Benchmark Dose Modeling – Cancer Models

Allen Davis, MSPH

Jeff Gift, Ph.D.

Jay Zhao, Ph.D.

National Center for Environmental Assessment, U.S. EPA



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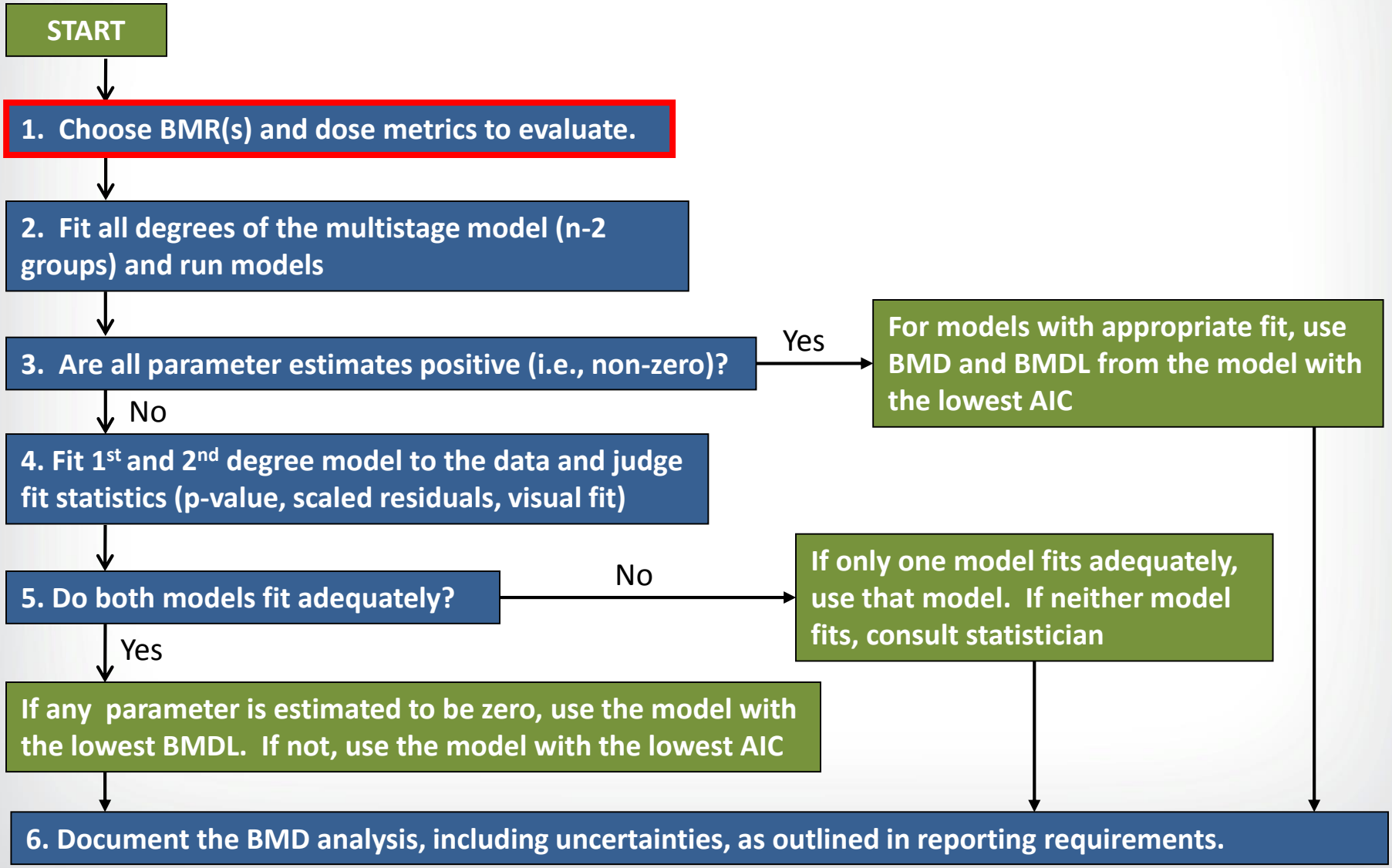
The views expressed in this presentation are those of the author(s) and do not necessarily reflect the views or policies of the US EPA.

Dichotomous Data - Cancer

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	•**Cancer: Tumor incidence**
Model Inputs	• Dose • Number of Subjects • Incidence or Percent Affected

BMD Cancer Analysis – Six Steps



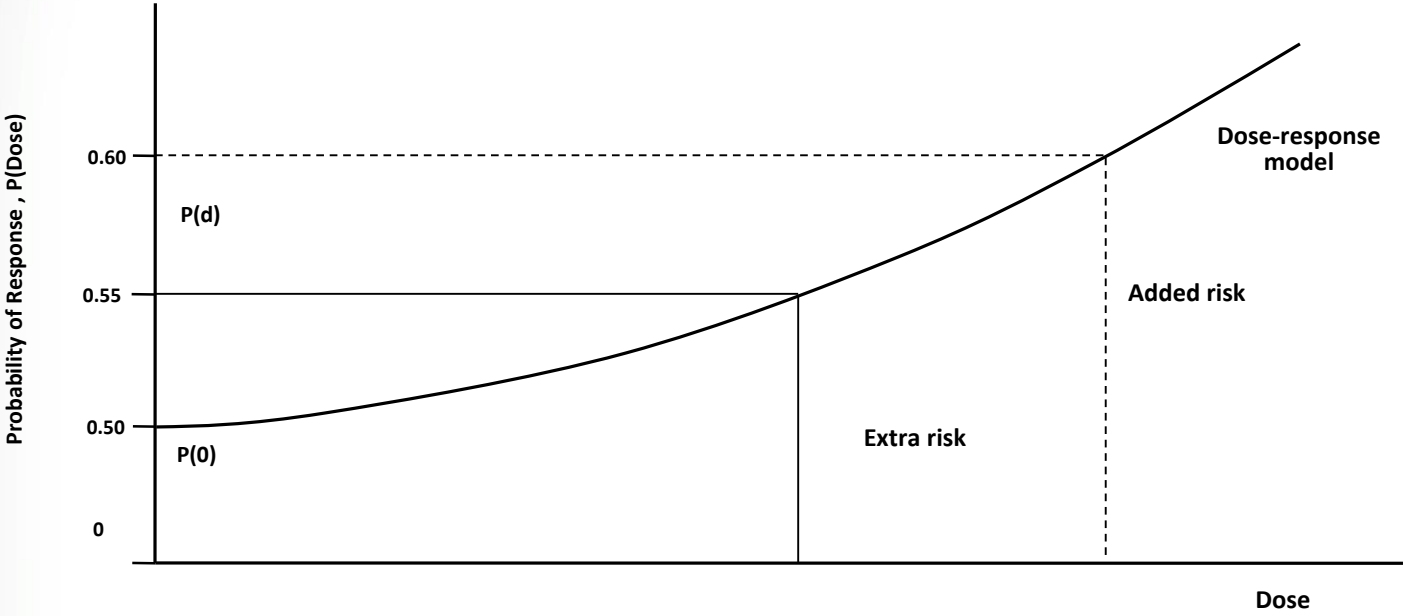
Select A Benchmark Response

- **BMR should be near the low end of the observable range of increased risks in a bioassay**
  - An **extra risk** of 10% is recommended as a standard (not default) reporting level for cancer data, it is at or near the limit of sensitivity in most cancer bioassays
  - Provided the increase in tumor incidence is considered **biologically significant**, the BMR does not need to correspond to a response that the bioassay could detect as statistically significant
- **Sometimes it may be necessary to raise the BMR (e.g. 20% extra risk) to get close to the low end of the observable range to avoid model uncertainty and underestimation of the cancer slope factor**
- **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 = **0.60**

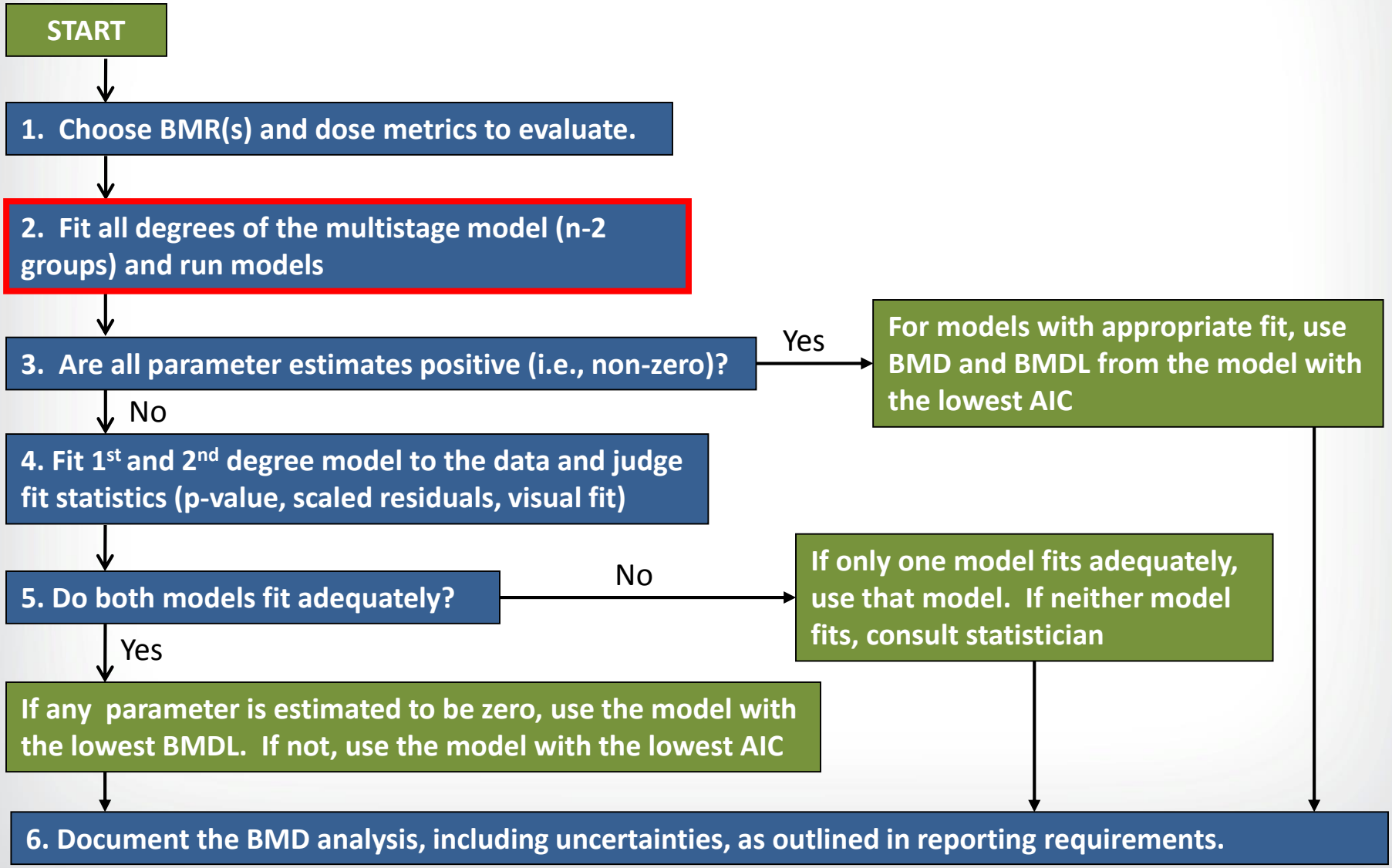
10% Extra Risk

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 Cancer Analysis – Six Steps



Selection of a Specific Model for Cancer Data

Biological Interpretation	Examples: • Various forms of the multistage model that attempt to describe the distinct stages in the progression towards cancer
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

Traditional Dichotomous Models

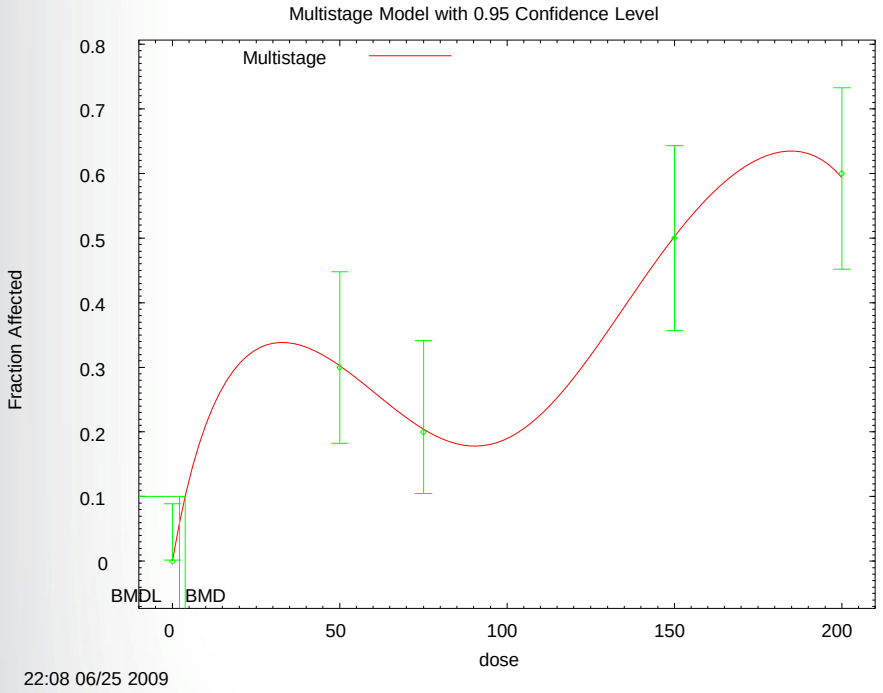
Model name	Functional form	# of Parameters[a]	Low Dose Linearity	Model fits
Multistage	$\gamma + (1-\gamma)\left[1 - \exp\left\{-\sum_{j=1}^{k} \beta_j X^j\right\}\right]$	1+k	Yes, if $\beta_1 > 0$ No, if $\beta_1 = 0$	All purpose
Logistic	$\frac{1}{1+\exp\{-(\alpha+\beta X)\}}$	2	Yes	Simple; no background
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	$\gamma+(1-\gamma)\left[\int_0^{\beta x} t^{\alpha-1}e^t dt\right] / \Gamma(\alpha)$	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

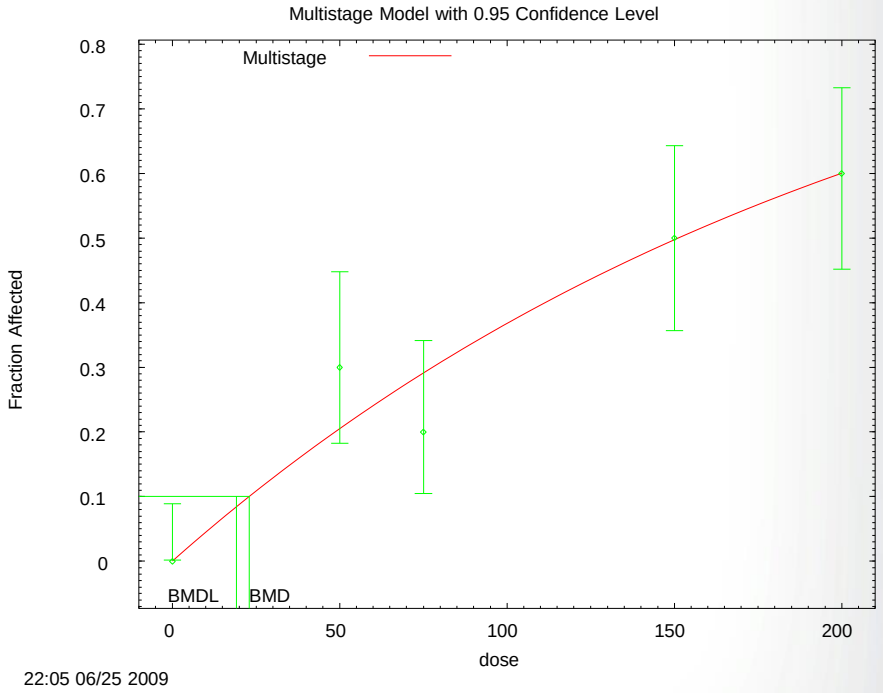
[a] Background parameter = γ. Background for hill model = v × g

Multistage-Cancer Model

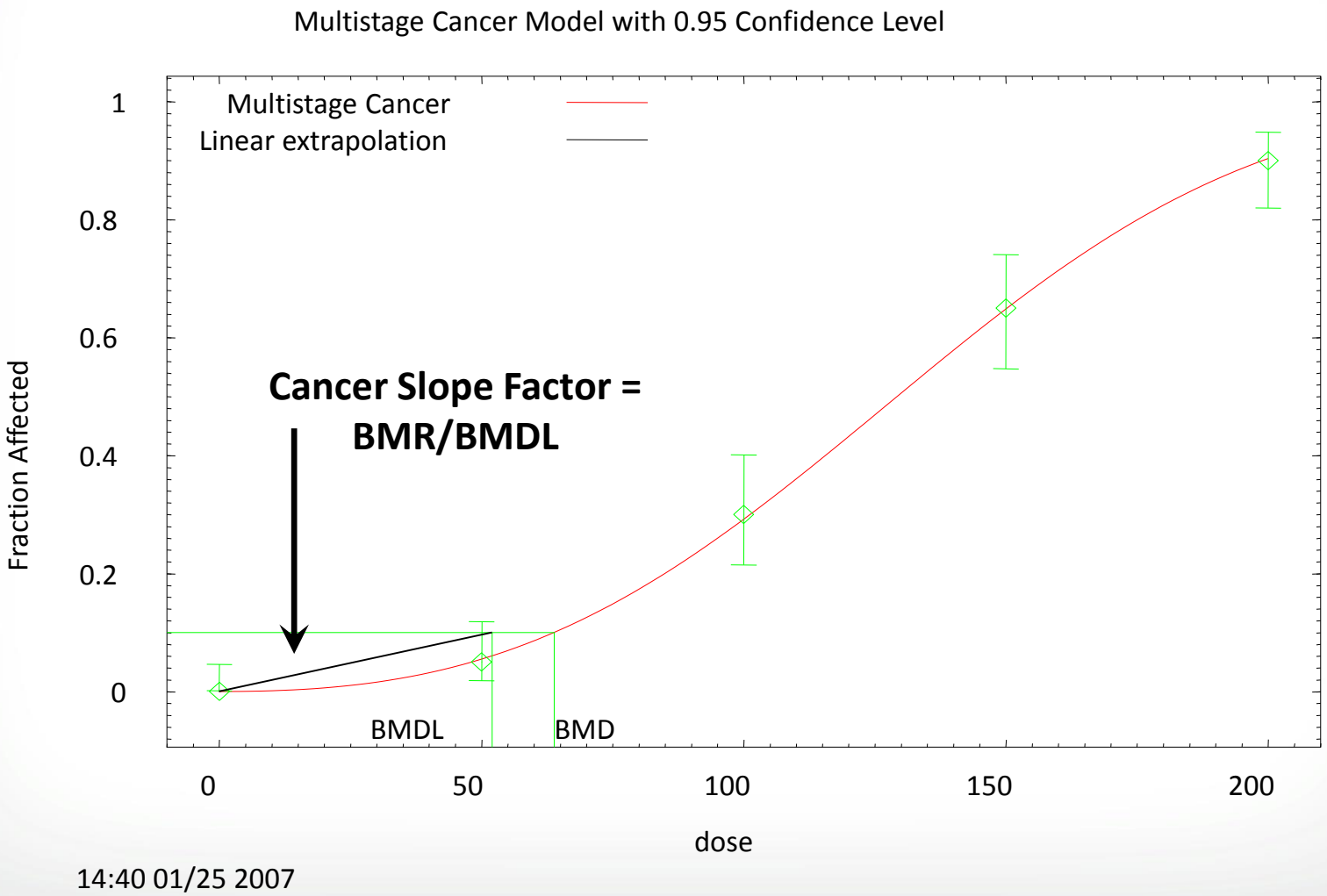
- **Difference between the Multistage-Cancer Model and the Multistage Model:**
  - β coefficients are always restricted to be positive
  - Cancer slope factor calculated and shown in output
  - Linear extrapolation appears on plot
  - Unlike other BMDS dichotomous models, both of the BMDS Multistage models present a BMDU (an estimate of the 95% upper confidence limit on the BMD)

Restriction of β Coefficients and Model Fitting

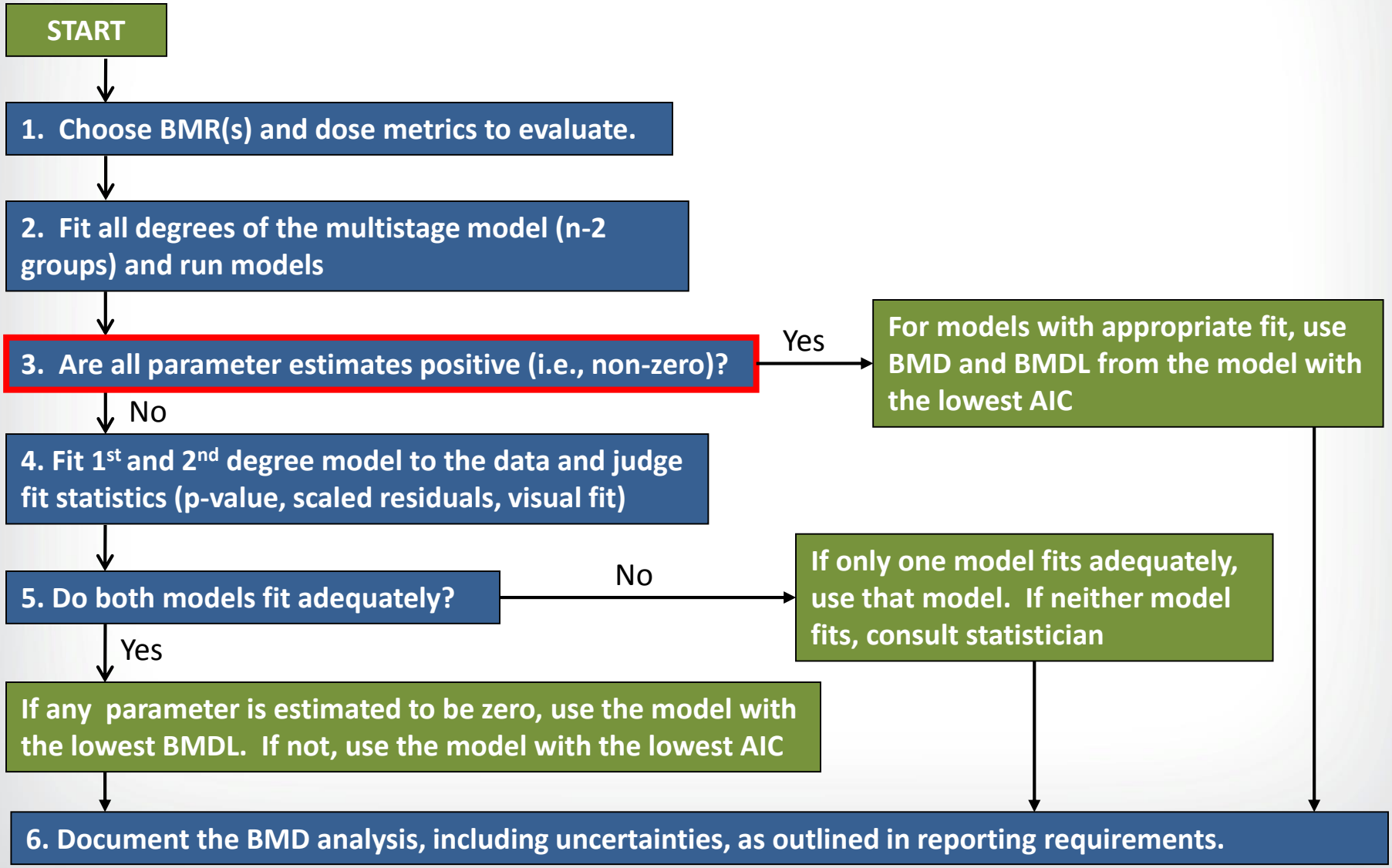




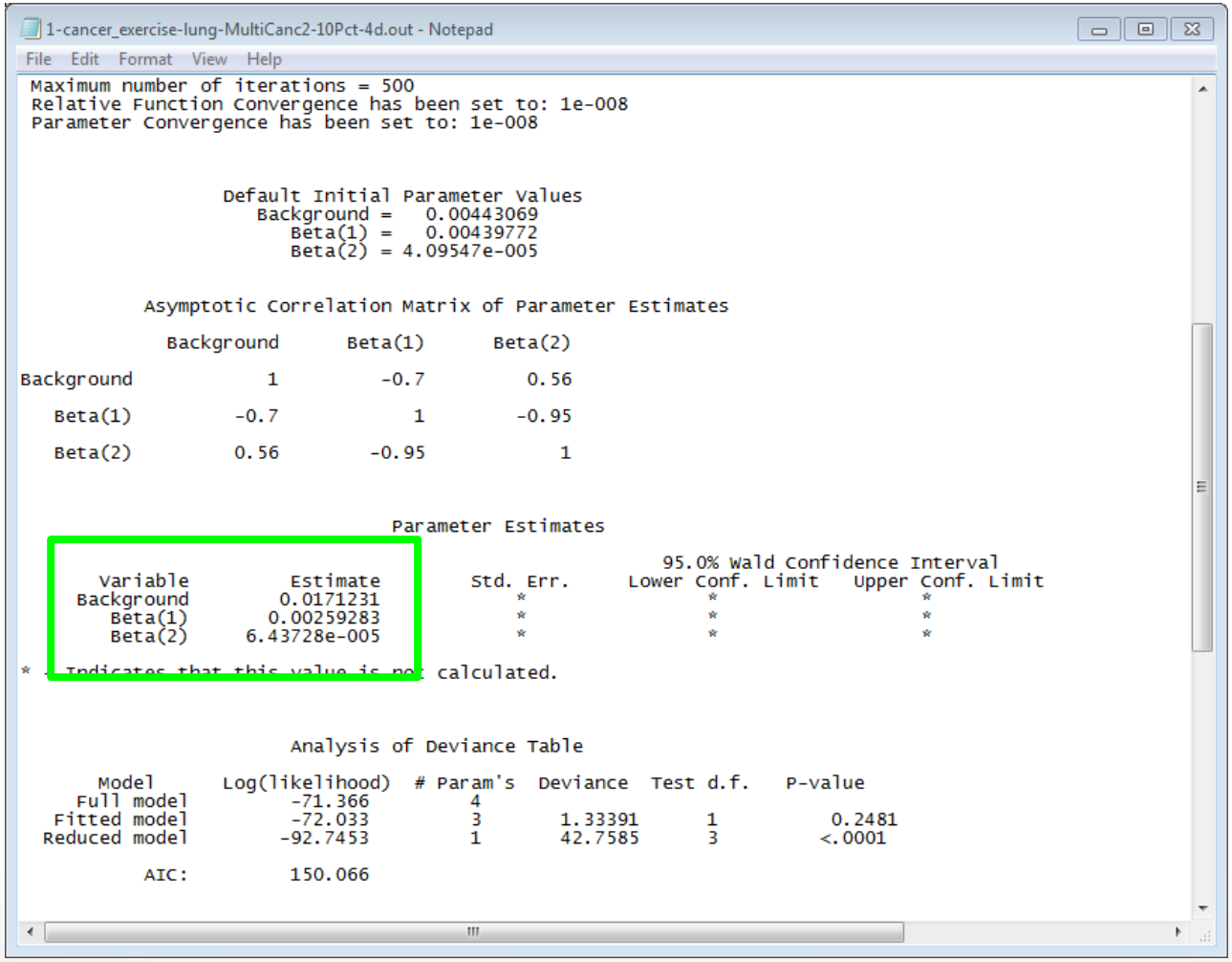
Cancer Slope Factor



BMD Cancer Analysis – Six Steps



Multistage Model Beta Parameters

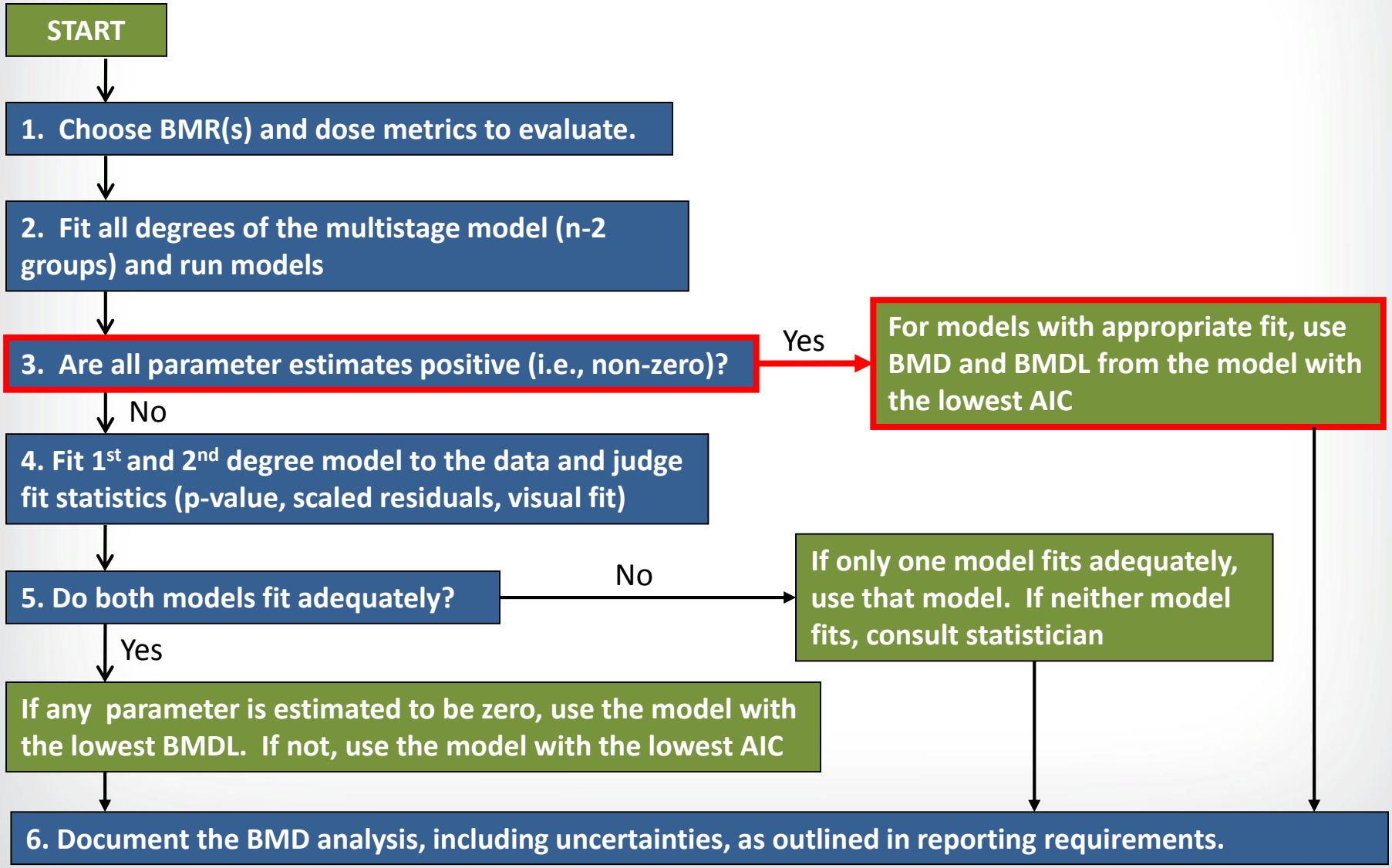


1-cancer_exercise-lung-MultiCanc2-10Pct-4d.out - Notepad

File Edit Format View Help

```
Maximum number of iterations = 500
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008


                Default Initial Parameter Values
                   Background =   0.00443069
                      Beta(1) =   0.00439772
                      Beta(2) = 4.09547e-005


          Asymptotic Correlation Matrix of Parameter Estimates

            Background      Beta(1)      Beta(2)

Background           1         -0.7         0.56

   Beta(1)       -0.7            1        -0.95

   Beta(2)       0.56        -0.95            1


                            Parameter Estimates

                                                          95.0% Wald Confidence Interval
     Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
   Background        0.0171231                *                     *                   *
      Beta(1)       0.00259283                *                     *                   *
      Beta(2)     6.43728e-005                *                     *                   *

* - Indicates that this value is not calculated.


                      Analysis of Deviance Table

      Model      Log(likelihood)  # Param's  Deviance  Test d.f.    P-value
 Full model          -71.366          4
Fitted model         -72.033          3       1.33391      1          0.2481
Reduced model       -92.7453          1       42.7585      3         <.0001

          AIC:        150.066
```

BMD Cancer Analysis – Six Steps



Does the Model Fit the Data?

- **For cancer data:**
  - ***Global measurement: goodness-of-fit p value (p > 0.1 or 0.05)***
  - 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* (e.g., multistage model for cancer endpoints), a cut-off value of $p = 0.05$ can be used

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

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.***

Comparing Model Fit Across Models

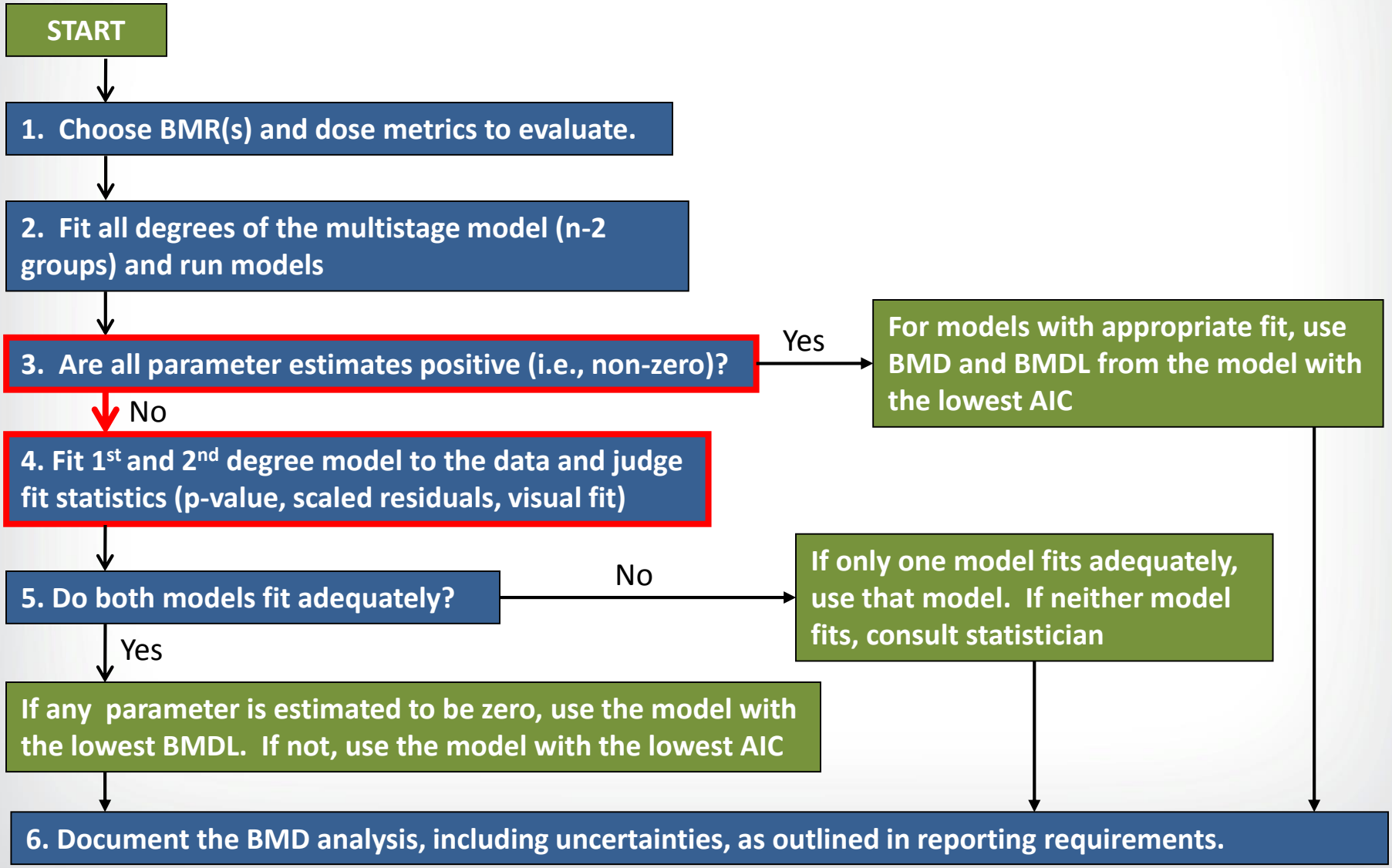
- **Within a family of models (e.g., 2nd degree vs. 1st degree multistage), addition of parameters will generally improve fit**
  - Likelihood ratio tests can determine whether the improvement in fit afforded by extra parameters is justified
  - However, these tests cannot be used to compare models from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

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

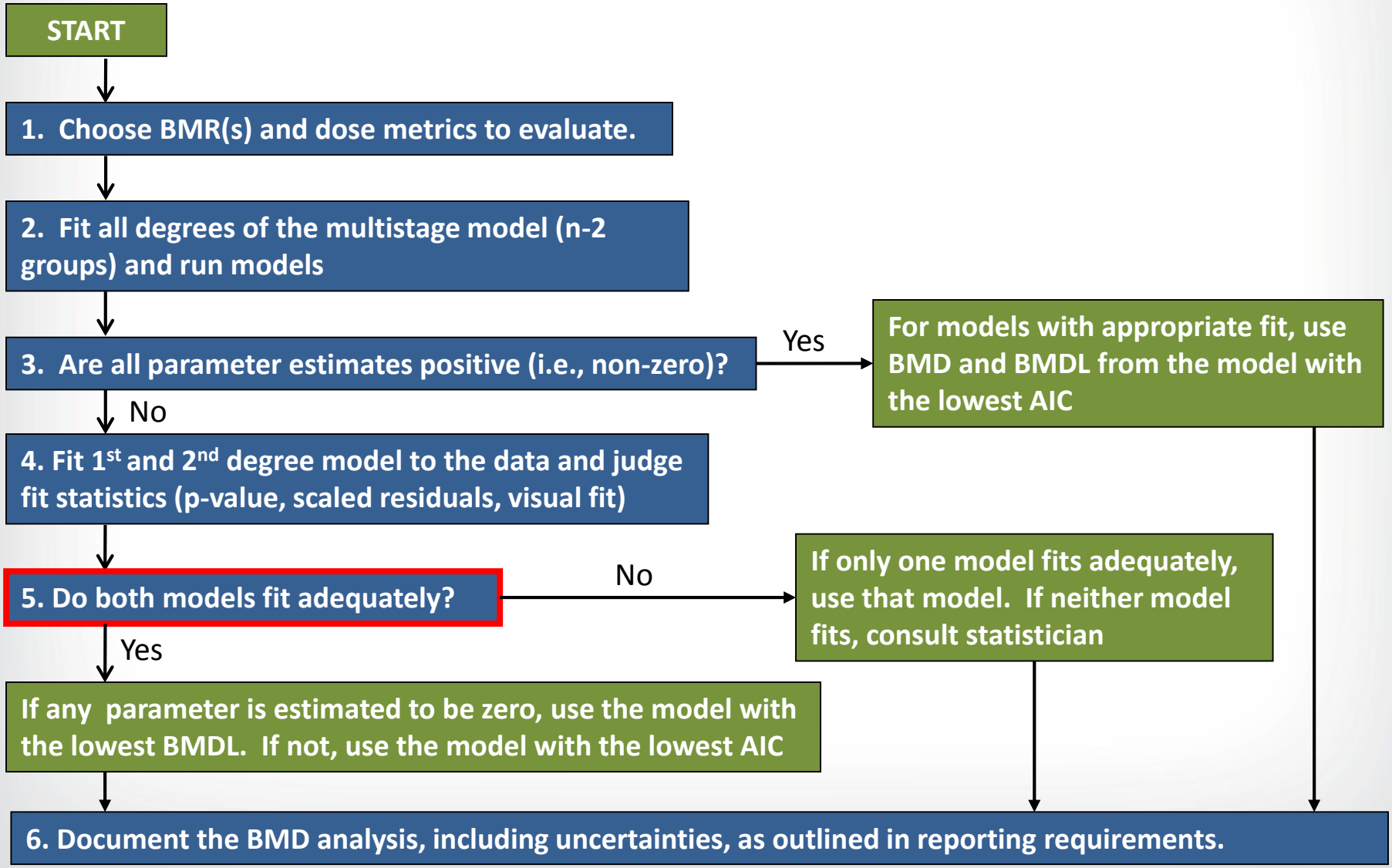
Akaike's Information Criterion (AIC)

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

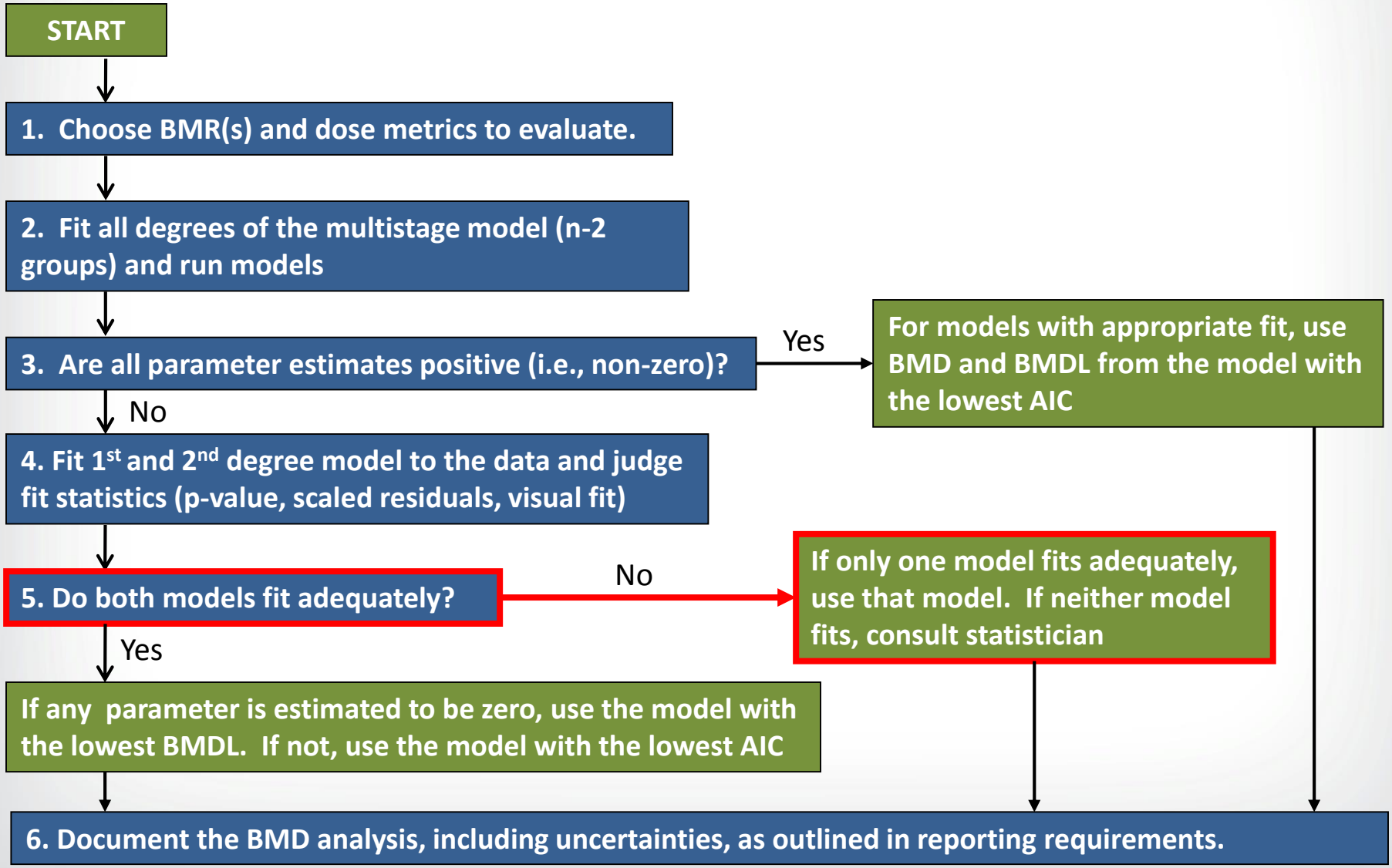
BMD Cancer Analysis – Six Steps



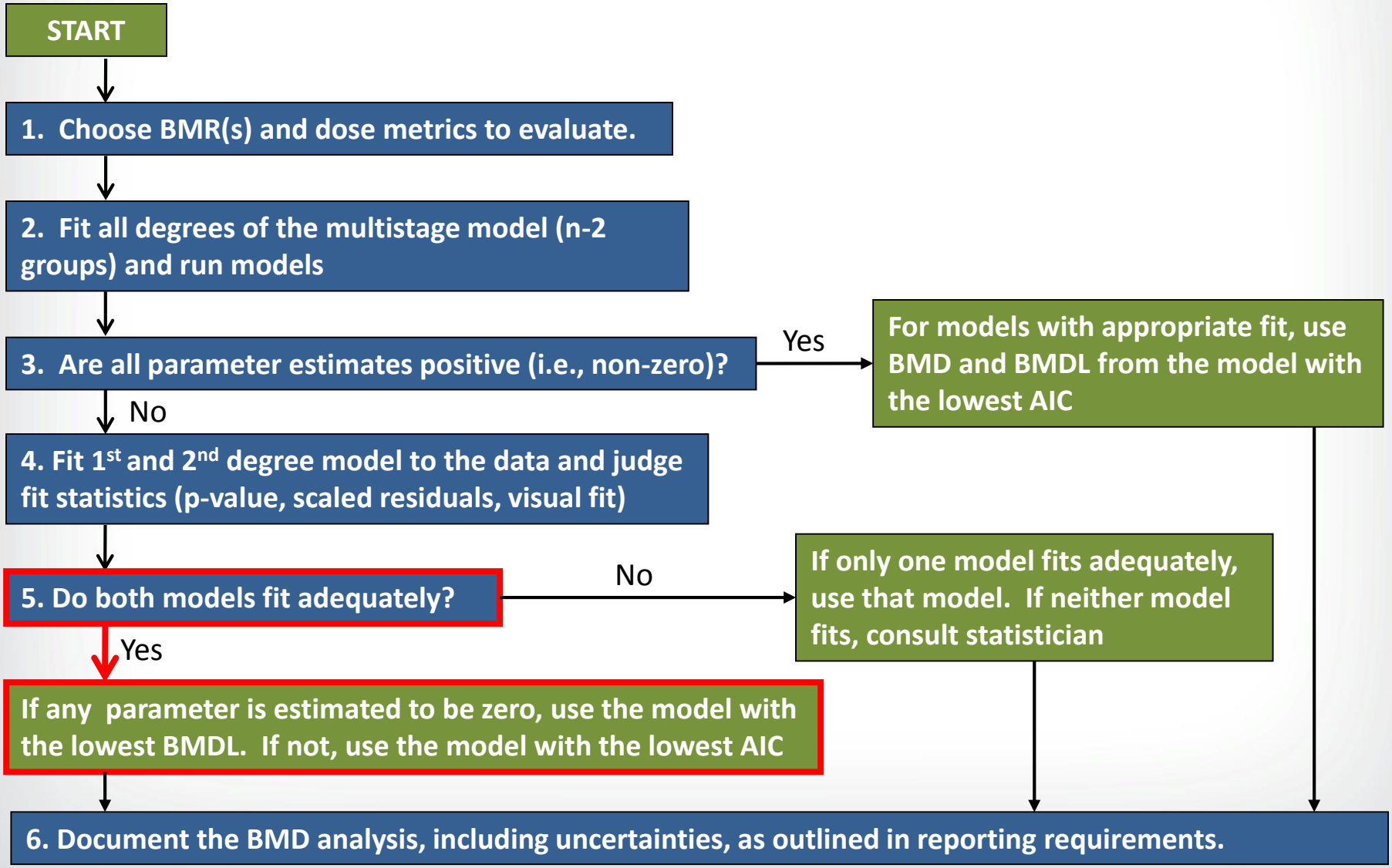
BMD Cancer Analysis – Six Steps



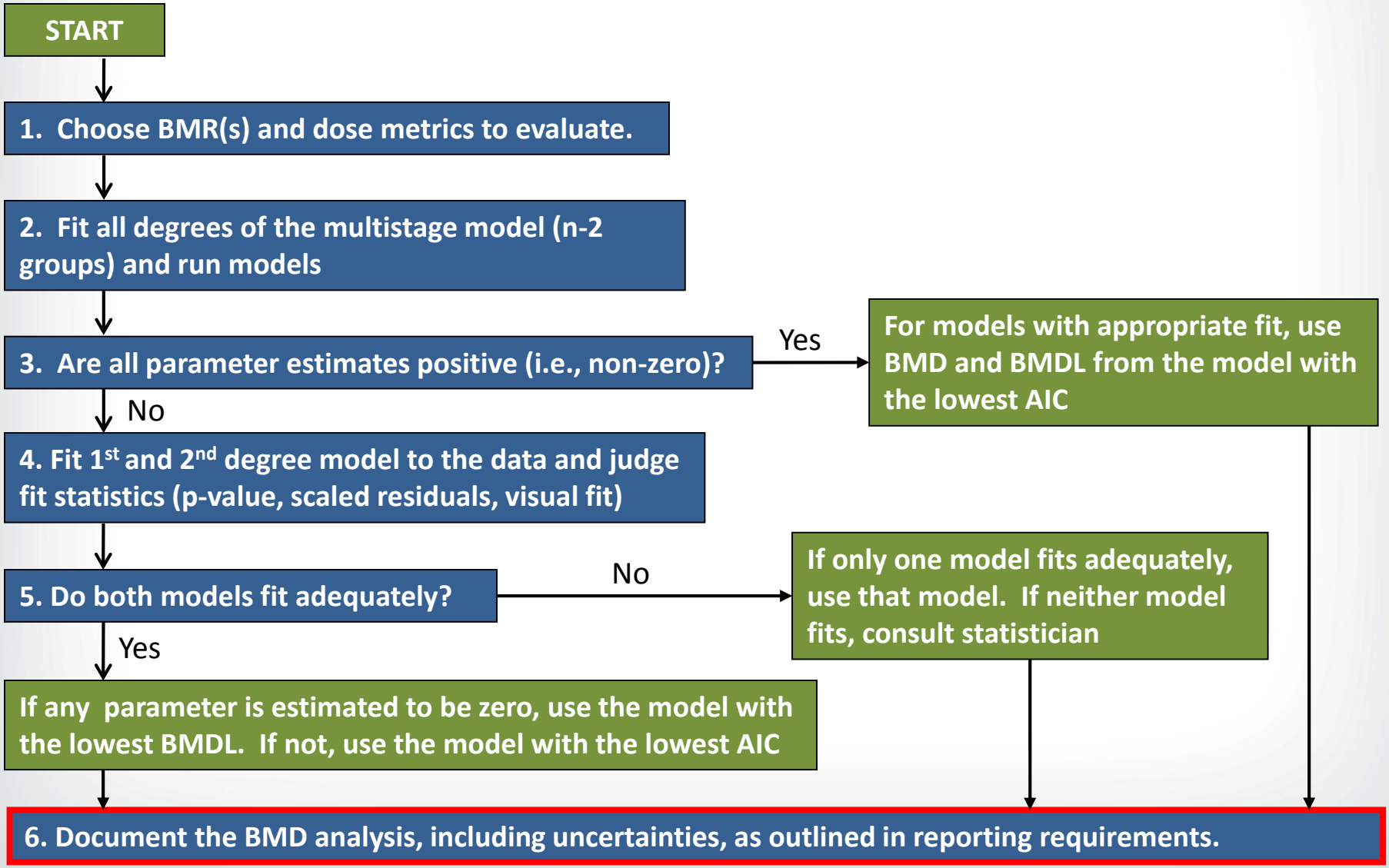
BMD Cancer Analysis – Six Steps



BMD Cancer Analysis – Six Steps



BMD Cancer Analysis – Six Steps



Cancer 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 "BMDS Wizard 1.9" folder in the BMDS240 directory**
  - To avoid possible problems running the Wizard, EPA recommends that the file path of the Wizard subdirectory not contain any non-alphanumeric characters
  - EPA users will need to locate their BMDS 250 and Wizard folders in the Users folder (C:\Users\name\BMDS250)
  - Non-EPA users can locate their folders in other directories, but the Wizard folder must be in the same directory as the BMDS executable

BMDS Wizard Macros

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

Excel 2003

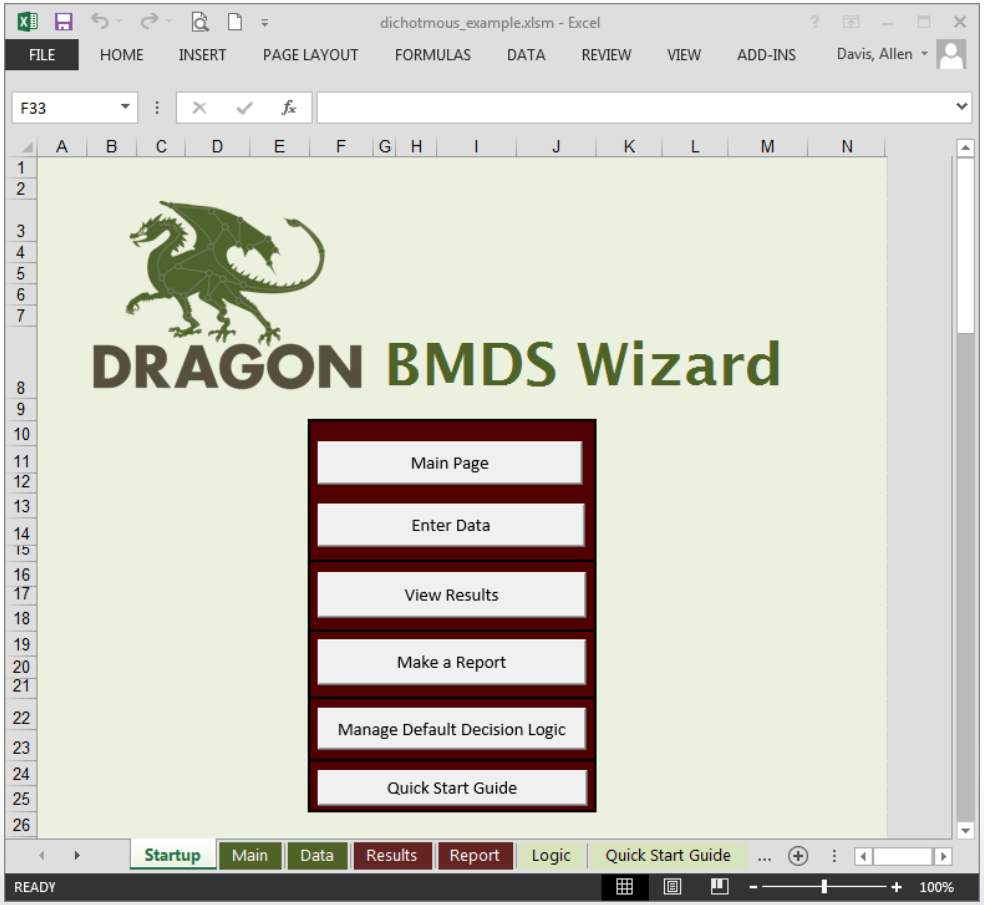
- Open Excel
- Select the "Tools" Menu
- Select Options
- Go to "Security" tab and click "Macro Security"
- Change security level to "Medium" or "Low"

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

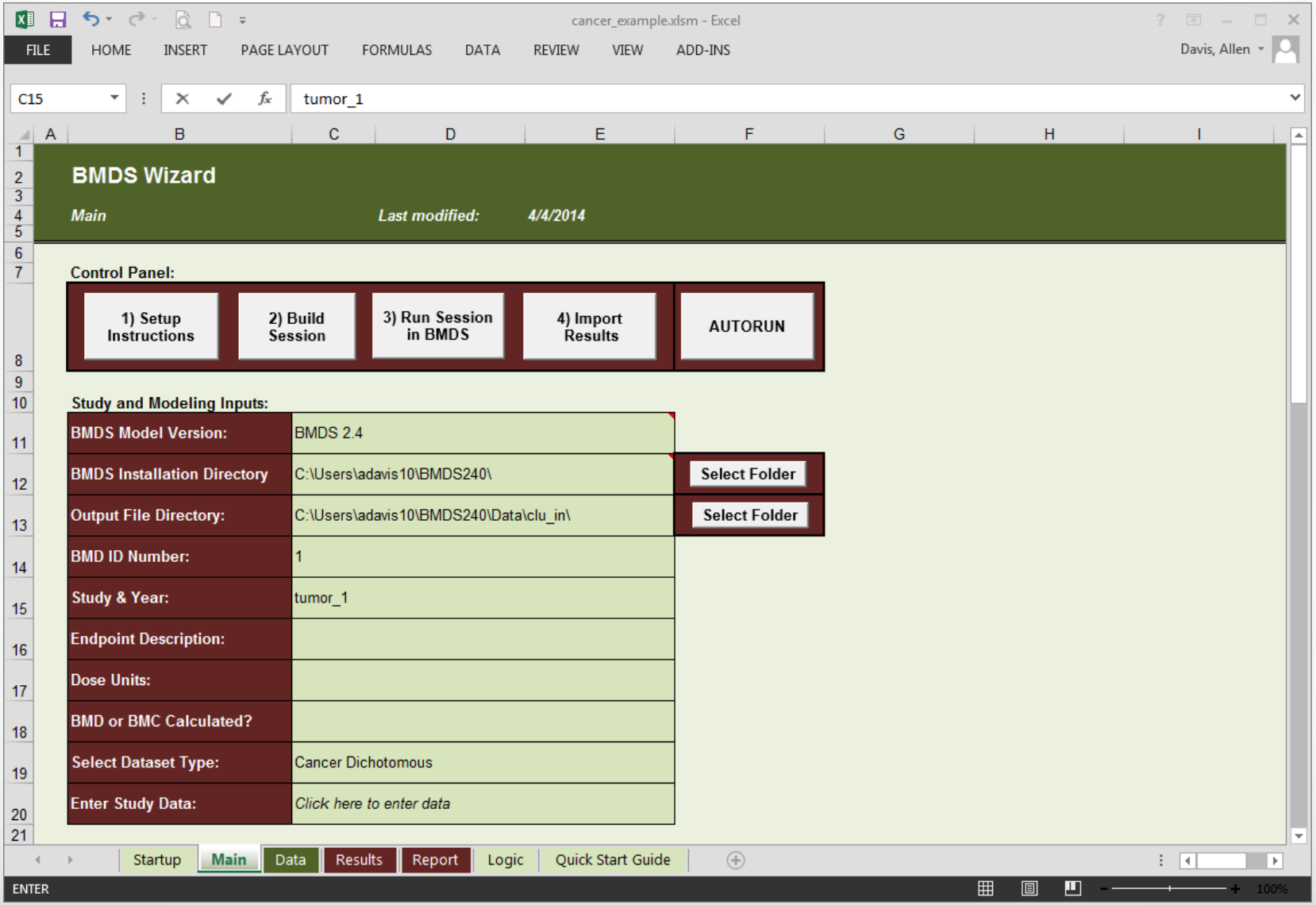
- **Excel 2010/2013**
- Open Excel
- Select "File" on the Ribbon toolbar and click "Options"
- Go to the "Trust Center" tab and click "Trust Center Settings"
- Change "Macro Settings" to "Disable all macros with notification" or "Enable all macros"

Starting a BMDS Wizard Session

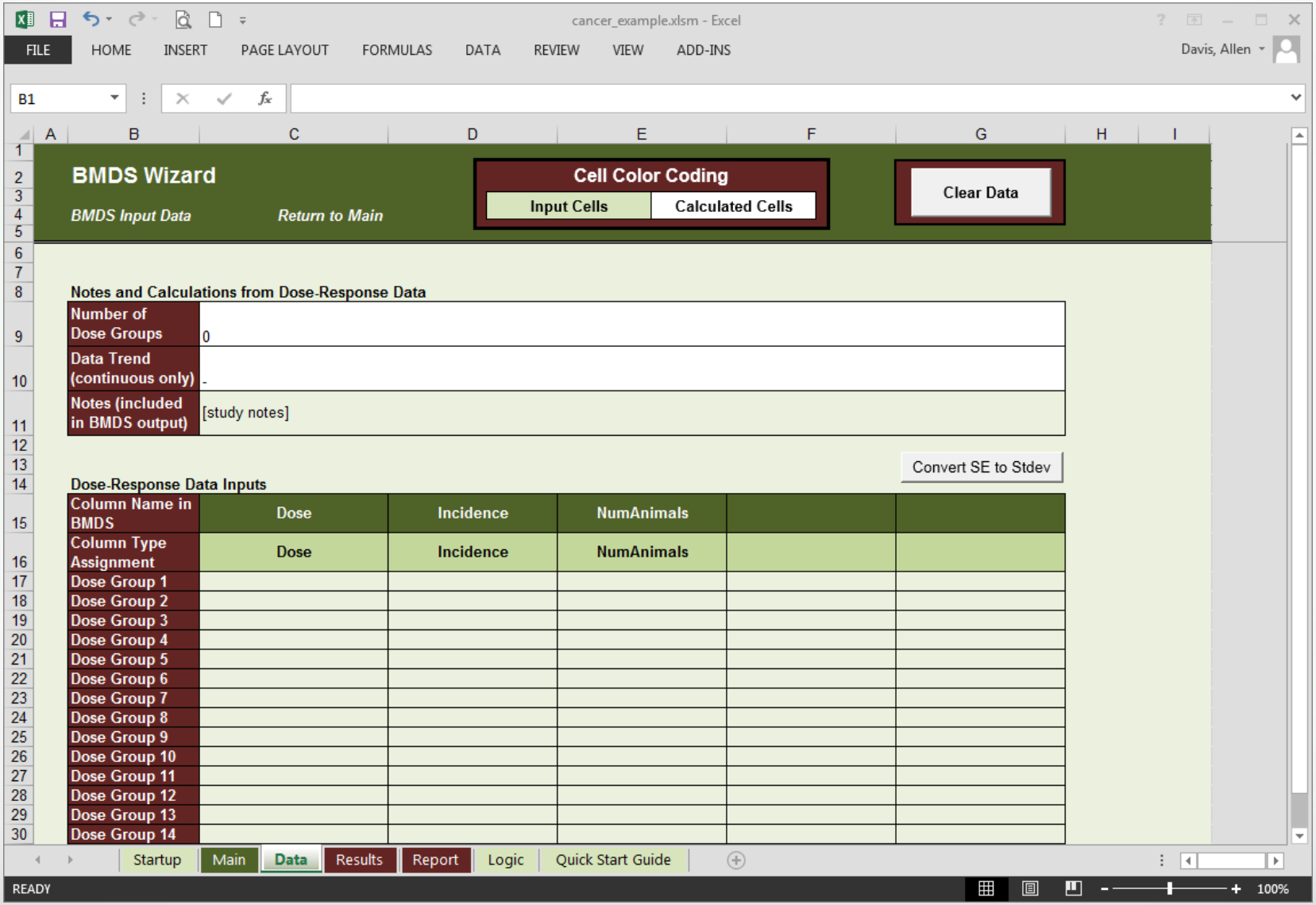
- **Open template file and "Save As" (Excel Macro-Enabled Workbook [*.xlsm]) to new BMDS Wizard file in desired working directory**



BMDS Wizard – Study and Modeling Inputs



BMDS Wizard – Entering Data



cancer_example.xlsm - Excel

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

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B1

BMDS Wizard

BMDS Input Data *Return to Main*

Cell Color Coding

Input Cells | Calculated Cells

Clear Data

Notes and Calculations from Dose-Response Data

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

Convert SE to Stdev

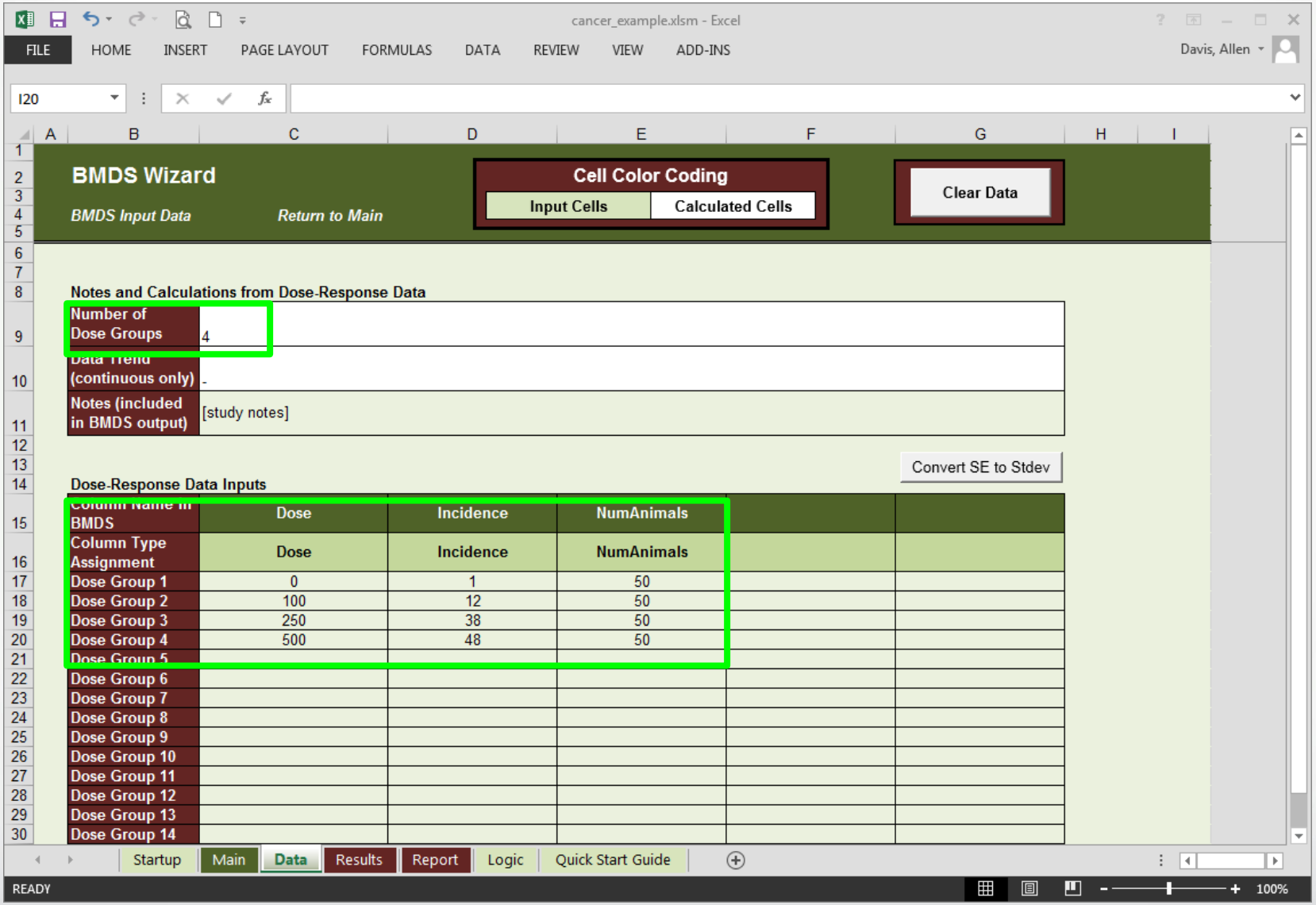
Dose-Response Data Inputs

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					

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

READY 100%

BMDS Wizard – Entering Data



cancer_example.xlsm - Excel

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

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I20

BMDS Wizard

BMDS Input Data *Return to Main*

Cell Color Coding

Input Cells | Calculated Cells

Clear Data

Notes and Calculations from Dose-Response Data

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

Convert SE to Stdev

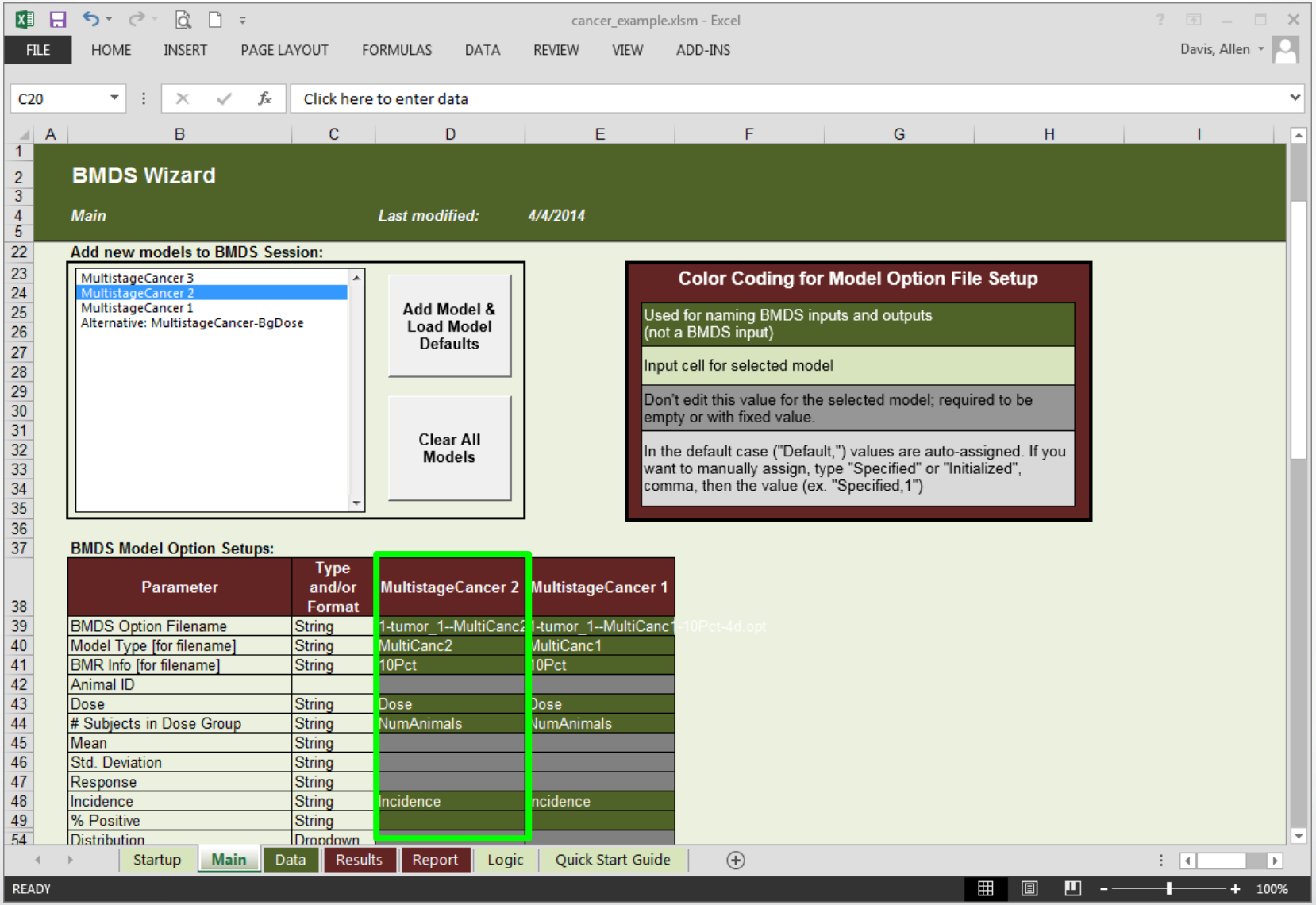
Dose-Response Data Inputs

Column Name in BMDS	Dose	Incidence	NumAnimals
Column Type Assignment	Dose	Incidence	NumAnimals
Dose Group 1	0	1	50
Dose Group 2	100	12	50
Dose Group 3	250	38	50
Dose Group 4	500	48	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			

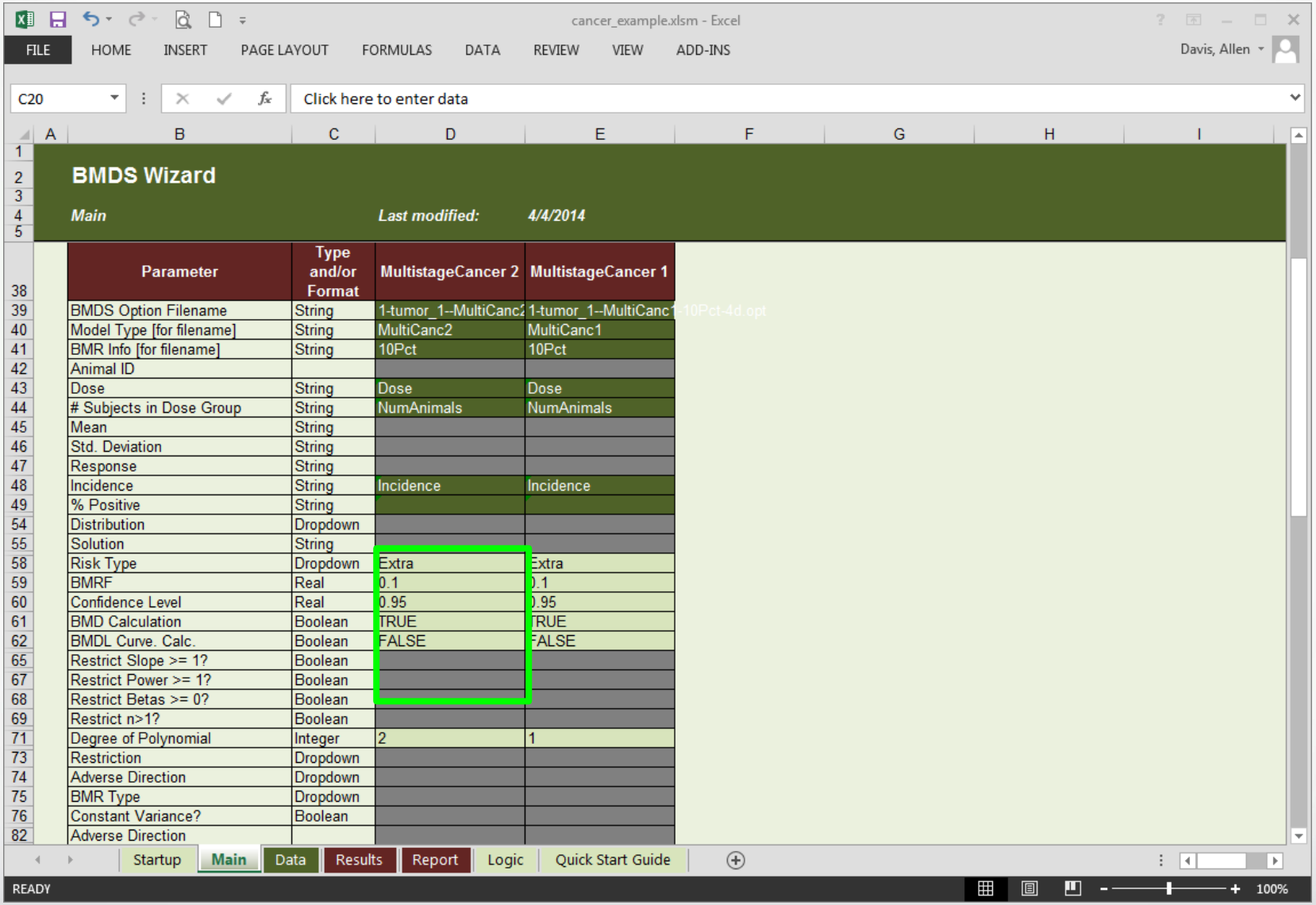
Startup | Main | Data | Results | Report | Logic | Quick Start Guide

READY 100%

BMDS Wizard – Model Parameters



BMDS Wizard – Model Parameters



cancer_example.xlsm - Excel

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

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C20 | Click here to enter data

BMDS Wizard

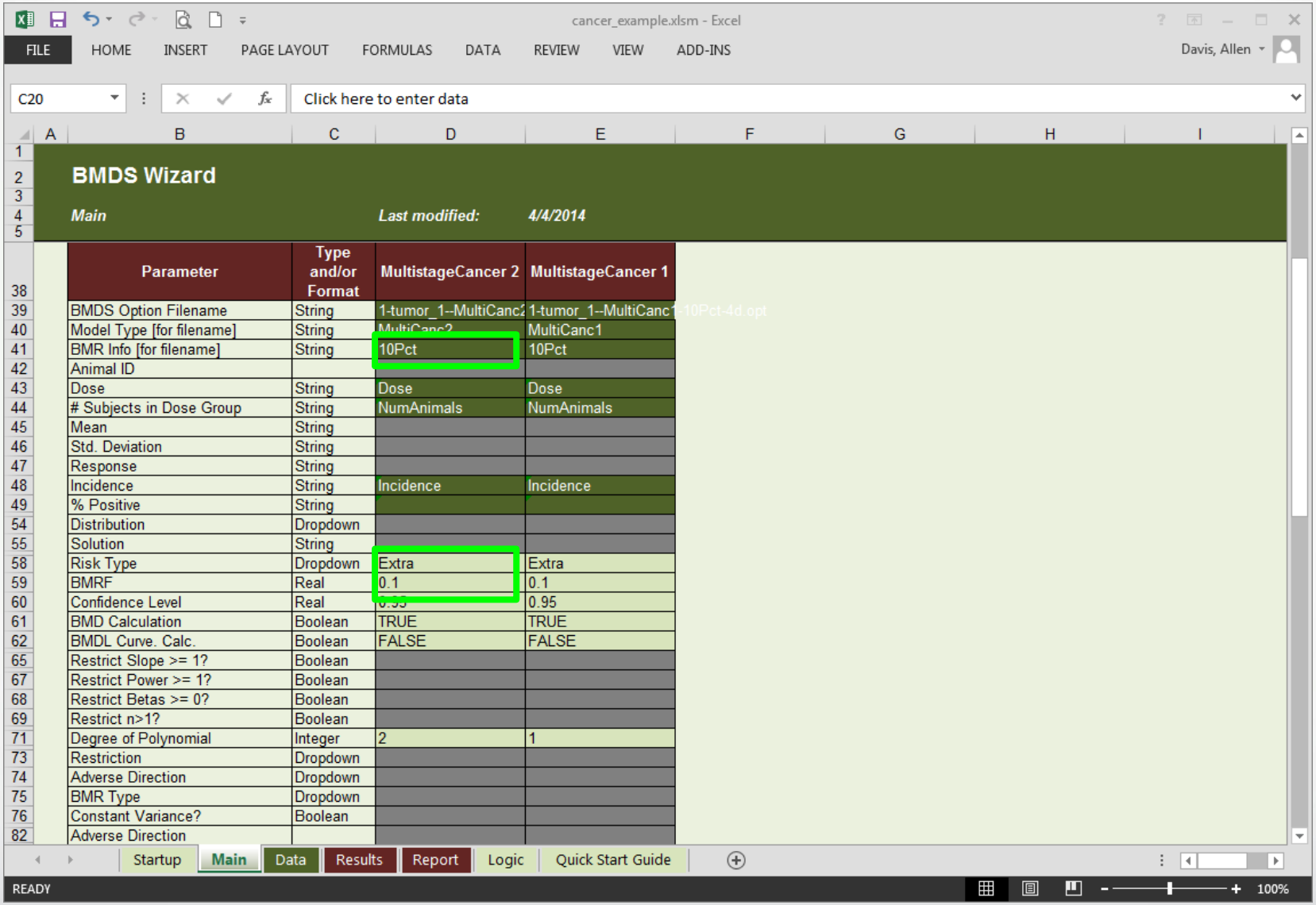
Main *Last modified:* *4/4/2014*

Parameter	Type and/or Format	MultistageCancer 2	MultistageCancer 1
BMDS Option Filename	String	1-tumor_1--MultiCanc2	1-tumor_1--MultiCanc1-10Pct-4d.opt
Model Type [for filename]	String	MultiCanc2	MultiCanc1
BMR Info [for filename]	String	10Pct	10Pct
Animal ID			
Dose	String	Dose	Dose
# Subjects in Dose Group	String	NumAnimals	NumAnimals
Mean	String		
Std. Deviation	String		
Response	String		
Incidence	String	Incidence	Incidence
% Positive	String		
Distribution	Dropdown		
Solution	String		
Risk Type	Dropdown	Extra	Extra
BMRF	Real	0.1	0.1
Confidence Level	Real	0.95	0.95
BMD Calculation	Boolean	TRUE	TRUE
BMDL Curve. Calc.	Boolean	FALSE	FALSE
Restrict Slope >= 1?	Boolean		
Restrict Power >= 1?	Boolean		
Restrict Betas >= 0?	Boolean		
Restrict n>1?	Boolean		
Degree of Polynomial	Integer	2	1
Restriction	Dropdown		
Adverse Direction	Dropdown		
BMR Type	Dropdown		
Constant Variance?	Boolean		
Adverse Direction			

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

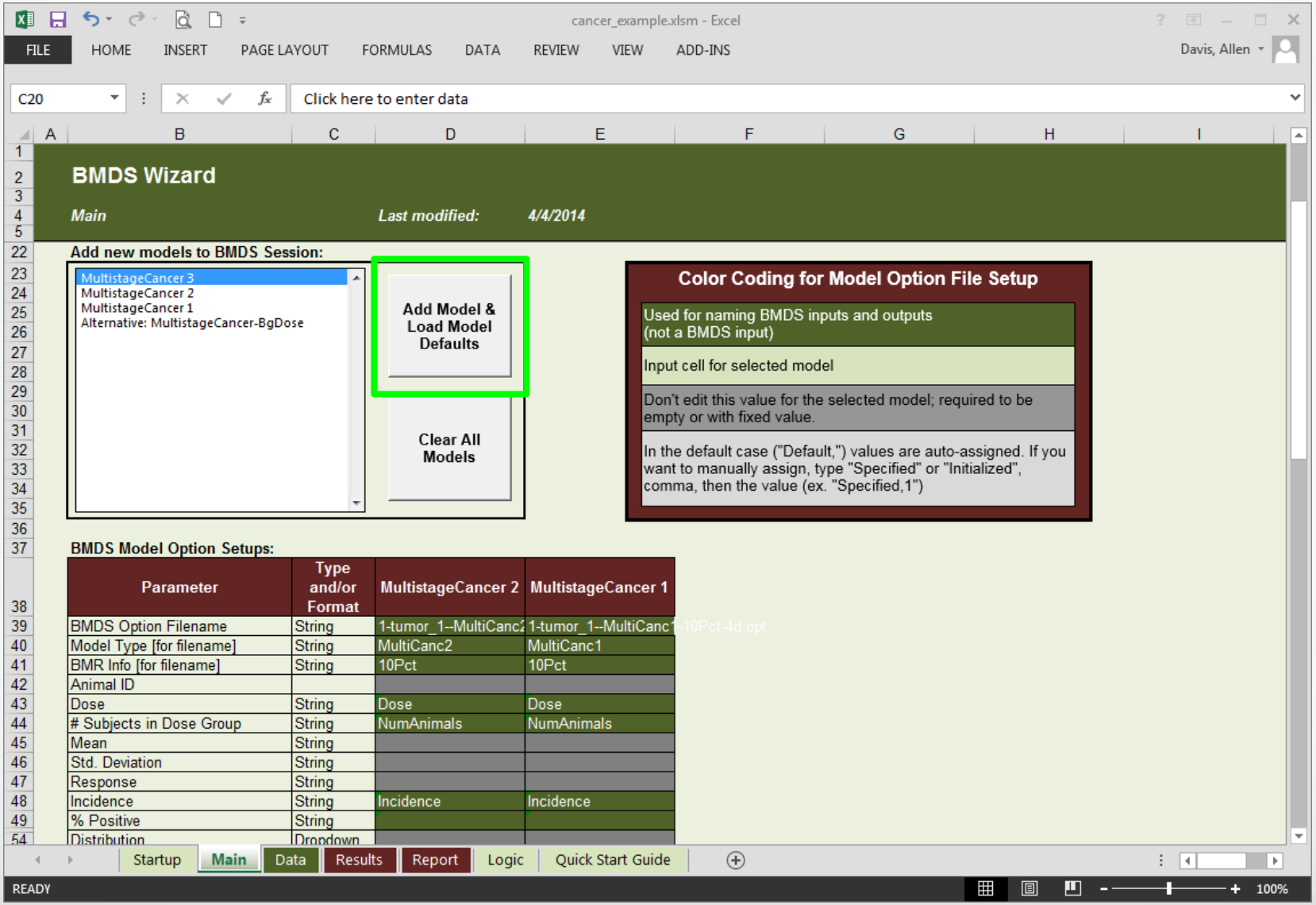
READY 100%

BMDS Wizard – Model Parameters

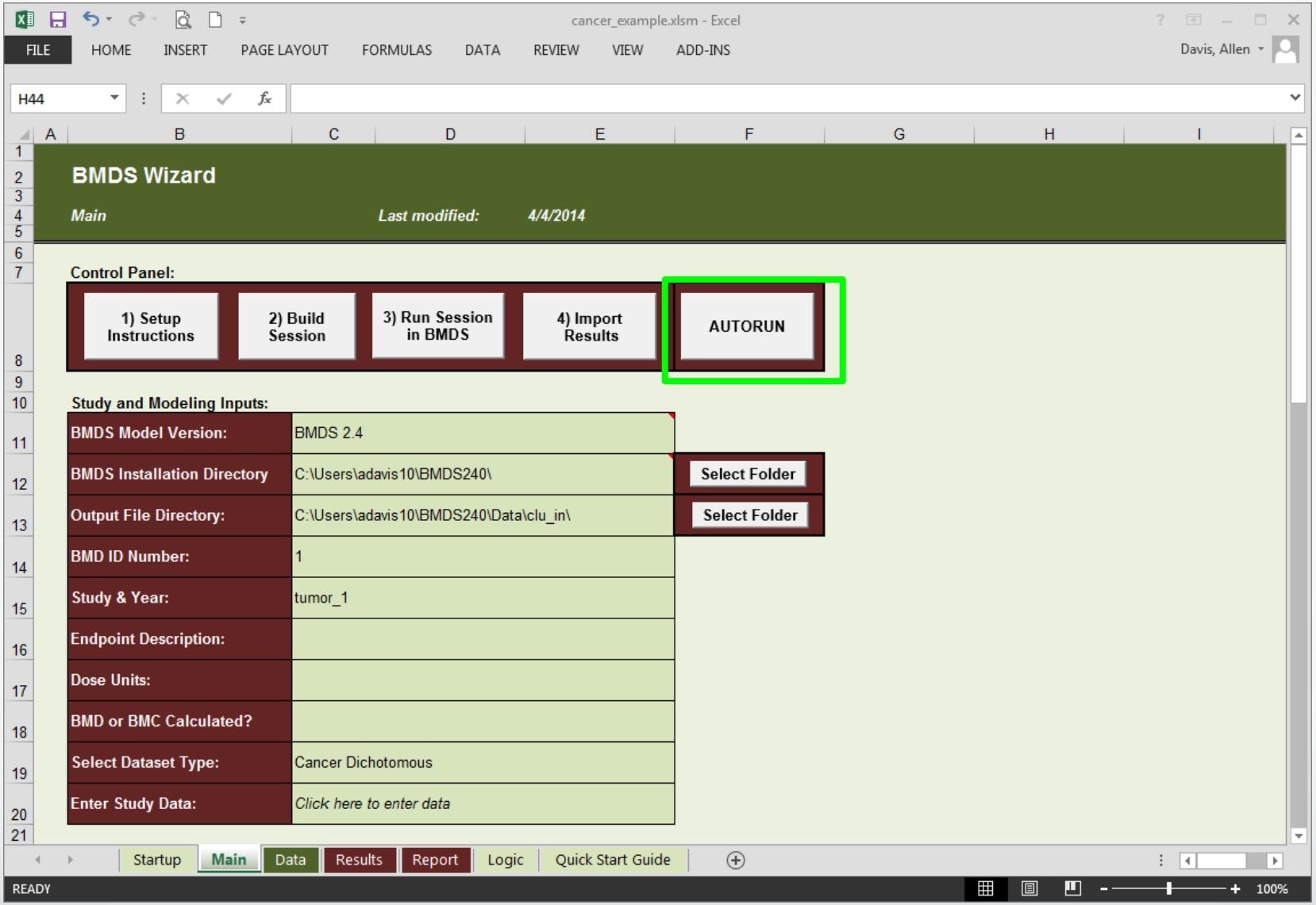


Parameter	Type and/or Format	MultistageCancer 2	MultistageCancer 1
BMDS Option Filename	String	1-tumor_1--MultiCanc2	1-tumor_1--MultiCanc1-10Pct-4d.opt
Model Type [for filename]	String	MultiCanc2	MultiCanc1
BMR Info [for filename]	String	10Pct	10Pct
Animal ID			
Dose	String	Dose	Dose
# Subjects in Dose Group	String	NumAnimals	NumAnimals
Mean	String		
Std. Deviation	String		
Response	String		
Incidence	String	Incidence	Incidence
% Positive	String		
Distribution	Dropdown		
Solution	String		
Risk Type	Dropdown	Extra	Extra
BMRF	Real	0.1	0.1
Confidence Level	Real	0.95	0.95
BMD Calculation	Boolean	TRUE	TRUE
BMDL Curve. Calc.	Boolean	FALSE	FALSE
Restrict Slope >= 1?	Boolean		
Restrict Power >= 1?	Boolean		
Restrict Betas >= 0?	Boolean		
Restrict n>1?	Boolean		
Degree of Polynomial	Integer	2	1
Restriction	Dropdown		
Adverse Direction	Dropdown		
BMR Type	Dropdown		
Constant Variance?	Boolean		
Adverse Direction			

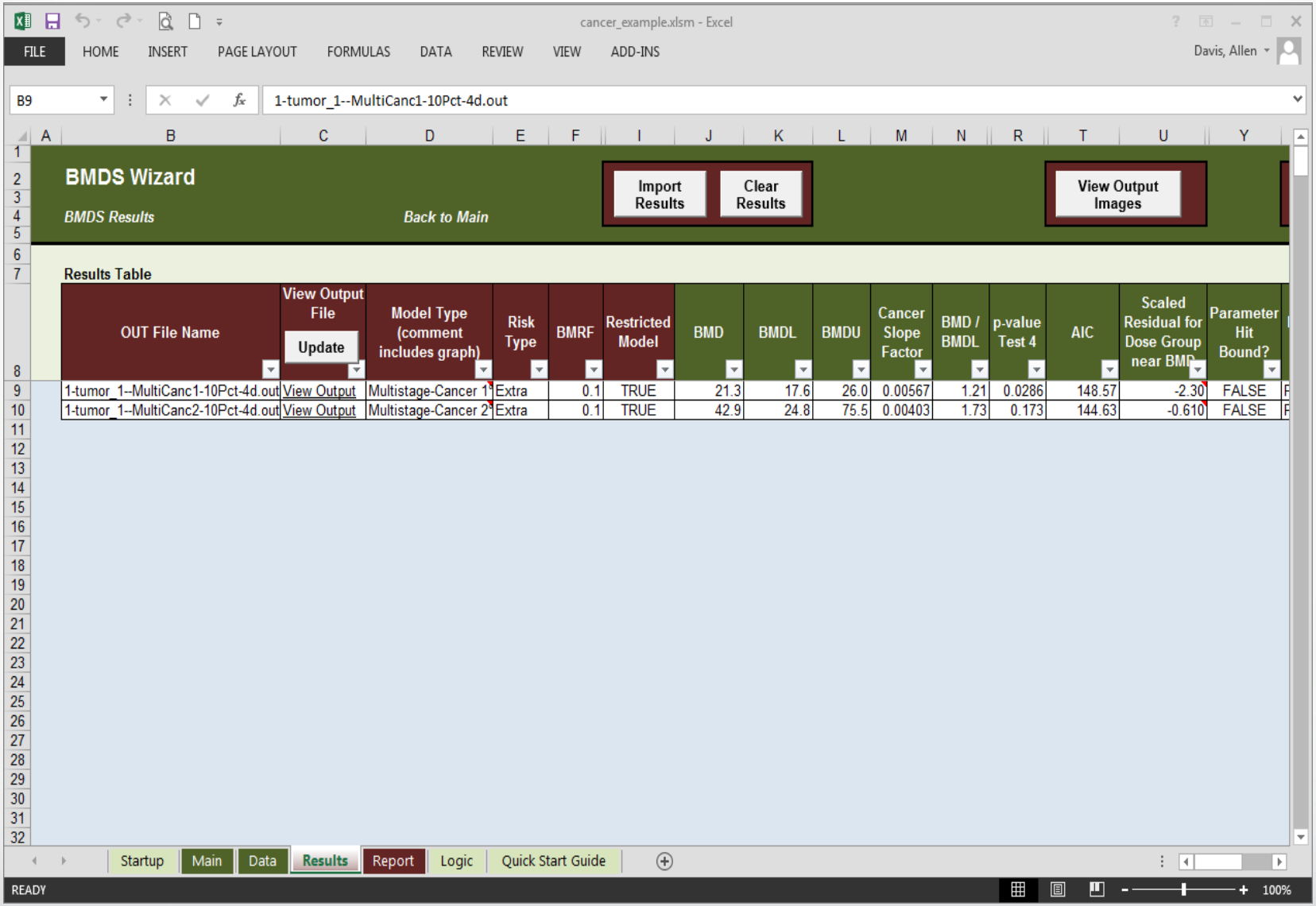
BMDS Wizard – Adding Models to Session



BMDS Wizard – AutoRunning BMDS



BMDS Wizard – Results

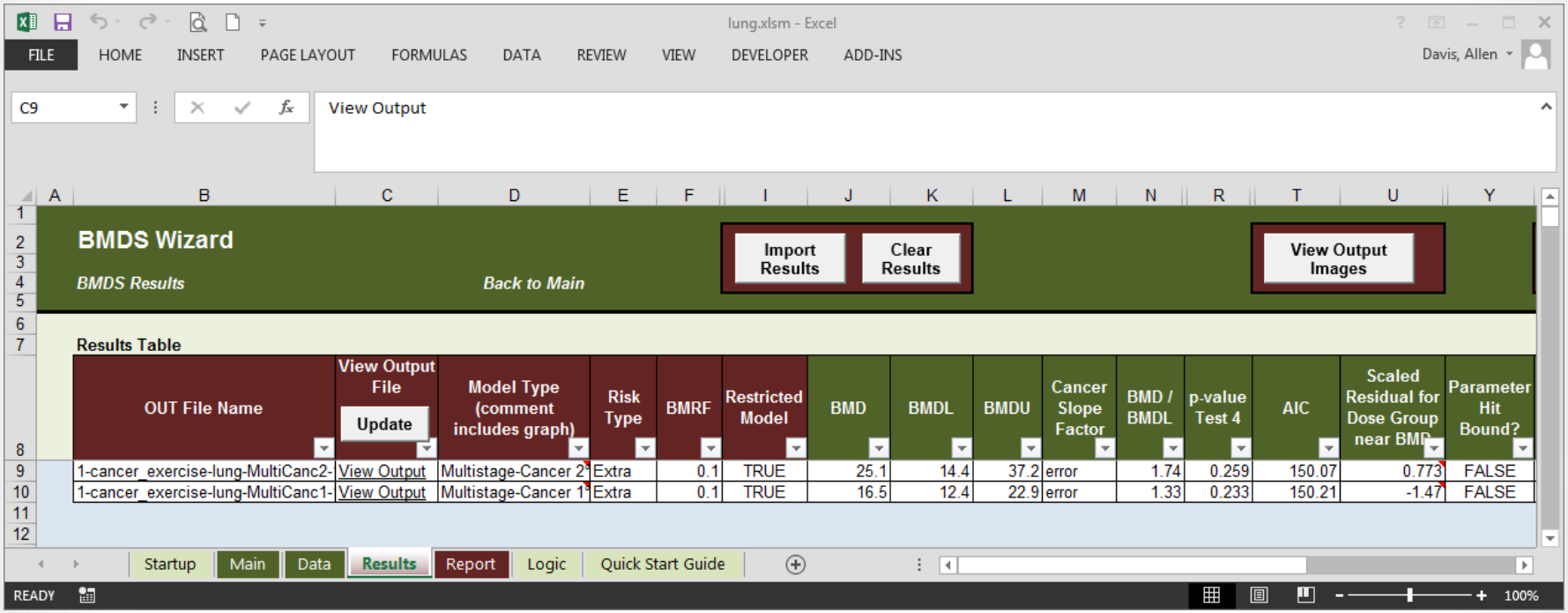


Cancer Data – Exercise #1

Cancer Exercise #1

- **Open the following Wizard cancer file: lung.xlsm**
- **Select the correct BMDS Installation directory and the desired Output file directory**
- **Autorun BMDS from Wizard file and select the appropriate Multistage model (make selection in column AE on Results tab)**

Cancer Exercise #1



The MS_Combo Combined Tumor Model

Multiple Tumor Analysis

- **Often, a individual cancer bioassay will report dose-related increases in multiple, independent tumor types**

- **Basing unit risk estimates on only one tumor type may underestimate the carcinogenic potential of a chemical that is observed to induce neoplasia at multiple sites in a bioassay (NRC, 1994)**

- **A method is needed to calculate composite risk (i.e., the risk of developing ANY COMBINATION of tumors at any site, NOT the risk of developing tumors at every site considered.**

Calculating Composite Risk

- **At first thought, modeling the number of tumor-bearing animals (i.e., counts of animals with one or more tumors of any kind) seems like an appropriate method of estimating composite risk**
  - Modeling tumor-bearing animals underestimates total risk when tumors occur at multiple sites independently of one another (NRC, 1994; Bogen, 1990)
  - Also, the use of only one dose-response model for all cancer types would not adequately characterize differences in dose-response shapes across different tumor types.

- **Therefore, a statistical approach is needed for calculation of composite risk**

The MS_Combo Model

- **Allows users to calculate the BMD and BMDL for any combination of tumors observed in a single bioassay.**

- **The major assumption of the MS_Combo model is that different tumor types are INDEPENDENT of one another**
  - Independence can be determined based on statistical or biological considerations

- **Individual tumor types must first be modeled with the multistage model to determine with degree model best fits the data**
  - This allows individual tumors to be fit with models that best characterize their specific dose-response shapes

The MS_Combo Approach to Calculating a BMD and BMDL

- **The probability function for the MS_Combo model has a multistage form:**

$$Prob\{response\} = p(d) = 1 - exp\{-(\beta_0 + \beta_1 d + \beta_2 d^2 + \cdots)\}$$

  - Where the terms of the combined probability function ($\beta_0, \beta_1, \ldots$) are functions of the β coefficient values obtained from the individual multistage model fits:

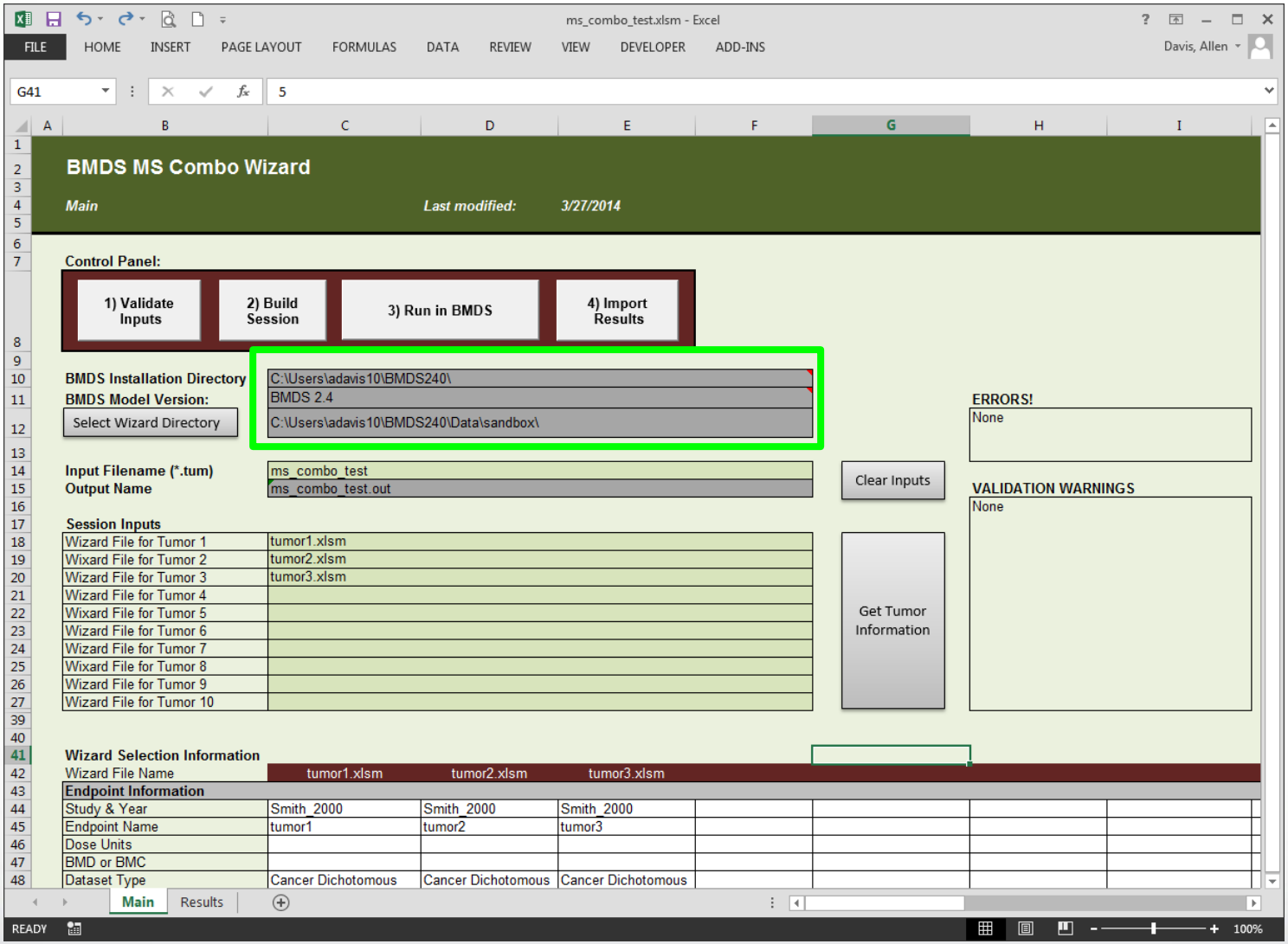
$$\beta_0 = \sum \beta_{0i}, \beta_1 = \sum \beta_{1i}, \ldots$$

- **The BMD is computed based on the combined parameter values and the user-specified BMR**

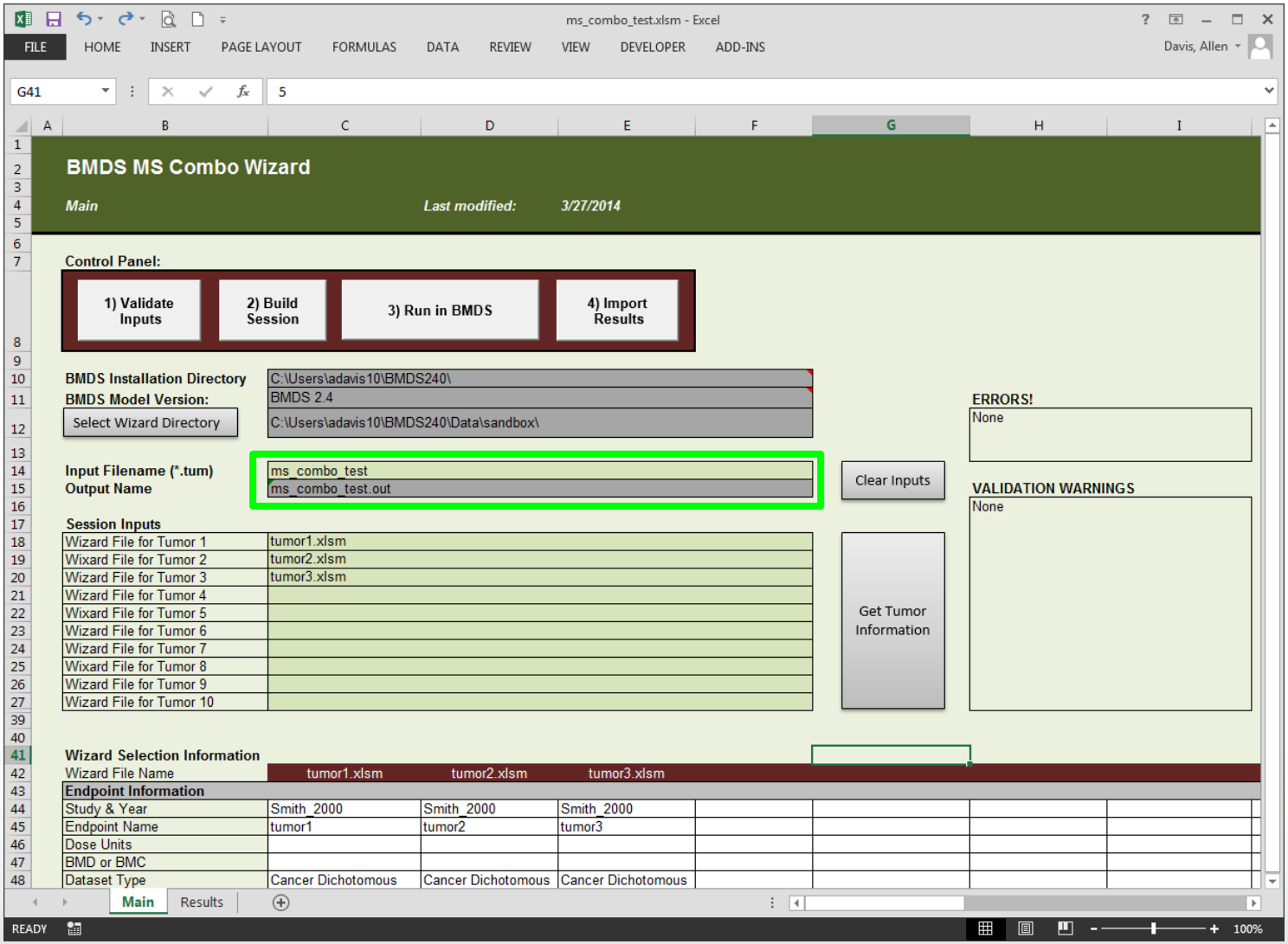
- **The BMDL is calculated via a profile likelihood approach**

Cancer Data – Running the MS_Combo Model using the BMDS Wizard Tool

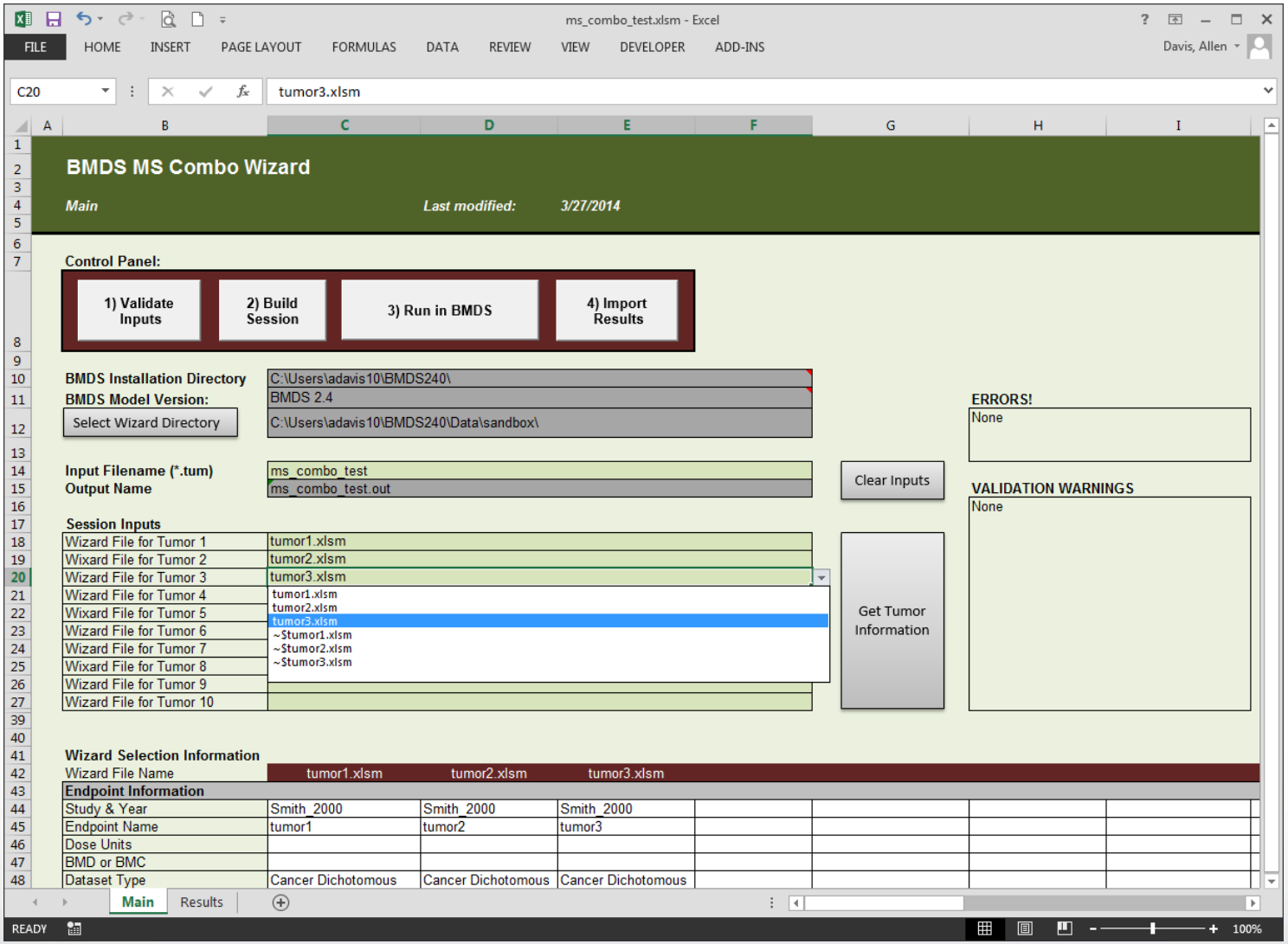
Wizard MS Combo



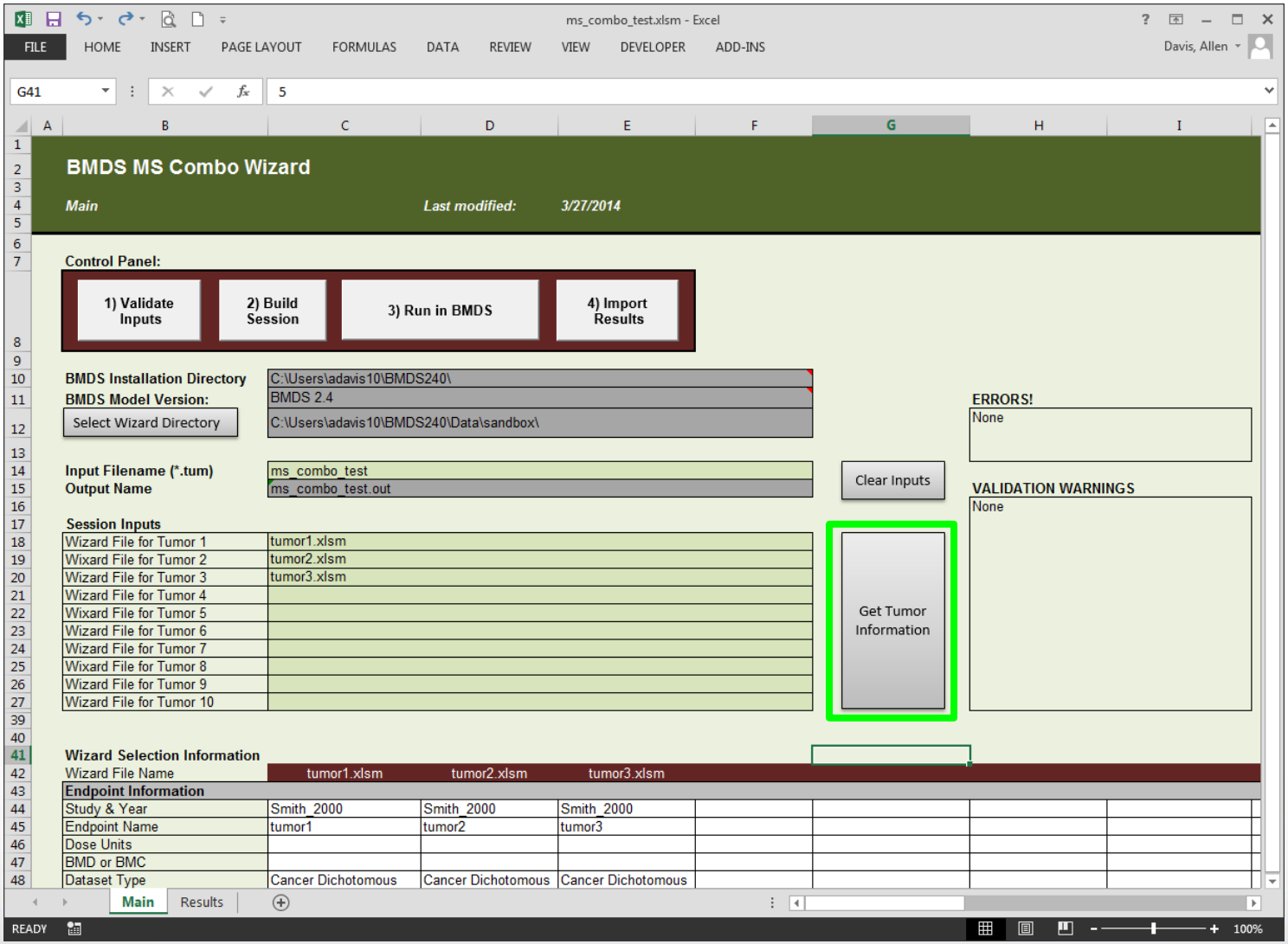
Wizard MS Combo



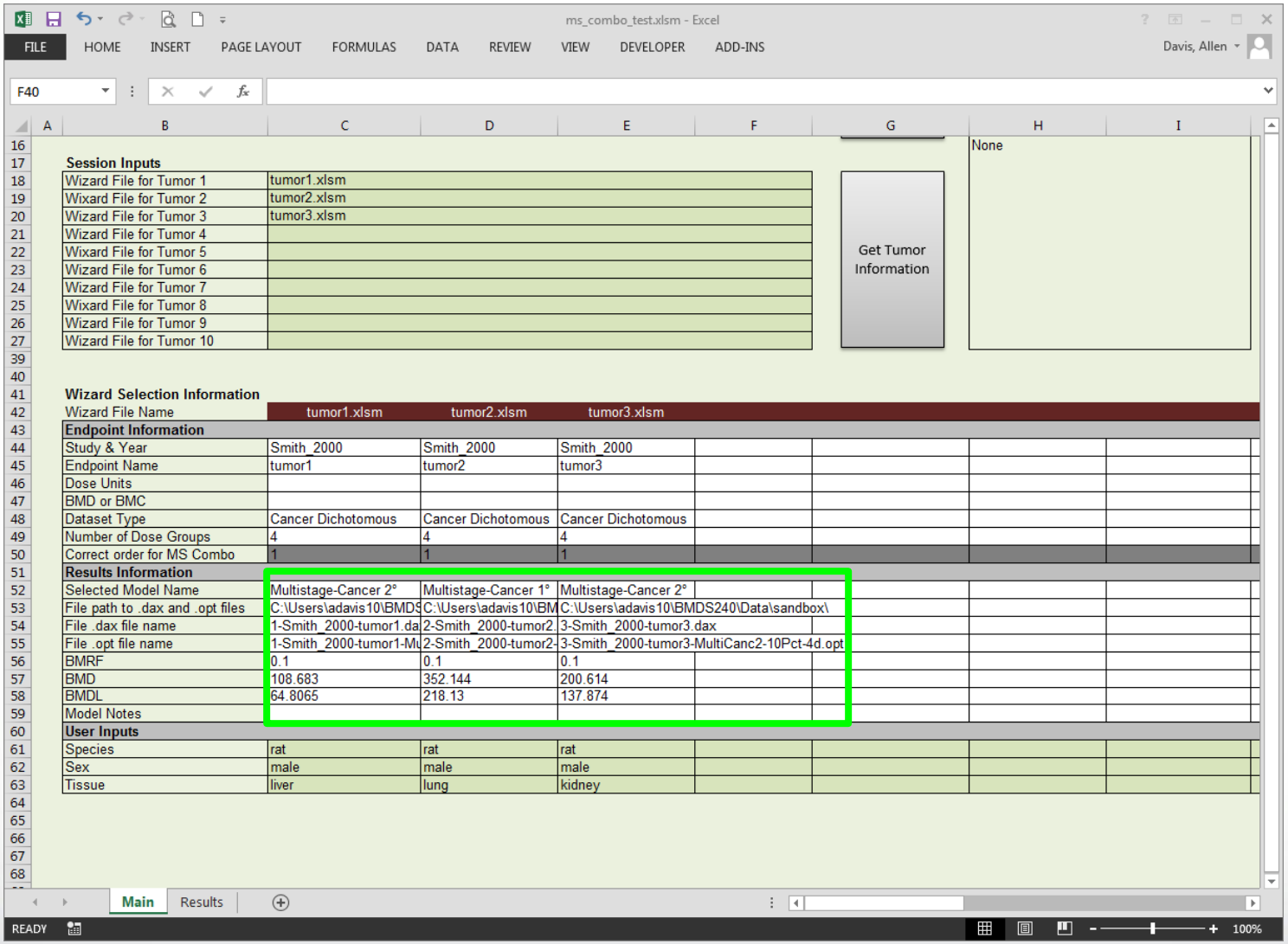
Wizard MS Combo



Wizard MS Combo



Wizard MS Combo



ms_combo_test.xlsm - Excel

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

Davis, Allen

F40

Session Inputs

Wizard File for Tumor 1	tumor1.xlsm
Wixard File for Tumor 2	tumor2.xlsm
Wizard File for Tumor 3	tumor3.xlsm
Wizard File for Tumor 4	
Wixard File for Tumor 5	
Wizard File for Tumor 6	
Wizard File for Tumor 7	
Wixard File for Tumor 8	
Wizard File for Tumor 9	
Wizard File for Tumor 10	

Get Tumor Information

None

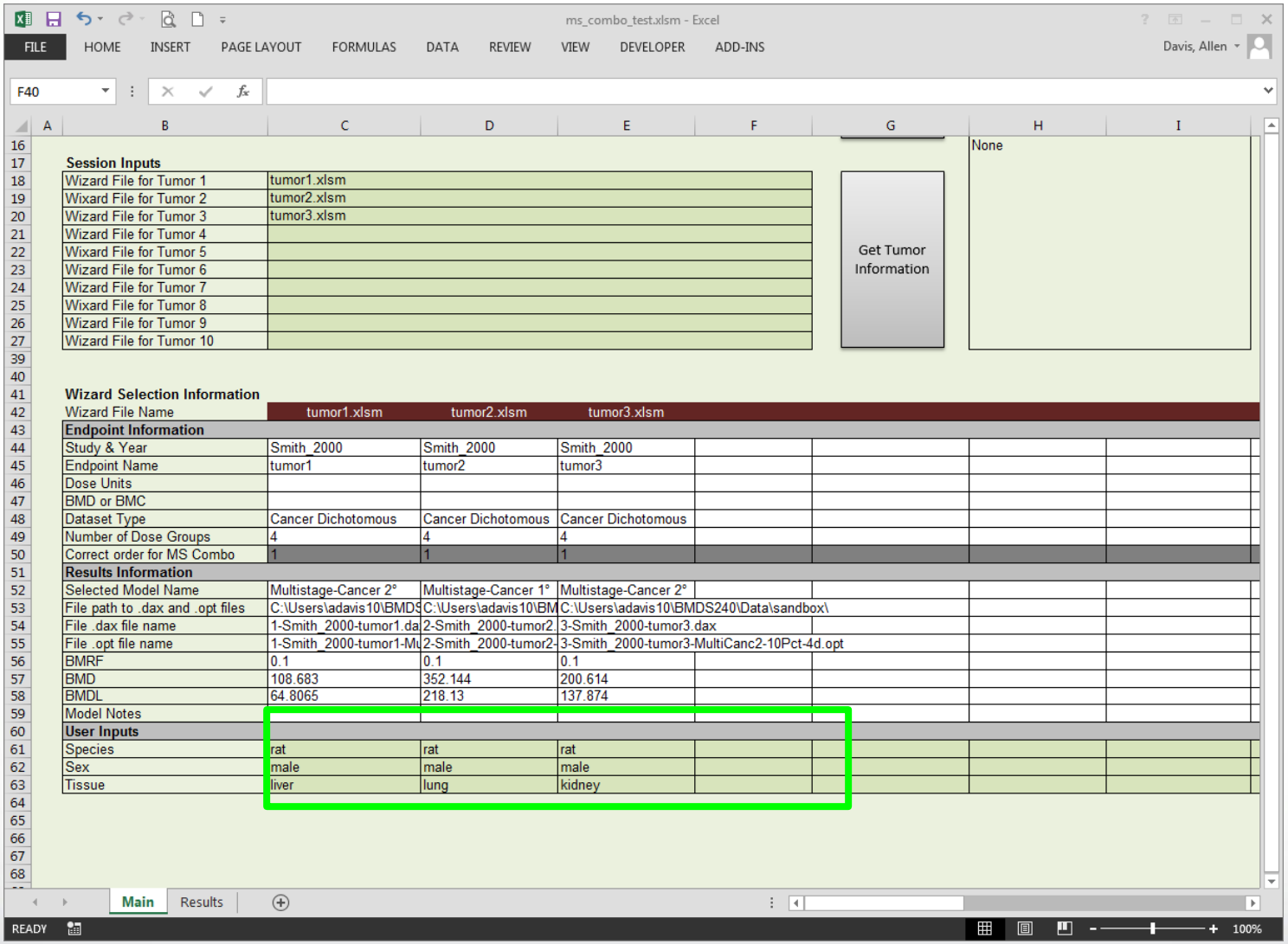
Wizard Selection Information

Wizard File Name	tumor1.xlsm	tumor2.xlsm	tumor3.xlsm
Endpoint Information			
Study & Year	Smith_2000	Smith_2000	Smith_2000
Endpoint Name	tumor1	tumor2	tumor3
Dose Units			
BMD or BMC			
Dataset Type	Cancer Dichotomous	Cancer Dichotomous	Cancer Dichotomous
Number of Dose Groups	4	4	4
Correct order for MS Combo	1	1	1
Results Information			
Selected Model Name	Multistage-Cancer 2°	Multistage-Cancer 1°	Multistage-Cancer 2°
File path to .dax and .opt files	C:\Users\adavis10\BMDS	C:\Users\adavis10\BM	C:\Users\adavis10\BMDS240\Data\sandbox\
File .dax file name	1-Smith_2000-tumor1.da	2-Smith_2000-tumor2	3-Smith_2000-tumor3.dax
File .opt file name	1-Smith_2000-tumor1-Mu	2-Smith_2000-tumor2-	3-Smith_2000-tumor3-MultiCanc2-10Pct-4d.opt
BMRF	0.1	0.1	0.1
BMD	108.683	352.144	200.614
BMDL	64.8065	218.13	137.874
Model Notes			
User Inputs			
Species	rat	rat	rat
Sex	male	male	male
Tissue	liver	lung	kidney

Main Results

READY 100%

Wizard MS Combo



ms_combo_test.xlsm - Excel

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

Davis, Allen

F40

Session Inputs

Wizard File for Tumor 1	tumor1.xlsm
Wixard File for Tumor 2	tumor2.xlsm
Wizard File for Tumor 3	tumor3.xlsm
Wizard File for Tumor 4	
Wixard File for Tumor 5	
Wizard File for Tumor 6	
Wizard File for Tumor 7	
Wixard File for Tumor 8	
Wizard File for Tumor 9	
Wizard File for Tumor 10	

Get Tumor Information

None

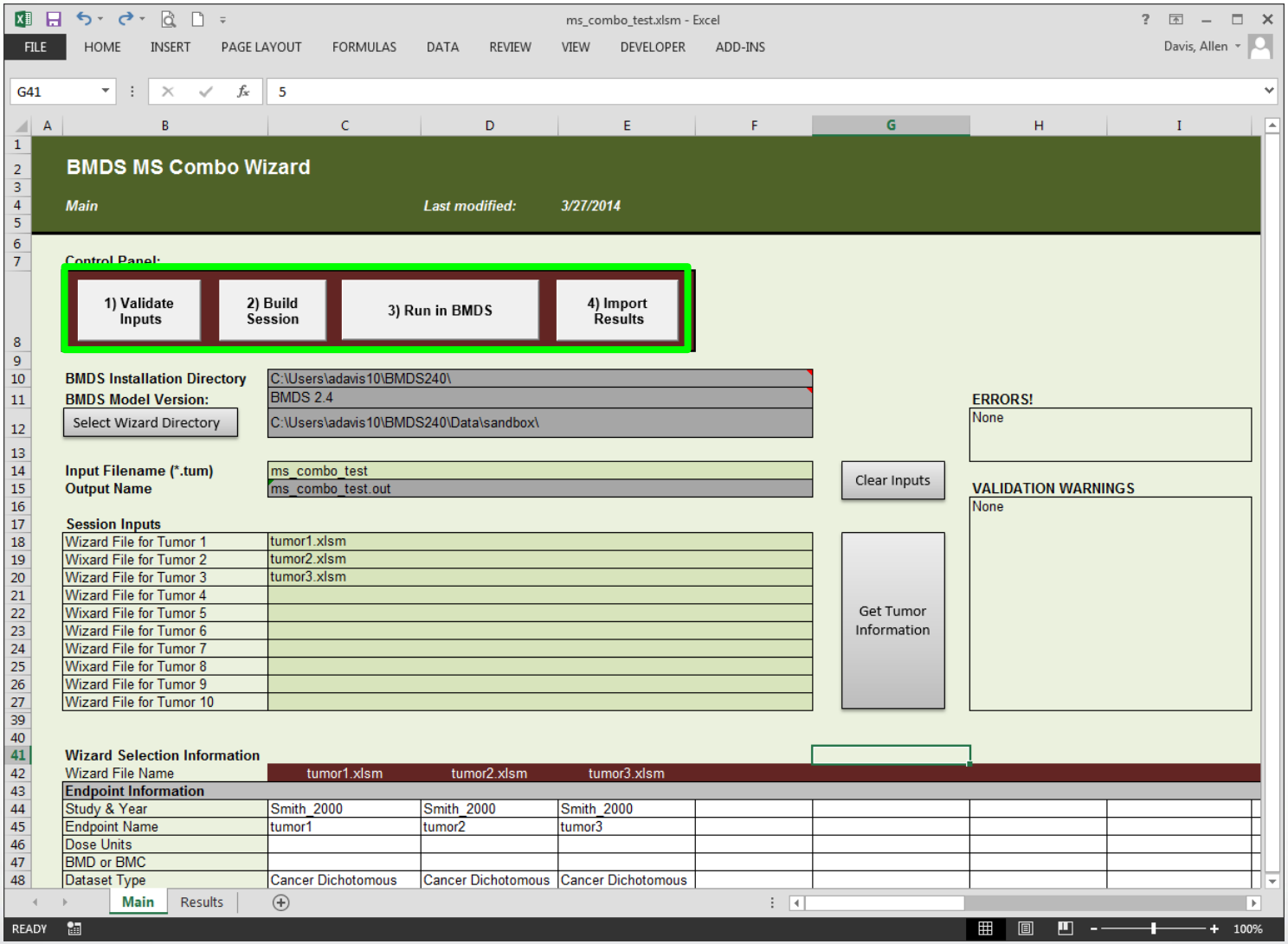
Wizard Selection Information

Wizard File Name	tumor1.xlsm	tumor2.xlsm	tumor3.xlsm
Endpoint Information			
Study & Year	Smith_2000	Smith_2000	Smith_2000
Endpoint Name	tumor1	tumor2	tumor3
Dose Units			
BMD or BMC			
Dataset Type	Cancer Dichotomous	Cancer Dichotomous	Cancer Dichotomous
Number of Dose Groups	4	4	4
Correct order for MS Combo	1	1	1
Results Information			
Selected Model Name	Multistage-Cancer 2°	Multistage-Cancer 1°	Multistage-Cancer 2°
File path to .dax and .opt files	C:\Users\adavis10\BMDS	C:\Users\adavis10\BM	C:\Users\adavis10\BMDS240\Data\sandbox\
File .dax file name	1-Smith_2000-tumor1.da	2-Smith_2000-tumor2	3-Smith_2000-tumor3.dax
File .opt file name	1-Smith_2000-tumor1-Mu	2-Smith_2000-tumor2-	3-Smith_2000-tumor3-MultiCanc2-10Pct-4d.opt
BMRF	0.1	0.1	0.1
BMD	108.683	352.144	200.614
BMDL	64.8065	218.13	137.874
Model Notes			
User Inputs			
Species	rat	rat	rat
Sex	male	male	male
Tissue	liver	lung	kidney

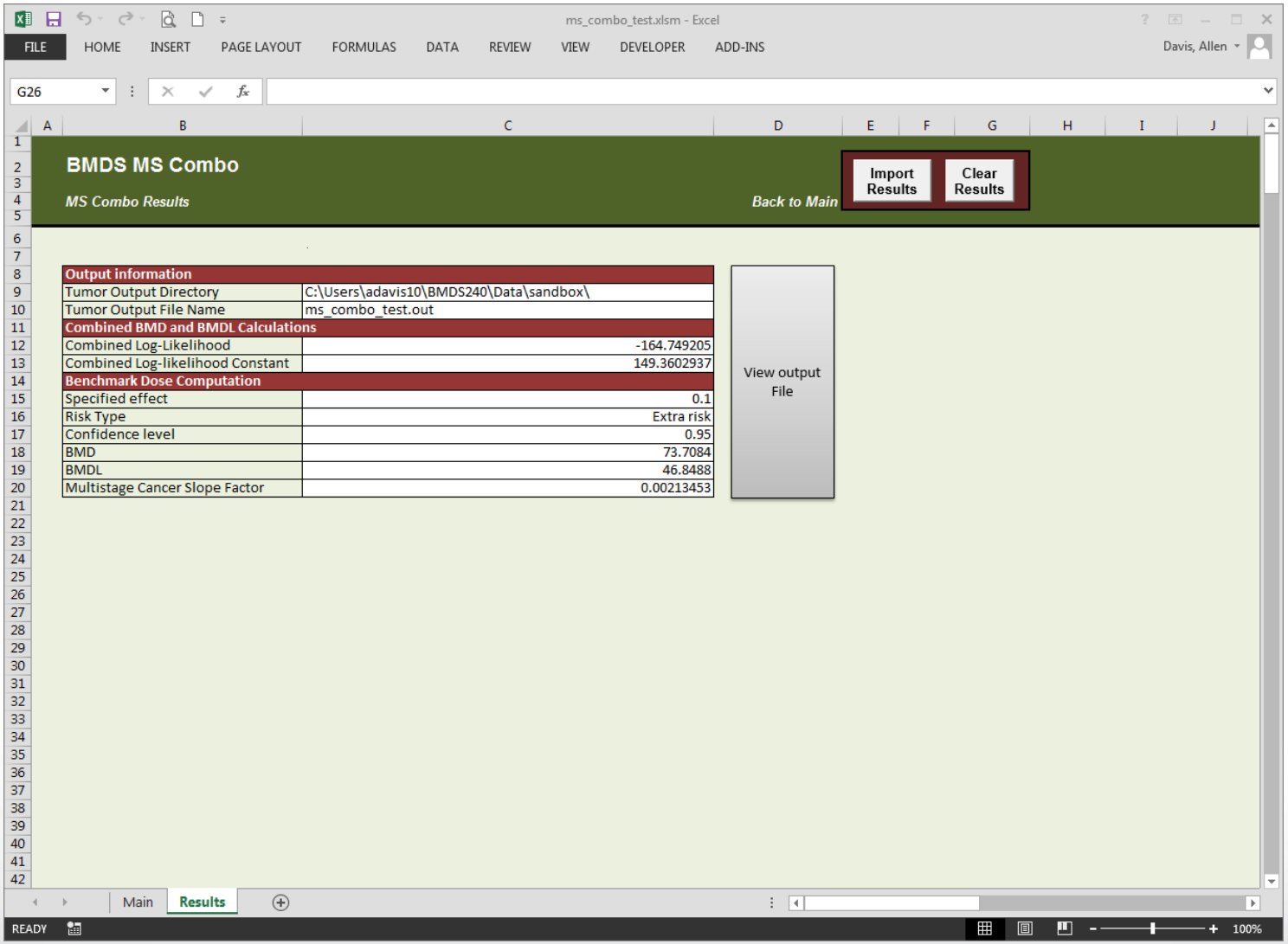
Main Results

READY 100%

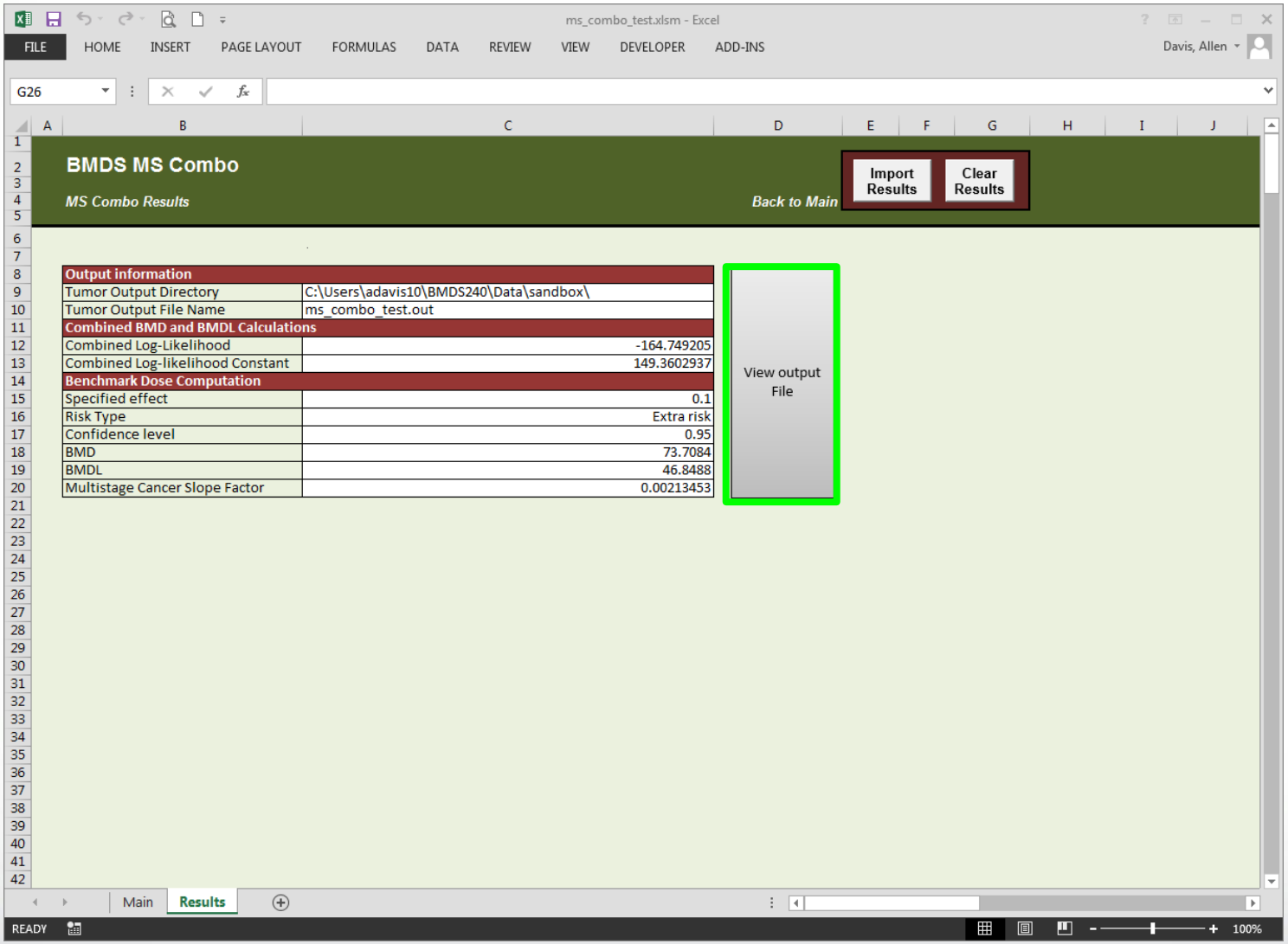
Wizard MS Combo



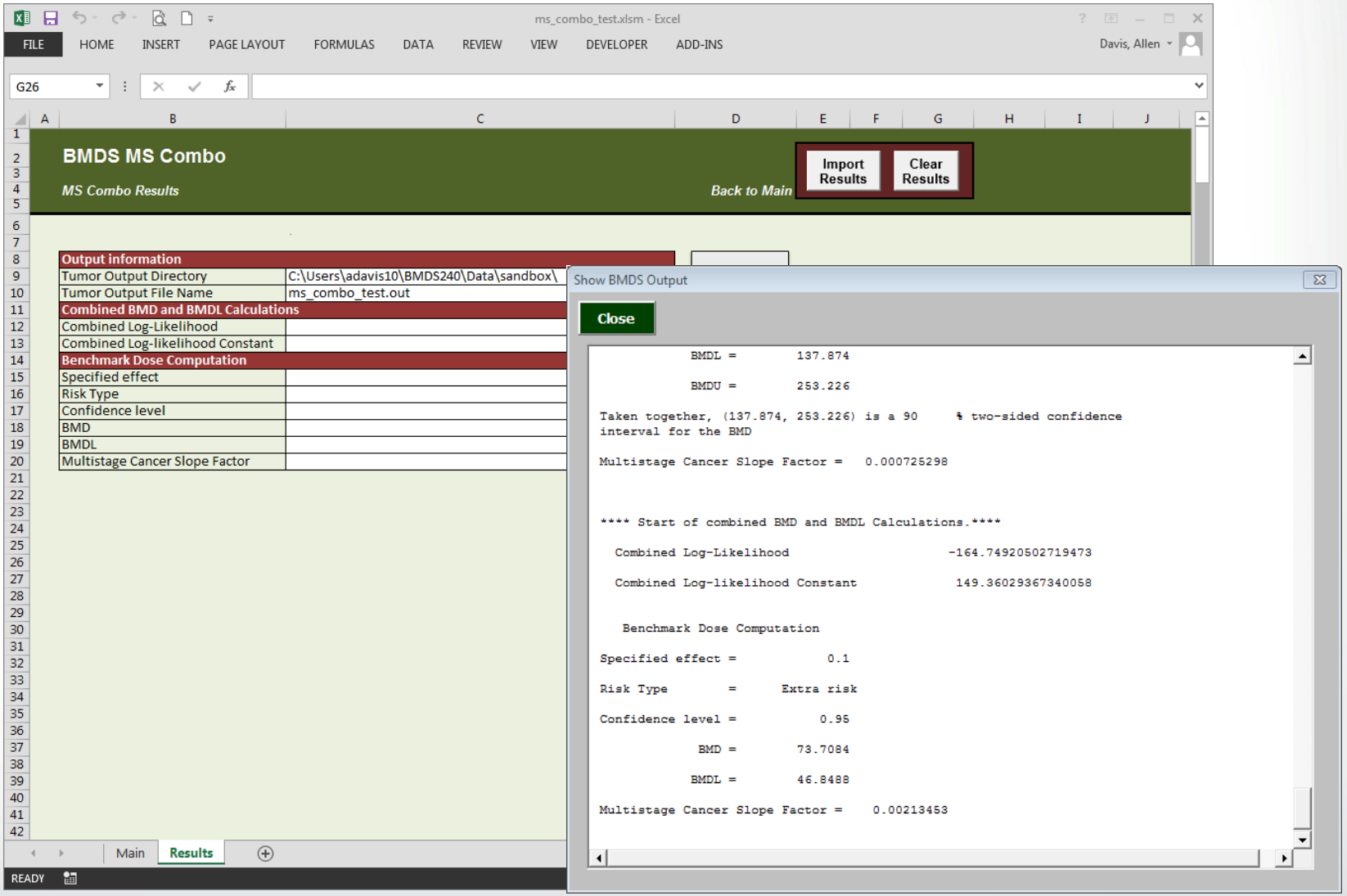
Wizard MS Combo



Wizard MS Combo



Wizard MS Combo



Cancer Data – Exercise #2

Cancer Exercise #2

- Open the following Wizard cancer files: liver.xlsm and kidney.xlsm
- In each, select the correct BMDS Installation directory and the desired Output file directory
- Autorun BMDS from the Wizard files and select the appropriate Multistage model (make selection in column AE on Results tab)
- Record model results for these tumors and the lung tumors modeled in Exercise #1

Cancer Exercise #2

	Lung	Liver	Kidney
Degree Multistage	2nd	1st	2nd
BMD_{10}	25.1	12.5	15.5
$BMDL_{10}$	14.4	9.75	9.47
CSF	0.0069	0.0103	0.0106
AIC	150.07	151.88	157.62
p value	0.259	0.752	0.276
Scaled residual	0.773	-0.407	-0.705

Cancer Exercise #2

- **Open MS_Combo Wizard template**
  - Select the correct BMDS Installation directory and the Wizard directory (i.e., the directory where the individual Wizard files were saved)
  - Choose name for Input Filename (i.e., the .tum file BMDS will use to run the MS_Combo model)
  - Select individual Wizard files previously created and get tumor information
  - Fill in User Inputs for species and sex (it doesn't matter what is used, but it must be the same for all three tumors)

- **Run MS_Combo model**
  - In the Control Panel: 1) Validate Inputs, 2) Build Session, 3) Run in BMDS, 4) Import Results

Cancer Exercise #2

	Lung	Liver	Kidney	MS_Combo
Degree Multistage	2nd	1st	2nd	n/a
BMD_{10}	25.1	12.5	15.5	6.48
$BMDL_{10}$	14.4	9.75	9.47	4.5
CSF	0.0069	0.0103	0.0106	0.0222
AIC	150.07	151.88	157.62	n/a
p value	0.259	0.752	0.276	n/a
Scaled residual	0.773	-0.407	-0.705	n/a

The Multistage Weibull Time-to-Tumor Model

Time-to-Tumor Analysis

- **Often, the dose group-specific mortality rates are different in cancer bioassays**
  - These differential rates of mortality between exposure groups could potentially bias modeling results and should be accounted for
  - Differences in the rate of mortality (i.e., numbers of dead) and increases in the onset of death (i.e., time to death) are important

- **There are a number of ways to account for differential mortality rates**
  - **For Grouped data**: estimate the number of animals at risk per dose group, i.e., number alive at week when first tumor was observed
  - **For Individual Animal data**: assemble data on individual times of death and tumor incidence for use in time-to-tumor modeling

The Multistage-Weibull Model

- **The Multistage-Weibull (MSW) time-to-tumor model describes the probability of some cancer response by observation time *t* given some dose *d***

- **Two forms of tumor-related response are considered**
  - Death of subject, with death resulting from cancer ("fatal tumors")
  - Appearance of a carcinogenic lesion that is detected by pathological methods, generally upon examination following death due to some other effect ("non-fatal tumors")

- **The MSW software allows the fitting of two distinct forms of the MSW model corresponding to these types of tumor responses**

Weibull Model for Fatal Tumors

- **The *k-stage* Weibull model for fatal tumors characterizes the probability of death from cancer prior to a specified observation time *t* at dose *d***

$$F(t, d|t_0, c, \beta_0, \beta_1, \ldots, \beta_k) = 1 - \exp\{-(t - t_0)^c \sum_{i=0}^{k} \beta_i d^i\}$$

  - Where:
  - c (shape parameter; ≥ 1) describes how rapidly the risk of death from tumor increases over time,
  - t_0 (induction time; ≥ 0; t > t_0) is the elapsed time that occurs between onset of fatal tumor and death from tumor, assumed to be the same for all subjects
  - $\beta_0, \beta_1, \ldots, \beta_k$ (polynomial coefficients; ≥ 0; k ≤ 6) determine curvature of the dose-resonse curve.

Weibull Model for Non-fatal Tumors

- **The *k-stage* Weibull model for non-fatal tumors characterizes the probability of observing the tumor prior to a specified observation time *t* at dose *d***

$$G(t, d|c, \beta_0, \beta_1, \ldots, \beta_k) = 1 - \exp\{-t^c \sum_{i=0}^{k} \beta_i d^i\}$$

  - Where:
  - c (shape parameter; ≥ 1) describes how rapidly the risk of developing a tumor increases over time,
  - t_0 is omitted
  - $\beta_0, \beta_1, \ldots, \beta_k$ (polynomial coefficients; ≥ 0; k ≤ 6) determine curvature of the dose-resonse curve.

Modeling Fatal vs. Non-fatal Tumors

- **Fatal tumor model – fit only if there is at least one observation with context "F"**
  - Optimally, there will be multiple "I" and "F" tumors to obtain reasonably estimates for time to death from tumor
  - The model can estimate the BMD for either "death from the cancer" (input file line 13, item 3 = 1) or "appearance of a detectable tumor" (input file line 13, item 3 = 0; requires "I" observations)
  - t_0 is explicitly estimated (input file line 9, item 2 = -9999)
  - Do not run the fatal tumor model if all tumors have context "I"
- **Non-fatal tumor model – fit if all observations are context "I"**
  - t_0 is set to 0 (input file line 9, item 2 = 0)
  - BMD can only be calculated for "appearance of a detectable tumor" (input file line 13, item 3 = 0)

Data and Tumor Context

- **Time-to-tumor data consist of dose, tumor response category (tumor context), and the time of observation**

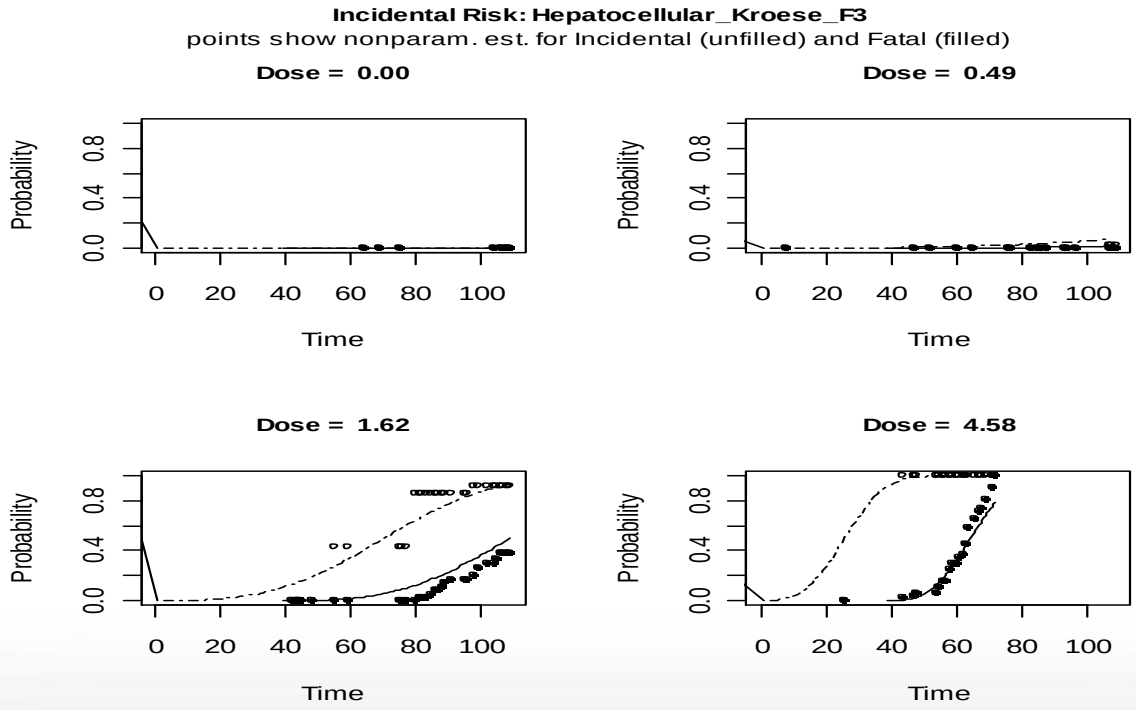
- **The subject's response is classified with one of the following contexts**
  - **Censored (C)**: subject is removed from the study at time *t* (because of sacrifice, or death from some other response) and no tumors are detected (right-censored)
  - **Death from fatal tumor (F)**: subject dies at time *t*, a cancer is detected when the subject is examined and death is attributed to the cancer (uncensored)
  - **Incidental tumor (I)**: subject is removed from the study at time *t* (because of sacrifice or death from some other response) and a tumor is detected upon examination, but death is not attributed to the cancer (left-censored)
  - **Unknown response observed (U)**: subject is removed from the study at time *t* but the presence/absence of tumors cannot be determined; subjects with context "U" should be removed from the dataset

Model Selection (Number of Stages)

- **The MSW model does not report a X^2 goodness-of-fit table (*p*-value or scaled residuals)**
- **Models differing in the maximum number of states should be evaluated by comparing the AICs, the log-likelihood, and graphical comparison of data to the fitted models**
- **Users are advised to choose the simplest adequate model (i.e., the model with the lowest AIC value that still affords a reasonable fit to the data)**

MSW Model Plots

- **Generated using the graphical module "gofplot_msw" in R – must request from EPA currently**
- **Plots can be used to judge model fit**



MSW Model Datafile Format

- **The MSW model datafile is a plain text file with ".(d)" extension**

lungMSW.(d) - Notepad

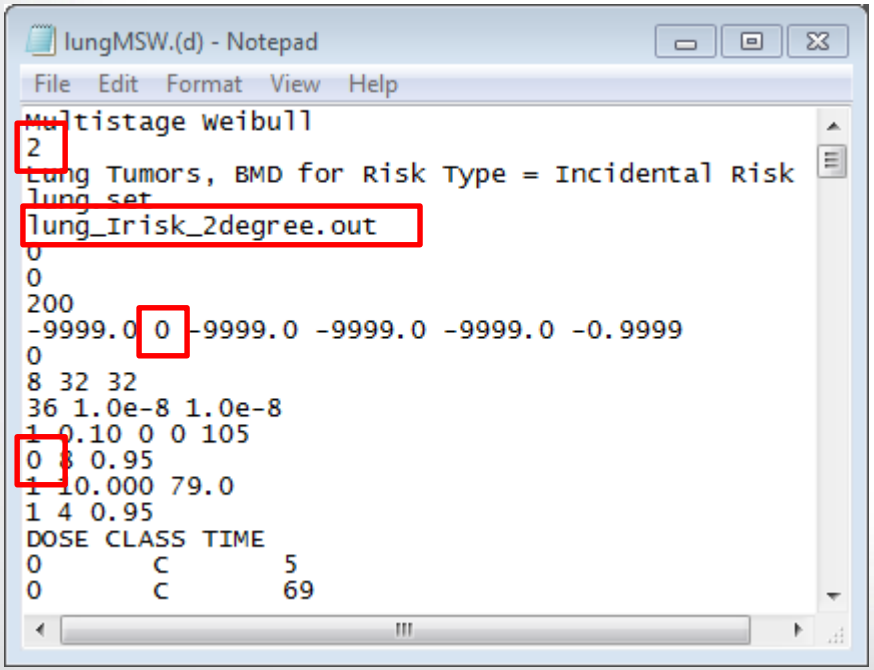
File Edit Format View Help

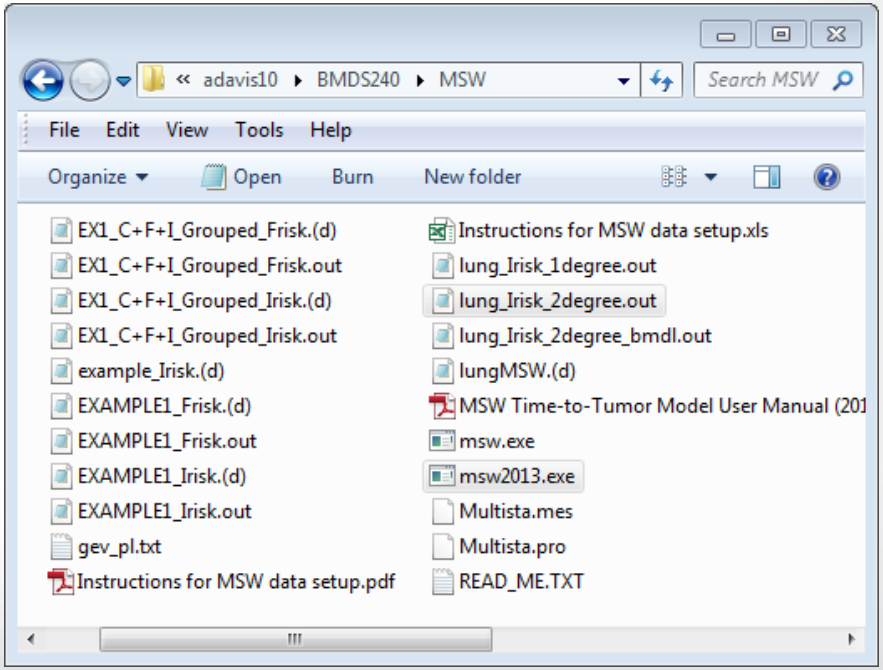
```
Multistage Weibull
2
Lung Tumors, BMD for Risk Type = Incidental Risk
lung.set
lung_Irisk_2degree_bmdl.out
0
0
200
-9999.0 -9999.0 -9999.0 -9999.0 -9999.0 -0.9999
0
8 32 32
36 1.0e-8 1.0e-8
1 0.10 0 0 105
1 8 0.95
1 10.000 79.0
1 4 0.95
DOSE CLASS TIME
0       C       5
0       C       69
0       C       70
0       C       71
0       C       76
0       C       78
0       C       88
0       C       91
0       C       91
0       C       95
0       C       97
0       C       98
0       C       101
0       C       101
0       C       105
0       C       105
0       C       105
0       C       105
0       C       105
0       C       105
0       C       105
0       C       105
0       C       105
0       C       105
0       C       105
0       C       105
0       C       105
0       C       105
0       C       105
0       C       105
0       C       105
0       C       105
0       C       105
0       C       105
0       I       105
```

1. Model name, do not change this text
2. Number of stages (order of model)
3. User specified title to appear in output file
4. Not used, but must have a text entry, "name.set" is recommended
5. Name of output file to be created
6. Append output file (1) or overwrite output file (0)
7. Grouped data (1) or ungrouped data (0)
8. Number of data lines (below)
9. Either a fixed (user-specified) or estimated (-9999) value used to solve MLE, in this order: c, t0, b0, b1, b2, b3, ...
10. Automatic initialization (0; recommended) or user-specified value (1)
11. If line #10 = 0; number of automatic initializations; controls search grid for shape parameter c; controls search grid for location parameter t_0
12. Optimization parameters
13. BMD estimation (1) or none (0); BMR value; incidental risk (0) or fatal risk (1); extra risk (0) or added risk (1); time for BMD
14. BMDL estimation (1) or none (0); multiple of BMD used for upper bound for BMDL search; 2-sided confidence level
15. Inactive slope calculations
16. Inactive slope calculations
17. Variable names
18. Data; Class = context indicators: C = censored, I = incidental, F = fatal, U = unknown

Steps for MSW Model Analysis – Incidental Risk

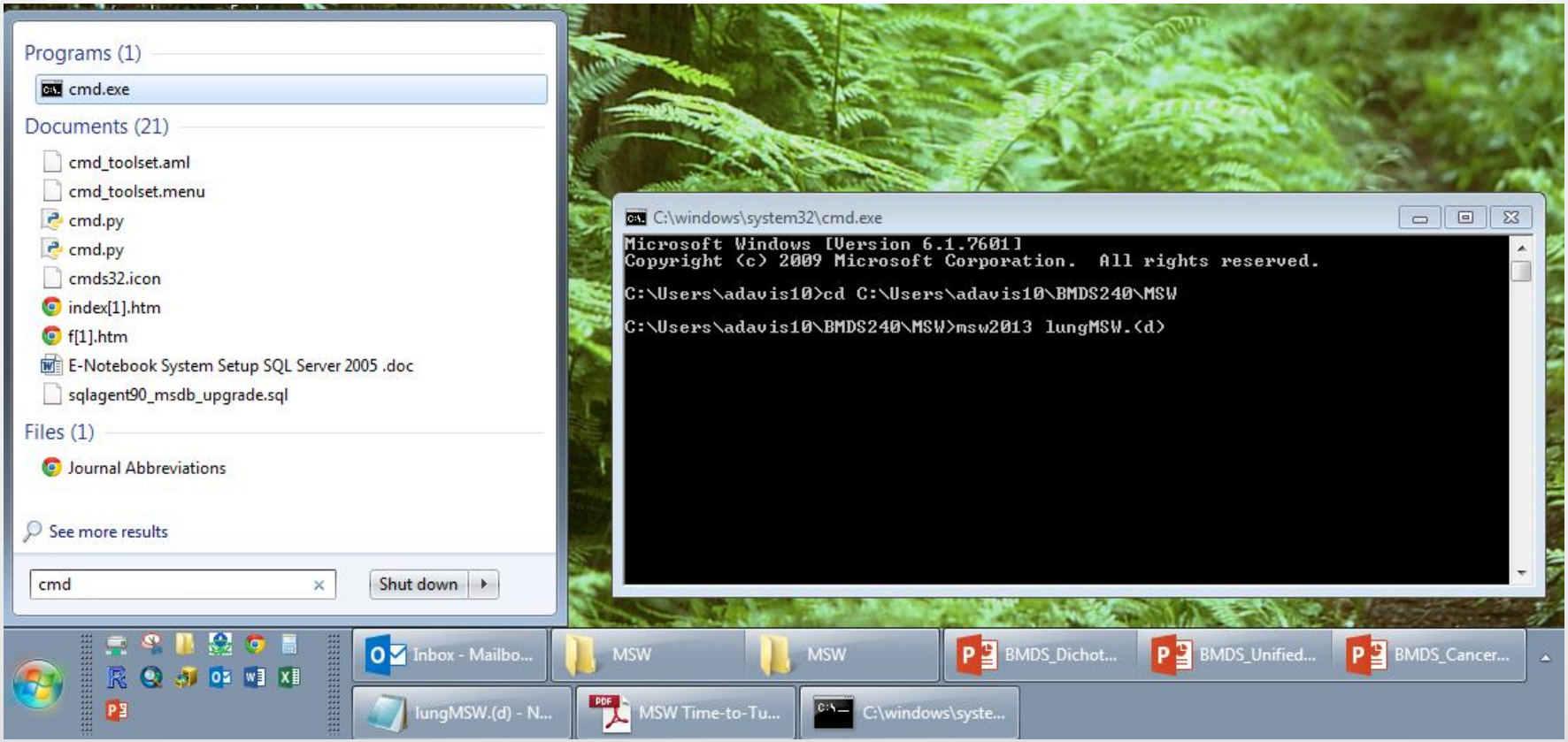
- Set the number of stages for 2nd degree MSW model (line 2 = 2)
- Set output file name, indicating the details of the model run (line 5)
- Parameterize for Incidental Risk (line 9, item 2 = "0", line 13, item 3 = "0")
- Turn BMDL "Off" in data files (line 14, item 1 = "0")
- Save msw.exe with data files in a "working directory"





Steps for MSW Model Analysis – Incidental Risk

- **Open a command line window and change directories to the directory where the .(d) file and model executable are saved**
- **Enter ">msw *filename*.(d)", press "Enter" to run model**



Steps for MSW Model Analysis – Incidental Risk

- **Examine output file, record results**

lung_Irisk_2degree.out - Notepad

File Edit Format View Help

```
    beta_1        -0.99         0.94            1         0.95

    beta_2        -0.98         0.95         0.95            1


                                Parameter Estimates
                                                          95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
          c                4.5321          1.06562               2.44353             6.62067
          beta_0      1.4239e-011     7.31328e-011       -1.29099e-010       1.57577e-010
          beta_1      9.06383e-012     4.48366e-011       -7.88144e-011        9.6942e-011
          beta_2      1.40115e-013     6.72233e-013       -1.17744e-012       1.45767e-012


                  Log(likelihood)    # Param            AIC
    Fitted Model           -157.8          4         323.601


                    Data Summary
                       CLASS
              C      F      I      U  Total  Expected Response
    DOSE
        0     49      0      1      0     50      0.86
       15     46      1      3      0     50      7.86
       30     34      5     11      0     50      9.54
       80     15     14     21      0     50     27.36

    Minimum observation time for F tumor context =         66


    Benchmark Dose Computation
Risk Response     =      Incidental
Risk Type         =           Extra
Specified effect  =             0.1
Time              =             105

              BMD =         7.22978
```

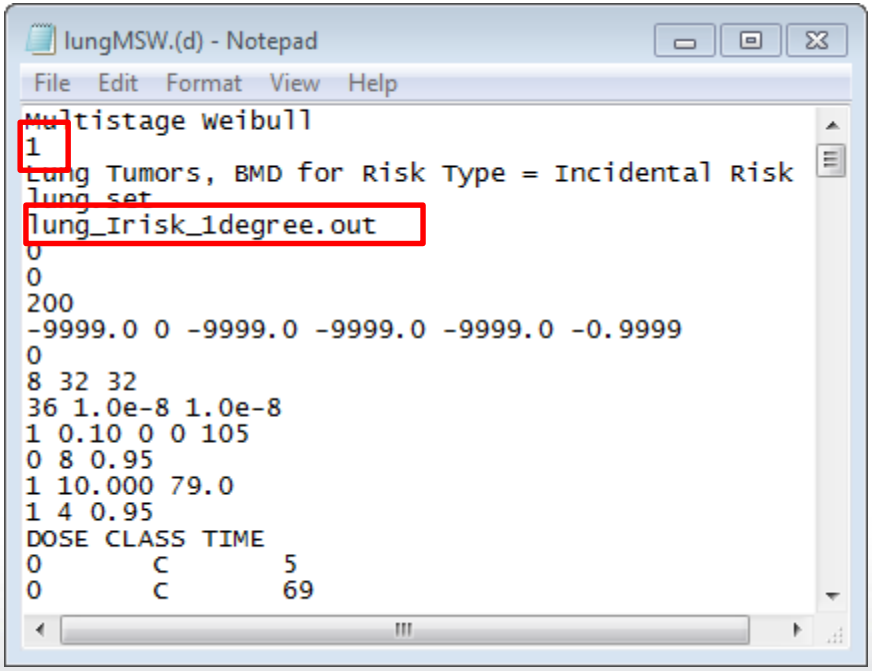
MSW Model Results - Incidental Risk

Model stages	AIC	BMD_{10}	Responses at mg/kg-d levels				Selected model parameter estimates	Model Selection
			0	15	30	80	c	
Lung Tumors								
1								
2	323.601	7.23	0.86	7.86	9.54	27.37	4.5321	

Observed incidence of tumors: 1/50, 3/50, 11/50, 21/50

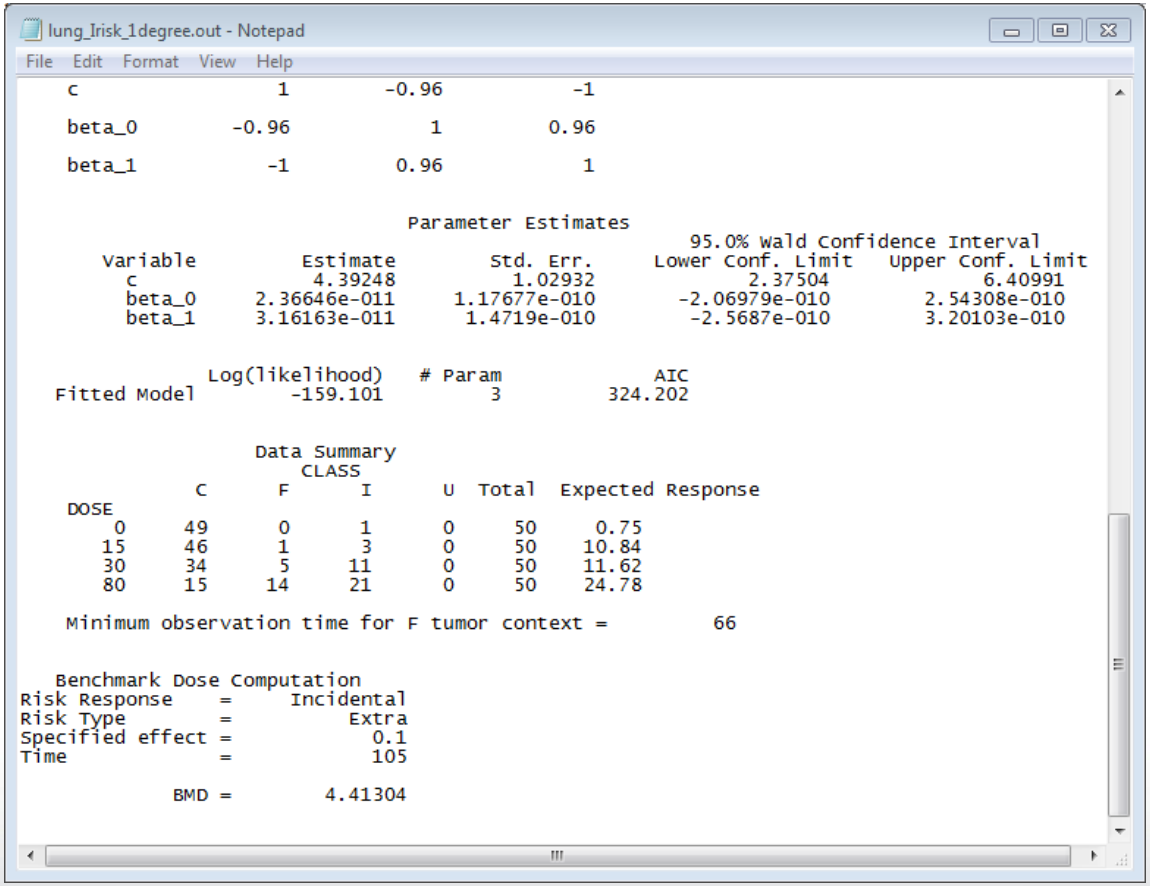
Steps for MSW Model Analysis – Incidental Risk

- **Set the number of stages for 1st degree MS model (line 2 = 1)**
- **Set output file name, indicating the details of the model run (line 5)**
- **Save msw.exe and repeat command line execution (up arrow recalls last command)**



Steps for MSW Model Analysis – Incidental Risk

- **Examine output file, record results**
- **Make final model selection for BMDL estimation**



lung_Irisk_1degree.out - Notepad

File Edit Format View Help

```
    c                  1          -0.96            -1

    beta_0         -0.96              1          0.96

    beta_1            -1           0.96             1


                                Parameter Estimates
                                                                 95.0% Wald Confidence Interval
       Variable          Estimate        Std. Err.      Lower Conf. Limit   Upper Conf. Limit
         c                4.39248          1.02932              2.37504             6.40991
         beta_0      2.36646e-011     1.17677e-010       -2.06979e-010       2.54308e-010
         beta_1      3.16163e-011      1.4719e-010        -2.5687e-010       3.20103e-010


                 Log(likelihood)    # Param            AIC
   Fitted Model          -159.101          3         324.202


                    Data Summary
                        CLASS
              C      F      I      U  Total  Expected Response
    DOSE
        0    49      0      1      0     50     0.75
       15    46      1      3      0     50    10.84
       30    34      5     11      0     50    11.62
       80    15     14     21      0     50    24.78

    Minimum observation time for F tumor context =         66


    Benchmark Dose Computation
Risk Response     =      Incidental
Risk Type         =           Extra
Specified effect  =             0.1
Time              =             105

              BMD =         4.41304
```

MSW Model Results - Incidental Risk

Model stages	AIC	BMD_{10}	Responses at mg/kg-d levels				Selected model parameter estimates	Model Selection
			0	15	30	80	c	
Lung Tumors								
1	324.202	4.41	0.75	10.84	11.62	24.78	4.3925	
2	323.601	7.23	0.86	7.86	9.54	27.37	4.5321	

Observed incidence of tumors: 1/50, 3/50, 11/50, 21/50

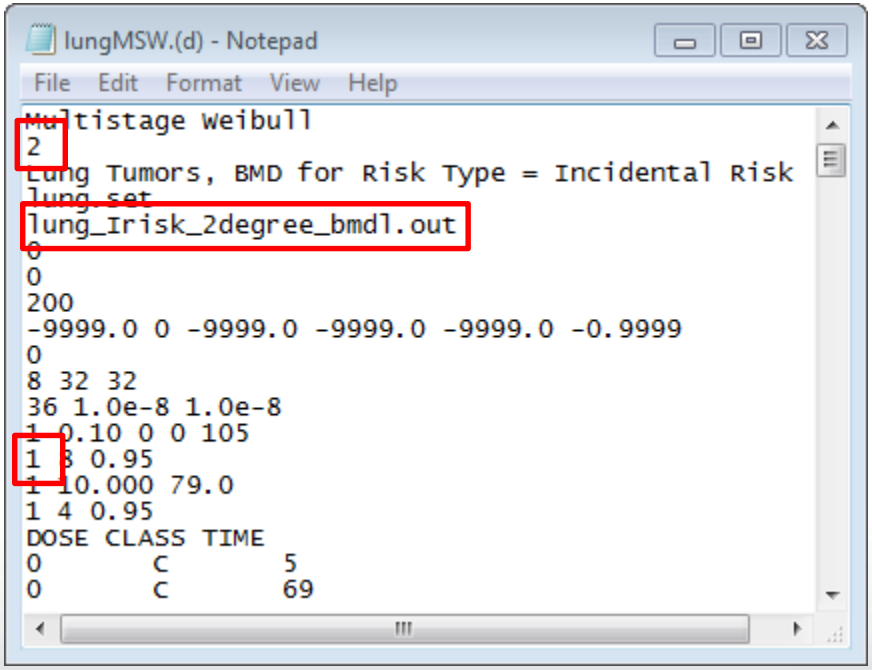
MSW Model Results - Incidental Risk

Model stages	AIC	BMD_{10}	Responses at mg/kg-d levels				Selected model parameter estimates	Model Selection
			0	15	30	80	c	
Lung Tumors								
1	324.202	4.41	0.75	10.84	11.62	24.78	4.3925	
2	**323.601**	**7.23**	**0.86**	**7.86**	**9.54**	**27.37**	**4.5321**	**Lowest AIC, better low-dose fit**

Observed incidence of tumors: 1/50, 3/50, 11/50, 21/50

Steps for MSW Model Analysis – Incidental Risk

- Set the number of stages for 2nd degree MS model (line 2 = 2)
- Set output file name, indicating the details of the model run (line 5)
- Turn BMDL "On" in data files (line 14, item 1 = "1")
- Save msw.exe and repeat command line execution (up arrow recalls last command)



MSW Model Results - Incidental Risk

lung_Irisk_2degree_bmdl.out - Notepad

File Edit Format View Help

```
                              Parameter Estimates
                                                        95.0% Wald Confidence Interval
      Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
        c                4.5321          1.06562           2.44353             6.62067
        beta_0       1.4239e-011     7.31328e-011      -1.29099e-010       1.57577e-010
        beta_1      9.06383e-012     4.48366e-011      -7.88144e-011        9.6942e-011
        beta_2      1.40115e-013     6.72233e-013      -1.17744e-012       1.45767e-012


              Log(likelihood)   # Param            AIC
   Fitted Model          -157.8         4         323.601


                  Data Summary
                      CLASS
             C      F      I      U  Total  Expected Response
   DOSE
       0    49      0      1      0     50      0.86
      15    46      1      3      0     50      7.86
      30    34      5     11      0     50      9.54
      80    15     14     21      0     50     27.36

   Minimum observation time for F tumor context =         66


   Benchmark Dose Computation
Risk Response     =     Incidental
Risk Type         =          Extra
Specified effect  =            0.1
Confidence level  =           0.95

Time              =            105

             BMD =        7.22978
            BMDL =        3.65949
            BMDU =        15.2971
```

Poly-3 Survival Adjustment

Poly-3 Survival Adjustment

- **While the MSW model can explicitly model time when survival rates differ between exposure groups, it can be difficult to run the model and interpret the results**

- **Poly-3 survival adjustment is an alternative method for incorporating survival information into a cancer modeling scheme**
  - The National Toxicology Program (NTP) uses a poly-3 adjustment to scale the number of animals able to exhibit a carcinogenic response to exposure
  - The poly-3 adjusted values are reported alongside un-adjusted values in NTP reports
  - One benefit of using a poly-3 adjustment scheme is that multiple poly-3 adjusted tumor datasets can be incorporated in a MS_Combo analysis

Poly-3 Survival Adjustment

- **The poly-3 survival adjustment is a method to calculate survival-adjusted lifetime tumor rates by fractionally weighting the number of exposed animals (i.e., sample size)**

- **It can be performed in multiple software packages, including R and Excel**
  - Must have individual animal data with times of death and tumor status
  - In R, the poly3test function is used to calculate the survival adjusted # of subjects (users must first download the MCPAN package)

- **"Poly-3" refers specifically to using a 3rd order polynomial to describe the tumor incidence function in time**
  - Other polynomials can be used, but estimating the correct polynomial can be difficult

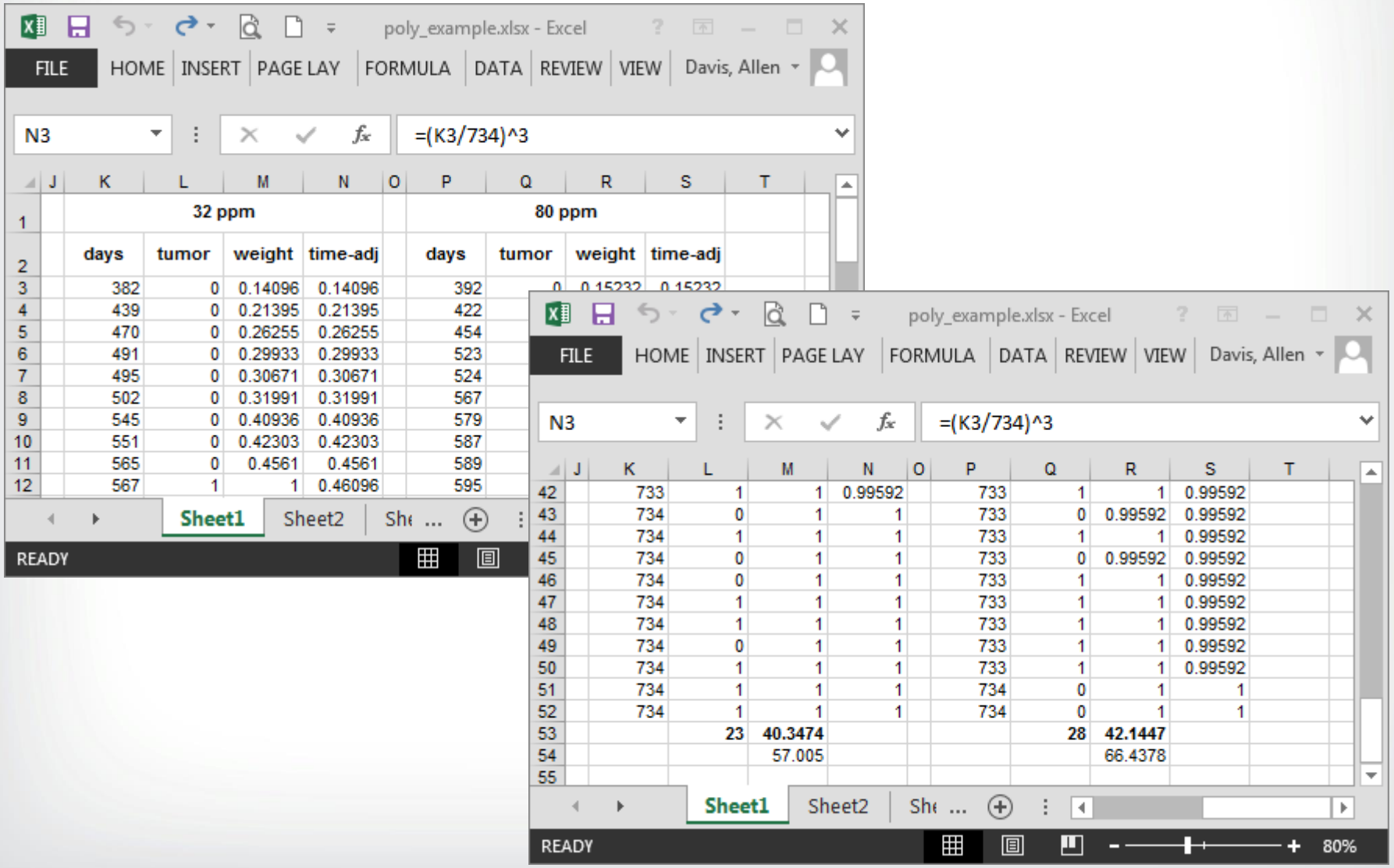
Calculating the Poly-3 Adjusted Tumor Rates

- **For a individual dose group (*i*), the poly-3 survival adjusted sample size is:**

$$n_i^* = \sum_{j=1}^{n_i} w_{ij}$$

  - Where,
  - $w_{ij} = 1$ if the *j*th animal in the *i*th dose group had a tumor at observation (i.e., necropsy)
  - Otherwise, $w_{ij} = t_{ij}^3$, where t_{ij} is the fraction of duration of the study for which the animal survived

Calculating the Poly-3 Adjusted Tumor Rates – Excel



Calculating the Poly-3 Adjusted Tumor Rates – R

R Console (64-bit)

File Edit Misc Packages Windows Help

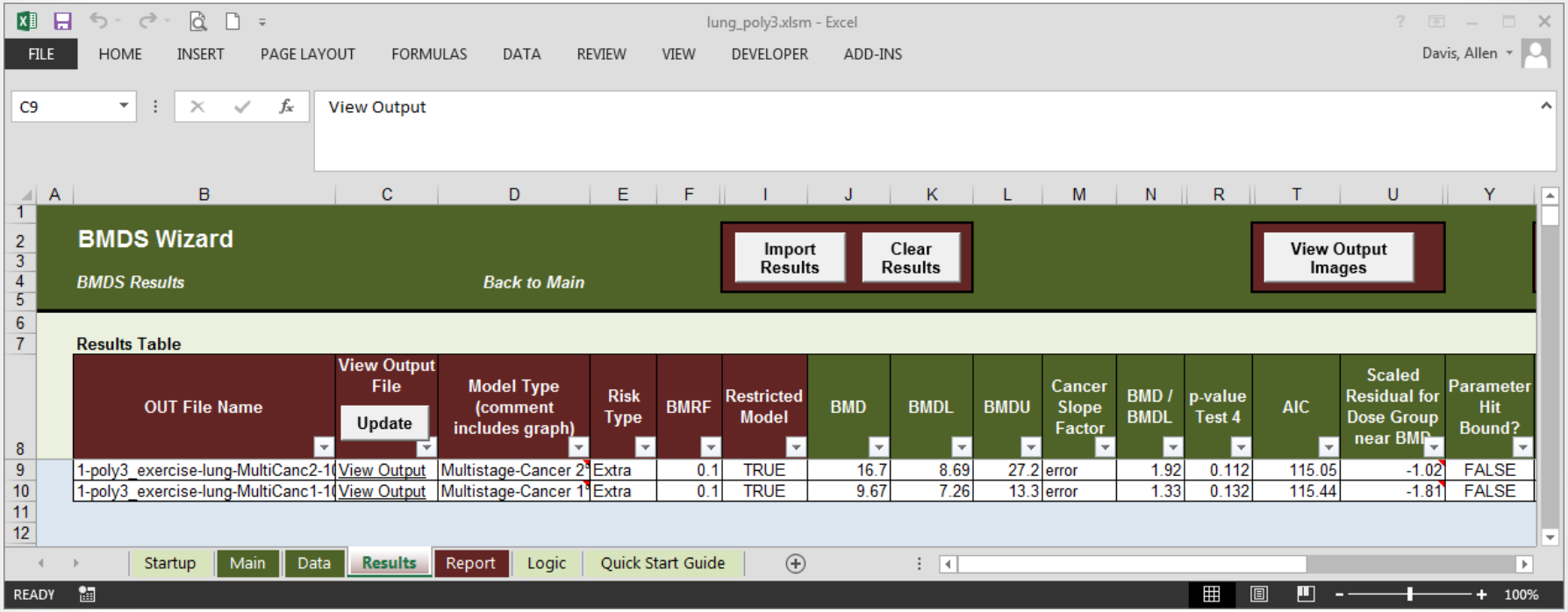
```
> setwd("M:\\BMDS_Training_Materials\\Cancer_2014\\training_files")
> example=read.csv("example.csv")
> local({pkg <- select.list(sort(.packages(all.available = TRUE)),graphics=TRUE)
+ if(nchar(pkg)) library(pkg, character.only=TRUE)})
Warning message:
package 'MCPAN' was built under R version 3.0.3
> poly3test(time=example$death,status=example$tumor,f=example$group,Method="BP",k=3)
Sample estimates using poly- 3 -adjustment
                         0    12.8      32      80
x                   6.0000 12.0000 23.0000 28.0000
n                  50.0000 50.0000 50.0000 50.0000
adjusted n         42.4216 42.3033 40.3474 42.1447
adjusted estimate  0.1414  0.2837  0.5700  0.6644

Contrast matrix:

         Multiple Comparisons of Means: Dunnett Contrasts

           0 12.8 32 80
12.8 - 0 -1    1  0  0
32 - 0   -1    0  1  0
80 - 0   -1    0  0  1

Union-Intersection test using Bailer-Portier  variance estimator:
P-value of the maximum test:
[1] 0

         estimate testat p.val.adj
12.8 - 0   0.1422 1.6244    0.2634
32 - 0     0.4286 4.5338    0.0000
80 - 0     0.5229 5.7914    0.0000

> |
```

Cancer Data – Exercise #3

Cancer Exercise #3

- **Open the following Wizard cancer file: lung_poly3.xlsm**
- **Select the correct BMDS Installation directory and the desired Output file directory**
- **Autorun BMDS from Wizard file and select the appropriate Multistage model (make selection in column AE on Results tab)**

Cancer Exercise #3



Cancer Data – Exercise #4

Cancer Exercise #4

- **Open the following Wizard cancer files: liver_poly3.xlsm and kidney_poly3.xlsm**
- **In each, select the correct BMDS Installation directory and the desired Output file directory**
- **Autorun BMDS from the Wizard files and select the appropriate Multistage model (make selection in column AE on Results tab)**
- **Record model results for these tumors and the lung_poly3 tumors modeled in Exercise #3**

Cancer Exercise #4

	Lung_poly3	Liver_poly3	Kidney_poly3
Degree Multistage	2nd	1st	2nd
BMD_{10}	16.7	8.10	10.9
$BMDL_{10}$	8.69	6.28	6.01
CSF	0.0115	0.0159	0.0167
AIC	115.05	117.65	116.46
p value	0.112	0.830	0.0965
Scaled residual	-1.02	-0.764	-1.01

Cancer Exercise #4

- **Open MS_Combo Wizard template**
  - Select the correct BMDS Installation directory and the Wizard directory (i.e., the directory where the individual poly3 Wizard files were saved)
  - Choose name for Input Filename (i.e., the .tum file BMDS will use to run the MS_Combo model)
  - Select individual poly3I Wizard files previously created and get tumor information
  - Fill in User Inputs for species and sex (it doesn't matter what is used, but it must be the same for all three tumors)

- **Run MS_Combo model**
  - In the Control Panel: 1) Validate Inputs, 2) Build Session, 3) Run in BMDS, 4) Import Results

Cancer Exercise #4

	Lung_poly3	Liver_poly3	Kidney_poly3	MS_Combo
Degree Multistage	2nd	1st	2nd	n/a
BMD_{10}	16.7	8.10	10.9	4.15
$BMDL_{10}$	8.69	6.28	6.01	2.33
CSF	0.0115	0.0159	0.0167	0.0430
AIC	115.05	117.65	116.46	n/a
p value	0.112	0.830	0.0965	n/a
Scaled residual	-1.02	-0.764	-1.01	n/a