



# Benchmark Dose Modeling – Cancer Models

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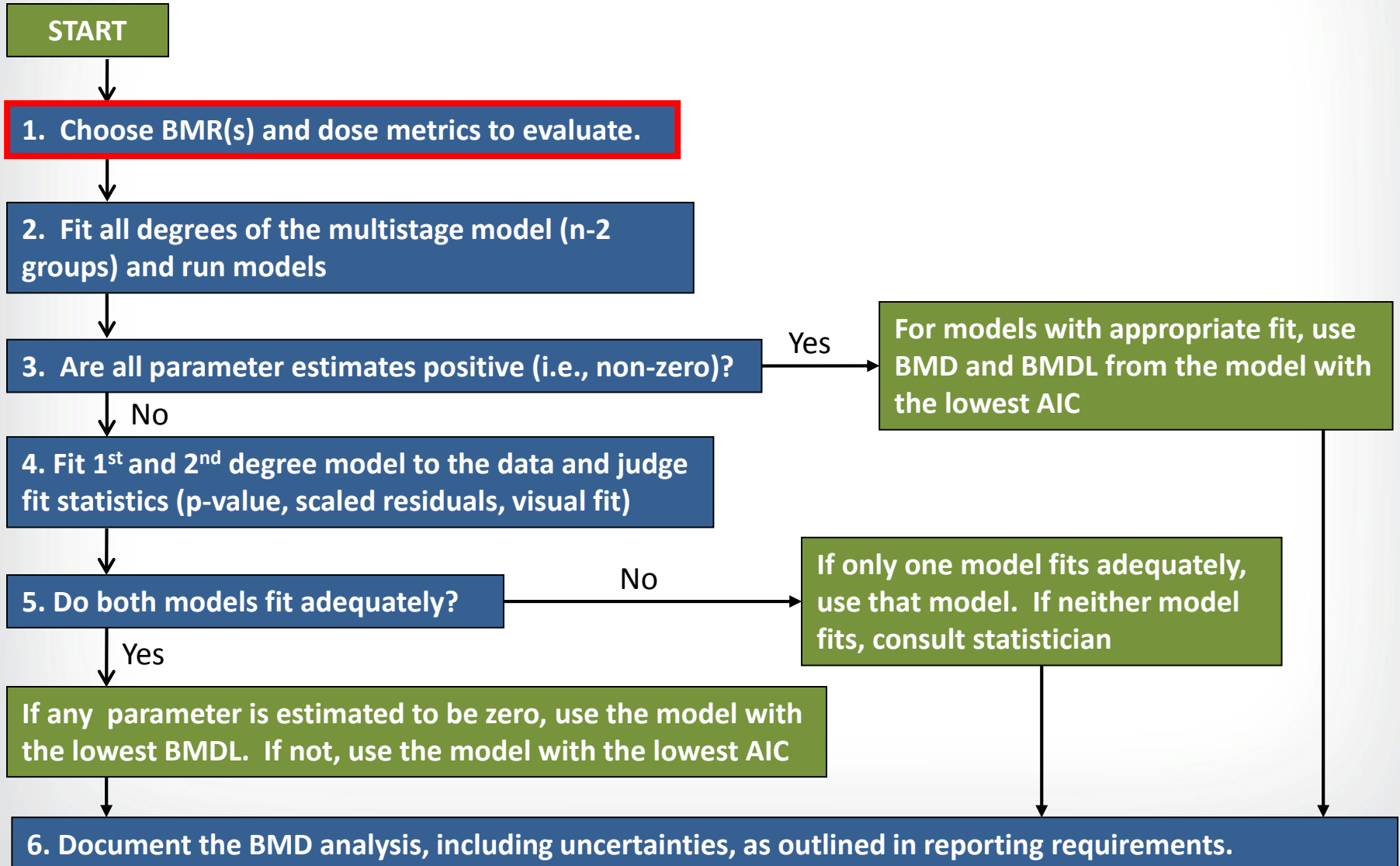
## Disclaimer

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

<b>Description</b>	<ul style="list-style-type: none"><li>• Response is measured as on/off or true/false</li><li>• You either have it or you don't</li><li>• BMDS can only model positive dose-response trends, where incidence increases with dose</li></ul>
<b>Example Endpoints</b>	<ul style="list-style-type: none"><li>• <b>Cancer: Tumor incidence</b></li></ul>
<b>Model Inputs</b>	<ul style="list-style-type: none"><li>• Dose</li><li>• Number of Subjects</li><li>• Incidence or Percent Affected</li></ul>



# BMD Cancer Analysis – Six Steps



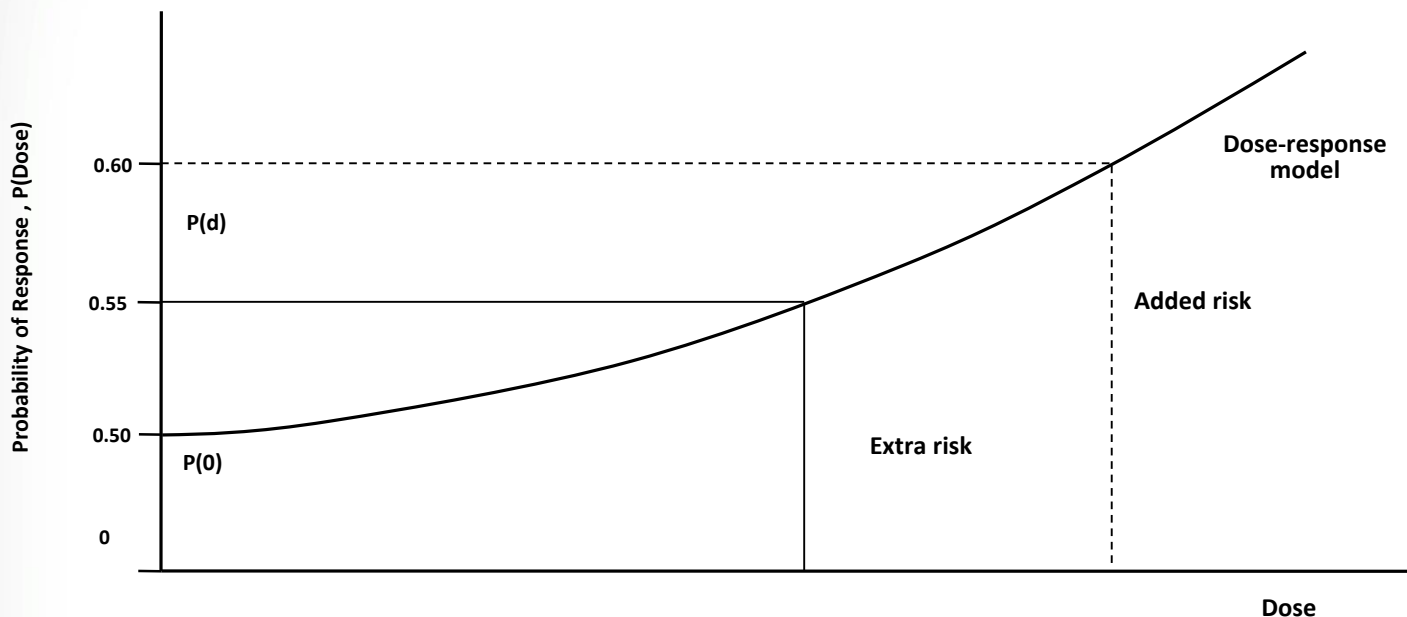


- **BMR should be near the low end of the observable range of increased risks in a bioassay**
  - An **extra risk** of 10% is recommended as a standard (not default) reporting level for cancer data, it is at or near the limit of sensitivity in most cancer bioassays
  - Provided the increase in tumor 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.**

- **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

$$0.10 = P(d) - P(0) ; \text{ if } P(0) = .50$$

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

10% Extra Risk

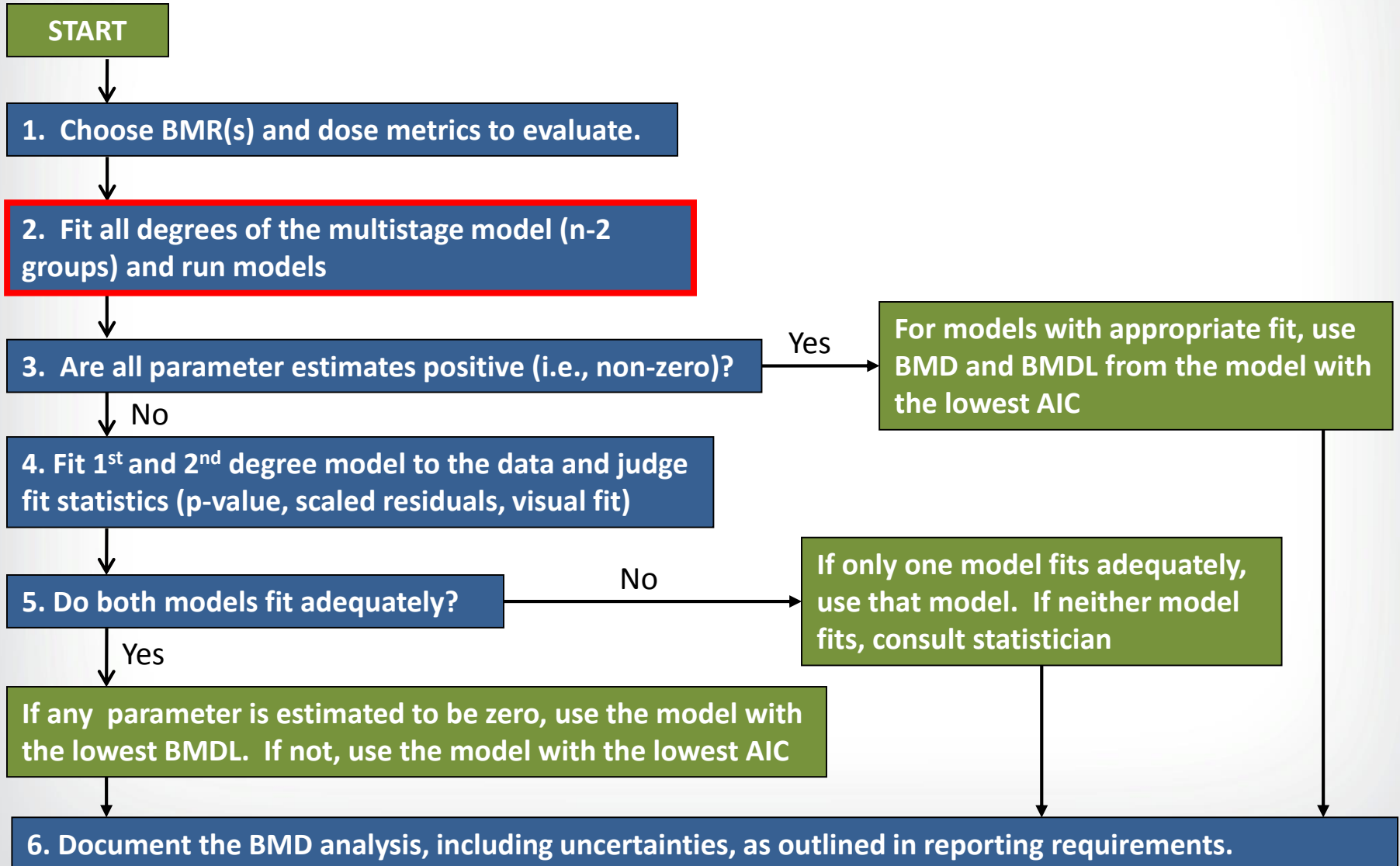
$$0.10 = [P(d) - P(0)] / [1 - P(0)]; \text{ if } P(0) = .50$$

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

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



# 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 <sup>a</sup>	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

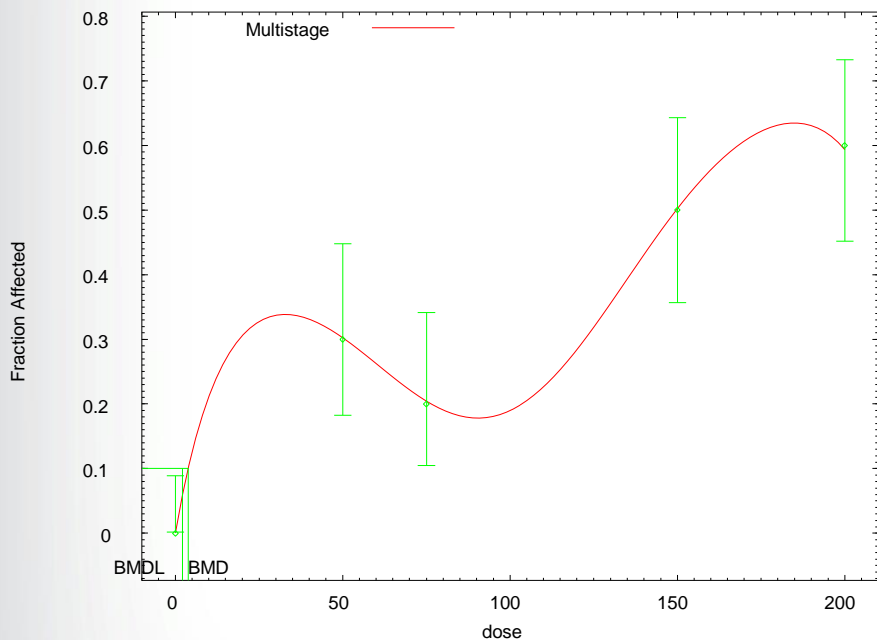
<sup>a</sup> Background parameter =  $\gamma$ . Background for hill model =  $v \times g$

- **Difference between the Multistage-Cancer Model and the Multistage Model:**
  - $\beta$  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)



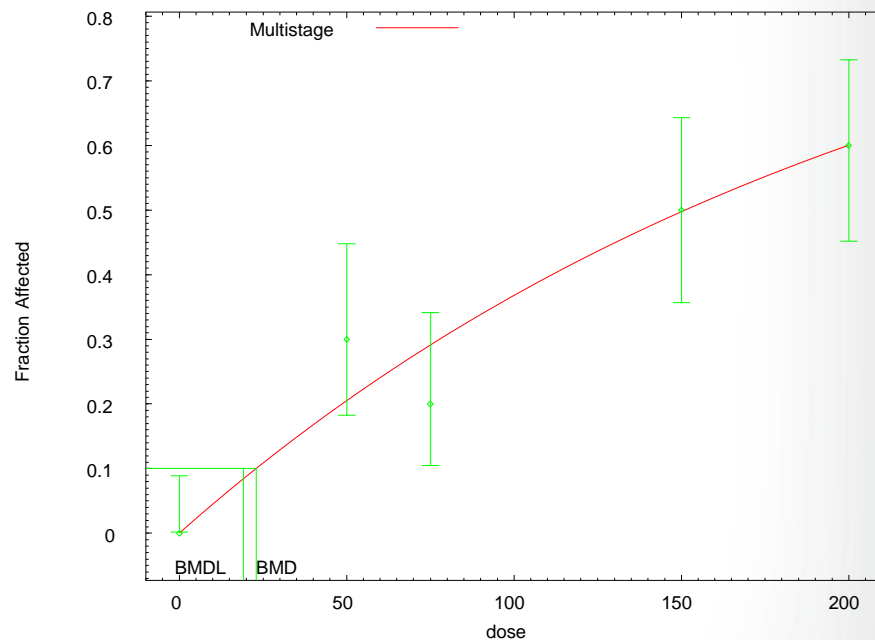
# Restriction of $\beta$ Coefficients and Model Fitting

Multistage Model with 0.95 Confidence Level



22:08 06/25 2009

Multistage Model with 0.95 Confidence Level



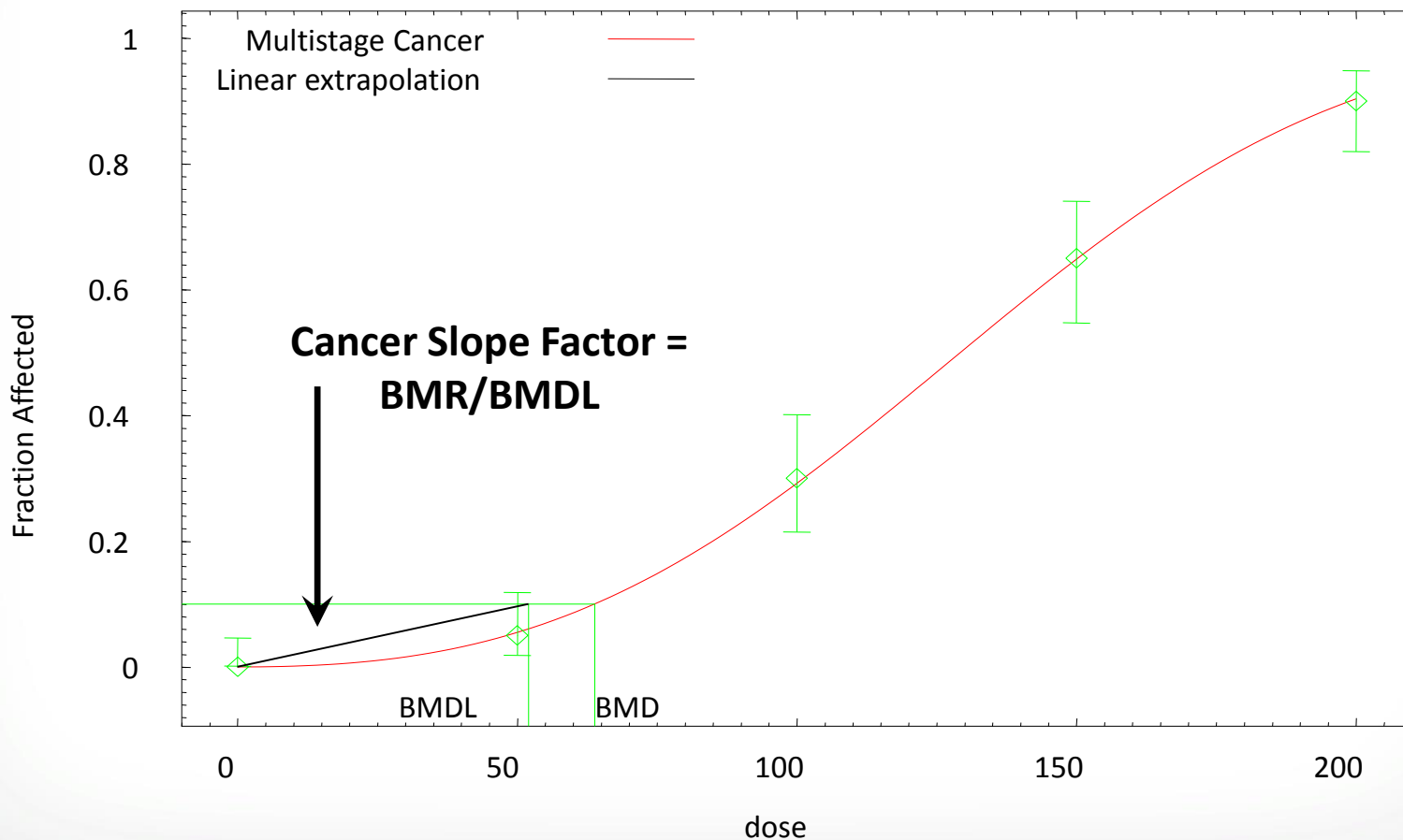
22:05 06/25 2009





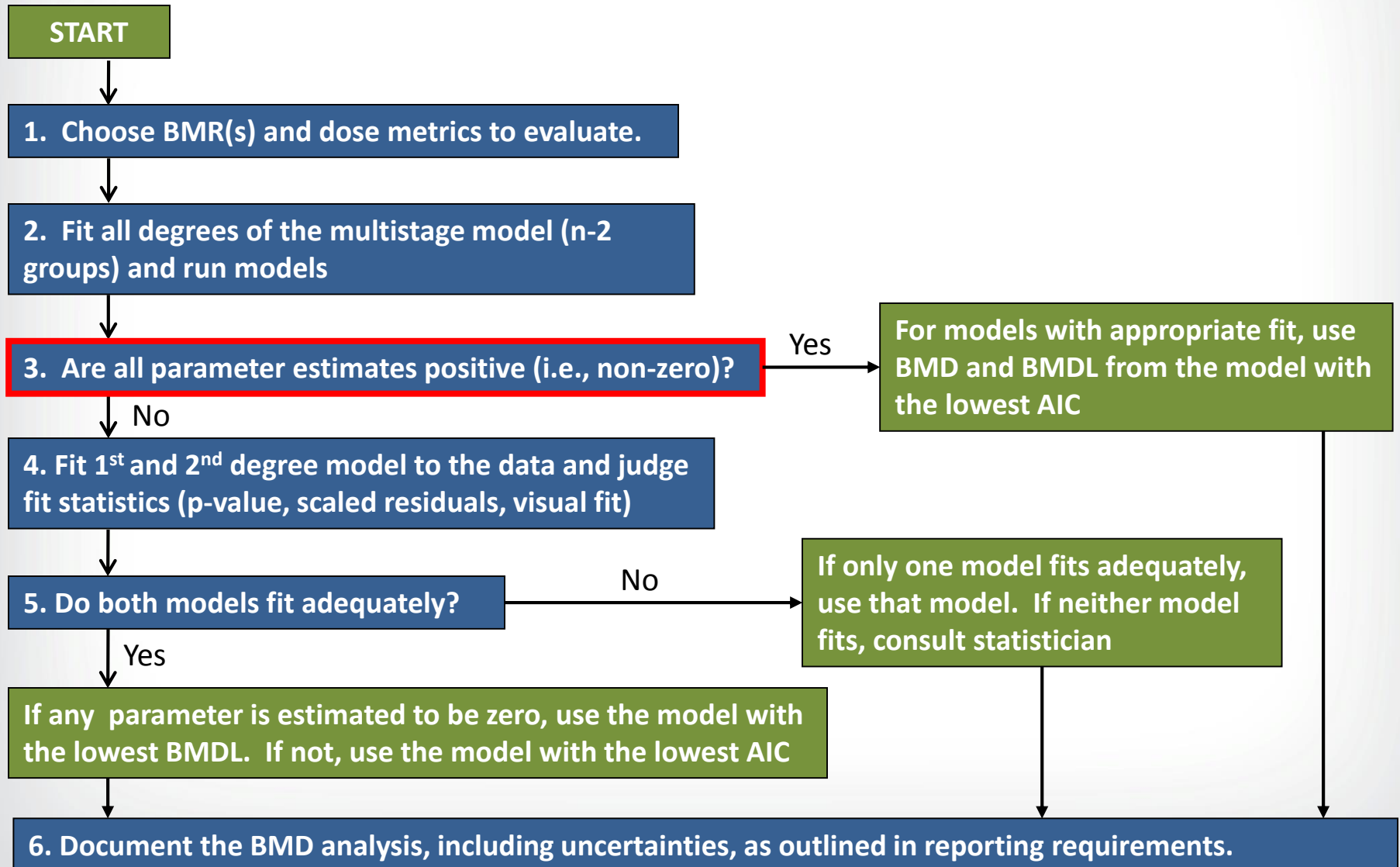
# Cancer Slope Factor

Multistage Cancer Model with 0.95 Confidence Level





# 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

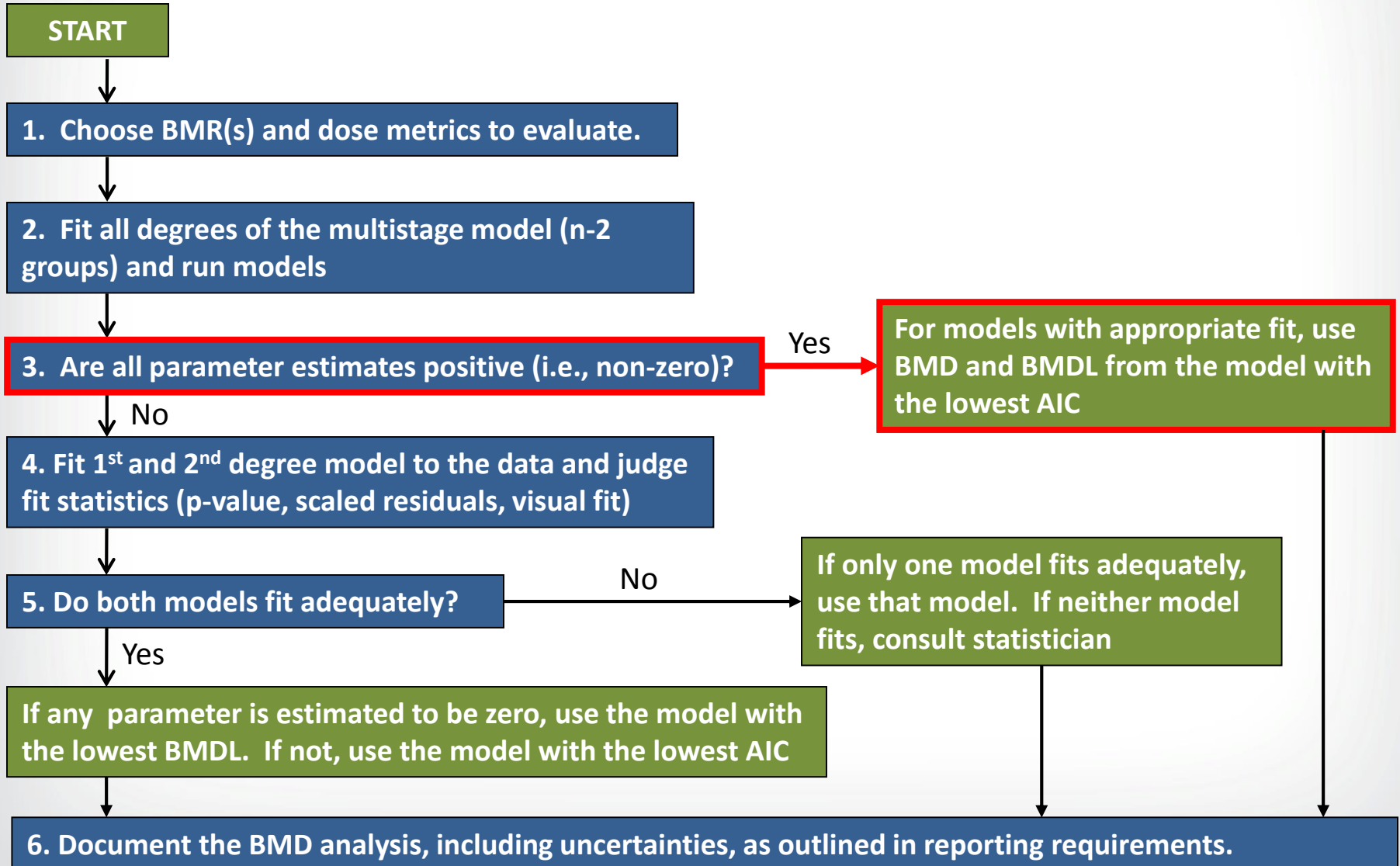
Parameter Estimates
Variable      Estimate      Std. Err.      95.0% wald Confidence Interval
Background    0.0171231    *              Lower Conf. Limit  Upper Conf. Limit
Beta(1)       0.00259283  *              *
Beta(2)       6.43728e-005 *              *
* Indicates that this value is not calculated.
```

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



- **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.

- **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

- **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 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



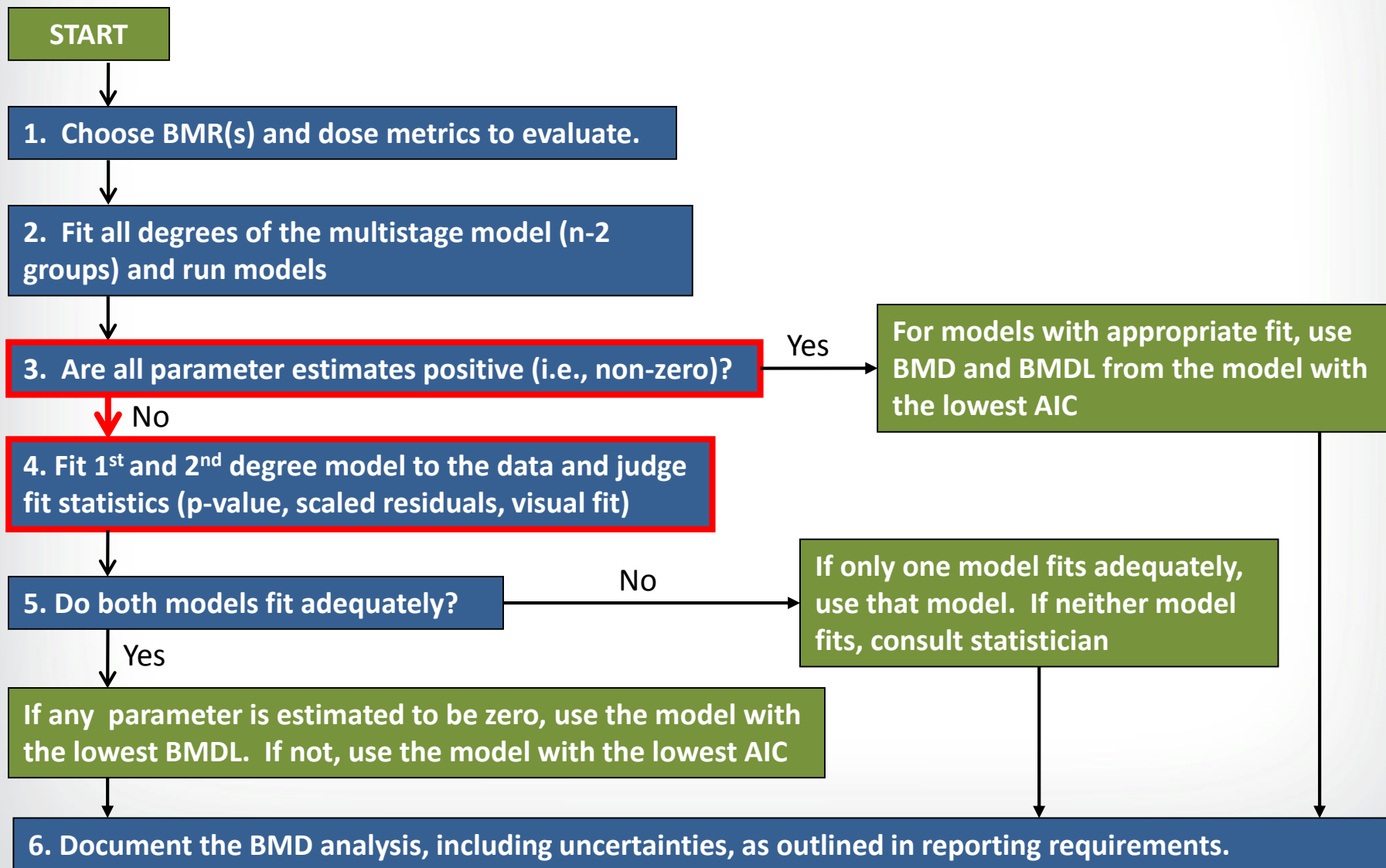
- **For dichotomous data:**
  - Global measurement: goodness-of-fit p value ( $p > 0.1$ )
  - ***Local measurement: Scaled residuals (absolute value  $< 2.0$ )***
  - ***Visual inspection of model fitting.***

- **Within a family of models (e.g., 2<sup>nd</sup> degree vs. 1<sup>st</sup> degree multistage), addition of parameters will generally improve fit**
  - Likelihood ratio tests can determine whether the improvement in fit afforded by extra parameters is justified
  - However, these tests cannot be used to compare models from different families (e.g., multistage vs. log-probit)
- **When comparing models from different families, Akaike's Information Criterion (AIC) is used to identify the best fitting model (the lower the AIC, the better)**

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

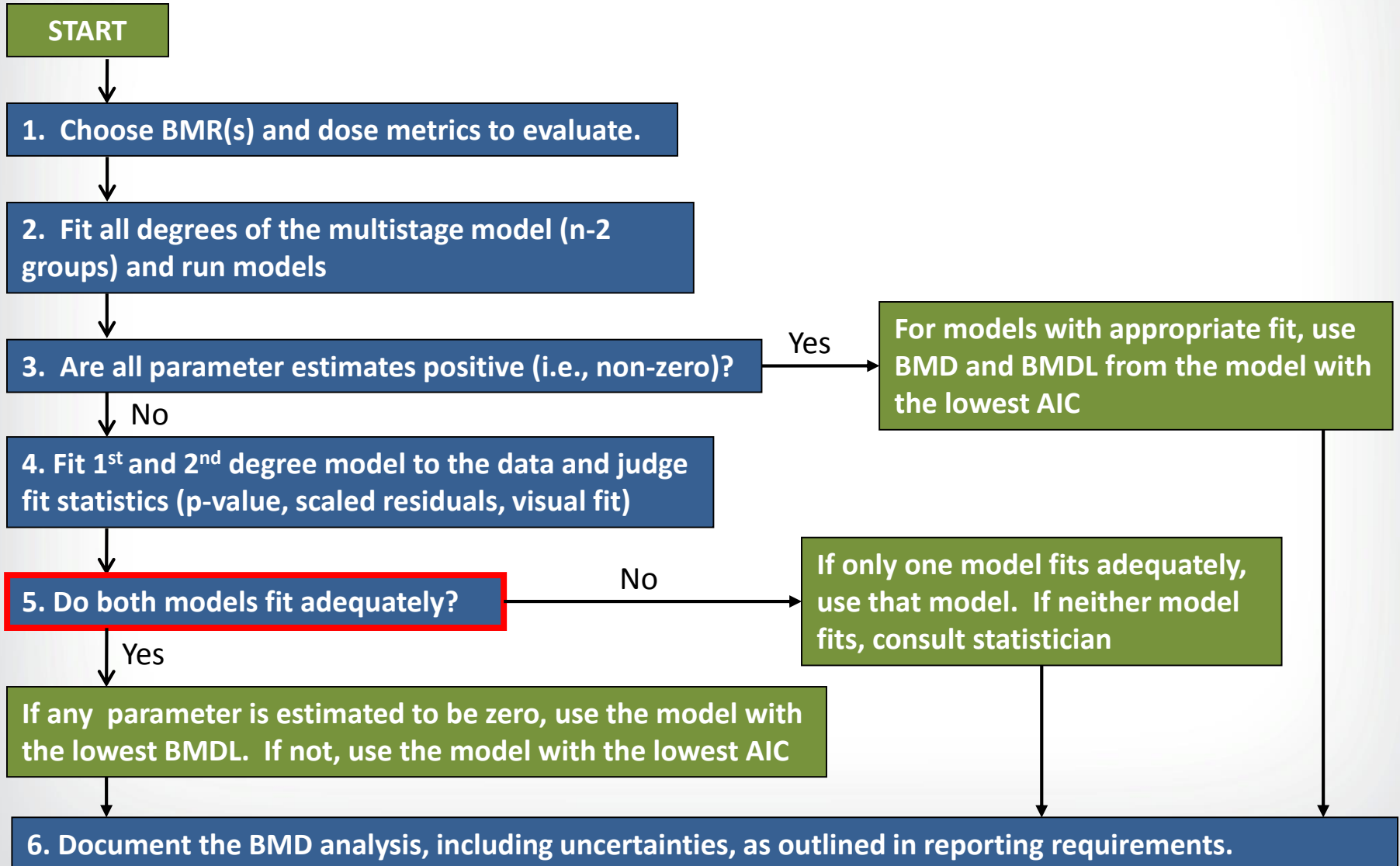


# BMD Cancer Analysis – Six Steps



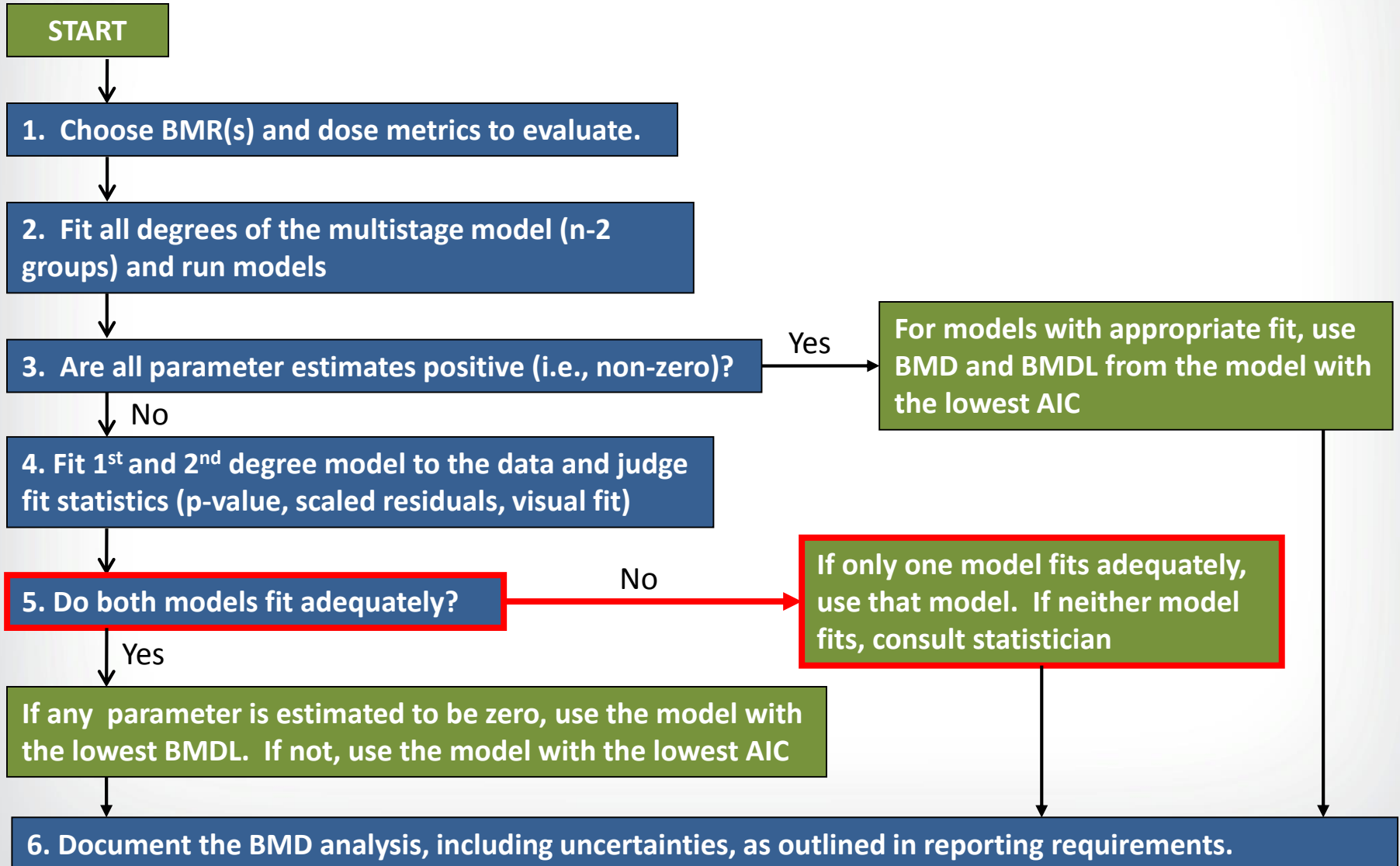


# BMD Cancer Analysis – Six Steps



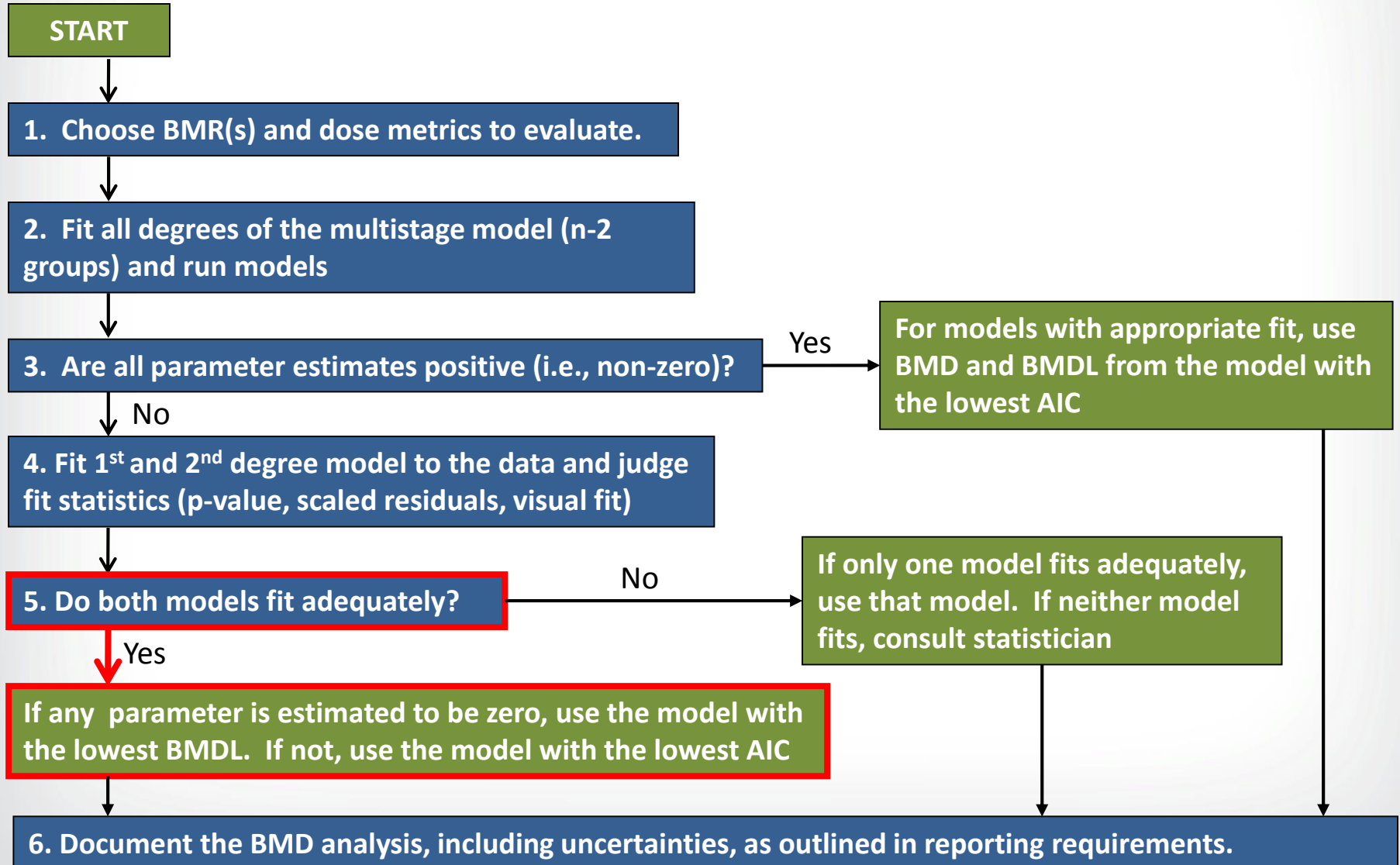


# BMD Cancer Analysis – Six Steps



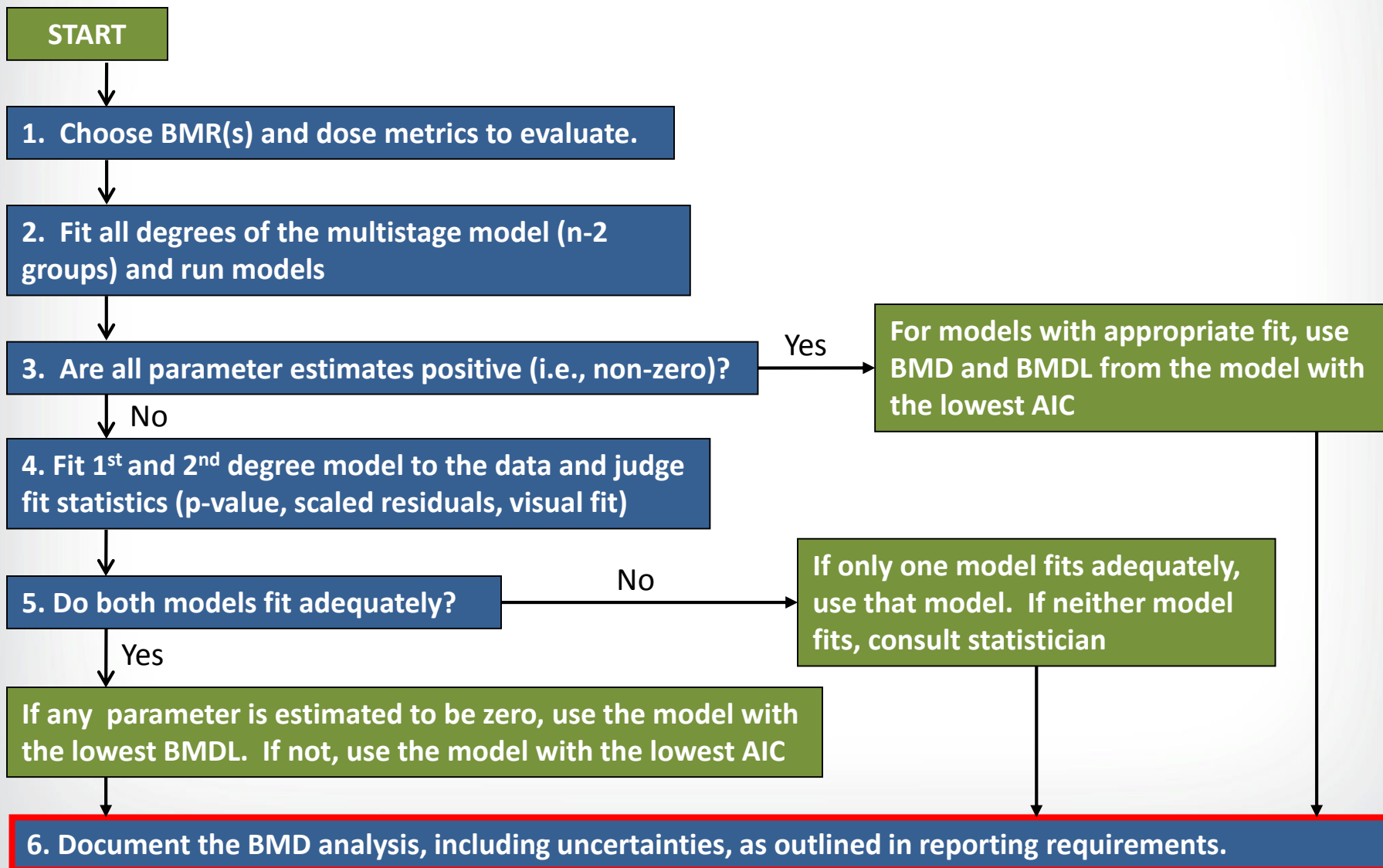


# BMD Cancer Analysis – Six Steps





# BMD Cancer Analysis – Six Steps







# ***Cancer Data – Batch Processing using the BMDS Wizard***

- **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

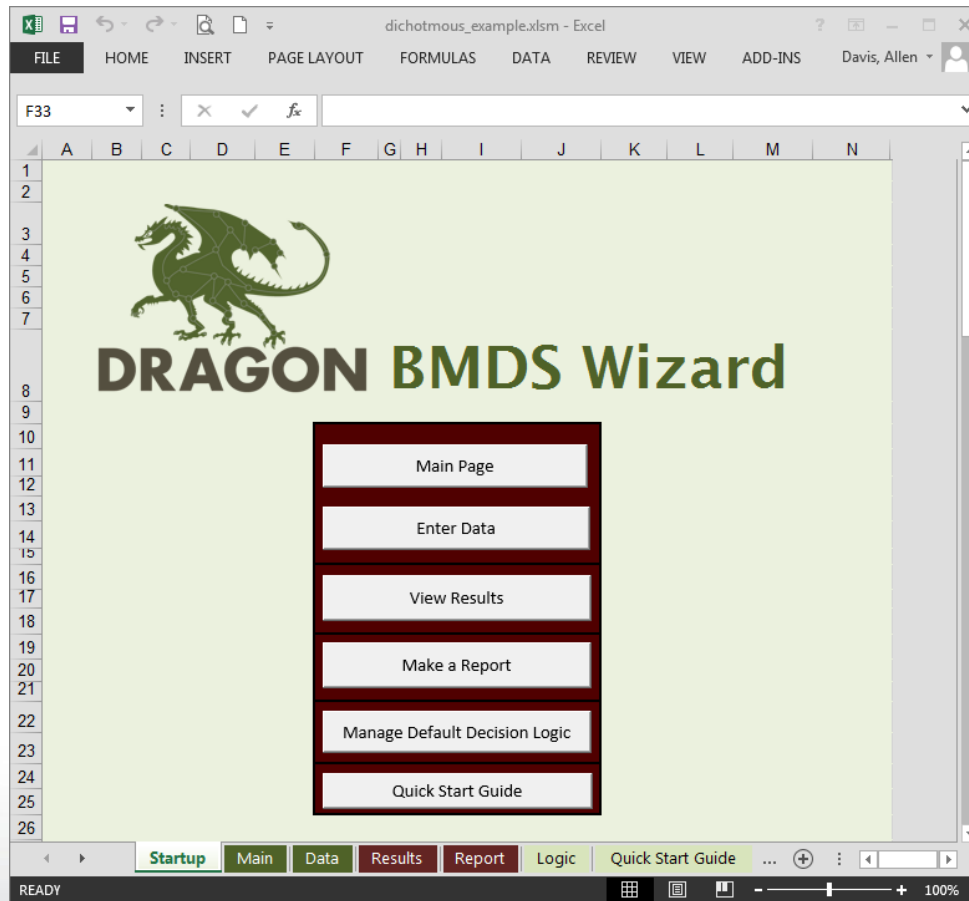
- Open Excel
- Press the “Office” button and select “Excel Options”
- Go to the “Trust Center” tab and click “Trust Center Settings”
- Change “Macro Settings” to “Disable all macros with notification” or “Enable all macros”

## 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

Excel window: cancer\_example.xlsm - Excel

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

Cell: C15, Formula: tumor\_1

BMDS Wizard				
Main	Last modified: 4/4/2014			
<b>Control Panel:</b>				
1) Setup Instructions	2) Build Session	3) Run Session in BMDS	4) Import Results	AUTORUN
<b>Study and Modeling Inputs:</b>				
BMDS Model Version:	BMDS 2.4			
BMDS Installation Directory	C:\Users\adavis10\BMDS240\	Select Folder		
Output File Directory:	C:\Users\adavis10\BMDS240\Data\clu_in\	Select Folder		
BMD ID Number:	1			
Study & Year:	tumor_1			
Endpoint Description:				
Dose Units:				
BMD or BMC Calculated?				
Select Dataset Type:	Cancer Dichotomous			
Enter Study Data:	<a href="#">Click here to enter data</a>			

Startup Main Data Results Report Logic Quick Start Guide

ENTER



# BMDS Wizard – Entering Data

Excel window: cancer\_example.xlsm - Excel

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

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

Excel window: cancer\_example.xlsm - Excel

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

120

**BMDS Wizard**

Cell Color Coding

Input Cells Calculated Cells

Clear Data

BMDS Input Data Return to Main

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

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# BMDS Wizard – Model Parameters

cancer\_example.xlsm - Excel

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

C20 : Click here to enter data

**BMDS Wizard**

Main Last modified: 4/4/2014

Add new models to BMDS Session:

- MultistageCancer 3
- MultistageCancer 2
- MultistageCancer 1
- Alternative: MultistageCancer-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	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	ncidence
% Positive	String		
Distribution	Dropdown		

Startup Main Data Results Report Logic Quick Start Guide

READY



# BMDS Wizard – Model Parameters

Excel window: cancer\_example.xlsm - Excel

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

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

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# BMDS Wizard – Model Parameters

cancer\_example.xlsm - Excel

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

C20 : Click here to enter data

**BMDS Wizard**

Main Last modified: 4/4/2014

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

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# BMDS Wizard – Adding Models to Session

cancer\_example.xlsm - Excel

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

C20 : Click here to enter data

**BMDS Wizard**

Main Last modified: 4/4/2014

**Add new models to BMDS Session:**

- MultistageCancer 3
- MultistageCancer 2
- MultistageCancer 1
- Alternative: MultistageCancer-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	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		

Startup Main Data Results Report Logic Quick Start Guide

READY



# BMDS Wizard – AutoRunning BMDS

cancer\_example.xlsm - Excel

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

H44

**BMDS Wizard**

Main Last modified: 4/4/2014

Control Panel:

1) Setup Instructions 2) Build Session 3) Run Session in BMDS 4) Import Results **AUTORUN**

Study and Modeling Inputs:

BMD Model Version:	BMDS 2.4	
BMD Installation Directory	C:\Users\adavis10\BMDS240\	Select Folder
Output File Directory:	C:\Users\adavis10\BMDS240\Data\clu_in\	Select Folder
BMD ID Number:	1	
Study & Year:	tumor_1	
Endpoint Description:		
Dose Units:		
BMD or BMC Calculated?		
Select Dataset Type:	Cancer Dichotomous	
Enter Study Data:	<a href="#">Click here to enter data</a>	

Startup Main Data Results Report Logic Quick Start Guide

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# BMDS Wizard – Results

Excel window: cancer\_example.xlsm - Excel

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

B9: 1-tumor\_1--MultiCanc1-10Pct-4d.out

**BMDS Wizard**

Buttons: Import Results, Clear Results, View Output Images

Back to Main

**Results Table**

OUT File Name	View Output File	Model Type (comment includes graph)	Risk Type	BMRF	Restricted Model	BMD	BMDL	BMDU	Cancer Slope Factor	BMD / BMDL	p-value Test 4	AIC	Scaled Residual for Dose Group near BMD	Parameter Hit Bound?
1-tumor_1--MultiCanc1-10Pct-4d.out	View Output	Multistage-Cancer 1	Extra	0.1	TRUE	21.3	17.6	26.0	0.00567	1.21	0.0286	148.57	-2.30	FALSE
1-tumor_1--MultiCanc2-10Pct-4d.out	View Output	Multistage-Cancer 2	Extra	0.1	TRUE	42.9	24.8	75.5	0.00403	1.73	0.173	144.63	-0.610	FALSE

Navigation: Startup Main Data Results Report Logic Quick Start Guide

READY 100%



# *Cancer Data – 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

lung.xlsm - Excel

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

C9 View Output

**BMDS Wizard**

BMDS Results [Back to Main](#) [Import Results](#) [Clear Results](#) [View Output Images](#)

**Results Table**

OUT File Name	View Output File <a href="#">Update</a>	Model Type (comment includes graph)	Risk Type	BMRF	Restricted Model	BMD	BMDL	BMDU	Cancer Slope Factor	BMD / BMDL	p-value Test 4	AIC	Scaled Residual for Dose Group near BMD	Parameter Hit Bound?
1-cancer_exercise-lung-MultiCanc2-	<a href="#">View Output</a>	Multistage-Cancer 2	Extra	0.1	TRUE	25.1	14.4	37.2	error	1.74	0.259	150.07	0.773	FALSE
1-cancer_exercise-lung-MultiCanc1-	<a href="#">View Output</a>	Multistage-Cancer 1	Extra	0.1	TRUE	16.5	12.4	22.9	error	1.33	0.233	150.21	-1.47	FALSE

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

READY 100%



# *The MS\_Combo Combined Tumor Model*

- **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.**

- **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**

- **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:**

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

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

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

- **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

ms\_combo\_test.xlsx - Excel

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

G41 : X ✓ fx 5

A B C D E F G H I

1 **BMDS MS Combo Wizard**

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7 **Control Panel:**

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10 **1) Validate Inputs** **2) Build Session** **3) Run in BMDS** **4) Import Results**

11 **BMDS Installation Directory** C:\Users\adavis10\BMDS240\

12 **BMDS Model Version:** BMDS 2.4

13 **Select Wizard Directory** C:\Users\adavis10\BMDS240\Data\sandbox\

14 **Input Filename (\*.tum)** ms\_combo\_test

15 **Output Name** ms\_combo\_test.out

16 **Clear Inputs**

17 **Session Inputs**

18 Wizard File for Tumor 1 tumor1.xlsx

19 Wizard File for Tumor 2 tumor2.xlsx

20 Wizard File for Tumor 3 tumor3.xlsx

21 Wizard File for Tumor 4

22 Wizard File for Tumor 5

23 Wizard File for Tumor 6

24 Wizard File for Tumor 7

25 Wizard File for Tumor 8

26 Wizard File for Tumor 9

27 Wizard File for Tumor 10

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41 **Wizard Selection Information**

42 Wizard File Name tumor1.xlsx tumor2.xlsx tumor3.xlsx

43 **Endpoint Information**

44 Study & Year	Smith 2000	Smith 2000	Smith 2000			
45 Endpoint Name	tumor1	tumor2	tumor3			
46 Dose Units						
47 BMD or BMC						
48 Dataset Type	Cancer Dichotomous	Cancer Dichotomous	Cancer Dichotomous			

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# Wizard MS Combo

ms\_combo\_test.xlsx - Excel

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1 **BMDS MS Combo Wizard**

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4 *Main* Last modified: 3/27/2014

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7 **Control Panel:**

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10 **1) Validate Inputs** **2) Build Session** **3) Run in BMDS** **4) Import Results**

11 **BMDS Installation Directory** C:\Users\adavis10\BMDS240\  
**BMDS Model Version:** BMDS 2.4  
**Select Wizard Directory** C:\Users\adavis10\BMDS240\Data\sandbox\  
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13 **Input Filename (\*.tum)** ms\_combo\_test  
**Output Name** ms\_combo\_test.out  
14  
15  
16 **Clear Inputs**

17 **Session Inputs**

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

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28 **Get Tumor Information**

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30 **ERRORS!**  
None

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32 **VALIDATION WARNINGS**  
None

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41 **Wizard Selection Information**

Wizard File Name	tumor1.xlsx	tumor2.xlsx	tumor3.xlsx
------------------	-------------	-------------	-------------

42

43 **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			

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# Wizard MS Combo

ms\_combo\_test.xlsx - Excel

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

C20 : X ✓ fx tumor3.xlsx

**BMDS MS Combo Wizard**

Main Last modified: 3/27/2014

**Control Panel:**

1) Validate Inputs    2) Build Session    3) Run in BMDS    4) Import Results

**BMDS Installation Directory:** C:\Users\adavis10\BMDS240\  
**BMDS Model Version:** BMDS 2.4  
 Select Wizard Directory: C:\Users\adavis10\BMDS240\Data\sandbox\  
**Input Filename (\*.tum):** ms\_combo\_test  
**Output Name:** ms\_combo\_test.out    Clear Inputs

**Session Inputs**

Wizard File for Tumor 1	tumor1.xlsx
Wizard File for Tumor 2	tumor2.xlsx
Wizard File for Tumor 3	tumor3.xlsx
Wizard File for Tumor 4	tumor1.xlsx
Wizard File for Tumor 5	tumor2.xlsx
Wizard File for Tumor 6	tumor3.xlsx
Wizard File for Tumor 7	~Stumor1.xlsx
Wizard File for Tumor 8	~Stumor2.xlsx
Wizard File for Tumor 9	~Stumor3.xlsx
Wizard File for Tumor 10	

Get Tumor Information

**ERRORS!**  
None

**VALIDATION WARNINGS**  
None

**Wizard Selection Information**

Wizard File Name	tumor1.xlsx	tumor2.xlsx	tumor3.xlsx
------------------	-------------	-------------	-------------

**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			

Main Results

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ms\_combo\_test.xlsx - Excel

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

G41 : X ✓ fx 5

A B C D E F G H I

1 **BMDS MS Combo Wizard**

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4 *Main* Last modified: 3/27/2014

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7 **Control Panel:**

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10 **1) Validate Inputs** **2) Build Session** **3) Run in BMDS** **4) Import Results**

11 **BMDS Installation Directory** C:\Users\adavis10\BMDS240\

12 **BMDS Model Version:** BMDS 2.4

13 **Select Wizard Directory** C:\Users\adavis10\BMDS240\Data\sandbox\

14 **Input Filename (\*.tum)** ms\_combo\_test

15 **Output Name** ms\_combo\_test.out

16 **Clear Inputs**

17 **Session Inputs**

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

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41 **Wizard Selection Information**

Wizard File Name	tumor1.xlsx	tumor2.xlsx	tumor3.xlsx
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43 **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			

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# Wizard MS Combo

ms\_combo\_test.xlsx - Excel

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

F40

A	B	C	D	E	F	G	H	I	
16								None	
17	<b>Session Inputs</b>								
18	Wizard File for Tumor 1	tumor1.xlsx				Get Tumor Information			
19	Wizard File for Tumor 2	tumor2.xlsx							
20	Wizard File for Tumor 3	tumor3.xlsx							
21	Wizard File for Tumor 4								
22	Wizard File for Tumor 5								
23	Wizard File for Tumor 6								
24	Wizard File for Tumor 7								
25	Wizard File for Tumor 8								
26	Wizard File for Tumor 9								
27	Wizard File for Tumor 10								
39									
40									
41	<b>Wizard Selection Information</b>								
42	Wizard File Name	tumor1.xlsx	tumor2.xlsx	tumor3.xlsx					
43	<b>Endpoint Information</b>								
44	Study & Year	Smith_2000	Smith_2000	Smith_2000					
45	Endpoint Name	tumor1	tumor2	tumor3					
46	Dose Units								
47	BMD or BMC								
48	Dataset Type	Cancer Dichotomous	Cancer Dichotomous	Cancer Dichotomous					
49	Number of Dose Groups	4	4	4					
50	Correct order for MS Combo	1	1	1					
51	<b>Results Information</b>								
52	Selected Model Name	Multistage-Cancer 2°	Multistage-Cancer 1°	Multistage-Cancer 2°					
53	File path to .dax and .opt files	C:\Users\adavis10\BMD\$	C:\Users\adavis10\BMD\$	C:\Users\adavis10\BMD\$240\Data\sandbox\					
54	File .dax file name	1-Smith_2000-tumor1.dax	2-Smith_2000-tumor2	3-Smith_2000-tumor3.dax					
55	File .opt file name	1-Smith_2000-tumor1-Mu	2-Smith_2000-tumor2	3-Smith_2000-tumor3-MultiCanc2-10Pct-4d.opt					
56	BMRP	0.1	0.1	0.1					
57	BMD	108.683	352.144	200.614					
58	BMDL	64.8065	218.13	137.874					
59	Model Notes								
60	<b>User Inputs</b>								
61	Species	rat	rat	rat					
62	Sex	male	male	male					
63	Tissue	liver	lung	kidney					
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67									
68									

Main Results

READY 100%



# Wizard MS Combo

ms\_combo\_test.xlsx - Excel

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

F40

A	B	C	D	E	F	G	H	I	
16								None	
17	<b>Session Inputs</b>								
18	Wizard File for Tumor 1	tumor1.xlsx				Get Tumor Information			
19	Wizard File for Tumor 2	tumor2.xlsx							
20	Wizard File for Tumor 3	tumor3.xlsx							
21	Wizard File for Tumor 4								
22	Wizard File for Tumor 5								
23	Wizard File for Tumor 6								
24	Wizard File for Tumor 7								
25	Wizard File for Tumor 8								
26	Wizard File for Tumor 9								
27	Wizard File for Tumor 10								
39									
40									
41	<b>Wizard Selection Information</b>								
42	Wizard File Name	tumor1.xlsx	tumor2.xlsx	tumor3.xlsx					
43	<b>Endpoint Information</b>								
44	Study & Year	Smith_2000	Smith_2000	Smith_2000					
45	Endpoint Name	tumor1	tumor2	tumor3					
46	Dose Units								
47	BMD or BMC								
48	Dataset Type	Cancer Dichotomous	Cancer Dichotomous	Cancer Dichotomous					
49	Number of Dose Groups	4	4	4					
50	Correct order for MS Combo	1	1	1					
51	<b>Results Information</b>								
52	Selected Model Name	Multistage-Cancer 2°	Multistage-Cancer 1°	Multistage-Cancer 2°					
53	File path to .dax and .opt files	C:\Users\adavis10\BMD\$	C:\Users\adavis10\BMD\$	C:\Users\adavis10\BMD\$240\Data\sandbox\					
54	File .dax file name	1-Smith_2000-tumor1.dax	2-Smith_2000-tumor2	3-Smith_2000-tumor3.dax					
55	File .opt file name	1-Smith_2000-tumor1-Mu	2-Smith_2000-tumor2	3-Smith_2000-tumor3-MultiCanc2-10Pct-4d.opt					
56	BMRP	0.1	0.1	0.1					
57	BMD	108.683	352.144	200.614					
58	BMDL	64.8065	218.13	137.874					
59	<b>Model Notes</b>								
60	<b>User Inputs</b>								
61	Species	rat	rat	rat					
62	Sex	male	male	male					
63	Tissue	liver	lung	kidney					
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Main Results

READY 100%

ms\_combo\_test.xlsm - Excel

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

G41 : X ✓ fx 5

A B C D E F G H I

1 **BMDS MS Combo Wizard**

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4 *Main* Last modified: 3/27/2014

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7 **Control Panel:**

8 **1) Validate Inputs** **2) Build Session** **3) Run in BMDS** **4) Import Results**

9

10 **BMDS Installation Directory** C:\Users\adavis10\BMDS240\

11 **BMDS Model Version:** BMDS 2.4

12 **Select Wizard Directory** C:\Users\adavis10\BMDS240\Data\sandbox\

13

14 **Input Filename (\*.tum)** ms\_combo\_test

15 **Output Name** ms\_combo\_test.out

16 **Clear Inputs**

17 **Session Inputs**

Wizard File for Tumor 1	tumor1.xlsm
Wizard File for Tumor 2	tumor2.xlsm
Wizard File for Tumor 3	tumor3.xlsm
Wizard File for Tumor 4	
Wizard File for Tumor 5	
Wizard File for Tumor 6	
Wizard File for Tumor 7	
Wizard File for Tumor 8	
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41 **Wizard Selection Information**

Wizard File Name	tumor1.xlsm	tumor2.xlsm	tumor3.xlsm
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43 **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				

44

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READY

100%



# Wizard MS Combo

**BMDS MS Combo**  
MS Combo Results

Back to Main

Import Results Clear Results

View output File

Output information	
Tumor Output Directory	C:\Users\adavis10\BMDS240\Data\sandbox\
Tumor Output File Name	ms_combo_test.out
Combined BMD and BMDL Calculations	
Combined Log-Likelihood	-164.749205
Combined Log-likelihood Constant	149.3602937
Benchmark Dose Computation	
Specified effect	0.1
Risk Type	Extra risk
Confidence level	0.95
BMD	73.7084
BMDL	46.8488
Multistage Cancer Slope Factor	0.00213453



# Wizard MS Combo

**BMD5 MS Combo**

MS Combo Results

Back to Main

Import Results

Clear Results

Output information	
Tumor Output Directory	C:\Users\adavis10\BMD5240\Data\sandbox\
Tumor Output File Name	ms_combo_test.out
Combined BMD and BMDL Calculations	
Combined Log-Likelihood	-164.749205
Combined Log-likelihood Constant	149.3602937
Benchmark Dose Computation	
Specified effect	0.1
Risk Type	Extra risk
Confidence level	0.95
BMD	73.7084
BMDL	46.8488
Multistage Cancer Slope Factor	0.00213453

View output File





# Wizard MS Combo

The screenshot shows an Excel spreadsheet titled "ms\_combo\_test.xlsxm" with a ribbon menu (FILE, HOME, INSERT, PAGE LAYOUT, FORMULAS, DATA, REVIEW, VIEW, DEVELOPER, ADD-INS) and a user profile for "Davis, Allen". The spreadsheet has a green header row with the text "BMD MS Combo" and "MS Combo Results". There are two buttons: "Import Results" and "Clear Results", and a link "Back to Main".

Output information	
Tumor Output Directory	C:\Users\adavis10\BMDs240\Data\sandbox\
Tumor Output File Name	ms_combo_test.out
Combined BMD and BMDL Calculations	
Combined Log-Likelihood	
Combined Log-likelihood Constant	
Benchmark Dose Computation	
Specified effect	
Risk Type	
Confidence level	
BMD	
BMDL	
Multistage Cancer Slope Factor	

The "Show BMDs Output" dialog box displays the following results:

```
BMDL = 137.874
BMDU = 253.226
Taken together, (137.874, 253.226) is a 90 % two-sided confidence interval for the BMD
Multistage Cancer Slope Factor = 0.000725298

**** Start of combined BMD and BMDL Calculations.****

Combined Log-Likelihood -164.74920502719473
Combined Log-likelihood Constant 149.36029367340058

Benchmark Dose Computation
Specified effect = 0.1
Risk Type = Extra risk
Confidence level = 0.95
BMD = 73.7084
BMDL = 46.8488
Multistage Cancer Slope Factor = 0.00213453
```



## ***Cancer Data – 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	2 <sup>nd</sup>	1 <sup>st</sup>	2 <sup>nd</sup>
BMD <sub>10</sub>	25.1	12.5	15.5
BMDL <sub>10</sub>	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

- **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	2 <sup>nd</sup>	1 <sup>st</sup>	2 <sup>nd</sup>	n/a
BMD <sub>10</sub>	25.1	12.5	15.5	6.48
BMDL <sub>10</sub>	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***

- **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 (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**

- 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*

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

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

- 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*

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

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



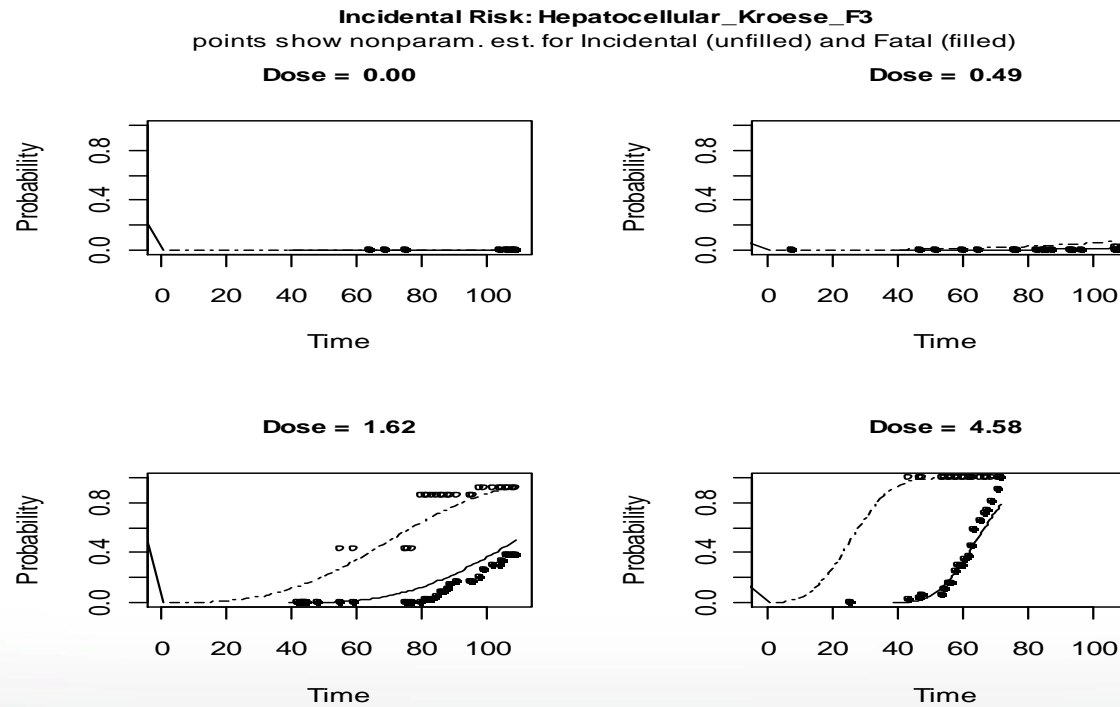
# Modeling Fatal vs. Non-fatal Tumors

- **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)

- **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

- **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)**

- **Generated using the graphical module “gofplot\_msw” in R – must request from EPA currently**
- **Plots can be used to judge model fit**





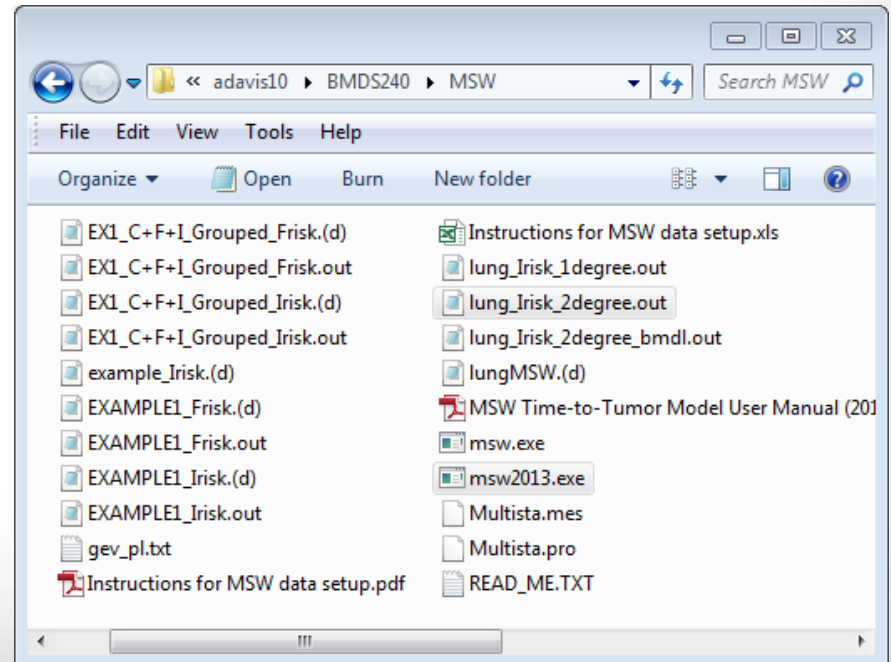




# Steps for MSW Model Analysis – Incidental Risk

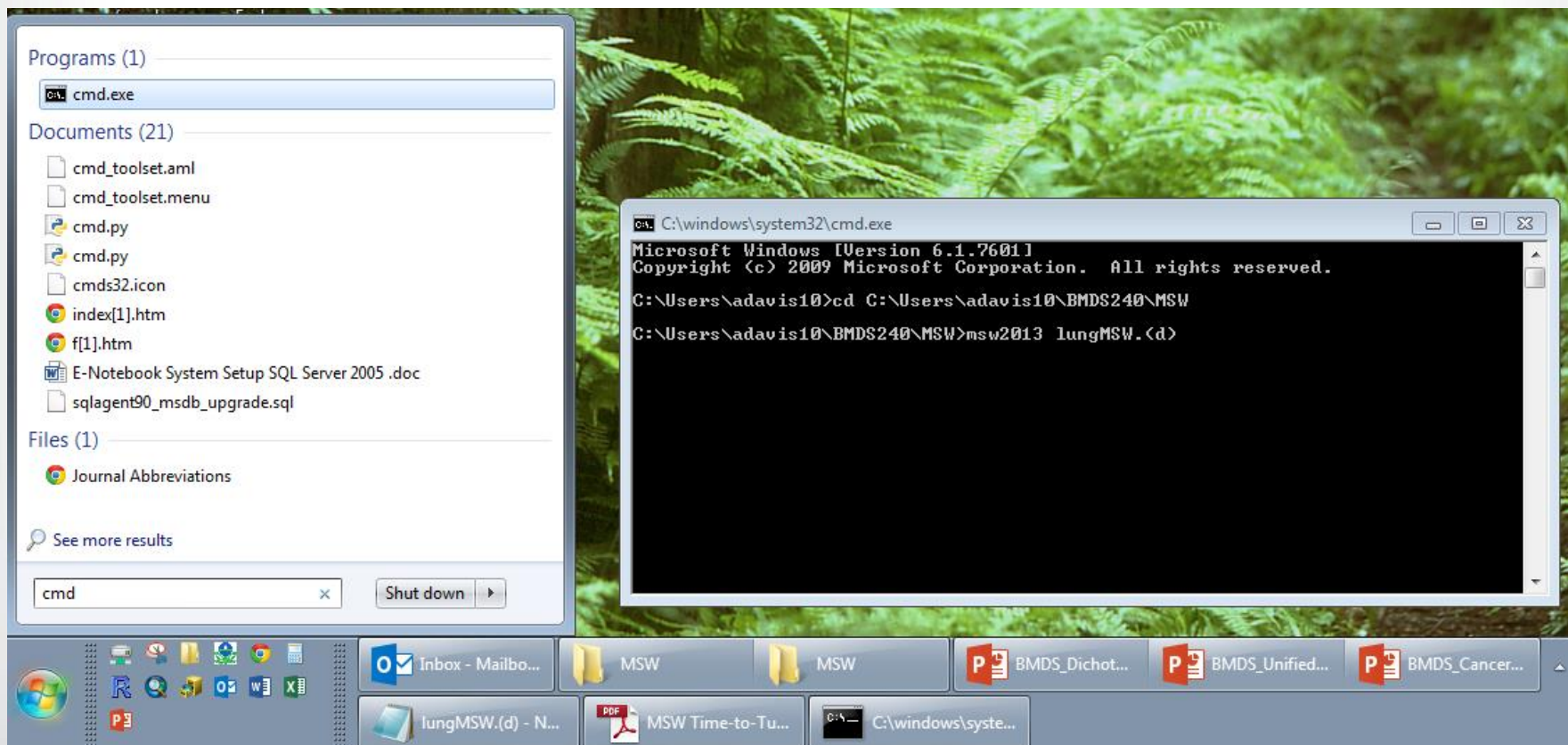
- **Set the number of stages for 2<sup>nd</sup> degree MSW model (line 2 = 2)**
- **Set output file name, indicating the details of the model run (line 5)**
- **Parameterize for Incidental Risk (line 9, item 2 = “0”, line 13, item 3 = “0”)**
- **Turn BMDL “Off” in data files (line 14, item 1 = “0”)**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

```
lungMSW.(d) - Notepad
File Edit Format View Help
Multistage weibull
2
Lung Tumors, BMD for Risk Type = Incidental Risk
lung set
lung_Irisk_2degree.out
0
0
200
-9999.0 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
0 0.95
1 10.000 79.0
1 4 0.95
DOSE CLASS TIME
0 C 5
0 C 69
```



# 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_Irsk_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
Variable      Estimate      Std. Err.      95.0% wald Confidence Interval
              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

Fitted Model  Log(likelihood)  # Param      AIC
              -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
```



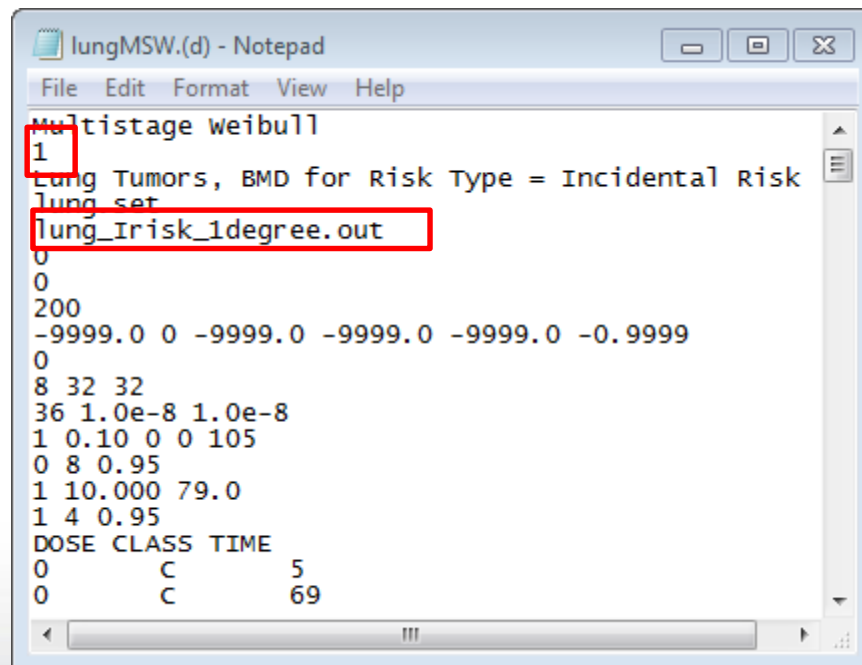
# MSW Model Results - Incidental Risk

Model stages	AIC	BMD <sub>10</sub>	Responses at mg/kg-d levels				Selected model parameter estimates	Model Selection
			0	15	30	80	c	
<b>Lung Tumors</b>								
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 1<sup>st</sup> 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)



```
lungMSW.(d) - Notepad
File Edit Format View Help
Multistage weibull
1
Lung Tumors, BMD for Risk Type = Incidental Risk
lung_set
lung_Irisk_1degree.out
0
0
200
-9999.0 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
0 8 0.95
1 10.000 79.0
1 4 0.95
DOSE CLASS TIME
0 C 5
0 C 69
```



# Steps for MSW Model Analysis – Incidental Risk

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

```
lung_Irsk_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
Variable      Estimate      Std. Err.      95.0% Wald Confidence Interval
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

Fitted Model  Log(likelihood)  # Param      AIC
              -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 <sub>10</sub>	Responses at mg/kg-d levels				Selected model parameter estimates	Model Selection
			0	15	30	80	c	
<b>Lung Tumors</b>								
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 <sub>10</sub>	Responses at mg/kg-d levels				Selected model parameter estimates	Model Selection
			0	15	30	80	c	
<b>Lung Tumors</b>								
1	324.202	4.41	0.75	10.84	11.62	24.78	4.3925	
2	<b>323.601</b>	<b>7.23</b>	<b>0.86</b>	<b>7.86</b>	<b>9.54</b>	<b>27.37</b>	<b>4.5321</b>	<b>Lowest AIC, better low-dose fit</b>

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 2<sup>nd</sup> 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)

```
lungMSW.(d) - Notepad
File Edit Format View Help
Multistage weibull
2
Lung Tumors, BMD for Risk Type = Incidental Risk
lung_set
lung_Irisk_2degree_bmd1.out
6
0
200
-9999.0 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
```



# MSW Model Results - Incidental Risk

lung\_Irisk\_2degree\_bmdl.out - Notepad

File Edit Format View Help

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% wald Confidence Interval	
			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

Fitted Model    Log(likelihood)    # Param    AIC

                             -157.8            4            323.601

Data Summary

DOSE	CLASS				Total	Expected Response
	C	F	I	U		
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***

- **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

- **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 3<sup>rd</sup> order polynomial to describe the tumor incidence function in time**
  - Other polynomials can be used, but estimating the correct polynomial can be difficult

- **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

poly\_example.xlsx - Excel

FILE HOME INSERT PAGE LAY FORMULA DATA REVIEW VIEW Davis, Allen

N3 :  $= (K3/734)^3$

	32 ppm				80 ppm			
	days	tumor	weight	time-adj	days	tumor	weight	time-adj
1								
2								
3	382	0	0.14096	0.14096	392	0	0.15232	0.15232
4	439	0	0.21395	0.21395	422			
5	470	0	0.26255	0.26255	454			
6	491	0	0.29933	0.29933	523			
7	495	0	0.30671	0.30671	524			
8	502	0	0.31991	0.31991	567			
9	545	0	0.40936	0.40936	579			
10	551	0	0.42303	0.42303	587			
11	565	0	0.4561	0.4561	589			
12	567	1	1	0.46096	595			

Sheet1 Sheet2 Sh...

READY

poly\_example.xlsx - Excel

FILE HOME INSERT PAGE LAY FORMULA DATA REVIEW VIEW Davis, Allen

N3 :  $= (K3/734)^3$

	J	K	L	M	N	O	P	Q	R	S	T
42		733	1	1	0.99592		733	1	1	0.99592	
43		734	0	1	1		733	0	0.99592	0.99592	
44		734	1	1	1		733	1	1	0.99592	
45		734	0	1	1		733	0	0.99592	0.99592	
46		734	0	1	1		733	1	1	0.99592	
47		734	1	1	1		733	1	1	0.99592	
48		734	1	1	1		733	1	1	0.99592	
49		734	0	1	1		733	1	1	0.99592	
50		734	1	1	1		733	1	1	0.99592	
51		734	1	1	1		734	0	1	1	
52		734	1	1	1		734	0	1	1	
53			23	40.3474				28	42.1447		
54				57.005					66.4378		
55											

Sheet1 Sheet2 Sh...

READY 80%



# 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***

- **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

lung\_poly3.xlsxm - Excel

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

C9 View Output

**BMDS Wizard**

Import Results Clear Results View Output Images

Back to Main

**Results Table**

OUT File Name	View Output File Update	Model Type (comment includes graph)	Risk Type	BMRF	Restricted Model	BMD	BMDL	BMDU	Cancer Slope Factor	BMD / BMDL	p-value Test 4	AIC	Scaled Residual for Dose Group near BMD	Parameter Hit Bound?
1-poly3_exercise-lung-MultiCanc2-1	View Output	Multistage-Cancer 2	Extra	0.1	TRUE	16.7	8.69	27.2	error	1.92	0.112	115.05	-1.02	FALSE
1-poly3_exercise-lung-MultiCanc1-1	View Output	Multistage-Cancer 1	Extra	0.1	TRUE	9.67	7.26	13.3	error	1.33	0.132	115.44	-1.81	FALSE

Startup Main Data Results Report Logic Quick Start Guide

READY 100%



## ***Cancer Data – Exercise #4***

- **Open the following Wizard cancer files: liver\_poly3.xlsx and kidney\_poly3.xlsx**
- **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	2 <sup>nd</sup>	1 <sup>st</sup>	2 <sup>nd</sup>
BMD <sub>10</sub>	16.7	8.10	10.9
BMDL <sub>10</sub>	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

- **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 poly3 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	2 <sup>nd</sup>	1 <sup>st</sup>	2 <sup>nd</sup>	n/a
BMD <sub>10</sub>	16.7	8.10	10.9	4.15
BMDL <sub>10</sub>	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