Benchmark Dose Modeling – Dichotomous Models

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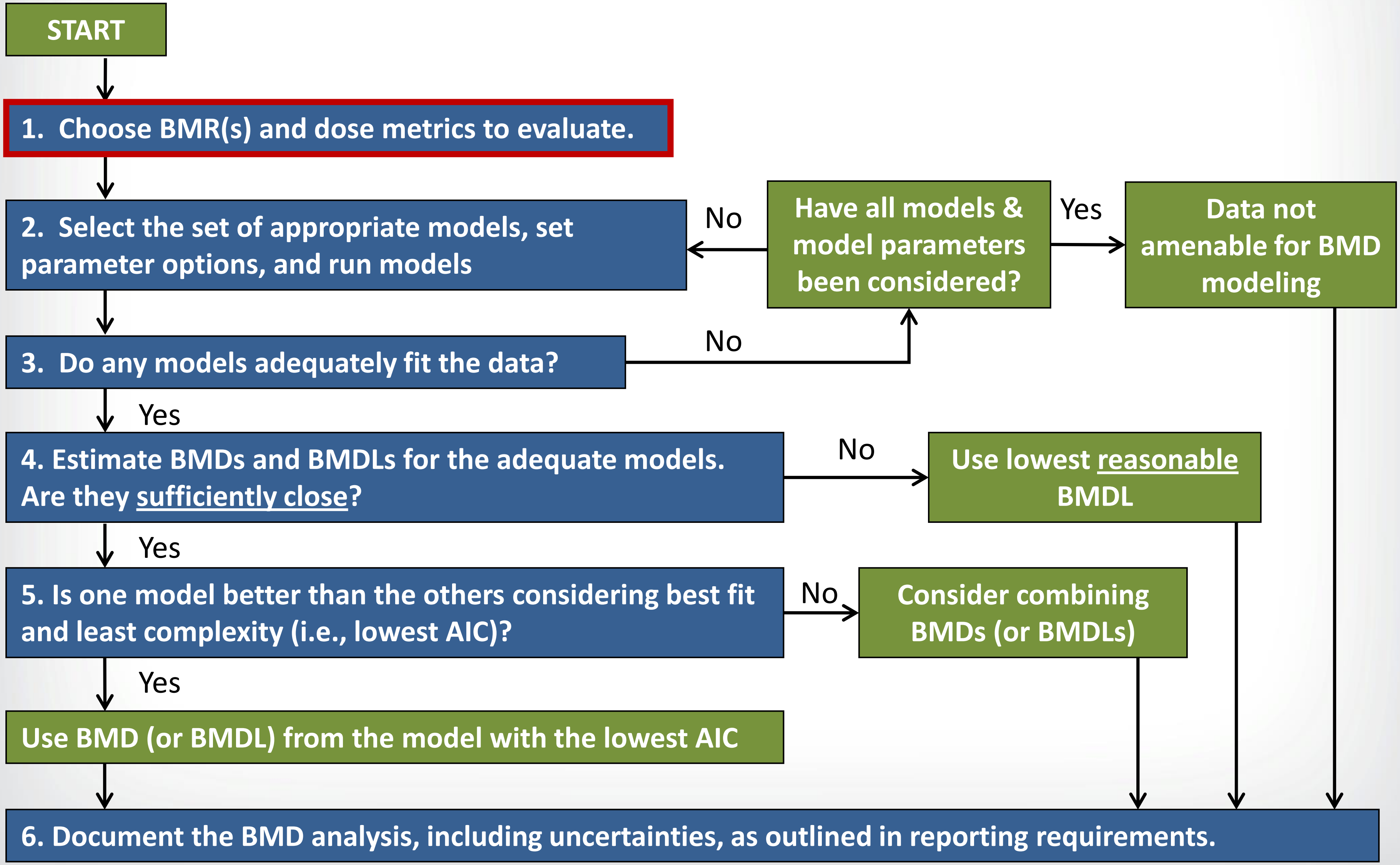
Dichotomous Data

Description	• Response is measured as on/off or true/false • You either have it or you don't • BMDS can only model positive dose-response trends, where incidence increases with dose
Example Endpoints	• Non-cancer: Precancerous lesions, tissue pathology incidence • Cancer: Tumor incidence
Model Inputs	• Dose • Number of Subjects • Incidence **OR** Percent Affected

BMD Analysis – Six Steps



START

1. Choose BMR(s) and dose metrics to evaluate.

2. Select the set of appropriate models, set parameter options, and run models

3. Do any models adequately fit the data?

No

Have all models & model parameters been considered?

No

Yes

Data not amenable for BMD modeling

Yes

4. Estimate BMDs and BMDLs for the adequate models. Are they sufficiently close?

No

Use lowest reasonable BMDL

Yes

5. Is one model better than the others considering best fit and least complexity (i.e., lowest AIC)?

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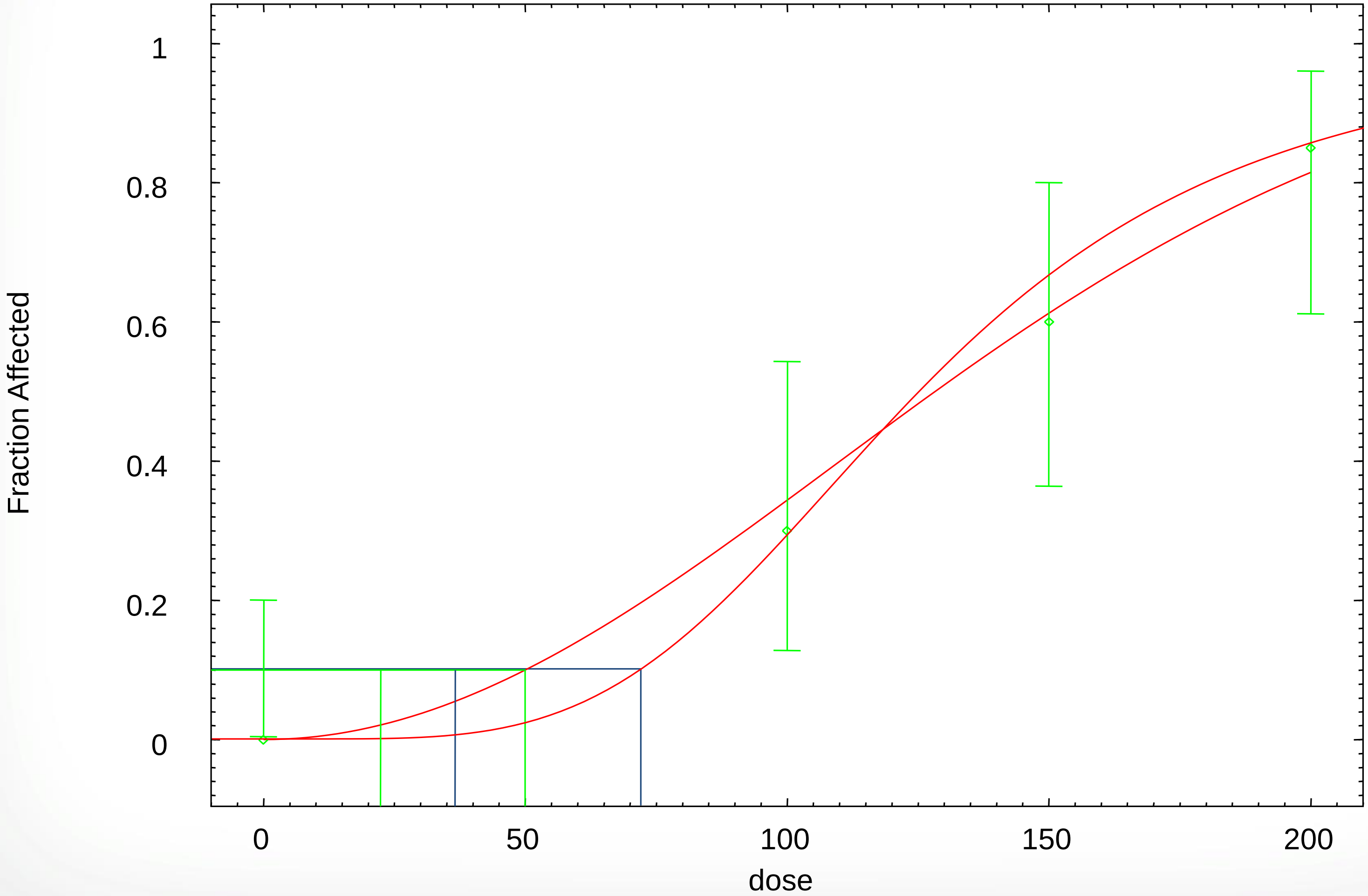
Select a Benchmark Response

- **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.**

Model-dependence of BMD in Low Dose Region (Step 1)



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BMR Selection: Choose BMR(s) to Evaluate

- **An extra risk of 10% is recommended as a standard (not default) reporting level for dichotomous data.**
  - Customarily used because it is at or near the limit of sensitivity in most cancer bioassays and in non-cancer bioassays of comparable size

- **In some situations, use of different BMRs is supported**
  - Biological considerations sometimes support different BMRs (5% for frank effects, >10% for precursor effects)
  - When a study has greater than usual sensitivity, a lower BMR can be used (5% for developmental studies)
  - Results for a 10% BMR should always be shown for comparison when using different BMRs.

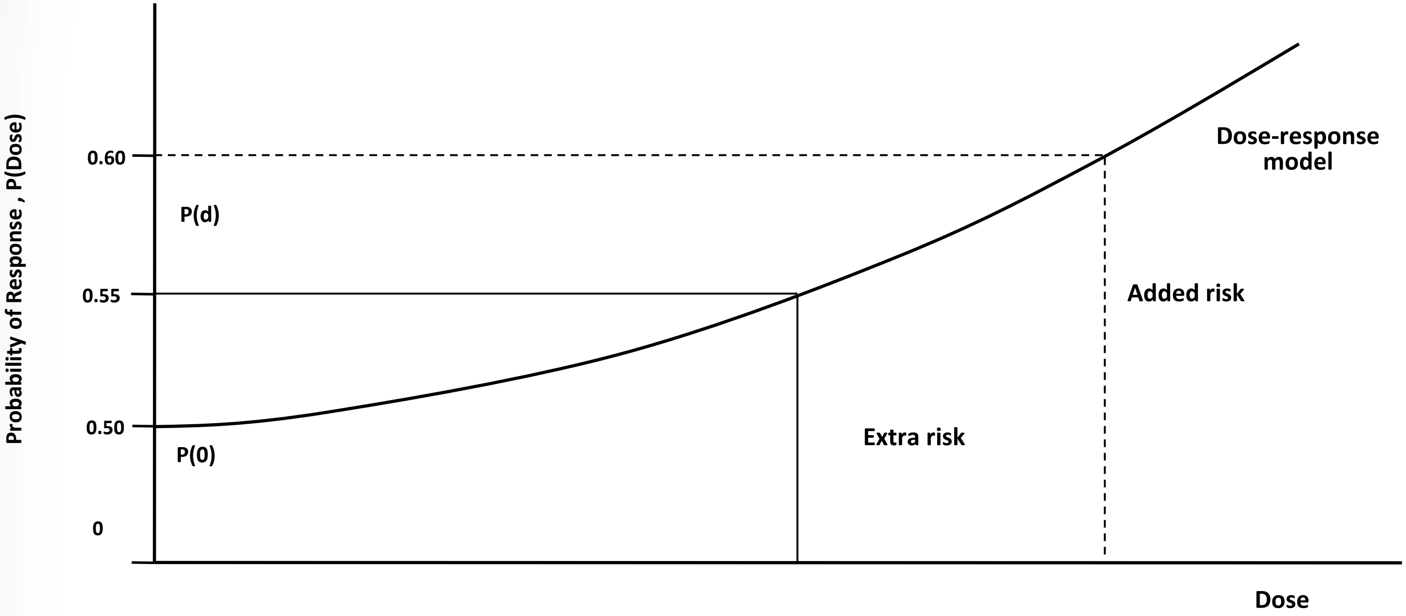
Measurement of Increased Risk

- **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 $P(0) = .50$

$P(d) = 0.10 + P(0) = 0.10 + 0.50 = \mathbf{0.60}$

10% Extra Risk

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

$P(d) = 0.10 \times [1 - P(0)] + P(0) = (0.10 \times 0.50) + 0.50 = \mathbf{0.55}$

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

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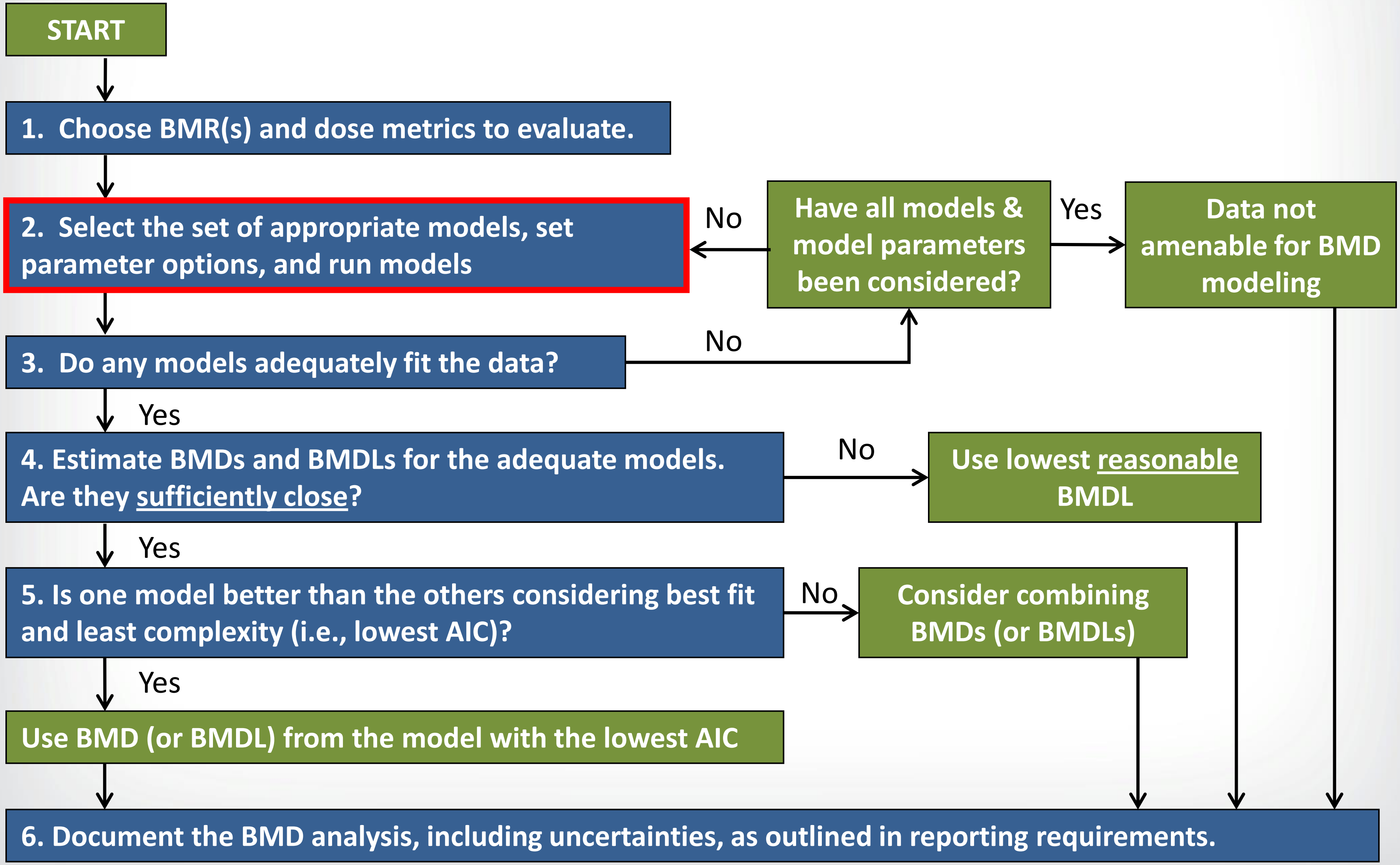

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Selection of a Specific Model

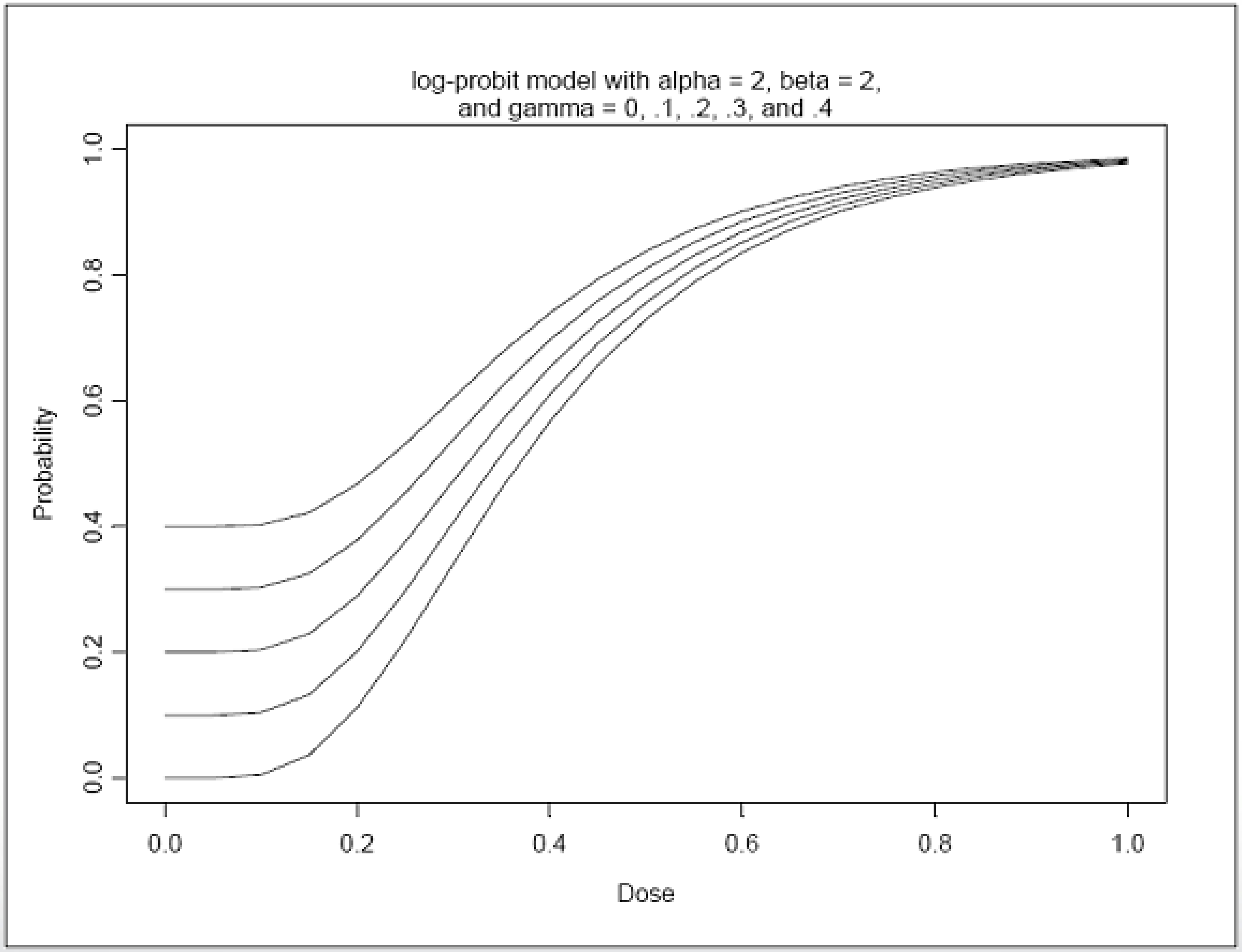
Biological Interpretation	Examples: • Saturable processes demonstrating Michaelis-Menten kinetics (Hill model) • Two-stage clonal expansion model (cancer endpoints)
Policy Decision	U.S. EPA's IRIS program uses the multistage model for cancer data • sufficiently flexible to fit most cancer bioassay data • provides consistency across cancer assessments
Otherwise	However, in the absence of biological or policy-driven considerations, criteria for final model selection are usually based on whether various models mathematically describe the data

Traditional Dichotomous Models

Model name	Functional form	# of Parameters[a]	Low Dose Linearity	Model fits
Multistage	$\gamma + (1-\gamma)\left[1-\exp\left\{-\sum_{j=1}^{k}\beta_j X^j\right\}\right]$	1+k	Yes, if $\beta_1 > 0$ No, if $\beta_1 = 0$	All purpose
Logistic	$\frac{1}{1+\exp\{-(\alpha+\beta X)\}}$	2	Yes	Simple; no background
Probit	$\Phi\,(\alpha+\beta X)$	2	Yes	Simple; no background
Log-logistic	$\frac{\gamma+(1-\gamma)}{1+\exp\{-[\alpha+\beta\ln(X)]\}}$	3	No	All purpose; S-shape with plateau at 100%
Log-probit	$\gamma+(1-\gamma)\ \Phi\{\alpha+\beta\ln(X)\}$	3	No	All purpose; plateau S-shape with plateau at 100%
Gamma	$\gamma+(1-\gamma)\left[\left[\int_0^{\beta x} t^{\alpha-1}e^{t}dt\right]/\,\Gamma(\alpha)\right.$	3	No	All purpose
Weibull	$\gamma+(1-\gamma)[1-\exp\{-\beta X^{\alpha}\}]$	3	No	"Hockey stick" shape
Dichotomous Hill	$v\times g+\frac{(v-v\times g)}{1+\exp\{-a-b\ \times\ln(X)\}}$	4	Yes	Symmetrical, S-shape with plateau

[a] Background parameter = γ. Background for hill model = $v \times g$

Curve Shapes with Increasing Background Response



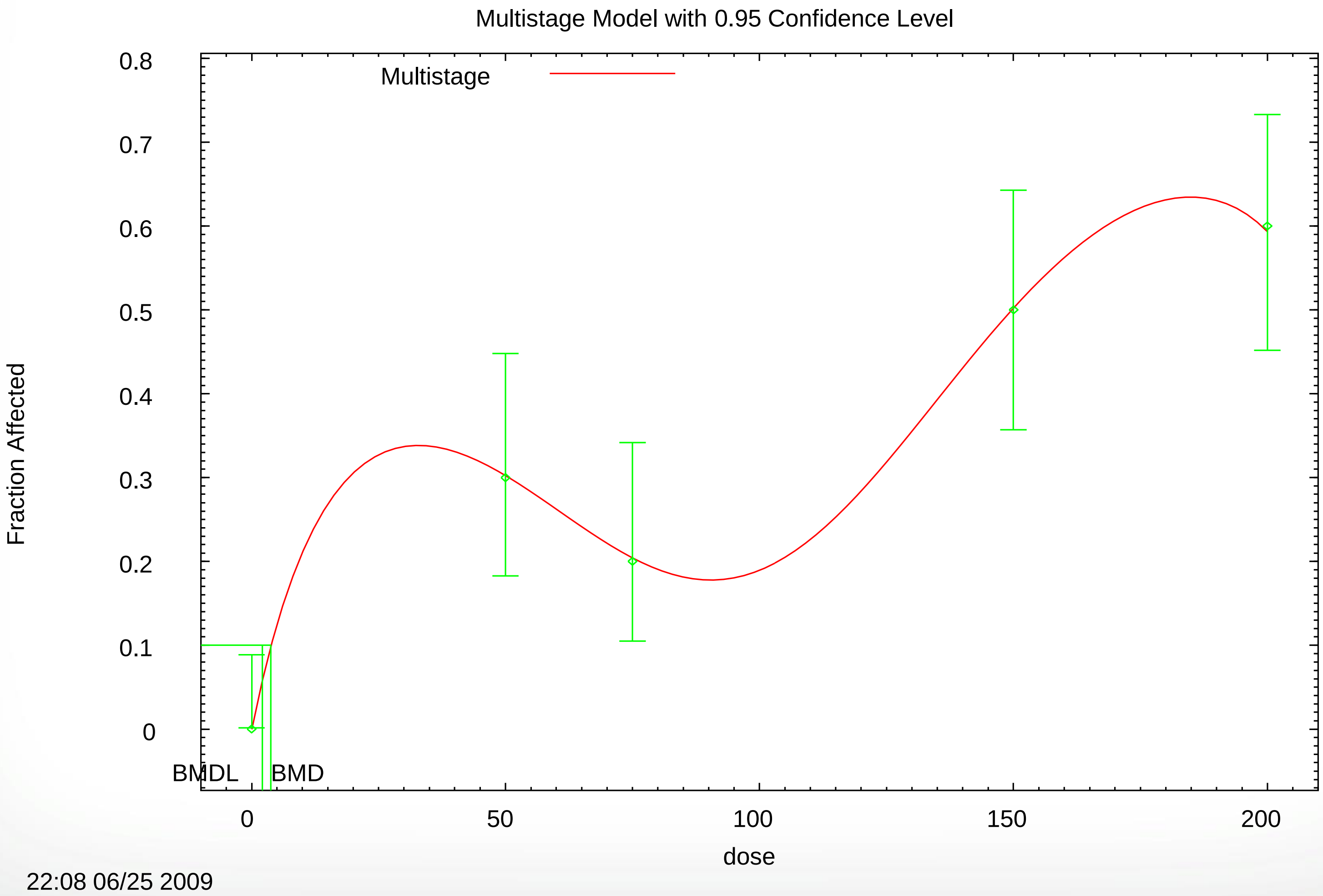
Restricting Parameters in Dichotomous Models

- **Dichotomous models are conceptually restricted so that probabilities are positive numbers no greater than one**

- **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 for *p*-value calculation)
    - 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)

Multistage Model – Betas not Restricted



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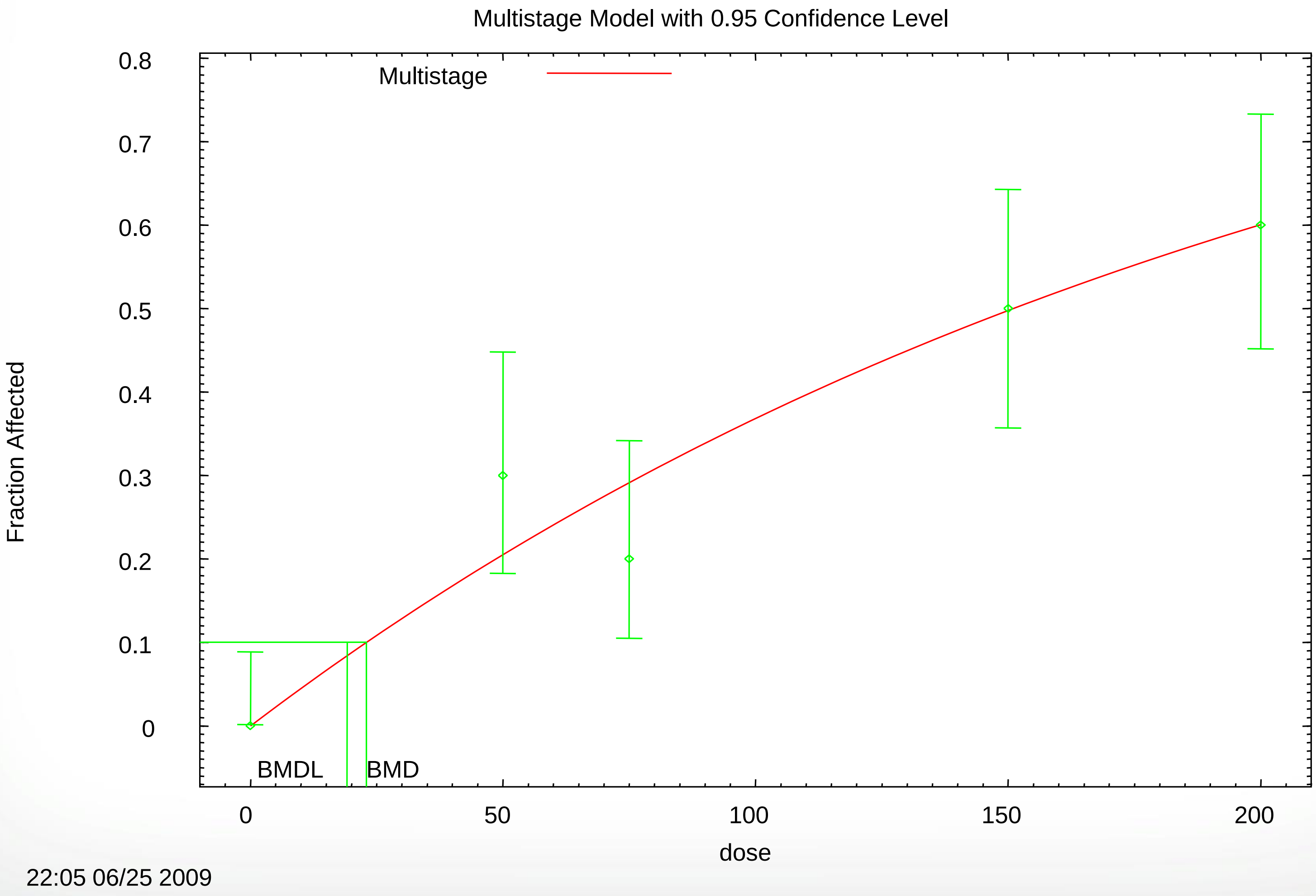
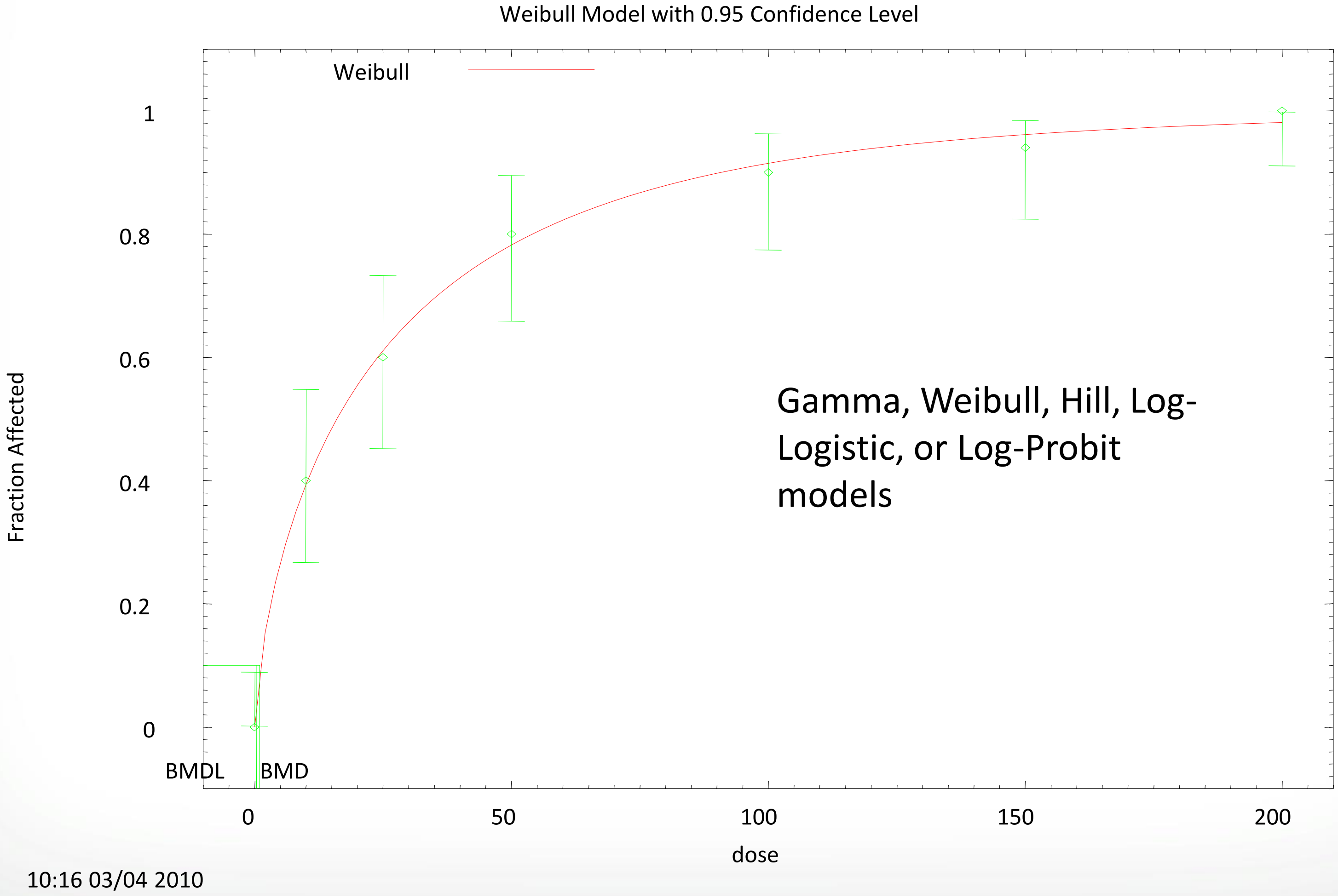


Models with Unrestricted Power or Slope Parameters



Gamma, Weibull, Hill, Log-Logistic, or Log-Probit models

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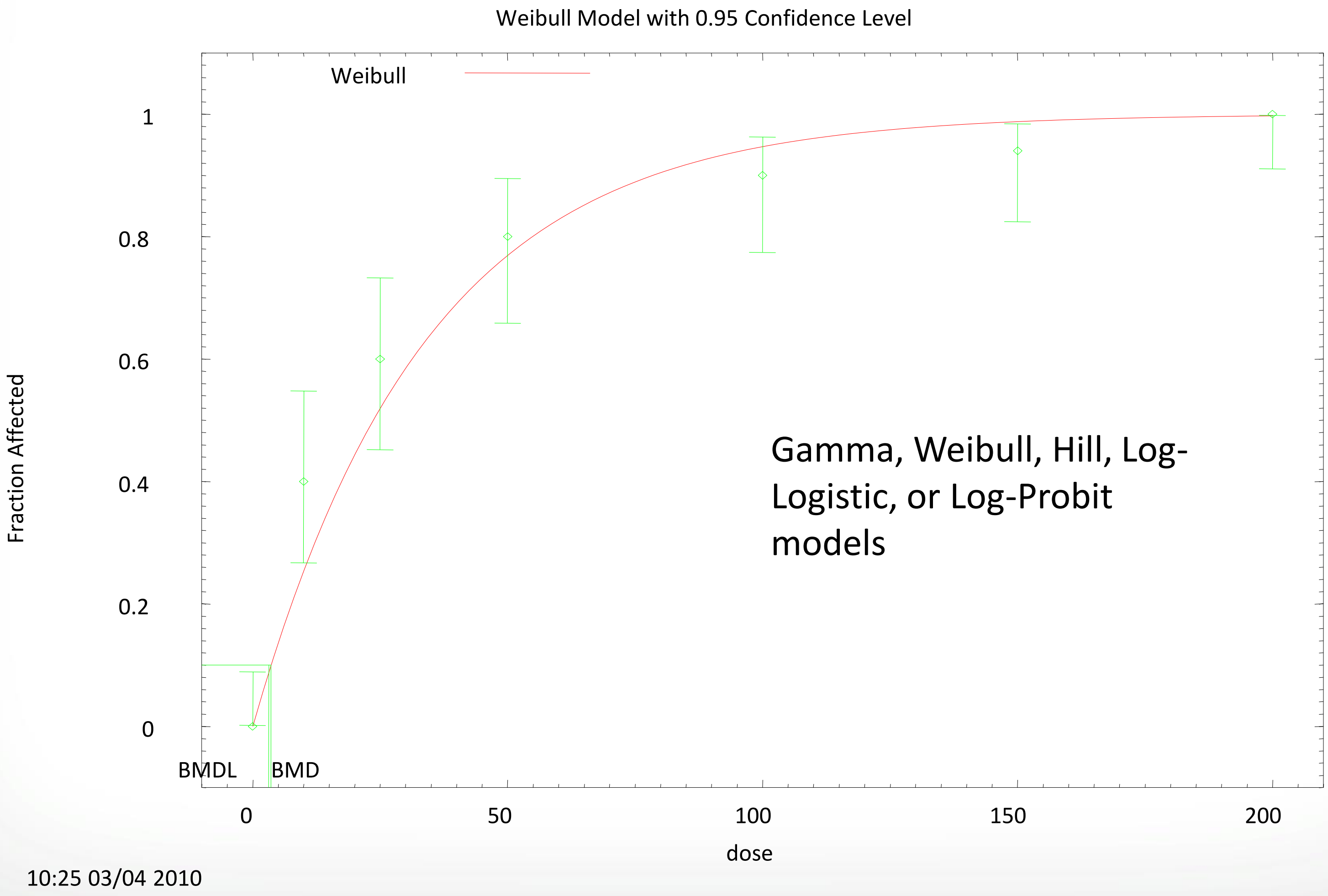

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Restricting Dichotomous Models – EPA Recommendations

- **User-specified Parameter Restrictions**
  - **Multistage beta coefficients** – restrict to be positive
  - **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 only available in nested dichotomous and C× T models in BMDS; other software packages (i.e., PROAST) can consider covariates for all data types

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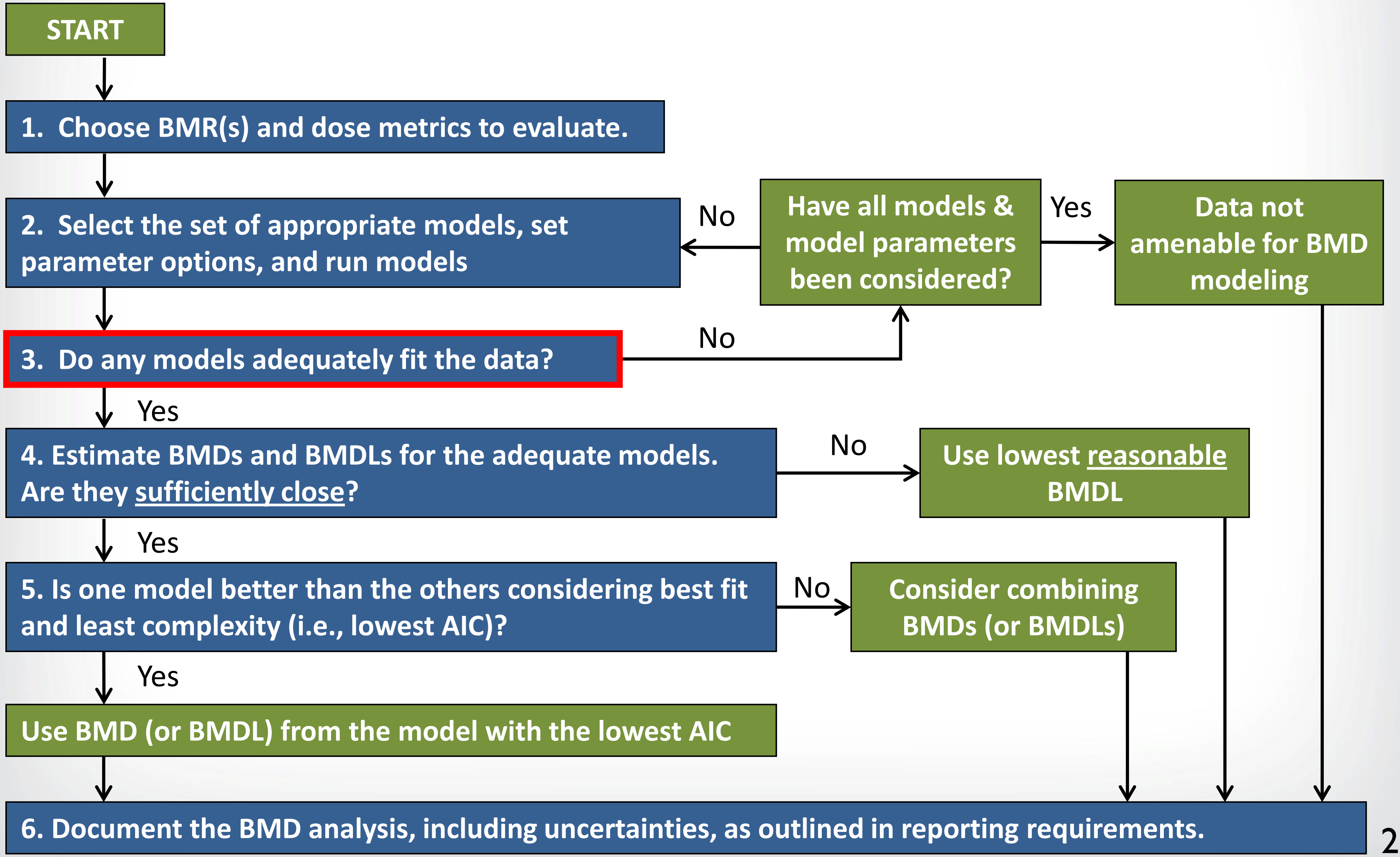

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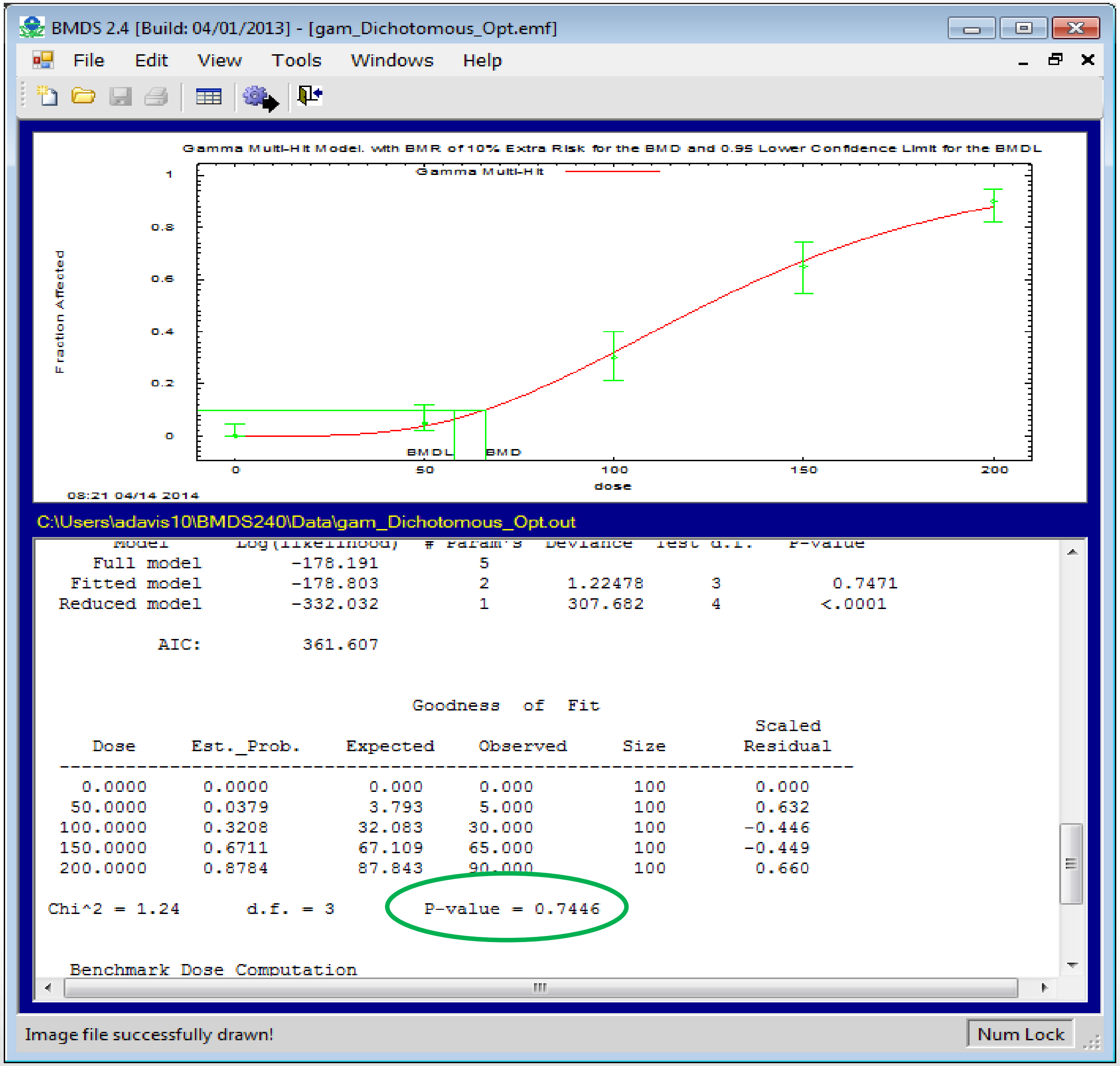
Does the Model Fit the Data?

- **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

- **BMDS provides a *p*-value to measure global goodness-of-fit**
  - Measures how model-predicted dose-group probability of responses differ from the actual responses
  - 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., multistage model for cancer endpoints), a cut-off value of $p = 0.05$ can be used

Global Goodness-of-Fit



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```
     Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
    Full model        -178.191         5
  Fitted model        -178.803         2       1.22478      3          0.7471
 Reduced model        -332.032         1       307.682      4         <.0001

          AIC:         361.607


                                  Goodness  of  Fit
                                                                 Scaled
    Dose       Est._Prob.     Expected    Observed     Size     Residual
  ------------------------------------------------------------------------
   0.0000       0.0000          0.000       0.000       100       0.000
  50.0000       0.0379          3.793       5.000       100       0.632
 100.0000       0.3208         32.083      30.000       100      -0.446
 150.0000       0.6711         67.109      65.000       100      -0.449
 200.0000       0.8784         87.843      90.000       100       0.660

 Chi^2 = 1.24      d.f. = 3        P-value = 0.7446


   Benchmark Dose Computation
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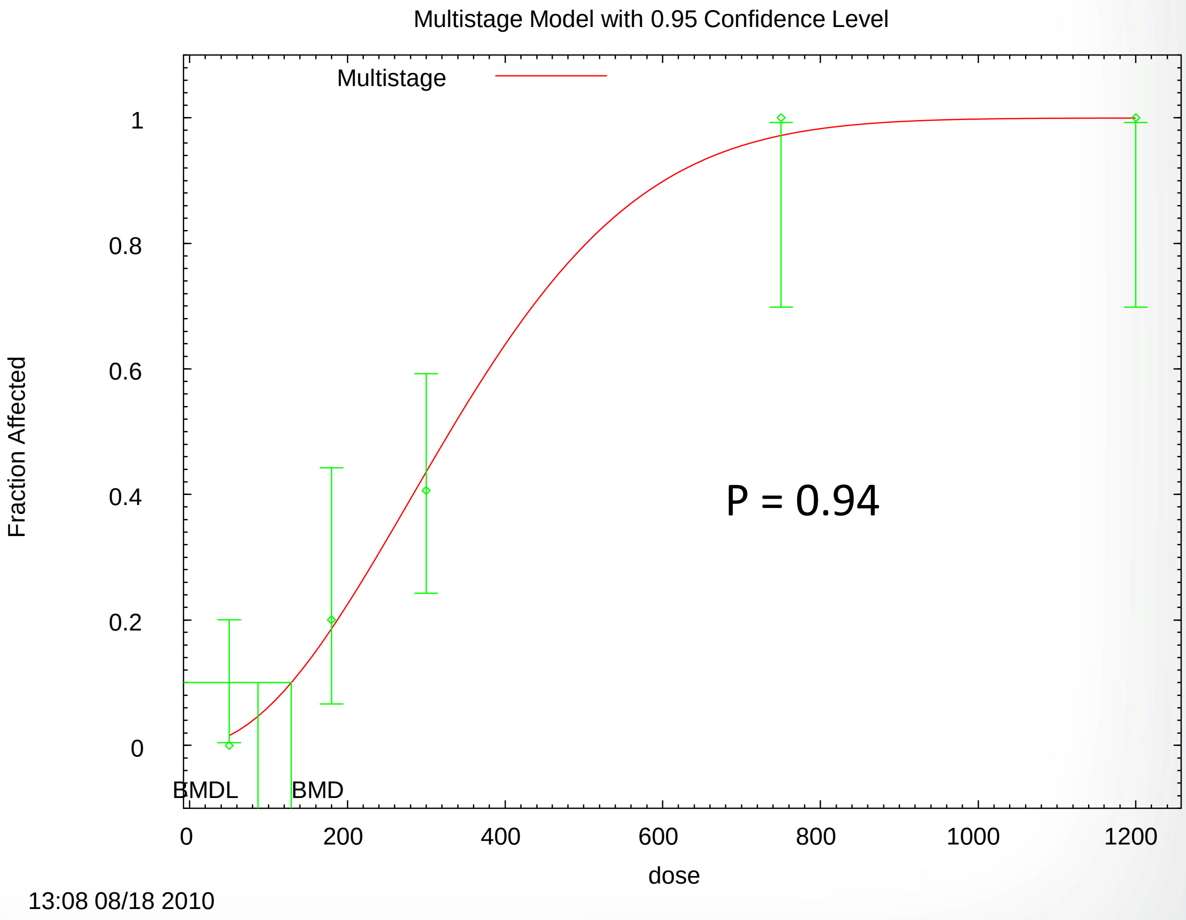
Modeling Recommendations – Poor Global Goodness-of-Fit

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

Example 1: When Not to Drop the High Dose

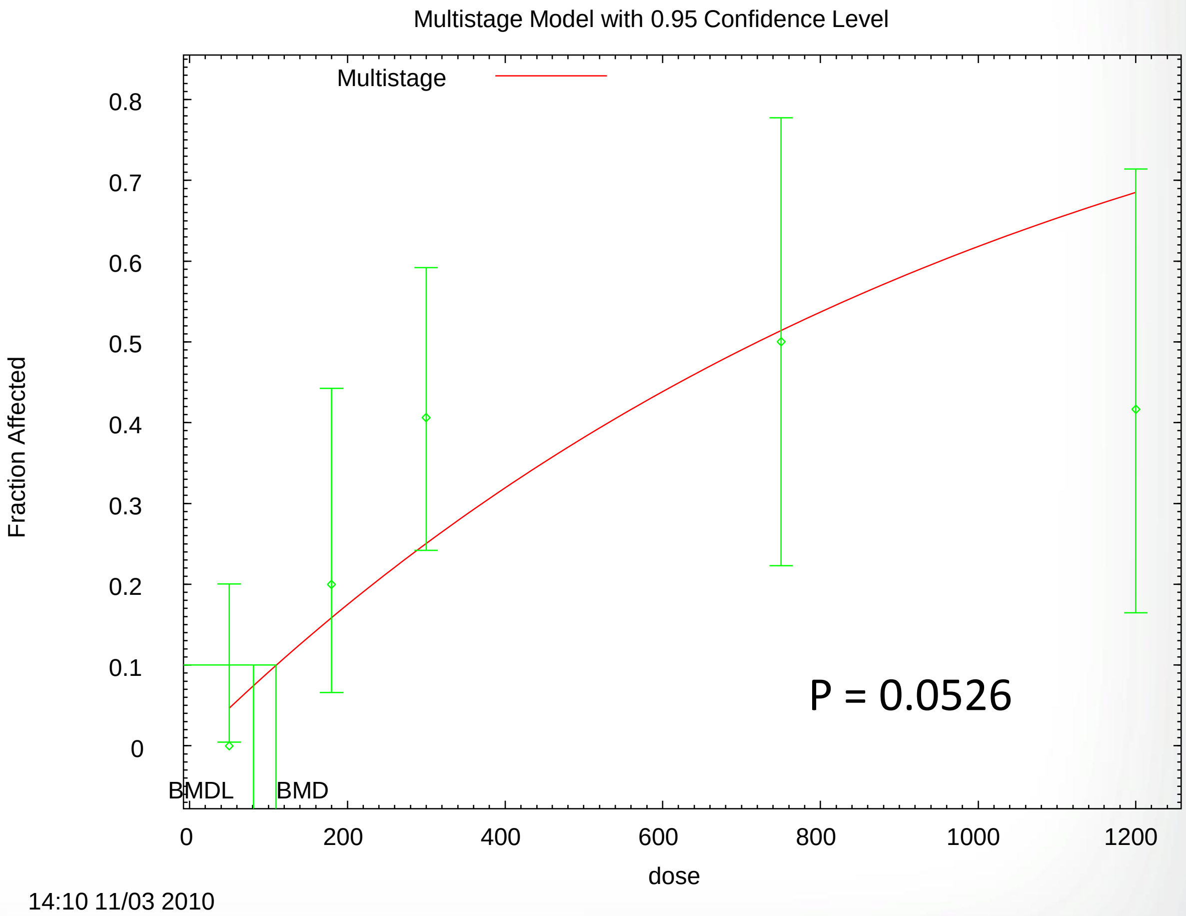
Dose (mg/m^3)	N	Incidence
50	20	0
180	20	4
300	32	13
750	12	12
1200	12	12



P = 0.94

Example 2: When to Drop the High Dose

Dose (mg/m^3)	N	Incidence
50	20	0
180	20	4
300	32	13
750	12	6
1200	12	5



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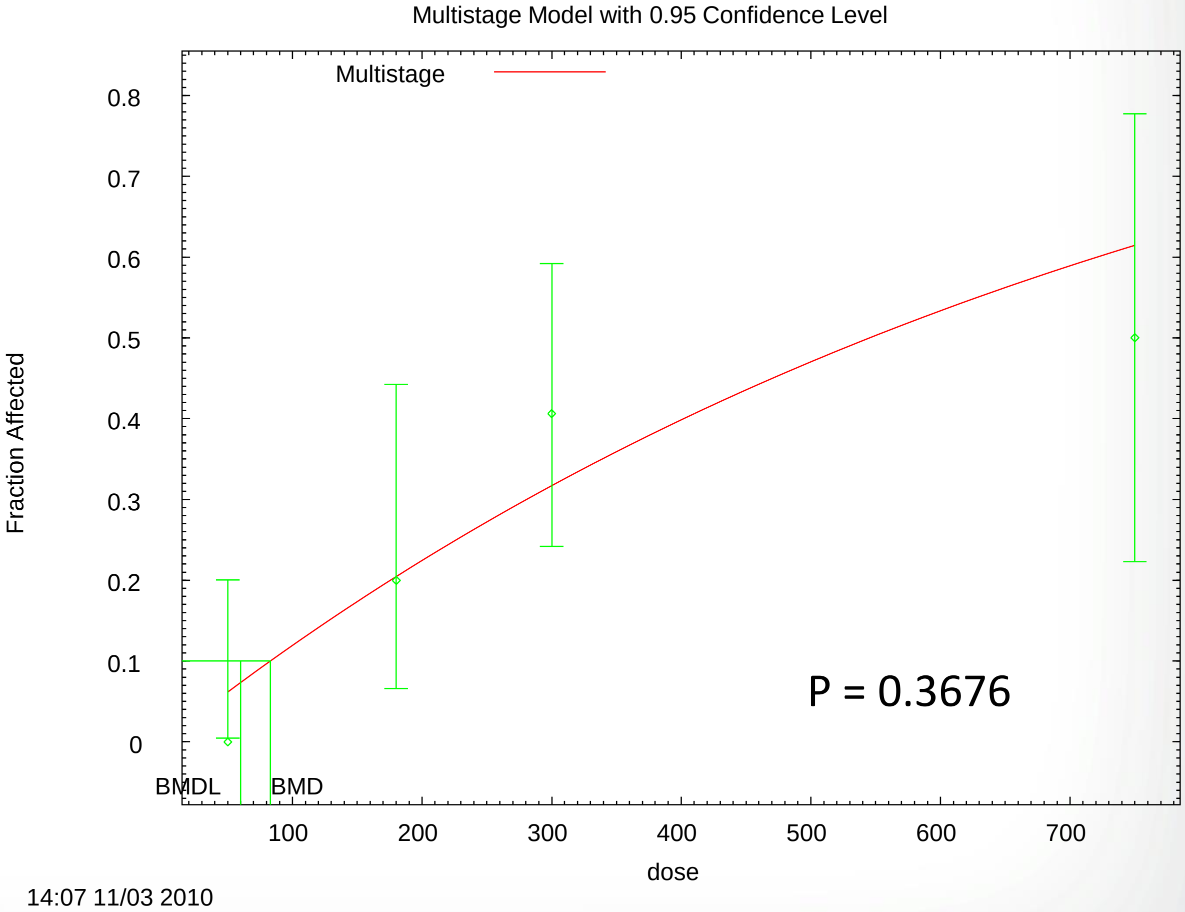

Example 3: Use of a Model with Asymptote Term

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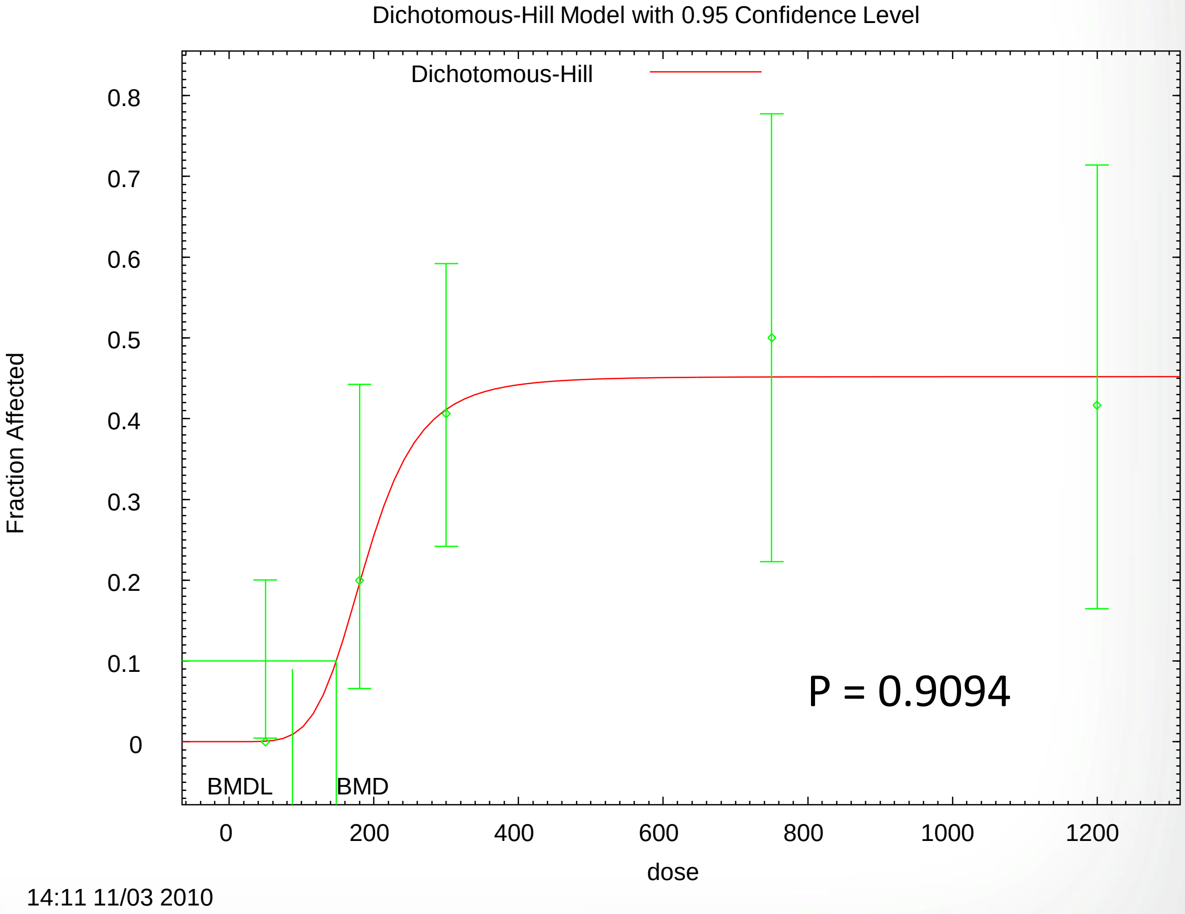


Further Recommendations – Poor Global Goodness-of-Fit

- **Log-transformation of doses**
  - Consult a statistician to determine if log-transformation is appropriate, special care often needs to be taken with the control dose (i.e., $\log_{10}(0)$ is undefined)
  - Both $\log_{10}$ and $\log_e$ transformations are available in BMDS

- **PBPK modeling can be very useful for BMD modeling**
  - For highly supralinear curves, use of internal dose metrics may be helpful, especially in cases of metabolic saturation (e.g., dose-response shape will be linearized)
  - If one particular dose metric fits the response data more closely, this may be an indication that this dose metric is the metric of interest (i.e., C_{max} vs. AUC)

PBPK Models and BMD Modeling

- **Care must be taken when performing BMD analyses with PBPK model-derived estimates of internal dose**

- **Most important question: Is the relationship between external and internal dose metrics linear across all doses?**

- **If yes, then it does not matter when BMD modeling occurs**
  - Can model external doses and then convert BMDs and BMDLs to internal doses (often advantageous if PBPK model is constantly updated or changed)

- **If no, then BMD analysis must be conducted using the internal dose metrics of interest**

Does the Model Fit the Data?

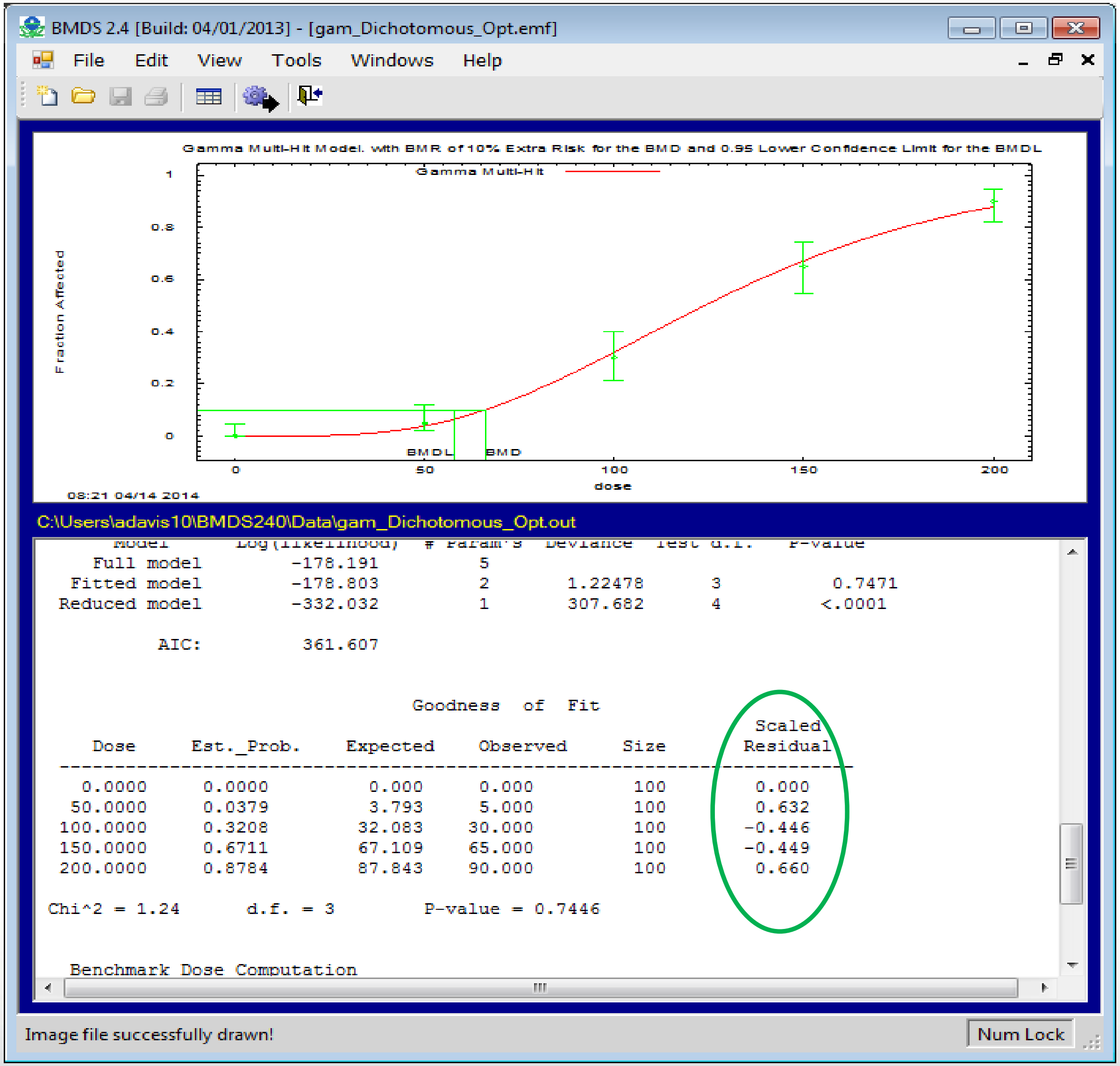
- **For dichotomous data:**
  - Global measurement: goodness-of-fit p value ($p > 0.1$)
  - ***Local measurement: Scaled residuals (absolute value < 2.0)***
  - Visual inspection of model fitting.

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**
  - $\frac{Obs - Exp}{\sqrt{(n*p(1-p))}}$
  - Absolute values near the BMR should be lowest
  - Question scaled residuals with absolute value > 2

Scaled Residuals



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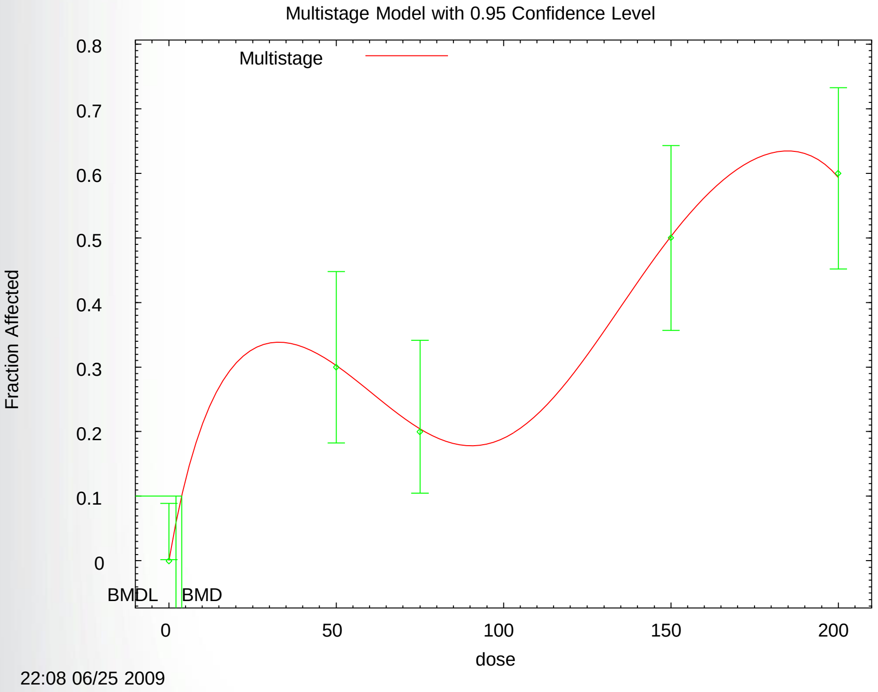
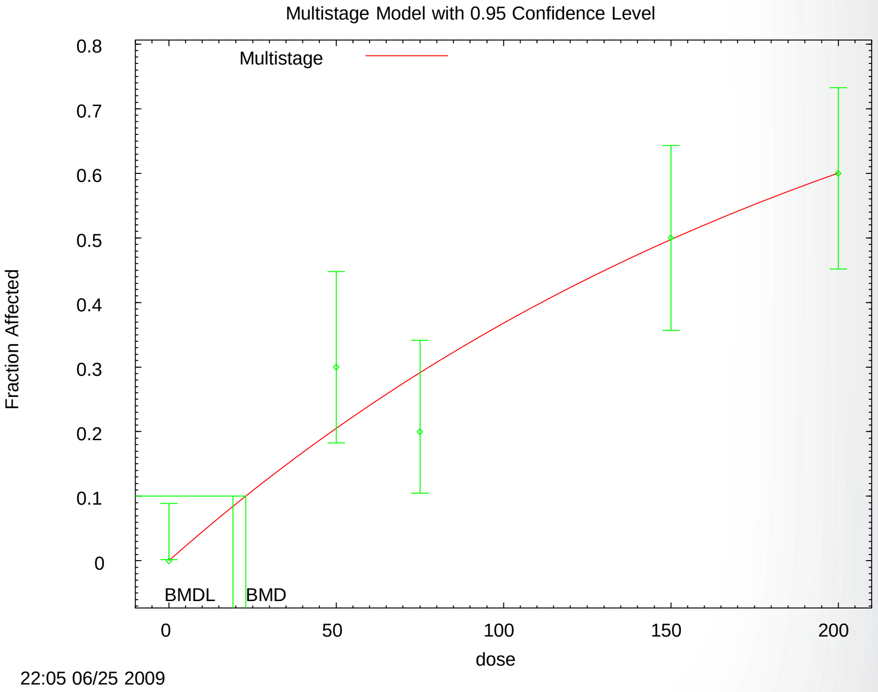
Visual Inspection of Fit





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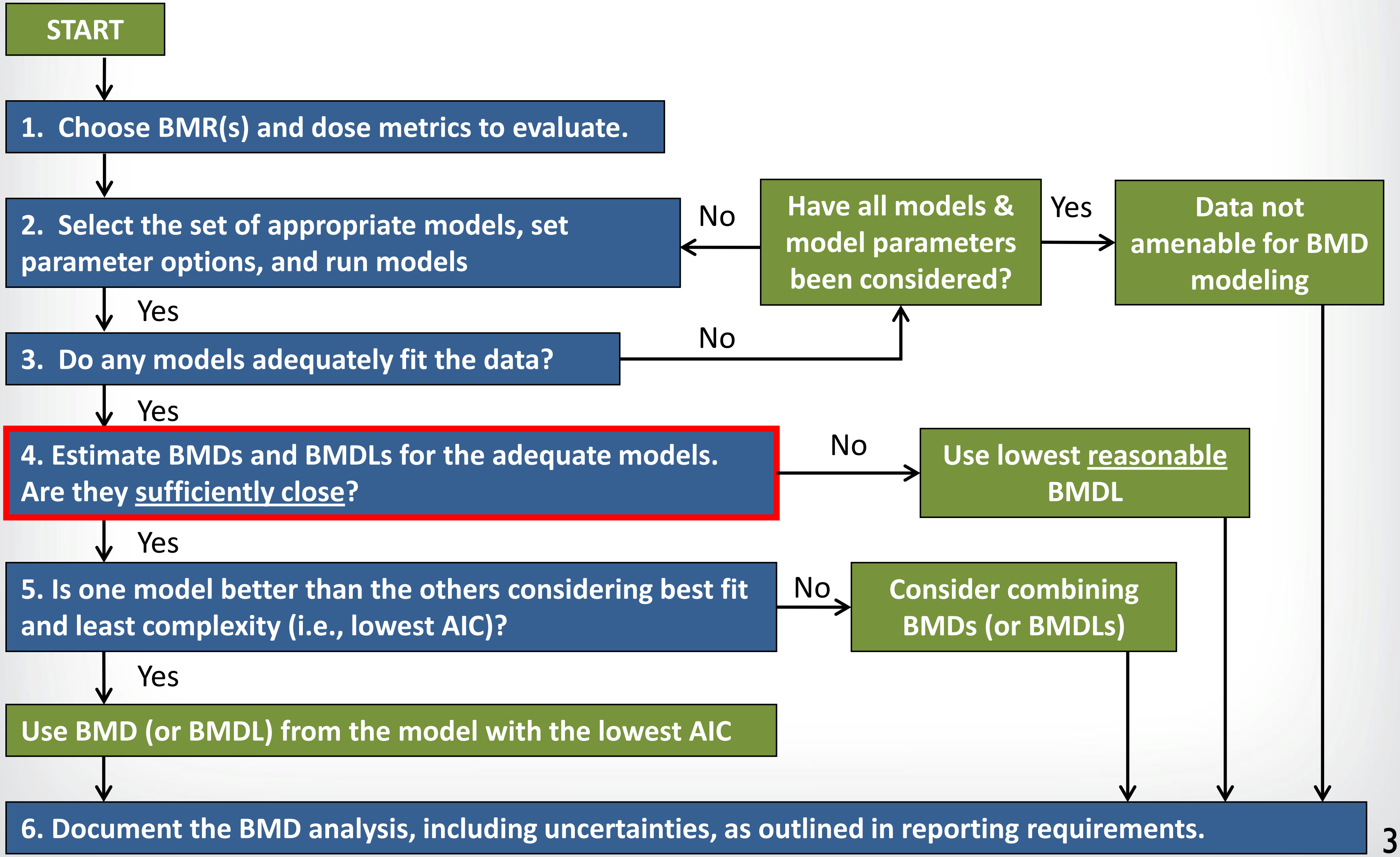

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Are BMDL Estimates "Sufficiently Close"?

- **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.**

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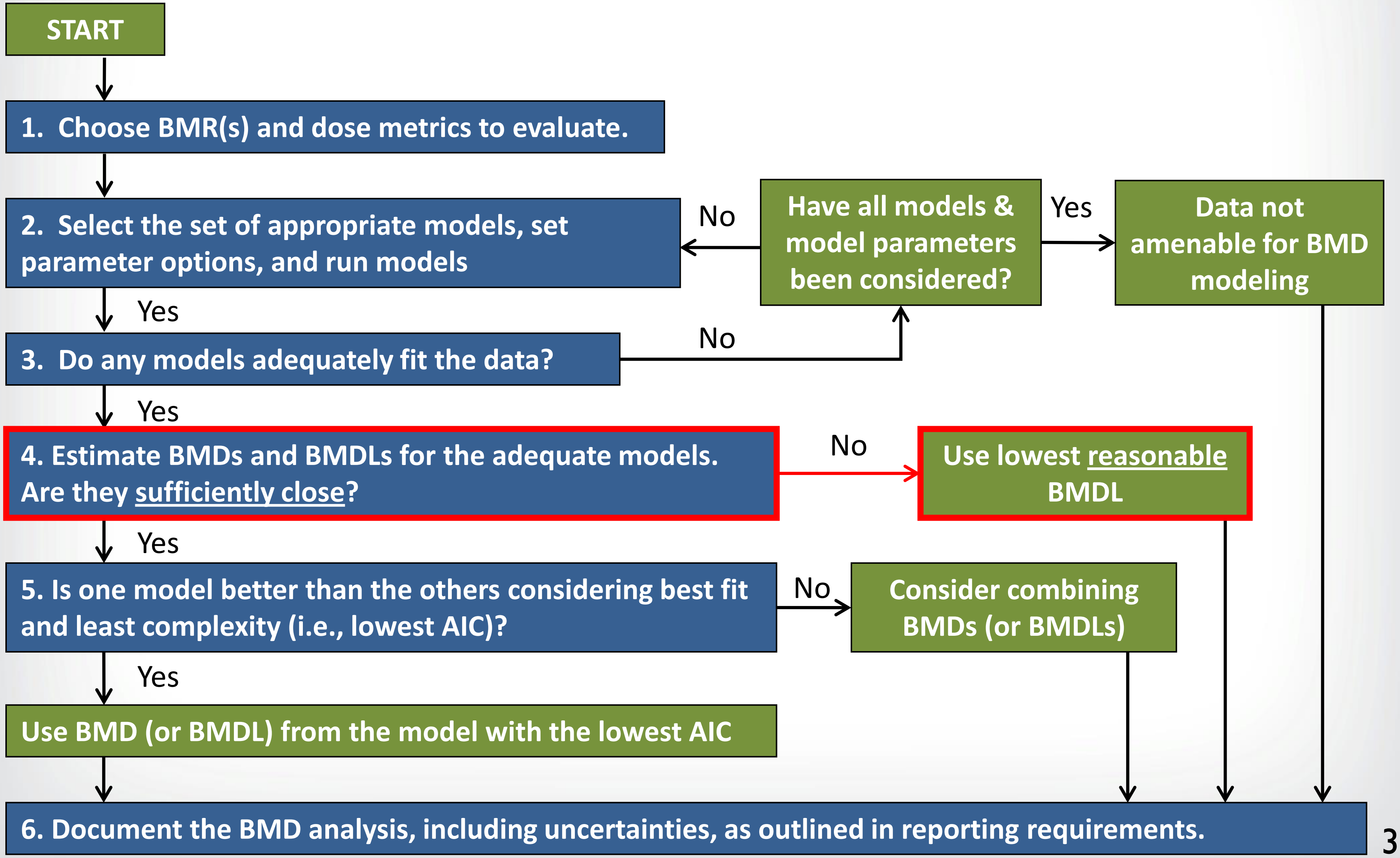

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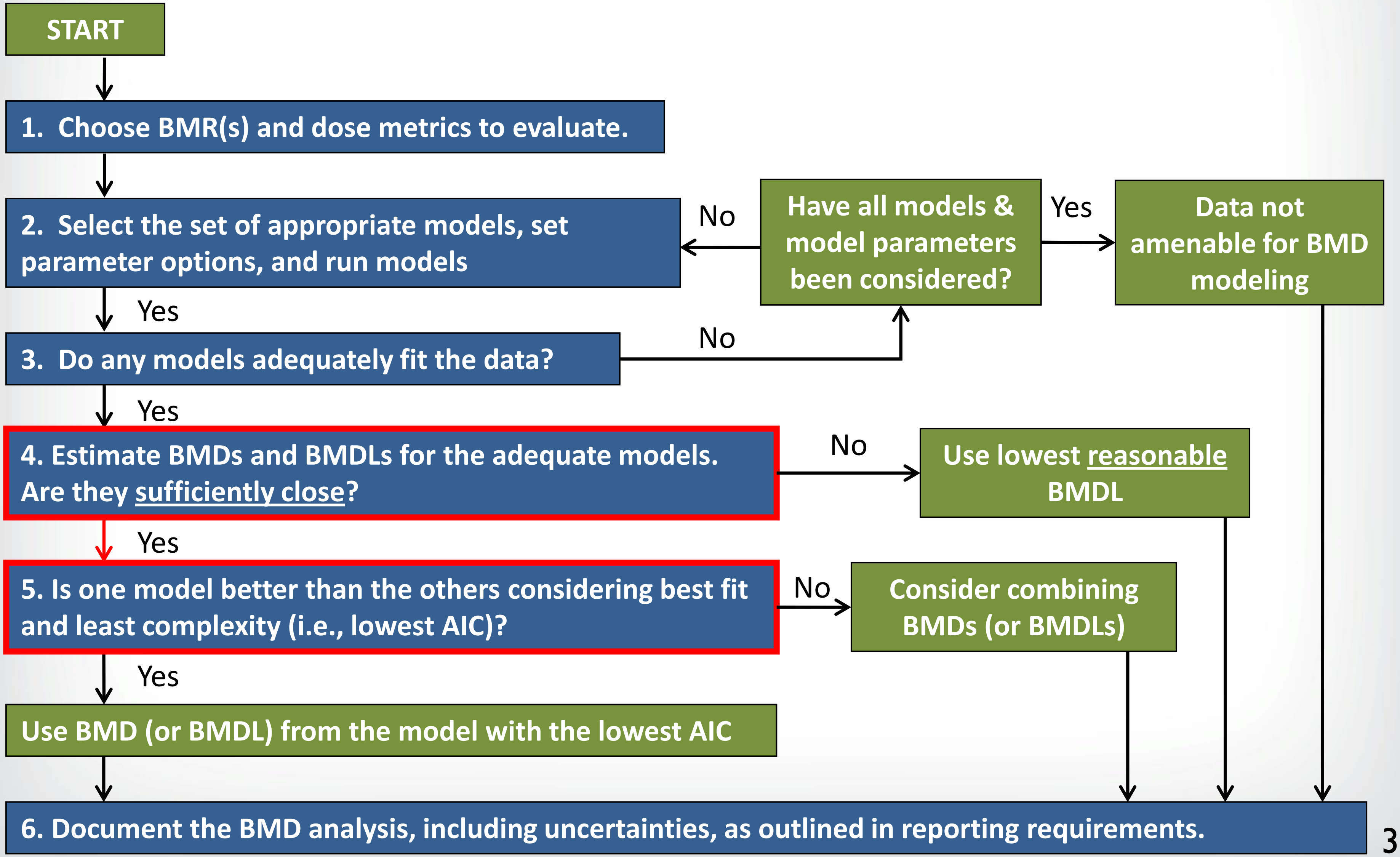

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Comparing Model Fit Across Models

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

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

Akaike's Information Criterion (AIC)

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

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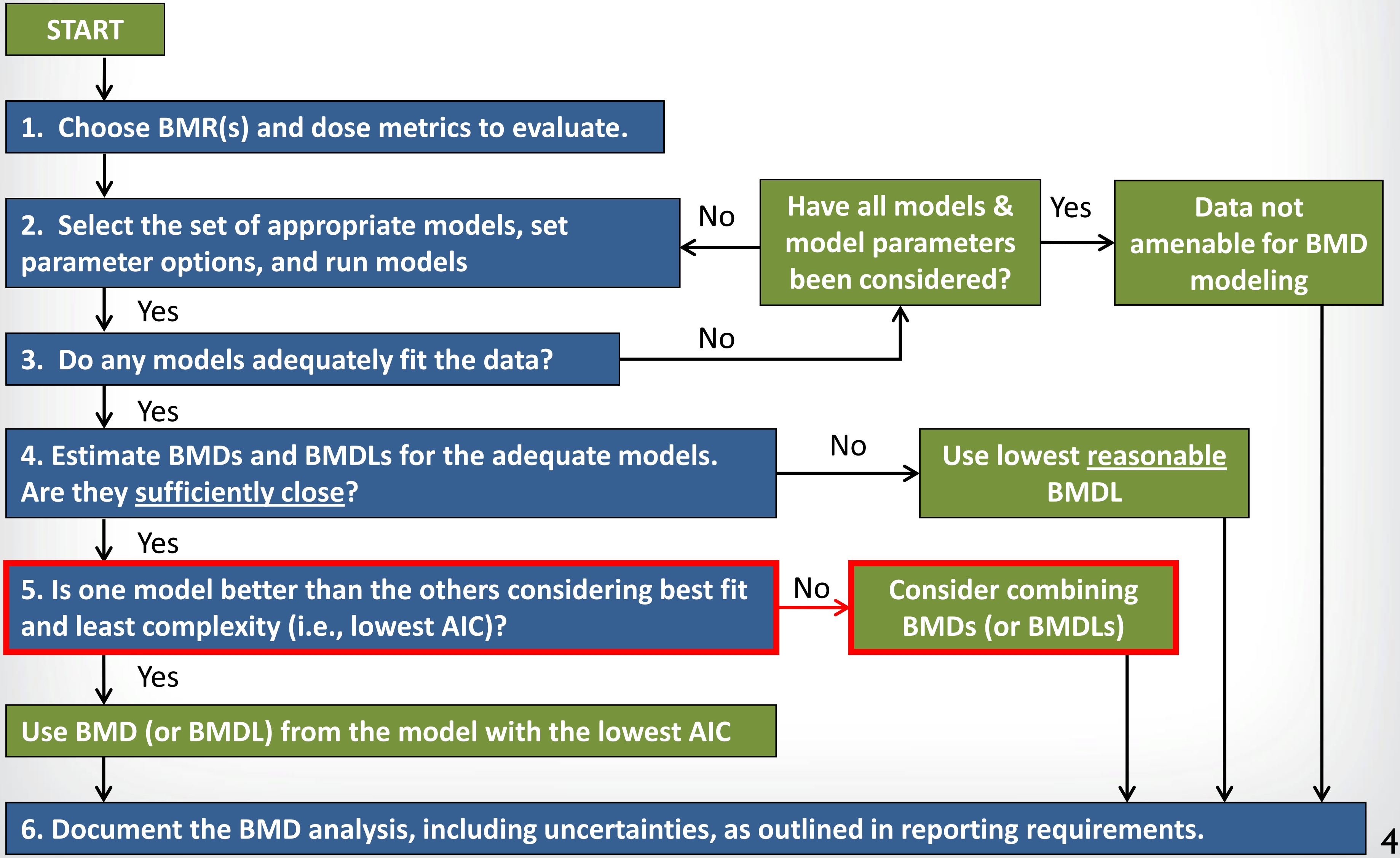

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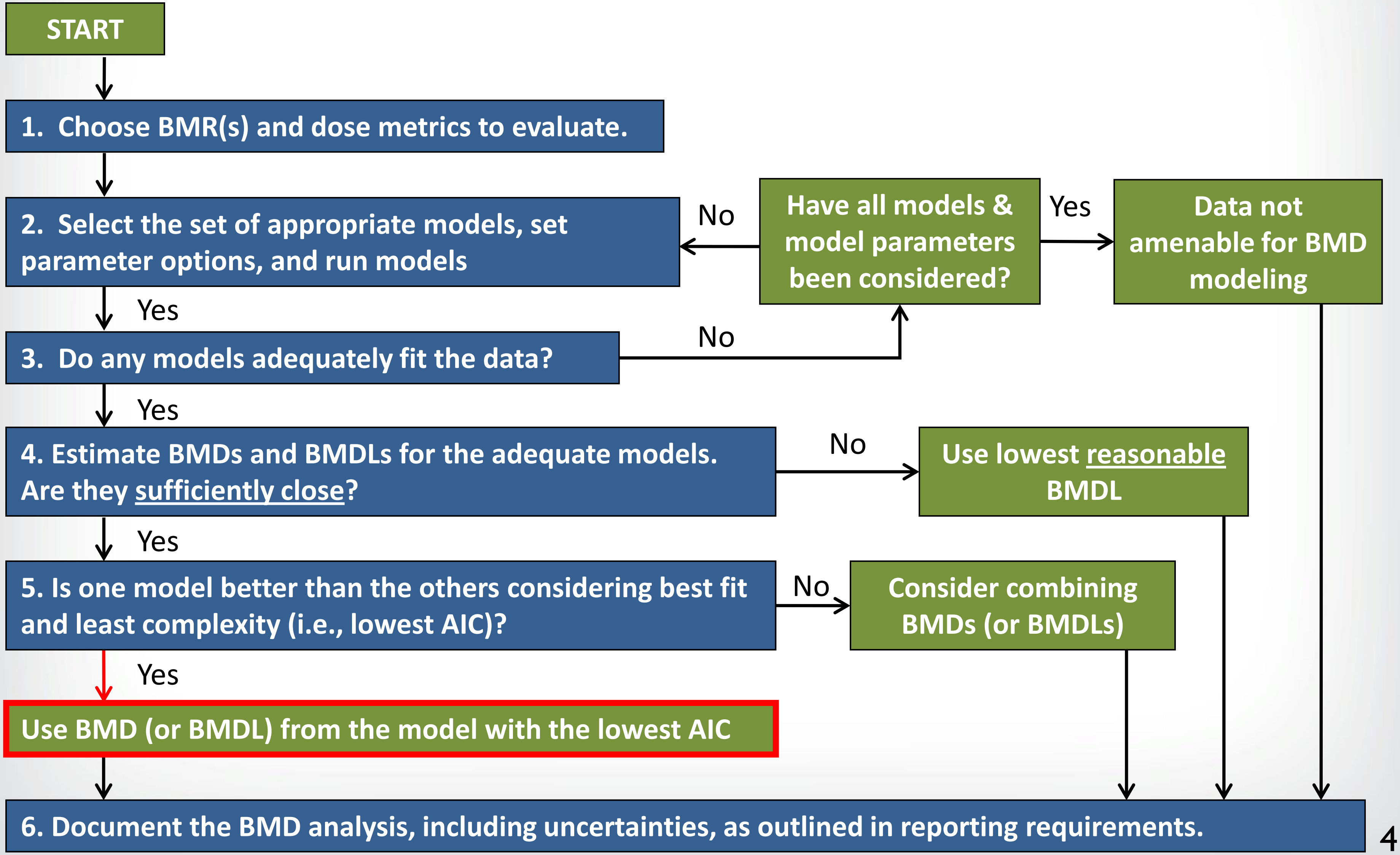

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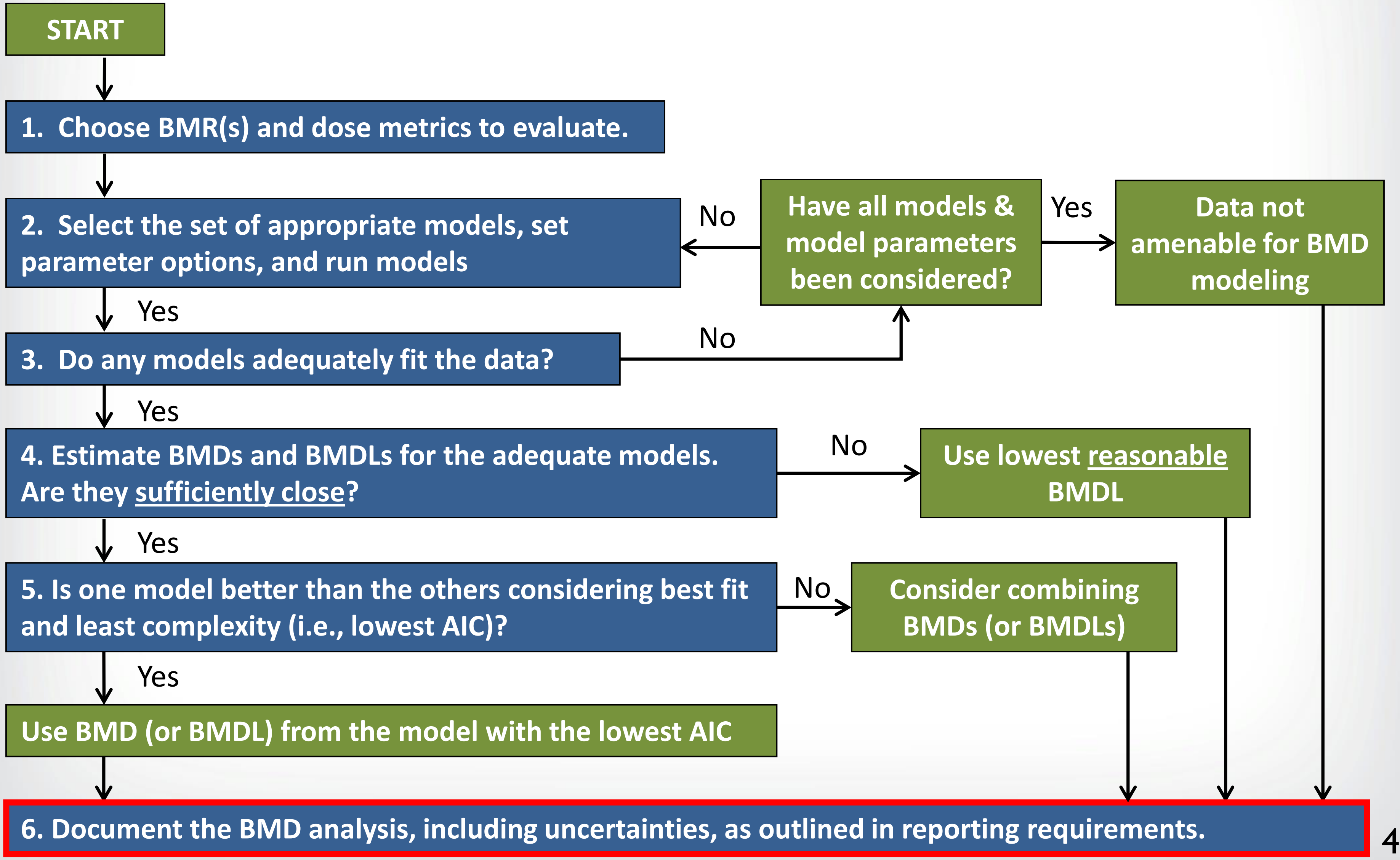

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No

Yes

Data not amenable for BMD modeling

Yes

4. Estimate BMDs and BMDLs for the adequate models. Are they sufficiently close?

No

Use lowest reasonable BMDL

Yes

5. Is one model better than the others considering best fit and least complexity (i.e., lowest AIC)?

No

Consider combining BMDs (or BMDLs)

Yes

Use BMD (or BMDL) from the model with the lowest AIC

6. Document the BMD analysis, including uncertainties, as outlined in reporting requirements.

Example of BMD Analysis Documentation

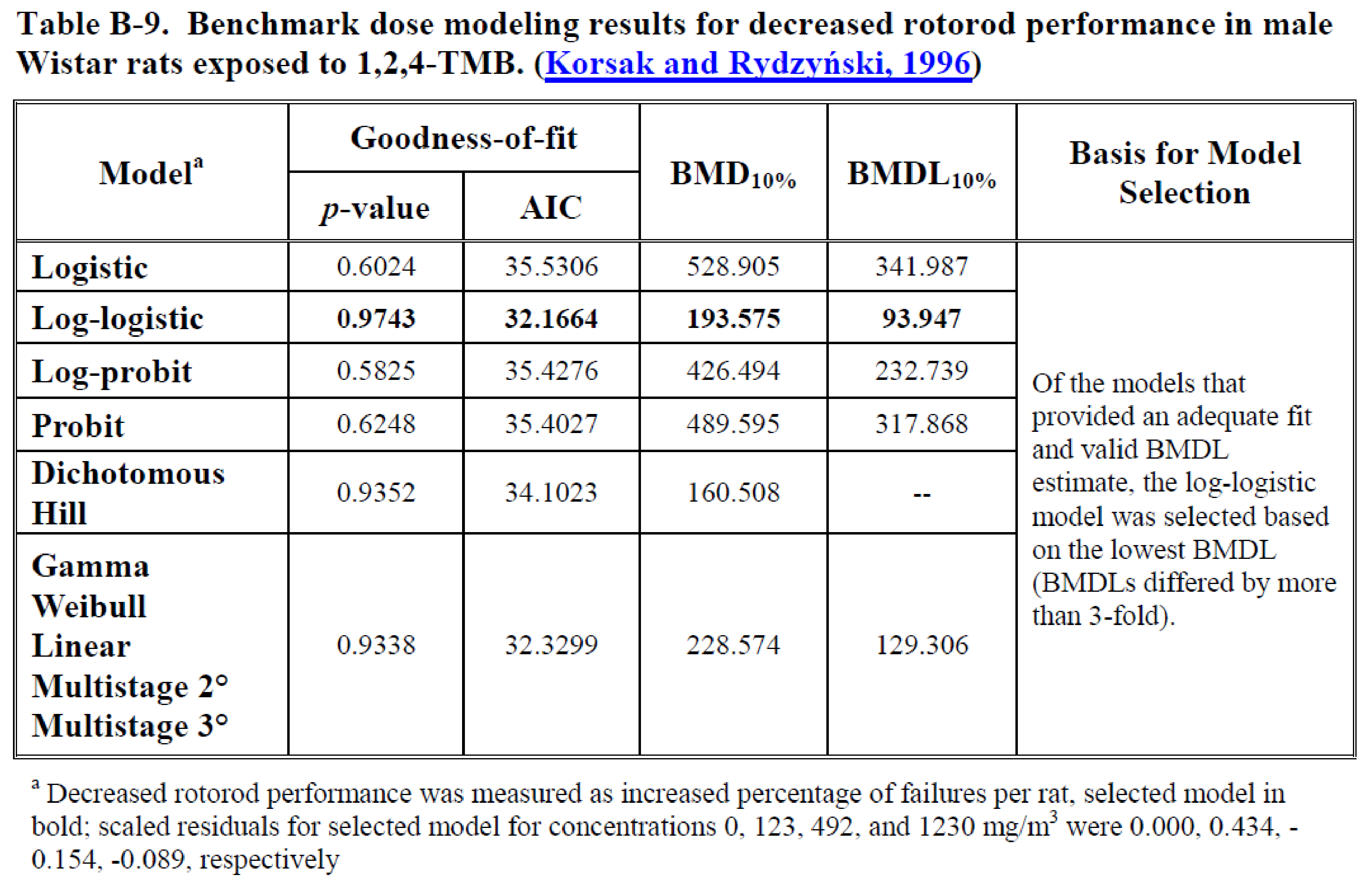


Table B-9. Benchmark dose modeling results for decreased rotorod performance in male Wistar rats exposed to 1,2,4-TMB. (Korsak and Rydzyński, 1996)

Model[a]	Goodness-of-fit		$BMD_{10\%}$	$BMDL_{10\%}$	Basis for Model Selection
	p-value	AIC			
Logistic	0.6024	35.5306	528.905	341.987	Of the models that provided an adequate fit and valid BMDL estimate, the log-logistic model was selected based on the lowest BMDL (BMDLs differed by more than 3-fold).
Log-logistic	**0.9743**	**32.1664**	**193.575**	**93.947**	
Log-probit	0.5825	35.4276	426.494	232.739	
Probit	0.6248	35.4027	489.595	317.868	
Dichotomous Hill	0.9352	34.1023	160.508	--	
Gamma **Weibull** **Linear** **Multistage 2°** **Multistage 3°**	0.9338	32.3299	228.574	129.306	

[a] Decreased rotorod performance was measured as increased percentage of failures per rat, selected model in bold; scaled residuals for selected model for concentrations 0, 123, 492, and 1230 mg/m^3 were 0.000, 0.434, -0.154, -0.089, respectively

Additional Models for Dichotomous Data

- **For most of the quantal models in BMDS, there are two alternative versions available:**
  - Background response parameter, γ:

    $$P(\beta, x, \gamma) = \gamma + (1-\gamma)*F\{\beta, x\}$$

  - Background parameter additive to dose, η:

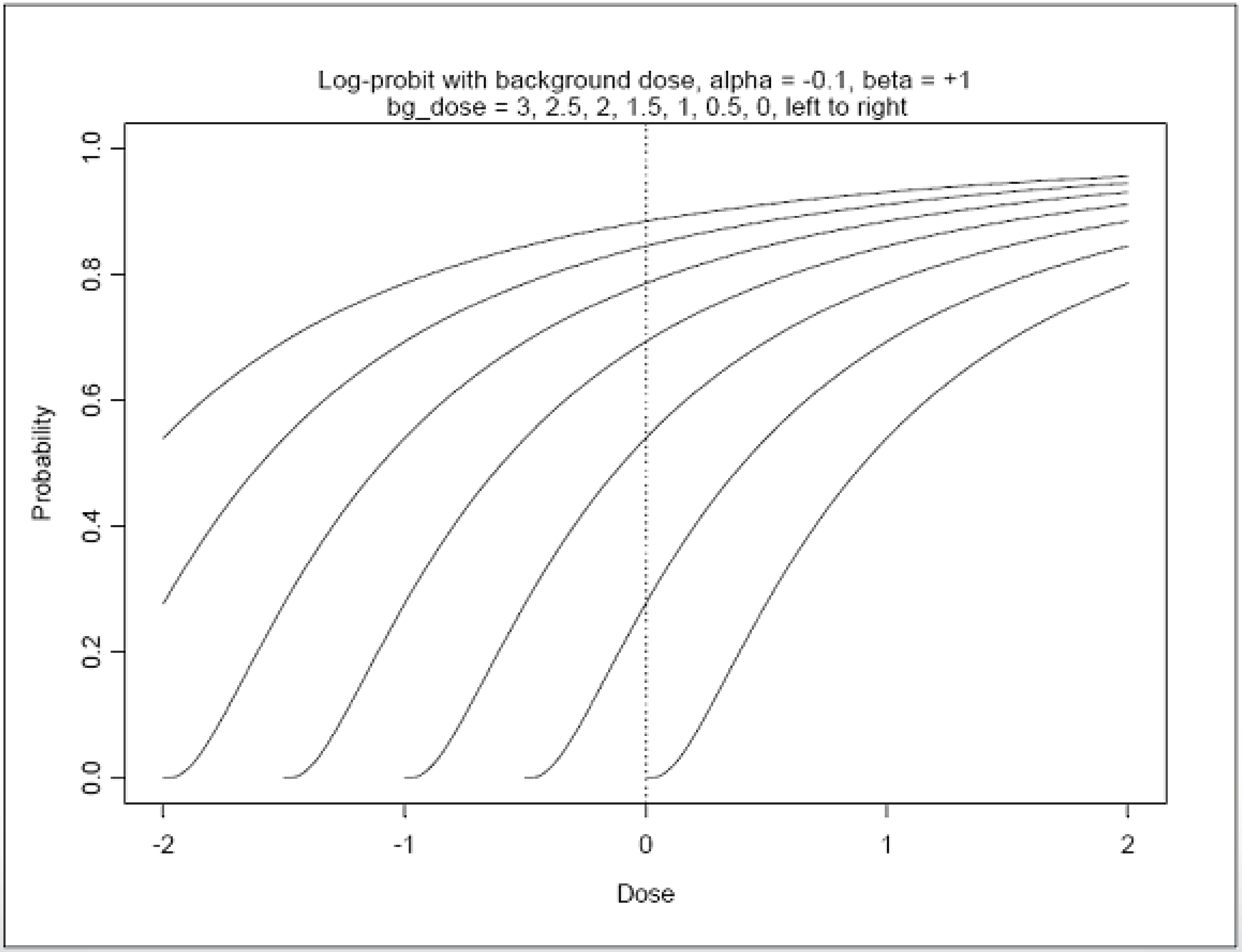
    $$P(\beta, x, \eta) = F\{\beta, (x+ \eta)\}$$

- **Background response models are the "traditional" models that are typically used in EPA assessments**

Available Models (and options) for Dichotomous Data

- **Gamma**
  - Background response
  - Background dose
- **Multi-stage**
  - Background response
  - Background dose
- **Multi-stage cancer**
  - Background response
  - Background dose
- **Weibull**
  - Quantal-Linear (power = 1)
  - Background response
  - Background dose
- **Dichotomous Hill**
- **Logistic**
  - Background response
  - Background dose
- **Log Logistic**
  - Background response
- **Probit**
  - Background response
  - Background dose
- **Log Probit**
  - Background response
  - Background dose

Curve Shapes with Increasing Background Dose



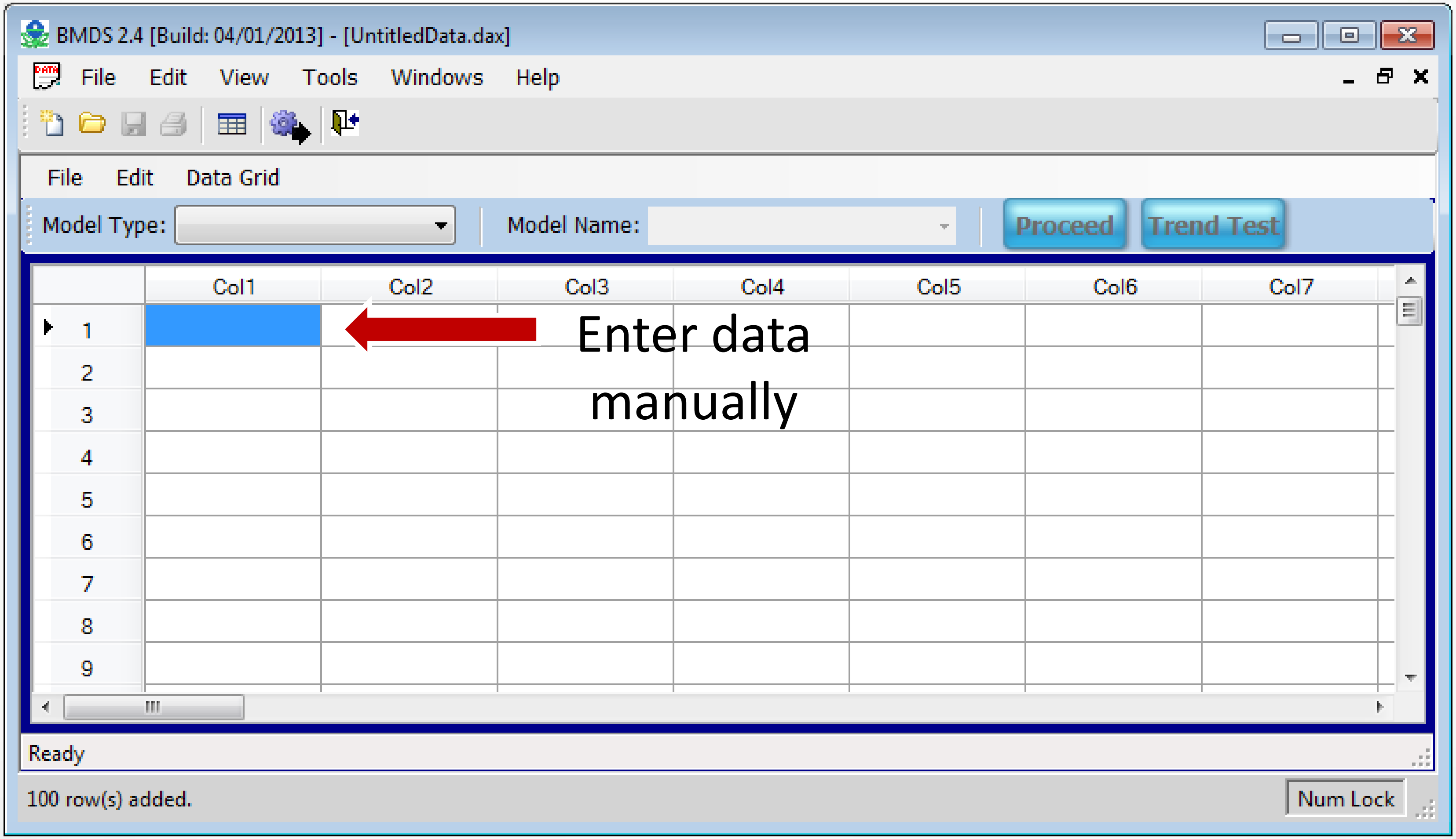
Dichotomous Data – Creating a Dataset in BMDS

Creating a Dataset - Options

- **Open new dataset and enter data manually**
- **Choose an existing dataset**
- **Import & export data in multiple formats**

Creating a Dataset – Open New Generic Dataset

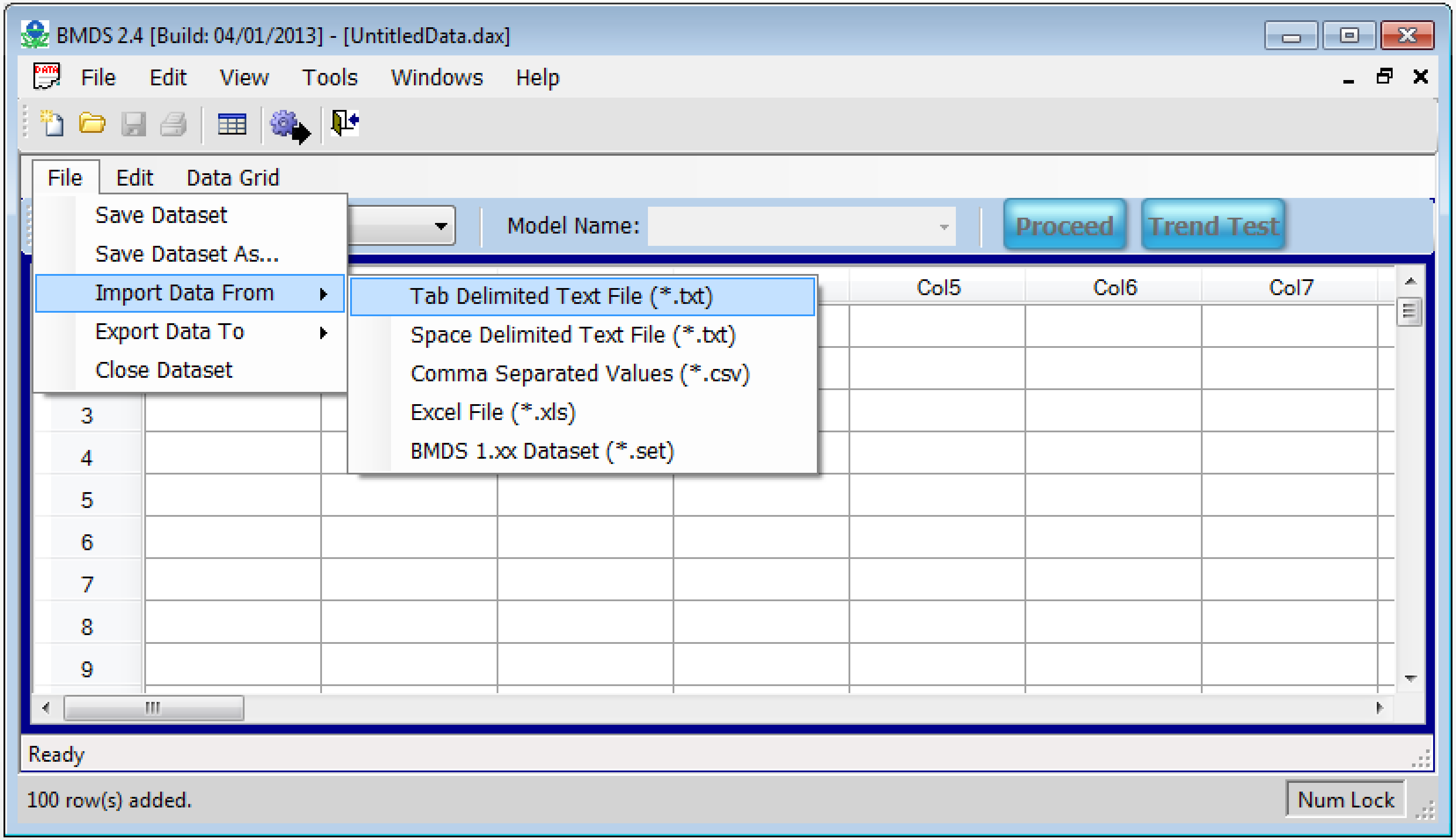
Creating a Dataset – Open New Generic Dataset



100 row(s) added.

Enter data manually

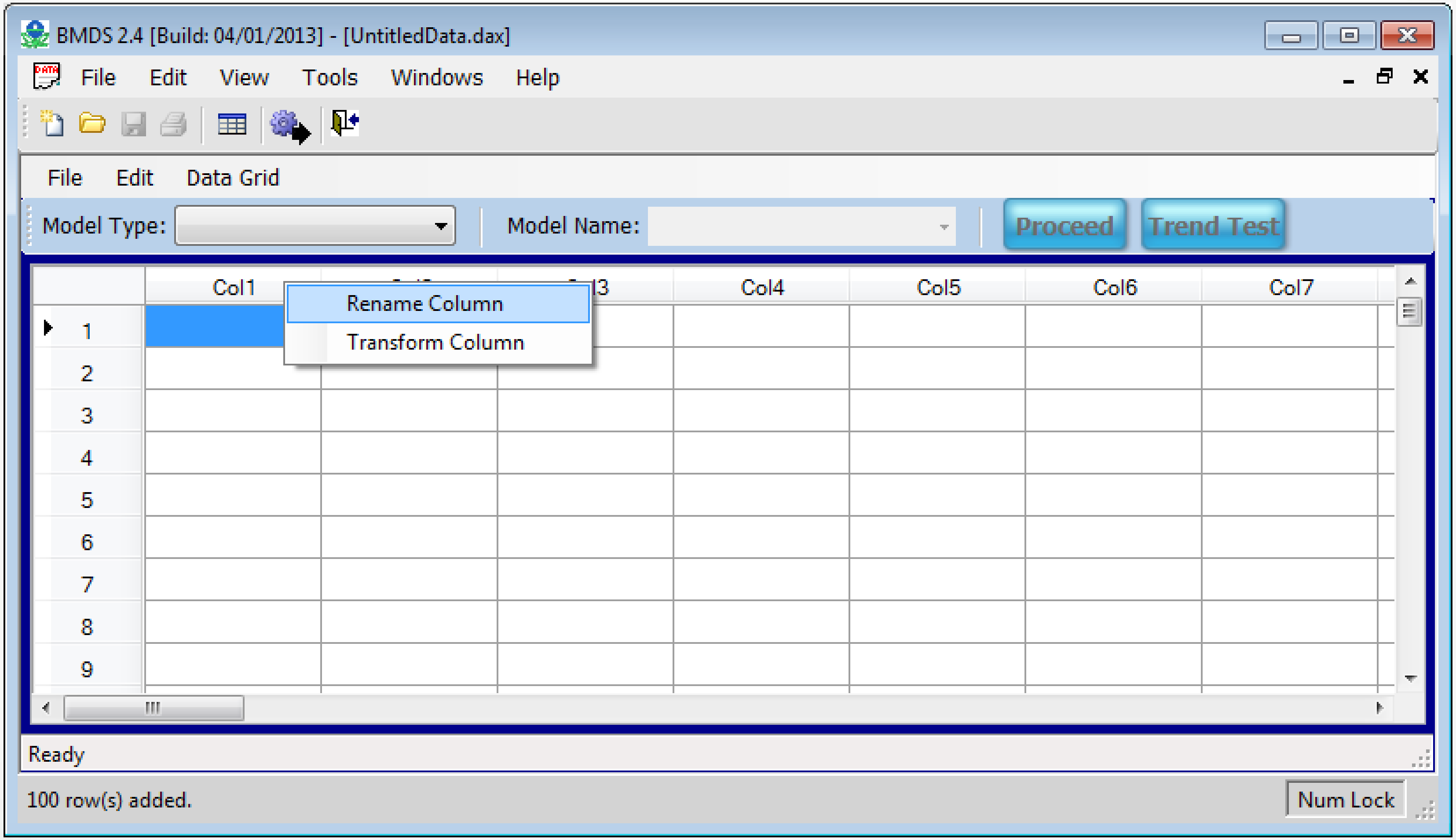
Creating a Dataset – Import an Existing Dataset



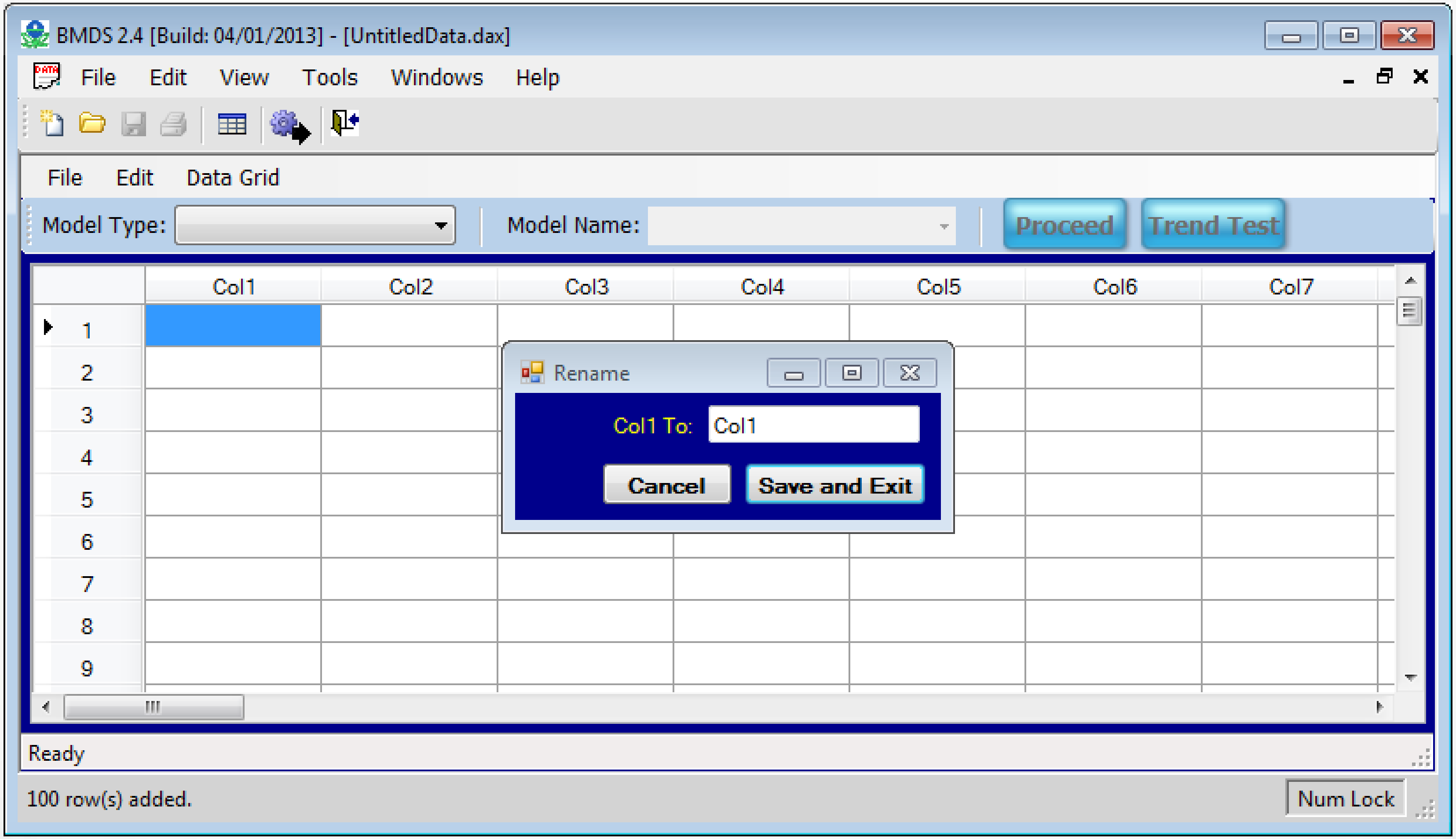
Ready

100 row(s) added.

Creating a Dataset – Renaming Column Headers

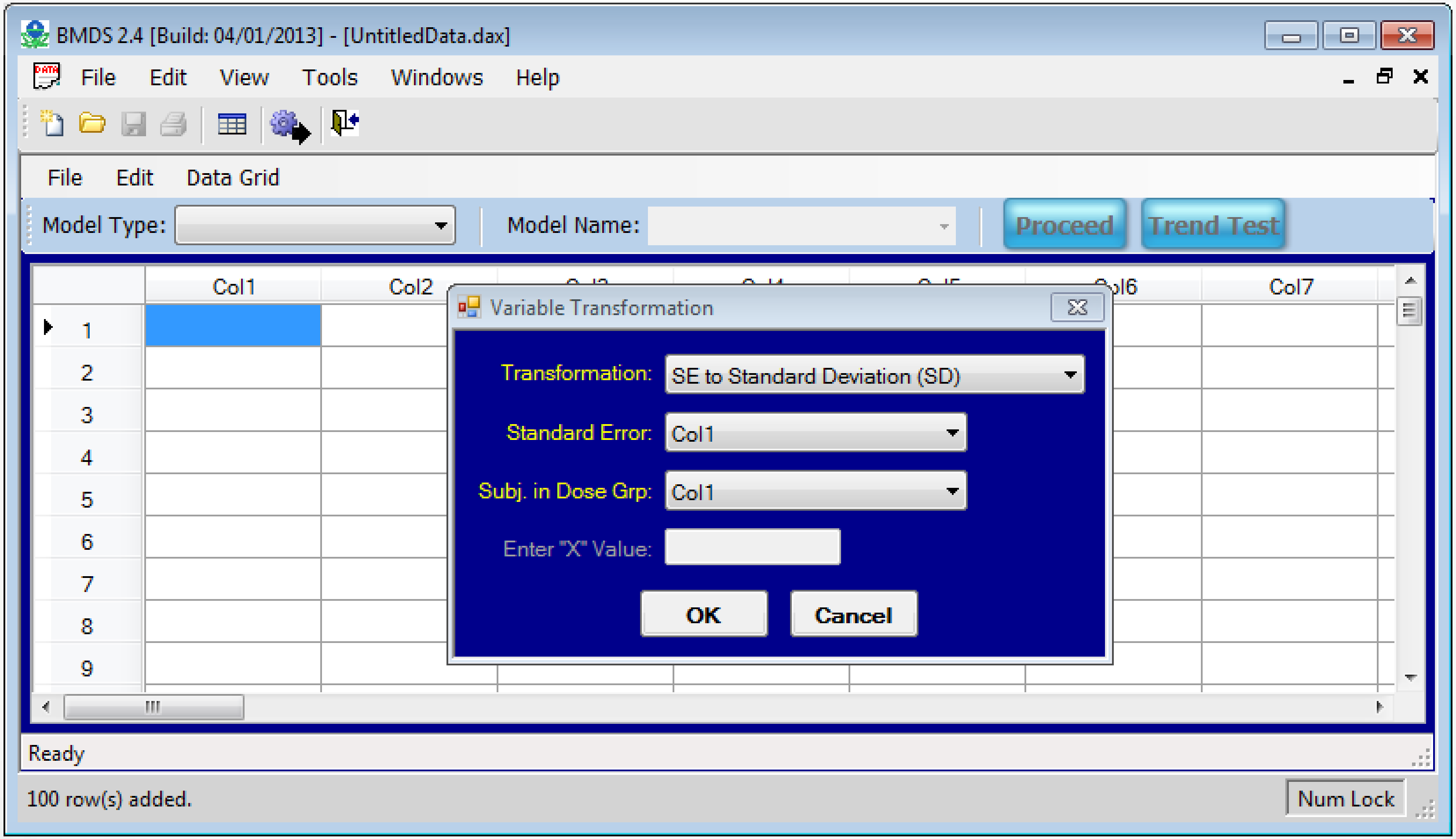


Creating a Dataset – Renaming Column Headers



Col1 To: Col1

Creating a Dataset – Data Transformations



Model Type:

Model Name:

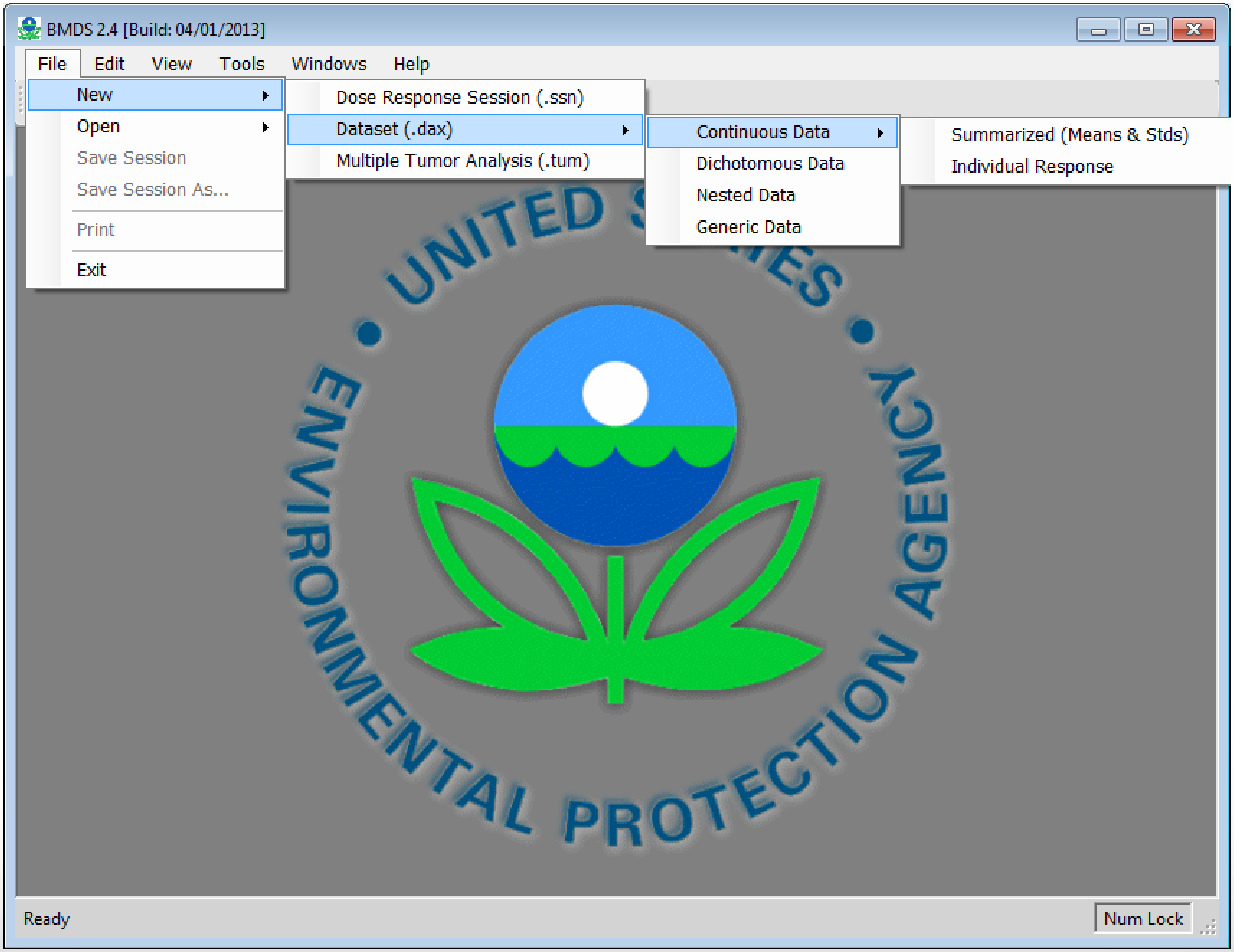
Transformation: SE to Standard Deviation (SD)

Standard Error: Col1

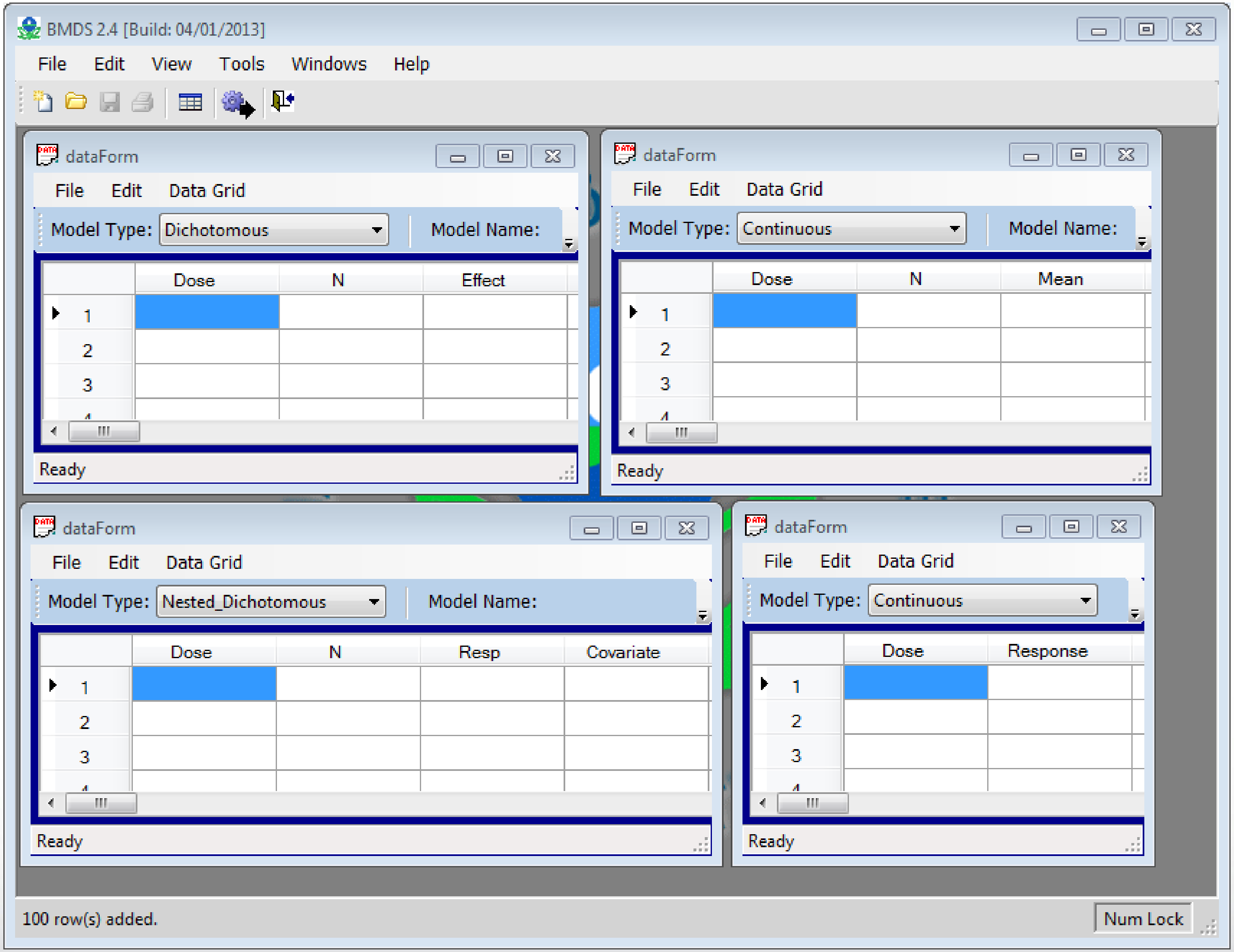
Subj. in Dose Grp: Col1

Enter "X" Value:

Creating a Dataset – Open new Formatted Dataset



Creating a Dataset – Open New Formatted Dataset



Model Type: Dichotomous
Model Name:

	Dose	N	Effect
1			
2			
3			

Model Type: Continuous
Model Name:

	Dose	N	Mean
1			
2			
3			

Model Type: Nested_Dichotomous
Model Name:

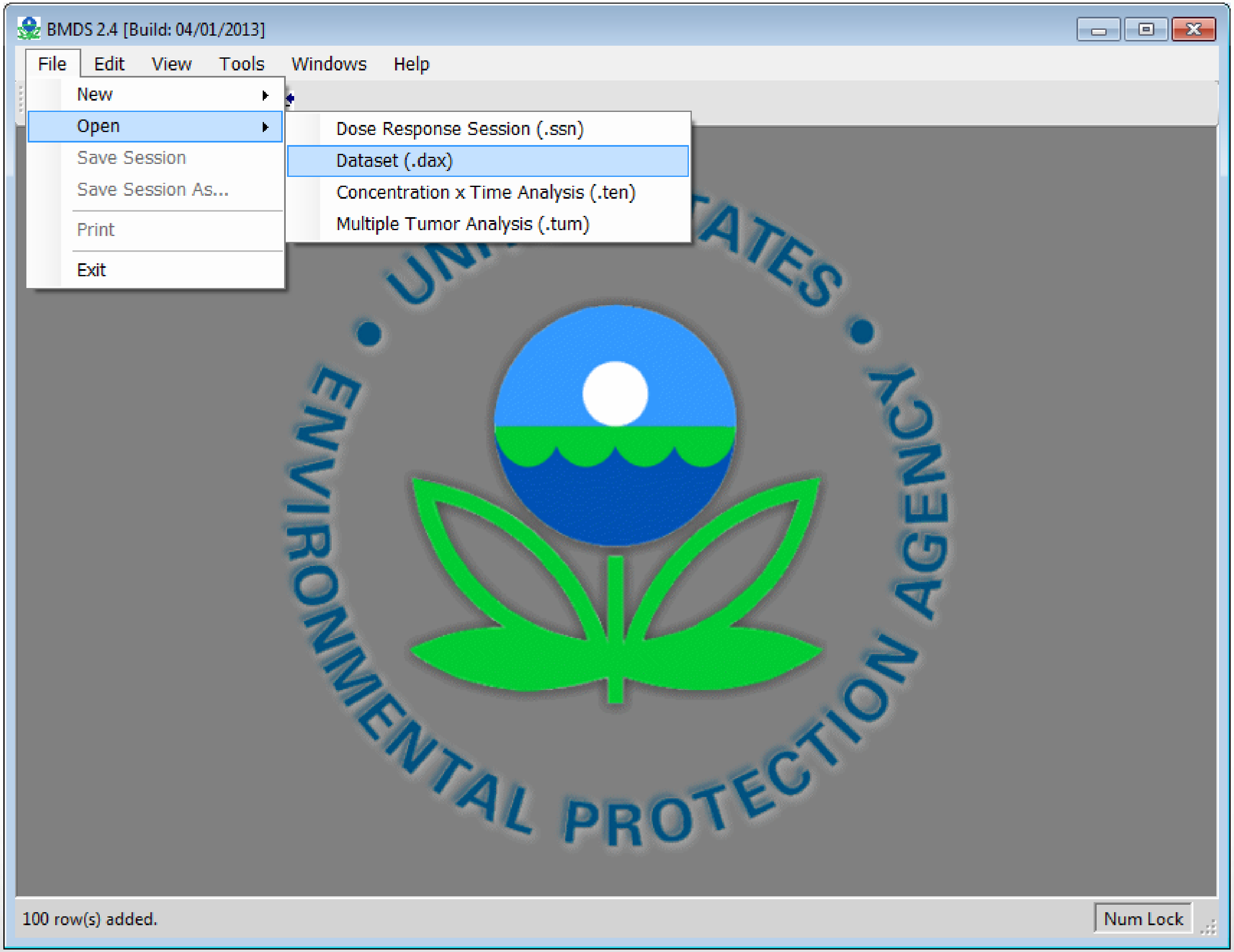
	Dose	N	Resp	Covariate
1				
2				
3				

Model Type: Continuous

	Dose	Response
1		
2		
3		

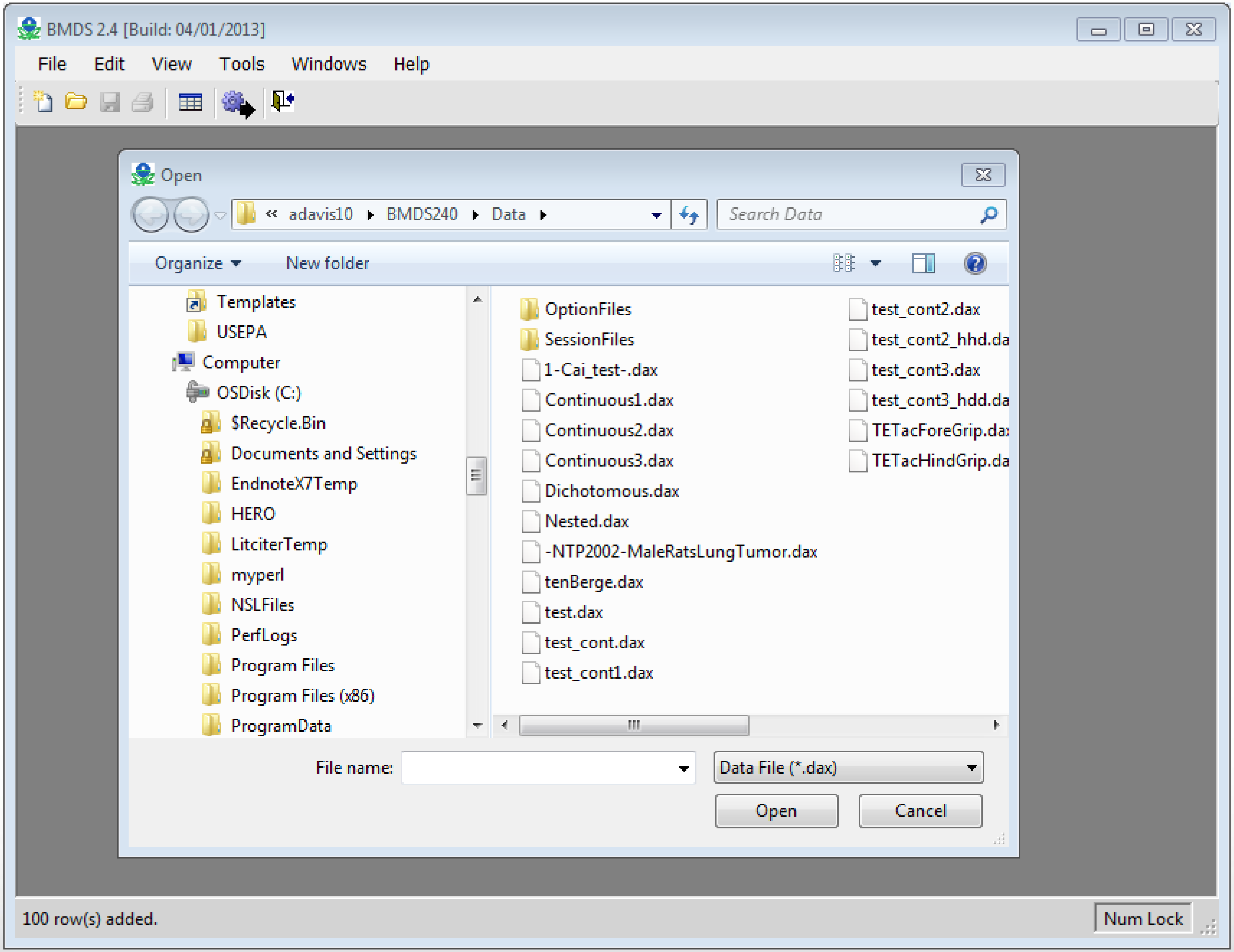
100 row(s) added.

Creating a Dataset – Open Existing Dataset



100 row(s) added.

Creating a Dataset – Open Existing Dataset



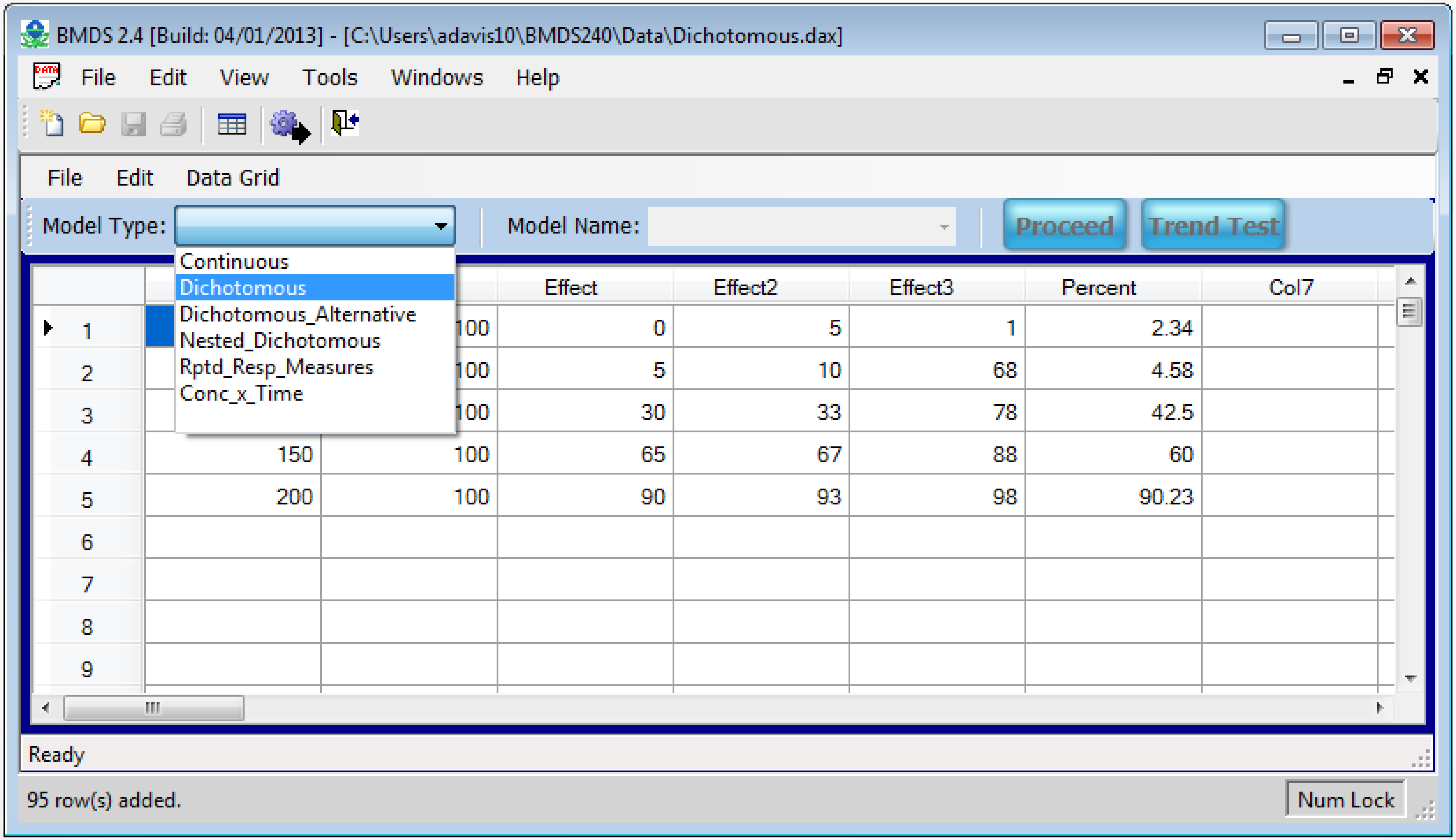
BMDS 2.4 [Build: 04/01/2013]

File name:

Data File (*.dax)

100 row(s) added.

Running an Individual Model – Select a Model Type

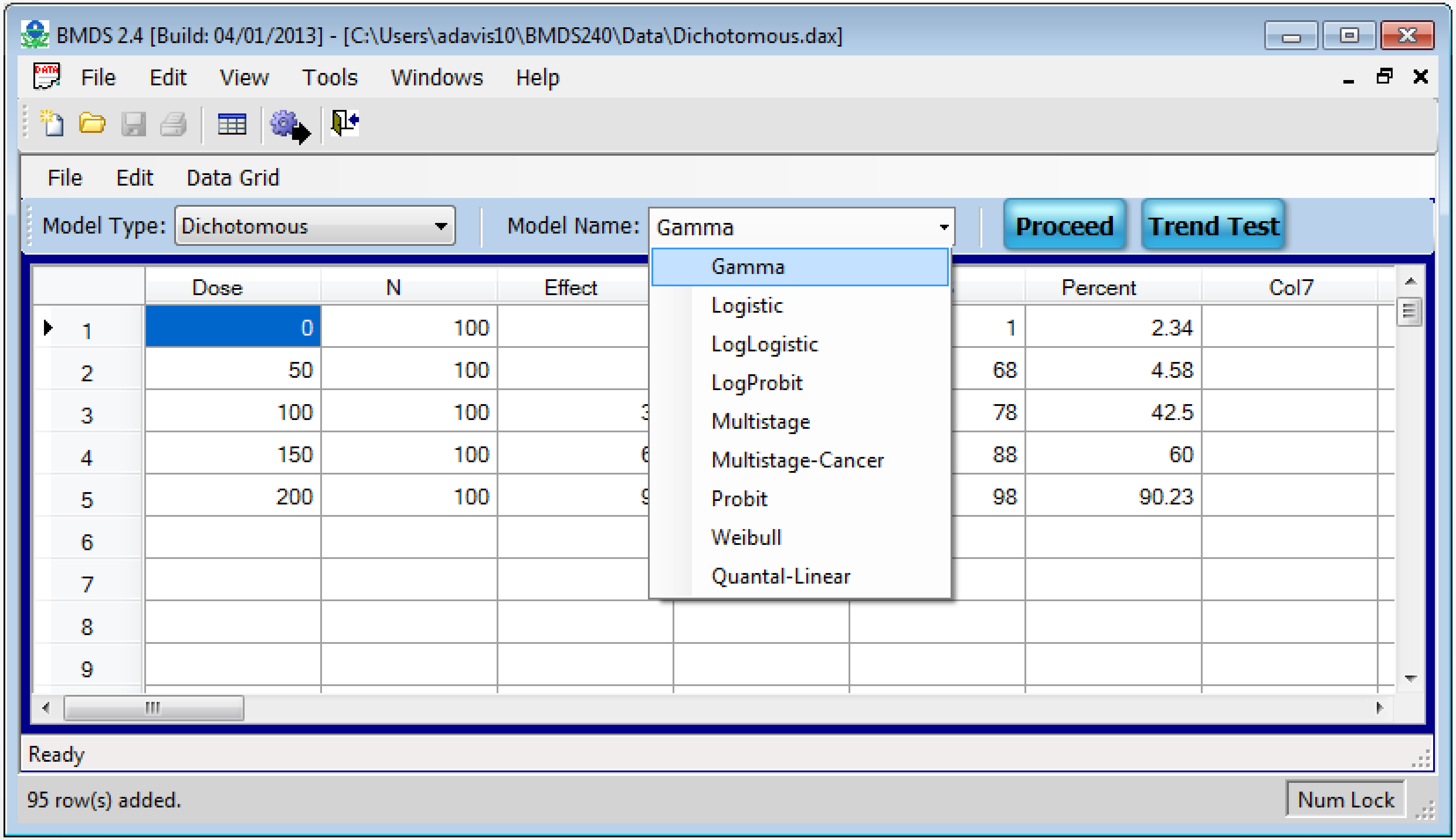


			Effect	Effect2	Effect3	Percent	Col7
1		100	0	5	1	2.34	
2		100	5	10	68	4.58	
3		100	30	33	78	42.5	
4	150	100	65	67	88	60	
5	200	100	90	93	98	90.23	
6							
7							
8							
9							

Ready

95 row(s) added.

Running an Individual Model – Select a Model



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

Model Type: Dichotomous

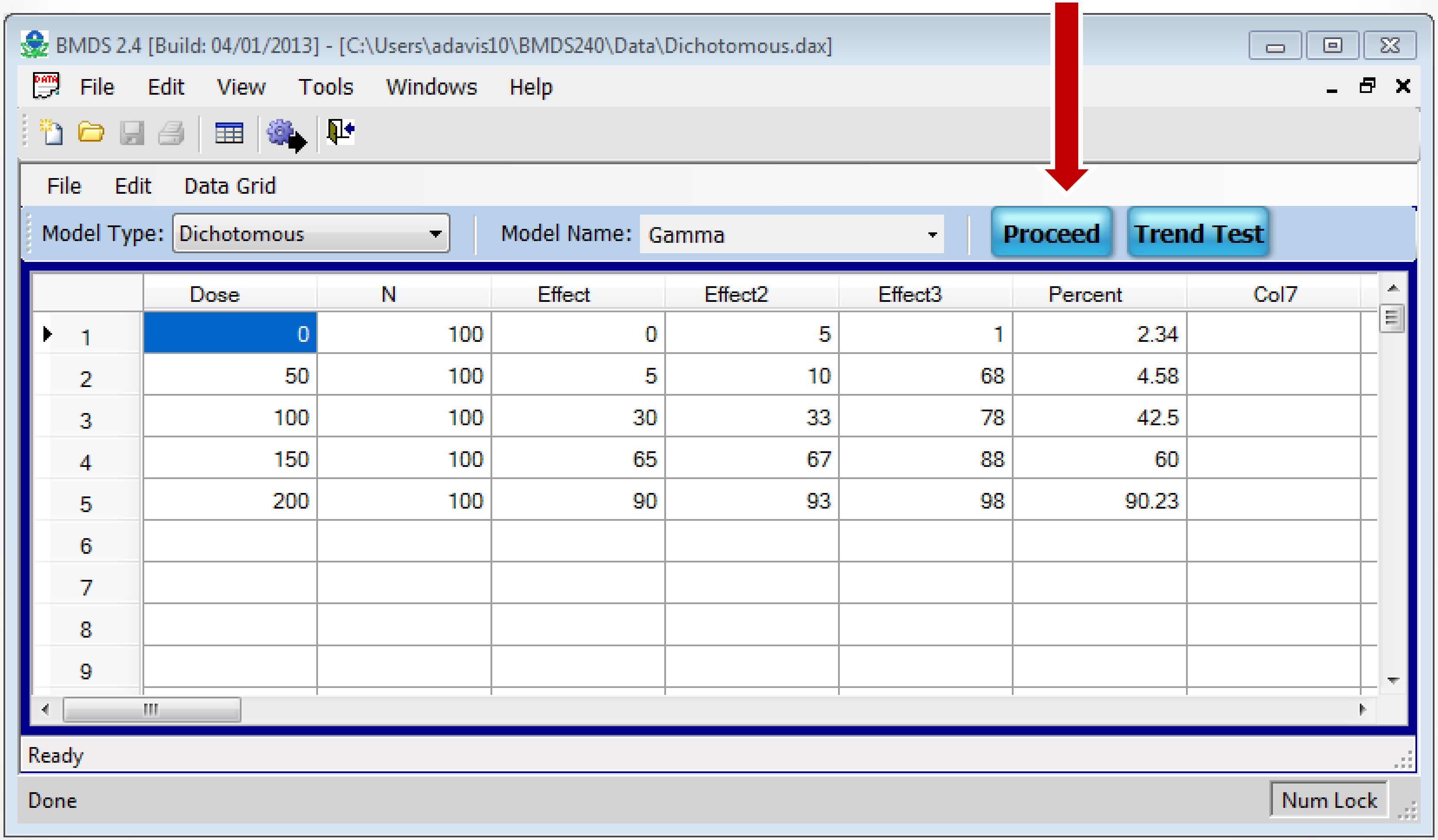
Model Name: Gamma

	Dose	N	Effect			Percent	Col7
1	0	100			1	2.34	
2	50	100			68	4.58	
3	100	100	3		78	42.5	
4	150	100	6		88	60	
5	200	100	9		98	90.23	
6							
7							
8							
9							

Ready

95 row(s) added.

Running an Individual Model – Proceed to Option Screen

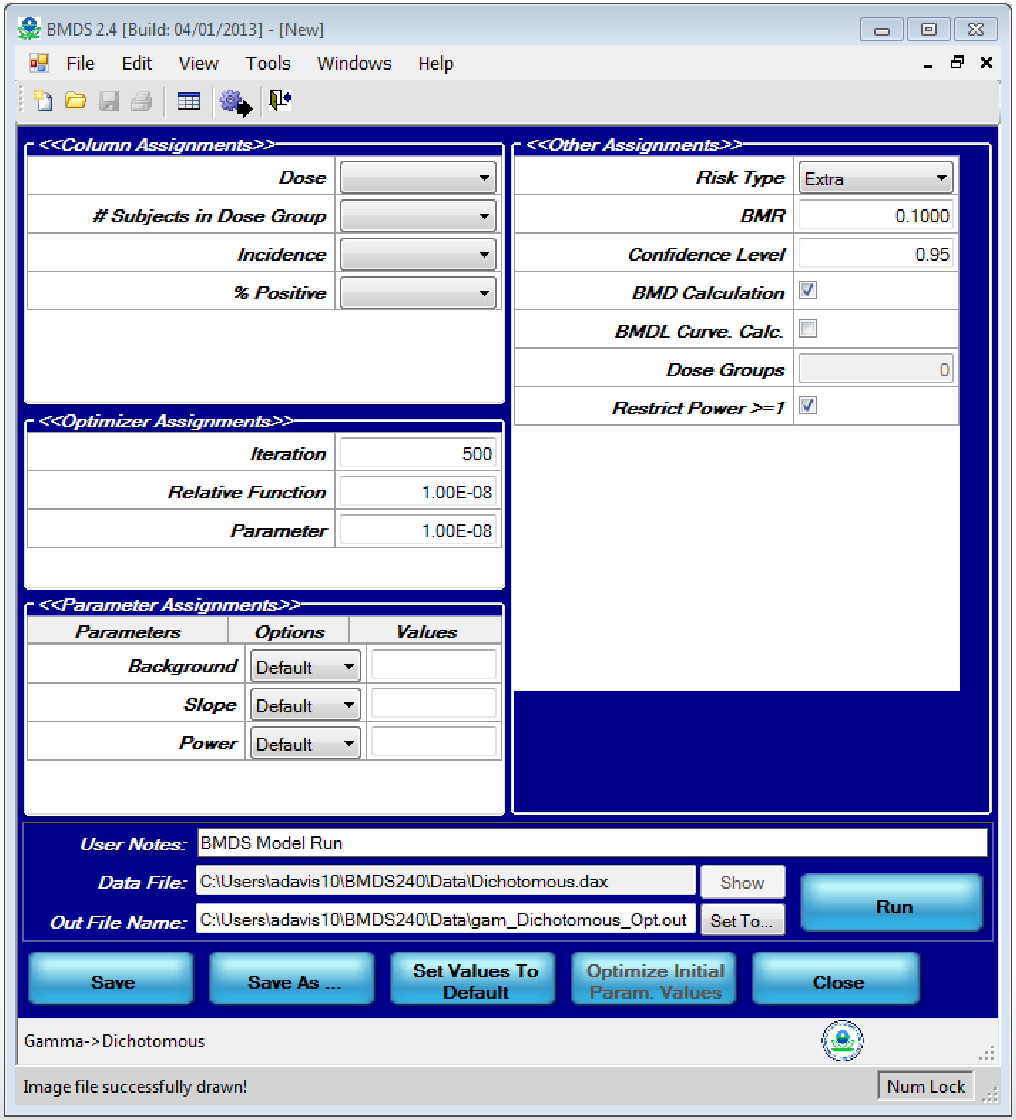


Model Type: Dichotomous

Model Name: Gamma

	Dose	N	Effect	Effect2	Effect3	Percent	Col7
1	0	100	0	5	1	2.34	
2	50	100	5	10	68	4.58	
3	100	100	30	33	78	42.5	
4	150	100	65	67	88	60	
5	200	100	90	93	98	90.23	
6							
7							
8							
9							

Model Option Screen



<<Column Assignments>>

Dose	
# Subjects in Dose Group	
Incidence	
% Positive	

<<Optimizer Assignments>>

Iteration	500
Relative Function	1.00E-08
Parameter	1.00E-08

<<Parameter Assignments>>

Parameters	Options	Values
Background	Default	
Slope	Default	
Power	Default	

<<Other Assignments>>

Risk Type	Extra
BMR	0.1000
Confidence Level	0.95
BMD Calculation	☑
BMDL Curve. Calc.	☐
Dose Groups	0
Restrict Power >=1	☑

User Notes: BMDS Model Run

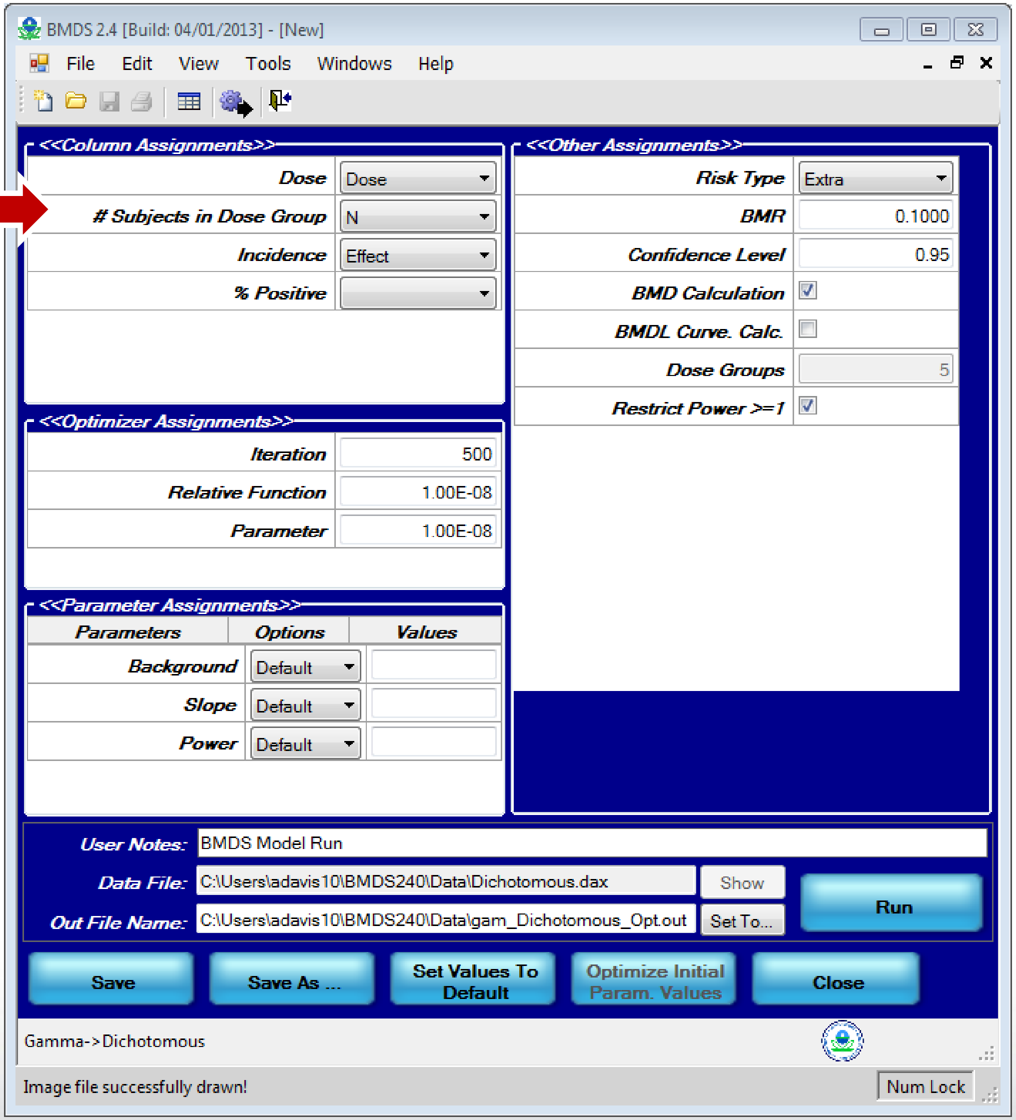
Data File: C:\Users\adavis10\BMDS240\Data\Dichotomous.dax

Out File Name: C:\Users\adavis10\BMDS240\Data\gam_Dichotomous_Opt.out

Gamma->Dichotomous

Image file successfully drawn!

Selecting Column Assignments



<<Column Assignments>>

Dose: Dose
Subjects in Dose Group: N
Incidence: Effect
% Positive:

<<Optimizer Assignments>>

Iteration: 500
Relative Function: 1.00E-08
Parameter: 1.00E-08

<<Parameter Assignments>>

Parameters	Options	Values
Background	Default	
Slope	Default	
Power	Default	

<<Other Assignments>>

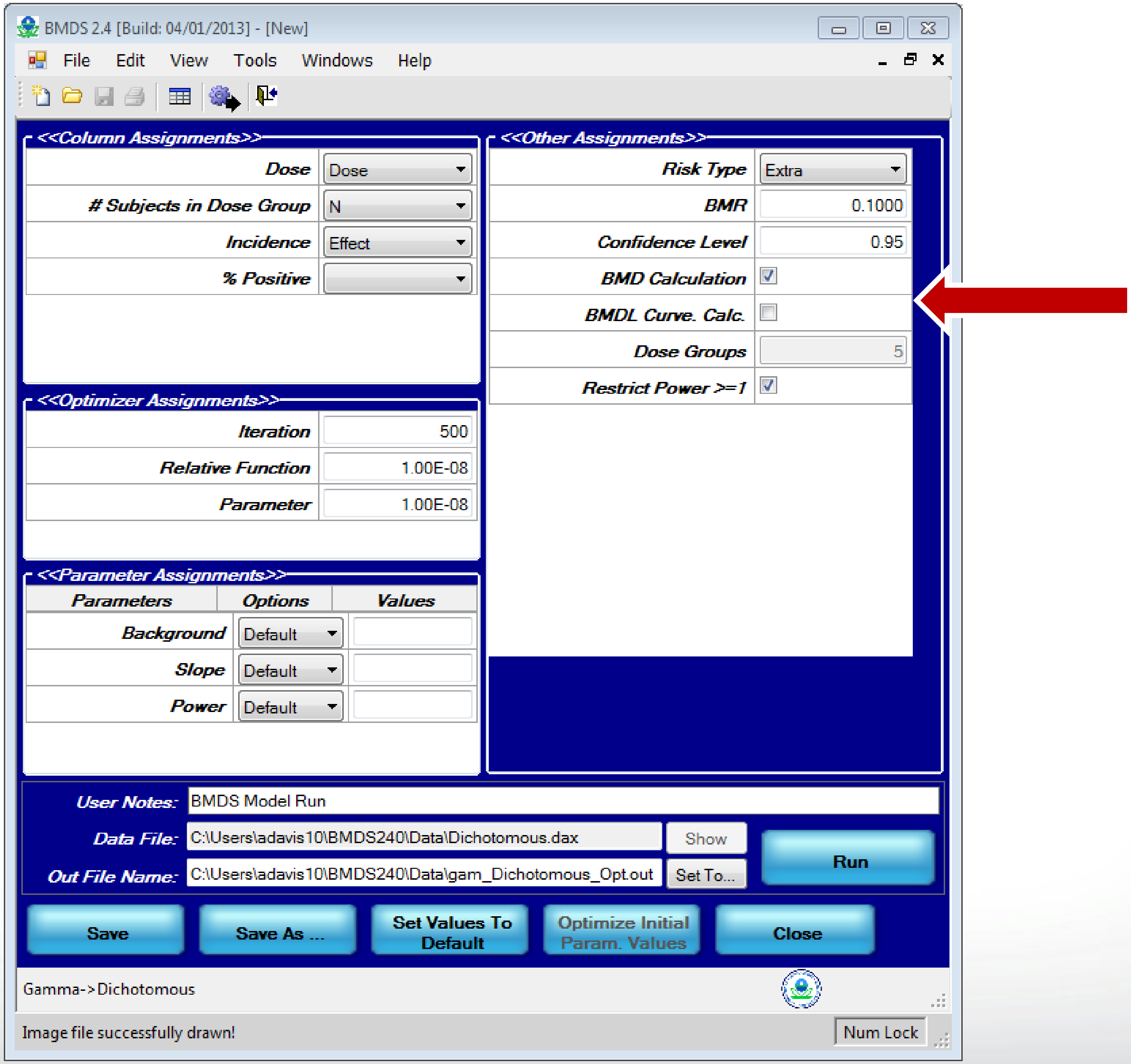
Risk Type: Extra
BMR: 0.1000
Confidence Level: 0.95
BMD Calculation: ☑
BMDL Curve. Calc.: ☐
Dose Groups: 5
Restrict Power >=1: ☑

User Notes: BMDS Model Run
Data File: C:\Users\adavis10\BMDS240\Data\Dichotomous.dax
Out File Name: C:\Users\adavis10\BMDS240\Data\gam_Dichotomous_Opt.out

Gamma->Dichotomous

Image file successfully drawn!

Selecting Model Options



<<Column Assignments>>

Dose	Dose
# Subjects in Dose Group	N
Incidence	Effect
% Positive	

<<Optimizer Assignments>>

Iteration	500
Relative Function	1.00E-08
Parameter	1.00E-08

<<Parameter Assignments>>

Parameters	Options	Values
Background	Default	
Slope	Default	
Power	Default	

<<Other Assignments>>

Risk Type	Extra
BMR	0.1000
Confidence Level	0.95
BMD Calculation	☑
BMDL Curve. Calc.	☐
Dose Groups	5
Restrict Power >=1	☑

User Notes: BMDS Model Run

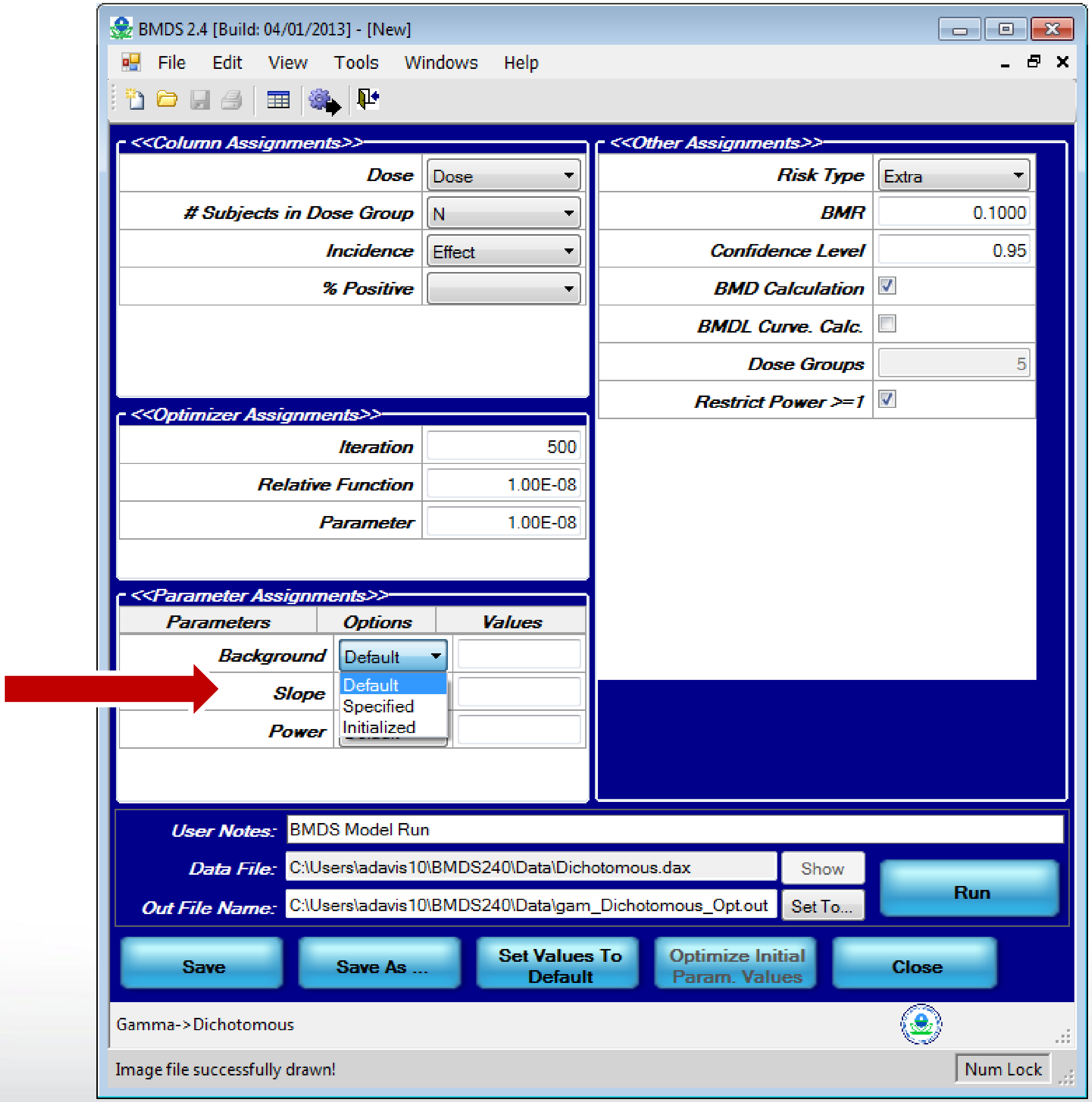
Data File: C:\Users\adavis10\BMDS240\Data\Dichotomous.dax

Out File Name: C:\Users\adavis10\BMDS240\Data\gam_Dichotomous_Opt.out

Gamma->Dichotomous

Image file successfully drawn!

Specifying Model Parameters



<<Column Assignments>>

Dose	Dose
# Subjects in Dose Group	N
Incidence	Effect
% Positive	

<<Optimizer Assignments>>

Iteration	500
Relative Function	1.00E-08
Parameter	1.00E-08

<<Parameter Assignments>>

Parameters	Options	Values
Background	Default Default Specified Initialized	
Slope		
Power		

<<Other Assignments>>

Risk Type	Extra
BMR	0.1000
Confidence Level	0.95
BMD Calculation	☑
BMDL Curve. Calc.	☐
Dose Groups	5
Restrict Power >=1	☑

User Notes: BMDS Model Run

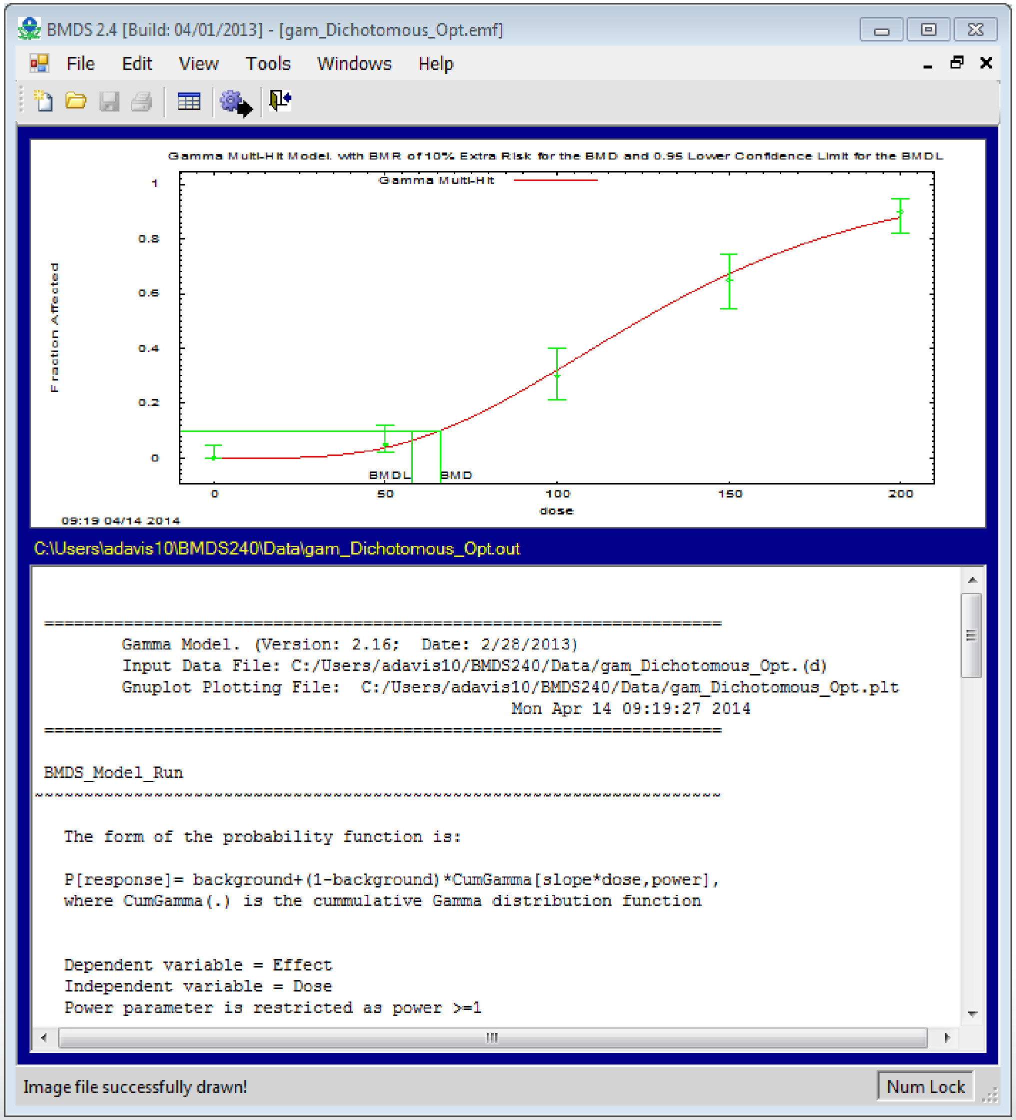
Data File: C:\Users\adavis10\BMDS240\Data\Dichotomous.dax

Out File Name: C:\Users\adavis10\BMDS240\Data\gam_Dichotomous_Opt.out

Gamma->Dichotomous

Image file successfully drawn!

Dichotomous Model Plot and Output Files



C:\Users\adavis10\BMDS240\Data\gam_Dichotomous_Opt.out

```
 ====================================================================
          Gamma Model. (Version: 2.16;  Date: 2/28/2013)
          Input Data File: C:/Users/adavis10/BMDS240/Data/gam_Dichotomous_Opt.(d)
          Gnuplot Plotting File:  C:/Users/adavis10/BMDS240/Data/gam_Dichotomous_Opt.plt
                                                  Mon Apr 14 09:19:27 2014
 ====================================================================

 BMDS_Model_Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

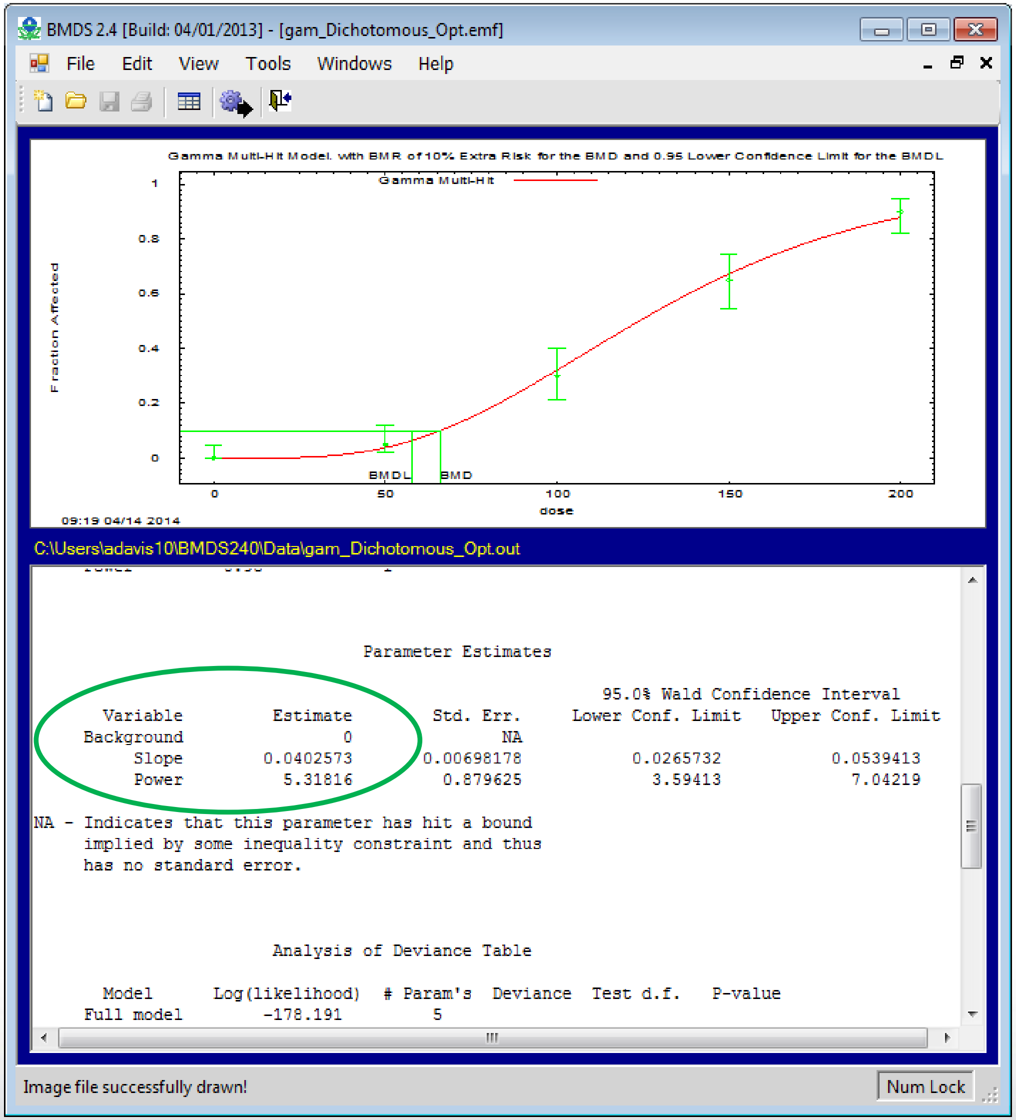
   The form of the probability function is:

   P[response]= background+(1-background)*CumGamma[slope*dose,power],
   where CumGamma(.) is the cummulative Gamma distribution function


   Dependent variable = Effect
   Independent variable = Dose
   Power parameter is restricted as power >=1
```

Image file successfully drawn!

Dichotomous Model Parameter Estimates



```
                           Parameter Estimates

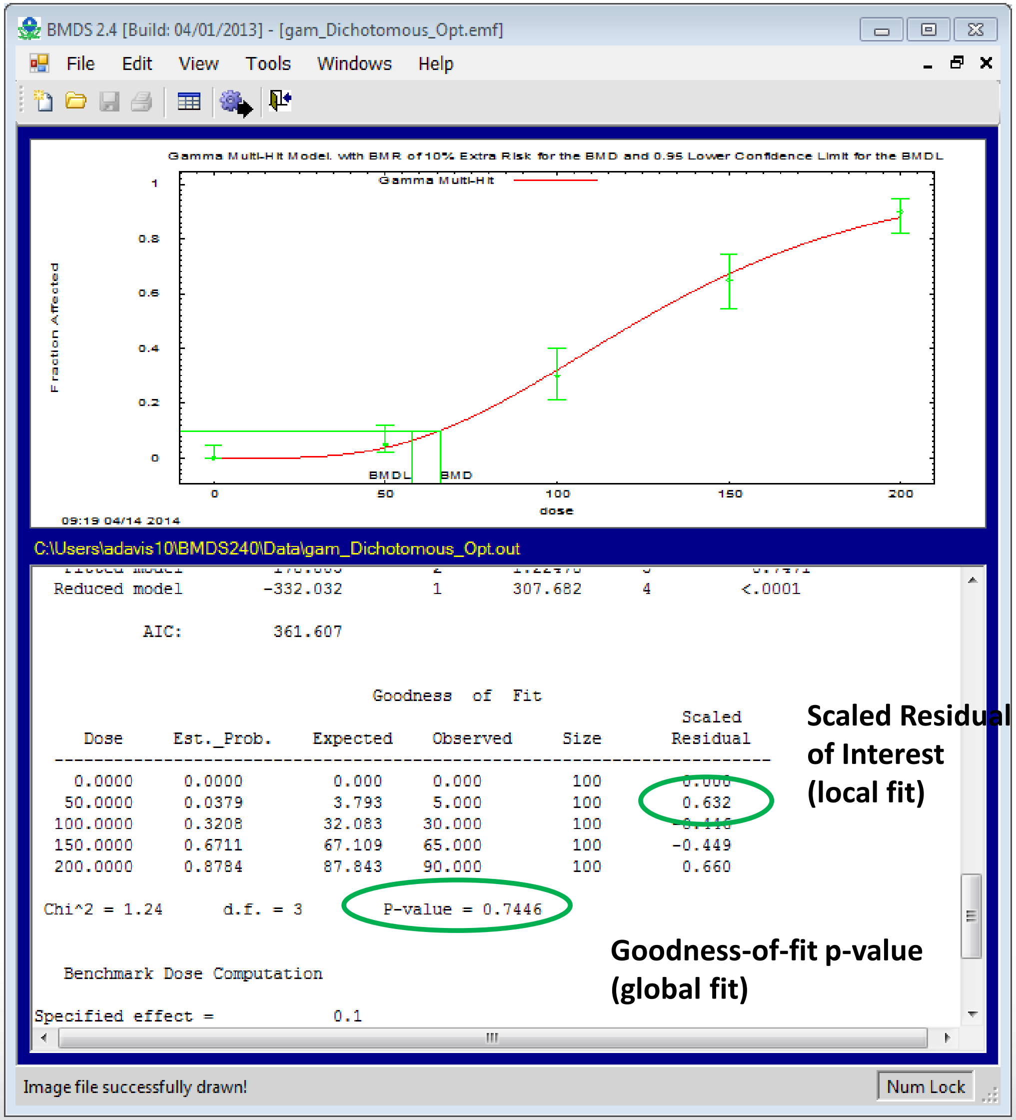
                                                95.0% Wald Confidence Interval
   Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
 Background                0              NA
      Slope        0.0402573      0.00698178            0.0265732           0.0539413
      Power          5.31816        0.879625              3.59413             7.04219

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


                      Analysis of Deviance Table

   Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
 Full model        -178.191         5
```

Dichotomous Model Fit Statistics



```
 Reduced model        -332.032         1        307.682       4          <.0001

          AIC:          361.607


                          Goodness  of  Fit
                                                                Scaled
     Dose      Est._Prob.    Expected    Observed     Size     Residual
  ------------------------------------------------------------------------
    0.0000     0.0000         0.000       0.000        100       0.000
   50.0000     0.0379         3.793       5.000        100       0.632
  100.0000     0.3208        32.083      30.000        100      -0.446
  150.0000     0.6711        67.109      65.000        100      -0.449
  200.0000     0.8784        87.843      90.000        100       0.660

 Chi^2 = 1.24      d.f. = 3        P-value = 0.7446


   Benchmark Dose Computation

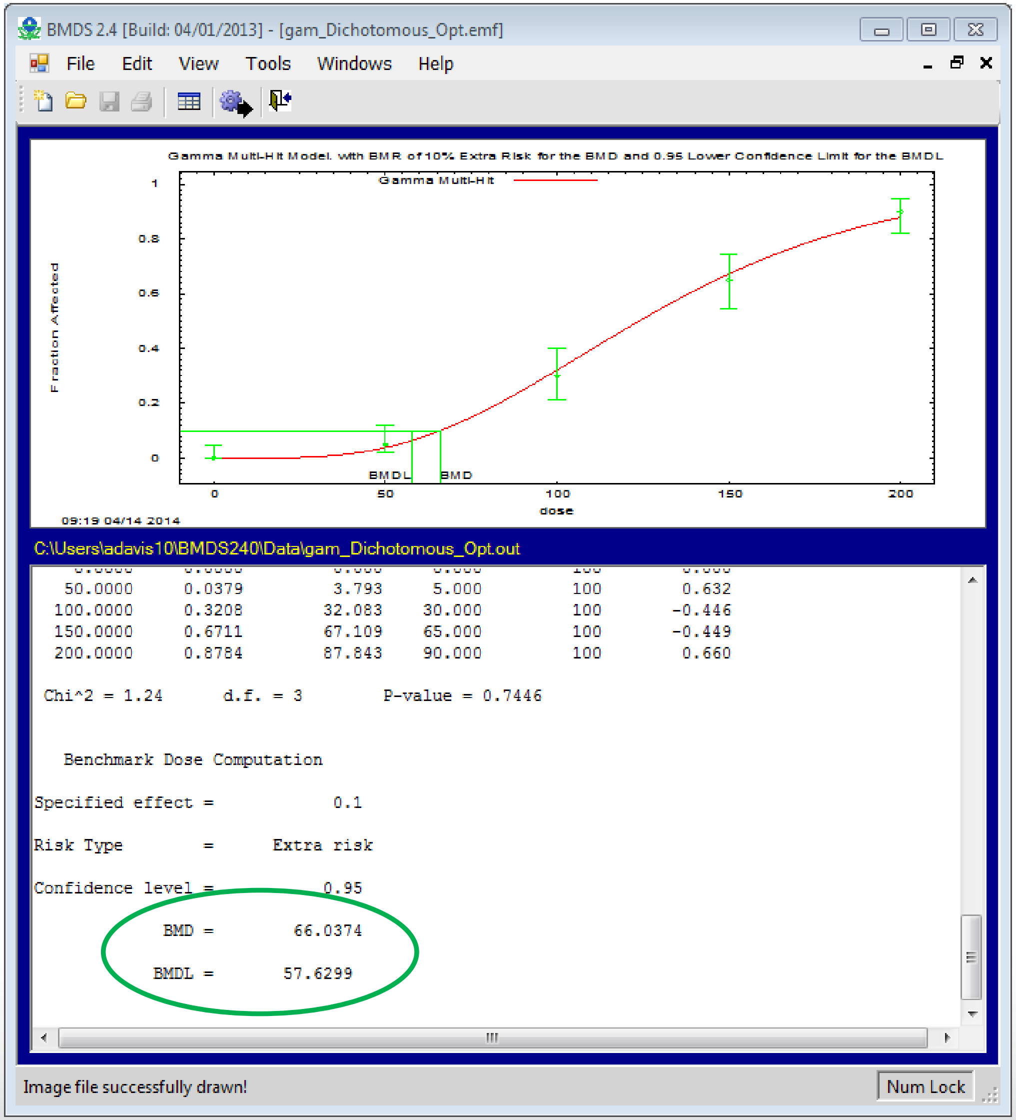
Specified effect =             0.1
```

Image file successfully drawn!

Scaled Residual of Interest (local fit)

Goodness-of-fit p-value (global fit)

BMD and BMDL Estimates



C:\Users\adavis10\BMDS240\Data\gam_Dichotomous_Opt.out

```
   50.0000     0.0379        3.793     5.000        100        0.632
  100.0000     0.3208       32.083    30.000        100       -0.446
  150.0000     0.6711       67.109    65.000        100       -0.449
  200.0000     0.8784       87.843    90.000        100        0.660

 Chi^2 = 1.24      d.f. = 3        P-value = 0.7446


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

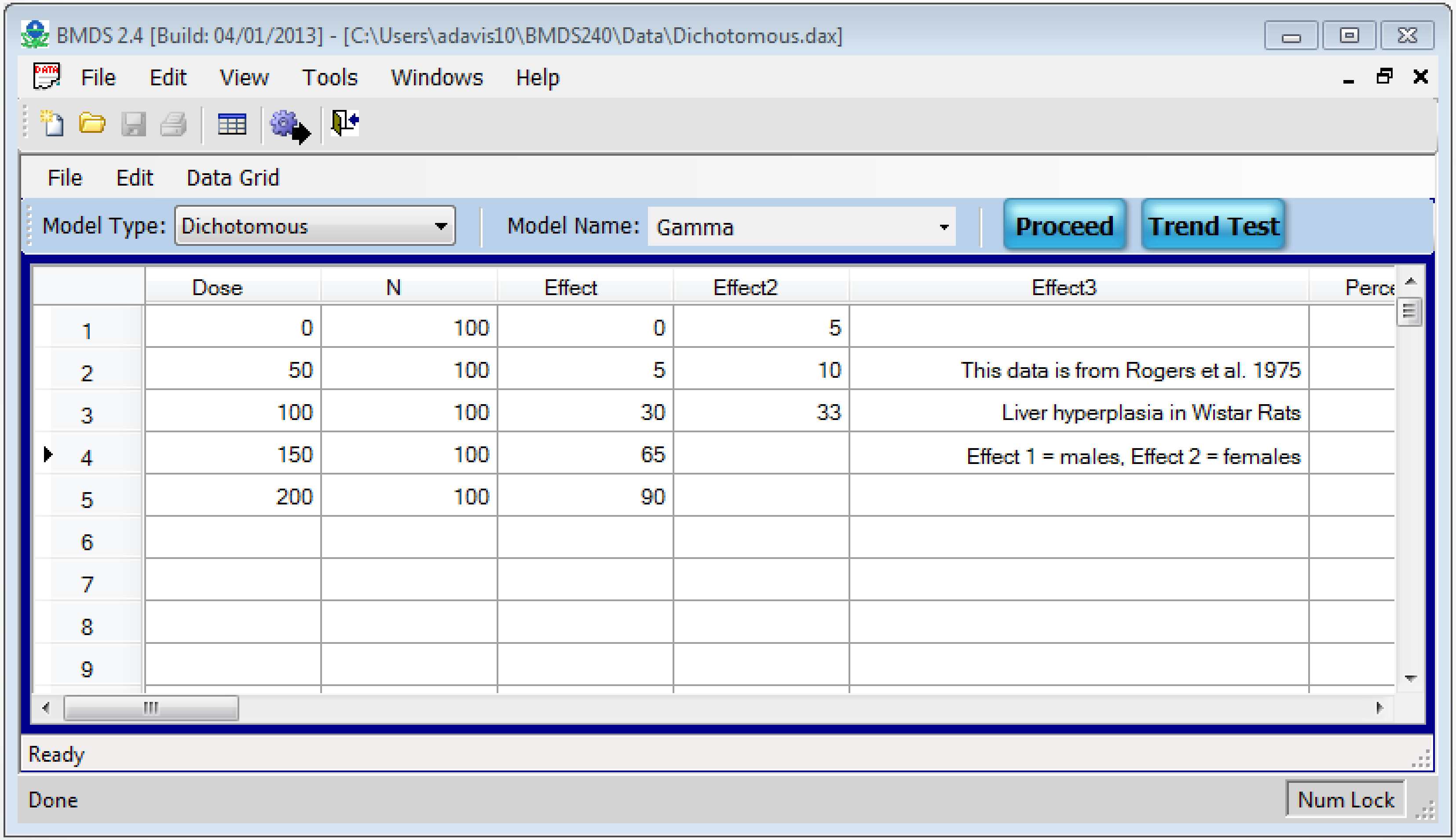
Confidence level =           0.95

             BMD =        66.0374

            BMDL =       57.6299
```

Opening Output and Plot Files after Analysis

New Flexibility in Datafile Structure



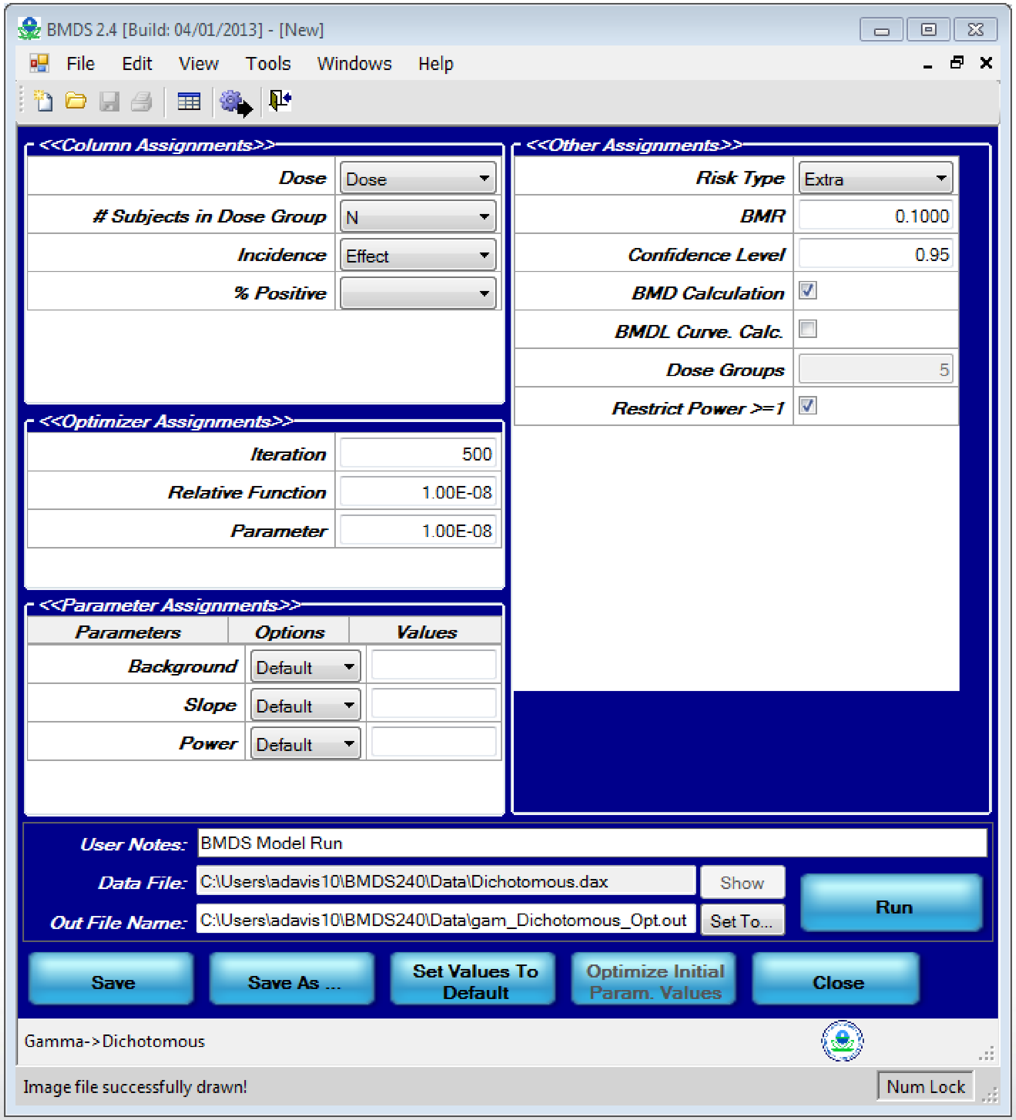
BMDS 2.4 [Build: 04/01/2013] - [C:\Users\adavis10\BMDS240\Data\Dichotomous.dax]

Model Type: Dichotomous

Model Name: Gamma

	Dose	N	Effect	Effect2	Effect3	Perce
1	0	100	0	5		
2	50	100	5	10	This data is from Rogers et al. 1975	
3	100	100	30	33	Liver hyperplasia in Wistar Rats	
4	150	100	65		Effect 1 = males, Effect 2 = females	
5	200	100	90			
6						
7						
8						
9						

New Flexibility in Datafile Structure



<<Column Assignments>>

Dose	Dose
# Subjects in Dose Group	N
Incidence	Effect
% Positive	

<<Optimizer Assignments>>

Iteration	500
Relative Function	1.00E-08
Parameter	1.00E-08

<<Parameter Assignments>>

Parameters	Options	Values
Background	Default	
Slope	Default	
Power	Default	

<<Other Assignments>>

Risk Type	Extra
BMR	0.1000
Confidence Level	0.95
BMD Calculation	☑
BMDL Curve. Calc.	☐
Dose Groups	5
Restrict Power >=1	☑

User Notes: BMDS Model Run

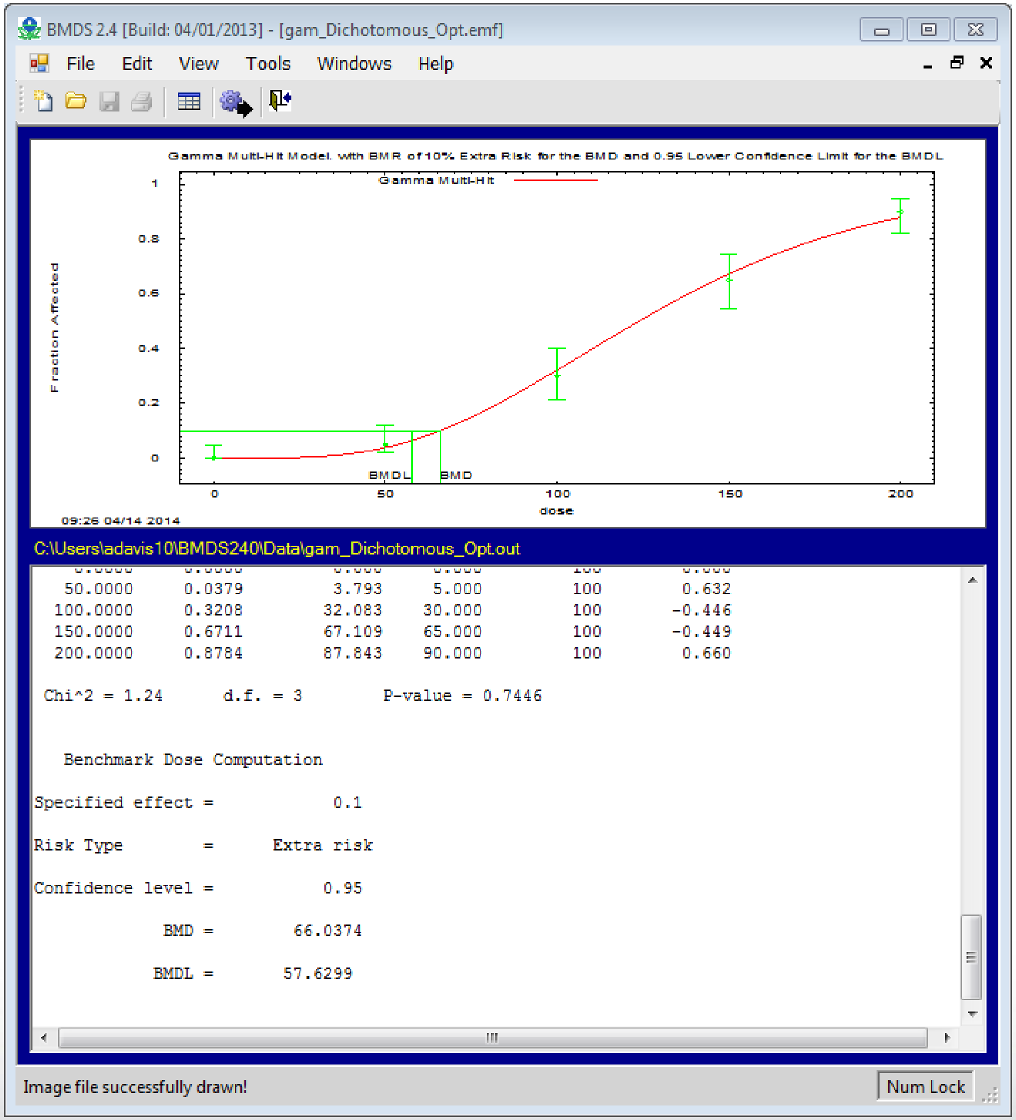
Data File: C:\Users\adavis10\BMDS240\Data\Dichotomous.dax

Out File Name: C:\Users\adavis10\BMDS240\Data\gam_Dichotomous_Opt.out

Gamma->Dichotomous

Image file successfully drawn!

New Flexibility in Datafile Structure



```
   50.0000     0.0379        3.793     5.000          100        0.632
  100.0000     0.3208       32.083    30.000          100       -0.446
  150.0000     0.6711       67.109    65.000          100       -0.449
  200.0000     0.8784       87.843    90.000          100        0.660

 Chi^2 = 1.24      d.f. = 3        P-value = 0.7446


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

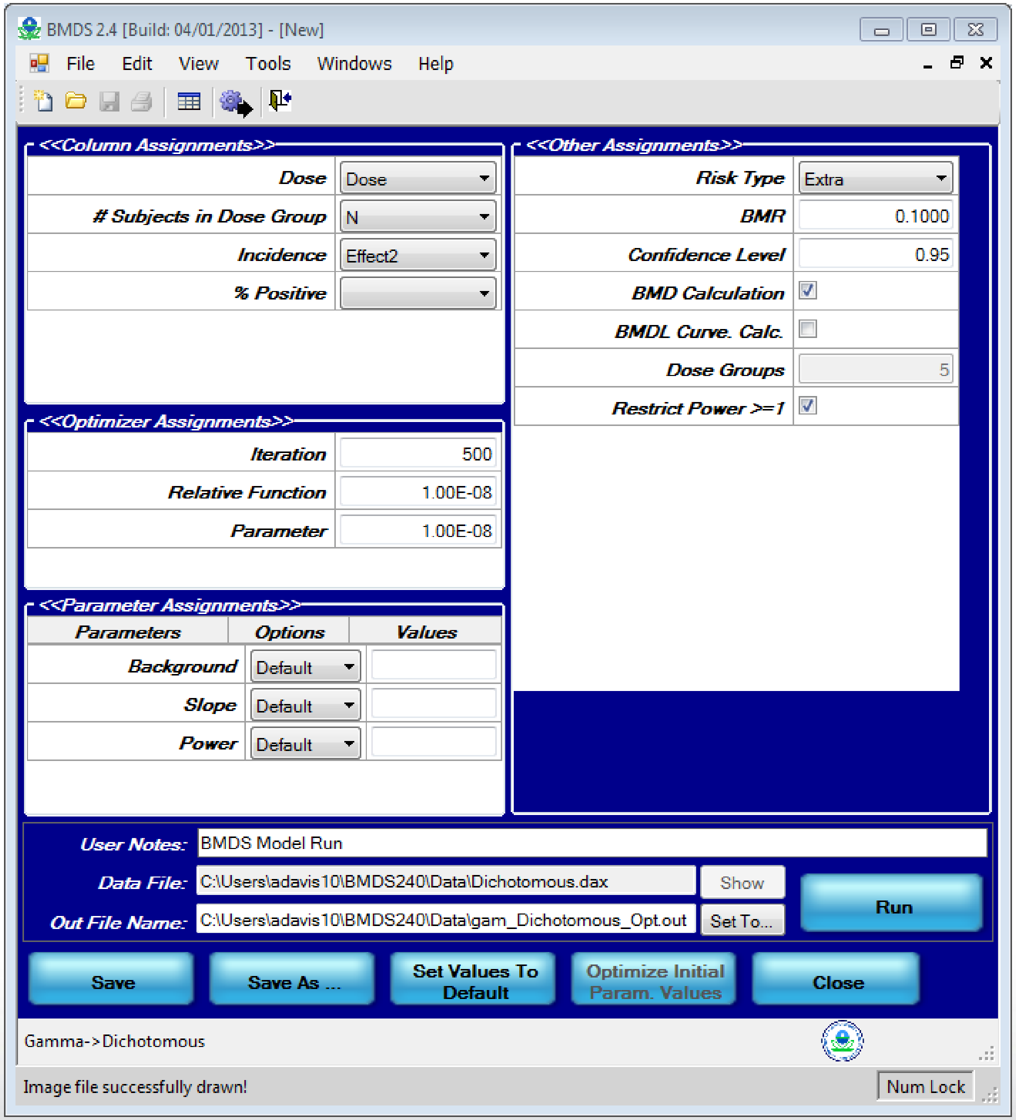
Confidence level =           0.95

             BMD =         66.0374

            BMDL =        57.6299
```

Image file successfully drawn!

New Flexibility in Datafile Structure



<<Column Assignments>>

Dose	Dose
# Subjects in Dose Group	N
Incidence	Effect2
% Positive	

<<Optimizer Assignments>>

Iteration	500
Relative Function	1.00E-08
Parameter	1.00E-08

<<Parameter Assignments>>

Parameters	Options	Values
Background	Default	
Slope	Default	
Power	Default	

<<Other Assignments>>

Risk Type	Extra
BMR	0.1000
Confidence Level	0.95
BMD Calculation	☑
BMDL Curve. Calc.	☐
Dose Groups	5
Restrict Power >=1	☑

User Notes: BMDS Model Run

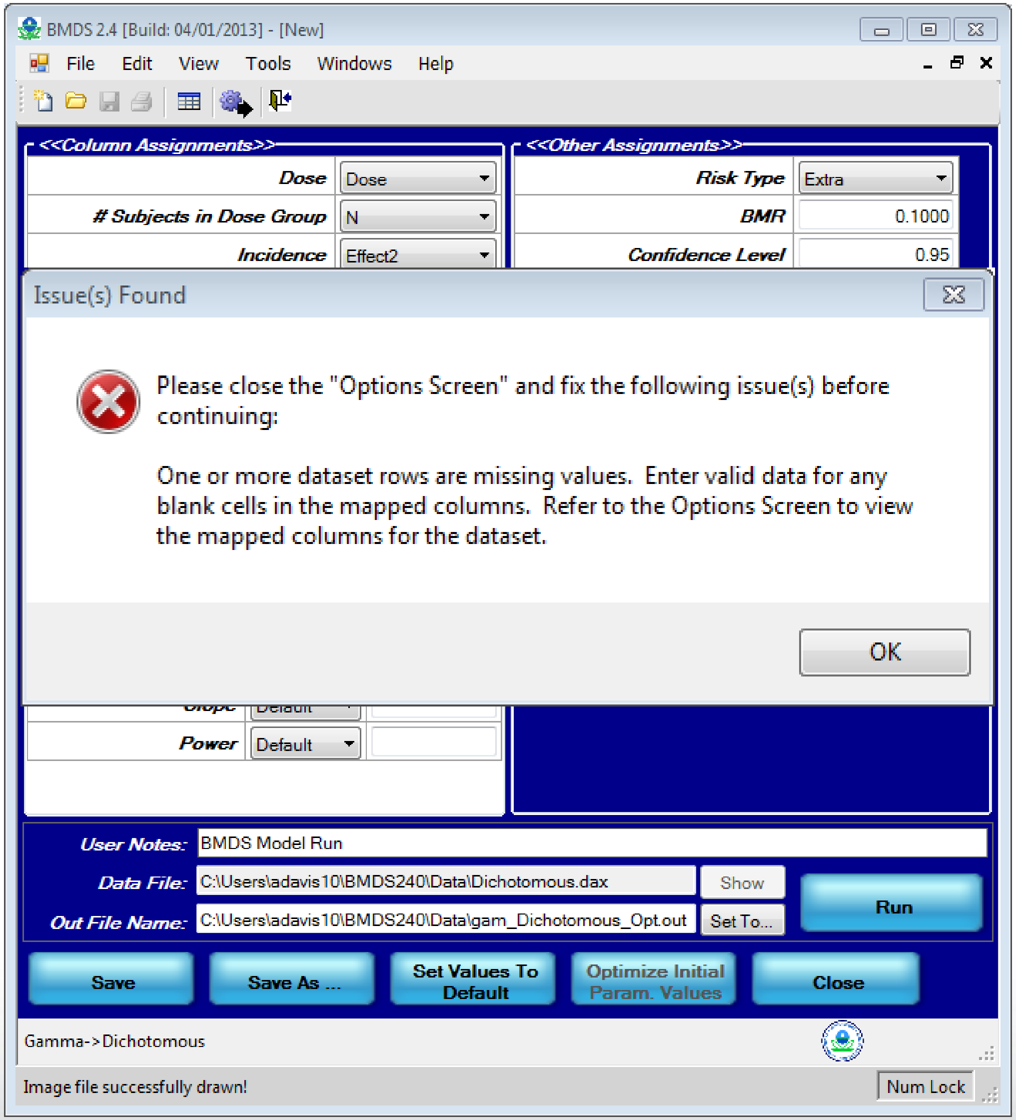
Data File: C:\Users\adavis10\BMDS240\Data\Dichotomous.dax

Out File Name: C:\Users\adavis10\BMDS240\Data\gam_Dichotomous_Opt.out

Gamma->Dichotomous

Image file successfully drawn!

New Flexibility in Datafile Structure



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

Dose: Dose

Subjects in Dose Group: N

Incidence: Effect2

Risk Type: Extra

BMR: 0.1000

Confidence Level: 0.95

Issue(s) Found

Please close the "Options Screen" and fix the following issue(s) before continuing:

One or more dataset rows are missing values. Enter valid data for any blank cells in the mapped columns. Refer to the Options Screen to view the mapped columns for the dataset.

Power: Default

User Notes: BMDS Model Run

Data File: C:\Users\adavis10\BMDS240\Data\Dichotomous.dax

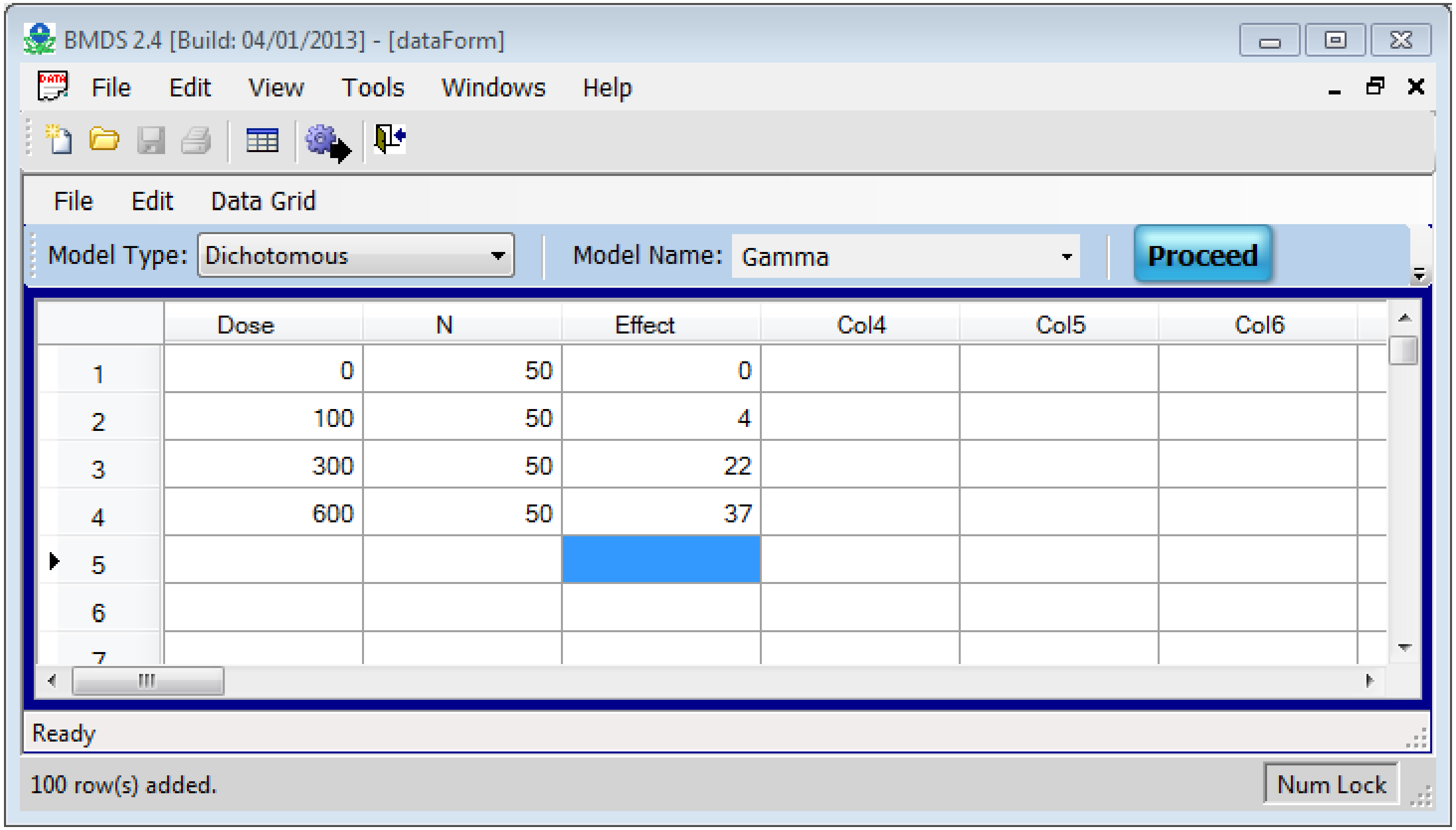
Out File Name: C:\Users\adavis10\BMDS240\Data\gam_Dichotomous_Opt.out

Gamma->Dichotomous

Image file successfully drawn!

Dichotomous Data – Exercise #1

Dichotomous Exercise #1



Model Type: Dichotomous

Model Name: Gamma

	Dose	N	Effect	Col4	Col5	Col6
1	0	50	0			
2	100	50	4			
3	300	50	22			
4	600	50	37			
5						
6						
7						

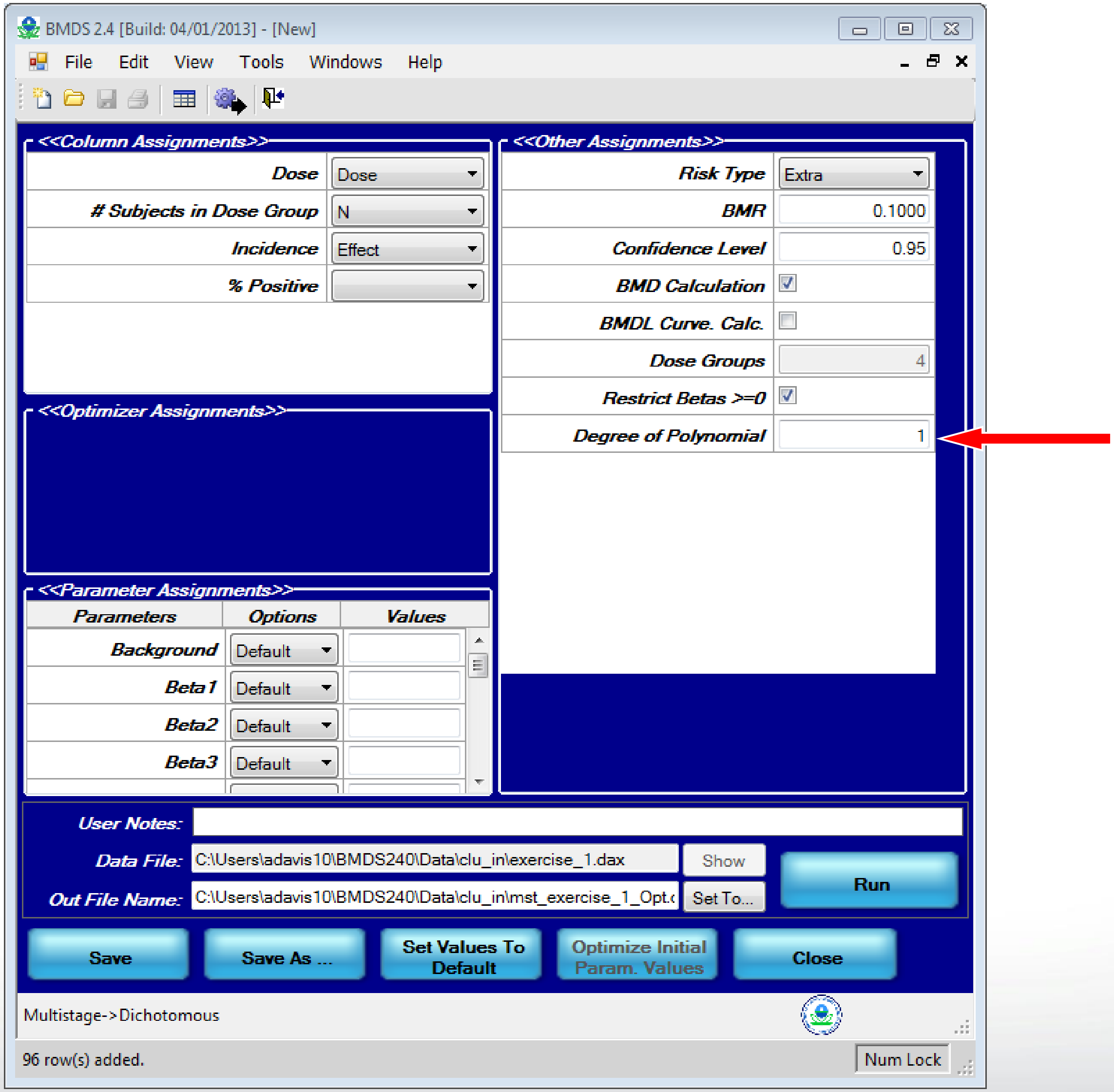
100 row(s) added.

Manually enter these data and save as Exercise_1.dax

Dichotomous Exercise #1

- **Run the Multistage (1st degree) model against the Exercise #1 data using the Individual Model Run option**
  - Make sure to change the Degree Polynomial =1

Dichotomous Exercise #1



<<Column Assignments>>

Dose	Dose
# Subjects in Dose Group	N
Incidence	Effect
% Positive	

<<Other Assignments>>

Risk Type	Extra
BMR	0.1000
Confidence Level	0.95
BMD Calculation	☑
BMDL Curve. Calc.	☐
Dose Groups	4
Restrict Betas >=0	☑
Degree of Polynomial	1

<<Parameter Assignments>>

Parameters	Options	Values
Background	Default	
Beta1	Default	
Beta2	Default	
Beta3	Default	

User Notes:

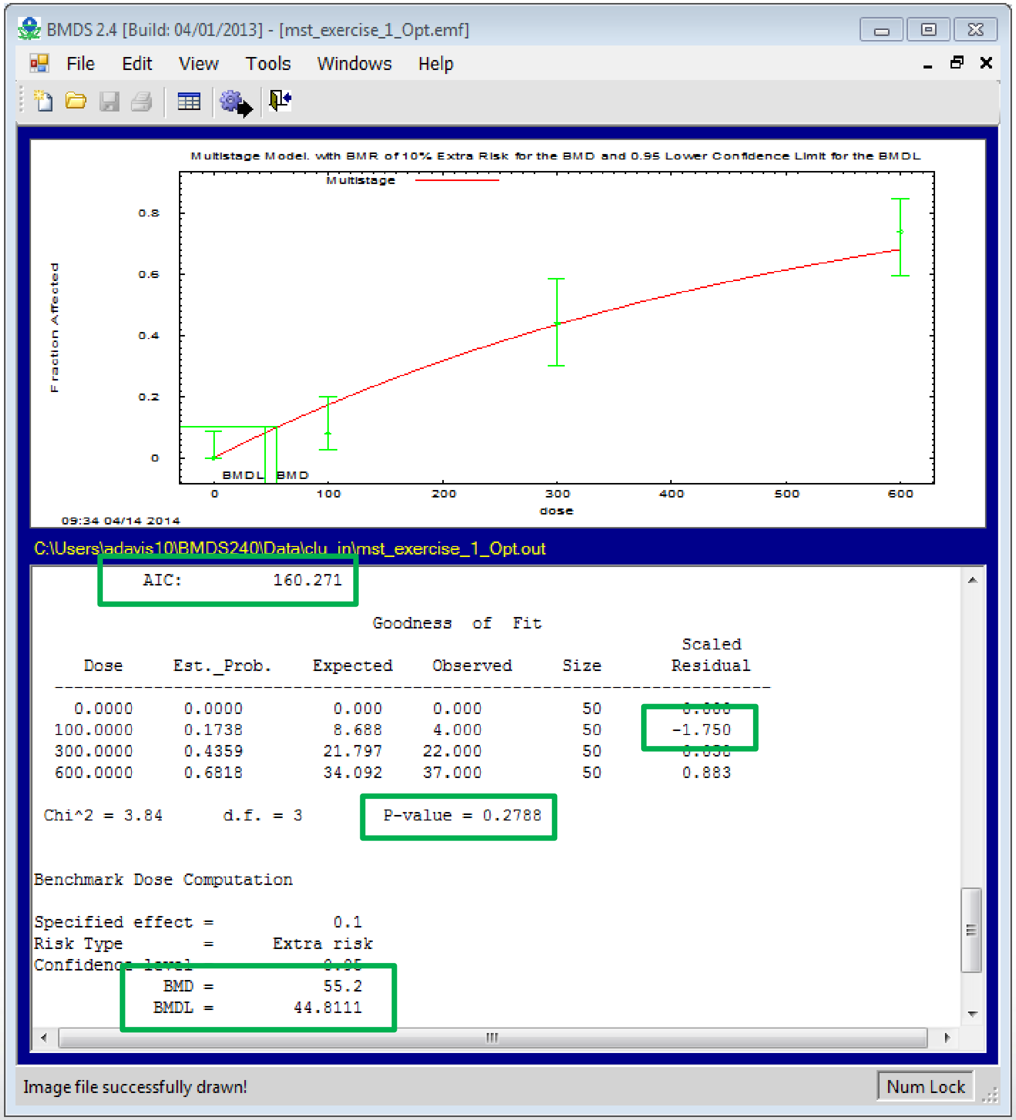
Data File: C:\Users\adavis10\BMDS240\Data\clu_in\exercise_1.dax

Out File Name: C:\Users\adavis10\BMDS240\Data\clu_in\mst_exercise_1_Opt.

Multistage->Dichotomous

96 row(s) added.

Dichotomous Exercise #1



```
     AIC:           160.271


                                  Goodness  of  Fit
                                                                  Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
  ------------------------------------------------------------------------
    0.0000     0.0000         0.000       0.000         50         0.000
  100.0000     0.1738         8.688       4.000         50        -1.750
  300.0000     0.4359        21.797      22.000         50         0.058
  600.0000     0.6818        34.092      37.000         50         0.883

 Chi^2 = 3.84      d.f. = 3        P-value = 0.2788


Benchmark Dose Computation

Specified effect =            0.1
Risk Type        =      Extra risk
Confidence level =           0.95
             BMD =           55.2
            BMDL =        44.8111
```

Dichotomous Exercise #1

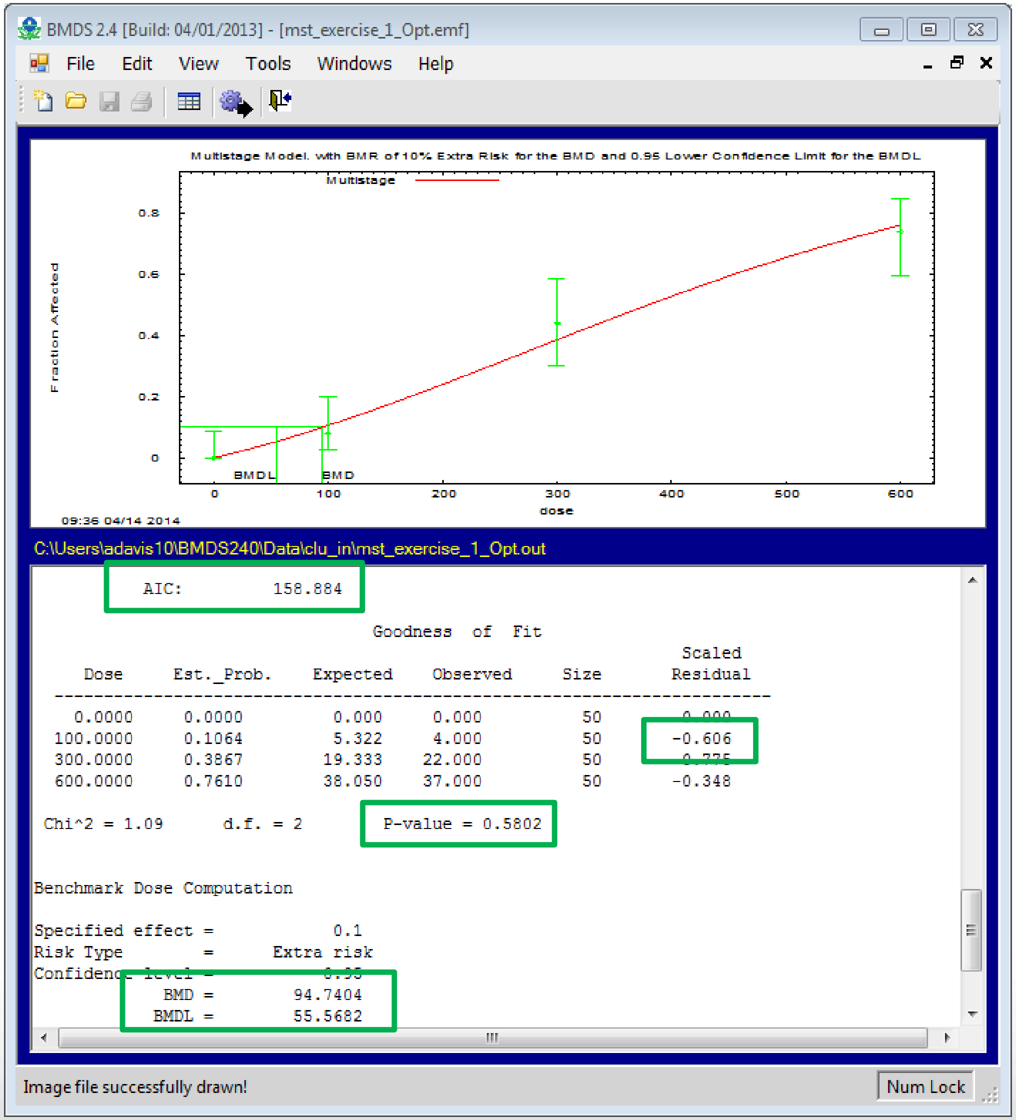
BMDS Summary Table

	Multistage 1^{st} degree		
BMD_{10}	55.2		
$BMDL_{10}$	44.81		
AIC	160.271		
p value	0.2788		
Scaled residual	-1.750		

Dichotomous Exercise #1

- **Run the Multistage (2nd degree) model against the Exercise #1 data using the Individual Model Run option**
    - Make sure to change the Degree Polynomial = 2

Dichotomous Exercise #1



C:\Users\adavis10\BMDS240\Data\clu_in\mst_exercise_1_Opt.out

```
        AIC:              158.884


                                  Goodness  of  Fit
                                                                 Scaled
     Dose      Est._Prob.    Expected    Observed     Size      Residual
  ------------------------------------------------------------------------
    0.0000     0.0000          0.000       0.000        50         0.000
  100.0000     0.1064          5.322       4.000        50        -0.606
  300.0000     0.3867         19.333      22.000        50         0.775
  600.0000     0.7610         38.050      37.000        50        -0.348

 Chi^2 = 1.09      d.f. = 2        P-value = 0.5802


Benchmark Dose Computation

Specified effect =            0.1
Risk Type        =      Extra risk
Confidence level =           0.95
             BMD =        94.7404
            BMDL =        55.5682
```

Image file successfully drawn!

Dichotomous Exercise #1

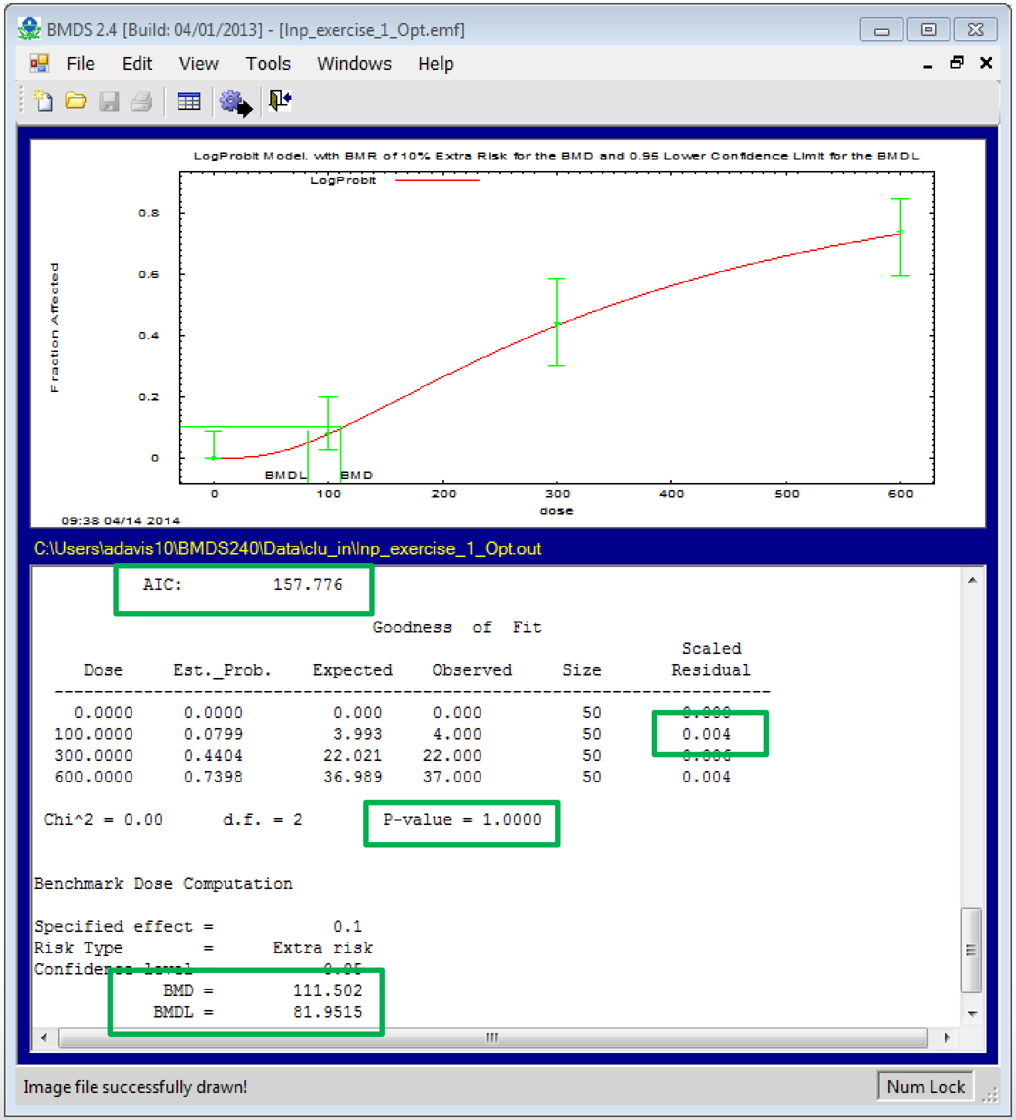
BMDS Summary Table

	Multistage 1st degree	Multistage 2nd degree	
BMD_{10}	55.2	94.7	
$BMDL_{10}$	44.81	55.6	
AIC	160.271	158.884	
p value	0.2788	0.5802	
Scaled residual	-1.750	-0.606	

Dichotomous Exercise #1

- **Run the Log-Probit model (restricted slope, must manually select in option file) against the Exercise #1 data using the Individual Model Run option**

Dichotomous Exercise #1



```
        AIC:          157.776


                                  Goodness  of  Fit
                                                                 Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
  ------------------------------------------------------------------------
    0.0000     0.0000         0.000       0.000        50         0.000
  100.0000     0.0799         3.993       4.000        50         0.004
  300.0000     0.4404        22.021      22.000        50         0.006
  600.0000     0.7398        36.989      37.000        50         0.004

 Chi^2 = 0.00       d.f. = 2        P-value = 1.0000


Benchmark Dose Computation

Specified effect =             0.1
Risk Type        =      Extra risk
Confidence level =            0.95
             BMD =         111.502
            BMDL =         81.9515
```

Dichotomous Exercise #1

BMDS Summary Table

	Multistage 1st degree	**Multistage 2nd degree**	**Log-probit**
BMD_{10}	55.2	94.74	111.50
$BMDL_{10}$	44.81	55.56	81.95
AIC	160.271	158.884	157.776
p value	0.2788	0.5802	1.000
Scaled residual	-1.750	-0.606	0.004

Dichotomous Exercise #1

- **Individual Model**
  - Visual inspection of model fit
  - Goodness of fit *p*-value
  - Chi-squared residuals (nearest BMD)

- **Across Models**
  - When BMDLs are "sufficiently close" – Akaike's Information Criterion (AIC) (the smaller, the better)
  - When BMDLs are not "sufficiently close – Smallest BMDL

Dichotomous Exercise #1

BMDS Summary Table

	Multistage 1st degree	**Multistage 2nd degree**	**Log-probit**
BMD_{10}	55.2	94.74	111.50
$BMDL_{10}$	44.81	55.56	81.95
AIC	160.271	158.884	157.776
p value	0.2788	0.5802	1.000
Scaled residual	-1.750	-0.606	0.004

Dichotomous Data – Batch Processing using the BMDS Wizard

The BMDS Wizard

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

BMDS Wizard Installation

- **When installing BMDS 2.5, preformatted BMDS Wizard templates will automatically be stored in the "Wizard" folder in the BMDS250 directory**
  - To avoid possible problems running the Wizard, EPA recommends that the file path of the Wizard subdirectory not contain any non-alphanumeric characters
  - EPA users will need to locate their BMDS 250 and Wizard folders in the Users folder (C:\Users\name\BMDS240)
  - Non-EPA users can locate their folders in other directories, but the Wizard folder must be in the same directory as the BMDS executable

BMDS Wizard Macros

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

Excel 2003

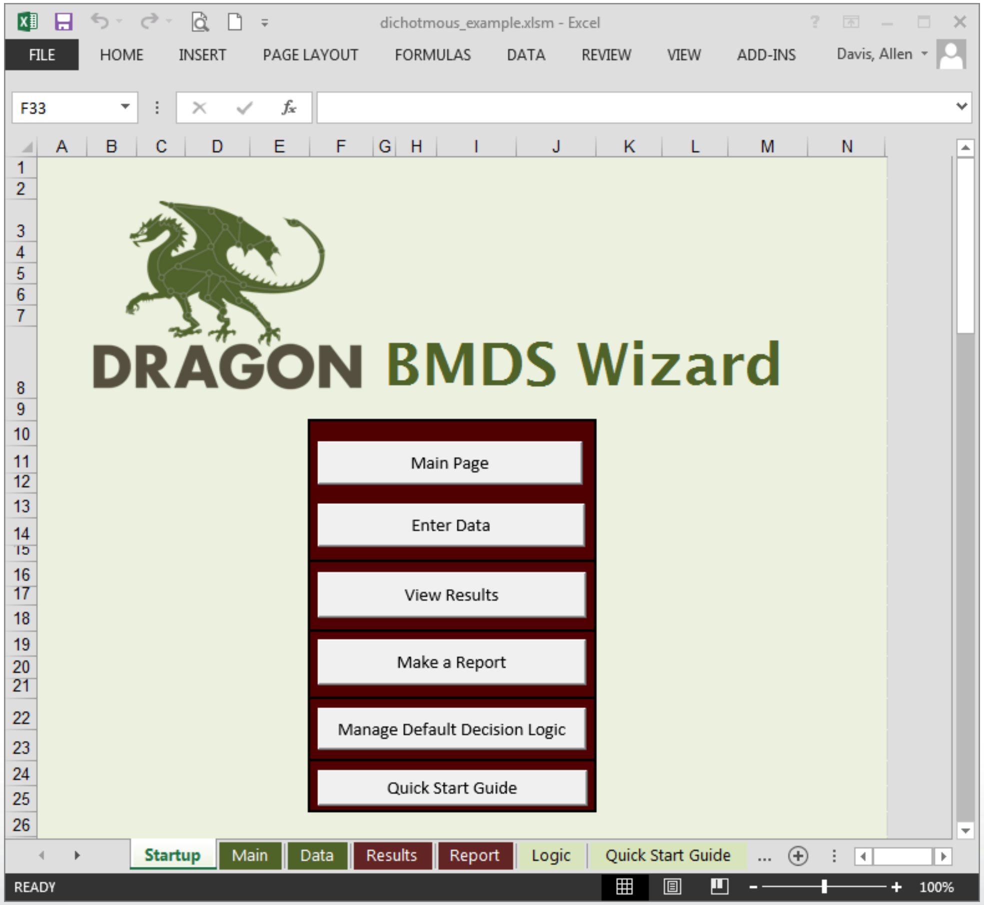
- Open Excel
- Select the "Tools" Menu
- Select Options
- Go to "Security" tab and click "Macro Security"
- Change security level to "Medium" or "Low"

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

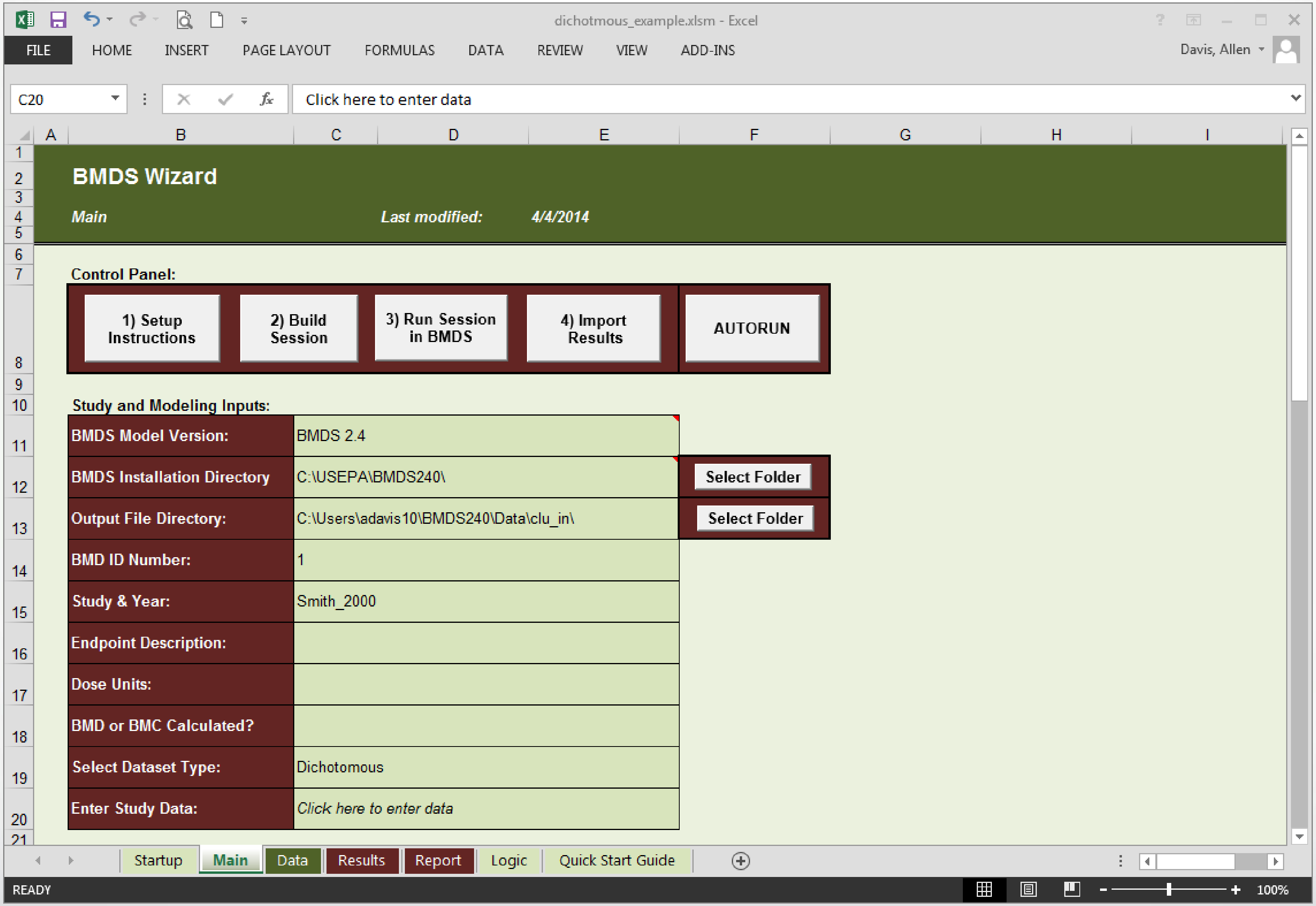
- **Excel 2010/2013**
- Open Excel
- Select "File" on the Ribbon toolbar and click "Options"
- Go to the "Trust Center" tab and click "Trust Center Settings"
- Change "Macro Settings" to "Disable all macros with notification" or "Enable all macros"

Starting a BMDS Wizard Session

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



BMDS Wizard – Study and Modeling Inputs



BMDS Wizard

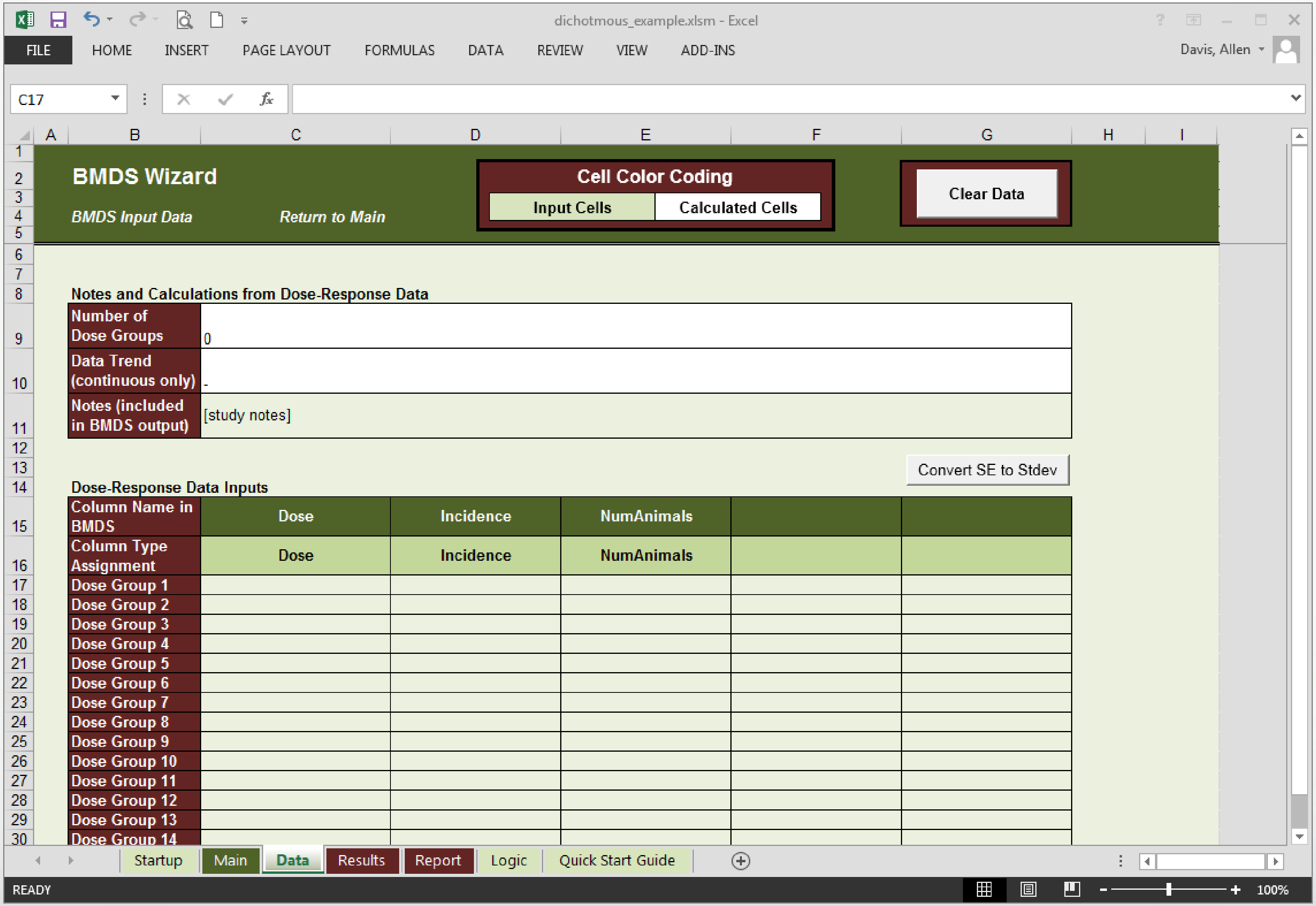
Main *Last modified:* *4/4/2014*

Control Panel:

Study and Modeling Inputs:

BMDS Model Version:	BMDS 2.4
BMDS Installation Directory	C:\USEPA\BMDS240\
Output File Directory:	C:\Users\adavis10\BMDS240\Data\clu_in\
BMD ID Number:	1
Study & Year:	Smith_2000
Endpoint Description:	
Dose Units:	
BMD or BMC Calculated?	
Select Dataset Type:	Dichotomous
Enter Study Data:	*Click here to enter data*

BMDS Wizard – Entering Data



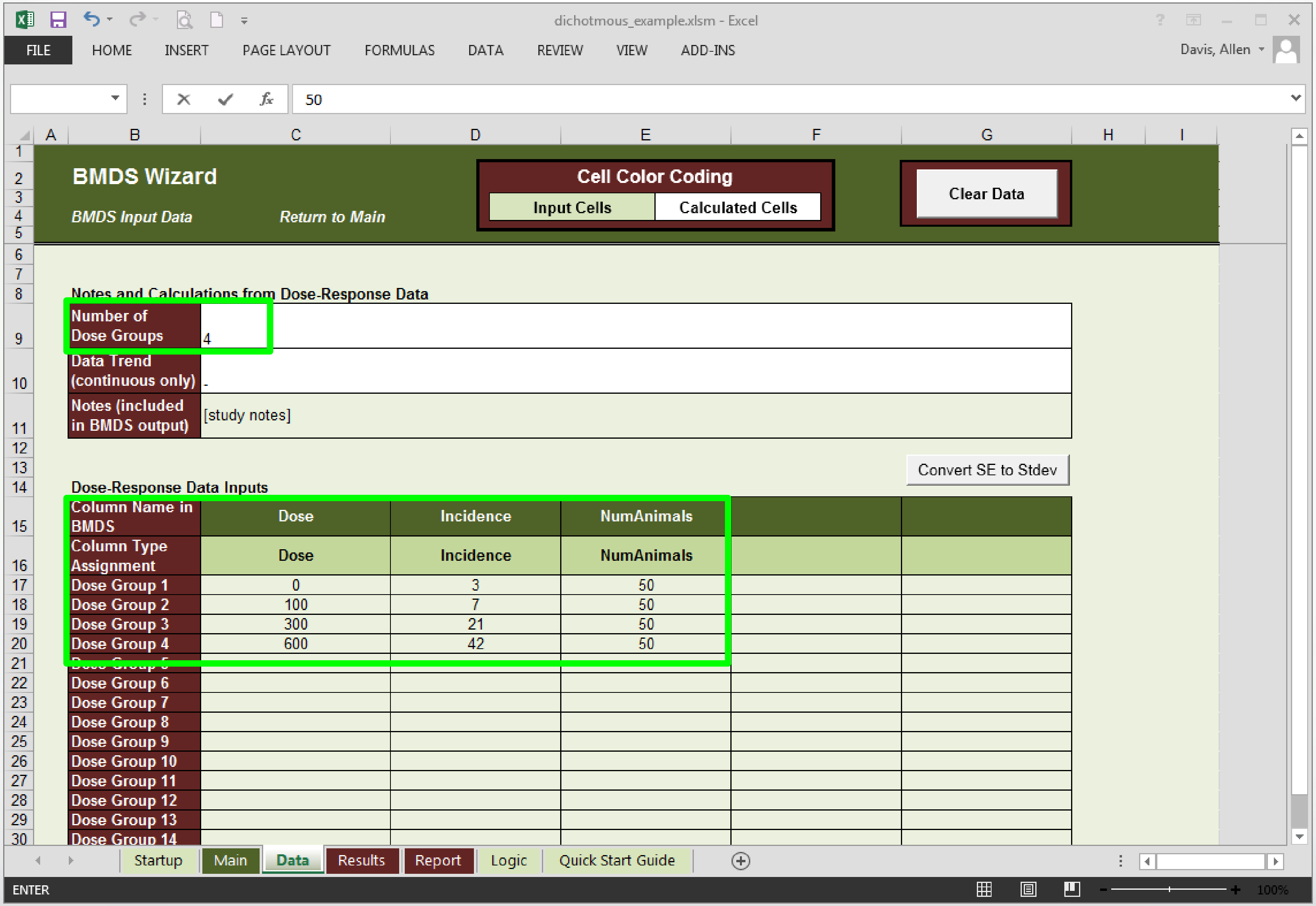
Notes and Calculations from Dose-Response Data

Number of Dose Groups	0
Data Trend (continuous only)	-
Notes (included in BMDS output)	[study notes]

Dose-Response Data Inputs

Column Name in BMDS	Dose	Incidence	NumAnimals		
Column Type Assignment	Dose	Incidence	NumAnimals		
Dose Group 1					
Dose Group 2					
Dose Group 3					
Dose Group 4					
Dose Group 5					
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					

BMDS Wizard – Entering Data



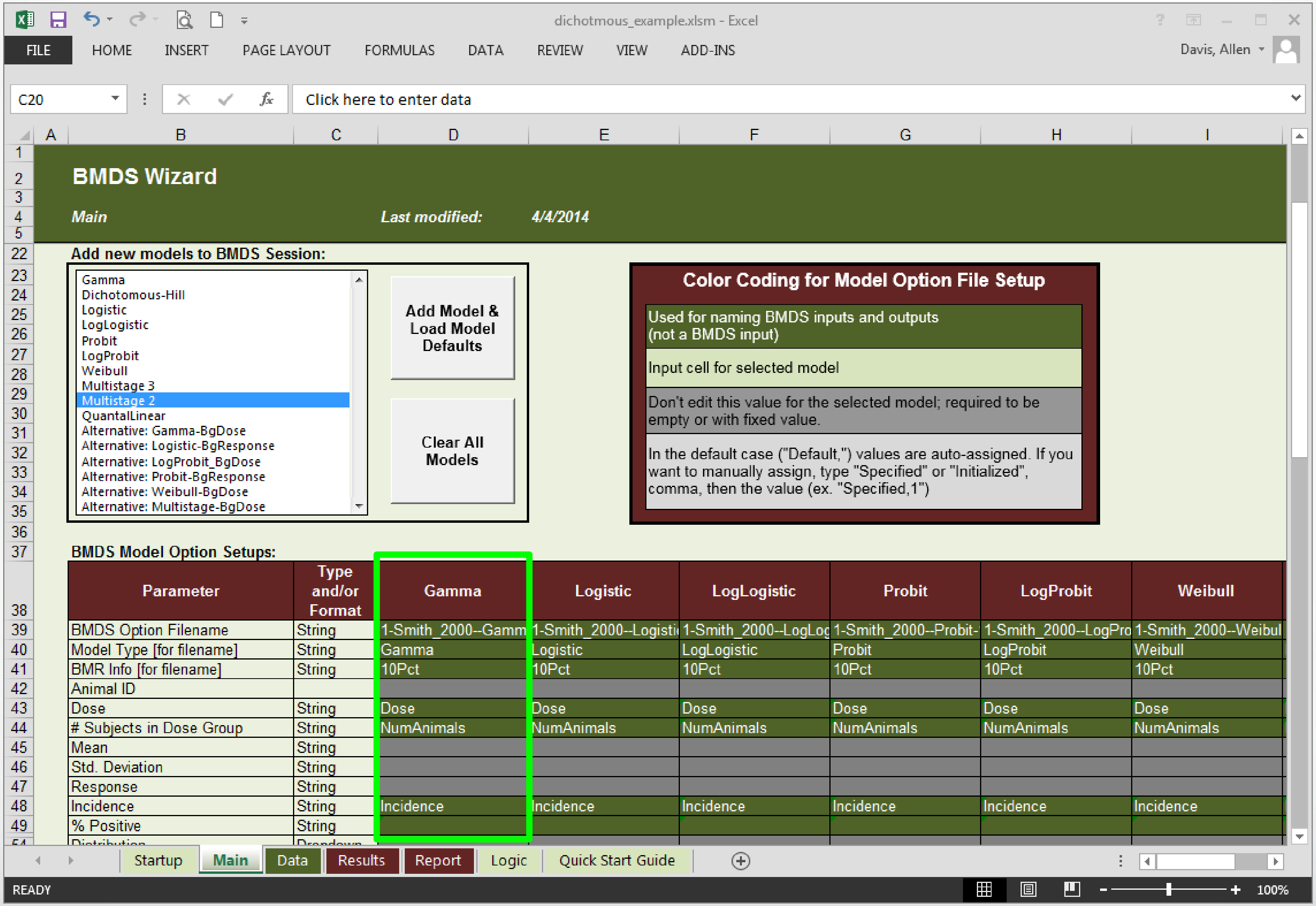
Notes and Calculations from Dose-Response Data

Number of Dose Groups	4
Data Trend (continuous only)	-
Notes (included in BMDS output)	[study notes]

Dose-Response Data Inputs

Column Name in BMDS	Dose	Incidence	NumAnimals		
Column Type Assignment	Dose	Incidence	NumAnimals		
Dose Group 1	0	3	50		
Dose Group 2	100	7	50		
Dose Group 3	300	21	50		
Dose Group 4	600	42	50		
Dose Group 5					
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					

BMDS Wizard – Model Parameters



BMDS Wizard

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

Add new models to BMDS Session:

- Gamma
- Dichotomous-Hill
- Logistic
- LogLogistic
- Probit
- LogProbit
- Weibull
- Multistage 3
- Multistage 2
- QuantalLinear
- Alternative: Gamma-BgDose
- Alternative: Logistic-BgResponse
- Alternative: LogProbit_BgDose
- Alternative: Probit-BgResponse
- Alternative: Weibull-BgDose
- Alternative: Multistage-BgDose

Color Coding for Model Option File Setup

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

Input cell for selected model

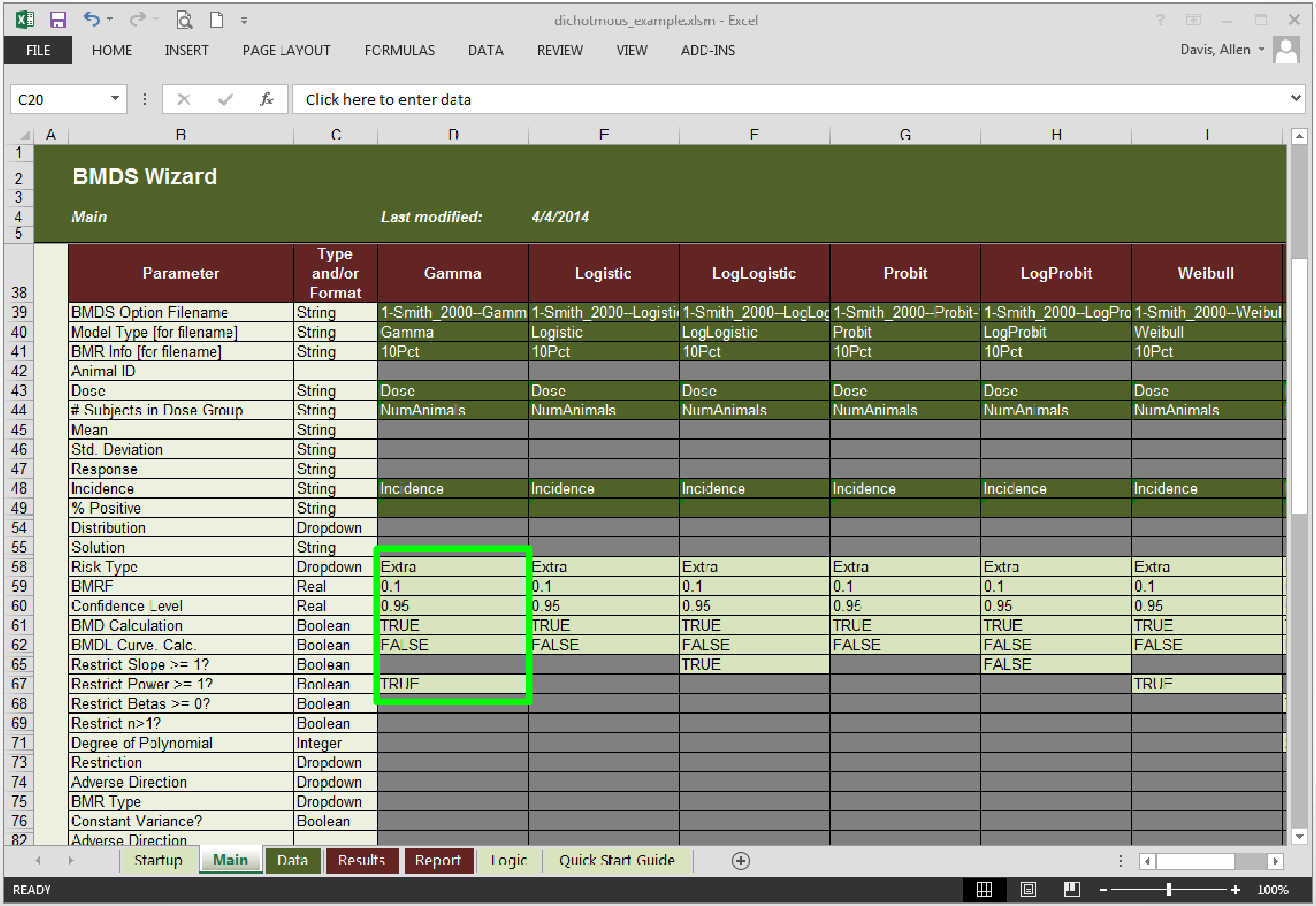
Don't edit this value for the selected model; required to be empty or with fixed value.

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	Gamma	Logistic	LogLogistic	Probit	LogProbit	Weibull
BMDS Option Filename	String	1-Smith_2000--Gamm	1-Smith_2000--Logisti	1-Smith_2000--LogLog	1-Smith_2000--Probit-	1-Smith_2000--LogPro	1-Smith_2000--Weibul
Model Type [for filename]	String	Gamma	Logistic	LogLogistic	Probit	LogProbit	Weibull
BMR Info [for filename]	String	10Pct	10Pct	10Pct	10Pct	10Pct	10Pct
Animal ID							
Dose	String	Dose	Dose	Dose	Dose	Dose	Dose
# Subjects in Dose Group	String	NumAnimals	NumAnimals	NumAnimals	NumAnimals	NumAnimals	NumAnimals
Mean	String						
Std. Deviation	String						
Response	String						
Incidence	String	Incidence	Incidence	Incidence	Incidence	Incidence	Incidence
% Positive	String						

BMDS Wizard – Model Parameters



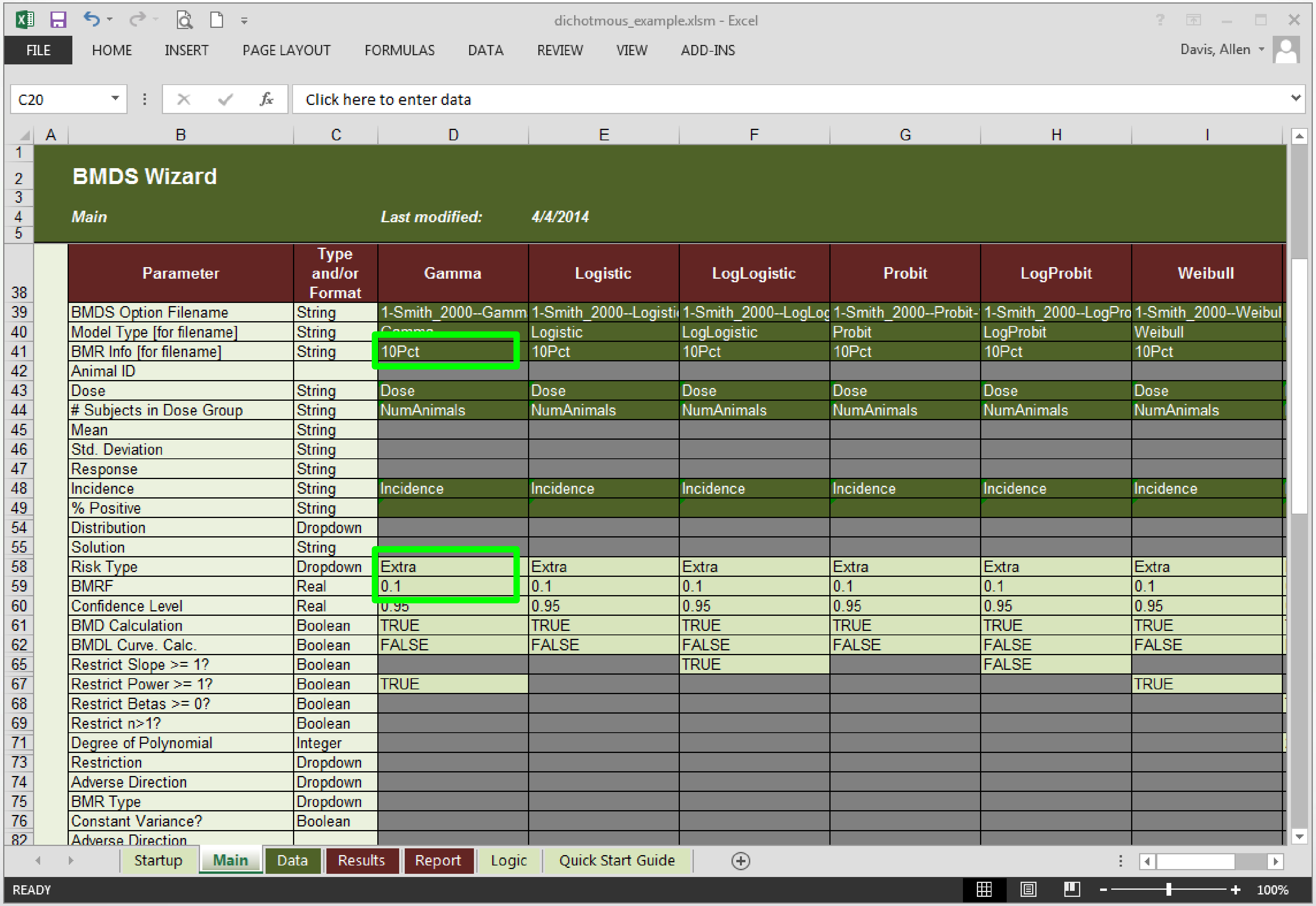
C20: Click here to enter data

BMDS Wizard

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

	Parameter	Type and/or Format	Gamma	Logistic	LogLogistic	Probit	LogProbit	Weibull
39	BMDS Option Filename	String	1-Smith_2000--Gamm	1-Smith_2000--Logisti	1-Smith_2000--LogLog	1-Smith_2000--Probit-	1-Smith_2000--LogPro	1-Smith_2000--Weibul
40	Model Type [for filename]	String	Gamma	Logistic	LogLogistic	Probit	LogProbit	Weibull
41	BMR Info [for filename]	String	10Pct	10Pct	10Pct	10Pct	10Pct	10Pct
42	Animal ID							
43	Dose	String	Dose	Dose	Dose	Dose	Dose	Dose
44	# Subjects in Dose Group	String	NumAnimals	NumAnimals	NumAnimals	NumAnimals	NumAnimals	NumAnimals
45	Mean	String						
46	Std. Deviation	String						
47	Response	String						
48	Incidence	String	Incidence	Incidence	Incidence	Incidence	Incidence	Incidence
49	% Positive	String						
54	Distribution	Dropdown						
55	Solution	String						
58	Risk Type	Dropdown	Extra	Extra	Extra	Extra	Extra	Extra
59	BMRF	Real	0.1	0.1	0.1	0.1	0.1	0.1
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	FALSE	FALSE
65	Restrict Slope >= 1?	Boolean			TRUE		FALSE	
67	Restrict Power >= 1?	Boolean	TRUE					TRUE
68	Restrict Betas >= 0?	Boolean						
69	Restrict n>1?	Boolean						
71	Degree of Polynomial	Integer						
73	Restriction	Dropdown						
74	Adverse Direction	Dropdown						
75	BMR Type	Dropdown						
76	Constant Variance?	Boolean						
82	Adverse Direction							

BMDS Wizard – Model Parameters



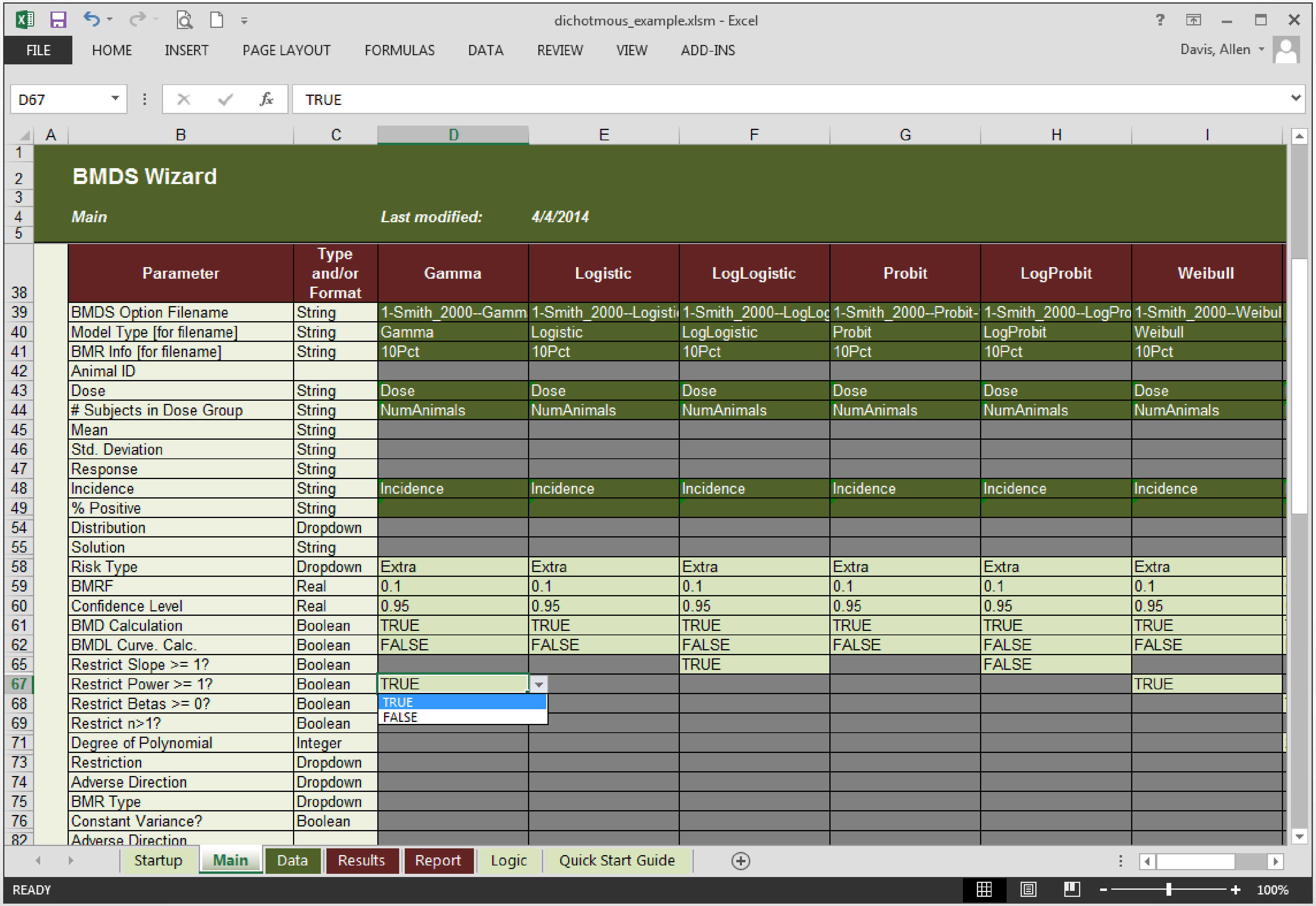
C20 | Click here to enter data

BMDS Wizard

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

	Parameter	Type and/or Format	Gamma	Logistic	LogLogistic	Probit	LogProbit	Weibull
39	BMDS Option Filename	String	1-Smith_2000--Gamm	1-Smith_2000--Logisti	1-Smith_2000--LogLog	1-Smith_2000--Probit-	1-Smith_2000--LogPro	1-Smith_2000--Weibul
40	Model Type [for filename]	String	Gamma	Logistic	LogLogistic	Probit	LogProbit	Weibull
41	BMR Info [for filename]	String	10Pct	10Pct	10Pct	10Pct	10Pct	10Pct
42	Animal ID							
43	Dose	String	Dose	Dose	Dose	Dose	Dose	Dose
44	# Subjects in Dose Group	String	NumAnimals	NumAnimals	NumAnimals	NumAnimals	NumAnimals	NumAnimals
45	Mean	String						
46	Std. Deviation	String						
47	Response	String						
48	Incidence	String	Incidence	Incidence	Incidence	Incidence	Incidence	Incidence
49	% Positive	String						
54	Distribution	Dropdown						
55	Solution	String						
58	Risk Type	Dropdown	Extra	Extra	Extra	Extra	Extra	Extra
59	BMRF	Real	0.1	0.1	0.1	0.1	0.1	0.1
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	FALSE	FALSE
65	Restrict Slope >= 1?	Boolean			TRUE		FALSE	
67	Restrict Power >= 1?	Boolean	TRUE					TRUE
68	Restrict Betas >= 0?	Boolean						
69	Restrict n>1?	Boolean						
71	Degree of Polynomial	Integer						
73	Restriction	Dropdown						
74	Adverse Direction	Dropdown						
75	BMR Type	Dropdown						
76	Constant Variance?	Boolean						
82	Adverse Direction							

BMDS Wizard – Model Parameters



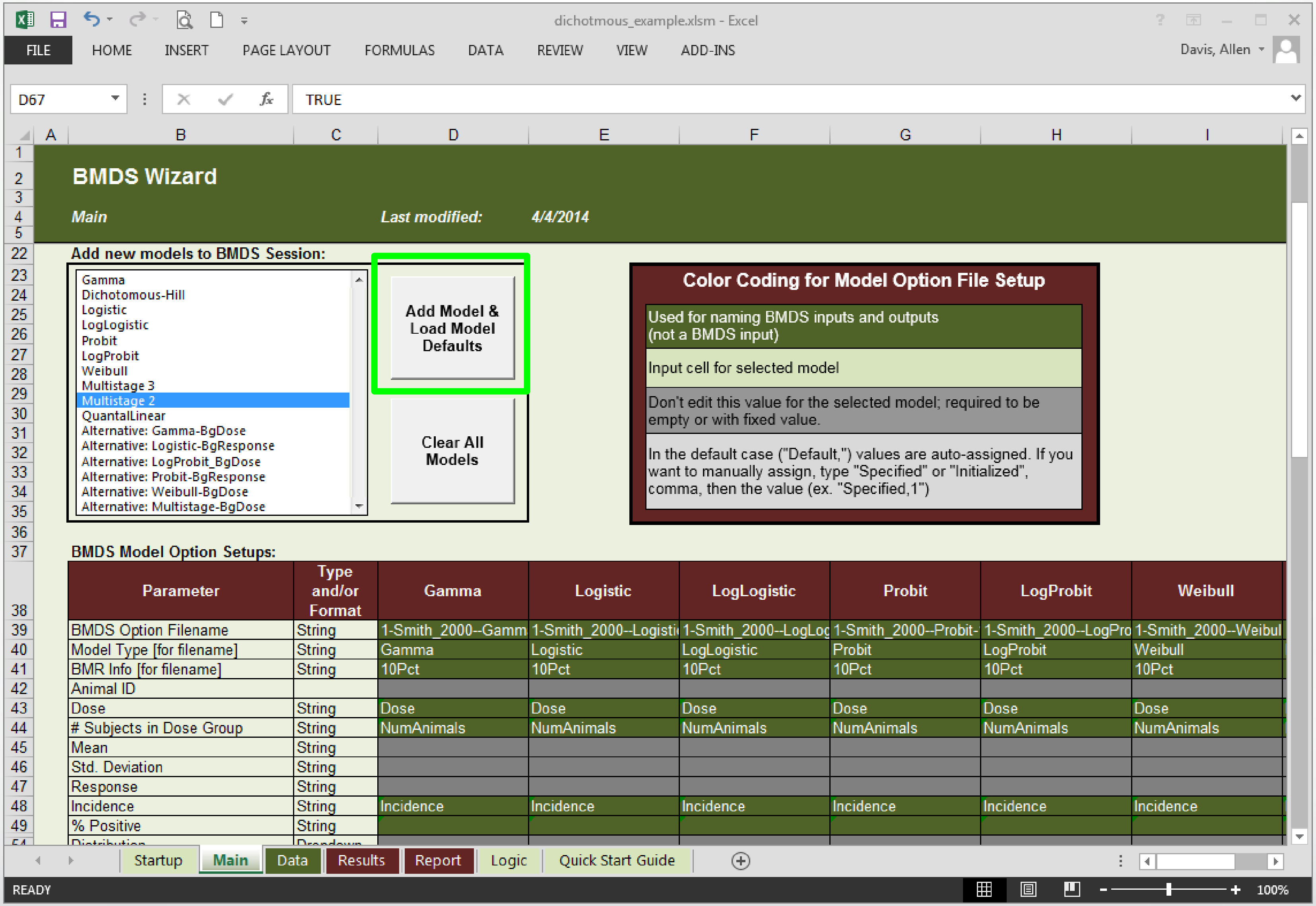
D67 = TRUE

BMDS Wizard

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

	Parameter	Type and/or Format	Gamma	Logistic	LogLogistic	Probit	LogProbit	Weibull
39	BMDS Option Filename	String	1-Smith_2000--Gamm	1-Smith_2000--Logisti	1-Smith_2000--LogLog	1-Smith_2000--Probit-	1-Smith_2000--LogPro	1-Smith_2000--Weibul
40	Model Type [for filename]	String	Gamma	Logistic	LogLogistic	Probit	LogProbit	Weibull
41	BMR Info [for filename]	String	10Pct	10Pct	10Pct	10Pct	10Pct	10Pct
42	Animal ID							
43	Dose	String	Dose	Dose	Dose	Dose	Dose	Dose
44	# Subjects in Dose Group	String	NumAnimals	NumAnimals	NumAnimals	NumAnimals	NumAnimals	NumAnimals
45	Mean	String						
46	Std. Deviation	String						
47	Response	String						
48	Incidence	String	Incidence	Incidence	Incidence	Incidence	Incidence	Incidence
49	% Positive	String						
54	Distribution	Dropdown						
55	Solution	String						
58	Risk Type	Dropdown	Extra	Extra	Extra	Extra	Extra	Extra
59	BMRF	Real	0.1	0.1	0.1	0.1	0.1	0.1
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	FALSE	FALSE
65	Restrict Slope >= 1?	Boolean			TRUE		FALSE	
67	Restrict Power >= 1?	Boolean	TRUE TRUE FALSE					TRUE
68	Restrict Betas >= 0?	Boolean						
69	Restrict n>1?	Boolean						
71	Degree of Polynomial	Integer						
73	Restriction	Dropdown						
74	Adverse Direction	Dropdown						
75	BMR Type	Dropdown						
76	Constant Variance?	Boolean						
82	Adverse Direction							

BMDS Wizard – Adding Models to Session



BMDS Wizard

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

Add new models to BMDS Session:

- Gamma
- Dichotomous-Hill
- Logistic
- LogLogistic
- Probit
- LogProbit
- Weibull
- Multistage 3
- Multistage 2
- QuantalLinear
- Alternative: Gamma-BgDose
- Alternative: Logistic-BgResponse
- Alternative: LogProbit_BgDose
- Alternative: Probit-BgResponse
- Alternative: Weibull-BgDose
- Alternative: Multistage-BgDose

Add Model & Load Model Defaults

Clear All Models

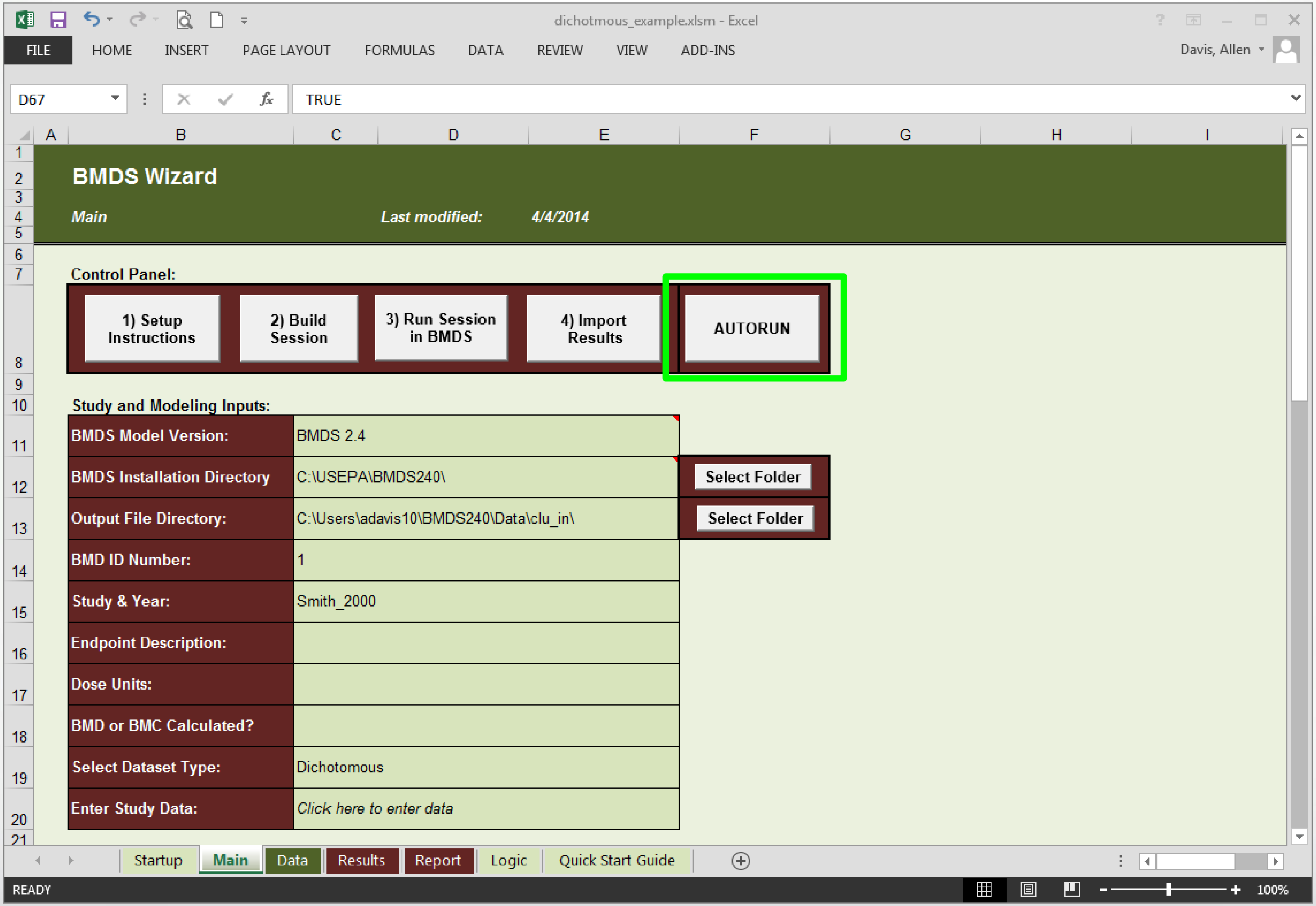
Color Coding for Model Option File Setup

- 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	Gamma	Logistic	LogLogistic	Probit	LogProbit	Weibull
BMDS Option Filename	String	1-Smith_2000--Gamm	1-Smith_2000--Logisti	1-Smith_2000--LogLog	1-Smith_2000--Probit-	1-Smith_2000--LogPro	1-Smith_2000--Weibul
Model Type [for filename]	String	Gamma	Logistic	LogLogistic	Probit	LogProbit	Weibull
BMR Info [for filename]	String	10Pct	10Pct	10Pct	10Pct	10Pct	10Pct
Animal ID							
Dose	String	Dose	Dose	Dose	Dose	Dose	Dose
# Subjects in Dose Group	String	NumAnimals	NumAnimals	NumAnimals	NumAnimals	NumAnimals	NumAnimals
Mean	String						
Std. Deviation	String						
Response	String						
Incidence	String	Incidence	Incidence	Incidence	Incidence	Incidence	Incidence
% Positive	String						

BMDS Wizard – AutoRunning BMDS



dichotmous_example.xlsm - Excel

D67 TRUE

BMDS Wizard

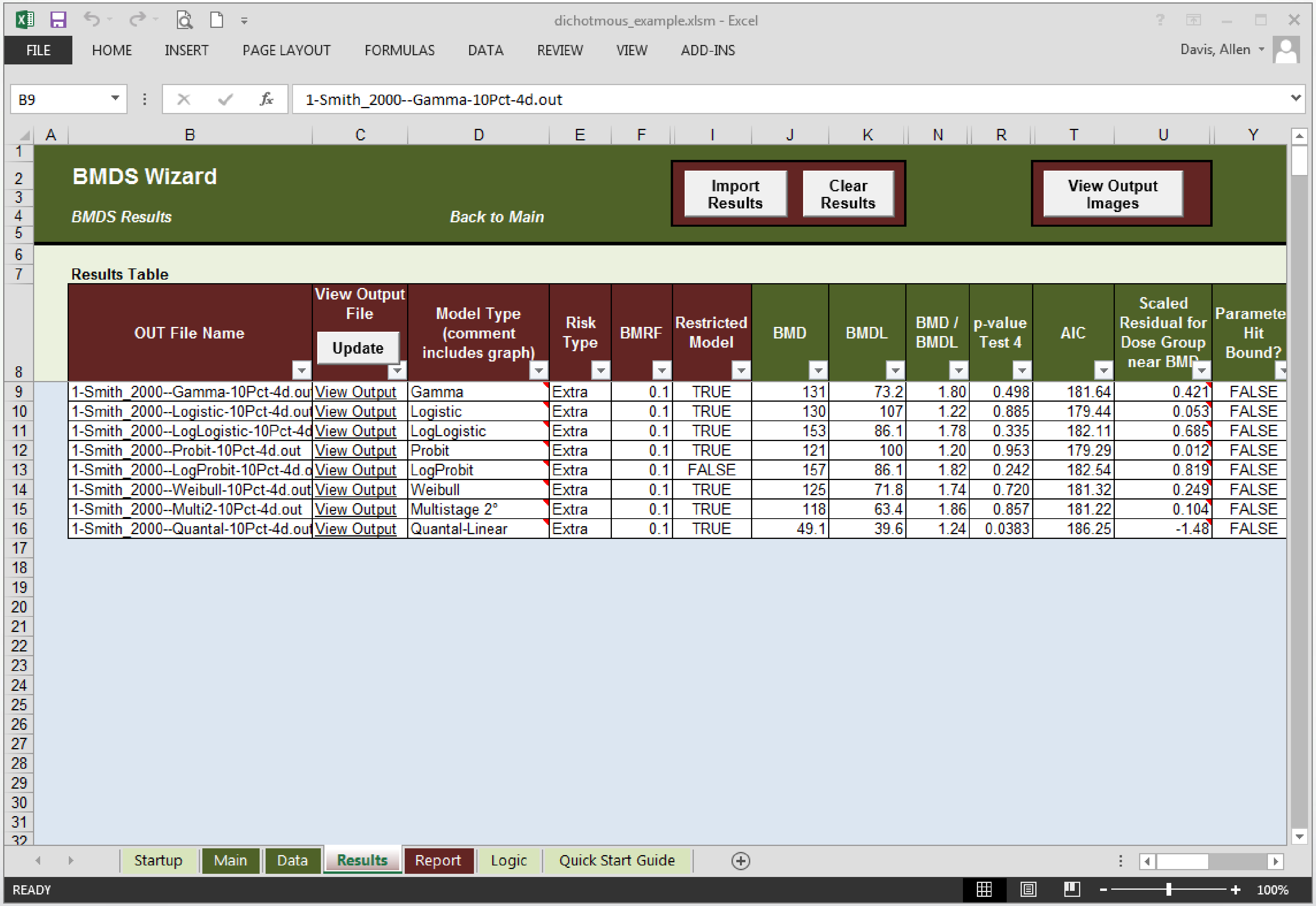
Main *Last modified:* *4/4/2014*

Control Panel:

Study and Modeling Inputs:

BMDS Model Version:	BMDS 2.4
BMDS Installation Directory	C:\USEPA\BMDS240\
Output File Directory:	C:\Users\adavis10\BMDS240\Data\clu_in\
BMD ID Number:	1
Study & Year:	Smith_2000
Endpoint Description:	
Dose Units:	
BMD or BMC Calculated?	
Select Dataset Type:	Dichotomous
Enter Study Data:	*Click here to enter data*

BMDS Wizard – Results



1-Smith_2000--Gamma-10Pct-4d.out

BMDS Wizard

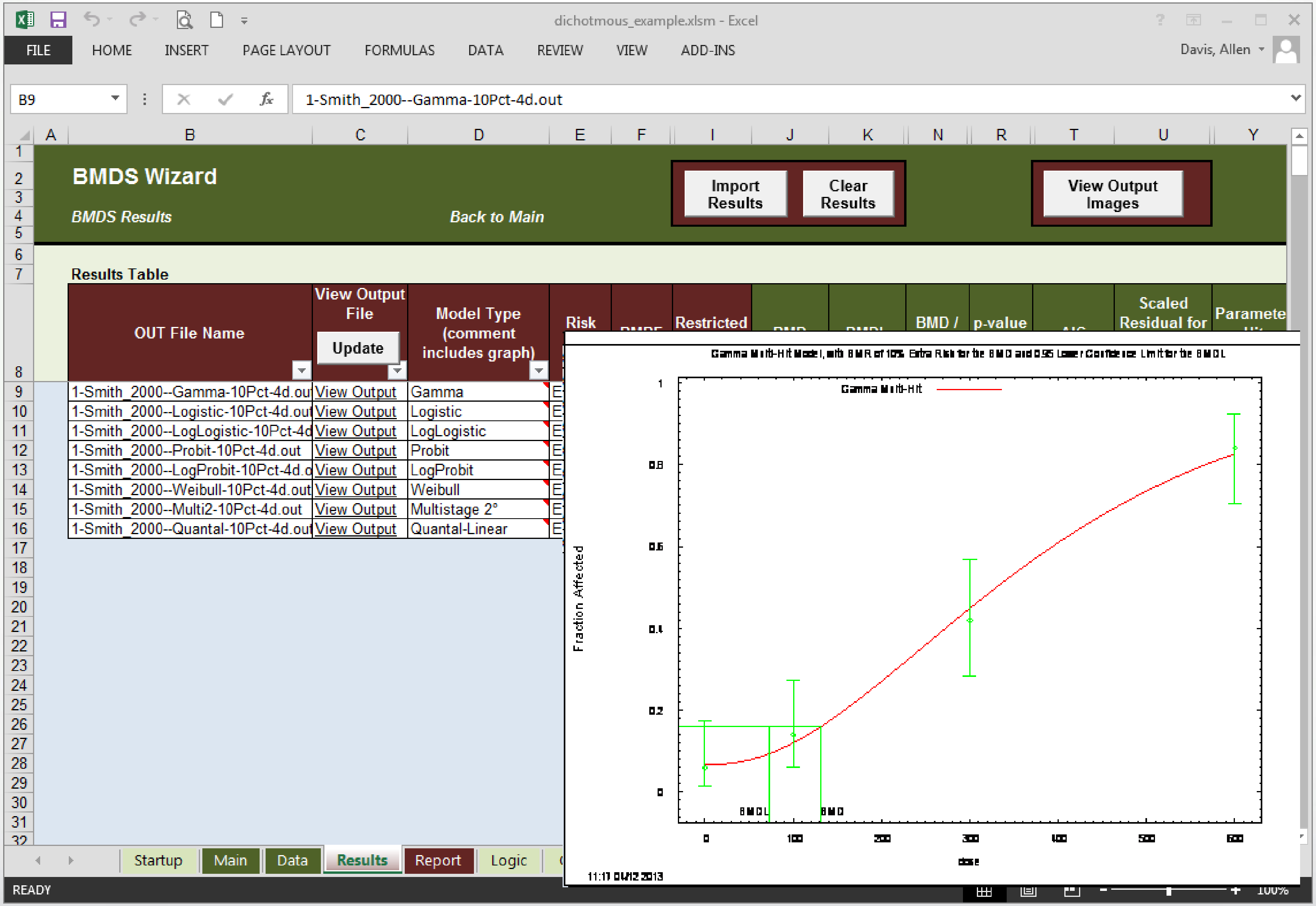
BMDS Results

Back to Main

Results Table

OUT File Name	View Output File Update	Model Type (comment includes graph)	Risk Type	BMRF	Restricted Model	BMD	BMDL	BMD / BMDL	p-value Test 4	AIC	Scaled Residual for Dose Group near BMD	Paramete Hit Bound?
1-Smith_2000--Gamma-10Pct-4d.ou	View Output	Gamma	Extra	0.1	TRUE	131	73.2	1.80	0.498	181.64	0.421	FALSE
1-Smith_2000--Logistic-10Pct-4d.ou	View Output	Logistic	Extra	0.1	TRUE	130	107	1.22	0.885	179.44	0.053	FALSE
1-Smith_2000--LogLogistic-10Pct-4d	View Output	LogLogistic	Extra	0.1	TRUE	153	86.1	1.78	0.335	182.11	0.685	FALSE
1-Smith_2000--Probit-10Pct-4d.out	View Output	Probit	Extra	0.1	TRUE	121	100	1.20	0.953	179.29	0.012	FALSE
1-Smith_2000--LogProbit-10Pct-4d.o	View Output	LogProbit	Extra	0.1	FALSE	157	86.1	1.82	0.242	182.54	0.819	FALSE
1-Smith_2000--Weibull-10Pct-4d.out	View Output	Weibull	Extra	0.1	TRUE	125	71.8	1.74	0.720	181.32	0.249	FALSE
1-Smith_2000--Multi2-10Pct-4d.out	View Output	Multistage 2°	Extra	0.1	TRUE	118	63.4	1.86	0.857	181.22	0.104	FALSE
1-Smith_2000--Quantal-10Pct-4d.ou	View Output	Quantal-Linear	Extra	0.1	TRUE	49.1	39.6	1.24	0.0383	186.25	-1.48	FALSE

BMDS Wizard – Results

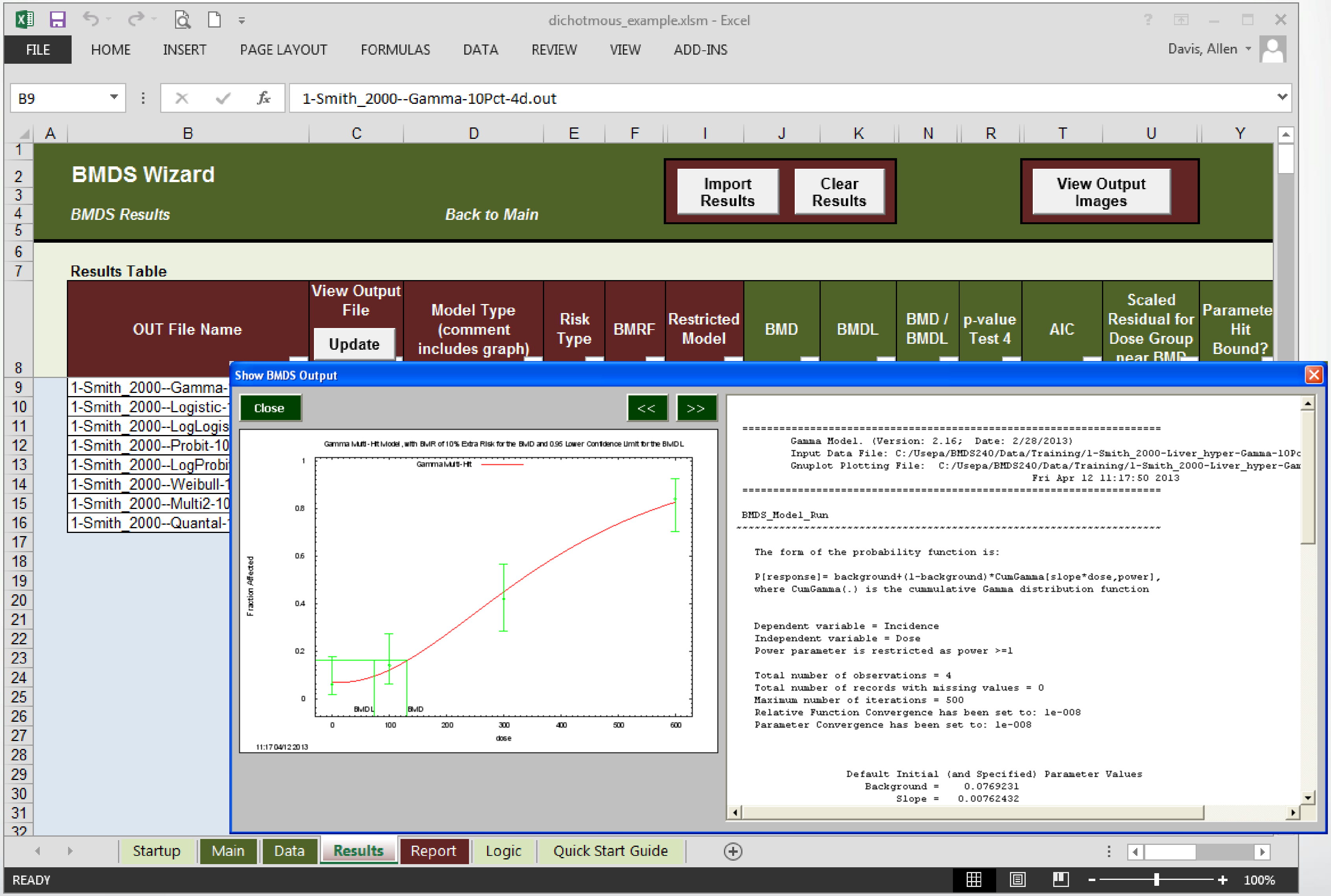


1-Smith_2000--Gamma-10Pct-4d.out

Results Table

OUT File Name	View Output File	Model Type (comment includes graph)	Risk
1-Smith_2000--Gamma-10Pct-4d.ou	View Output	Gamma	E
1-Smith_2000--Logistic-10Pct-4d.ou	View Output	Logistic	E
1-Smith_2000--LogLogistic-10Pct-4d	View Output	LogLogistic	E
1-Smith_2000--Probit-10Pct-4d.out	View Output	Probit	E
1-Smith_2000--LogProbit-10Pct-4d.o	View Output	LogProbit	E
1-Smith_2000--Weibull-10Pct-4d.out	View Output	Weibull	E
1-Smith_2000--Multi2-10Pct-4d.out	View Output	Multistage 2°	E
1-Smith_2000--Quantal-10Pct-4d.ou	View Output	Quantal-Linear	E

BMDS Wizard – Results



Formula bar (B9): 1-Smith_2000--Gamma-10Pct-4d.out

1-Smith_2000--Gamma-
1-Smith_2000--Logistic-
1-Smith_2000--LogLogis
1-Smith_2000--Probit-10
1-Smith_2000--LogProbi
1-Smith_2000--Weibull-1
1-Smith_2000--Multi2-10
1-Smith_2000--Quantal-

```
 ====================================================================
        Gamma Model. (Version: 2.16;  Date: 2/28/2013)
        Input Data File: C:/Usepa/BMDS240/Data/Training/1-Smith_2000-Liver_hyper-Gamma-10Pc
        Gnuplot Plotting File:  C:/Usepa/BMDS240/Data/Training/1-Smith_2000-Liver_hyper-Gam
                                                    Fri Apr 12 11:17:50 2013
 ====================================================================

 BMDS_Model_Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response]= background+(1-background)*CumGamma[slope*dose,power],
   where CumGamma(.) is the cummulative Gamma distribution function

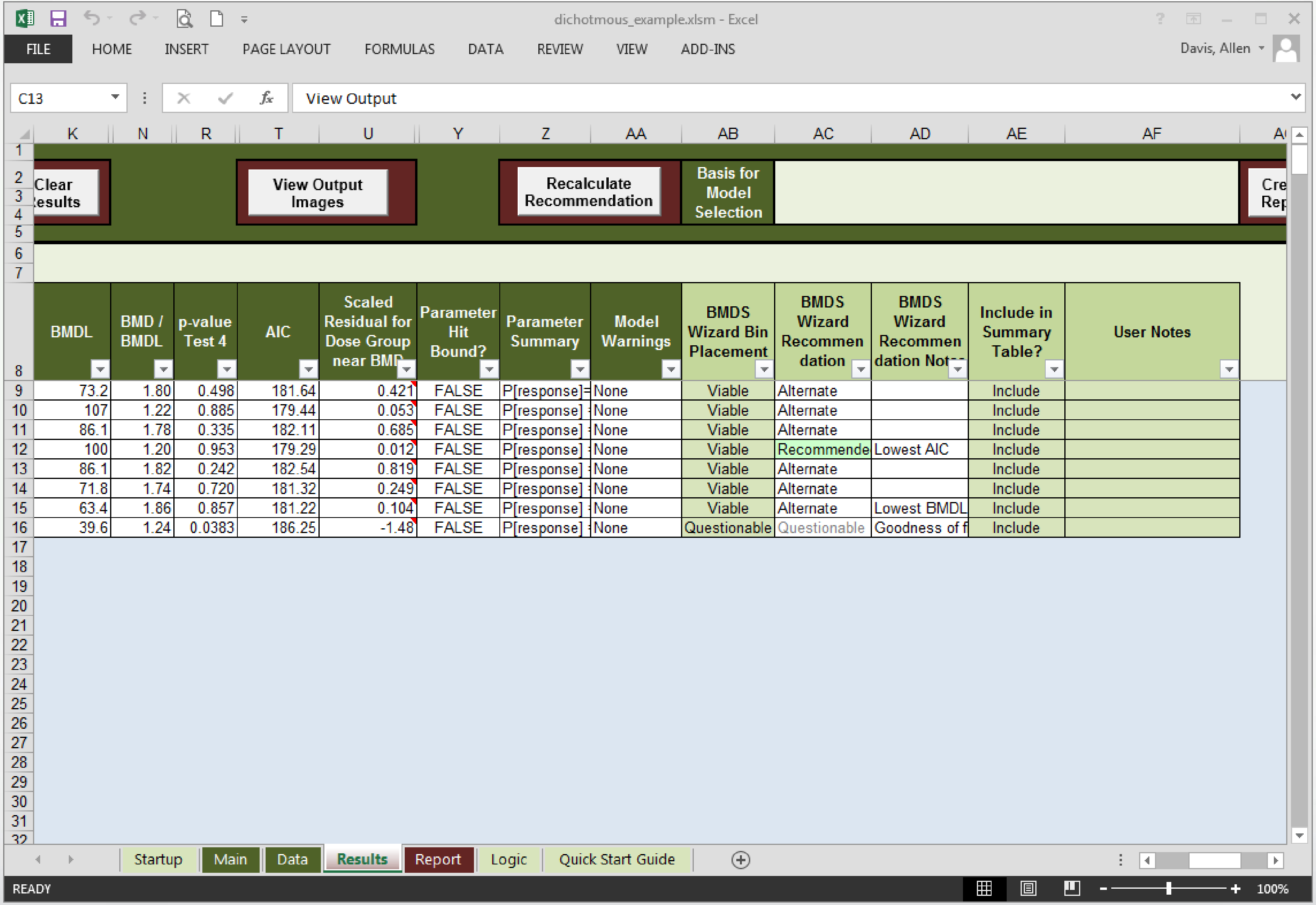

   Dependent variable = Incidence
   Independent variable = Dose
   Power parameter is restricted as power >=1

   Total number of observations = 4
   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



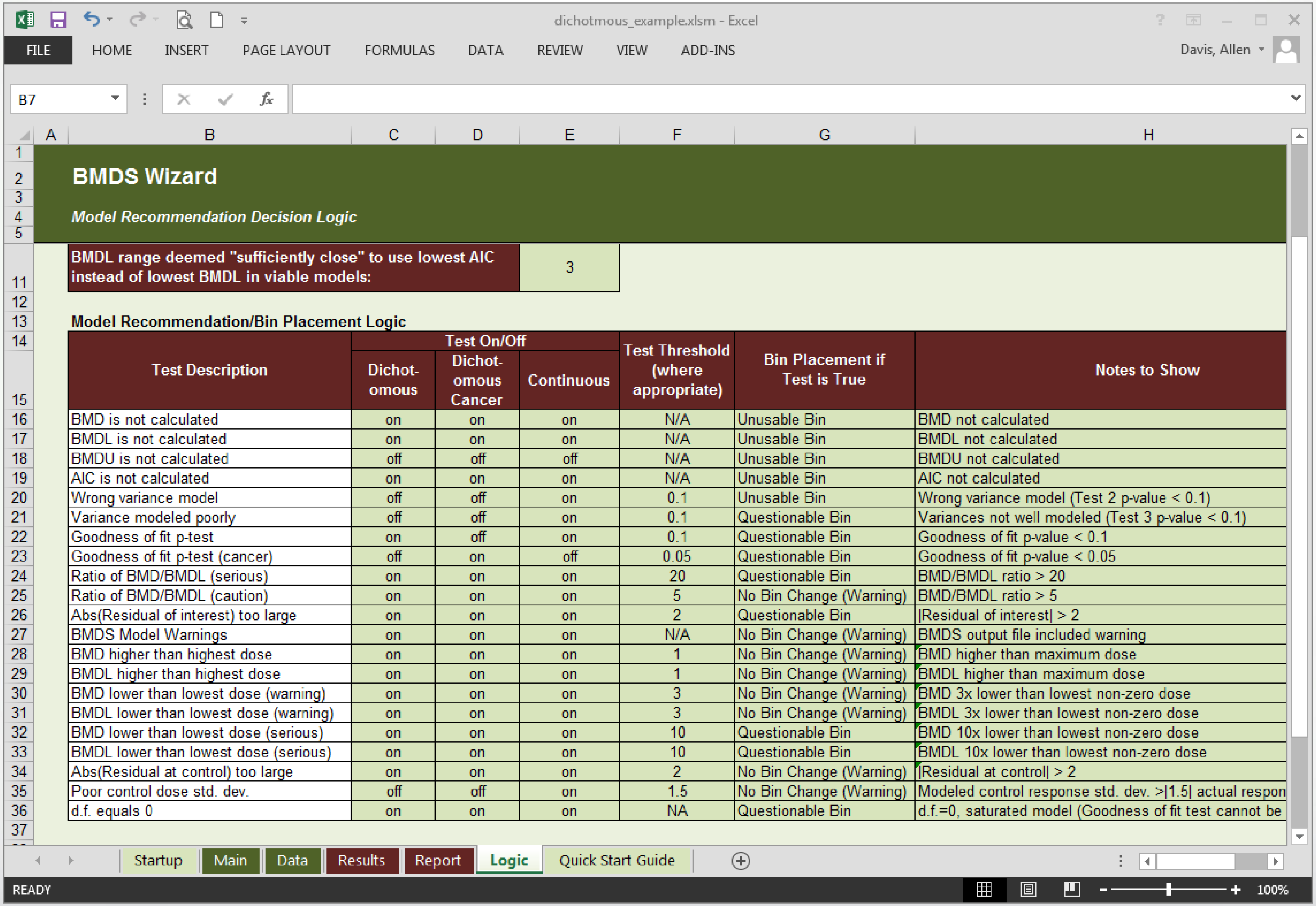
                  Default Initial (and Specified) Parameter Values
                     Background =     0.0769231
                          Slope =    0.00762432
```

BMDS Wizard – Results



	BMDL	BMD / BMDL	p-value Test 4	AIC	Scaled Residual for Dose Group near BMD	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	73.2	1.80	0.498	181.64	0.421	FALSE	P[response]=	None	Viable	Alternate		Include	
10	107	1.22	0.885	179.44	0.053	FALSE	P[response]	None	Viable	Alternate		Include	
11	86.1	1.78	0.335	182.11	0.685	FALSE	P[response]	None	Viable	Alternate		Include	
12	100	1.20	0.953	179.29	0.012	FALSE	P[response]	None	Viable	Recommende	Lowest AIC	Include	
13	86.1	1.82	0.242	182.54	0.819	FALSE	P[response]	None	Viable	Alternate		Include	
14	71.8	1.74	0.720	181.32	0.249	FALSE	P[response]	None	Viable	Alternate		Include	
15	63.4	1.86	0.857	181.22	0.104	FALSE	P[response]	None	Viable	Alternate	Lowest BMDL	Include	
16	39.6	1.24	0.0383	186.25	-1.48	FALSE	P[response]	None	Questionable	Questionable	Goodness of f	Include	

BMDS Wizard – Logic



BMDS Wizard

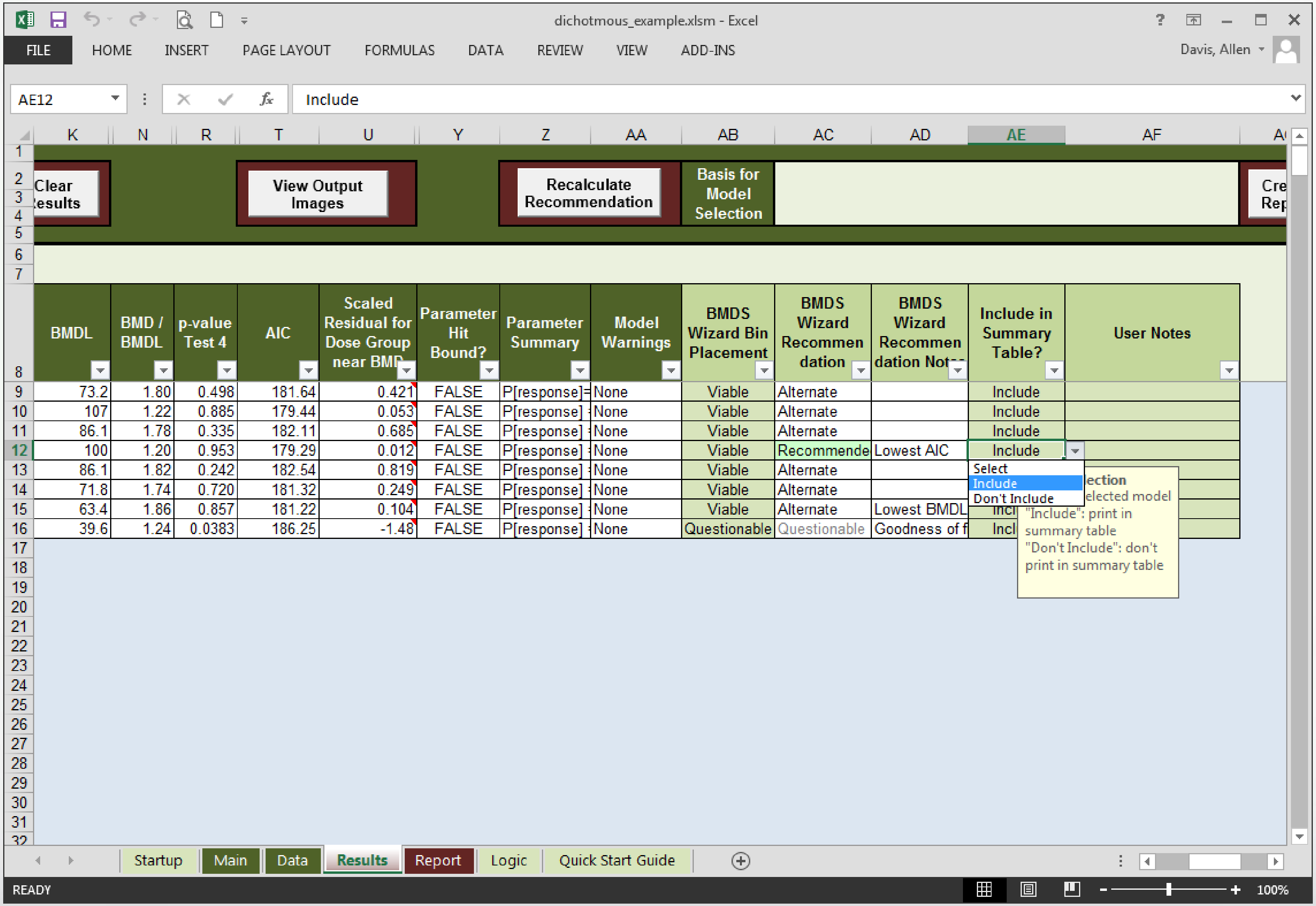
Model Recommendation Decision Logic

BMDL range deemed "sufficiently close" to use lowest AIC instead of lowest BMDL in viable models:	3

Model Recommendation/Bin Placement Logic

Test Description	Test On/Off			Test Threshold (where appropriate)	Bin Placement if Test is True	Notes to Show
	Dichotomous	Dichotomous Cancer	Continuous			
BMD is not calculated	on	on	on	N/A	Unusable Bin	BMD not calculated
BMDL is not calculated	on	on	on	N/A	Unusable Bin	BMDL not calculated
BMDU is not calculated	off	off	off	N/A	Unusable Bin	BMDU not calculated
AIC is not calculated	on	on	on	N/A	Unusable Bin	AIC not calculated
Wrong variance model	off	off	on	0.1	Unusable Bin	Wrong variance model (Test 2 p-value < 0.1)
Variance modeled poorly	off	off	on	0.1	Questionable Bin	Variances not well modeled (Test 3 p-value < 0.1)
Goodness of fit p-test	on	off	on	0.1	Questionable Bin	Goodness of fit p-value < 0.1
Goodness of fit p-test (cancer)	off	on	off	0.05	Questionable Bin	Goodness of fit p-value < 0.05
Ratio of BMD/BMDL (serious)	on	on	on	20	Questionable Bin	BMD/BMDL ratio > 20
Ratio of BMD/BMDL (caution)	on	on	on	5	No Bin Change (Warning)	BMD/BMDL ratio > 5
Abs(Residual of interest) too large	on	on	on	2	Questionable Bin	|Residual of interest| > 2
BMDS Model Warnings	on	on	on	N/A	No Bin Change (Warning)	BMDS output file included warning
BMD higher than highest dose	on	on	on	1	No Bin Change (Warning)	BMD higher than maximum dose
BMDL higher than highest dose	on	on	on	1	No Bin Change (Warning)	BMDL higher than maximum dose
BMD lower than lowest dose (warning)	on	on	on	3	No Bin Change (Warning)	BMD 3x lower than lowest non-zero dose
BMDL lower than lowest dose (warning)	on	on	on	3	No Bin Change (Warning)	BMDL 3x lower than lowest non-zero dose
BMD lower than lowest dose (serious)	on	on	on	10	Questionable Bin	BMD 10x lower than lowest non-zero dose
BMDL lower than lowest dose (serious)	on	on	on	10	Questionable Bin	BMDL 10x lower than lowest non-zero dose
Abs(Residual at control) too large	on	on	on	2	No Bin Change (Warning)	|Residual at control| > 2
Poor control dose std. dev.	off	off	on	1.5	No Bin Change (Warning)	Modeled control response std. dev. >|1.5| actual respon
d.f. equals 0	on	on	on	NA	Questionable Bin	d.f.=0, saturated model (Goodness of fit test cannot be

BMDS Wizard – Results



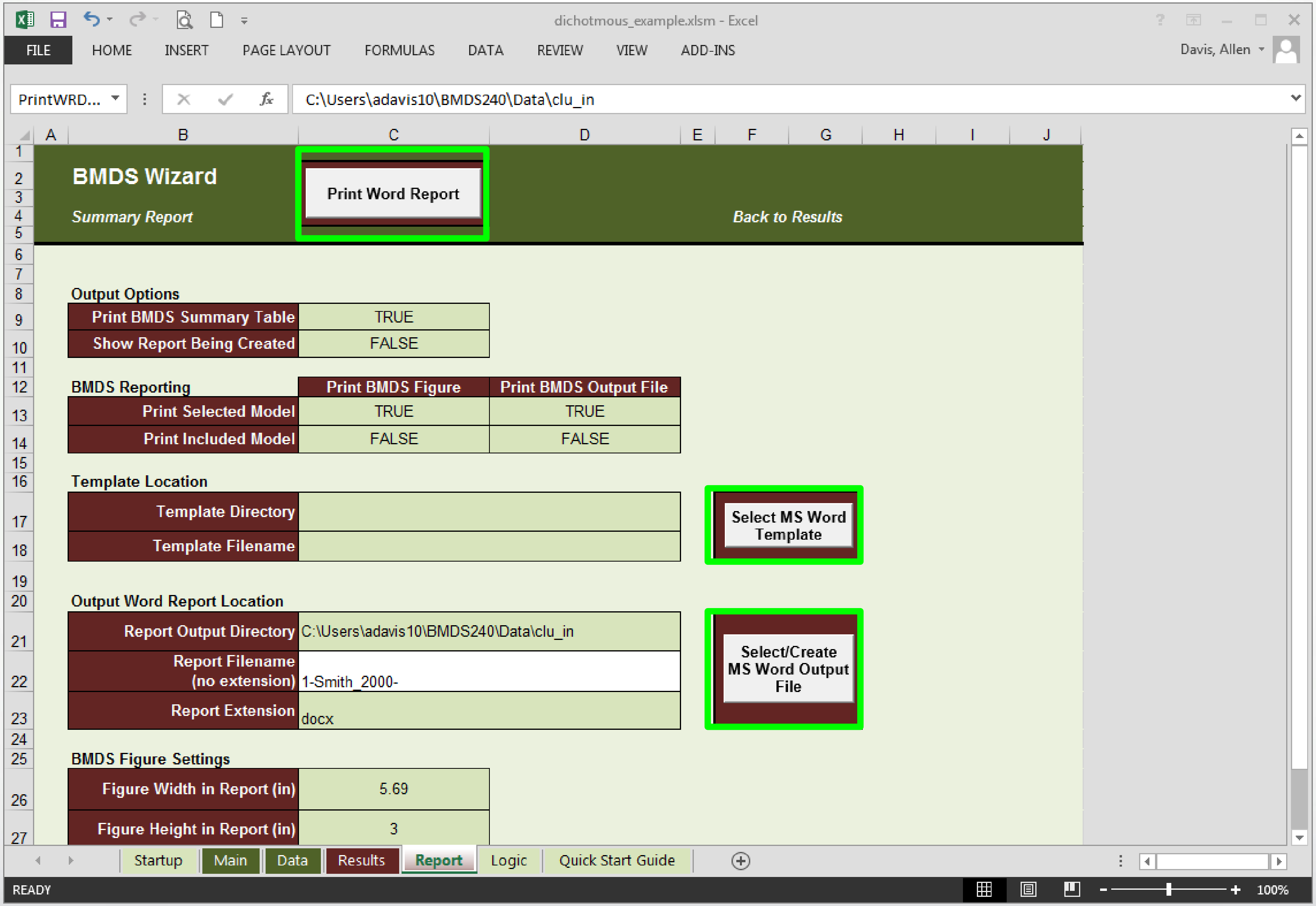
AE12 Include

	BMDL	BMD / BMDL	p-value Test 4	AIC	Scaled Residual for Dose Group near BMD	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	73.2	1.80	0.498	181.64	0.421	FALSE	P[response]=	None	Viable	Alternate		Include	
10	107	1.22	0.885	179.44	0.053	FALSE	P[response]	None	Viable	Alternate		Include	
11	86.1	1.78	0.335	182.11	0.685	FALSE	P[response]	None	Viable	Alternate		Include	
12	100	1.20	0.953	179.29	0.012	FALSE	P[response]	None	Viable	Recommende	Lowest AIC	Include	
13	86.1	1.82	0.242	182.54	0.819	FALSE	P[response]	None	Viable	Alternate			
14	71.8	1.74	0.720	181.32	0.249	FALSE	P[response]	None	Viable	Alternate			
15	63.4	1.86	0.857	181.22	0.104	FALSE	P[response]	None	Viable	Alternate	Lowest BMDL	Incl	
16	39.6	1.24	0.0383	186.25	-1.48	FALSE	P[response]	None	Questionable	Questionable	Goodness of f	Incl	

Select
Include
Don't Include

ection
elected model
"Include": print in summary table
"Don't Include": don't print in summary table

BMDS Wizard – Automatic Report Generation



C:\Users\adavis10\BMDS240\Data\clu_in

BMDS Wizard

Summary Report

Output Options

Print BMDS Summary Table	TRUE
Show Report Being Created	FALSE

BMDS Reporting	Print BMDS Figure	Print BMDS Output File
Print Selected Model	TRUE	TRUE
Print Included Model	FALSE	FALSE

Template Location

Template Directory	
Template Filename	

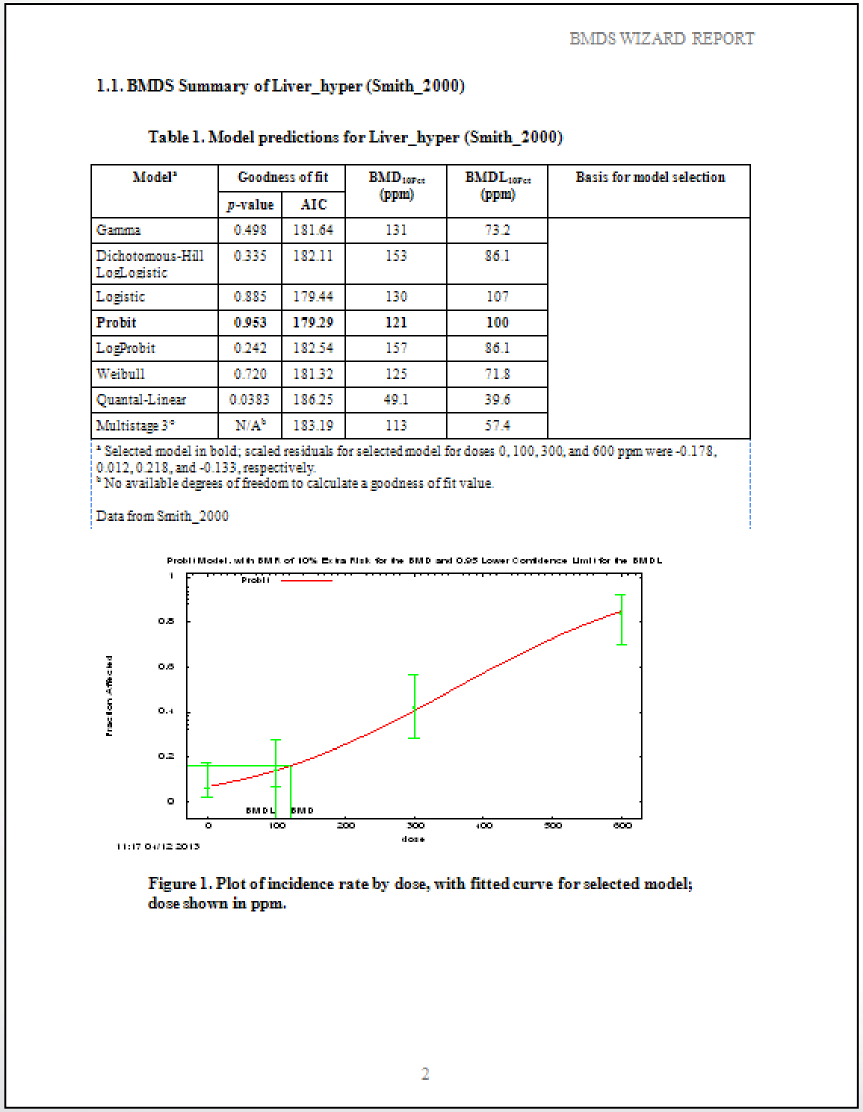
Output Word Report Location

Report Output Directory	C:\Users\adavis10\BMDS240\Data\clu_in
Report Filename (no extension)	1-Smith_2000-
Report Extension	docx

BMDS Figure Settings

Figure Width in Report (in)	5.69
Figure Height in Report (in)	3

BMDS Wizard – EPA Formated Report in Microsoft Word



BMDS WIZARD REPORT

1.1. BMDS Summary of Liver_hyper (Smith_2000)

Table 1. Model predictions for Liver_hyper (Smith_2000)

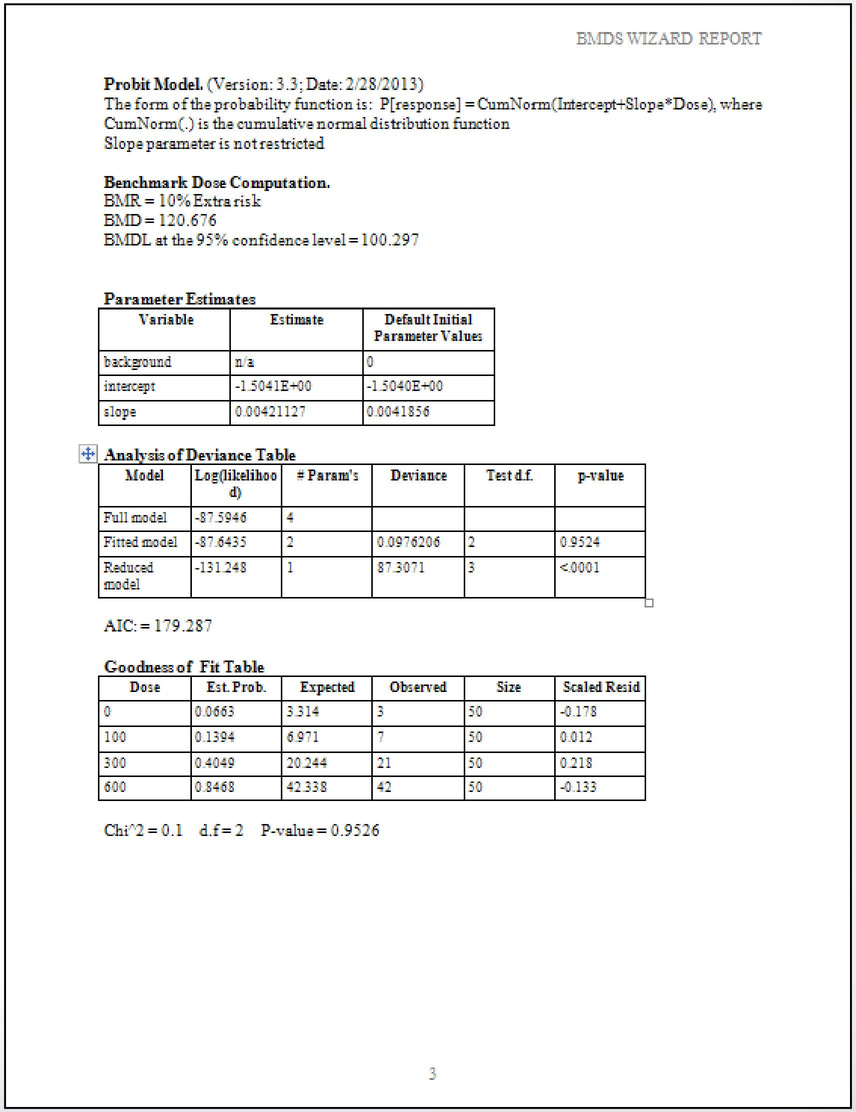
Model[a]	Goodness of fit		BMD$_{10Pct}$ (ppm)	BMDL$_{10Pct}$ (ppm)	Basis for model selection
	p-value	AIC			
Gamma	0.498	181.64	131	73.2	
Dichotomous-Hill LogLogistic	0.335	182.11	153	86.1	
Logistic	0.885	179.44	130	107	
Probit	**0.953**	**179.29**	**121**	**100**	
LogProbit	0.242	182.54	157	86.1	
Weibull	0.720	181.32	125	71.8	
Quantal-Linear	0.0383	186.25	49.1	39.6	
Multistage 3°	N/A[b]	183.19	113	57.4	

[a] Selected model in bold; scaled residuals for selected model for doses 0, 100, 300, and 600 ppm were -0.178, 0.012, 0.218, and -0.133, respectively.
[b] No available degrees of freedom to calculate a goodness of fit value.

Data from Smith_2000

Figure 1. Plot of incidence rate by dose, with fitted curve for selected model; dose shown in ppm.

2



BMDS WIZARD REPORT

Probit Model. (Version: 3.3; Date: 2/28/2013)
The form of the probability function is: P[response] = CumNorm(Intercept+Slope*Dose), where CumNorm(.) is the cumulative normal distribution function
Slope parameter is not restricted

Benchmark Dose Computation.
BMR = 10% Extra risk
BMD = 120.676
BMDL at the 95% confidence level = 100.297

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
background	n/a	0
intercept	-1.5041E+00	-1.5040E+00
slope	0.00421127	0.0041856

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-87.5946	4			
Fitted model	-87.6435	2	0.0976206	2	0.9524
Reduced model	-131.248	1	87.3071	3	<.0001

AIC: = 179.287

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0.0663	3.314	3	50	-0.178
100	0.1394	6.971	7	50	0.012
300	0.4049	20.244	21	50	0.218
600	0.8468	42.338	42	50	-0.133

Chi^2 = 0.1 d.f = 2 P-value = 0.9526

3

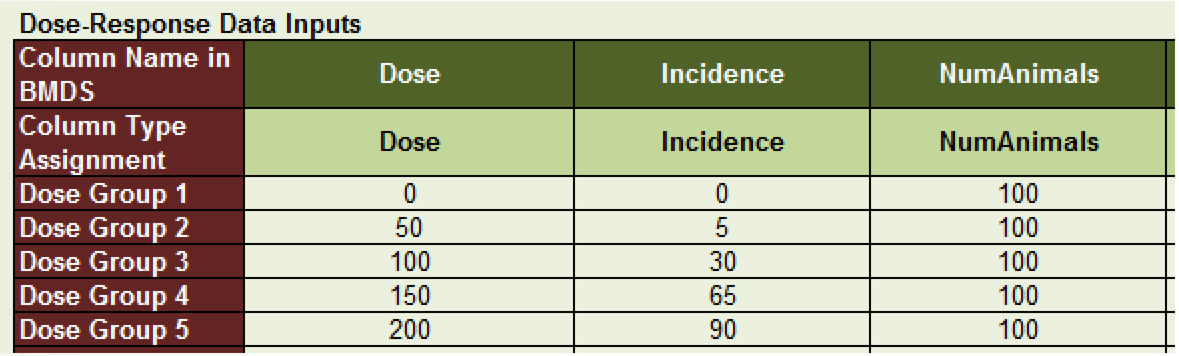
Dichotomous Data – Exercise #2

Dichotomous Exercise #2

- **Open the default Wizard Template named "BMDS Wizard-dichotomous.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**

Dichotomous Exercise #2

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



Dose-Response Data Inputs

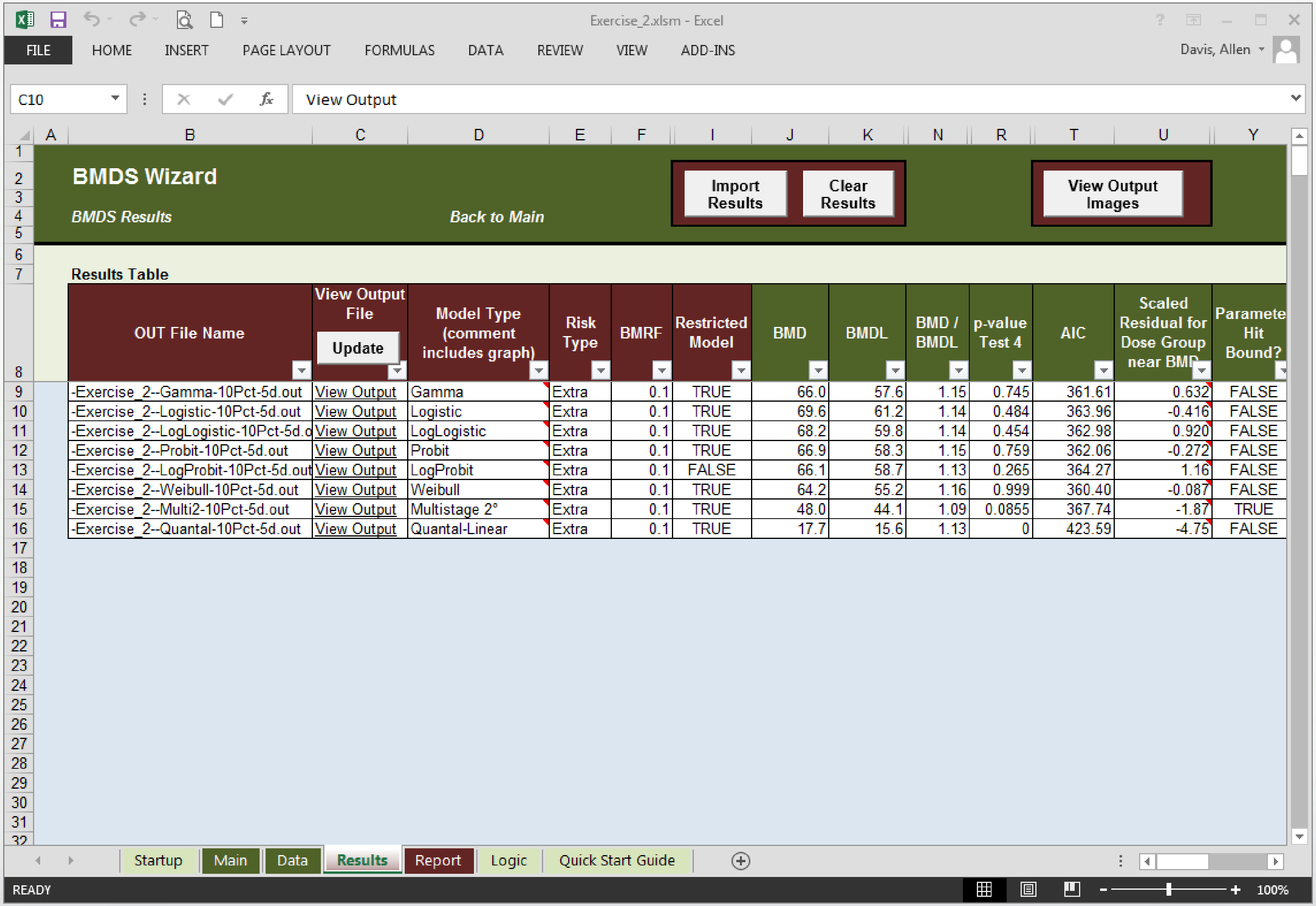
Column Name in BMDS	Dose	Incidence	NumAnimals
Column Type Assignment	Dose	Incidence	NumAnimals
Dose Group 1	0	0	100
Dose Group 2	50	5	100
Dose Group 3	100	30	100
Dose Group 4	150	65	100
Dose Group 5	200	90	100

- **On Main worksheet tab, click "AUTORUN"**

- **Results will automatically import to Results worksheet tab**

- **Which model would you pick, and why?**

Dichotomous Exercise #2



C10 View Output

BMDS Wizard

BMDS Results

Back to Main

Import Results

Clear Results

View Output Images

Results Table

OUT File Name	View Output File Update	Model Type (comment includes graph)	Risk Type	BMRF	Restricted Model	BMD	BMDL	BMD / BMDL	p-value Test 4	AIC	Scaled Residual for Dose Group near BMD	Paramete Hit Bound?
-Exercise_2--Gamma-10Pct-5d.out	View Output	Gamma	Extra	0.1	TRUE	66.0	57.6	1.15	0.745	361.61	0.632	FALSE
-Exercise_2--Logistic-10Pct-5d.out	View Output	Logistic	Extra	0.1	TRUE	69.6	61.2	1.14	0.484	363.96	-0.416	FALSE
-Exercise_2--LogLogistic-10Pct-5d.o	View Output	LogLogistic	Extra	0.1	TRUE	68.2	59.8	1.14	0.454	362.98	0.920	FALSE
-Exercise_2--Probit-10Pct-5d.out	View Output	Probit	Extra	0.1	TRUE	66.9	58.3	1.15	0.759	362.06	-0.272	FALSE
-Exercise_2--LogProbit-10Pct-5d.out	View Output	LogProbit	Extra	0.1	FALSE	66.1	58.7	1.13	0.265	364.27	1.16	FALSE
-Exercise_2--Weibull-10Pct-5d.out	View Output	Weibull	Extra	0.1	TRUE	64.2	55.2	1.16	0.999	360.40	-0.087	FALSE
-Exercise_2--Multi2-10Pct-5d.out	View Output	Multistage 2°	Extra	0.1	TRUE	48.0	44.1	1.09	0.0855	367.74	-1.87	TRUE
-Exercise_2--Quantal-10Pct-5d.out	View Output	Quantal-Linear	Extra	0.1	TRUE	17.7	15.6	1.13	0	423.59	-4.75	FALSE