Benchmark Dose Modeling – Nested Dichotomous Models

Allen Davis, MSPH

Jeff Gift, Ph.D.

Jay Zhao, Ph.D.

National Center for Environmental Assessment, U.S. EPA

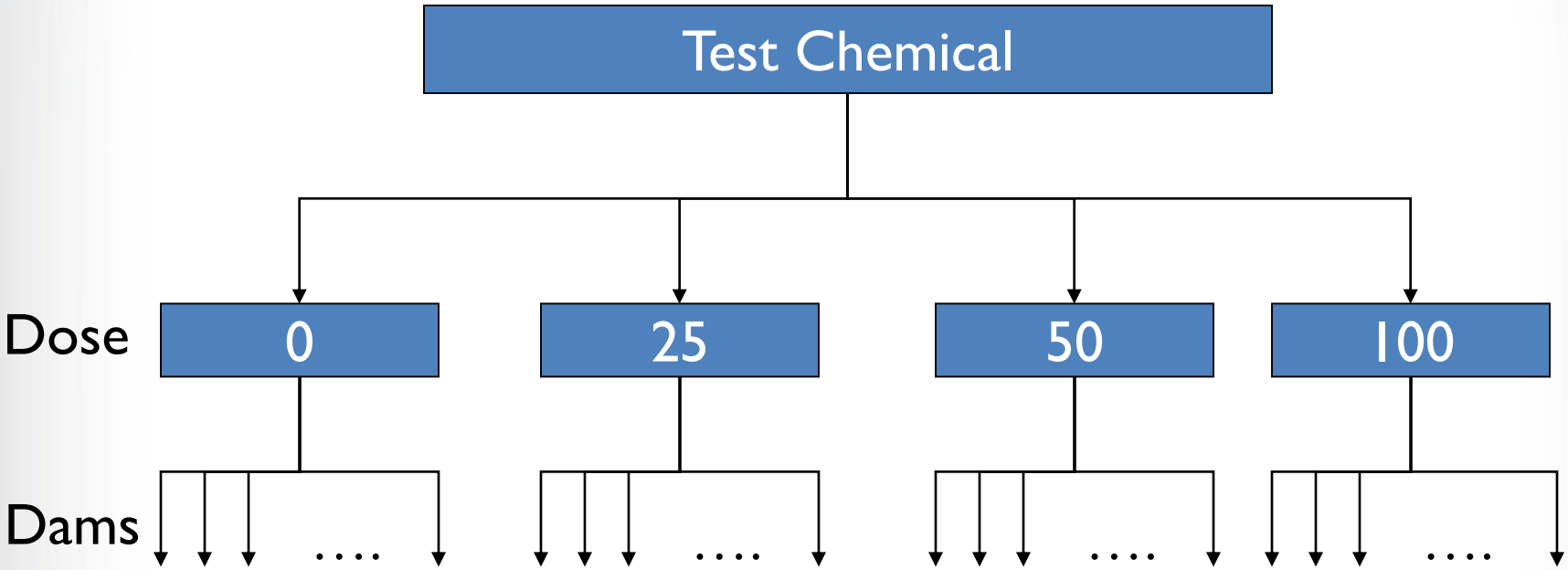
Disclaimer

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

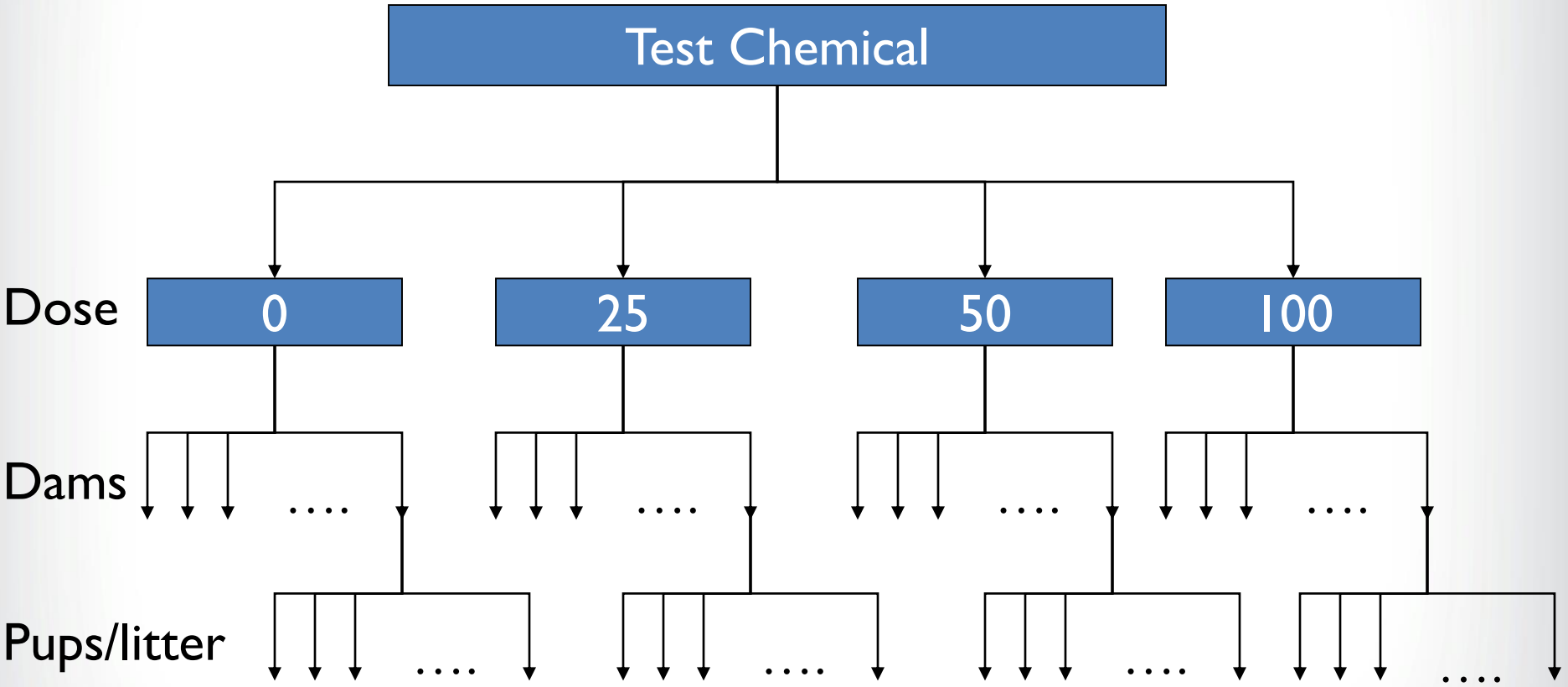
Nested Dichotomous Data

Description	• Response is measured as on/off or true/false • Outcomes are measured in the offspring of exposed, pregnant animals • BMDS can only model positive dose-response trends, where incidence increases with dose
Example Endpoints	• Structural abnormalities – malformations (e.g., cleft palate) or variations (ossification changes) • Mortality – resorptions (early mortality) or fetal death (late mortality)
Model Inputs	• Dose • Individual animal (i.e., dam) data – number of offspring experiencing the effect per exposed dam

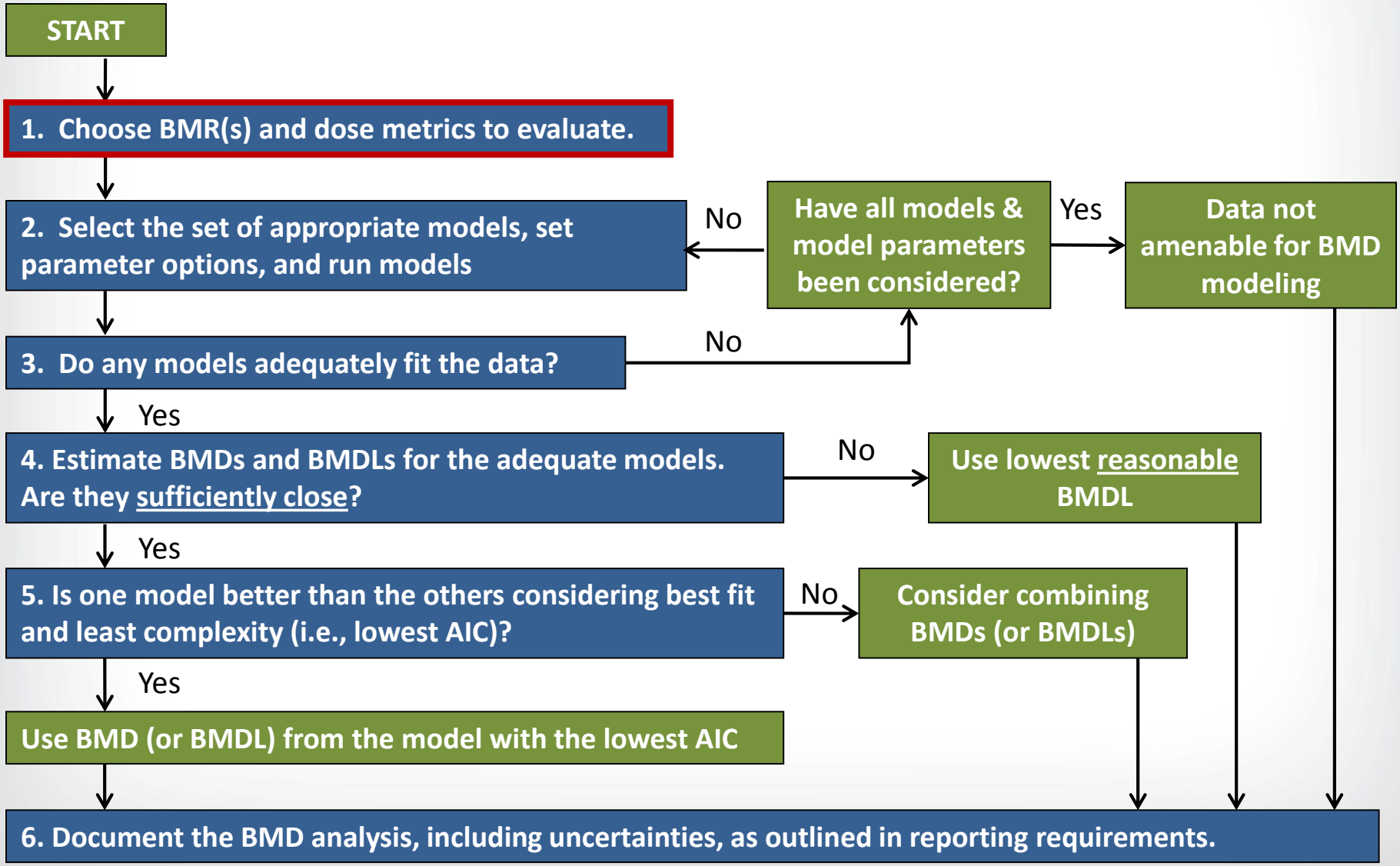
Regular Toxicity Study



Developmental Toxicity Study



BMD Analysis – Six Steps



Select A Benchmark Response

- **BMR should be near the low end of the observable range of increased risks in a bioassay**

- **BMRs that are too low can impart high model dependence, i.e., different models have different shapes in the extreme low dose area and will provide different BMDL estimates.**

Select a Benchmark Response

- **Although an excess risk of 10% is usually a standard BMR for dichotomous data, an excess risk of 5% approximates the NOAEL for most developmental studies.**

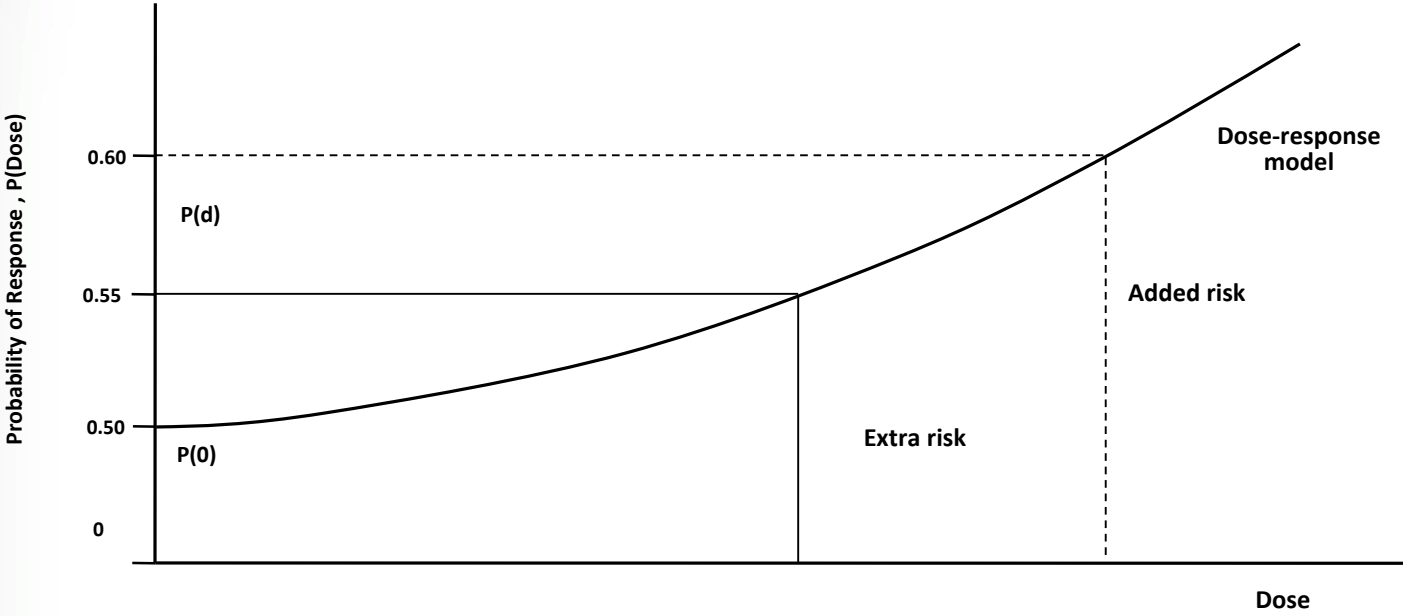
- **In a series of papers (Faustman et al., 1994; Allen et al., 1994a,b), it was shown that the BMDL for 5% extra risk corresponded on average with NOAELs identified from a large developmental toxicity database**

- **Support for using a BMR of 5% for developmental data**
  - Developmental studies provide increased statistical power compared to regular toxicity studies due the increase in sample size (i.e., use of pups as the observational subject)
  - Developmental effects are often considered to be severe, or sometimes frank (i.e., fetal mortality)

Measurement of Increased Risk

- **For dichotomous data, BMRs are expressed as:**
  - **Added risk –** AR(d) = P(d) – P(0)
  - **Extra risk –** ER(d) = [P(d) – P(0)]/[1 – P(0)]
- **Extra risk is recommended by the IRIS, and is used in IRIS risk assessments.**

Added vs. Extra Risk



10% Added Risk

0.10 =P(d) – P(0) ; if P(0)=.50

P(d) = 0.10 + P(0) = 0.10 + 0. 50 = **0.60**

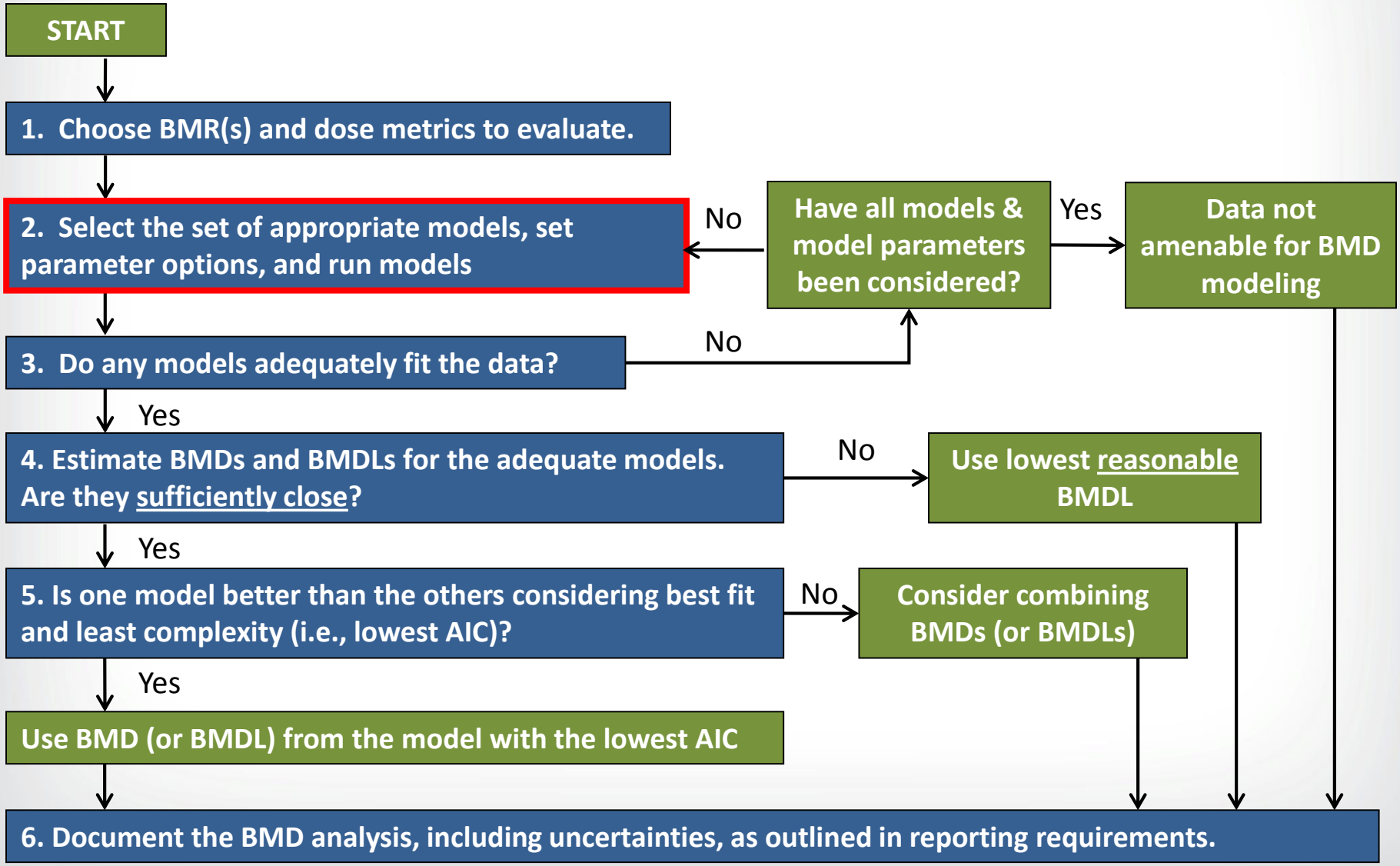
10% Extra Risk

0.10 =[P(d) –P(0)]/[1-P(0)]; if P(0) = .50

P(d) = 0.10 x [1 - P(0)] + P(0) = (0.10 x 0.50) + 0.50 = **0.55**

The dose will be lower for a 10% Extra risk than for a 10% Added risk if P(0) > 0

BMD Analysis – Six Steps



Nested Dichotomous Models

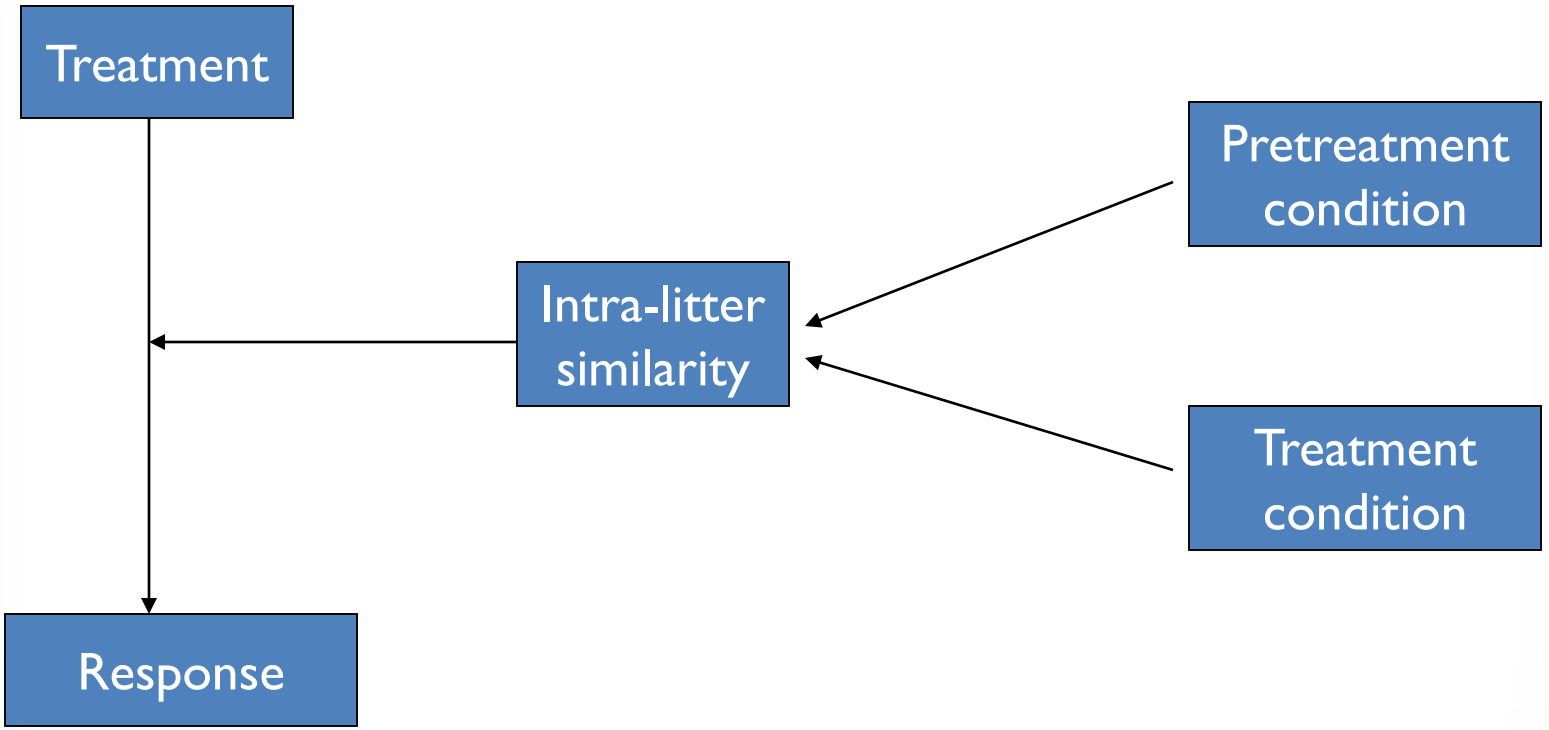
Model name	Functional form	Notes
Nested Logistic[a]	$\frac{\alpha + \theta_1 r_{ij} + [1 - \alpha - \theta_1 r_{ij}]}{(1 + \exp[-\beta - \theta_2 r_{ij} - \rho * \ln(X)])}$	r_{ij} is the litter specific covariate for the jth litter in the ith dose group, there are g intra-litter correlation coefficients , $0 < \Phi_i < 1$ (i = 1, …, g)
NCTR	$1 - \exp[-(\alpha + \theta_1[r_{ij} - r_m]) - (\beta + \theta_2[r_{ij} - r_m]) * dose_\rho]$	r_{ij} is the litter specific covariate for the jth litter in the ith dose group, and r_m is the overall mean for the litter-specific covariate, there are g intra-litter correlation coefficients , $0 < \Phi_i < 1$ (i = 1, …, g)
Rai and van Ryzin	$[1 - \exp(-\alpha - \beta(dose_\rho)] * \exp(-(\theta_1 + \theta_2 dose) * r_{ij})$	r_{ij} is the litter specific covariate for the jth litter in the ith dose group, there are g intra-litter correlation coefficients , $0 < \Phi_i < 1$ (i = 1, …, g)

[a] The nested Logistic model is the Log-logistic model modified to include a litter-specific covariate. Log-logistic model form: $\frac{\gamma + (1 - \gamma)}{1 + \exp\{-[\alpha + \beta \ln(X)]\}}$

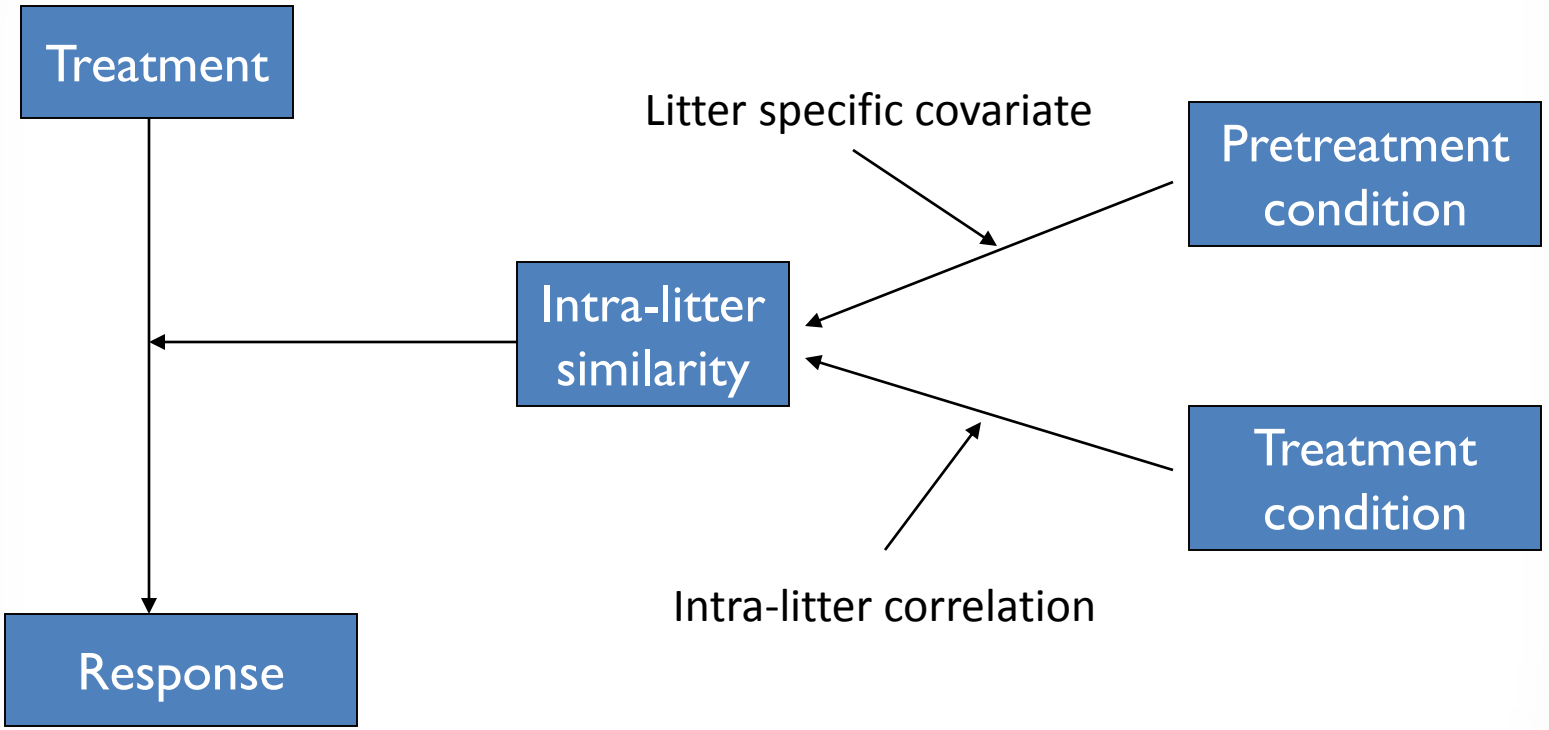
Parameters Specific to the Nested Dichotomous Models

- **It is usual for the responses of pups in the same litter to be more similar to each other than to the responses of pups in different litters**
  - This is typically called "intra-litter similarity" or "litter effects"
- **Models for nested dichotomous data incorporate two parameters to address this issue**
  - Litter specific covariate (θ coefficients)
  - Intra-litter correlation (Φ coefficients)

Developmental Toxicity Responses



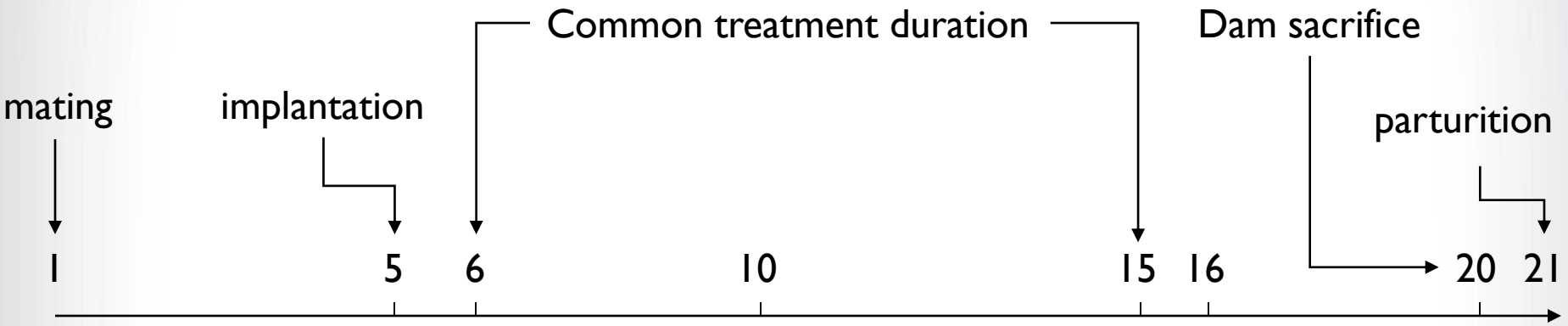
Developmental Toxicity Responses

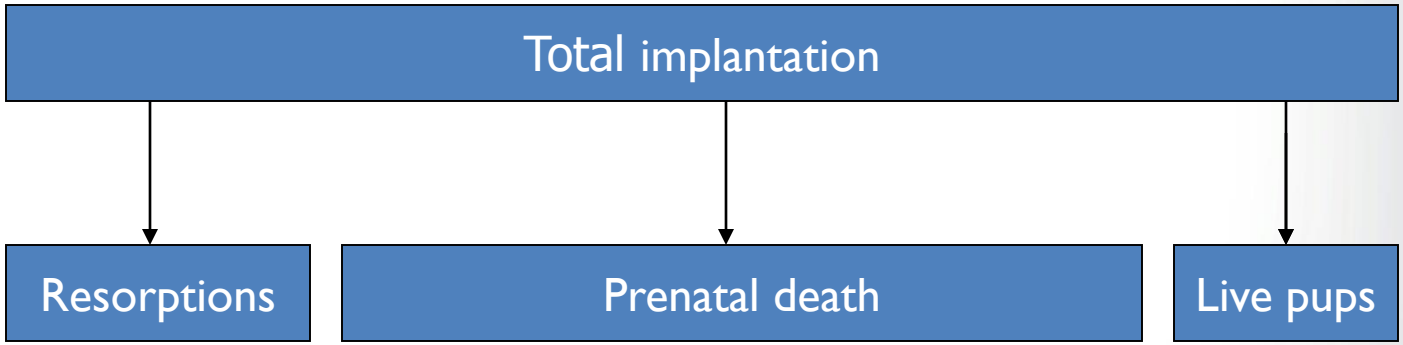


Litter Specific Covariate

- **A litter specific covariate (θ coefficients) takes into account the condition of the exposed dam prior to the onset of dosing/exposure.**
- **The pre-treatment condition of the dam should account for some of the observed "litter effect"**
- **The litter specific covariate should NOT be affected by treatment**
- **Commonly used litter specific covariates include:**
  - Litter size
  - Dam weight
  - Implantation sites

Rat Developmental Milestones





Litter Specific Covariate

- **Implantation sites**
  - In a normal guideline developmental toxicity study, where dosing begins after implantation takes place, the number implantation sites is the preferred litter specific covariate
  - However, these data are not reported in some toxicity studies

- **Litter size**
  - Litter size is an appropriate litter specific covariate as long as there are not treatment-related resorptions or prenatal deaths

Use of Litter Specific Covariate

- **The litter specific covariate should only be used when ALL of the following 3 criteria are met:**
  - The chosen litter specific covariate is not affected by treatment
  - θ coefficients are estimated by BMDS to be non-zero (currently, the software does not estimate coefficent standard errors, so some judgement is required when making this determination)
    - If the model estimates the θ coefficients to be EXACTLY 0, the modeling results (including AIC) should be the same as when running the model with the litter specific covariate turned off.
  - When the litter specific covariate is included in the modeling scheme, the model fit becomes better (e.g., per AIC or scaled residual comparison)

- **NOTE: regardless of whether an appropriate litter specific covariate can be identified, the modeled dataset MUST contain "covariate" data (even if it's dummy data)**

Intra-litter Correlation

- **The intra-litter correlation statistically describes the similarity of responses among pups in the same litter**

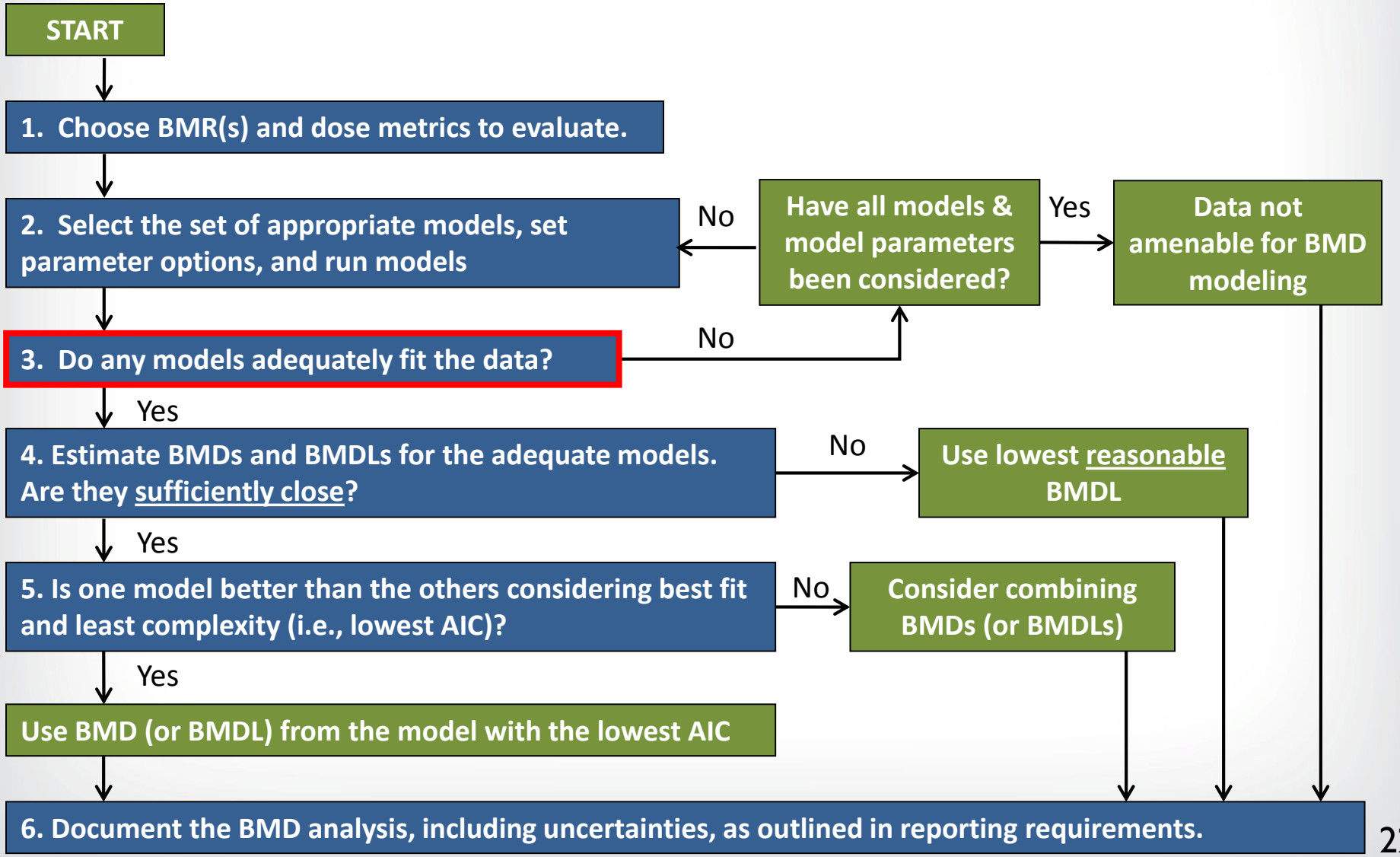
- **Intra-litter correlation should only be used when BOTH of the following 2 criteria are met:**
  - Φ coefficients are estimated by BMDS to be non-zero (currently, the software does not estimate coefficent standard errors, so some judgement is required when making this determination)
  - When the intra-liter correlation is included in the modeling scheme, the model fit becomes better (e.g., per AIC or scaled residual comparison)

- **When intra-litter correlation is used, if the range of the scaled residuals for the litters with the same litter specific covariate is not reduced, consult a statistician to determine a course of action**

Model Parameter Selection for Nested Dichotomous Data

- **For a single dataset, run the desired nested dichotomous model 4 times (assuming there is a covariate appropriate for the litter specific covariate):**
  - Litter specific covariate = -, intra-litter covariate = +
  - Litter specific covariate = + intra-litter covariate = -
  - Litter specific covariate = -, intra-litter covariate = +
  - Litter specific covariate = +, intra-litter covariate = +
- **Applying the criteria in the previous slides, final model selection can be made based on global goodness-of-fit p-value, scaled residuals, and AIC**

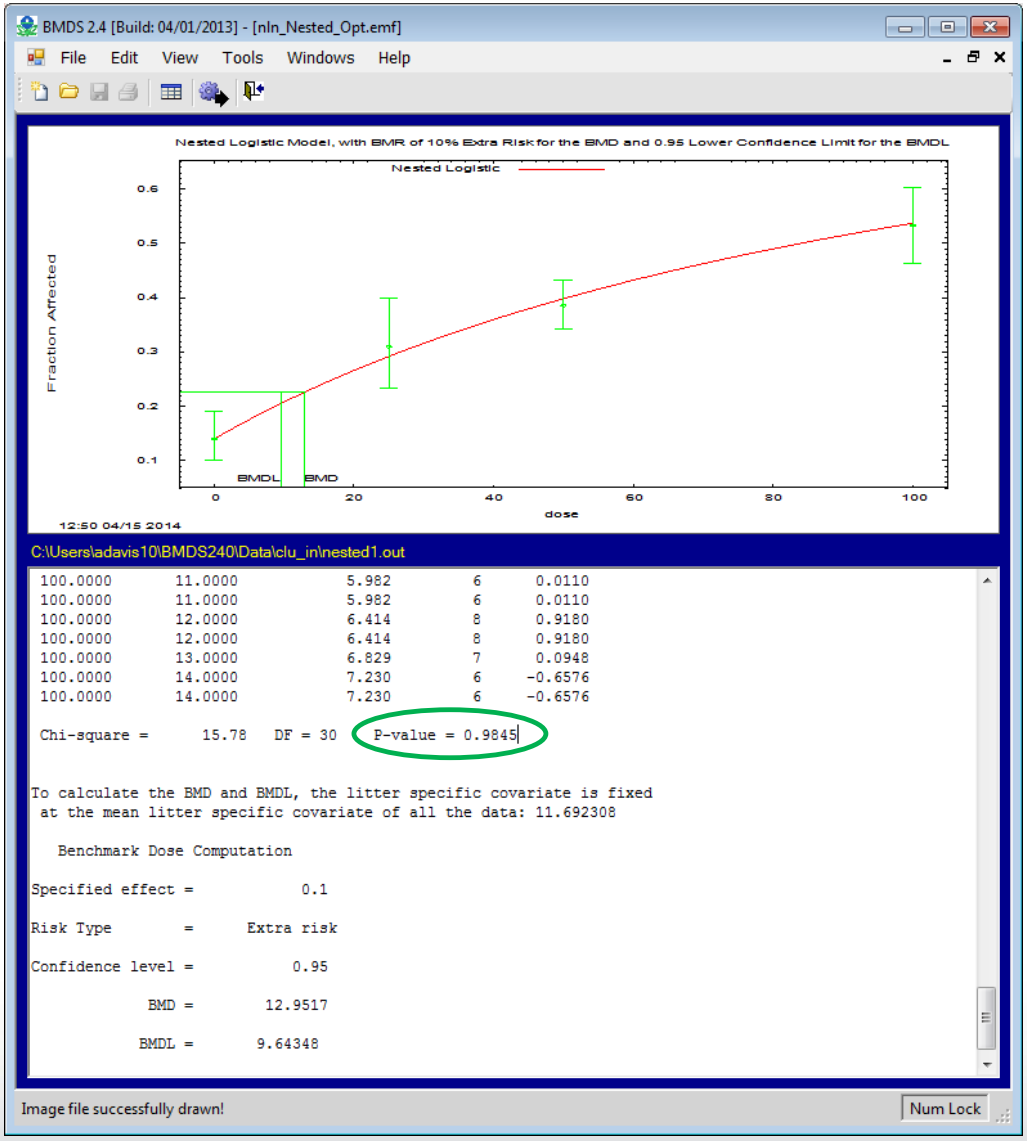
BMD Analysis – Six Steps



Does the Model Fit the Data?

- **For dichotomous data:**
  - ***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



Modeling Recommendations – Poor Global Goodness-of-Fit

- **Consider dropping high dose group(s) that negatively impact low dose fit**

- **Use PBPK models if available to calculate internal dose metrics that may facilitate better model fitting**
  - 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)

- **Log-transform 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)

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 nested dichotomous data:**
  - 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.

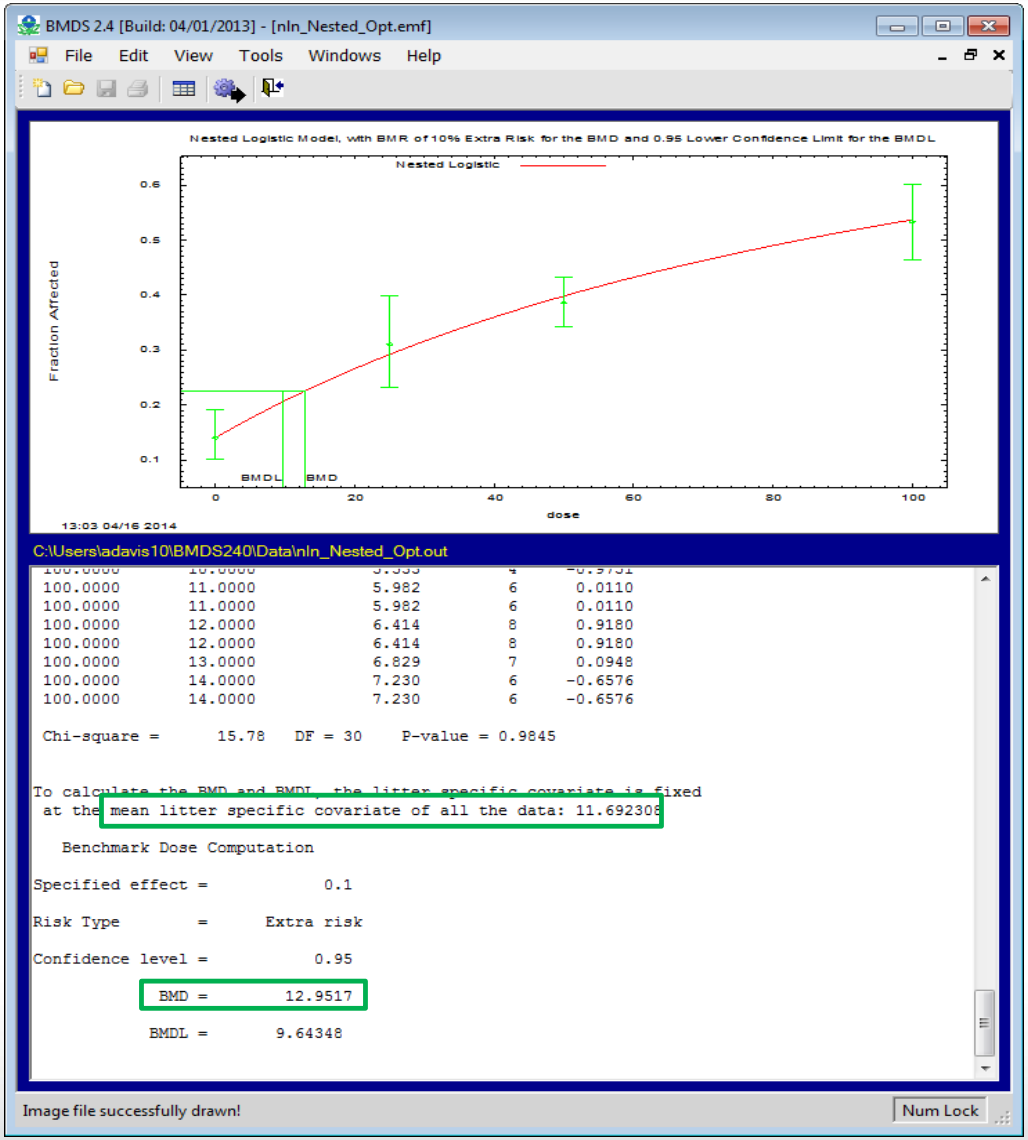
- **Scaled Residuals – measure of how closely the model fits the data at each point; 0 = exact fit**
  - Absolute values near the BMR should be lowest
  - Question scaled residuals with absolute value > 2

Scaled Residuals in Nested Dichotomous Models

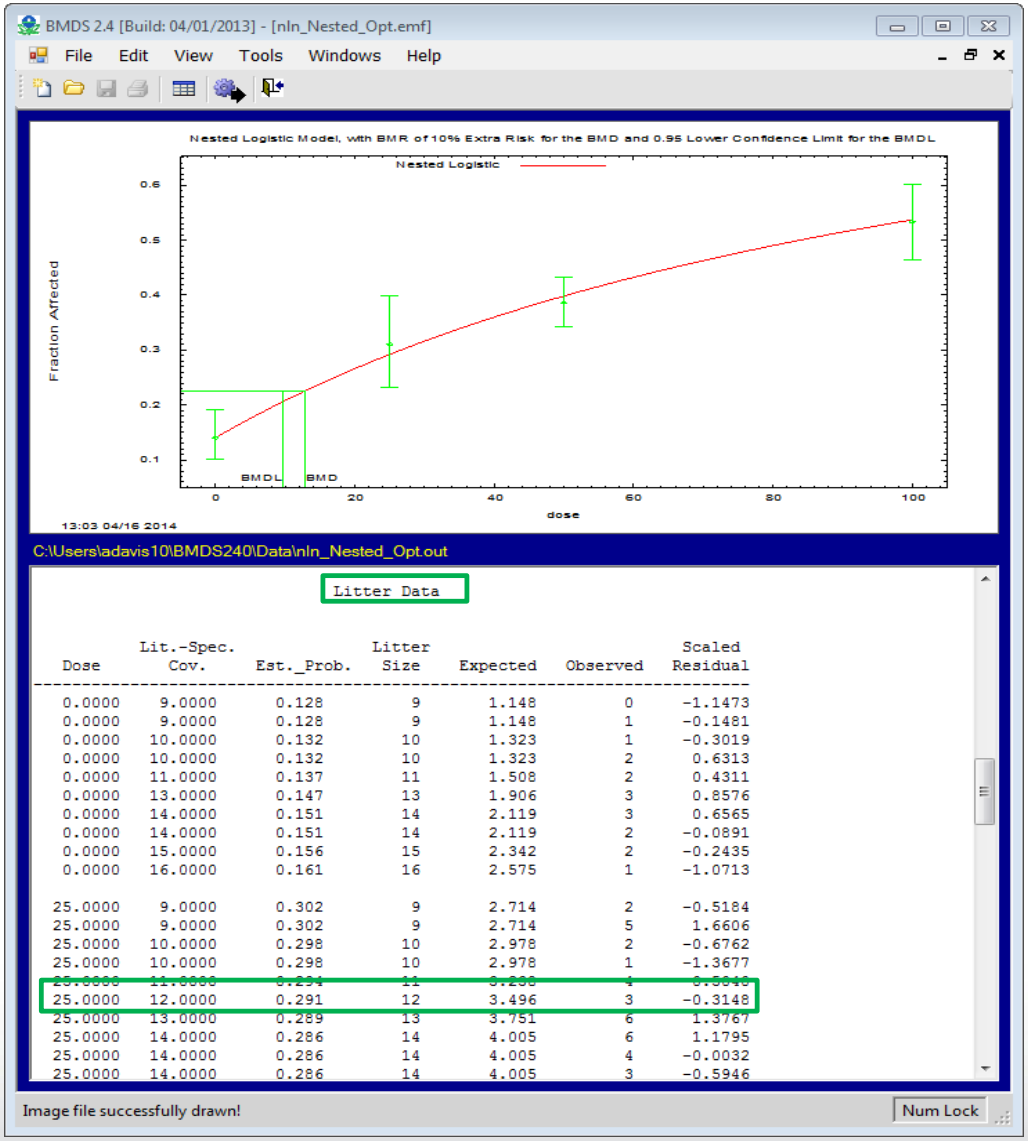
- **The scaled residual of interest is estimated from the scaled residuals from the Litter Data for litters with a litter specific covariate value closest to the *mean litter specific covariate of all the data***

- **When multiple scaled residuals are obtained from samples with the same litter specific covariate, there are a number of options for assessing local fit**
  - **Maximum (absolute) scaled residual value**
  - Average (absolute) scaled residual value
  - Range of scaled residual values

Scaled Residuals in Nested Dichotomous Models



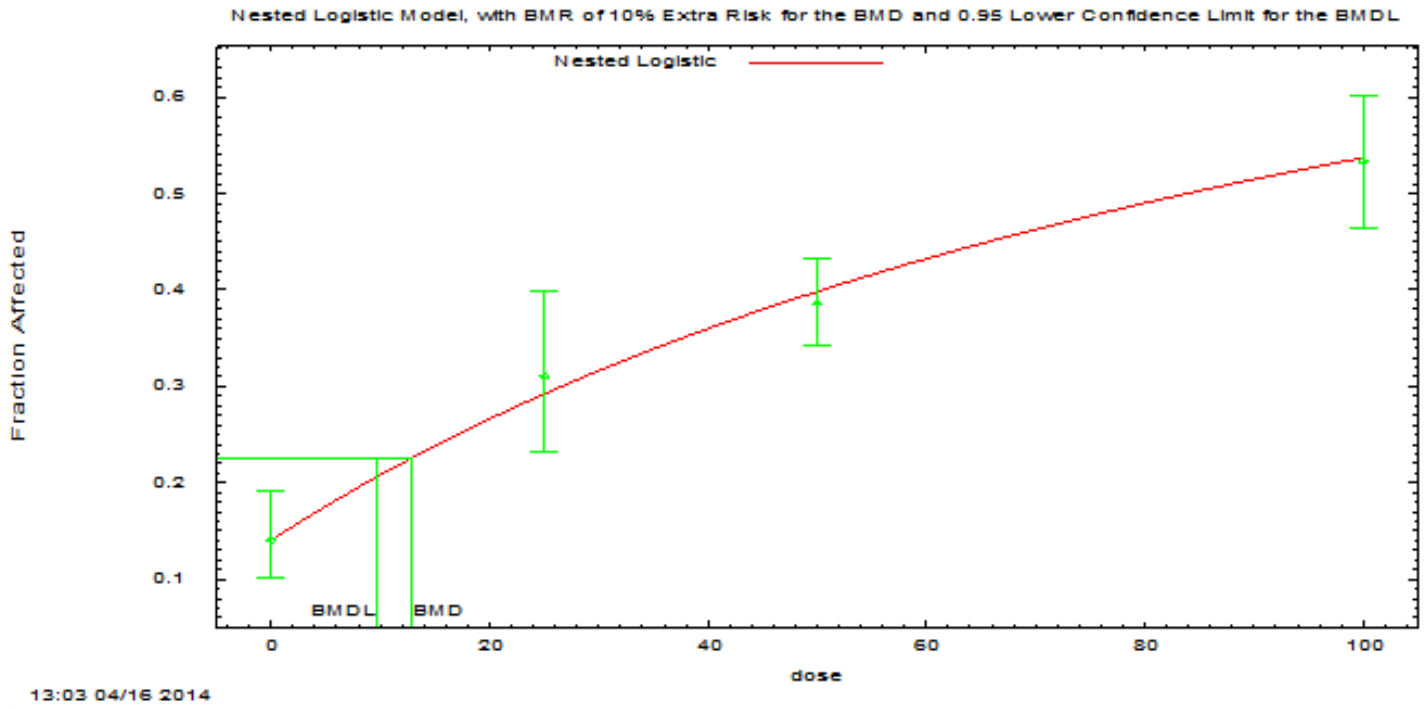
Scaled Residuals in Nested Dichotomous Models



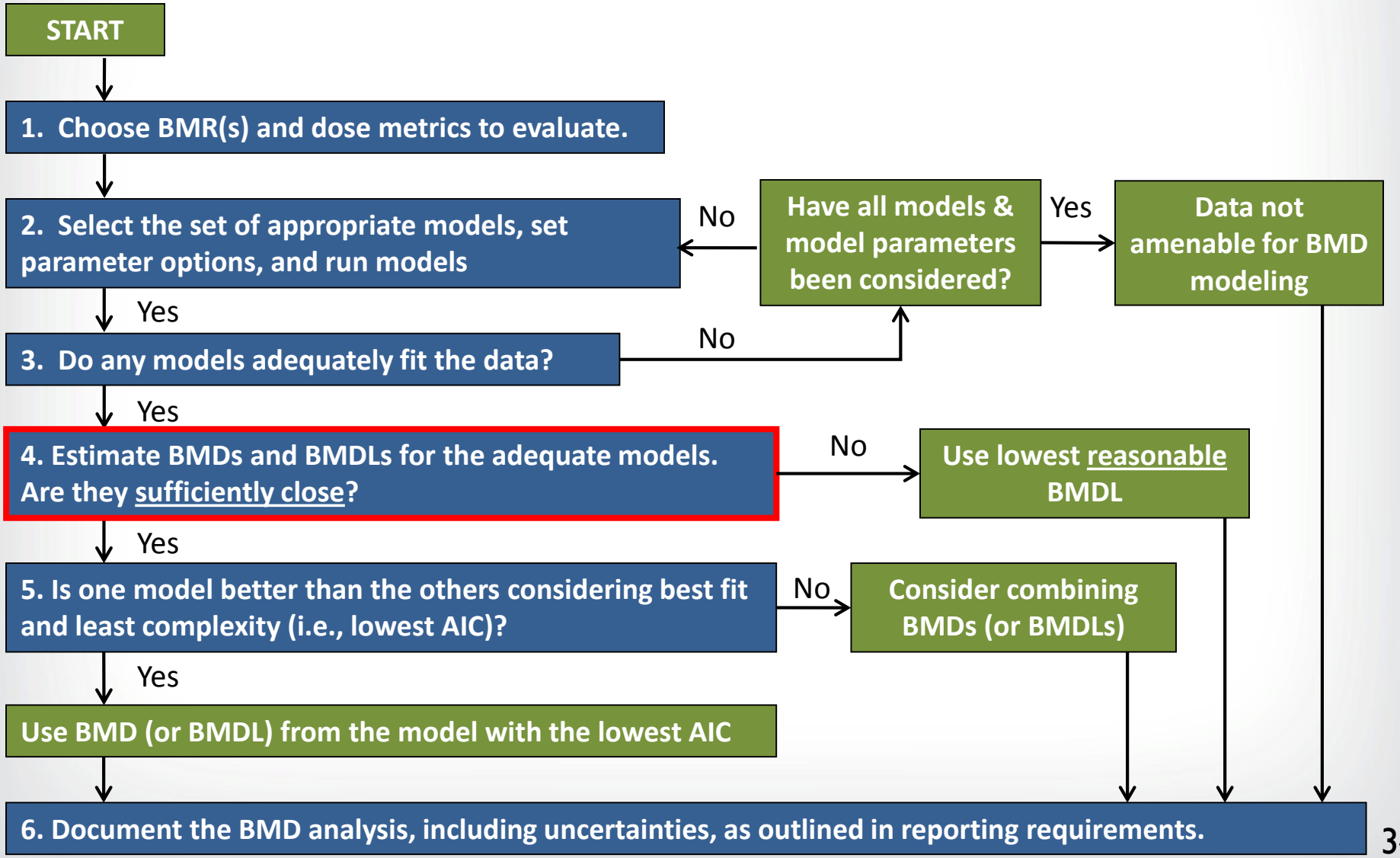
Does the Model Fit the Data?

- **For nested dichotomous data:**
  - Global measurement: goodness-of-fit p value ($p > 0.1$)
  - Local measurement: Scaled residuals (absolute value < 2.0)
  - ***Visual inspection of model fitting***

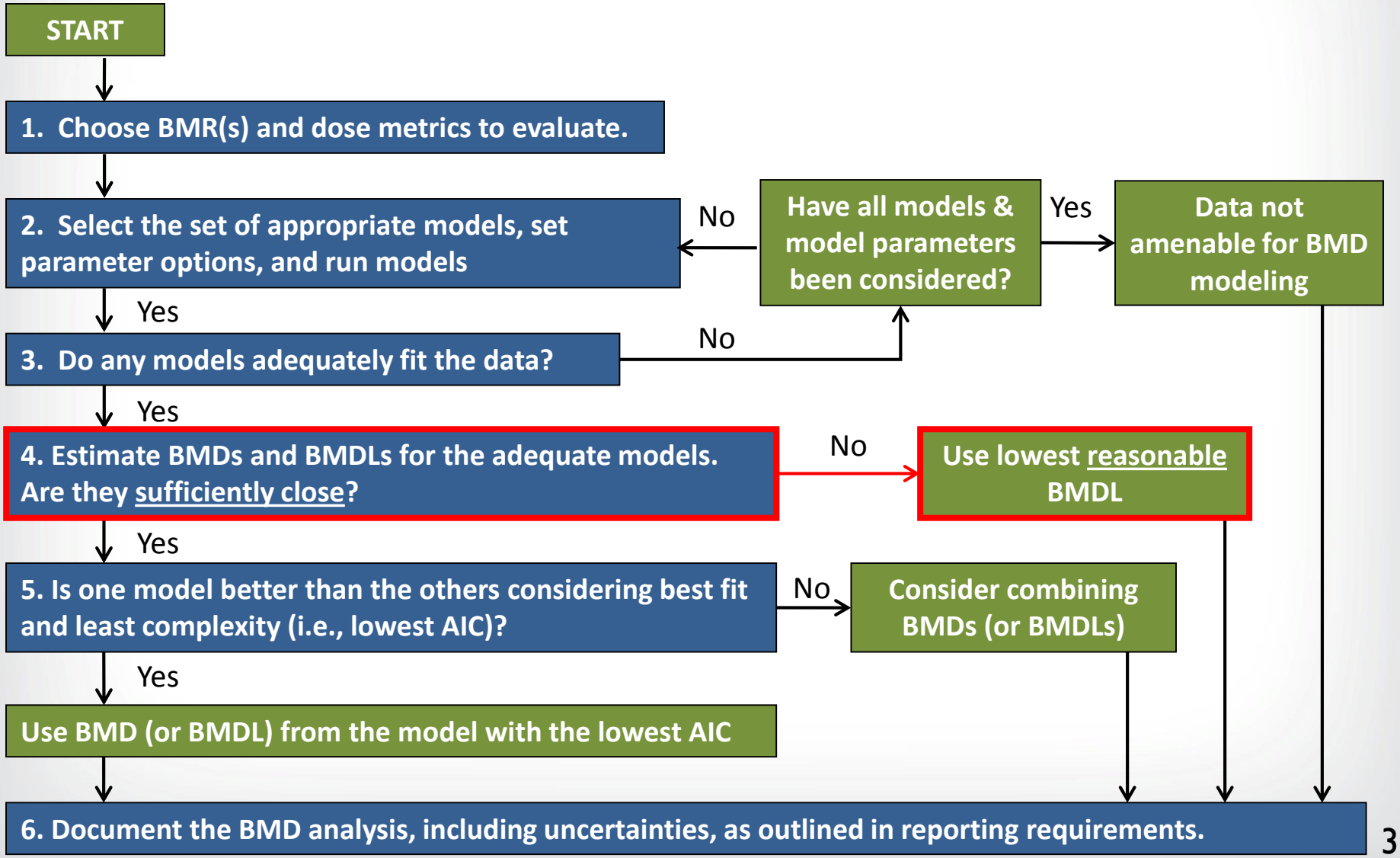
Visual Fit


Nested Logistic Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMDL
Nested Logistic
Fraction Affected
0.6
0.5
0.4
0.3
0.2
0.1
BMDL
BMD
0
20
40
60
80
100
dose
13:03 04/16 2014

BMD Analysis – Six Steps



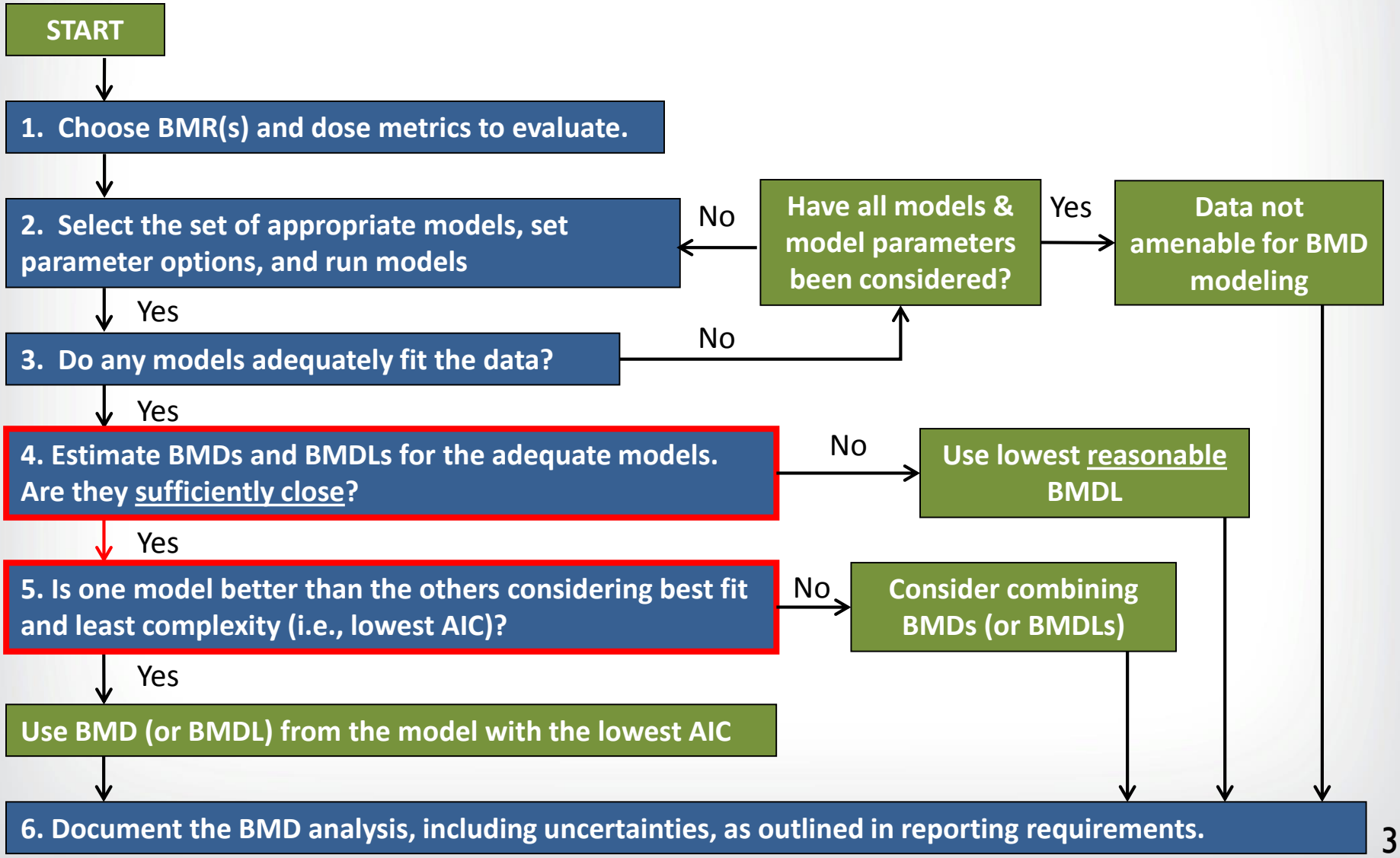
BMD Analysis – Six Steps



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.**

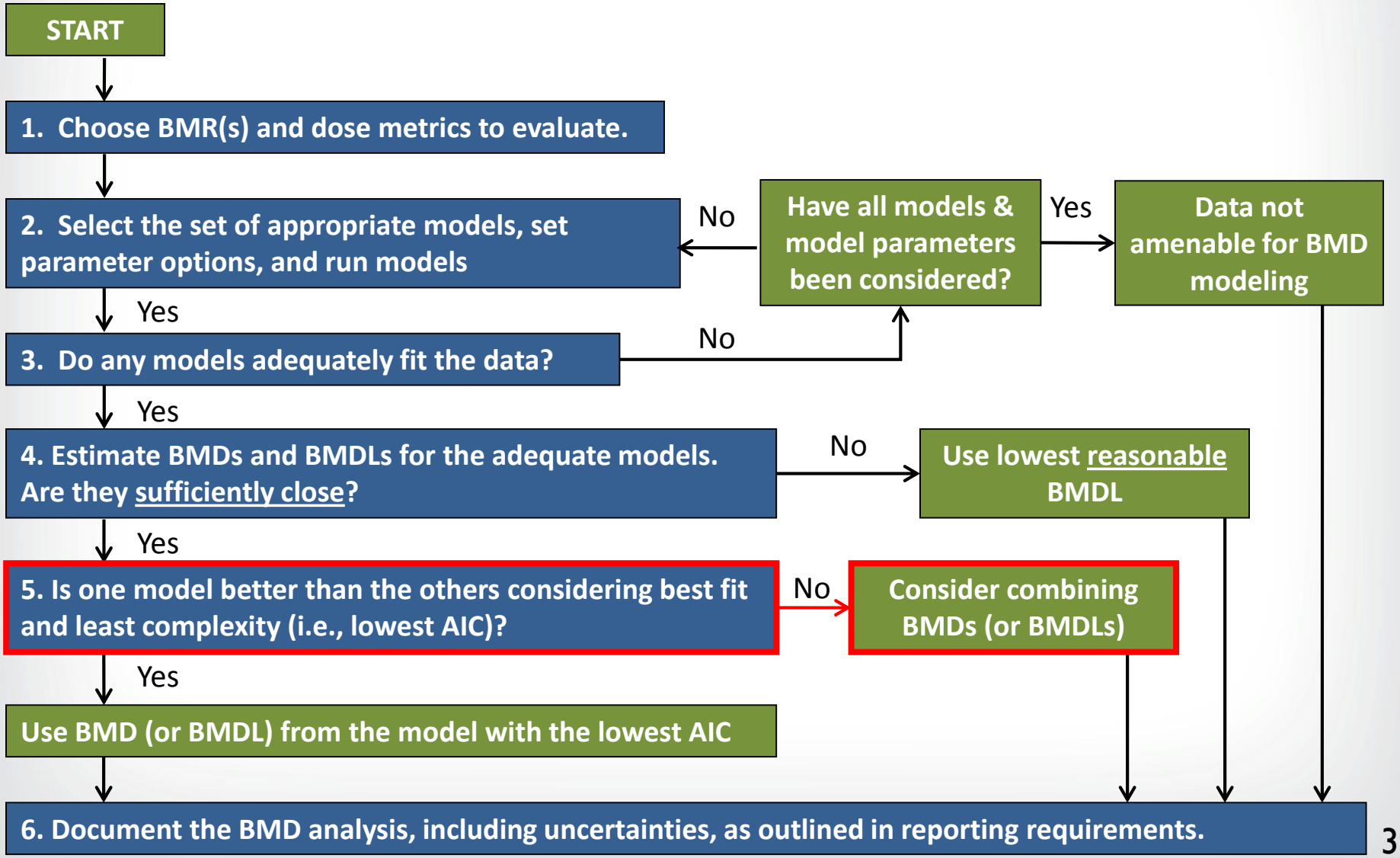
BMD Analysis – Six Steps



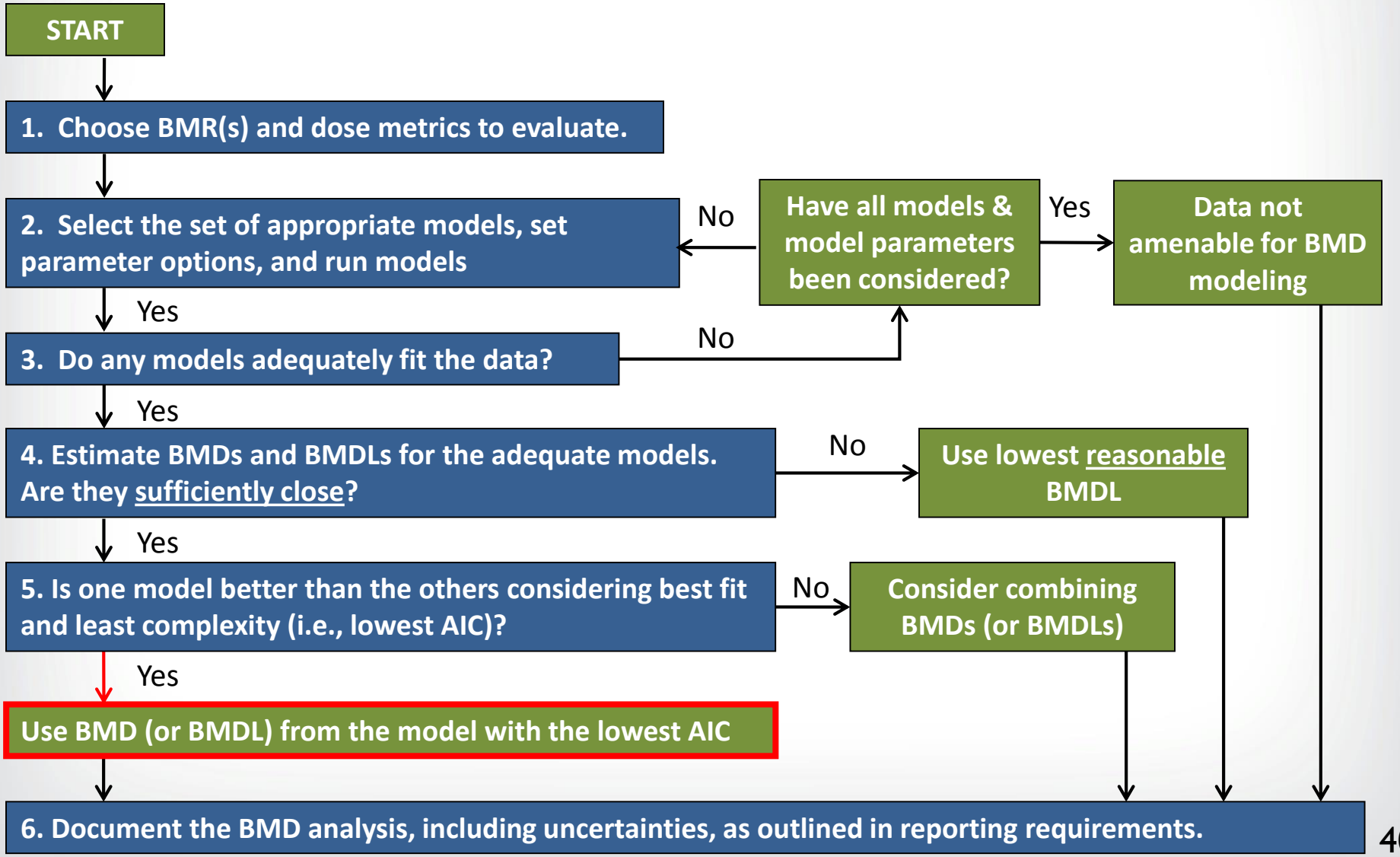
Akaike's Information Criterion (AIC)

- **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"**

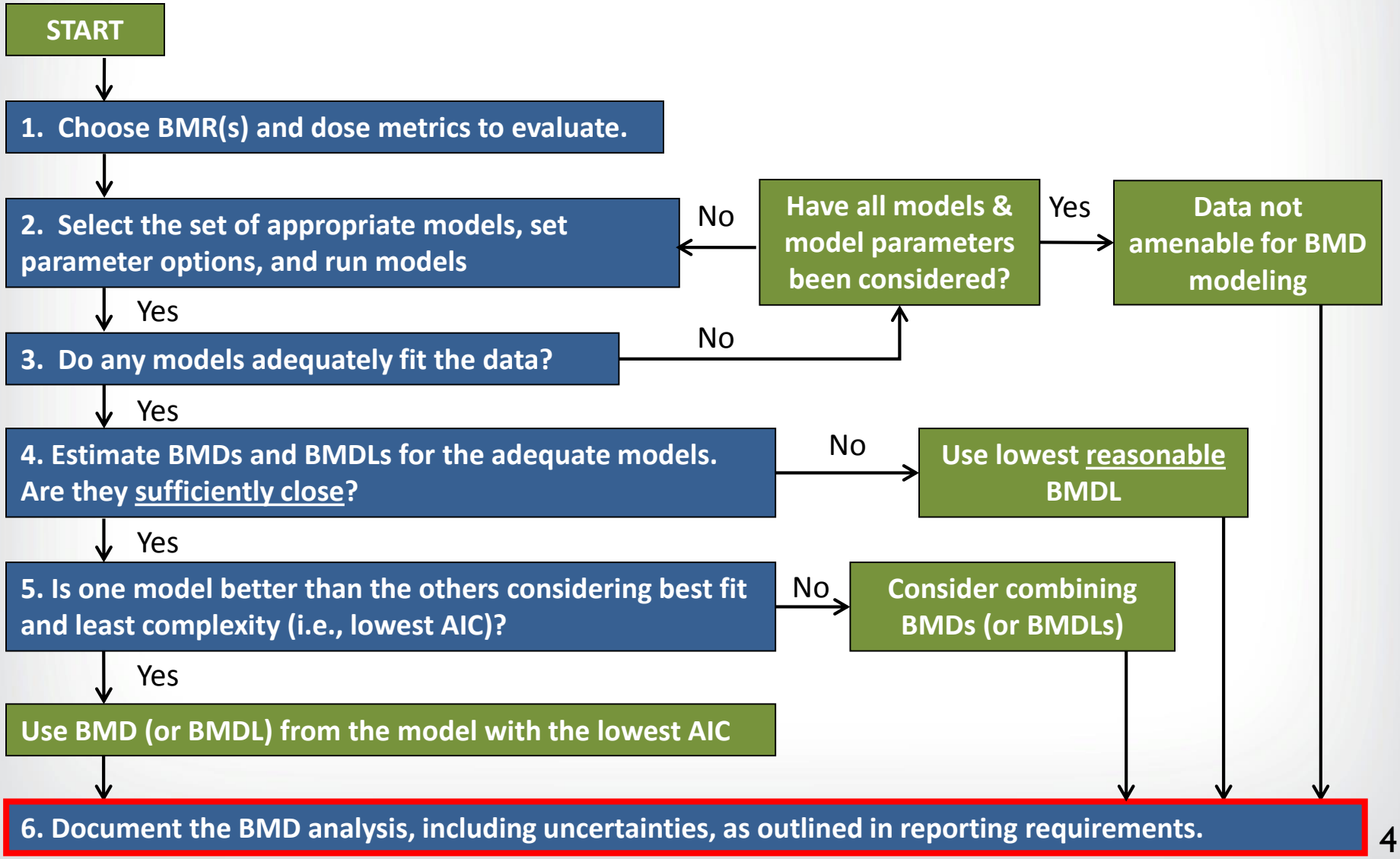
BMD Analysis – Six Steps



BMD Analysis – Six Steps



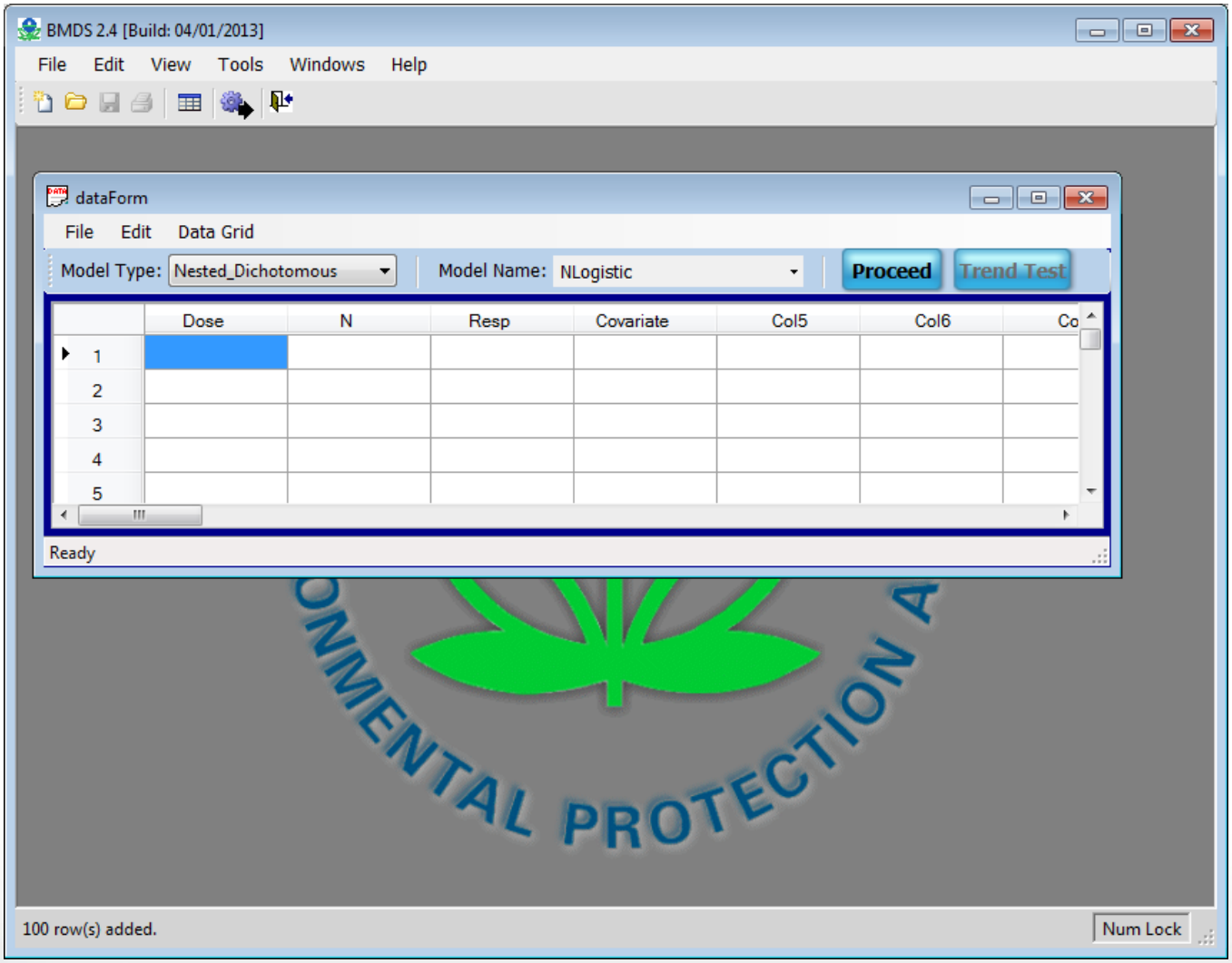
BMD Analysis – Six Steps



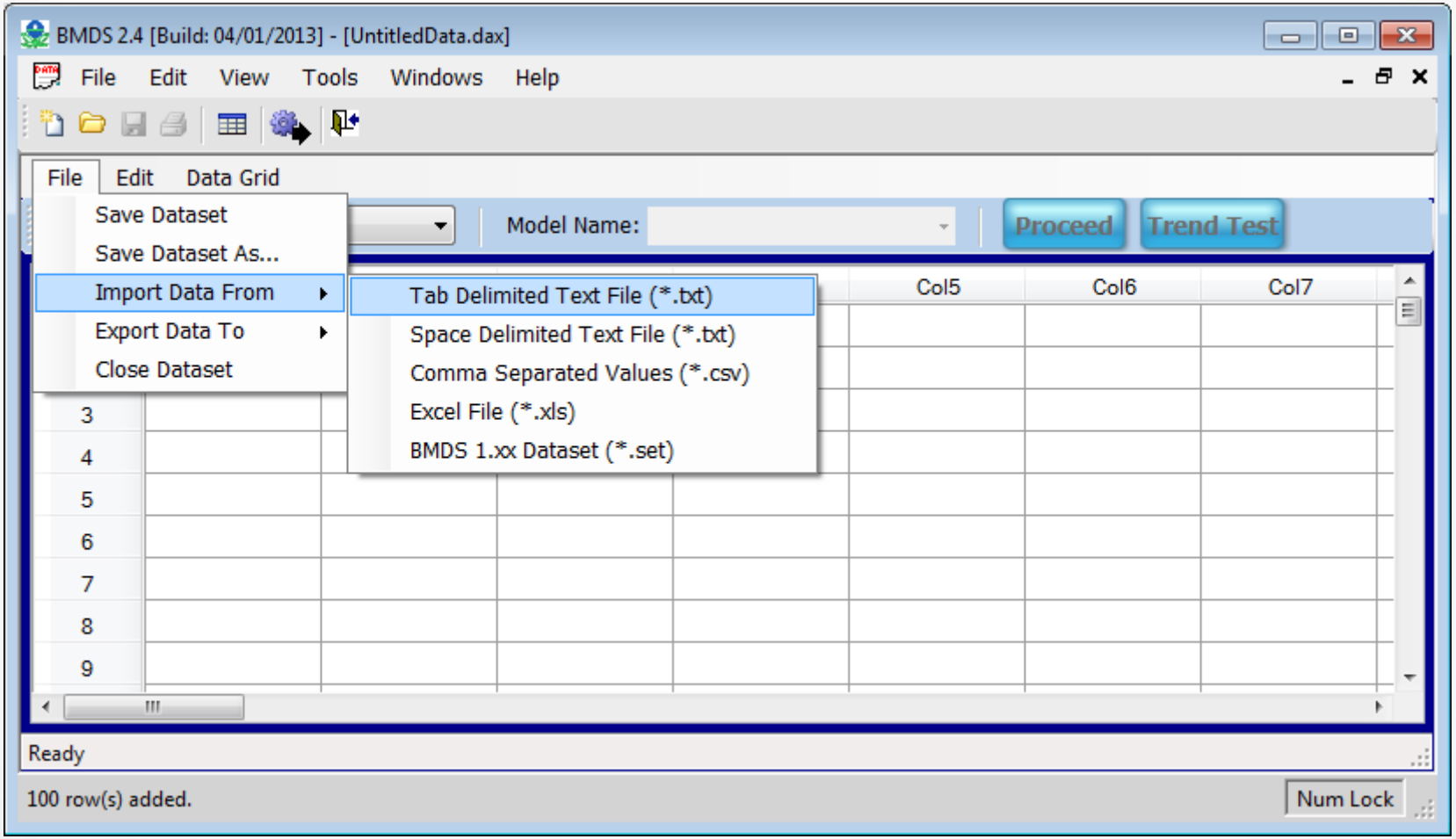
Nested Dichotomous Data – Running the models in BMDS

Creating a Dataset – Open New Nested Dataset

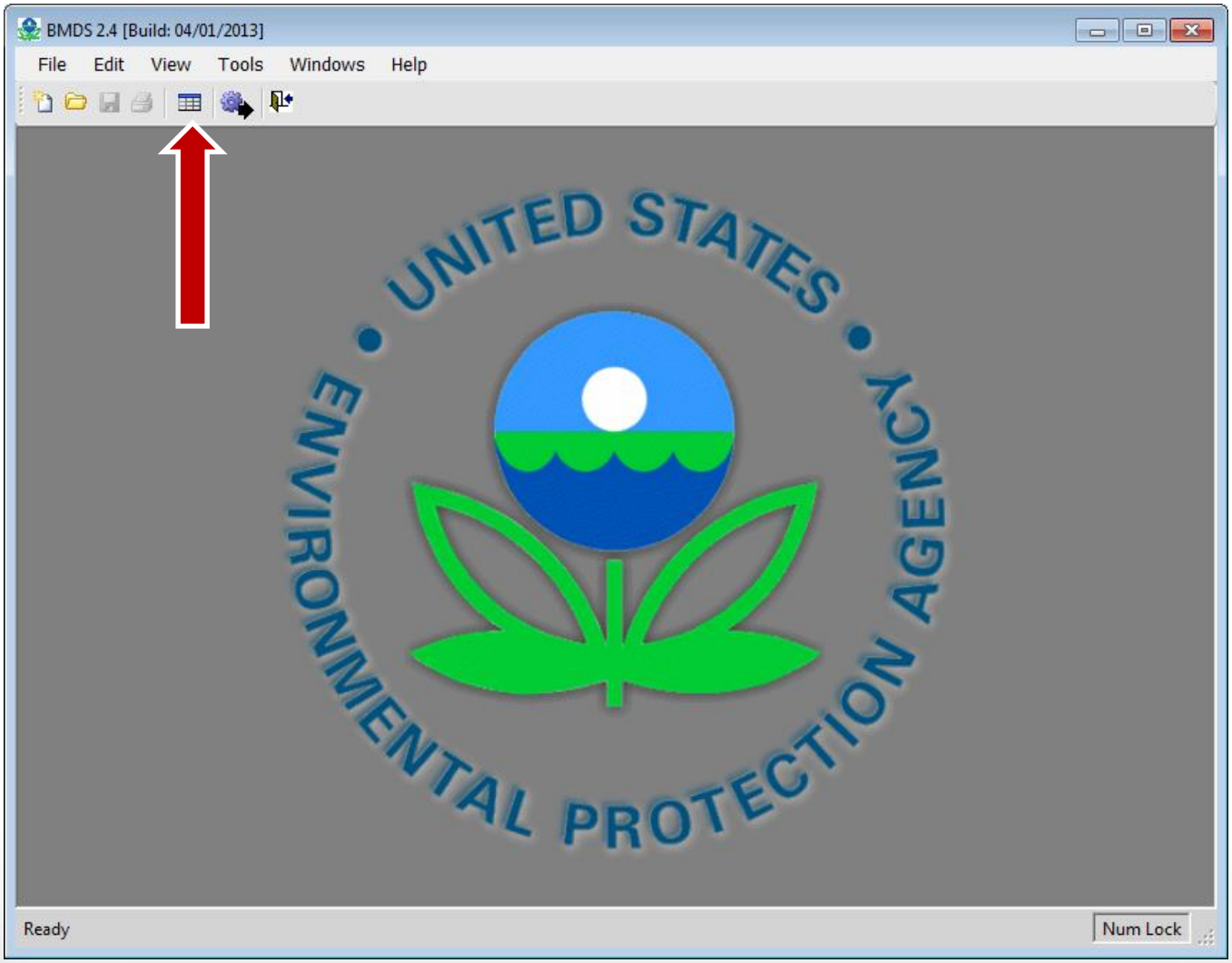
Creating a Dataset – Open New Nested Dataset



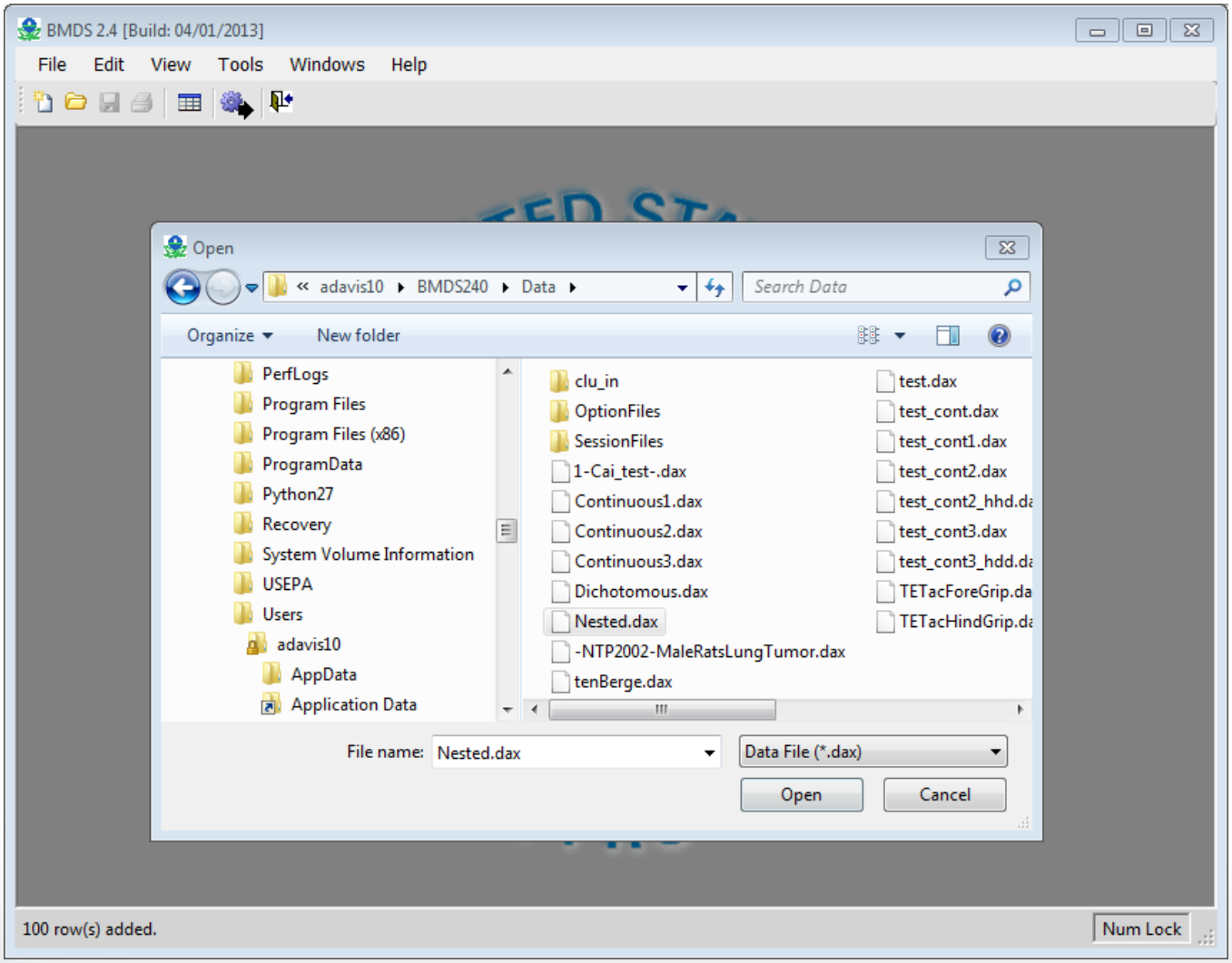
Creating a Dataset – Import an Existing Dataset



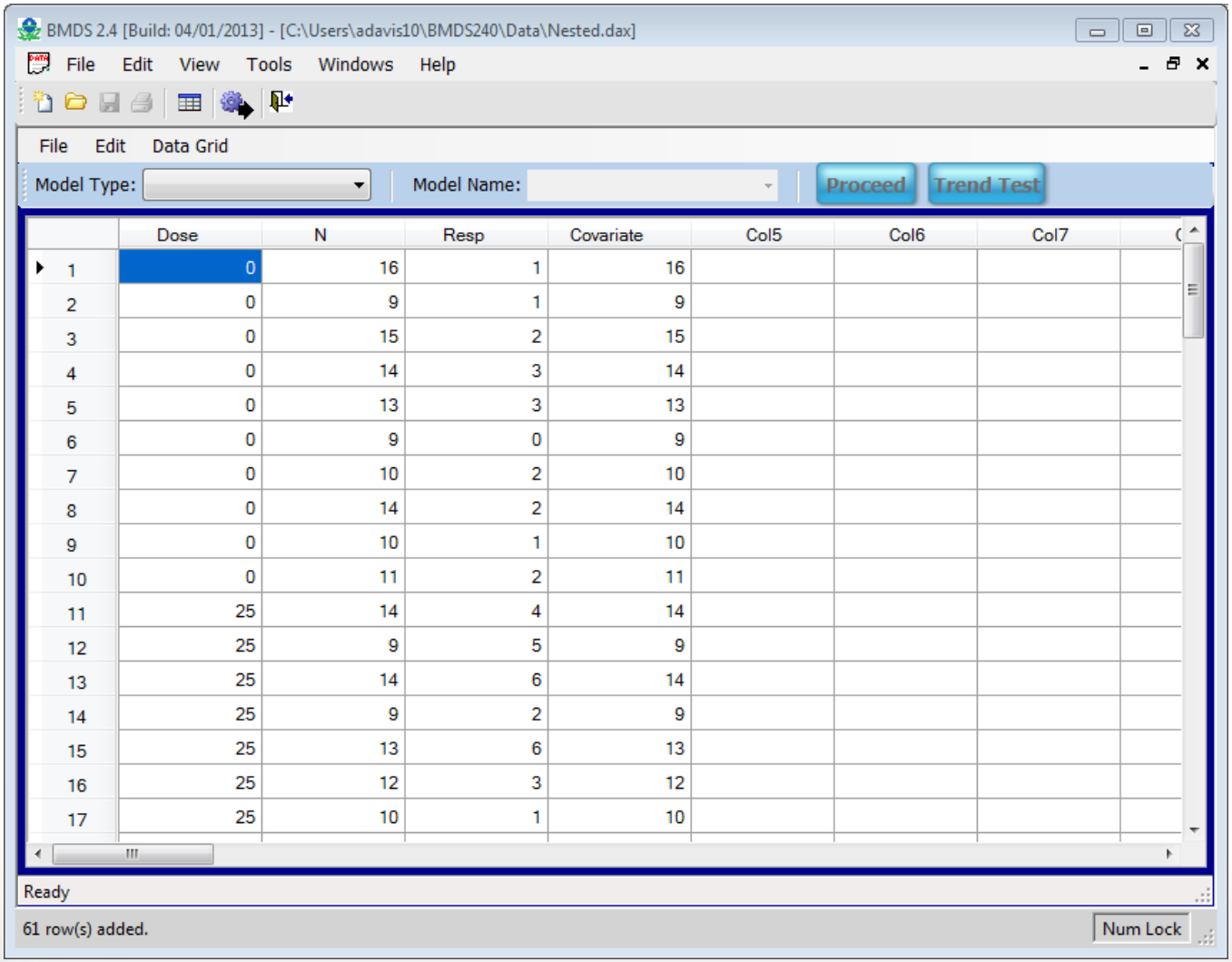
Creating a Dataset – Open Existing Dataset



Creating a Dataset – Open Existing Dataset

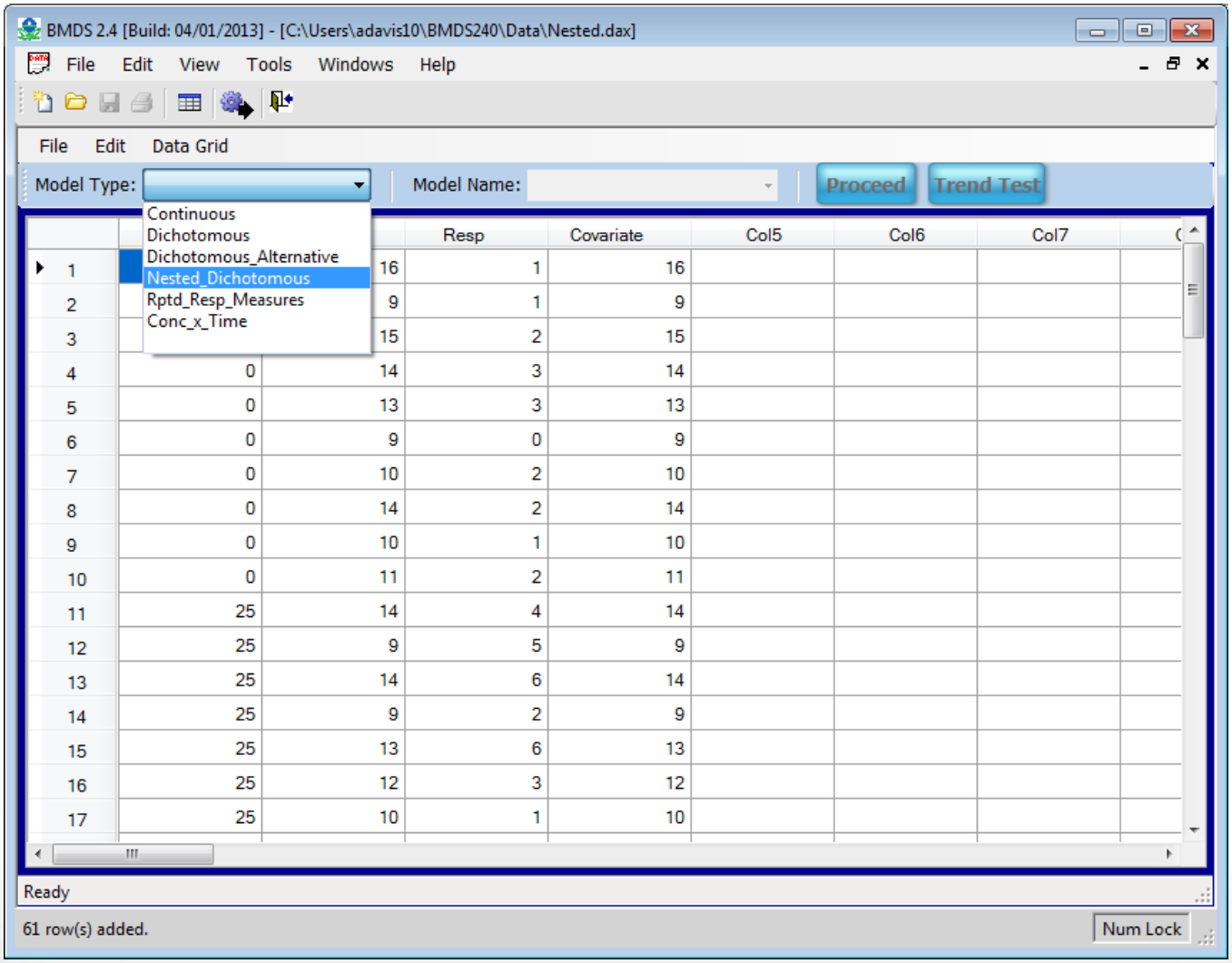


Nested Dichotomous Datafile Structure

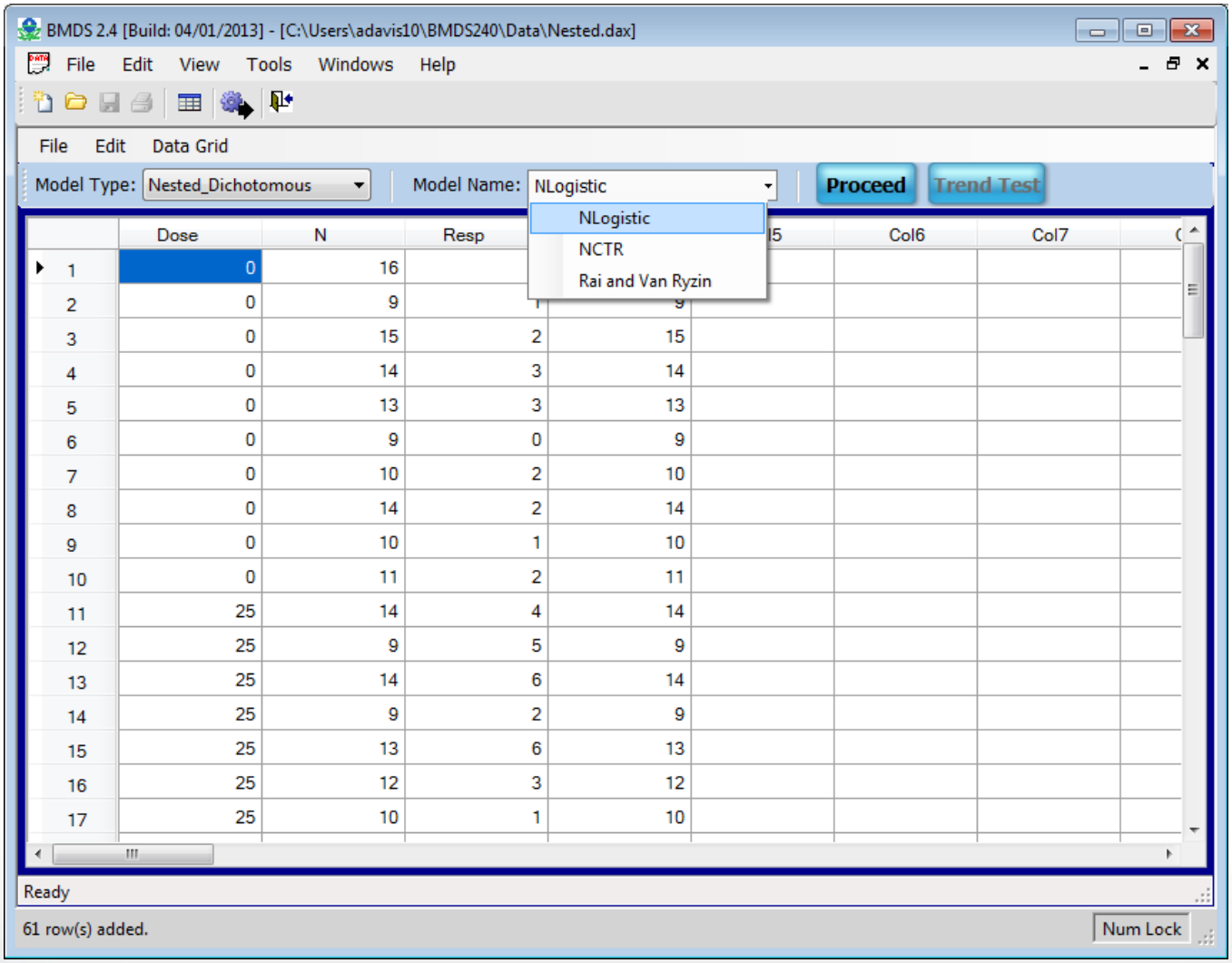


	Dose	N	Resp	Covariate	Col5	Col6	Col7
1	0	16	1	16			
2	0	9	1	9			
3	0	15	2	15			
4	0	14	3	14			
5	0	13	3	13			
6	0	9	0	9			
7	0	10	2	10			
8	0	14	2	14			
9	0	10	1	10			
10	0	11	2	11			
11	25	14	4	14			
12	25	9	5	9			
13	25	14	6	14			
14	25	9	2	9			
15	25	13	6	13			
16	25	12	3	12			
17	25	10	1	10			

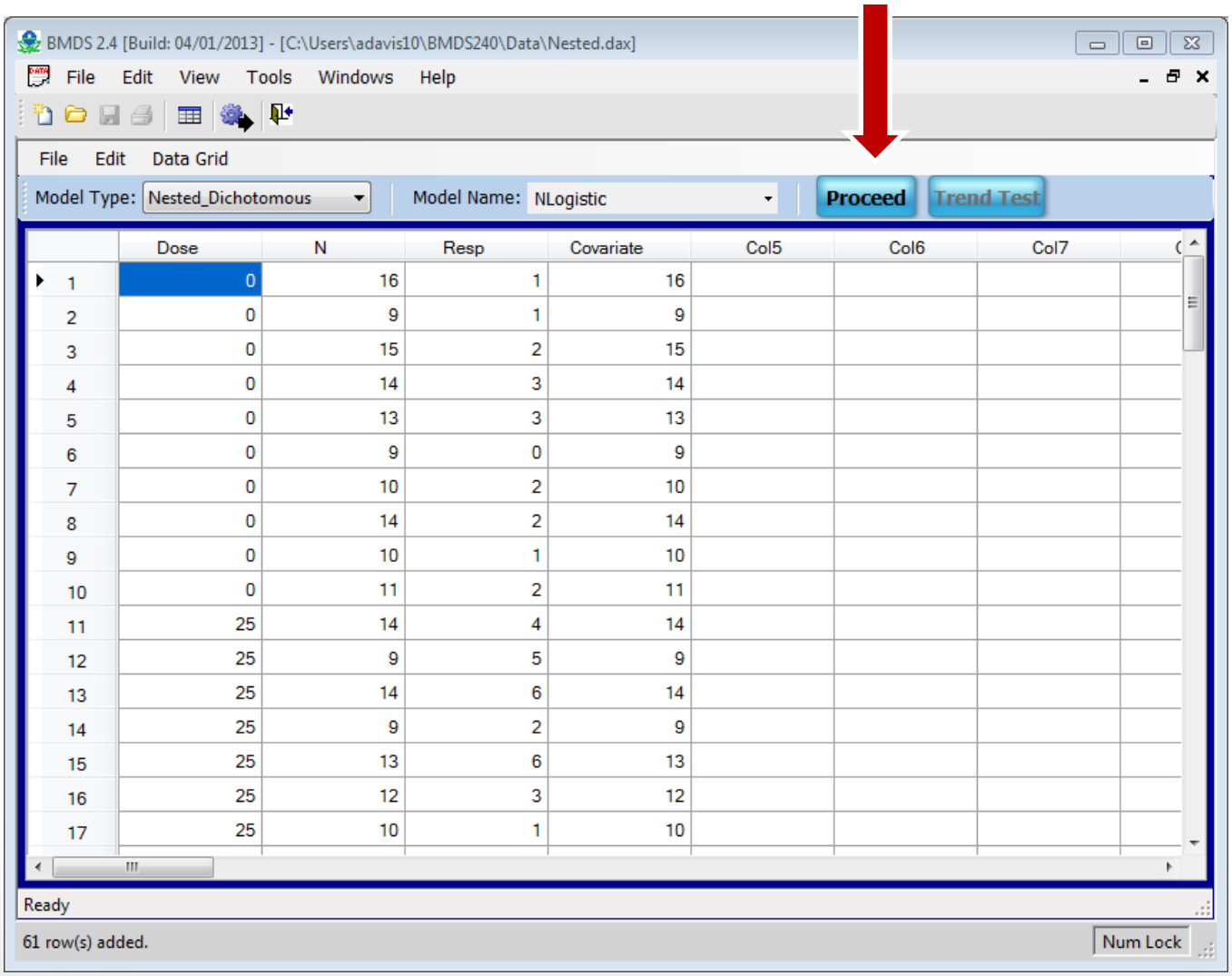
Running an Individual Model – Select a Model Type



Running an Individual Model – Select a Model

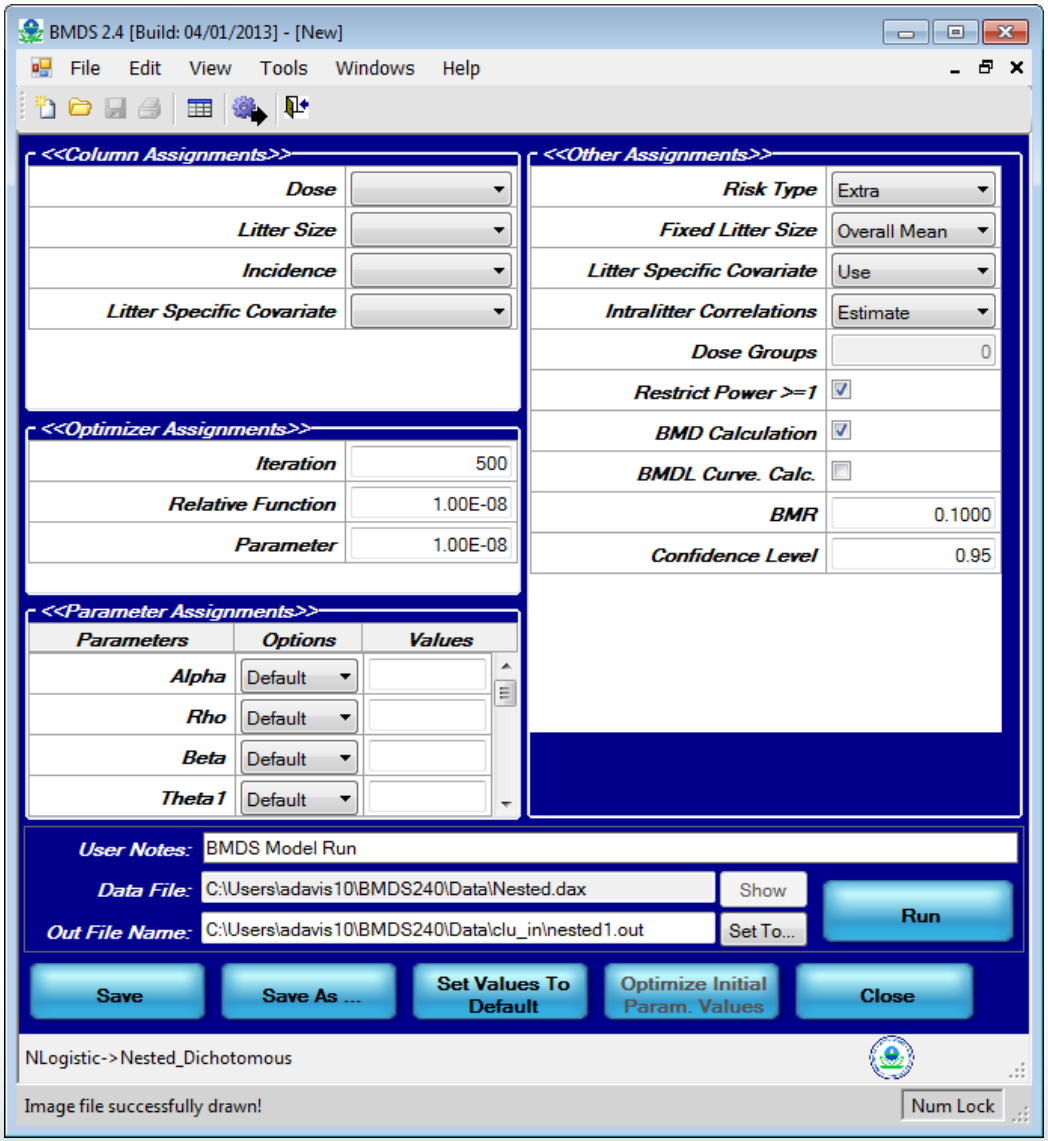


Running an Individual Model – Proceed to Option Screen

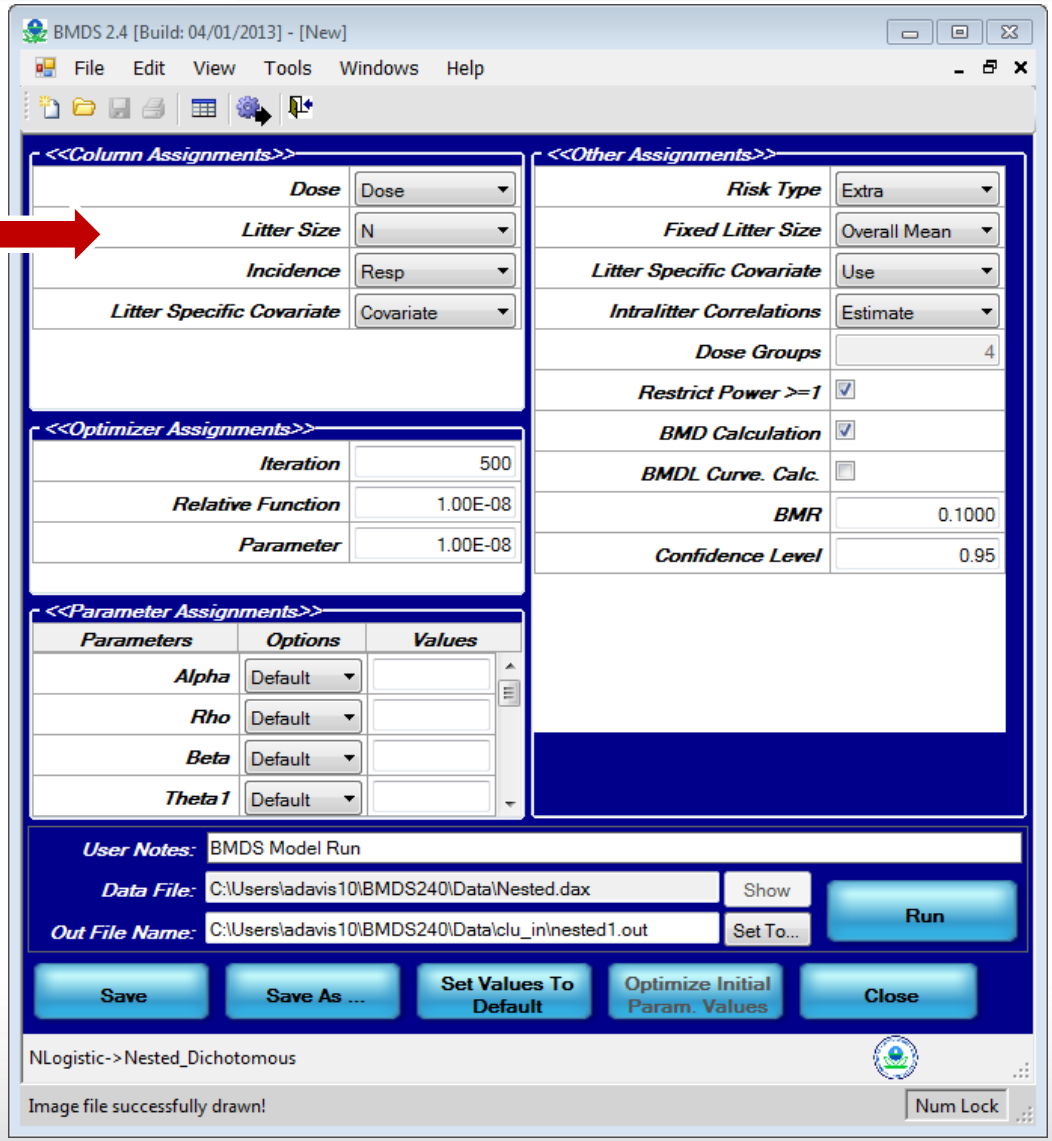


	Dose	N	Resp	Covariate	Col5	Col6	Col7
1	0	16	1	16			
2	0	9	1	9			
3	0	15	2	15			
4	0	14	3	14			
5	0	13	3	13			
6	0	9	0	9			
7	0	10	2	10			
8	0	14	2	14			
9	0	10	1	10			
10	0	11	2	11			
11	25	14	4	14			
12	25	9	5	9			
13	25	14	6	14			
14	25	9	2	9			
15	25	13	6	13			
16	25	12	3	12			
17	25	10	1	10			

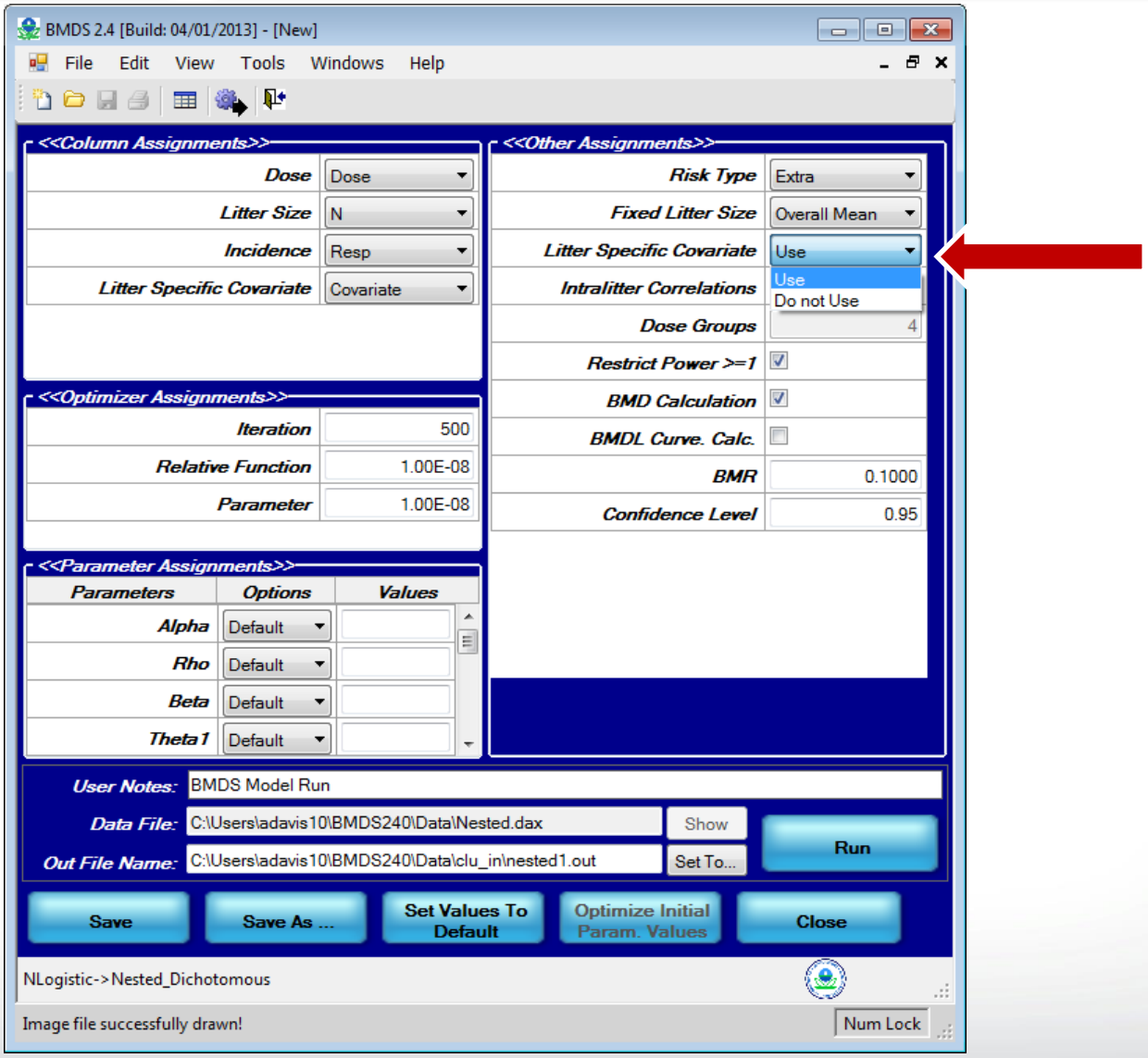
Model Option Screen



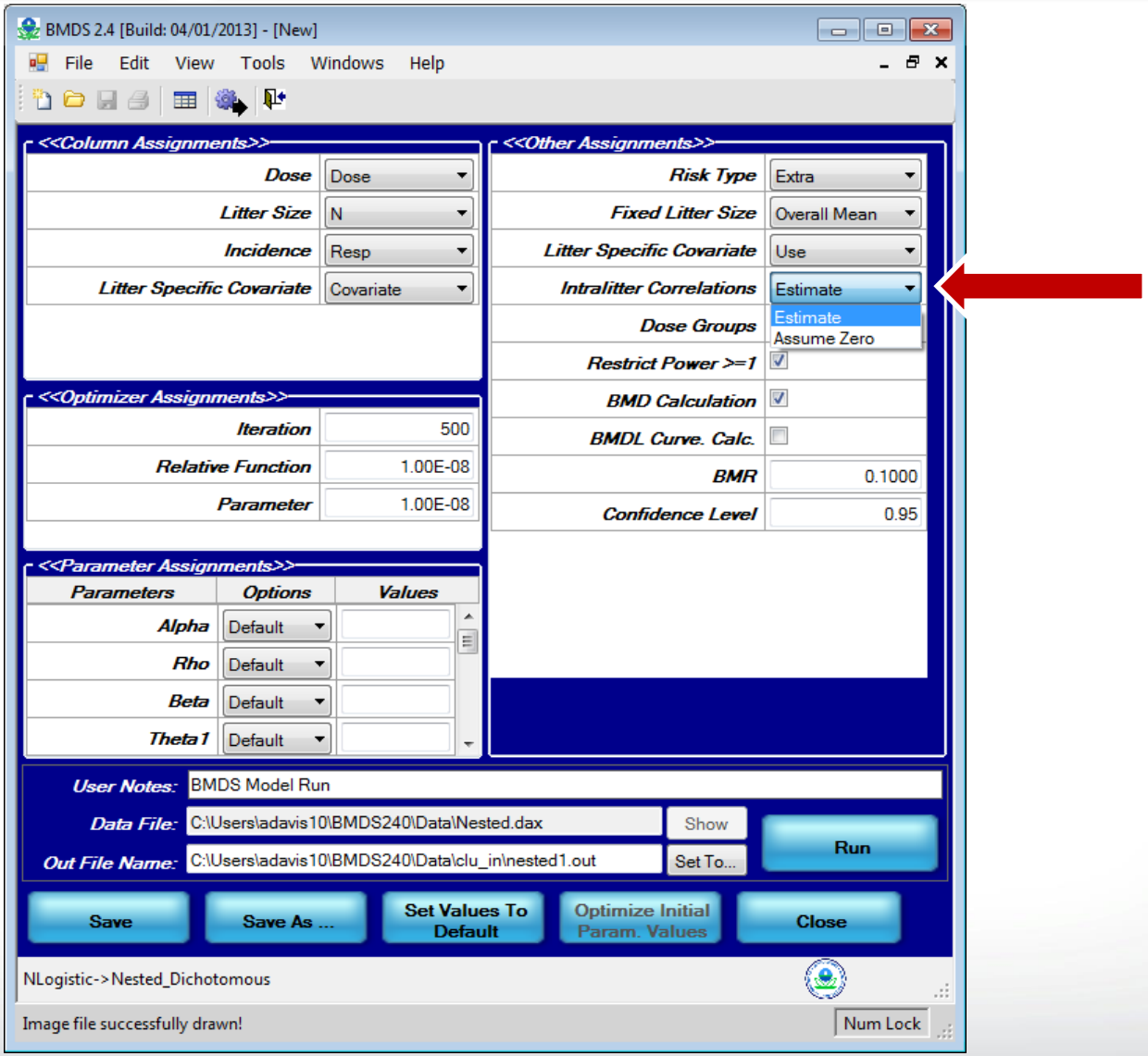
Selecting Column Assignments



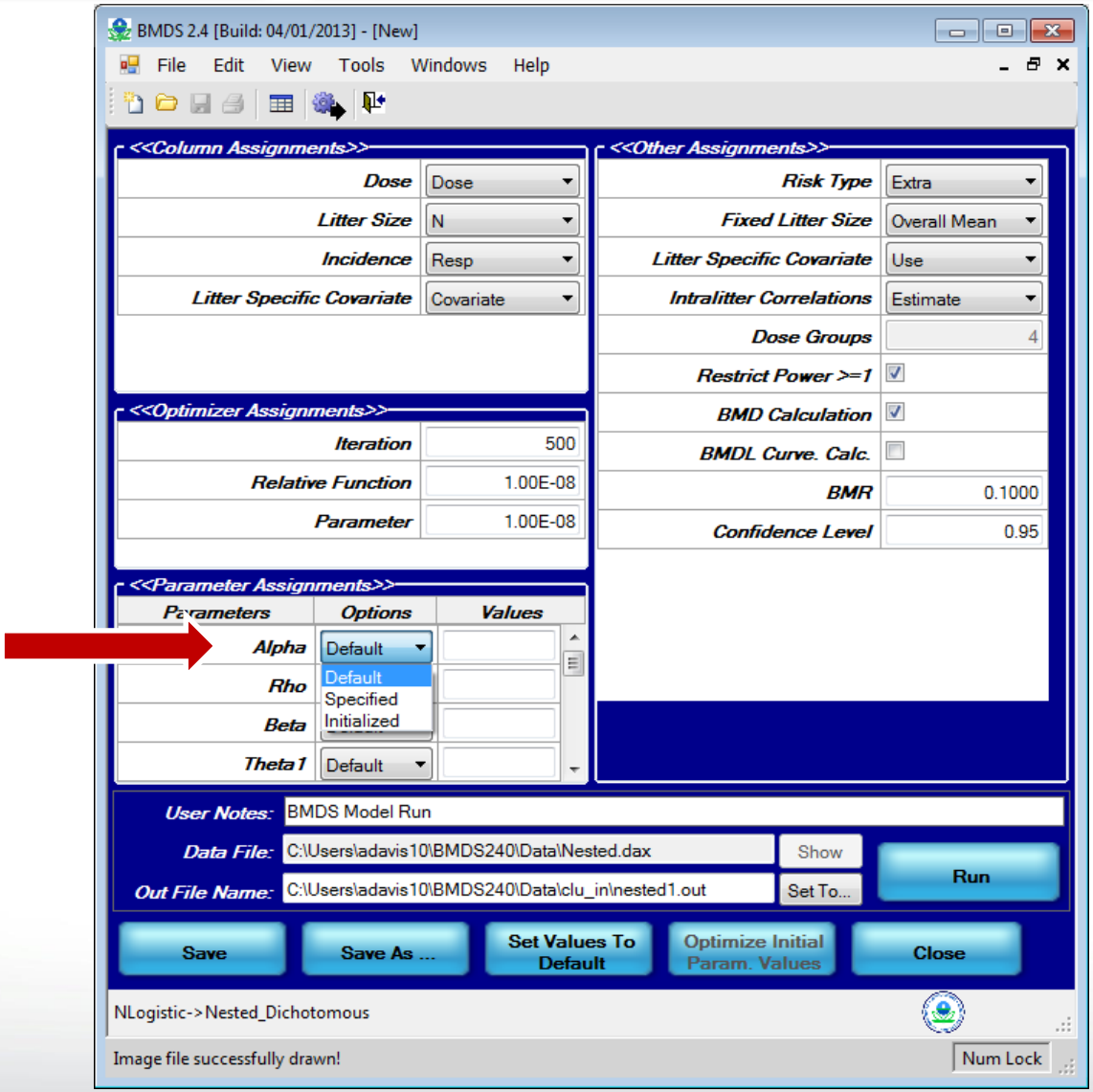
Selecting Model Options – Litter Specific Covariate



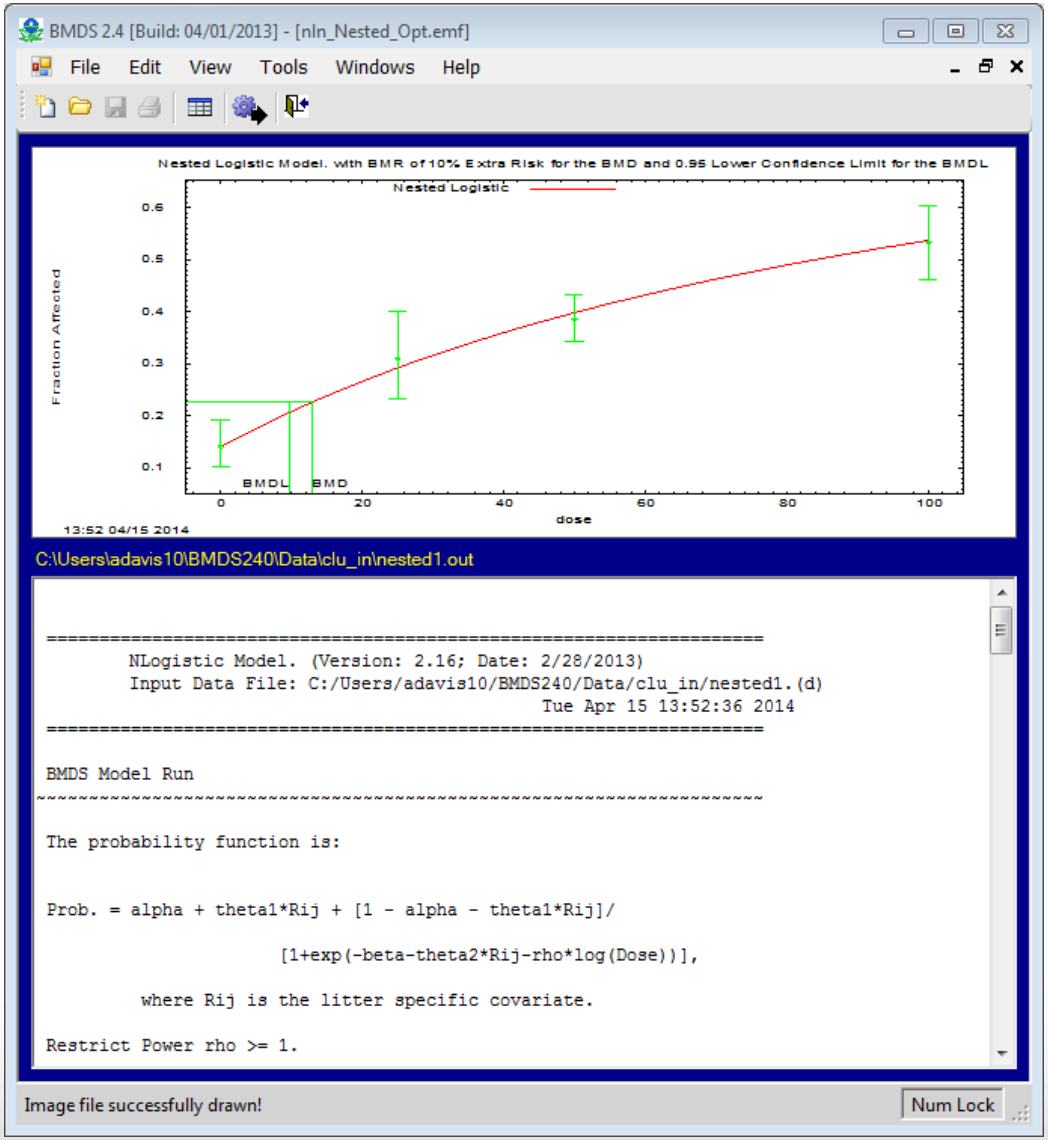
Selecting Model Options – Intra-litter Correlation



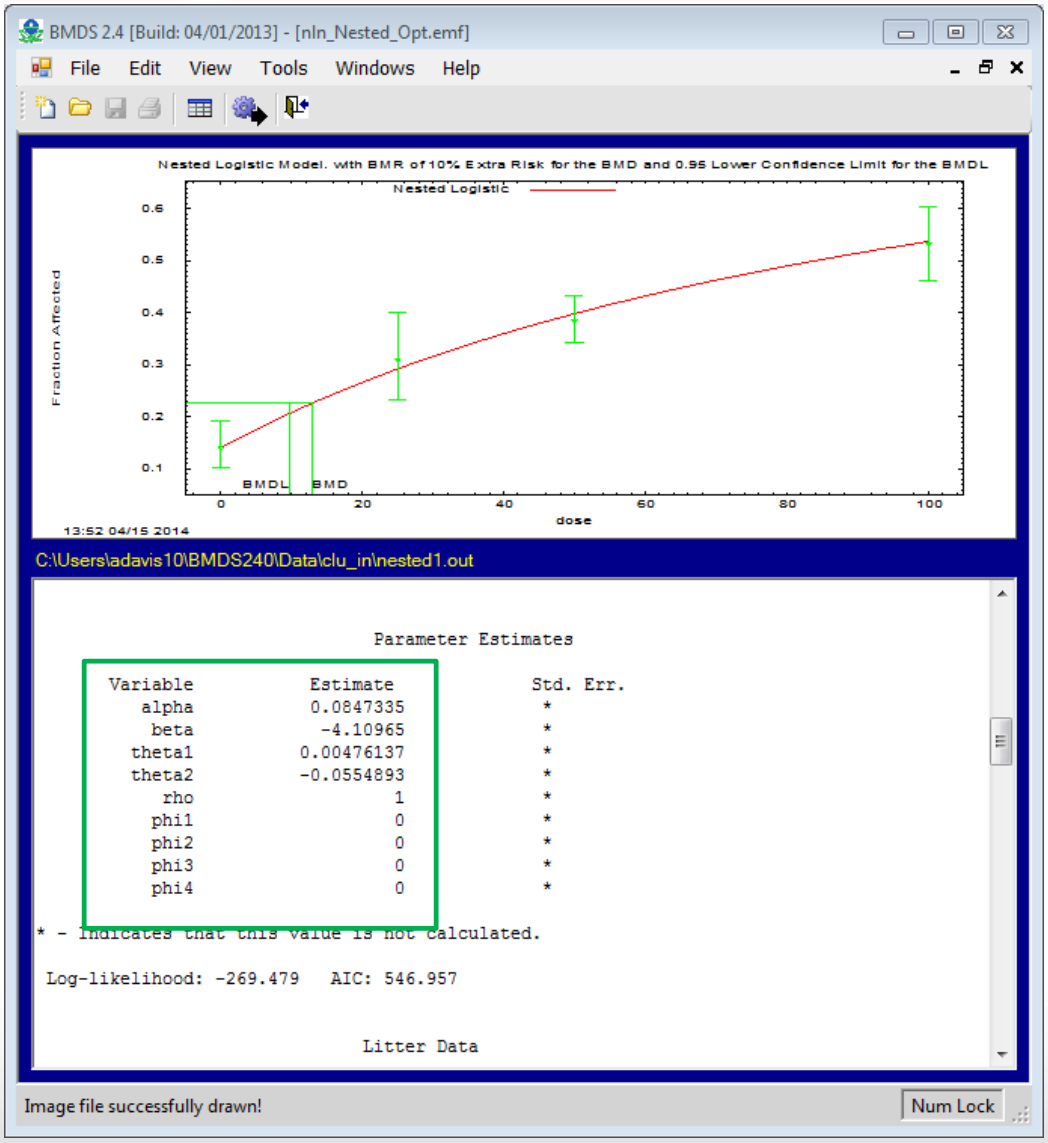
Specifying Model Parameters



Nested Dichotomous Plot and Output Files



Nested Dichotomous Model Parameter Estimates



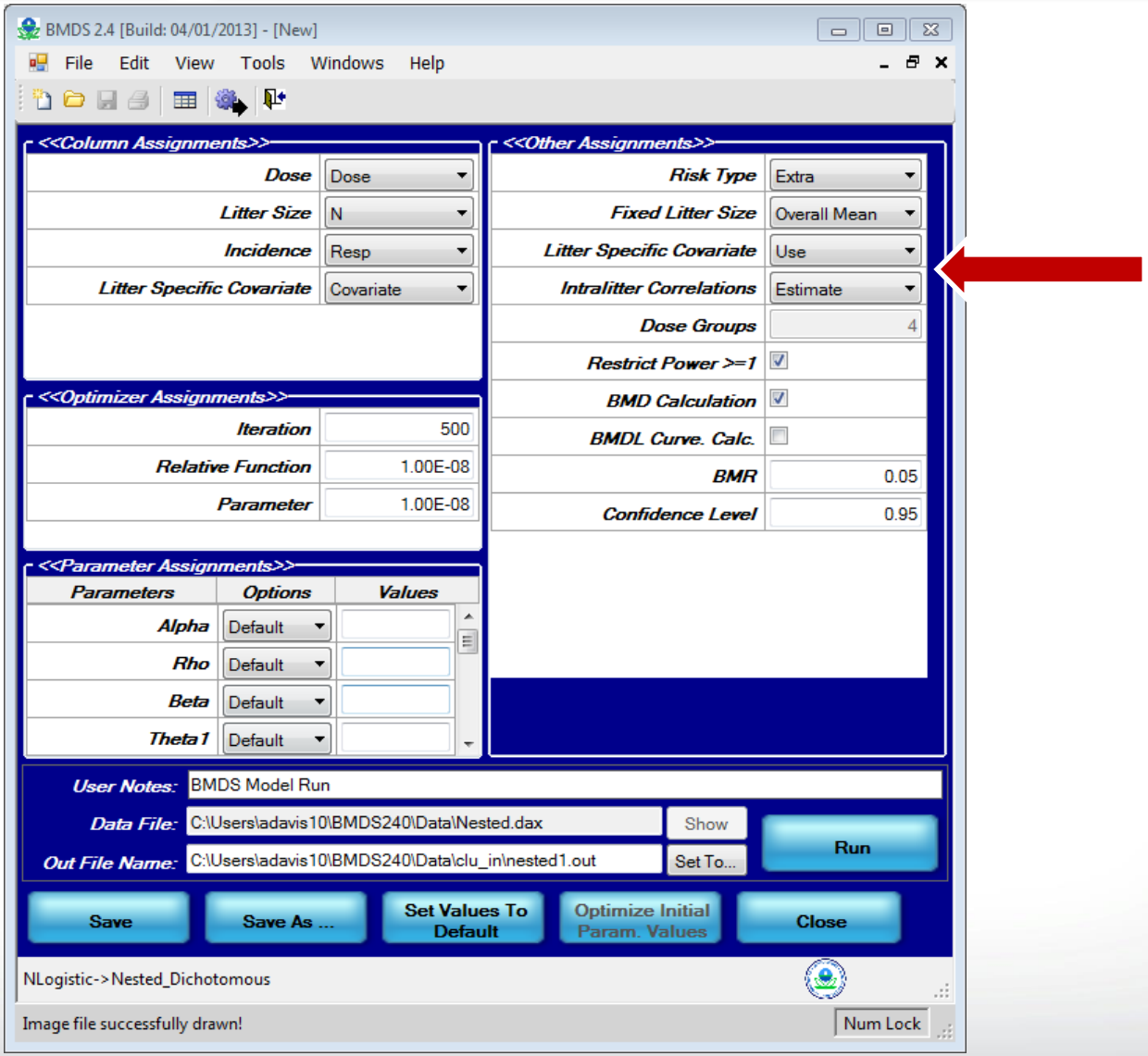
Opening Output and Plot Files after Analysis

Nested Dichotomous Data – Exercise

Nested Dichotomous Exercise

- **Open the provided dataset titled "Nested_Exercise.dax"**
- **Run the Nested Logistic model against the data with the following parameterizations**
  - Litter Specific Covariate – Use (select "Covariate" for the Litter Specific Covariate)
  - Intra-litter Correlation – Estimate
  - BMR = 5% Extra risk
- **Record the following data:**
  - BMD and BMDL
  - p-value, AIC, and Scaled Residual of Interest (1. find "mean litter specific covariate"; 2. look at grouped data and dose group closest to BMD; 3. find individual rows for which reported mean litter specific covariate is closes to the value for all data; 4. average multiple values if necessary)
  - Parameter estimates for θ and Φ coefficients

Nested Dichotomous Exercise



Nested Dichotomous Exercise

	Litter Specific Covariate; Intralitter Correlation	No Litter Specific Covariate; Intralitter Correlation	Litter Specific Covariate; No Intralitter Correlation	No Litter Specific Covariate; No Intralitter Correlation
BMD_{05}	505			
$BMDL_{05}$	174.24			
AIC	1049.33			
p-value	0.2752			
Grouped Scaled residual (max value)	1.3312			
θ_1 estimate	0.0331164			
θ_2 estimate	-0.410957			
Φ_1 estimate	0.200123			
Φ_2 estimate	0.313042			
Φ_3 estimate	0.213544			
Φ_4 estimate	0.370267			

Nested Dichotomous Exercise

- **Open the provided dataset titled "Nested_Exercise.dax"**
- **Run the Nested Logistic model against the data with the following parameterizations**
  - Litter Specific Covariate – Do Not Use
  - Intra-litter Correlation – Estimate
  - BMR = 5% Extra risk
- **Record the following data:**
  - BMD and BMDL
  - p-value, AIC, and Scaled Residual of Interest (1. find "mean litter specific covariate"; 2. look at grouped data and dose group closest to BMD; 3. find individual rows for which reported mean litter specific covariate is closes to the value for all data; 4. average multiple values if necessary)
  - Parameter estimates for θ and Φ coefficients

Nested Dichotomous Exercise

	Litter Specific Covariate; Intralitter Correlation	No Litter Specific Covariate; Intralitter Correlation	Litter Specific Covariate; No Intralitter Correlation	No Litter Specific Covariate; No Intralitter Correlation
BMD_{05}	505	658.131		
$BMDL_{05}$	174.24	216.749		
AIC	1049.33	1053.46		
p-value	0.2752	0.1601		
Grouped Scaled residual	1.3312	1.3538		
θ_1 estimate	0.0331164	--		
θ_2 estimate	-0.410957	--		
Φ_1 estimate	0.200123	0.212445		
Φ_2 estimate	0.313042	0.312581		
Φ_3 estimate	0.213544	0.219964		
Φ_4 estimate	0.370267	0.371497		

Nested Dichotomous Exercise

- **Open the provided dataset titled "Nested_Exercise.dax"**
- **Run the Nested Logistic model against the data with the following parameterizations**
  - Litter Specific Covariate – Use (select "Covariate" for the Litter Specific Covariate)
  - Intra-litter Correlation – Assume Zero
  - BMR = 5% Extra risk
- **Record the following data:**
  - BMD and BMDL
  - p-value, AIC, and Scaled Residual of Interest (1. find "mean litter specific covariate"; 2. look at grouped data and dose group closest to BMD; 3. find individual rows for which reported mean litter specific covariate is closes to the value for all data; 4. average multiple values if necessary)
  - Parameter estimates for θ and Φ coefficients

Nested Dichotomous Exercise

	Litter Specific Covariate; Intralitter Correlation	No Litter Specific Covariate; Intralitter Correlation	Litter Specific Covariate; No Intralitter Correlation	No Litter Specific Covariate; No Intralitter Correlation
BMD_{05}	505	658.131	526.799	
$BMDL_{05}$	174.24	216.749	266.212	
AIC	1049.33	1053.46	1133.43	
p-value	0.2752	0.1601	0.00	
Grouped Scaled residual	1.3312	1.3538	2.0286	
θ_1 estimate	0.0331164	--	0.0340365	
θ_2 estimate	-0.410957	--	-0.431175	
Φ_1 estimate	0.200123	0.212445	--	
Φ_2 estimate	0.313042	0.312581	--	
Φ_3 estimate	0.213544	0.219964	--	
Φ_4 estimate	0.370267	0.371497	--	

Nested Dichotomous Exercise

- **Open the provided dataset titled "Nested_Exercise.dax"**
- **Run the Nested Logistic model against the data with the following parameterizations**
  - Litter Specific Covariate – Do Not Use
  - Intra-litter Correlation – Assume Zero
  - BMR = 5% Extra risk
- **Record the following data:**
  - BMD and BMDL
  - p-value, AIC, and Scaled Residual of Interest (1. find "mean litter specific covariate"; 2. look at grouped data and dose group closest to BMD; 3. find individual rows for which reported mean litter specific covariate is closes to the value for all data; 4. average multiple values if necessary)
  - Parameter estimates for θ and Φ coefficients

Nested Dichotomous Exercise

	Litter Specific Covariate; Intralitter Correlation	No Litter Specific Covariate; Intralitter Correlation	Litter Specific Covariate; No Intralitter Correlation	No Litter Specific Covariate; No Intralitter Correlation
BMD_{05}	505	658.131	526.799	728.281
$BMDL_{05}$	174.24	216.749	266.212	392.351
AIC	1049.33	1053.46	1133.43	1144.08
p-value	0.2752	0.1601	0.00	0.00
Grouped Scaled residual	1.3312	1.3538	2.0286	2.0499
θ_1 estimate	0.0331164	--	0.0340365	--
θ_2 estimate	-0.410957	--	-0.431175	--
Φ_1 estimate	0.200123	0.212445	--	--
Φ_2 estimate	0.313042	0.312581	--	--
Φ_3 estimate	0.213544	0.219964	--	--
Φ_4 estimate	0.370267	0.371497	--	--

Nested Dichotomous Exercise

	Litter Specific Covariate; Intralitter Correlation	No Litter Specific Covariate; Intralitter Correlation	Litter Specific Covariate; No Intralitter Correlation	No Litter Specific Covariate; No Intralitter Correlation
BMD_{05}	505	658.131	526.799	728.281
$BMDL_{05}$	174.24	216.749	266.212	392.351
AIC	1049.33	1053.46	1133.43	1144.08
p-value	0.2752	0.1601	0.00	0.00
Grouped Scaled residual	-0.7259	-0.7061	-1.06127	-1.04193
θ_1 estimate	0.0331164	--	0.0340365	--
θ_2 estimate	-0.410957	--	-0.431175	--
Φ_1 estimate	0.200123	0.212445	--	--
Φ_2 estimate	0.313042	0.312581	--	--
Φ_3 estimate	0.213544	0.219964	--	--
Φ_4 estimate	0.370267	0.371497	--	--

References

- Faustman, EM; Allen, BC; Kavlock, RJ; Kimmel, CA. (1994) Dose-response assessment for developmental toxicity: I. Characterization of data base and determination of NOAELs. Fundam Appl Toxicol 23:478-486.

- Allen, BC; Kavlock, RJ; Kimmel, CA; Faustman, EM. (1994a) Dose-response assessment for developmental toxicity: II. Comparison of generic benchmark dose estimates with NOAELs. Fundam Appl Toxicol 23:487-495.

- Allen, BC; Kavlock, RJ; Kimmel, CA; Faustman, EM. (1994b) Dose-response assessment for development toxicity: III. Statistical models. Fundam Appl Toxicol 23:496-509.