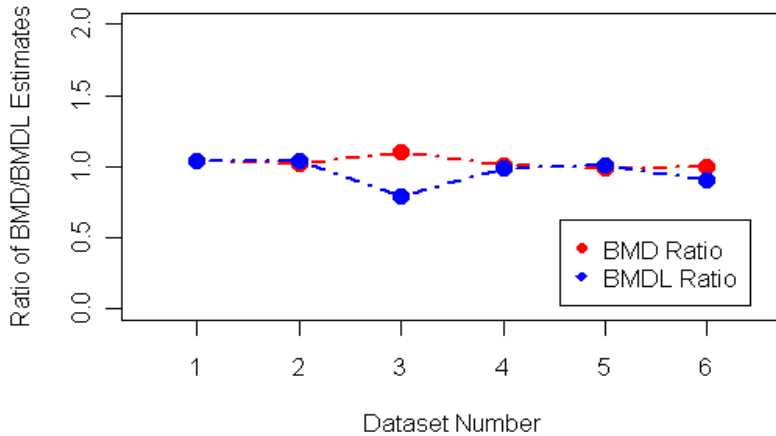
Quadratic Model



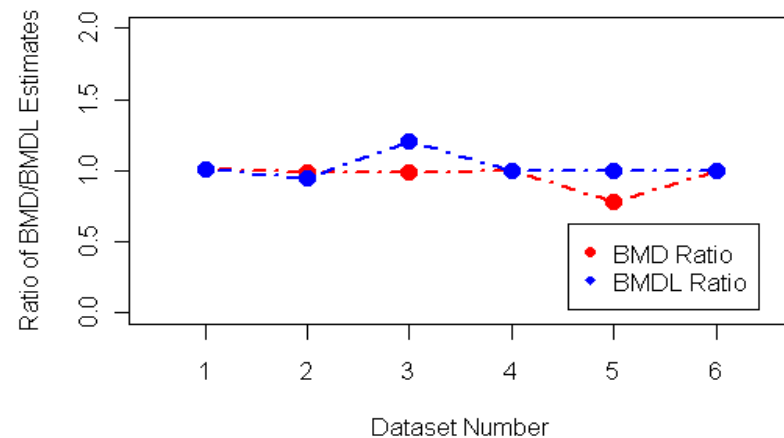
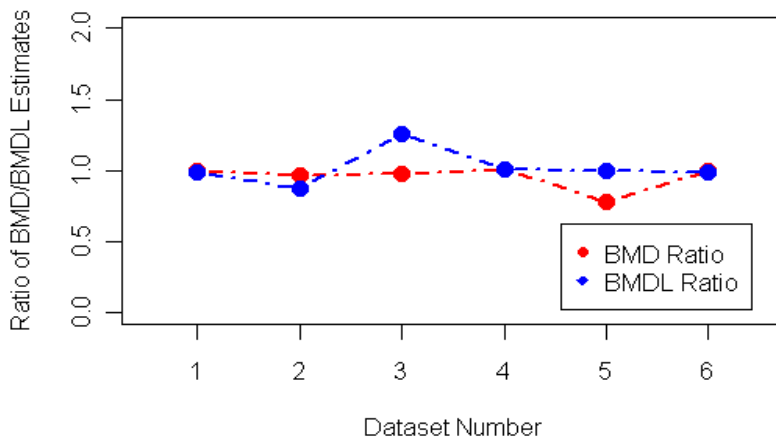


Normality vs. Log-normality – Difference in BMDs and BMDLs

Ratios of BMD and BMDL Estimates from Quadratic Model using 5%(left) and 10%(right) Relative Deviation



Ratios of BMD and BMDL Estimates from Hill Model using 5%(left) and 10%(right) Relative Deviation





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)



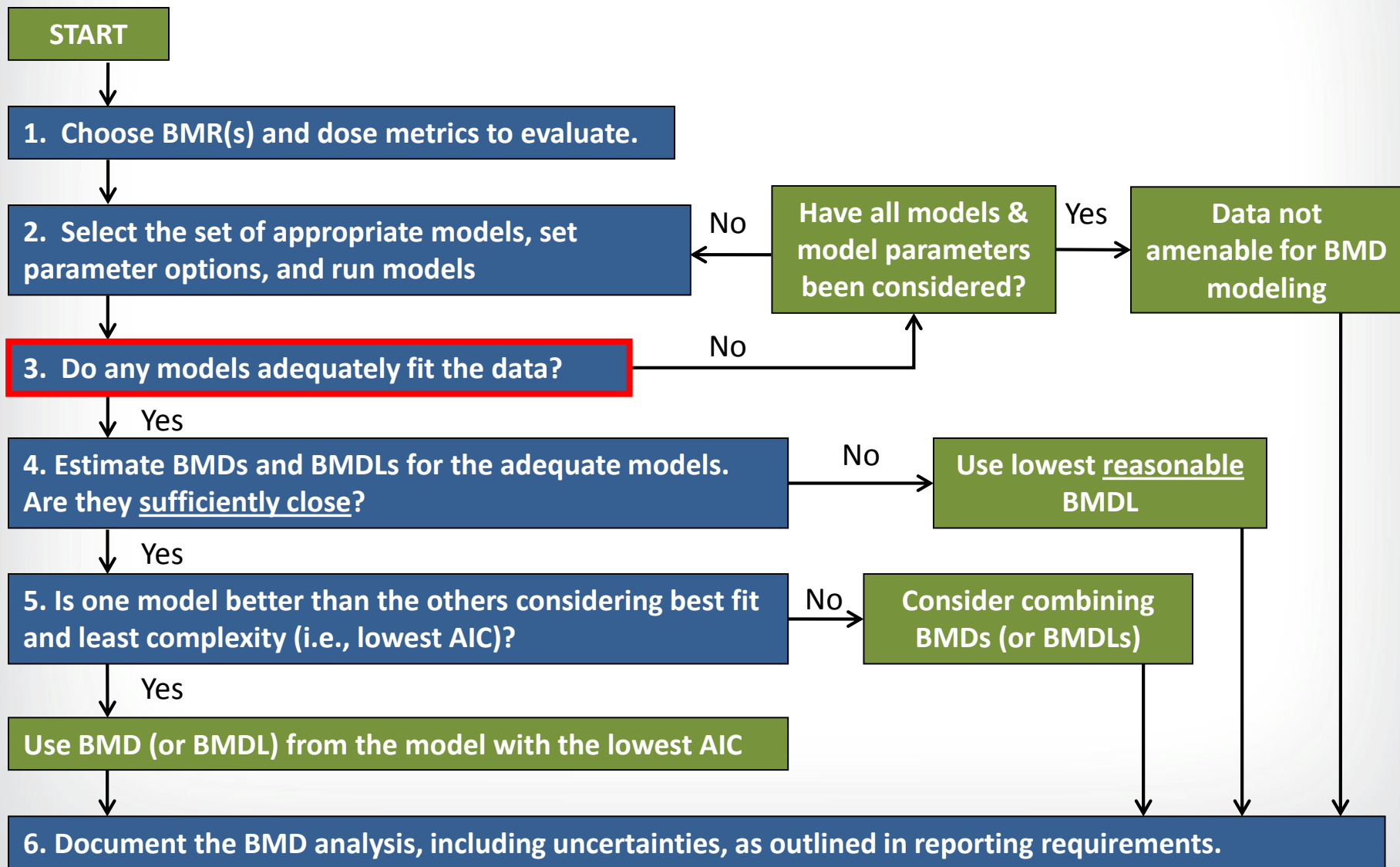
Restricting Continuous Models – EPA Recommendations

- **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

- **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

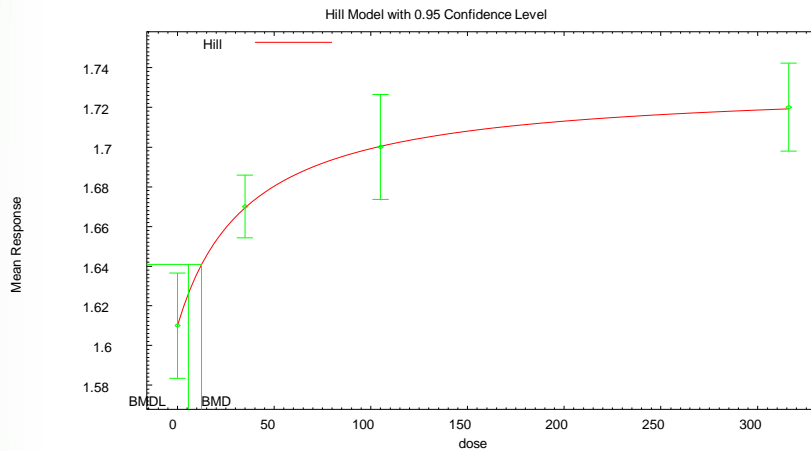


- **For continuous data:**
 - *Tests of interest (response/variance modeling)*
 - Global measurement: goodness-of-fit p value ($p > 0.1$)
 - Local measurement: Scaled residuals (absolute value < 2.0)
 - Visual inspection of model fitting.

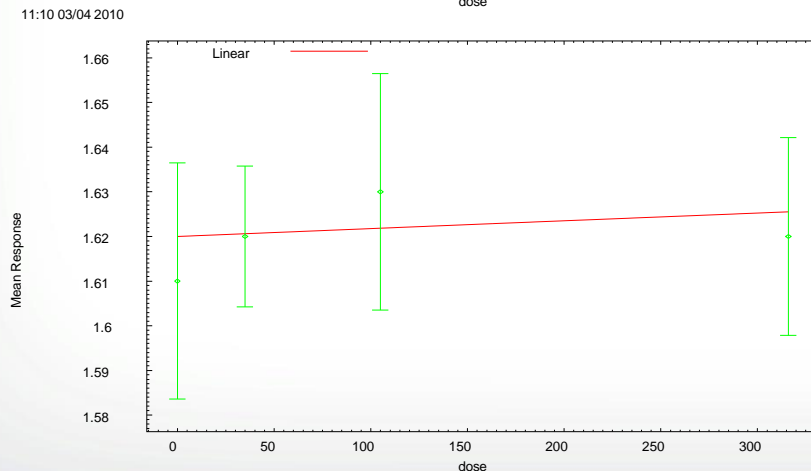


Tests of Interest – Differences in Responses/Variances

- **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

- **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**
 - $\text{Var}(i) = \alpha[\text{mean}(i)]^\rho$
 - $\rho(\text{rho}) = 0$, constant variance
 - $\rho(\text{rho}) \neq 0$, modeled variance
- **Test 2 – Are variances homogenous?**
- **Test 3 – Are variances adequately modeled?**
- **Always assume constant variance unless data clearly indicate otherwise**

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. 0)
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.

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. B)
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          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.

Continuous data with variance modeled as power function of mean

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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          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.

Continuous data with variance modeled as power function of mean

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Explanation of Tests

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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

- **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.

- **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


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Explanation of Tests

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Tests of Interest

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Modeling Recommendations – Poor Global Goodness-of-Fit

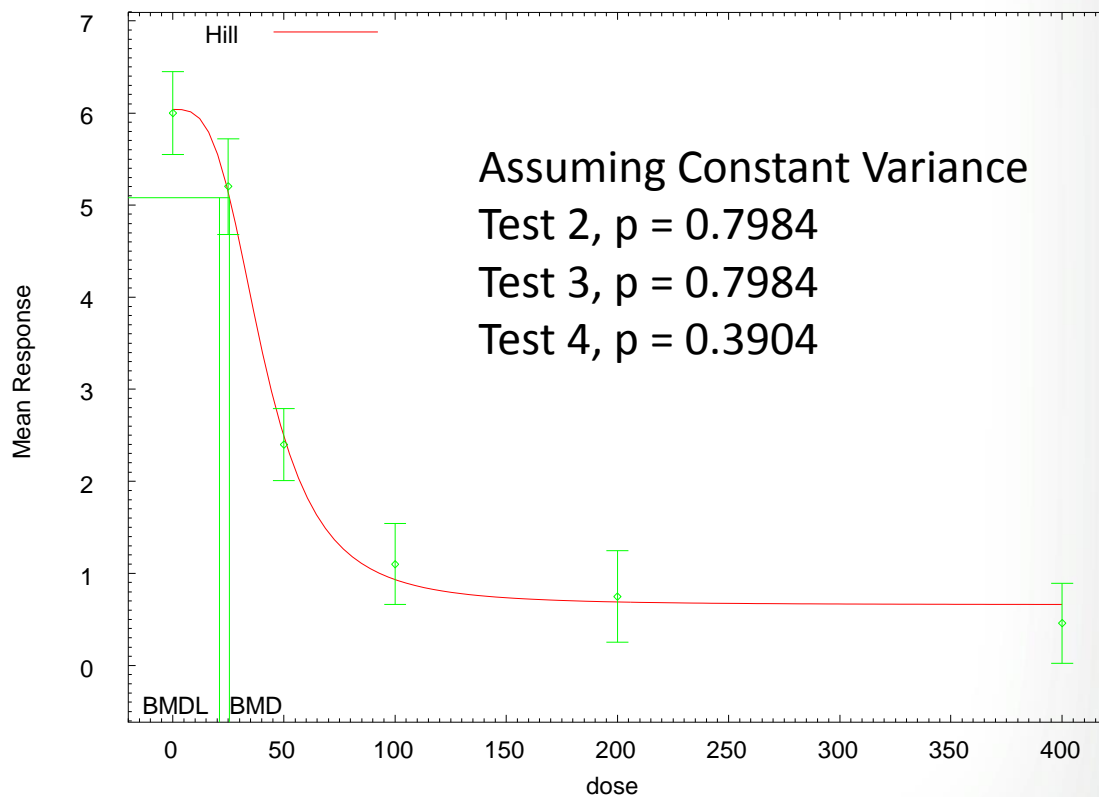
- **Consider dropping high dose group(s) that negatively impact low dose fit**
- **Don't drop doses solely to improve fit**
- **To model a high dose “plateau” consider using a Hill or other models that contain an asymptote term**
- **Use PBPK models if available to calculate internal dose metrics that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



Example I: 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

Hill Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

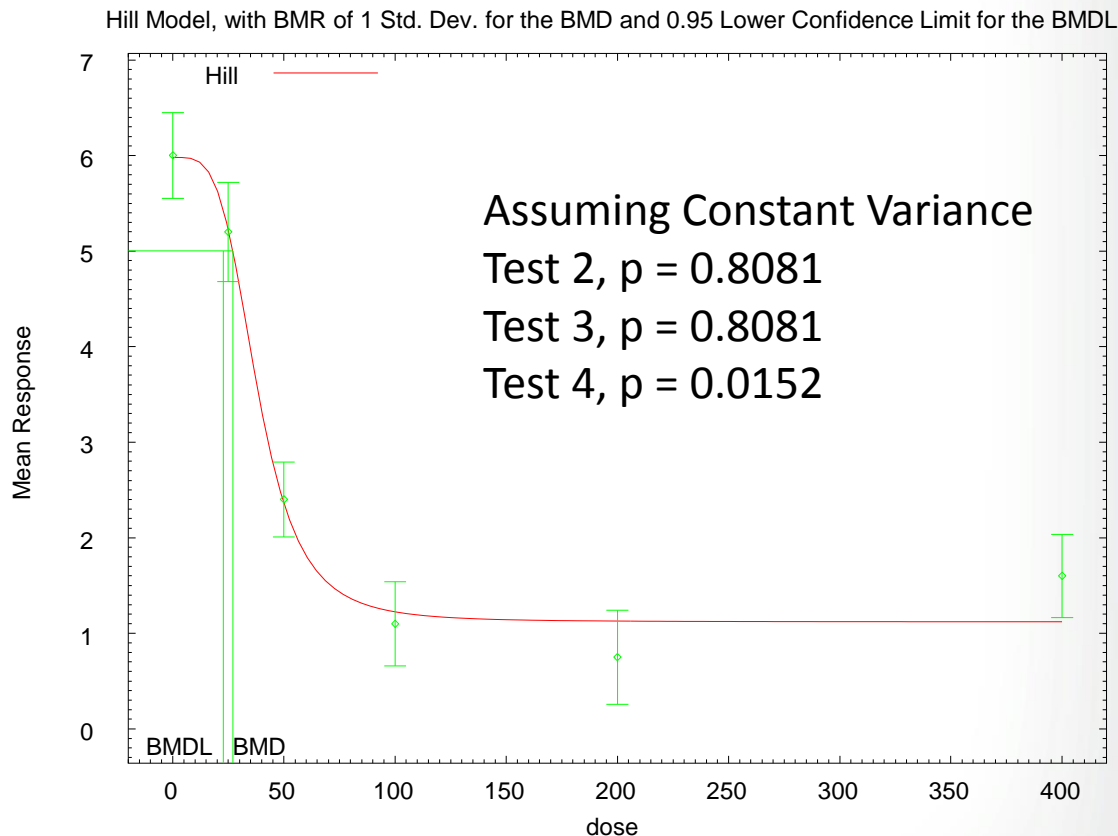


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Example I: When to Drop the High Dose

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

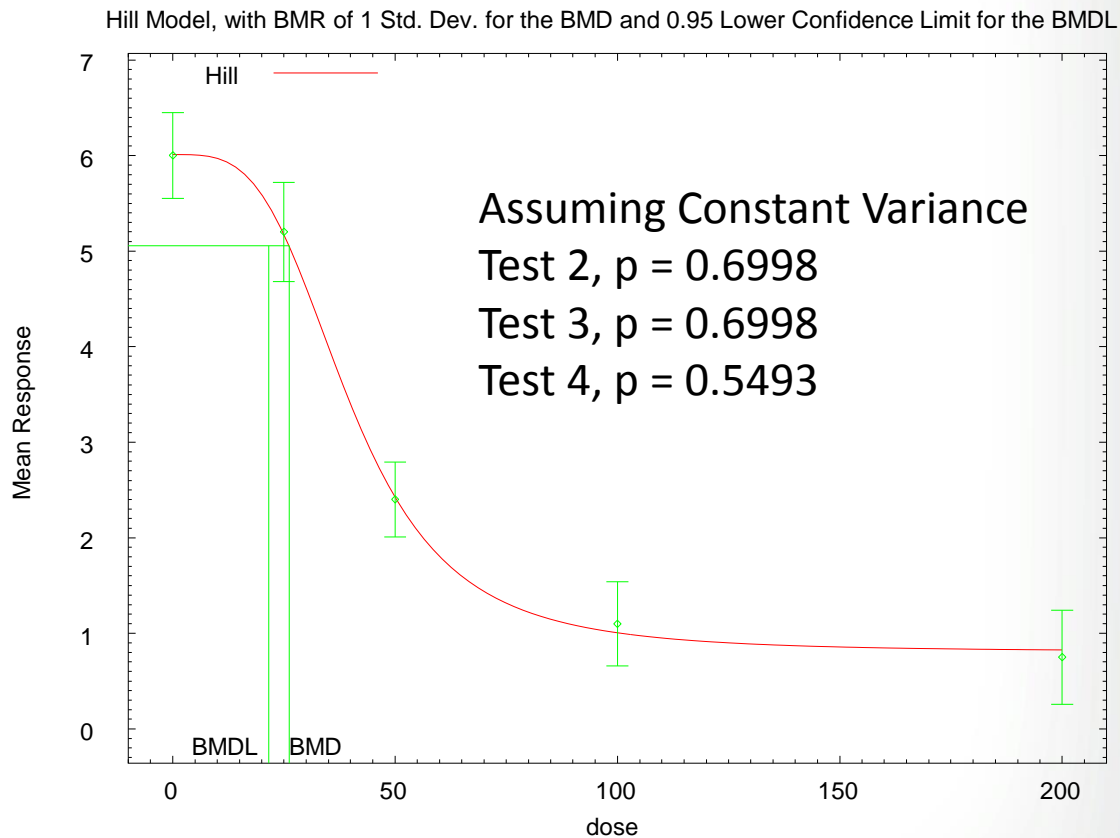


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Example I: When to Drop the High Dose

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

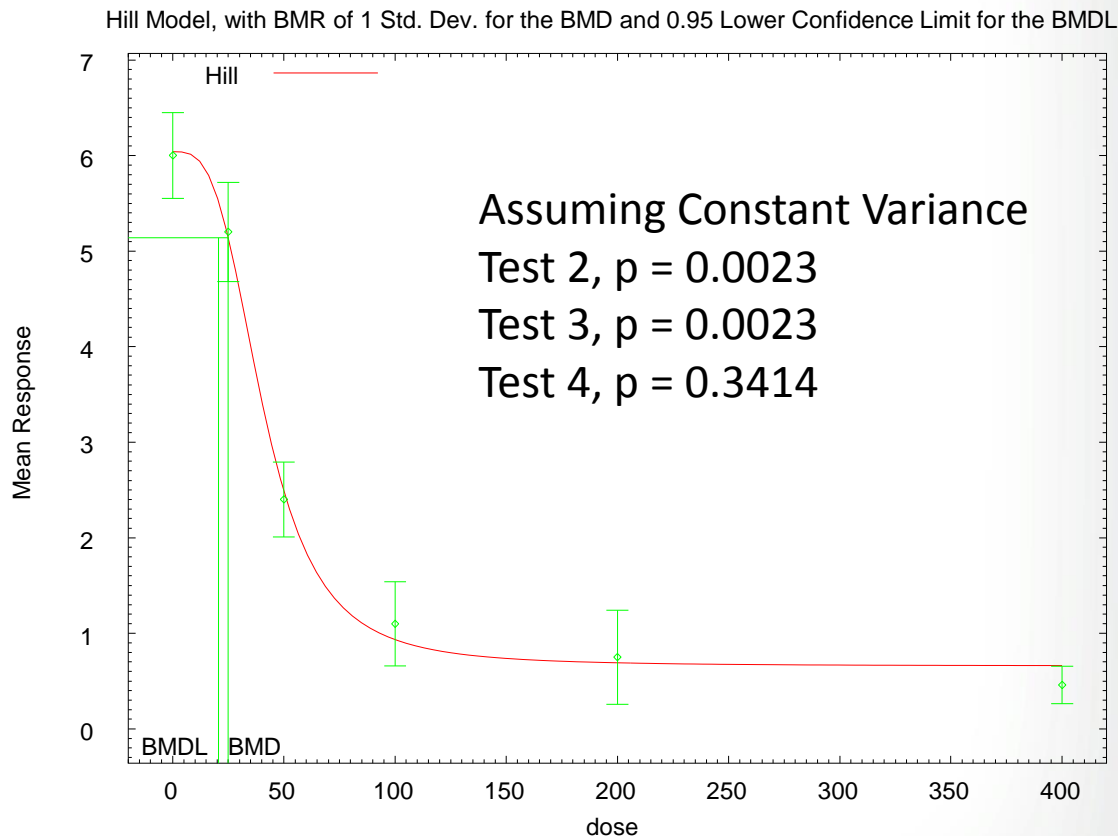


11:27 04/11 2014



Example I: 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

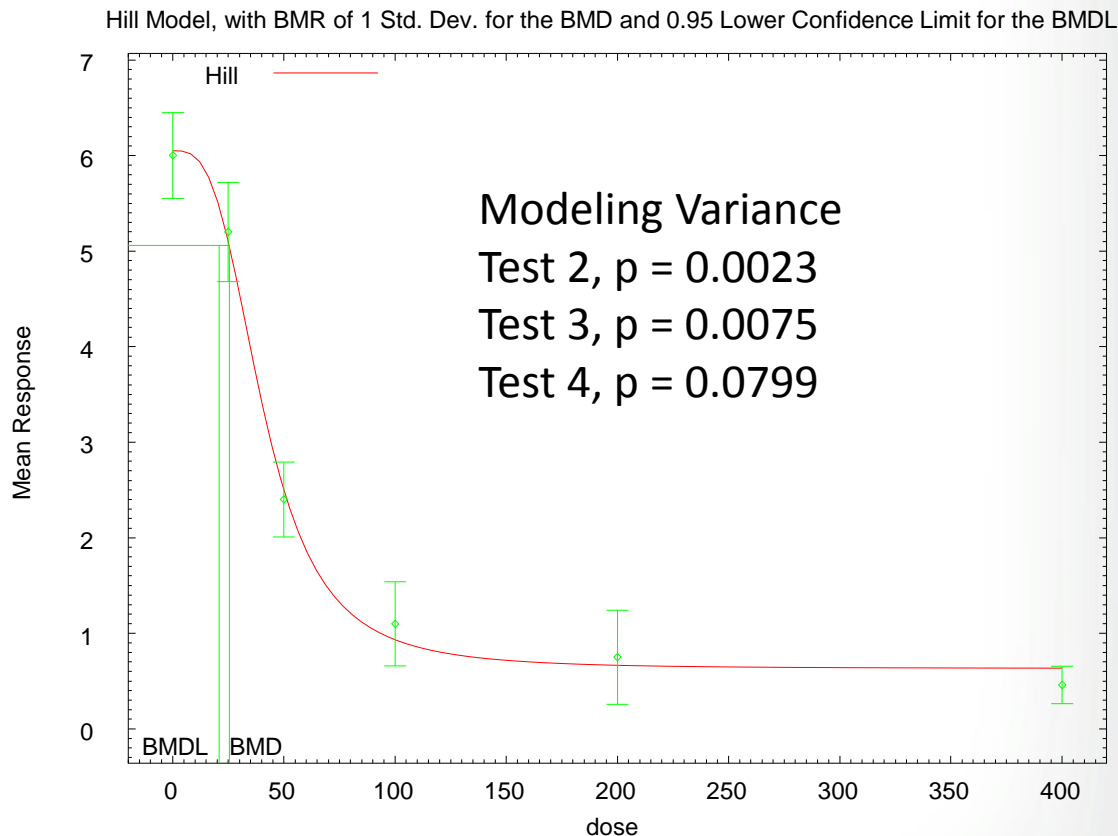


11:35 04/11 2014



Example I: 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

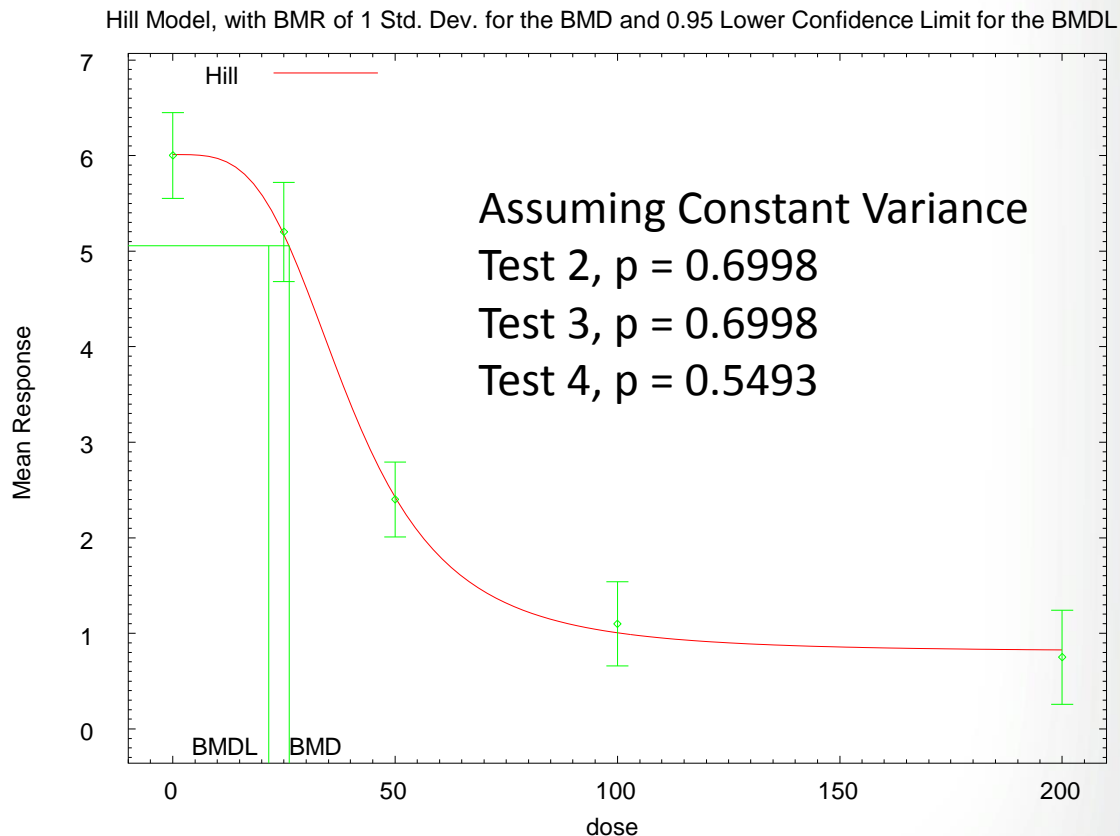


11:46 04/11 2014



Example I: 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



11:27 04/11 2014

- **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**

- **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 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

```

hil_cont_constant_Opt.out - Notepad
File Edit Format View Help
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
35        10       1.66       1.66       0.13         0.123
105       10       1.75       1.73       0.11         0.123
316       10       1.81       1.83       0.15         0.123
625       10       1.89       1.88       0.13         0.123
          -0.0165
          -0.123
          0.389
          -0.505
          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

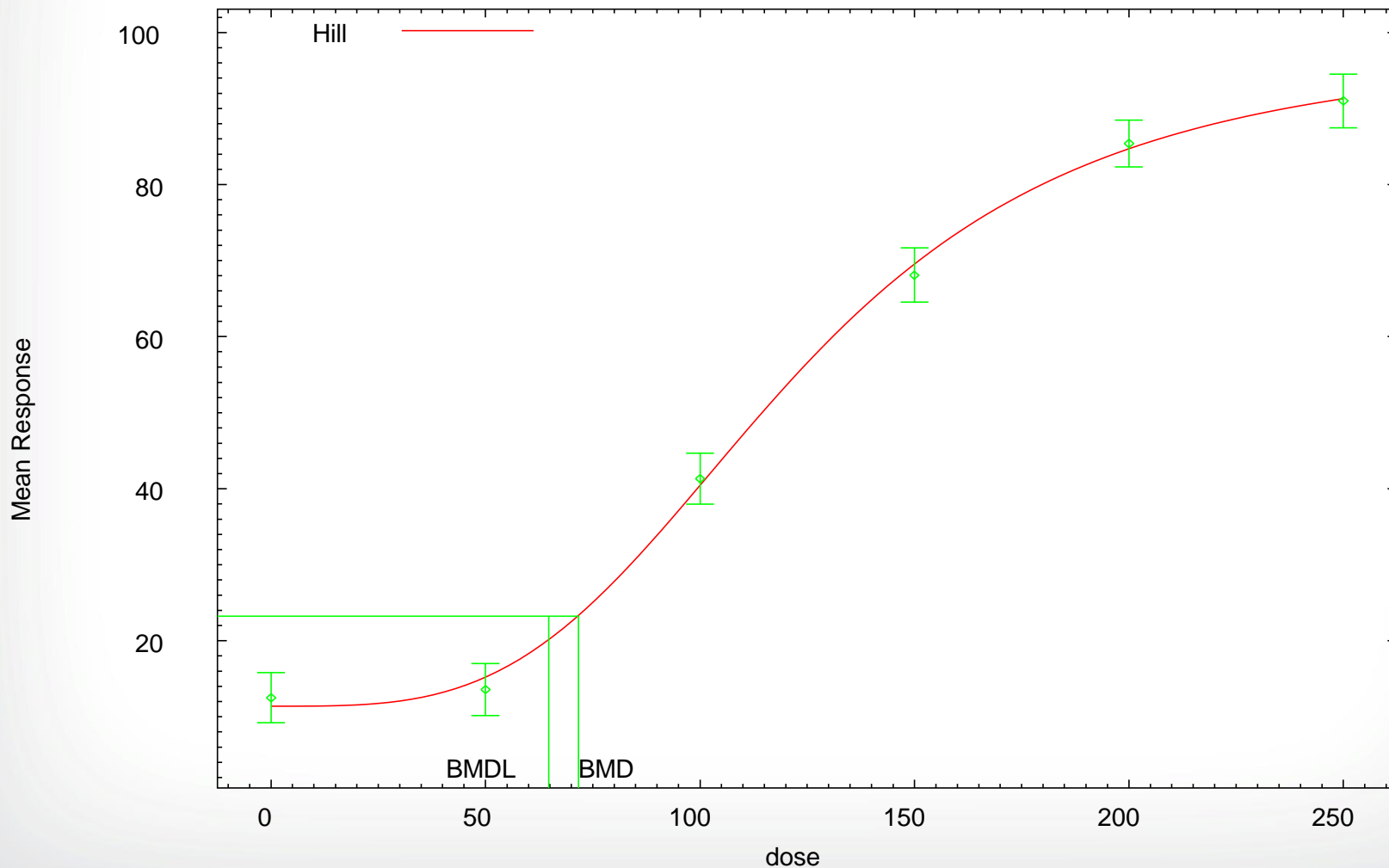
Model A3:      Yij = Mu(i) + e(ij)
               var{e(ij)} = Sigma^2
Model A3 uses any fixed variance parameters that
were specified by the user
  
```

- **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.*



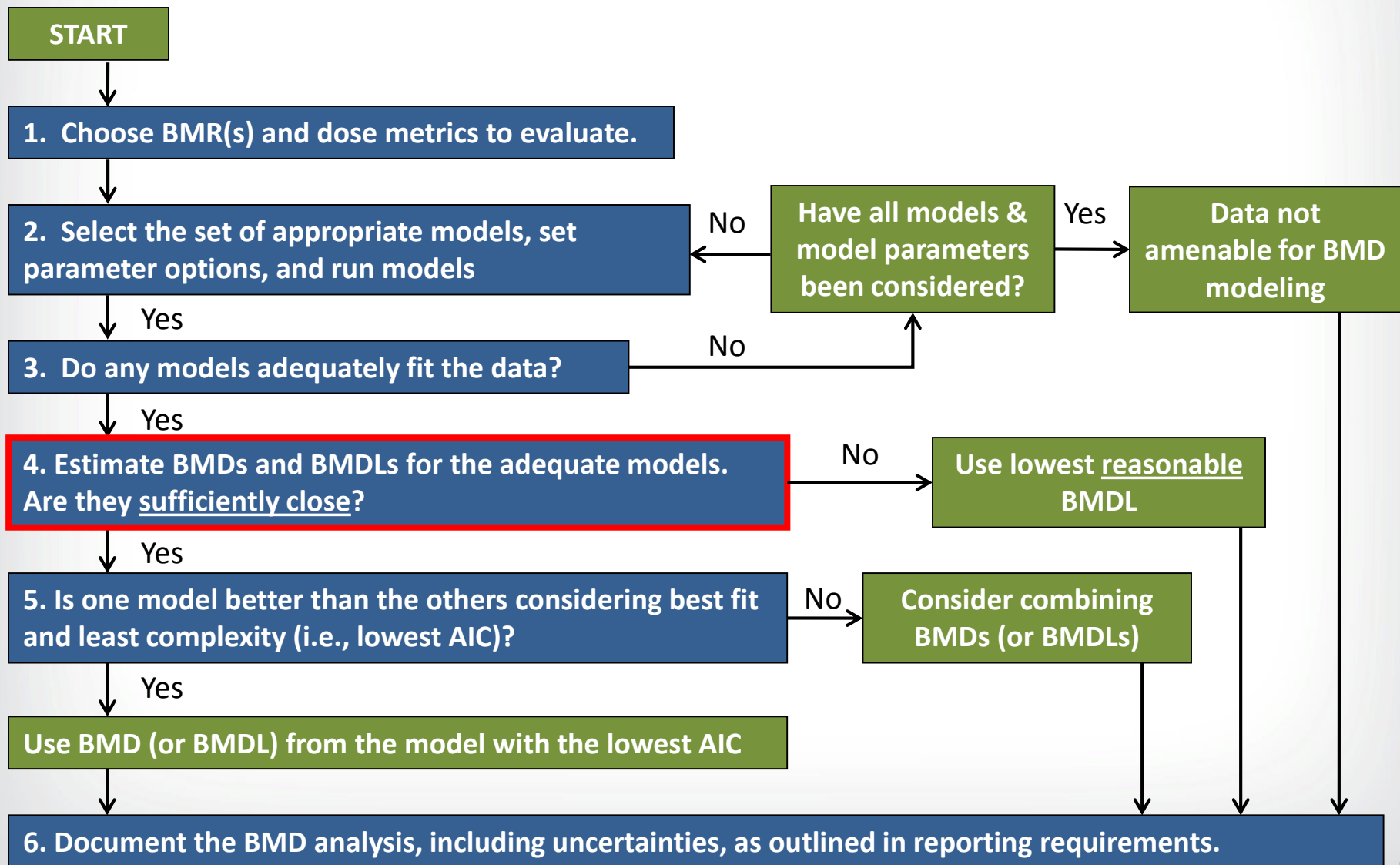
Visual Inspection of Model Fit

Hill Model with 0.95 Confidence Level





BMD Analysis – Six Steps



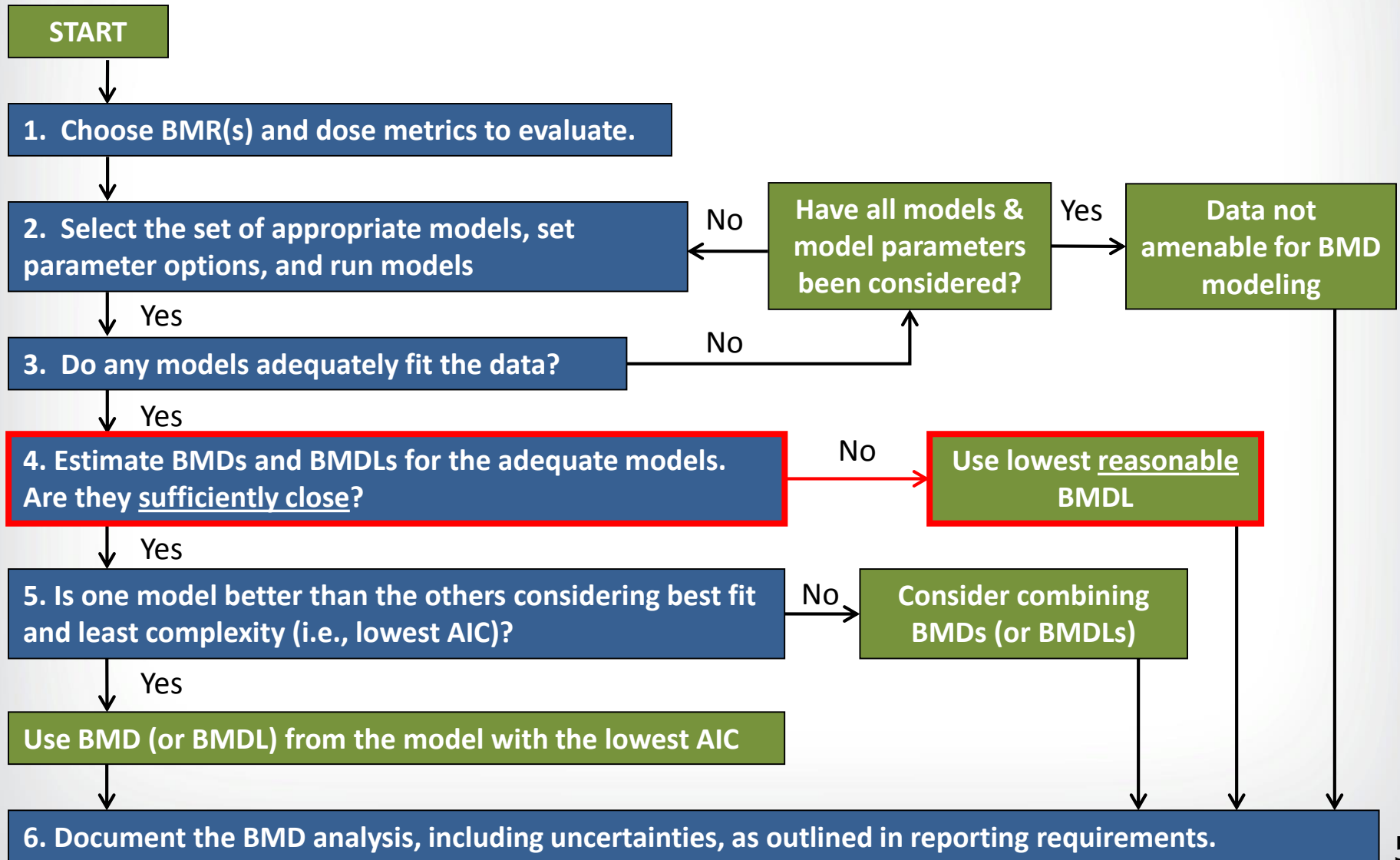


Are BMDL Estimates “Sufficiently Close”?

- **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.**

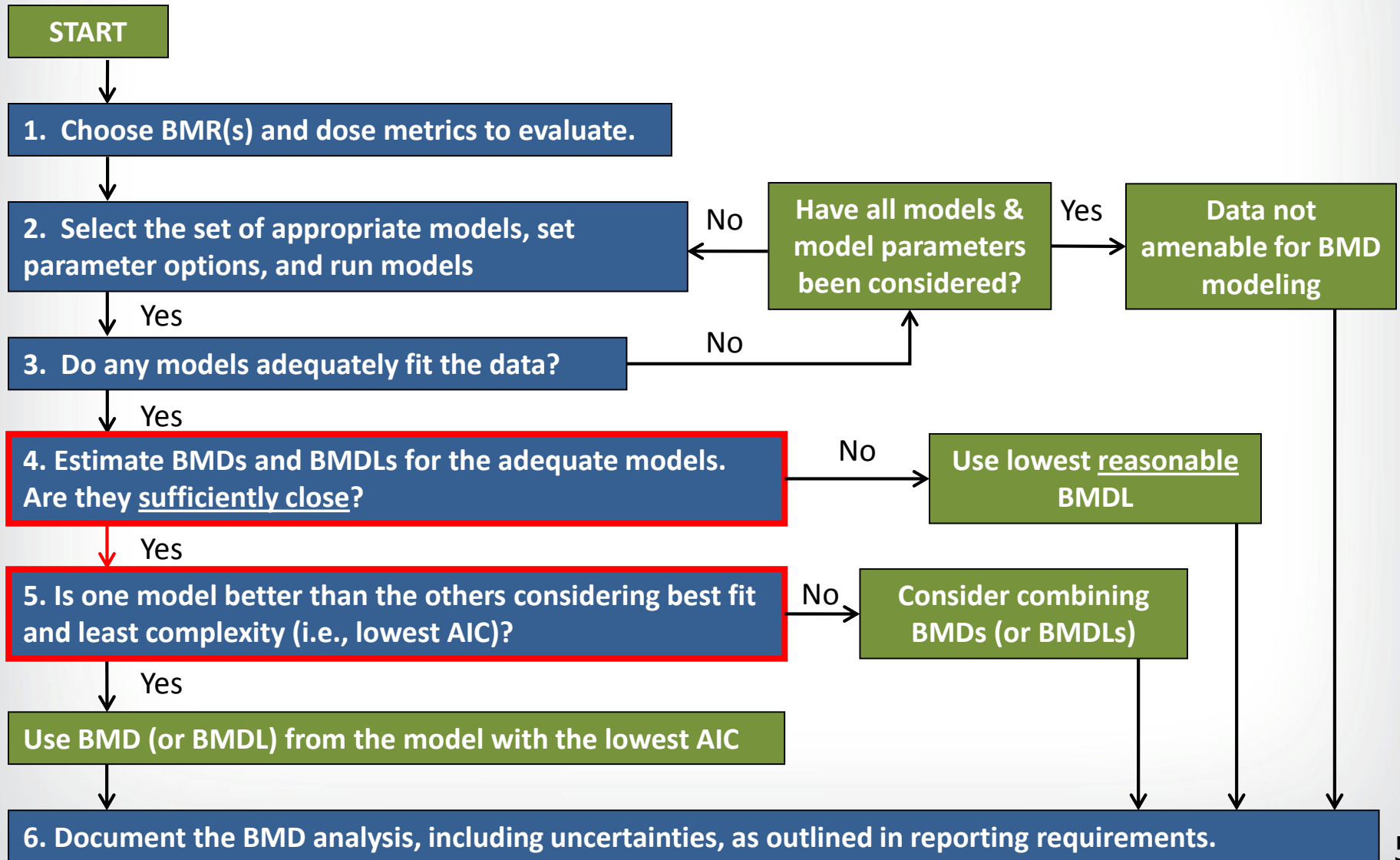


BMD Analysis – Six Steps





BMD Analysis – Six Steps

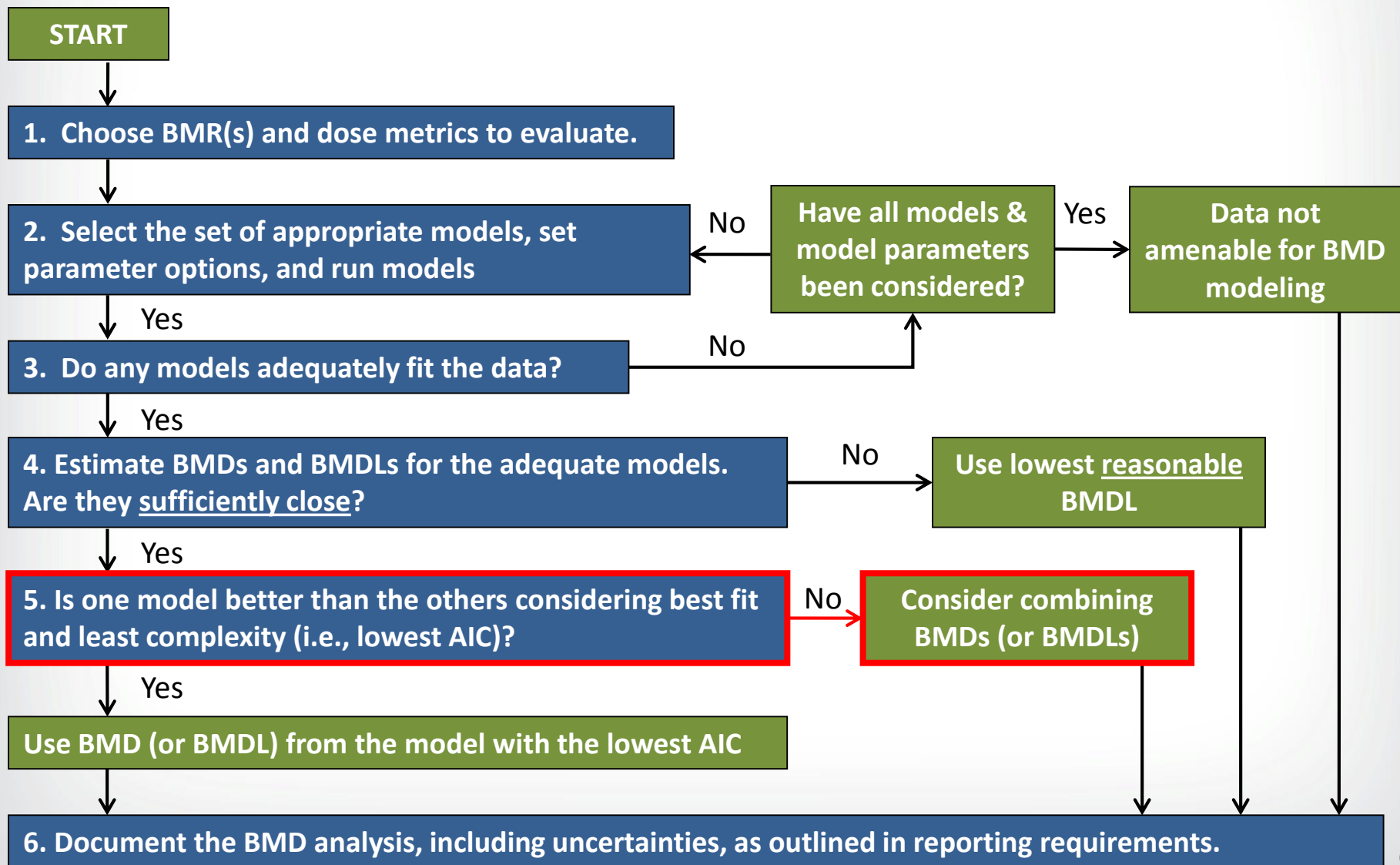


- **Within a family of models (e.g., 2nd degree vs. 1st degree multistage), addition of parameters will generally improve fit**
 - Likelihood ratio tests can determine whether the improvement in fit afforded by extra parameters is justified
 - However, these tests cannot be used to compare models from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

- **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”**

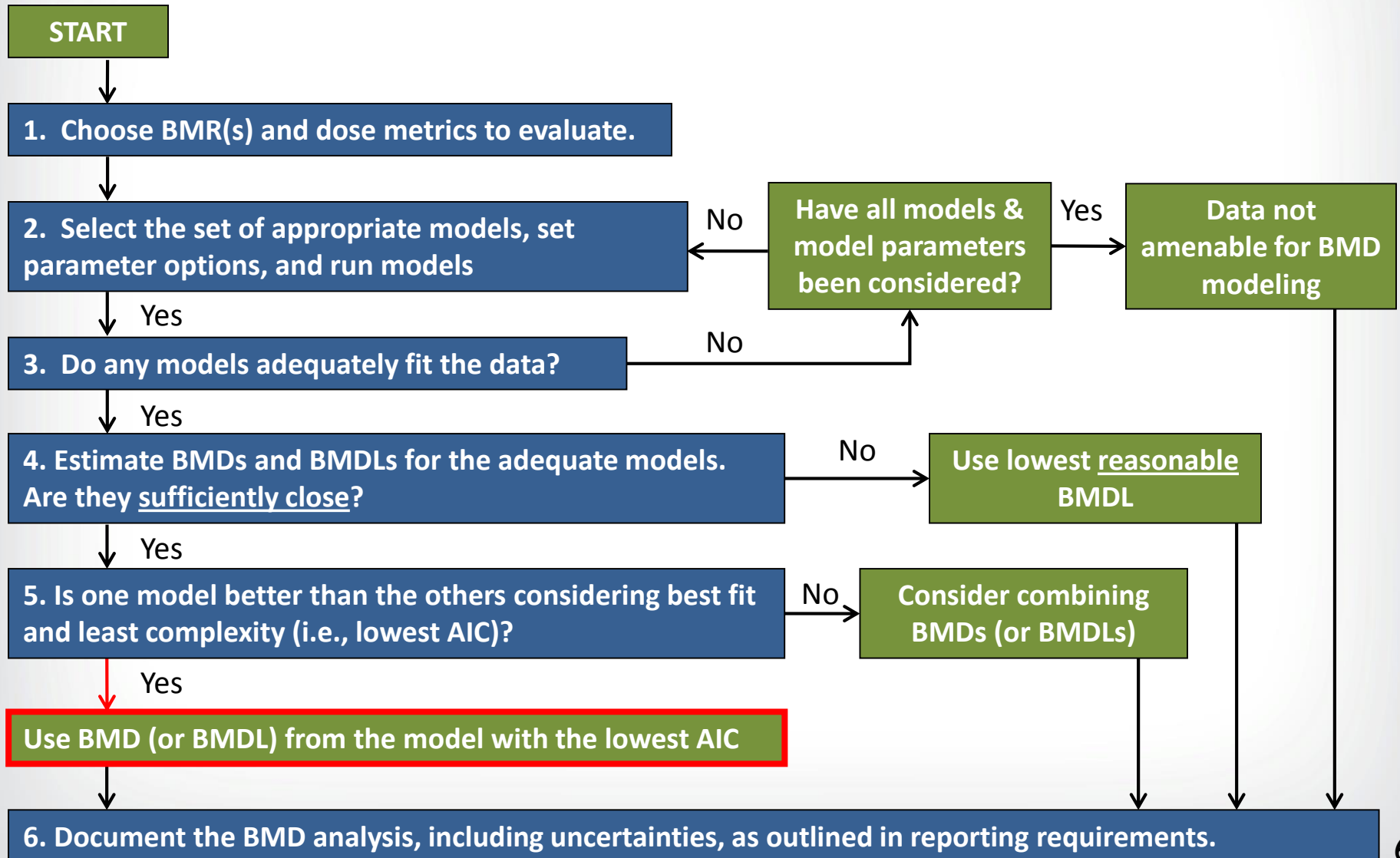


BMD Analysis – Six Steps



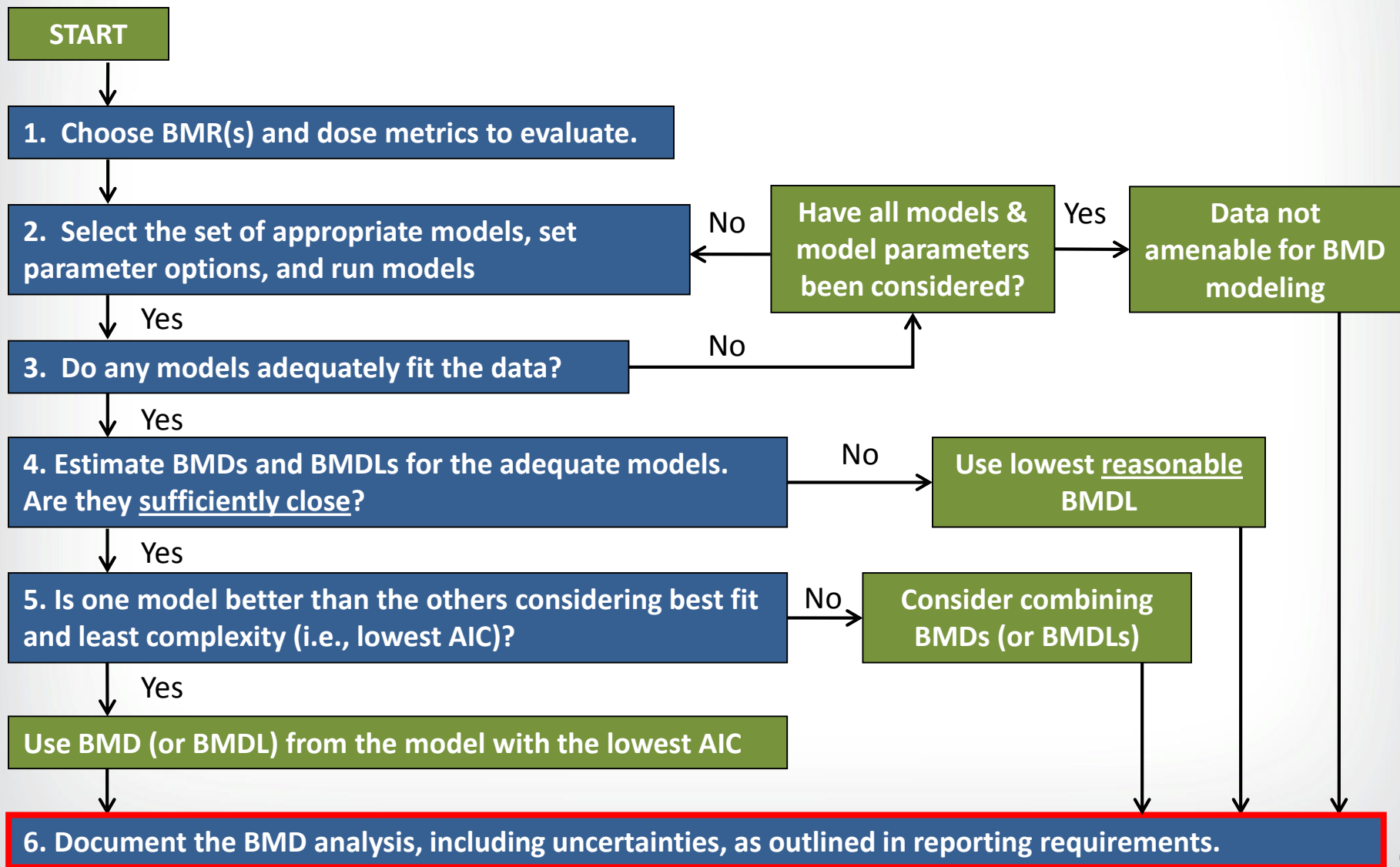


BMD Analysis – Six Steps





BMD Analysis – Six Steps



Continuous Data – Running an Individual Model in BMDS



Running an Individual Model – Select a Model Type

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

File Edit View Tools Windows Help

File Edit Data Grid

Model Type: Model Name: Proceed

			Mean	Std	Col5	Col6
▶ 1			10	1.61	0.12	
2			10	1.66	0.13	
3			10	1.75	0.11	
4		316	10	1.81	0.15	
5		625	10	1.89	0.13	
6						
7						

Ready

95 row(s) added.

Num Lock



Running an Individual Model – Select a Model

The screenshot shows the BMDS 2.4 software interface. The title bar indicates the file path: [C:\Users\adavis10\BMDS240\Data\clu_in\cont_constant.dax]. The menu bar includes File, Edit, View, Tools, Windows, and Help. The toolbar contains icons for file operations and settings. The main window is titled "Data Grid" and shows a table with columns for Dose, N, Mean, Col5, and Col6. A dropdown menu is open over the "Model Name" field, which is currently set to "Hill". The dropdown menu lists the following model types: Exponential, Hill (highlighted), Linear, Polynomial, and Power. A "Proceed" button is visible to the right of the model selection field. The status bar at the bottom shows "Ready" and "95 row(s) added." with a "Num Lock" indicator.

	Dose	N	Mean	Col5	Col6
1	0	10	1.6		
2	35	10	1.6		
3	105	10	1.7		
4	316	10	1.81	0.15	
5	625	10	1.89	0.13	
6					
7					



Running an Individual Model – Proceed to Option Screen

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

File Edit View Tools Windows Help

File Edit Data Grid

Model Type: Continuous | Model Name: Hill | **Proceed**

	Dose	N	Mean	Std	Col5	Col6
▶ 1	0	10	1.61	0.12		
2	35	10	1.66	0.13		
3	105	10	1.75	0.11		
4	316	10	1.81	0.15		
5	625	10	1.89	0.13		
6						
7						

Ready

95 row(s) added. Num Lock



Model Option Screen

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

File Edit View Tools Windows Help

File Edit View Tools Windows Help

<<Column Assignments>>

Dose	▼
# Subjects in Dose Group	▼
Mean	▼
Std. Deviation	▼
Response	▼

<<Optimizer Assignments>>

<<Parameter Assignments>>

Parameters	Options	Values
Alpha	Default ▼	
Rho	Default ▼	
Intercept	Default ▼	

<<Other Assignments>>

Adverse Direction	Automatic ▼
BMR Type	Std. Dev. ▼
BMRF	1
Confidence Level	0.95
Constant Variance(Rho=0)	<input checked="" type="checkbox"/>
BMD Calculation	<input checked="" type="checkbox"/>
Restrict n > 1	<input checked="" type="checkbox"/>

User Notes: BMDS Model Run

Data File: C:\Users\ladavis10\BMDS240\Data\clu_in\cont_constant.dax Show

Out File Name: C:\Users\ladavis10\BMDS240\Data\clu_in\hil_cont_constant_Or Set To...

Run

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

Hill-> Continuous

95 row(s) added.

Num Lock



Selecting Column Assignments



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

File Edit View Tools Windows Help

<<Column Assignments>>

<i>Dose</i>	Dose
<i># Subjects in Dose Group</i>	N
<i>Mean</i>	Mean
<i>Std. Deviation</i>	Std
<i>Response</i>	

<<Optimizer Assignments>>

<<Parameter Assignments>>

Parameters	Options	Values
<i>Alpha</i>	Default	
<i>Rho</i>	Default	
<i>Intercept</i>	Default	

<<Other Assignments>>

<i>Adverse Direction</i>	Automatic
<i>BMR Type</i>	Std. Dev.
<i>BMRF</i>	1
<i>Confidence Level</i>	0.95
<i>Constant Variance(Rho=0)</i>	<input checked="" type="checkbox"/>
<i>BMD Calculation</i>	<input checked="" type="checkbox"/>
<i>Restrict n > 1</i>	<input checked="" type="checkbox"/>

User Notes: BMDS Model Run

Data File: C:\Users\adavis10\BMDS240\Data\clu_in\cont_constant.dax Show

Out File Name: C:\Users\adavis10\BMDS240\Data\clu_in\hil_cont_constant_Or Set To...

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

Hill-> Continuous

95 row(s) added.

Num Lock

Selecting Model Options

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

File Edit View Tools Windows Help

<<Column Assignments>>
 <<Other Assignments>>

Column Assignments	Other Assignments
<i>Dose</i> Dose	<i>Adverse Direction</i> Automatic
<i># Subjects in Dose Group</i> N	<i>BMR Type</i> Std. Dev.
<i>Mean</i> Mean	<i>BMRF</i> 1
<i>Std. Deviation</i> Std	<i>Confidence Level</i> 0.95
<i>Response</i>	<i>Constant Variance(Rho=0)</i> <input checked="" type="checkbox"/>
	<i>BMD Calculation</i> <input checked="" type="checkbox"/>
	<i>Restrict n > 1</i> <input checked="" type="checkbox"/>

<<Optimizer Assignments>>

<<Parameter Assignments>>

Parameters	Options	Values
<i>Alpha</i>	Default	
<i>Rho</i>	Default	
<i>Intercept</i>	Default	

User Notes: BMDS Model Run

Data File: C:\Users\ladavis10\BMDS240\Data\clu_in\cont_constant.dax Show

Out File Name: C:\Users\ladavis10\BMDS240\Data\clu_in\hil_cont_constant_Or Set To...

Run

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

Hill-> Continuous

95 row(s) added. Num Lock

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

File Edit View Tools Windows Help

<<Column Assignments>>

<i>Dose</i>	Dose
<i># Subjects in Dose Group</i>	N
<i>Mean</i>	Mean
<i>Std. Deviation</i>	Std
<i>Response</i>	

<<Optimizer Assignments>>

<i>Adverse Direction</i>	Automatic
<i>BMR Type</i>	Std. Dev.
<i>BMRF</i>	1
<i>Confidence Level</i>	0.95
<i>Constant Variance(Rho=0)</i>	<input checked="" type="checkbox"/>
<i>BMD Calculation</i>	<input checked="" type="checkbox"/>
<i>Restrict n > 1</i>	<input checked="" type="checkbox"/>

<<Parameter Assignments>>

Parameters	Options	Values
<i>Alpha</i>	Default	
<i>Rho</i>	Default	
<i>Intercept</i>	Default	

User Notes: BMDS Model Run
 Data File: C:\Users\ladavis10\BMDS240\Data\clu_in\cont_constant.dax Show
 Out File Name: C:\Users\ladavis10\BMDS240\Data\clu_in\hil_cont_constant_Or Set To... Run

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

Hill-> Continuous

95 row(s) added. Num Lock



Dichotomous Model Plot and Output Files

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

File Edit View Tools Windows Help

Hill Model with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

dose	Mean Response	Lower Bound	Upper Bound
0	1.65	1.55	1.75
100	1.75	1.65	1.85
300	1.85	1.75	1.95
600	1.90	1.80	2.00

13:17 04/14 2014

C:\Users\adavis10\BMDS240\Data\clu_in\hil_cont_constant_Opt.out

```
=====
Hill Model. (Version: 2.17; Date: 01/28/2013)
Input Data File: C:/Users/adavis10/BMDS240/Data/clu_in/hil_cont_constant_Opt.(d)
Gnuplot Plotting File: C:/Users/adavis10/BMDS240/Data/clu_in/hil_cont_constant_Opt
                               Mon Apr 14 13:17:41 2014
=====

BMDS Model Run
=====

The form of the response function is:

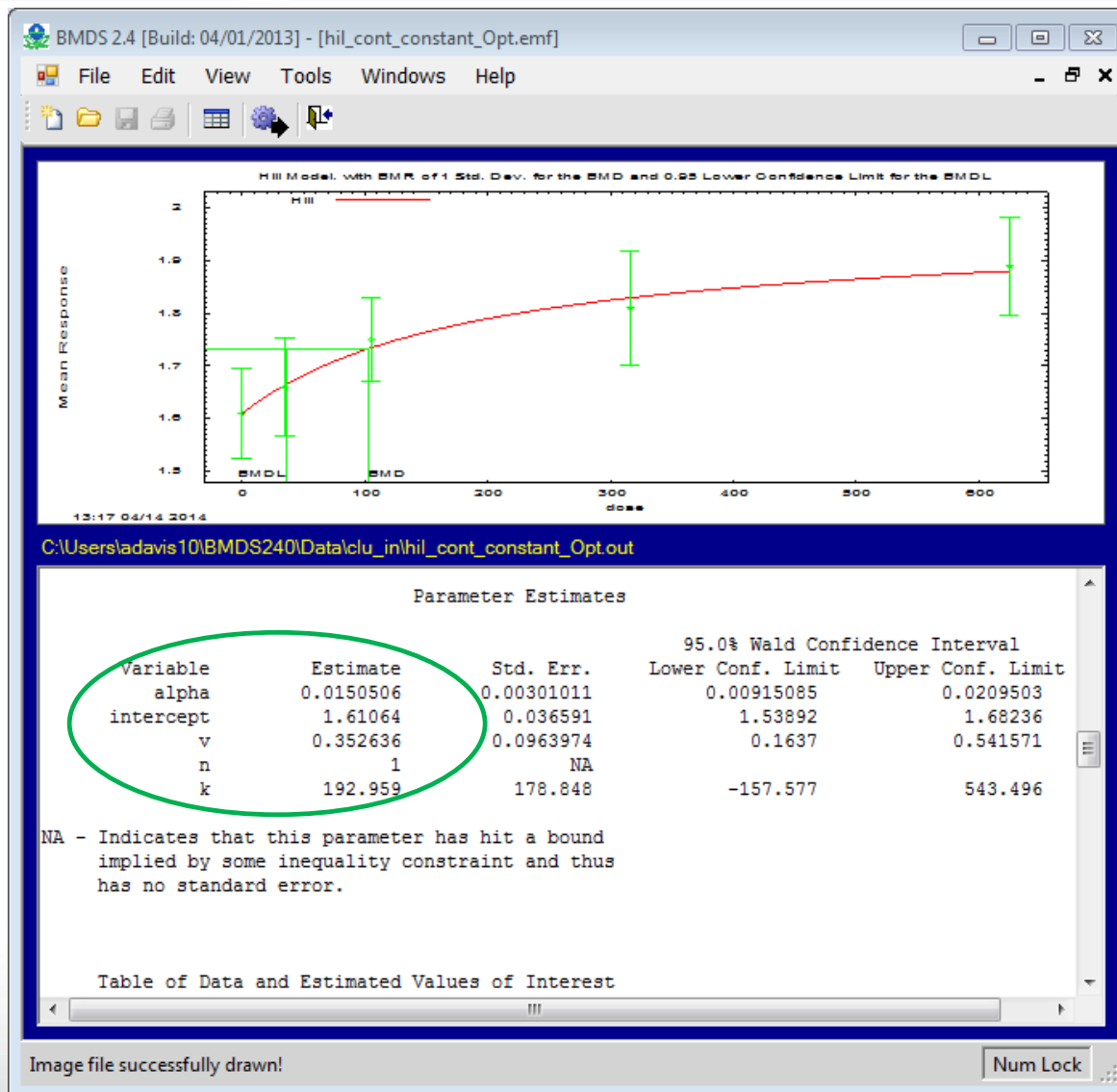
Y[dose] = intercept + v*dose^n/(k^n + dose^n)

Dependent variable = Mean
```

Image file successfully drawn! Num Lock

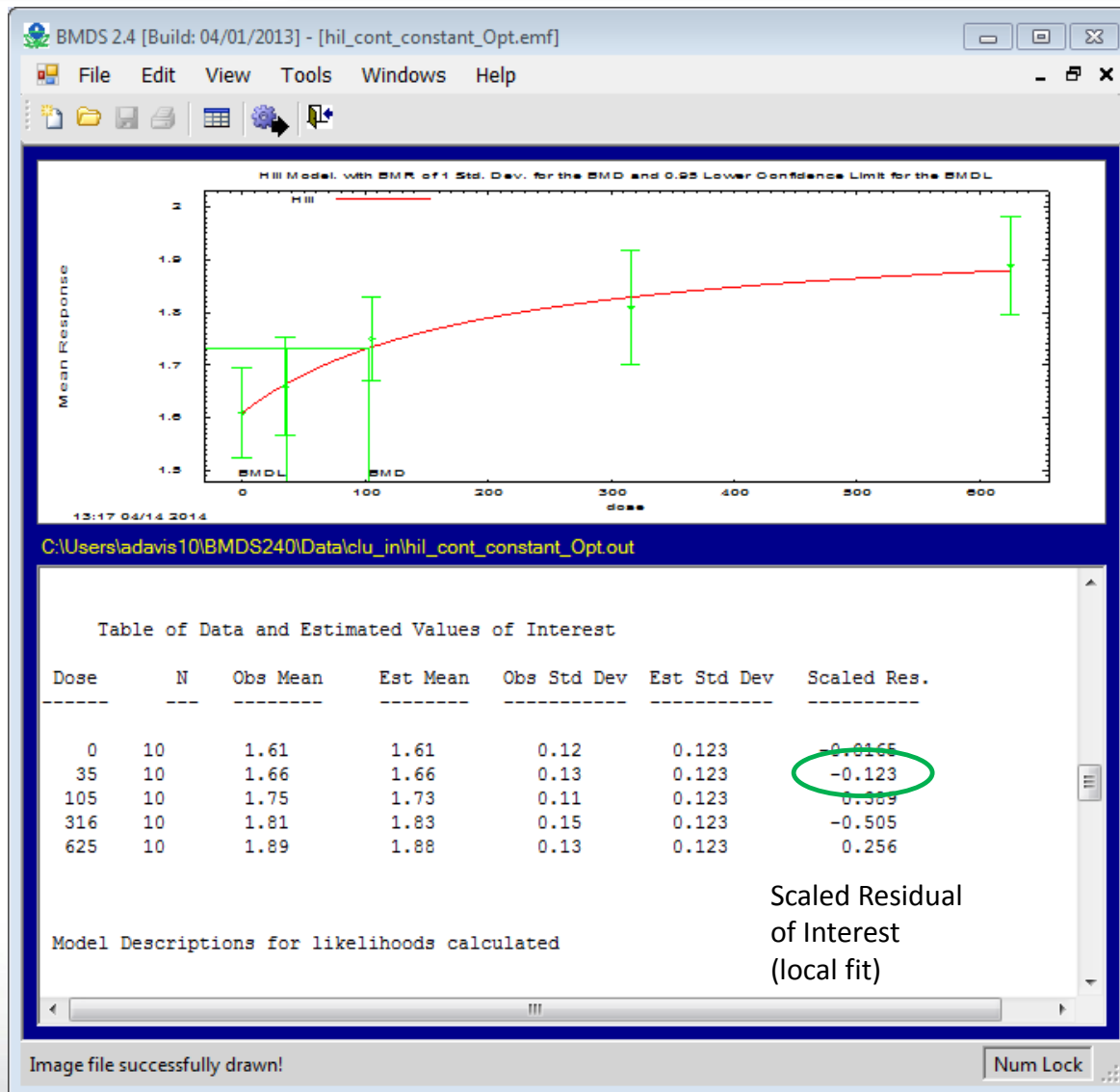


Dichotomous Model Parameter Estimates



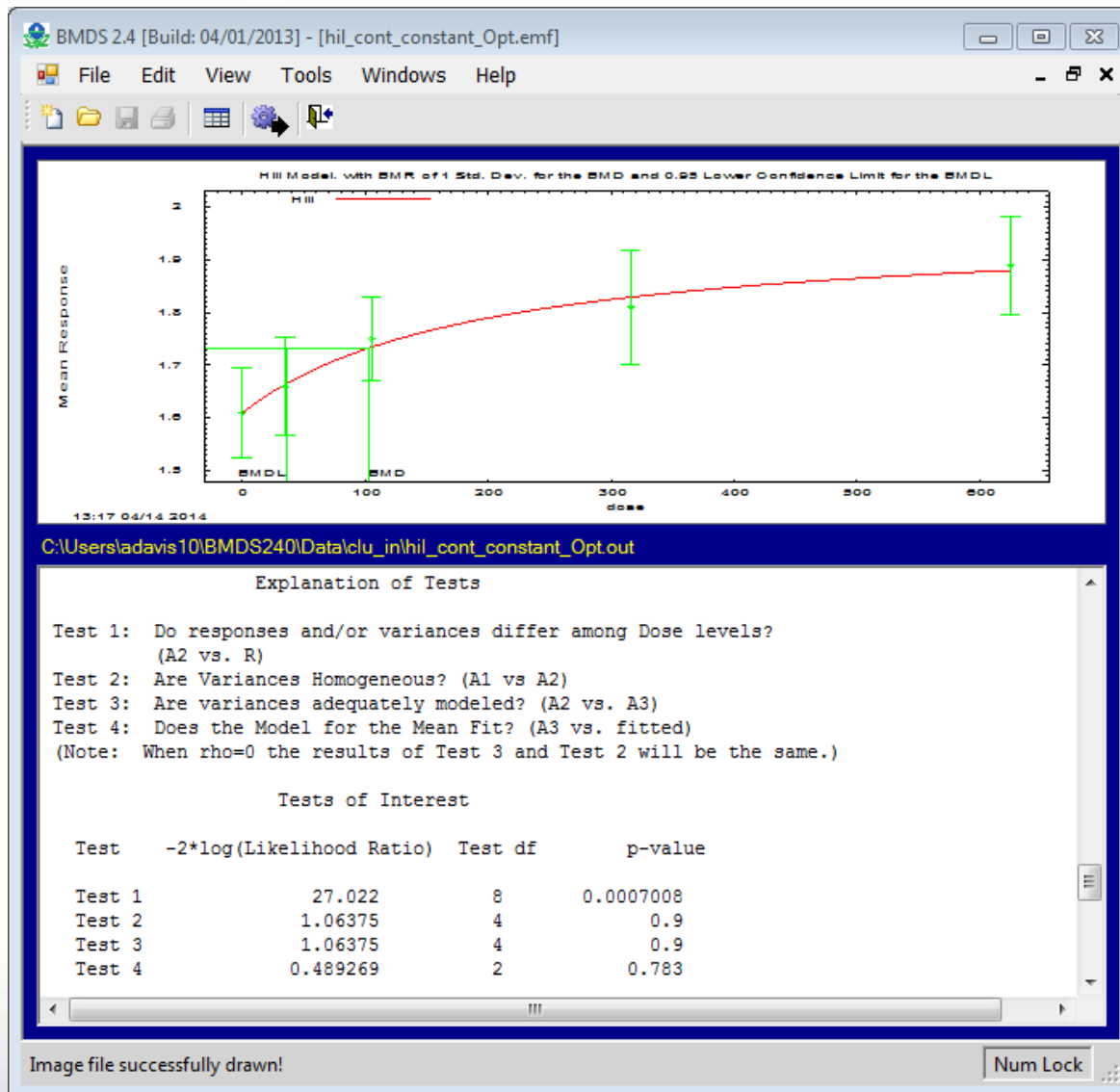


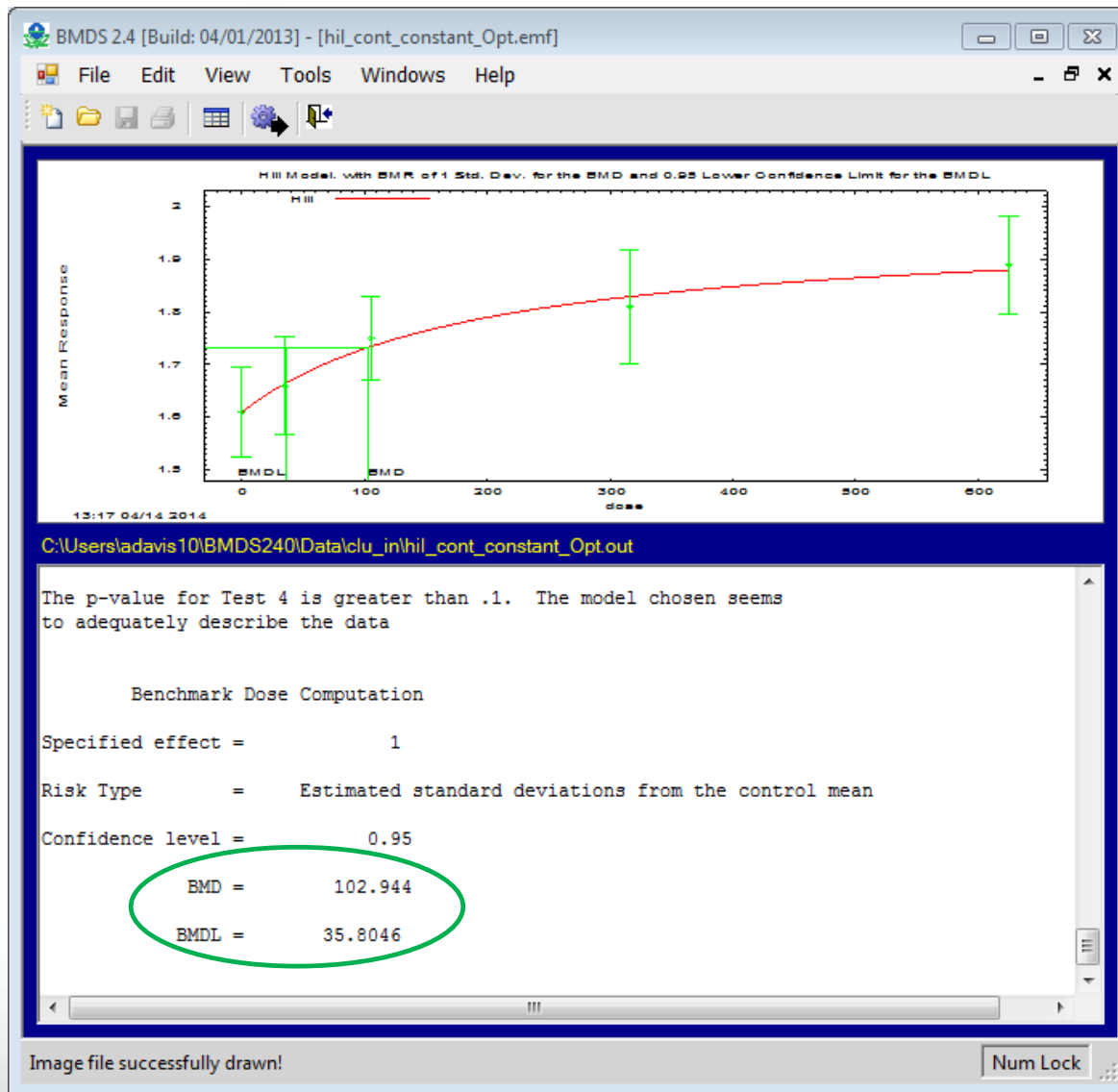
Dichotomous Model Fit Statistics





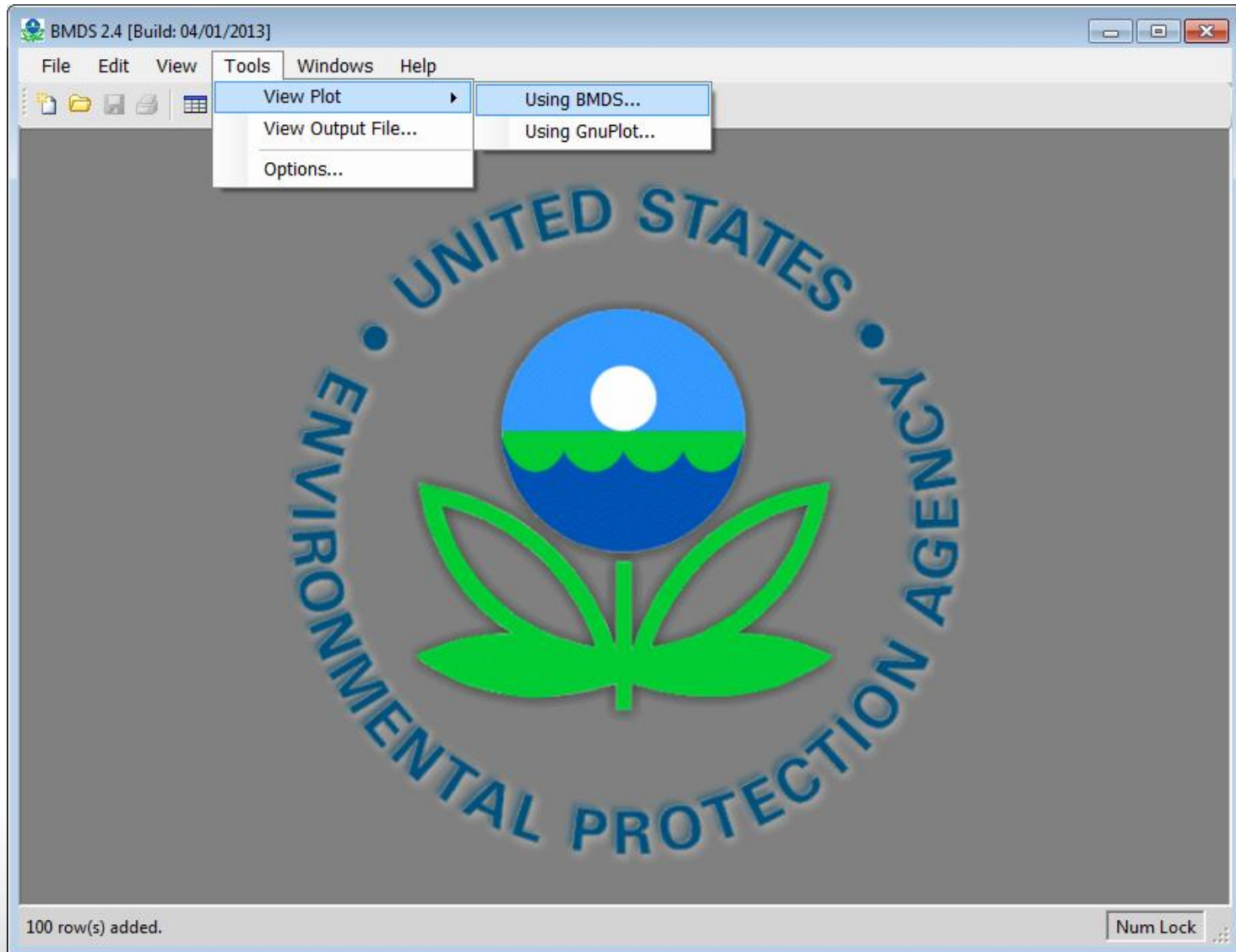
Dichotomous Model Fit Statistics





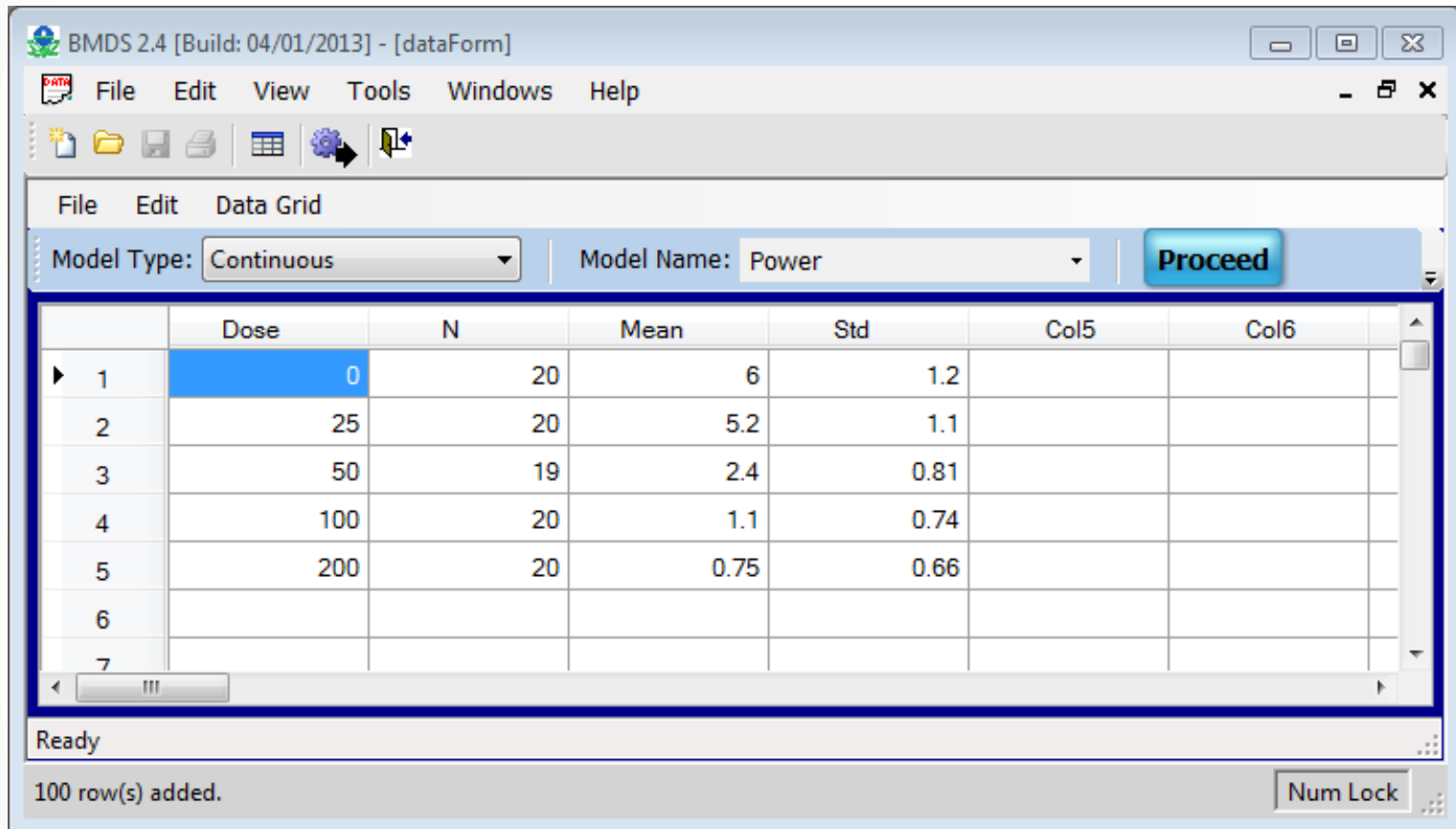


Opening Output and Plot Files after Analysis





Continuous Data – Exercise #1



The screenshot shows the BMDS 2.4 software interface. The window title is "BMDS 2.4 [Build: 04/01/2013] - [dataForm]". The menu bar includes File, Edit, View, Tools, Windows, and Help. The toolbar contains icons for file operations and settings. The "Data Grid" tab is active, showing a table with the following data:

	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						

The status bar at the bottom indicates "Ready" and "100 row(s) added." A "Num Lock" button is visible in the bottom right corner.

Manually enter these data and save as
Exercise_1.dax

- **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

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

File Edit View Tools Windows Help

<<Column Assignments>>

Dose	Dose
# Subjects in Dose Group	N
Mean	Mean
Std. Deviation	Std
Response	

<<Other Assignments>>

Adverse Direction	Automatic
BMR Type	Std. Dev.
BMRF	1
Confidence Level	0.95
Constant Variance($Rho=0$)	<input checked="" type="checkbox"/>
BMD Calculation	<input checked="" type="checkbox"/>
BMDL Curve. Calc.	<input type="checkbox"/>
Restrict Power ≥ 1	<input checked="" type="checkbox"/>

<<Optimizer Assignments>>

<<Parameter Assignments>>

Parameters	Options	Values
Alpha	Default	
Rho	Default	
Control	Default	

User Notes: BMDS Model Run

Data File: C:\Users\ladavis10\BMDS240\Data\clu_in\cont_exercise1.dax Show

Out File Name: C:\Users\ladavis10\BMDS240\Data\clu_in\pow_cont_exercise1 Set To...

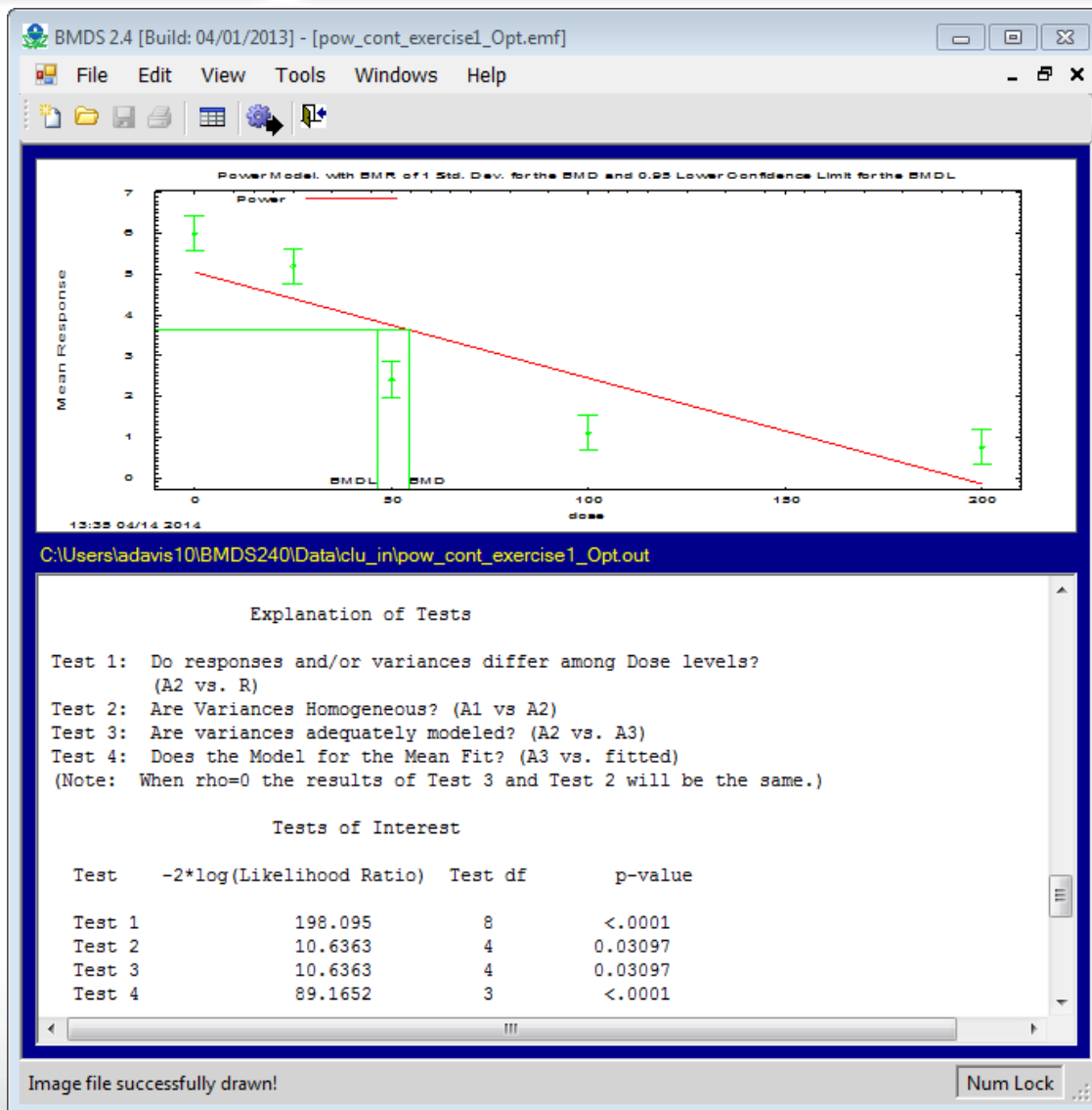
Run

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

Power-> Continuous

95 row(s) added.

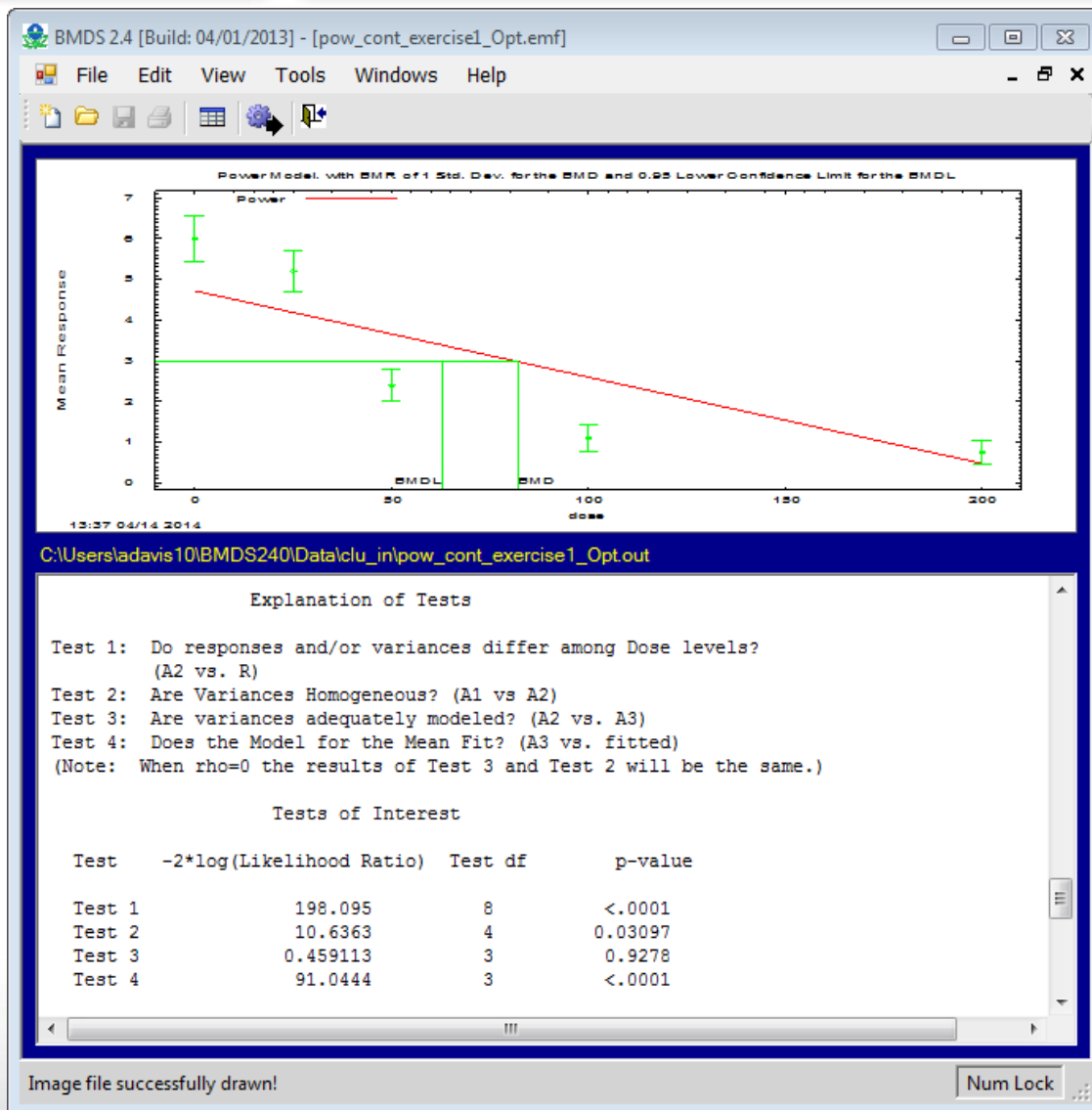
Num Lock



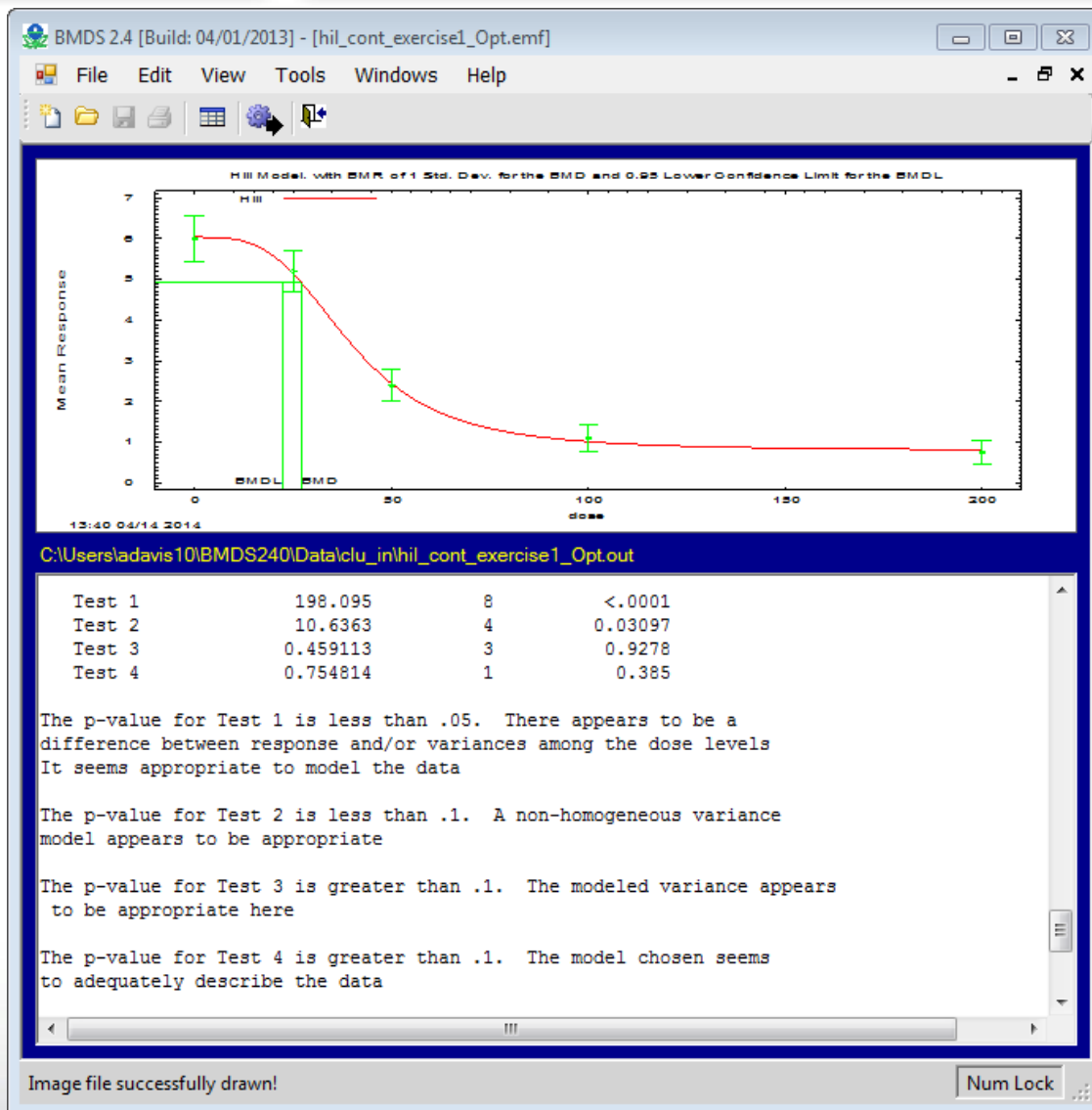
- **Re-run the Power model against the Exercise #1 data using the Individual Model Run option**
 - Deselect the option to run with constant variance



Continuous Exercise #1



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





Continuous Exercise #1

BMDS 2.4 [Build: 04/01/2013] - [hil_cont_exercise1_Opt.emf]

File Edit View Tools Windows Help

Hill Model, with BMD of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

13:40 04/14 2014

C:\Users\ladavis10\BMDS240\Data\clu_in\hil_cont_exercise1_Opt.out

to be appropriate here

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

Benchmark Dose Computation

Specified effect = 1

Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 27.116

BMDL = 22.2687

Image file successfully drawn! Num Lock



Continuous Data – Batch Processing using 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

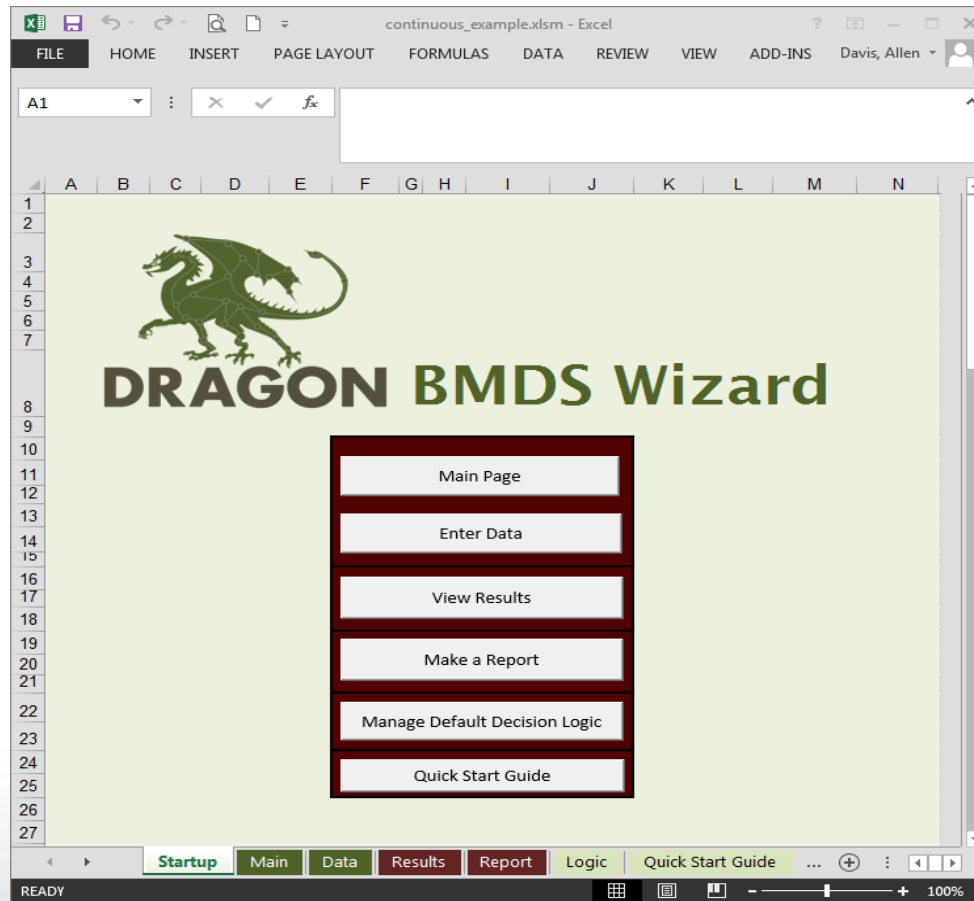
- Open Excel
- Press the “Office” button and select “Excel Options”
- Go to the “Trust Center” tab and click “Trust Center Settings”
- Change “Macro Settings” to “Disable all macros with notification” or “Enable all macros”

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

continuous_example.xlsm - Excel

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

G18

A	B	C	D	E	F	G	H	I
1	BMDS Wizard							
2								
3								
4	<i>Main</i>		<i>Last modified:</i>		<i>4/4/2014</i>			
5								
6								
7	Control Panel:							
8	1) Setup Instructions		2) Build Session		3) Run Session in BMDS		4) Import Results	AUTORUN
9								
10	Study and Modeling Inputs:							
11	BMDS Model Version:		BMDS 2.4					
12	BMDS Installation Directory		C:\Users\adavis10\BMDS240\				Select Folder	
13	Output File Directory:		C:\Users\adavis10\BMDS240\Data\clu_in\				Select Folder	
14	BMD ID Number:		2					
15	Study & Year:		Bob_2010					
16	Endpoint Description:							
17	Dose Units:							
18	BMD or BMC Calculated?							
19	Select Dataset Type:		Continuous					
20	Enter Study Data:		<i>Click here to enter data</i>					

Startup Main Data Results Report Logic Quick Start Guide

READY

100%



BMDS Wizard – Entering Data

continuous_example.xlsxm - Excel

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

F17 : X ✓ fx 0.12

BMDS Wizard

BMDS Input Data Return to Main

Cell Color Coding

Input Cells Calculated Cells

Clear Data

Notes and Calculations from Dose-Response Data

Number of Dose Groups	5
Data Trend (continuous only)	increasing
Notes (included in BMDS output)	[study notes]

Convert SE to Stdev

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	0.12	
Dose Group 2	35	10	1.66	0.13	
Dose Group 3	105	10	1.75	0.11	
Dose Group 4	316	10	1.81	0.15	
Dose Group 5	625	10	1.89	0.13	
Dose Group 6					
Dose Group 7					
Dose Group 8					
Dose Group 9					
Dose Group 10					
Dose Group 11					
Dose Group 12					
Dose Group 13					
Dose Group 14					

Startup Main Data Results Report Logic Quick Start Guide

ENTER

100%



BMDS Wizard – Model Parameters

continuous_example.xlsm - Excel

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

C20 : Click here to enter data

BMDS Wizard

Main Last modified: 4/4/2014

Add new models to BMDS Session:

- Exponential CV
- Hill CV
- Power CV
- Polynomial 4 CV
- Polynomial 3 CV
- Polynomial 2 CV
- Linear CV
- Exponential NCV
- Hill NCV
- Power NCV
- Polynomial 4 NCV
- Polynomial 3 NCV
- Polynomial 2 NCV
- Linear NCV

Add Model & Load Model Defaults

Clear All Models

Color Coding for Model Option File Setup

Used for naming BMDS inputs and outputs (not a BMDS input)

Input cell for selected model

Don't edit this value for the selected model; required to be empty or with fixed value.

In the default case ("Default,") values are auto-assigned. If you want to manually assign, type "Specified" or "Initialized", comma, then the value (ex. "Specified,1")

BMDS Model Option Setups:

Parameter	Type and/or Format	Exponential CV	Power CV	Polynomial 2 CV	Linear CV	Exponential NCV	Power NCV
BMDS Option Filename	String	2-Bob_2010-ExpCV-1	2-Bob_2010-PowerCV	2-Bob_2010-Poly2CV	2-Bob_2010-LinearCV	2-Bob_2010-ExpNCV	2-Bob_2010-PowerNCV
Model Type [for filename]	String	ExpCV	PowerCV	Poly2CV	LinearCV	ExpNCV	PowerNCV
BMR Info [for filename]	String	1SD	1SD	1SD	1SD	1SD	1SD
Animal ID							
Dose	String	Dose	Dose	Dose	Dose	Dose	Dose
# Subjects in Dose Group	String	NumAnimals	NumAnimals	NumAnimals	NumAnimals	NumAnimals	NumAnimals
Mean	String	MeanResponse	MeanResponse	MeanResponse	MeanResponse	MeanResponse	MeanResponse
Std. Deviation	String	Stdev	Stdev	Stdev	Stdev	Stdev	Stdev
Response	String						
Incidence	String						
% Positive	String						

Startup Main Data Results Report Logic Quick Start Guide

READY 100%



BMDS Wizard – Model Parameters

continuous_example.xlsm - Excel

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

O38 : Linear NCV

BMDS Wizard								
Main			Last modified:			4/4/2014		
48	Incidence	String						
49	% Positive	String						
54	Distribution	Dropdown	Normal					
55	Solution	String	Exact					
58	Risk Type	Dropdown						
59	BMR	Real	1		1	1	1	1
60	Confidence Level	Real	0.95	0.95	0.95	0.95	0.95	0.95
61	BMD Calculation	Boolean	TRUE	TRUE	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	Dropdown				Non-negative	Non-negative	None
74	Adverse Direction	Dropdown	Up	Automatic	Automatic	Automatic	Automatic	Automatic
75	BMR Type	Dropdown	Std. Dev.	Std. Dev.	Std. Dev.	Std. Dev.	Std. Dev.	Std. Dev.
76	Constant Variance?	Boolean	TRUE	TRUE	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

continuous_example.xlsxm - Excel

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

E76 : TRUE

BMDS Wizard								
Main			Last modified:			4/4/2014		
54	Distribution	Dropdown	Normal					
55	Solution	String	Exact					
58	Risk Type	Dropdown						
59	BMRf	Real	1	1	1	1	1	1
60	Confidence Level	Real	0.95	0.95	0.95	0.95	0.95	0.95
61	BMD Calculation	Boolean	TRUE	TRUE	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	Dropdown				Non-negative	Non-negative	None
74	Adverse Direction	Dropdown	Up	Automatic	Automatic	Automatic	Automatic	Automatic
75	BMR Type	Dropdown	Std. Dev.	Std. Dev.	Std. Dev.	Std. Dev.	Std. Dev.	Std. Dev.
76	Constant Variance?	Boolean	TRUE	TRUE	TRUE	TRUE	TRUE	TRUE
82	Adverse Direction			TRUE				
88	Confidence Level			FALSE				
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,			
105	Power	Light Gray			Default,			
106	Alpha	Light Gray		Default,	Default,	Default,	Default,	Default,

Startup Main Data Results Report Logic Quick Start Guide

READY



BMDS Wizard – AutoRunning BMDS

continuous_example.xlsm - Excel
Davis, Allen

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

G8

A	B	C	D	E	F	G	H	I	
1	BMDS Wizard								
2	<i>Main</i> Last modified: 4/4/2014								
6	Control Panel:								
7	<div style="display: flex; justify-content: space-around;"><div style="border: 1px solid black; padding: 5px;">1) Setup Instructions</div><div style="border: 1px solid black; padding: 5px;">2) Build Session</div><div style="border: 1px solid black; padding: 5px;">3) Run Session in BMDS</div><div style="border: 1px solid black; padding: 5px;">4) Import Results</div><div style="border: 1px solid black; padding: 5px;">AUTORUN</div></div>								
10	Study and Modeling Inputs:								
11	BMDS Model Version:	BMDS 2.4							
12	BMDS Installation Directory	C:\Users\adavis10\BMDS240\					Select Folder		
13	Output File Directory:	C:\Users\adavis10\BMDS240\Data\clu_in\					Select Folder		
14	BMD ID Number:	2							
15	Study & Year:	Bob_2010							
16	Endpoint Description:								
17	Dose Units:								
18	BMD or BMC Calculated?								
19	Select Dataset Type:	Continuous							
20	Enter Study Data:	Click here to enter data							

Startup Main Data Results Report Logic Quick Start Guide

READY 100%



BMDS Wizard – Results

continuous_example.xlsm - Excel

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

B9 : 2-Bob_2010--M2ExpCV-1SD-5d.out

BMDS Wizard

BMDS Results *Back to Main* **Import Results** **Clear Results** **View Output Image**

Results Table

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

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

READY 7 OF 18 RECORDS FOUND



BMDS Wizard – Results

continuous_example.xlsm - Excel

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

B9 : 2-Bob_2010--M2ExpCV-1SD-5d.out

BMDS Wizard

BMDS Results Back to Main Import Results Clear Results View Output Image

Results Table

OUT File Name	View Output File	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)	Sort Smallest to Largest				TRUE	326	246	1.33	0.9	0.9	0.250	-150.19
2-Bob_2010--M3ExpCV-1SD-5d.out	View Output	Exponential (M3)	Sort Largest to Smallest				TRUE	326	246	1.33	0.9	0.9	0.250	-150.19
2-Bob_2010--M4ExpCV-1SD-5d.out	View Output	Exponential (M4)	Sort by Color				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)					TRUE	119	44.9	2.65	0.9	0.9	0.666	-151.49
2-Bob_2010--HillCV-1SD-5d.out	View Output	Hill	Clear Filter From "Correct Variance ..."				TRUE	103	35.8	2.88	0.9	0.9	0.783	-151.82
2-Bob_2010--PowerCV-1SD-5d.out	View Output	Power	Filter by Color				TRUE	311	230	1.35	0.9	0.9	0.282	-150.49
2-Bob_2010--Poly3CV-1SD-5d.out	View Output	Polynomial 3°	Number Filters				TRUE	311	230	1.35	0.9	0.9	0.282	-150.49

Startup Main Data **Results** Report Logic

READY 7 OF 18 RECORDS FOUND

OK Cancel



BMDS Wizard – Results

continuous_example.xlsx - Excel

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

B9 : 2-Bob_2010--M2ExpCV-1SD-5d.out

BMDS Wizard

BMDS Results Back to Main Import Results Clear Results View Output Image

Results Table

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	R
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.out	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.out	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.out	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.out	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	

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

READY 100%



BMDS Wizard – Results

continuous_example.xlsxm - Excel

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

AE13 : Include

	P	Q	R	T	U	Y	Z	AA	AB	AC	AD	AE	AF	AG	AH
1	<div style="display: flex; justify-content: space-between; align-items: center;"> <div style="border: 1px solid black; padding: 5px;">View Output Images</div> <div style="border: 1px solid black; padding: 5px;">Recalculate Recommendation</div> <div style="border: 1px solid black; padding: 5px;">Basis for Model Selection</div> <div style="border: 1px solid black; padding: 5px;">Create Report</div> </div>														
2															
3															
4															
5															
6															
7															
8	p-value Test 2	p-value Test 3	p-value Test 4	AIC	Scaled Residual for Dose Group near BMP	Parameter Hit Bound?	Parameter Summary	Model Warnings	BMDS Wizard Bin Placement	BMDS Wizard Recommendation	BMDS Wizard Recommendation Not	Include in Summary Table?	User Notes		
9	0.9	0.9	0.250	-150.19	0.710	FALSE	Y[dose] = a *	None	Viable	Alternate		Include			
10	0.9	0.9	0.250	-150.19	0.710	TRUE	Y[dose] = a *	None	Viable	Alternate		Include			
11	0.9	0.9	0.666	-151.49	0.538	FALSE	Y[dose] = a *	None	Viable	Alternate		Include			
12	0.9	0.9	0.666	-151.49	0.538	TRUE	Y[dose] = a *	None	Viable	Alternate		Include			
13	0.9	0.9	0.783	-151.82	0.389	TRUE	Y[dose] = int	None	Viable	Recommend	Lowest BMDL	Include			
14	0.9	0.9	0.282	-150.49	0.63	TRUE	Y[dose] = co	None	Viable	Alternate		Select			
15	0.9	0.9	0.282	-150.49	0.63	TRUE	Y[dose] = be	None	Viable	Alternate		Include			
16	<div style="border: 1px solid black; padding: 5px;"> Don't Include "Include": print in summary table "Don't Include": don't print in summary table </div>														
17															
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Startup Main Data Results Report Logic Quick Start Guide

READY 7 OF 18 RECORDS FOUND



BMDS Wizard – Automatic Report Generation

The screenshot shows the 'Report' tab of the BMDS Wizard in Excel. The interface is organized into several sections for configuring report output:

- Summary Report:** A green header bar containing the text 'BMDS Wizard', 'Print Word Report' (highlighted with a red box), 'Summary Report', and 'Back to Results'.
- Output Options:** A table with two rows:

Print BMDS Summary Table	TRUE
Show Report Being Created	FALSE
- BMDS Reporting:** A table with two rows:

BMDS Reporting	Print BMDS Figure	Print BMDS Output File
Print Selected Model	TRUE	TRUE
Print Included Model	FALSE	FALSE
- Template Location:** A table with two rows:

Template Directory	C:\Users\adavis10\BMDS240\BMDS Wizard\
Template Filename	BMDS Wizard Report Template.dotx

 A 'Select MS Word Template' button is located to the right.
- Output Word Report Location:** A table with three rows:

Report Output Directory	C:\Users\adavis10\BMDS240\Data\clu_in
Report Filename (no extension)	2-Bob_2010-
Report Extension	docx

 A 'Select/Create MS Word Output File' button is located to the right.
- BMDS Figure Settings:** A section header at the bottom of the visible area.

The Excel status bar at the bottom shows the 'Report' tab is active, and the system tray indicates 'READY' and '100%' zoom.



BMDs Wizard – EPA Format Report in Microsoft Word

BMDs WIZARD REPORT

1.1. BMDs Summary of (Exercise_4)

Table 1. Model predictions for (Exercise_4)

Model ^a	Goodness of fit		BMD ₁₀₀ (0)	BMDL ₁₀₀ (0)	Basis for model selection
	p-value	AIC			
Exponential (M2)	0.250	-150.19	326	246	
Exponential (M3) ^b					
Exponential (M4)	0.666	-151.49	119	44.9	
Exponential (M5) ^c					
Hill	0.783	-151.82	103	35.8	
Power ^d	0.282	-150.49	311	230	
Polynomial 4 ^e					
Linear					

^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^e 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

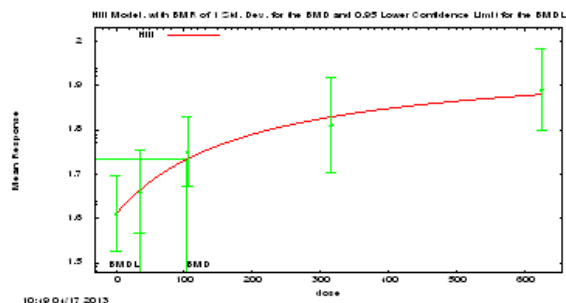


Figure 1. Plot of mean response by dose, with fitted curve for selected model; dose shown in .

BMDs WIZARD REPORT

Hill Model. (Version: 2.17; Date: 01/28/2013)

The form of the response function is: $Y[\text{dose}] = \text{intercept} + v * \text{dose}^n / (k^n + \text{dose}^n)$

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

- **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**

- 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

Exercise_2.xlsm - Excel

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

C13 View Output

BMDs Wizard

BMDS Results Back to Main Import Results Clear Results View Output Image

Results Table

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	R D
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	

Startup Main Data Results Report Logic Quick Start Guide

READY 9 OF 18 RECORDS FOUND

- **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**