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Benchmark Dose Modeling – Cancer Models

Allen Davis, MSPH Jeff Gift, Ph.D. Jay Zhao, Ph.D. National Center for Environmental Assessment, U.S. EPA



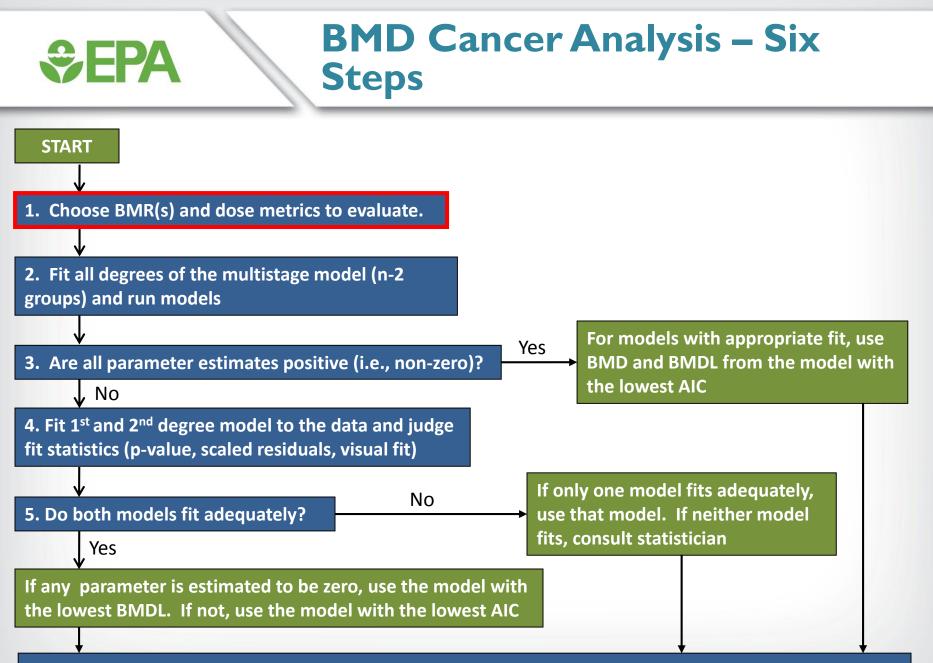


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Dichotomous Data - Cancer

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

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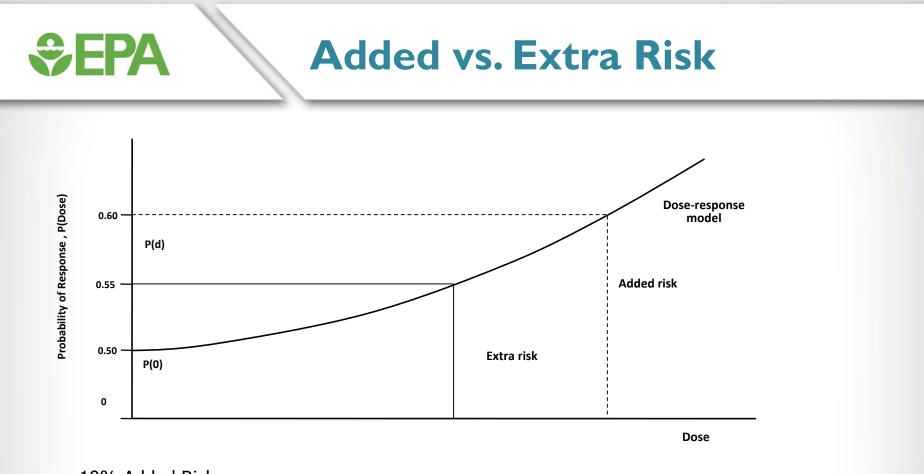
Select A Benchmark Response

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

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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)]/[I P(0)]
- Extra risk is recommended by the IRIS, and is used in IRIS risk assessments.

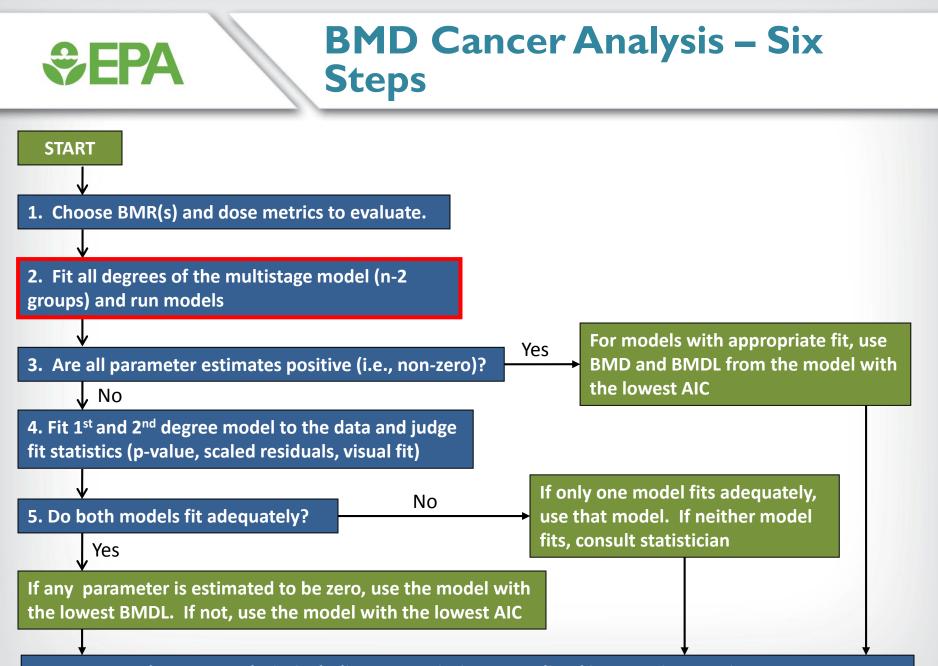


10% Added Risk 0.10 = P(d) - P(0); if P(0)=.50P(d) = 0.10 + P(0) = 0.10 + 0.50 = 0.60

10% Extra Risk 0.10 = [P(d) - P(0)]/[1 - P(0)]; if P(0) = .50 $P(d) = 0.10 \times [1 - P(0)] + P(0) = (0.10 \times 0.50) + 0.50 = 0.55$

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

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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

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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 = $v \times g$

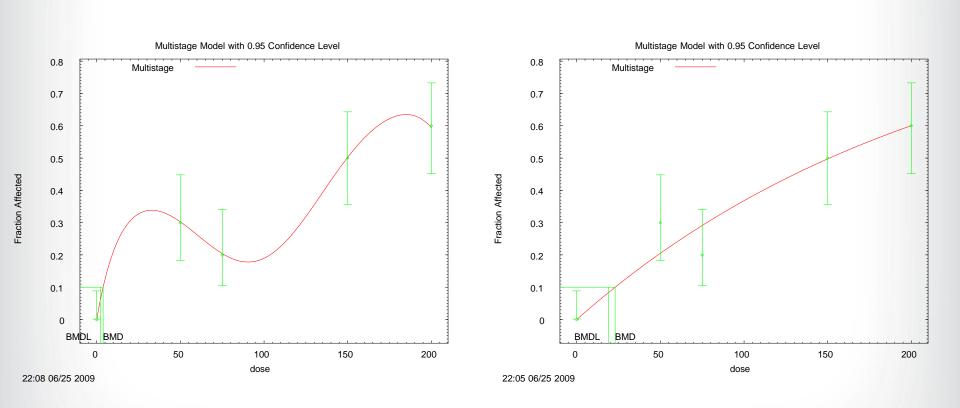
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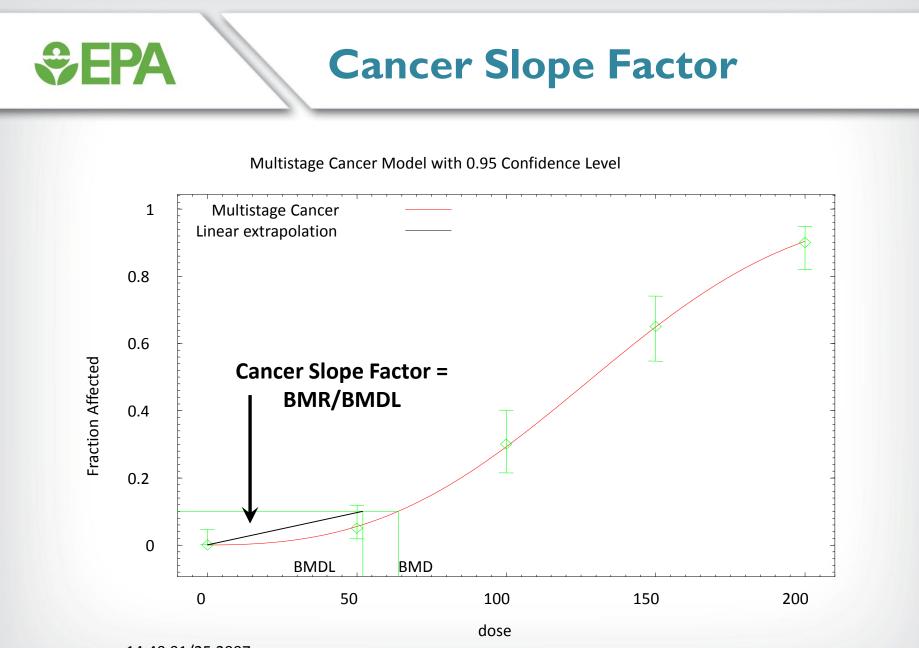
Multistage-Cancer Model

- 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)

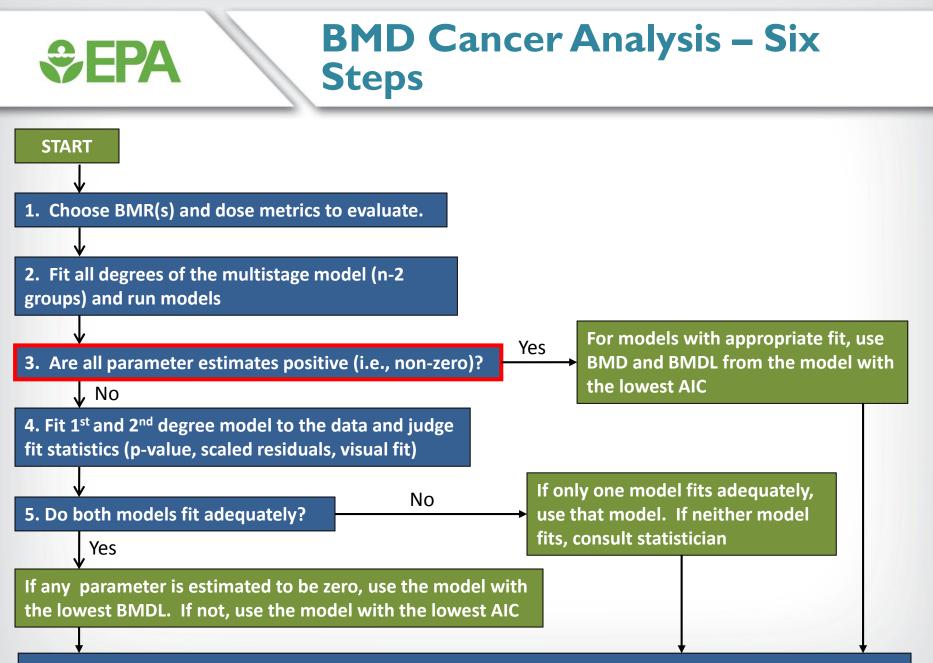
Restriction of β Coefficients and Model Fitting



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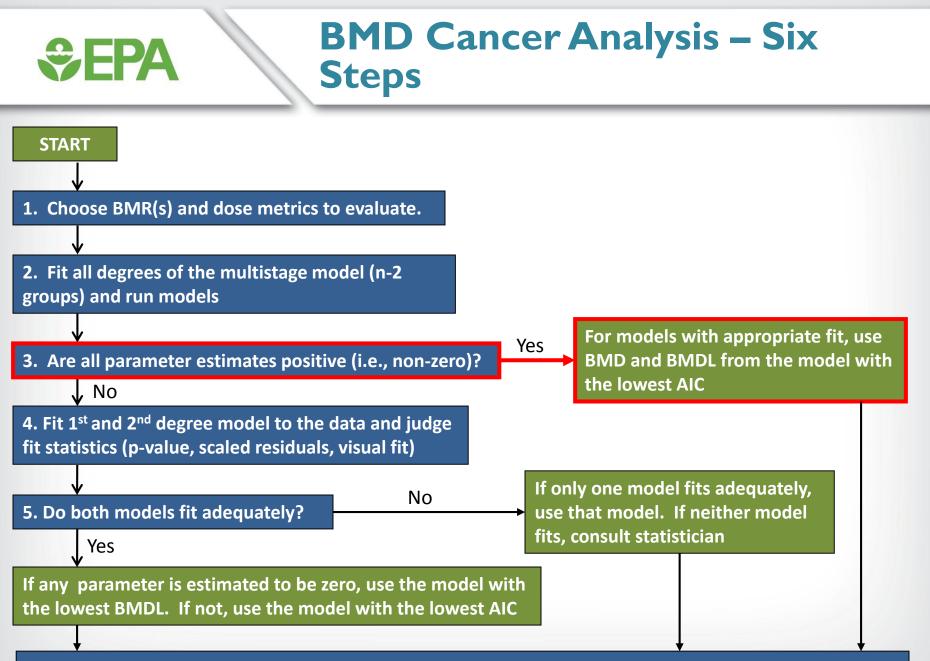
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Multistage Model Beta Parameters

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Beta(2)	0.56	-0.95	1			
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Does the Model Fit the Data?

For cancer data:

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- 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.

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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:

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

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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:

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- 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

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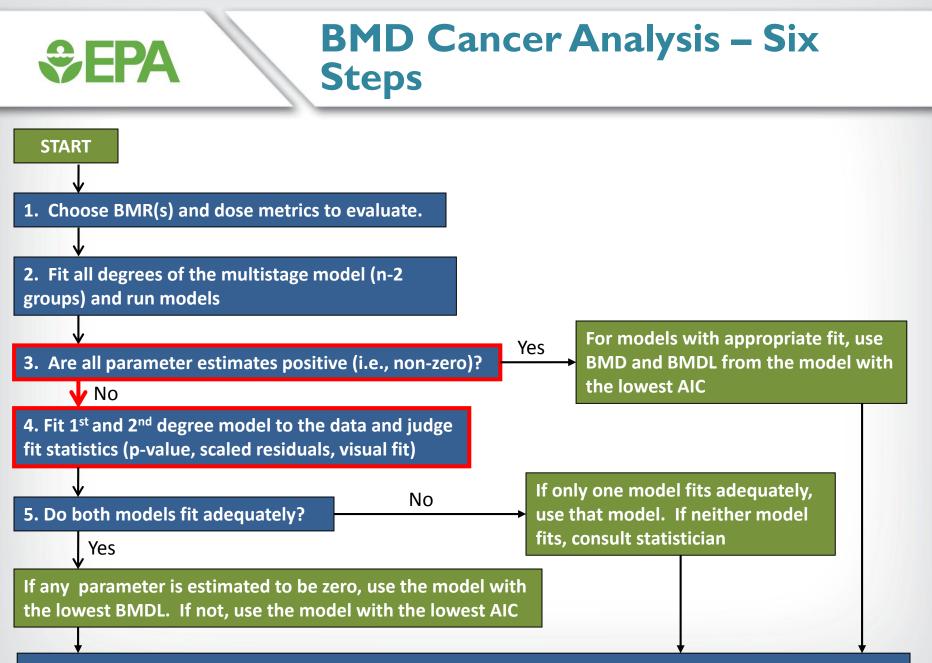
- Likelihood ratio tests can determine whether the improvement in fit afforded by extra parameters is justified
- However, these tests cannot be used to compare models from different families (e.g., multistage vs. log-probit)
- When comparing models from different families, Akaike's Information Criterion (AIC) is used to identify the best fitting model (the lower the AIC, the better)

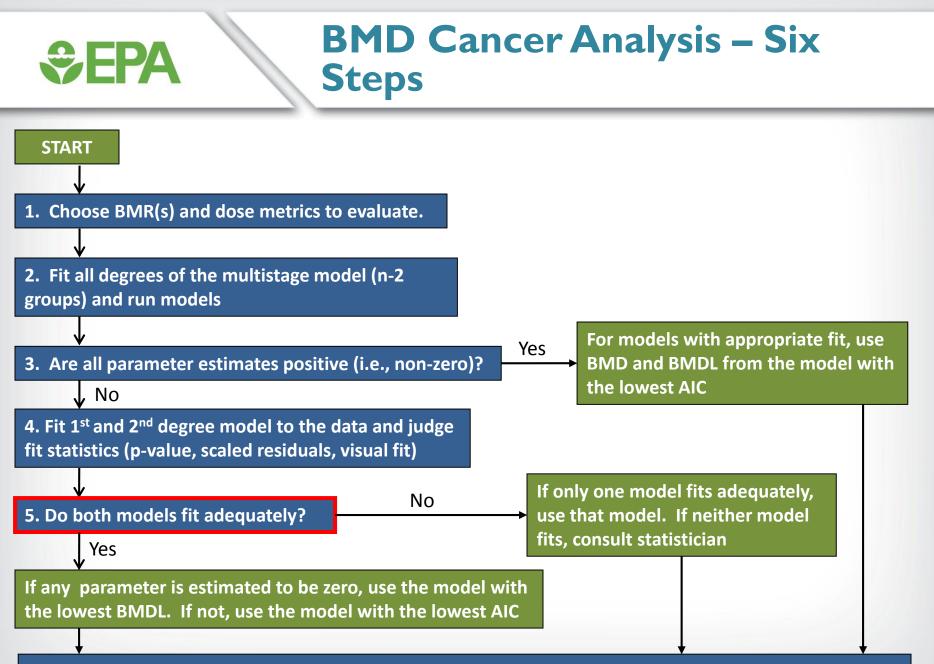
Akaike's Information Criterion (AIC)

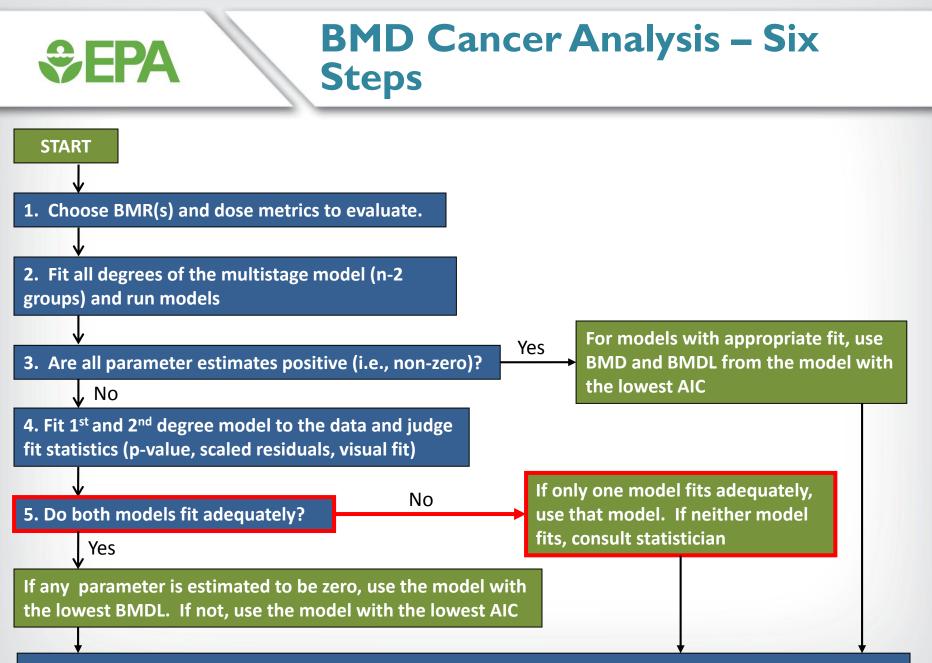
• AIC = $-2 \times LL + 2 \times p$

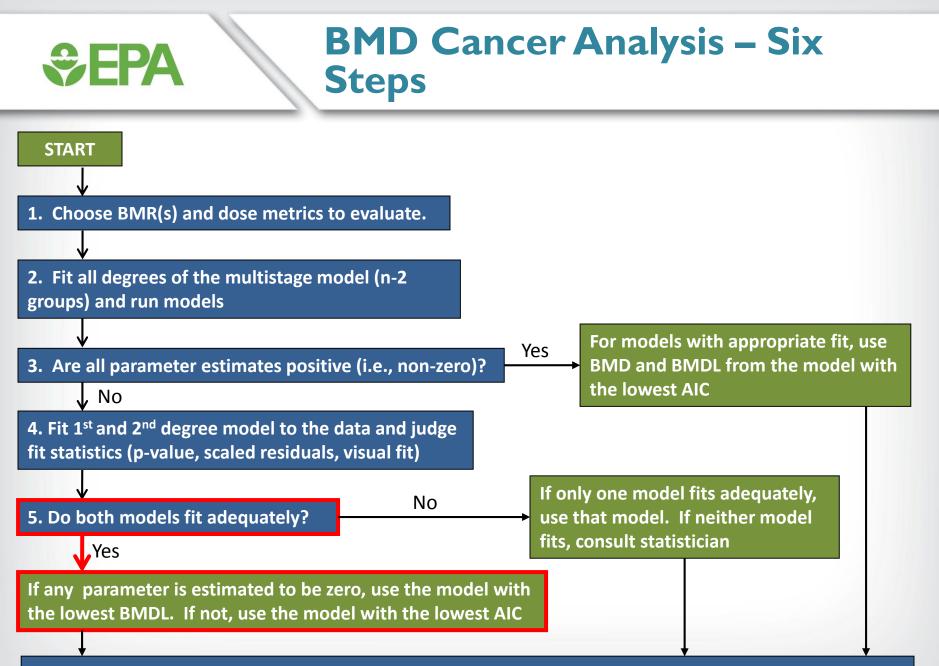
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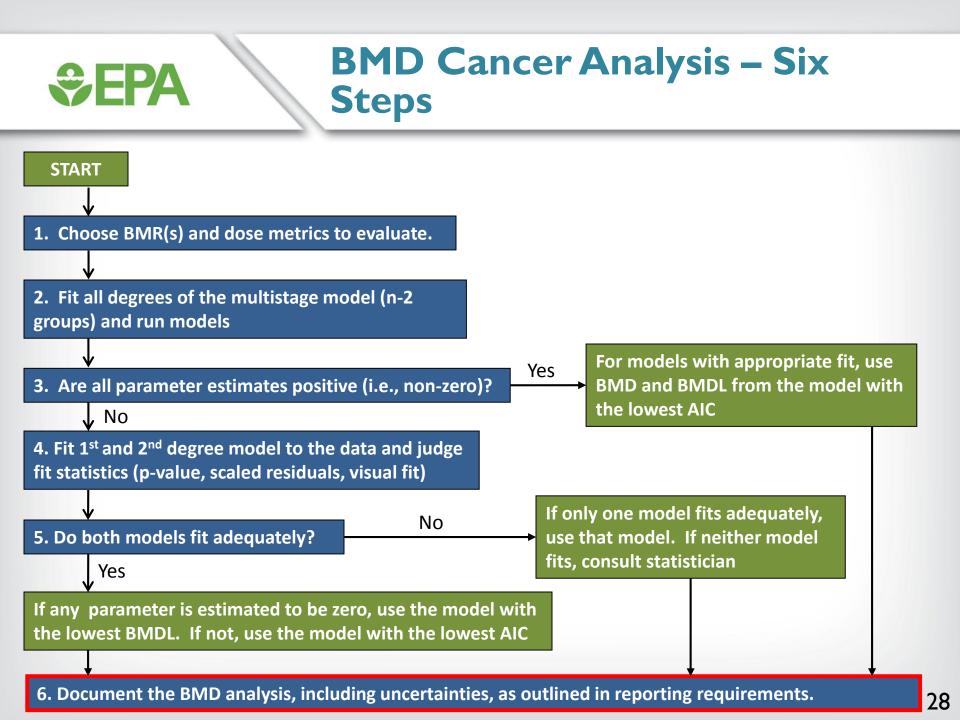
- LL = log-likelihood at the maximum likelihood estimates for parameters
- p = number of model degrees of freedom (dependent on total number of model parameters, number of model parameters that hit a bound, and the number of dose groups in your dataset)
- Only the DIFFERENCE in AIC is important, not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













Cancer Data – Batch Processing using the BMDS Wizard

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- 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

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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

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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

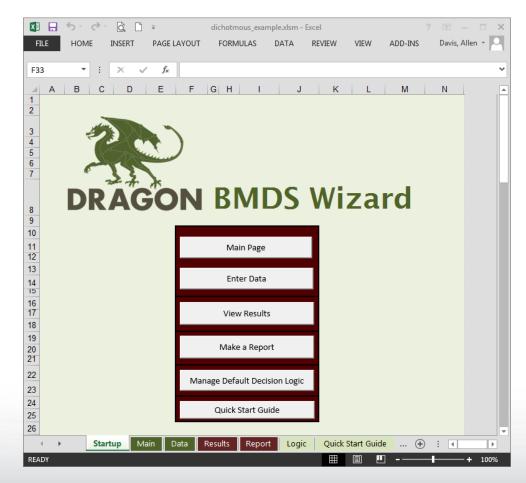
- Open Excel
- Select the "Tools" Menu
- Select Options
- Go to "Security" tab and click "Macro Security"
- Change security level to "Medium" or "Low"

- 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



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BMDS Wizard – Study and Modeling Inputs

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BMDS Wizard – Model Parameters

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BMDS Wizard – Adding Models to Session

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BMDS Wizard – AutoRunning BMDS

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BMDS Wizard – Results

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Cancer Data – Exercise #1

©EPA Cancer Exercise #I

- 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)

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The MS_Combo Combined Tumor Model

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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

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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 (β₀, β₁, ...) are functions of the β 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

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Wizard MS Combo

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Wixard File for Tumor 2	tumor2.xlsm				1		
Wizard File for Tumor 3	tumor3.xlsm						
Wizard File for Tumor 4							
Wixard File for Tumor 5					Get Tumor		
Wizard File for Tumor 6					Information		
Wizard File for Tumor 7							
Wixard File for Tumor 8							
Wizard File for Tumor 9							
Wizard File for Tumor 10							
Wizard Selection Information Wizard File Name Endpoint Information	tumor1.xlsm	tumor2.xlsm	tumor3.xlsm				
Study & Year	Smith 2000	Smith 2000	Smith 2000				
Endpoint Name	tumor1	tumor2	tumor3				
Dose Units	turnori	turnorz	tumors				
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 1°					
File path to .dax and .opt files	C:\Users\adavis10\BMD				/xod		
File .dax file name	1-Smith_2000-tumor1.da						
File .opt file name	1-Smith_2000-tumor1-M			MultiCanc2-10Pct-	4d.opt		
BMRF	0.1	0.1	0.1				
BMD	108.683	352.144	200.614				
BMDL Madel Neter	64.8065	218.13	137.874		+ - -		
Model Notes User Inputs			1				
Species	rat	rat	rat		1		
Sex	male	male	male				
	liver	lung	kidney				
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	BMRF			0.1	0.1		0.1								
	BMD			108.683	352.144		200.614					_			
	BMDL			64.8065	218.13		137.874								
	Model I														
	User In									_				 	
	Specie	S		rat	rat		rat					_		 	
	Sex			male	male		male							 	
	Tissue			liver	lung		kidney								
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Wizard MS Combo

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Wizard MS Combo

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D	Tumor Output Directory C:\Users\adavi Tumor Output File Name ms_combo_tes		vata\sandbox	Show BMDS Ou	tput		X
1 2 3	Combined BMD and BMDL Calculations Combined Log-Likelihood Combined Log-likelihood Constant			Close			
4	Benchmark Dose Computation				BMDL = 137.874		
5	Specified effect			_	BMDU = 253.226		
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	BMD				<pre>gether, (137.874, 253.226) is a 90 % two-side for the BMD</pre>	ed confidence	
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	Main Results (+)			•			الحر
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Cancer Data – Exercise #2

• Open the following Wizard cancer files: liver.xlsm and kidney.xlsm

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- 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 #I

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	Lung	Liver	Kidney
Degree Multistage	2 nd	1 st	2 nd
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

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

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

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	Lung	Liver	Kidney	MS_Combo
Degree Multistage	2 nd	1 st	2 nd	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

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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

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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

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 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

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

• Where:

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- c (shape parameter; ≥ 1) describes how rapidly the risk of death from tumor increases over time,
- t₀ (induction time; ≥ 0; t > t₀) is the elapsed time that occurs between onset of fatal tumor and death from tumor, assumed to be the same for all subjects
- $\beta_0, \beta_1, ..., \beta_k$ (polynomial coefficients; ≥ 0 ; k ≤ 6) determine curvature of the doseresonse 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

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

• Where:

SEPA

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

SEPA 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

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- 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

Sepa Model Selection (Number of Stages)

- The MSW model does not report a X² 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)

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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

Incidental Risk: Hepatocellular_Kroese_F3 points show nonparam. est. for Incidental (unfilled) and Fatal (filled) Dose = 0.00Dose = 0.49Probability 0.8 0.8 Probability 0.4 0.4 0.0 0.0 0 80 100 0 20 20 40 60 40 60 80 100 Time Time Dose = 1.62 Dose = 4.580.8 0.8 Probability Probability 0.4 0.4 0.0 0.0 ο 20 60 80 100 0 20 40 60 80 100 40 Time Time

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MSW Model Datafile Format

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

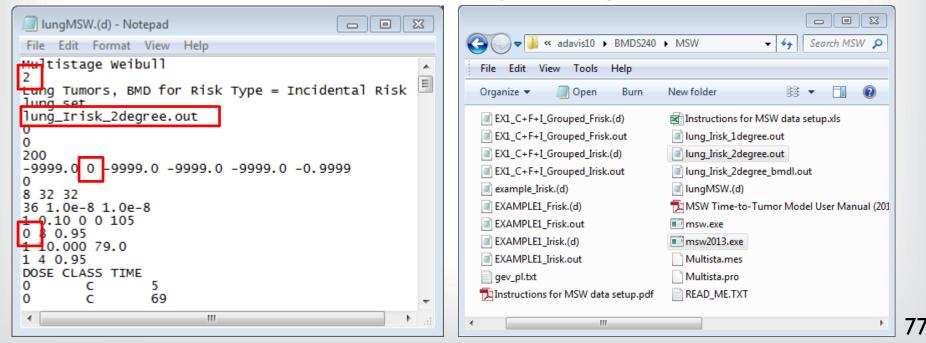
١.	Model name, do not change this text
2.	Number of stages (order of model)
3.	User specified title to appear in output file
4.	Not used, but must have a text entry, "name.set" is recommended
5.	Name of output file to be created
6.	Append output file (1) or overwrite output file (0)
7.	Grouped data (1) 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

- 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")

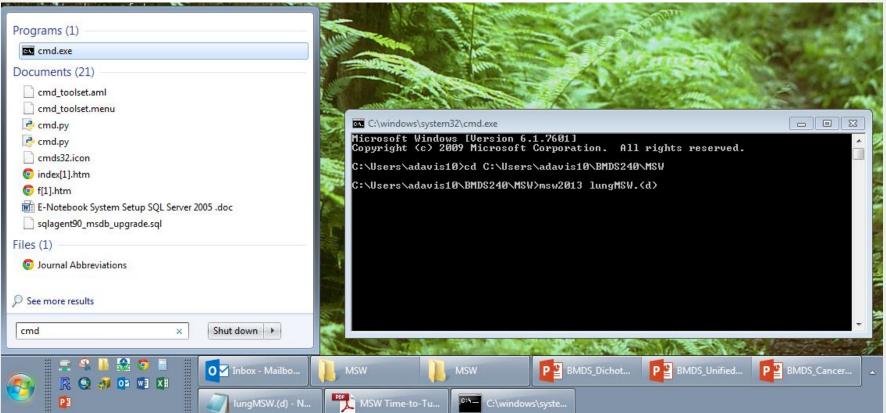
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Save msw.exe with data files in a "working directory"



- 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

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• Examine output file, record results

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lung_Irisk_2degree.out - File Edit Format Viev						3
beta_1	-0.99	0.94	1	0.95		^
beta_2	-0.98	0.95	0.95	1		
		Parameter E	stimates			
Variable c beta_0 beta_1 beta_2	Estimate 4.5321 1.4239e-011 9.06383e-012 1.40115e-013	1. 7.31328 4.48366	e-011	95.0% Wald Conf Lower Conf. Limit 2.44353 -1.29099e-010 -7.88144e-011 -1.17744e-012	idence Interval Upper Conf. Limit 6.62067 1.57577e-010 9.6942e-011 1.45767e-012	
Lo Fitted Model	og(likelihood) -157.8	# Param 4	323.	AIC 601		
c	Data Summary CLASS F I		Expected	d Response		
DOSE 0 49 15 46 30 34 80 15	$\begin{array}{ccc} 0 & 1 \\ 1 & 3 \\ 5 & 11 \\ 14 & 21 \end{array}$	0 50 0 50 0 50 0 50 0 50	7.86 9.54		[
Minimum observ	ation time for	F tumor con	text =	66		
Benchmark Dose Risk Response = Risk Type = Specified effect = Time = BMD =	Incidenta Extr 0.	a 1)5				m
			III			▼



MSW Model Results -Incidental Risk

Model stages	AIC	BMD ₁₀	Respo	onses at i	mg/kg-d∣	levels	Selected model parameter estimates	Model Selection
			0	15	30	80	с	
				Lun	g Tumors	5		
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

Set the number of stages for Ist degree MS model (line 2 = I)

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- 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)

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File Edit Format View Help
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tung Tumors, BMD for Risk Type = Incidental Risk
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lung_Irisk_1degree.out
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0
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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
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                 5
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0
                 69
        C
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- Examine output file, record results
- Make final model selection for BMDL estimation

Iung_Irisk_1degree.o											
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 c beta_0 beta_1	Esti 4.3 2.36646e 3.16163e	9248 -011 1	Std. Er 1.029 L.17677e-0 1.4719e-0	32 10	Lower Conf. Limit Upp 2.37504 -2.06979e-010	er Conf. Limit 6.40991 2.54308e-010 3.20103e-010					
Fitted Model	Log(likeliho -159.		aram 3	324.	AIC 202						
	Data Sum CLAS F	s	Total C	wheeted	Despense						
DOSE			Total E		Response						
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Minimum obse	rvation time	for F tun	nor contex	t =	66						
Benchmark Dos Risk Response Risk Type Specified effect Time BMD	= Incid = =					E					
•			m			▼ 					



MSW Model Results -Incidental Risk

Model stages	AIC	BMD ₁₀	Respo	onses at I	mg/kg-d∣	levels	Selected model parameter estimates	Model Selection
			0	15	30	80	с	
				Lun	g Tumors	5		
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

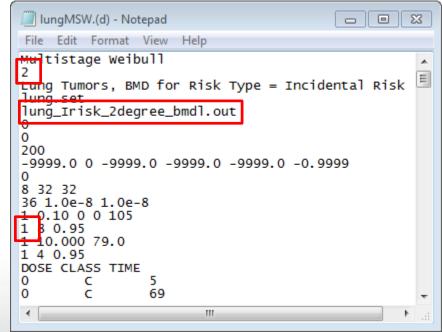
Model stages	AIC	BMD ₁₀	Respo	onses at i	mg/kg-d	levels	Selected model parameter estimates	Model Selection
			0	15	30	80	с	
				Lun	g Tumors	5		
1	324.202	4.41	0.75	10.84	11.62	24.78	4.3925	
2	323.601	7.23	0.86	7.86	9.54	27.37	4.5321	Lowest AIC, better low-dose fit

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

- 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")

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 Save msw.exe and repeat command line execution (up arrow recalls last command)



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MSW Model Results -Incidental Risk

arameter Es Std. 1.0 7.31328e 4.48366e 6.72233e # Param	Err. 1 6562 -011 -011 -013	95.0% wald conf Lower Conf. Limit 2.44353 -1.29099e-010 -7.88144e-011 -1.17744e-012	idence Interval Upper Conf. Limit 6.62067 1.57577e-010 9.6942e-011 1.45767e-012	*
5td. 1.0 7.31328e 4.48366e 6.72233e	Err. 1 6562 -011 -011 -013	Lower Conf. Limit 2.44353 -1.29099e-010 -7.88144e-011	Upper Conf. Limit 6.62067 1.57577e-010 9.6942e-011	
1.0 7.31328e 4.48366e 6.72233e	6562 011 011 013	Lower Conf. Limit 2.44353 -1.29099e-010 -7.88144e-011	Upper Conf. Limit 6.62067 1.57577e-010 9.6942e-011	
1.0 7.31328e 4.48366e 6.72233e	6562 011 011 013	2.44353 -1.29099e-010 -7.88144e-011	6.62067 1.57577e-010 9.6942e-011	
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6.72233e	-013			
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Poly-3 Survival Adjustment

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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

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Poly-3 Survival Adjustment

- The poly-3 survival adjustment is a method to calculate survivaladjusted 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:

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

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- 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

N3		▼ E	×	f _x	=(K3/	734)^3	3				*							
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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")	·
<pre>> setwd("M:\\BMD5_fraining_Materials\\Cancer_2014\\training_ffles") > example=read.csv("example.csv")</pre>	
<pre>> local({pkg <- select.list(sort(.packages(all.available = TRUE)),graphics=TRUE</pre>	n –
<pre>if(nchar(pkg)) library(pkg, character.only=TRUE)})</pre>	·/
Varning message:	
package 'MCPAN' was built under R version 3.0.3	
<pre>> poly3test(time=example\$death,status=example\$tumor,f=example\$group,Method="BP"</pre>	, k=3)
Sample estimates using poly- 3 -adjustment	
0 12.8 32 80	
6.0000 12.0000 23.0000 28.0000	
1 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:	
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estimate testat p.val.adj	
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32 - 0 0.4286 4.5338 0.0000	
30 - 0 0.5229 5.7914 0.0000	
	-
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Cancer Data – Exercise #3

©EPA 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)

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5 6 7	Results Table OUT File Name	File Update	Model Type (comment includes graph) Multistage-Cancer	Risk Type ▼ ▼ ▼ 2ªExtra	•	Restricted Model	BMD	BMDL	BMDU Slope Factor	BMDL	Test 4	AIC	Scaled Residual for Dose Group near BMP	Hit Bound? ▼
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Cancer Data – Exercise #4

SEPA 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

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	Lung_poly3	Liver_poly3	Kidney_poly3
Degree Multistage	2 nd	1 st	2 nd
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

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 poly3l 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

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

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	Lung_poly3	Liver_poly3	Kidney_poly3	MS_Combo
Degree Multistage	2 nd	1 st	2 nd	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