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Benchmark Dose Modeling – Dichotomous Models

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Dichotomous Data

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

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Select a Benchmark Response

- BMR should be near the low end of the observable range of increased risks in a bioassay
- BMRs that are too low can impart high model dependence, i.e., different models have different shapes in the extreme low dose area and will provide different BMDL estimates.

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



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BMR Selection: Choose BMR(s) to Evaluate

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

• In some situations, use of different BMRs is supported

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

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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.



P% 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



Selection of a Specific Model

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

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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	$\Phi\left(\alpha+\beta X\right)$	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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Curve Shapes with Increasing Background Response



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Restricting Parameters in Dichotomous Models

- Dichotomous models are conceptually restricted so that probabilities are positive numbers no greater than one
- Model parameters (i.e., slope, background response, etc.) can be bounded to prevent biologically implausible results
 - Bounding model parameters restricts the shape the dose-response curve can assume
- These restrictions can impact statistical calculations such as the goodness-of-fit p-value and AIC
 - Currently, a parameter estimate that "hits a bound" impacts a model's degrees of freedom (DF) (in BMDS, DF is increased by 1 for p-value calculation)
 - When a parameter hits a bound, that parameter is not counted towards the AIC penalization (EPA's Statistical Working Group may modify this approach in the future)

Multistage Model – Betas not Restricted



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Multistage Model – Betas Restricted



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Models with Unrestricted Power or Slope Parameters



Models with Restricted Power or Slope Parameters



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18

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Restricting Dichotomous Models – EPA Recommendations

User-specified Parameter Restrictions

- Multistage beta coefficients restrict to be positive
- **Power and slope terms** restrict to be 1 or greater
- **Background** do not set to zero unless biologically justifiable

• Other Modeling Options

- Threshold parameter currently not recommended as the parameter can be misconstrued to have more biological meaning than appropriate
- Multivariate modeling currently only available in nested dichotomous and C×T models in BMDS; other software packages (i.e., PROAST) can consider covariates for all data types



Does the Model Fit the Data?

For dichotomous data:

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- Global measurement: goodness-of-fit φ value (φ > 0.1)
- 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 due to biological or policy preferences (e.g., multistage model for cancer endpoints), a cut-off value of p = 0.05 can be used

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Global Goodness-of-Fit



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Modeling Recommendations – Poor Global Goodness-of-Fit

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

Example I:When <u>Not</u> to Drop the High Dose

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

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Multistage Model with 0.95 Confidence Level



Example 2: When <u>to</u> Drop the High Dose

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

Fraction Affected

Multistage Model with 0.95 Confidence Level



Example 2: When <u>to</u> Drop the High Dose

Multistage

Dose (mg/m ³)	Ν	Incidence
50	20	0
180	20	4
300	32	13
750	12	6

0.7 0.6 0.5 0.4 0.3 0.2 0.1 P = 0.36760 BMDL BMD 200 500 700 100 300 400 600 dose

Multistage Model with 0.95 Confidence Level

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Fraction Affected

Example 3: Use of a Model with Asymptote Term

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

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Dichotomous-Hill Model with 0.95 Confidence Level



Further Recommendations – Poor Global Goodness-of-Fit

Log-transformation of doses

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- Consult a statistician to determine if log-transformation is appropriate, special care
 often needs to be taken with the control dose (i.e., log₁₀(0) is undefined)
- Both log₁₀ and log_e transformations are available in BMDS

• **PBPK** modeling can be very useful for **BMD** modeling

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

PBPK Models and BMD Modeling

- Care must be taken when performing BMD analyses with PBPK model-derived estimates of internal dose
- Most important question: Is the relationship between external and internal dose metrics linear across all doses?
- If yes, then it does not matter when BMD modeling occurs
 - Can model external doses and then convert BMDs and BMDLs to internal doses (often advantageous if PBPK model is constantly updated or changed)
- If no, then BMD analysis must be conducted using the internal dose metrics of interest

Does the Model Fit the Data?

For dichotomous data:

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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

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Scaled Residuals



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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Visual Inspection of Fit



35


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Are BMDL Estimates "Sufficiently Close"?

- Often, more than one model or modeling options will result in an acceptable fit to the data.
- Consider using the lowest BMDL if BMDL estimates from acceptable models are not sufficiently close, indicating model dependence
- What is "sufficiently close" can vary based on the needs of the assessment, but generally should not be more than 3-fold.





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"







Example of BMD Analysis Documentation

 Table B-9. Benchmark dose modeling results for decreased rotorod performance in male

 Wistar rats exposed to 1,2,4-TMB. (Korsak and Rydzyński, 1996)

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Madala	Goodne	ess-of-fit	BMD	PMDI	Basis for Model Selection	
Widder	<i>p</i> -value	AIC	BMD _{10%}	BMDL _{10%}		
Logistic	0.6024	35.5306	528.905	341.987		
Log-logistic	0.9743	32.1664	193.575	93.947		
Log-probit	0.5825	35.4276	426.494	232.739	Of the models that	
Probit	0.6248	35.4027	489.595	317.868	provided an adequate fit	
Dichotomous Hill	0.9352	34.1023	160.508		estimate, the log-logistic model was selected based	
Gamma Weibull Linear Multistage 2° Multistage 3°	0.9338	32.3299	228.574	129.306	on the lowest BMDL (BMDLs differed by more than 3-fold).	

^a Decreased rotorod performance was measured as increased percentage of failures per rat, selected model in bold; scaled residuals for selected model for concentrations 0, 123, 492, and 1230 mg/m³ were 0.000, 0.434, - 0.154, -0.089, respectively

SEPA Additional Models for Dichotomous Data

- For most of the quantal models in BMDS, there are two alternative versions available:
 - Background response parameter, γ:
 P(β, x, γ) = γ + (Ι-γ)*F{β, x}
 - Background parameter additive to dose, η:
 P(β, x, η) = F{β, (x+ η)}

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

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Available Models (and options) for Dichotomous Data

- Gamma
 - Background response
 - Background dose
- Multi-stage
 - Background response
 - Background dose
- Multi-stage cancer
 - Background response
 - Background dose

• Weibull

- Quantal-Linear (power = 1)
- Background response
- Background dose

- Dichotomous Hill
- Logistic
 - Background response
 - Background dose
- Log Logistic
 - Background response
- Probit
 - Background response
 - Background dose
- Log Probit
 - Background response
 - Background dose

Curve Shapes with Increasing Background Dose



48



Dichotomous Data – Creating a Dataset in BMDS

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Creating a Dataset - Options

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

Creating a Dataset – Open New Generic Dataset



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Creating a Dataset – Open New Generic Dataset

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Creating a Dataset – Open new Formatted Dataset



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Creating a Dataset – Open Existing Dataset



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Creating a Dataset – Open Existing Dataset

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Specifying Model Parameters

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Dichotomous Model Plot and Output Files



Dichotomous Model Parameter Estimates



Dichotomous Model Fit Statistics



BMD and **BMDL** Estimates



SEPA

Opening Output and Plot Files after Analysis



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New Flexibility in Datafile Structure

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New Flexibility in Datafile Structure

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New Flexibility in Datafile Structure



New Flexibility in Datafile Structure

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New Flexibility in Datafile Structure

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Dichotomous Data – Exercise #1

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Dichotomous Exercise #I

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Manually enter these data and save as Exercise_I.dax

EPA Dichotomous Exercise #1

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

SEPA

Dichotomous Exercise #I

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Dichotomous Exercise #I



Dichotomous Exercise #I

BMDS Summary Table

	Multistage 1 st degree	
BMD ₁₀	55.2	
BMDL ₁₀	44.81	
AIC	160.271	
p value	0.2788	
Scaled residual	-1.750	

EPA Dichotomous Exercise #1

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

Dichotomous Exercise #I



Dichotomous Exercise #I

BMDS Summary Table

	Multistage 1 st degree	Multistage 2 nd degree	
BMD ₁₀	55.2	94.7	
BMDL ₁₀	44.81	55.6	
AIC	160.271	158.884	
p value	0.2788	0.5802	
Scaled residual	-1.750	-0.606	

SEPA Dichotomous Exercise #1

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

Dichotomous Exercise #I



Dichotomous Exercise #I

BMDS Summary Table

	Multistage 1 st degree	Multistage 2 nd degree	Log-probit
BMD ₁₀	55.2	94.74	111.50
BMDL ₁₀	44.81	55.56	81.95
AIC	160.271	158.884	157.776
p value	0.2788	0.5802	1.000
Scaled residual	-1.750	-0.606	0.004

Dichotomous Exercise #I

Individual Model

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

Across Models

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

Dichotomous Exercise #I

BMDS Summary Table

	Multistage 1 st degree	Multistage 2 nd degree	Log-probit
BMD ₁₀	55.2	94.74	111.50
BMDL ₁₀	44.81	55.56	81.95
AIC	160.271	158.884	157.776
p value	0.2788	0.5802	1.000
Scaled residual	-1.750	-0.606	0.004



Dichotomous Data – Batch Processing using the BMDS Wizard

SEPA The BMDS Wizard

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

BMDS Wizard Installation

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

BMDS Wizard Macros

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

Excel 2003

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

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

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

Starting a BMDS Wizard Session

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



BMDS Wizard – Study and Modeling Inputs

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BMDS Wizard – Model Parameters

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BMDS Wizard – Model Parameters

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Std. Deviation	String						
Response	String						
Incidence	String	Incidence	Incidence	Incidence	Incidence	Incidence	Incidence
% Positive	String						
Distribution	Dropdown						
Solution	String						
Risk Type	Dropdown	Extra	Extra	Extra	Extra	Extra	Extra
BMRF	Real	0.1	0.1	0.1	0.1	0.1	0.1
Confidence Level	Real	0.95	0.95	0.95	0.95	0.95	0.95
BMD Calculation	Boolean	TRUE	TRUE	TRUE	TRUE	TRUE	TRUE
BMDL Curve. Calc.	Boolean	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE
Restrict Slope >= 1?	Boolean			TRUE		FALSE	
Restrict Power >= 1?	Boolean	TRUE					TRUE
Restrict Betas >= 0?	Boolean						
Restrict n>1?	Boolean						
Degree of Polynomial	Integer						
Restriction	Dropdown						
Adverse Direction	Dropdown						
BMR Type	Dropdown						
Constant Variance?	Boolean						

101

BMDS Wizard – Model Parameters

Image: Second secon	chere to enter data C D Last modified: Last modified: Camma 1-Smith_2000-Gami 10Pct Dose NumAnimals Incidence	 E 4/4/2014 Logistic 1-Smith_2000-Logistic Logistic 10Pct Dose NumAnimals Incidence 	F LogLogistic 1-Smith_2000LogLog LogLogistic 10Pct Dose NumAnimals	G Probit 1-Smith_2000Probit- Probit 10Pct Dose NumAnimals	H LogProbit 1-Smith_2000LogPro LogProbit 10Pct Dose NumAnimals	Weibull 1-Smith_2000Weit Weibull 10Pct Dose NumAnimals
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Degree of Polynomial Integer	r					
Restriction Dropdov	own					
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102

BMDS Wizard – Model Parameters

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	TRUE						
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PMDC Wizard							
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Animal ID	- Ching						
Dose	String	Dose	Dose	Dose	Dose	Dose	Dose
# Subjects in Dose Group	String	NumAnimals	NumAnimals	NumAnimals	NumAnimals	NumAnimals	NumAnimals
Mean	String						
Std. Deviation	String						
Response	String						
Incidence	String	Incidence	Incidence	Incidence	Incidence	Incidence	Incidence
% Positive	String						
Distribution	Dropdown						
Solution	String						
Risk Type	Dropdown	Extra	Extra	Extra	Extra	Extra	Extra
BMRF	Real	0.1	0.1	0.1	0.1	0.1	0.1
Confidence Level	Real	0.95	0.95	0.95	0.95	0.95	0.95
BMD Calculation	Boolean	TRUE	TRUE	TRUE	TRUE	TRUE	TRUE
BIVIDE Curve, Calc.	Boolean	FALSE	FALSE	TALSE	FALSE	FALSE	FALSE
Restrict Slope >= 1/	Boolean	TDUE		IRUE		FALSE	TOUE
Restrict Power >= 1?	Booloan	TRUE					IRUE
Restrict n>12	Boolean	FALSE					
Degree of Polynomial	Integer						
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BMDS Wizard – Adding Models to Session

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BMDS N	odel Option Setups:	T						
	Parameter	Type and/or Format	Gamma	Logistic	LogLogistic	Probit	LogProbit	Weibull
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Model Ty	pe [for filename]	String	Gamma	Logistic	LogLogistic	Probit	LogProbit	Weibull
BMR Info	[for filename]	String	10Pct	10Pct	10Pct	10Pct	10Pct	10Pct
Animal I)	01.1						
Dose		String	Dose	Dose	Dose	Dose	Dose	Dose
# Subjec	is in Dose Group	String	NumAnimals	NumAnimals	NumAnimals	NumAnimals	NumAnimals	NumAnimals
Std. Davi	ation	String						
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BMDS Wizard – AutoRunning BMDS

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• : ×	√ fx	TRUE										
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BMDS Wizar	d											
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Control Panel:												
1) Setup Instructions	2) Se	Build	3) Rui in	n Session BMDS	4) li Re	mport esults	AUTOR	UN				
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BMDS Installation	Directory	C:\USEF	PA\BMDS24	40\			Select Fo	lder				
Output File Direct	ry:	C:\Users	\adavis10\E	BMDS240\D	ata\clu_in\		Select Fo	older				
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€PA **BMDS Wizard – Results** Gù □ = 🕅 🗖 5- edichotmous_example.xlsm - Excel ? 🗹 – 🗆 🗙 Davis, Allen 👻 🔍 FILE HOME INSERT PAGE LAYOUT FORMULAS DATA REVIEW VIEW ADD-INS B9 - \times \checkmark fx 1-Smith 2000--Gamma-10Pct-4d.out A В С D Е F K N R Т U Υ . 1 **BMDS Wizard** 2 Import Clear View Output Results Results Images 4 **BMDS Results** Back to Main 5 6 7 **Results Table** View Output Scaled File Model Type Paramete Risk Restricted BMD Residual for p-value **OUT File Name** (comment Update includes graph) Gamma Muth-Hit Model, with 8M R. of 10%. Entra Risk for the 8M Claud 0.95 Lower Countering Limit for the 8M CL -8 1 Gamma Mutt-Hit 9 1-Smith 2000--Gamma-10Pct-4d.ou View Output E Gamma 10 1-Smith 2000--Logistic-10Pct-4d.outView Output E Logistic F 11 1-Smith 2000--LogLogistic-10Pct-4d View Output LogLogistic 12 1-Smith 2000--Probit-10Pct-4d.out View Output Probit F 1-Smith 2000--LogProbit-10Pct-4d.qView Output ∎₿ 13 EEE LogProbit 14 1-Smith 2000--Weibull-10Pct-4d.out View Output Weibull 15 1-Smith 2000--Multi2-10Pct-4d.out View Output Multistage 2° 16 1-Smith 2000--Quantal-10Pct-4d.out View Output Quantal-Linear E 17 8.6 Fraction Affected 18 19 20 21 0.4 22 23 24 25 82 26 27 28 29 30 BMDL 8 M D 31 100 700 3 LED. 500 600 32 Main Data Results -1 Startup Report Logic 11:17 04/12 2013 READY 100% *** Ш ÷

EPA **BMDS Wizard – Results** à □ ≠ 🕅 🔒 S- C-? 🖬 – 🗖 🗙 dichotmous_example.xlsm - Excel Davis, Allen 👻 🔍 FILE HOME INSERT PAGE LAYOUT FORMULAS DATA REVIEW VIEW ADD-INS B9 Ŧ 1 \times fx 1-Smith 2000--Gamma-10Pct-4d.out K N В С D Е F R Т U Y Α J 1 . 1 **BMDS** Wizard 2 3 Import Clear View Output Results Results Images 4 **BMDS Results** Back to Main 5 6 7 **Results Table** View Output Scaled File Model Type Paramete Residual for Risk BMD / p-value Restricted AIC **OUT File Name** (comment BMRF BMD BMDI Hit Model BMDL Test 4 Dose Group Туре Update includes graph) Bound? near BMP 8 Show BMDS Output 9 1-Smith 2000--Gamma-10 1-Smith 2000--Logistic-Close ٠ 1-Smith_2000--LogLogis 11 -----12 1-Smith 2000--Probit-10 Gamma Mutti - Ht Model , with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMD L Gamma Model. (Version: 2.16; Date: 2/28/2013) Input Data File: C:/Usepa/BMDS240/Data/Training/l-Smith_2000-Liver_hyper-Gamma-10Pc 13 1-Smith 2000--LogProbi Gamma Mutt-Ht Gnuplot Plotting File: C:/Usepa/BMDS240/Data/Training/1-Smith 2000-Liver hyper-Gam Fri Apr 12 11:17:50 2013 14 1-Smith 2000--Weibull-15 1-Smith 2000--Multi2-10 0.8 BMDS Model Run 16 1-Smith 2000--Quantal 17 The form of the probability function is: 0.6 18 P[response]= background+(1-background)*CumGamma[slope*dose,power], 19 where CumGamma(.) is the cummulative Gamma distribution function 20 0.4 21 Dependent variable = Incidence 22 Independent variable = Dose 02 Power parameter is restricted as power >=1 23 24 Total number of observations = 4 Total number of records with missing values = 0 25 Maximum number of iterations = 500 BMD Relative Function Convergence has been set to: 1e-008 26 100 200 300 400 500 600 Parameter Convergence has been set to: le-008 27 dose 1117 04/12 2013 28 29 Default Initial (and Specified) Parameter Values Background = 0.0769231 30 Slope = 0.00762432 31 4 32 Main Data Results Ð -d Startup Report Logic Quick Start Guide ۱Þ. READY 100%
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вм	IDL T	BMD / BMDL	p₋value Test 4	AIC	Scaled Residual for Dose Group near BMP	Parameter Hit Bound?	Parameter Summary	Model Warnings	BMDS Wizard Bin Placement	BMDS Wizard Recommen dation	BMDS Wizard Recommen dation Not	Include in Summary Table?	User Notes	
	73.2	1.80	0.498	181.64	0.421	FALSE	P[response]=	None	Viable	Alternate		Include		
	86.1	1.22	0.335	179.44	0.053	FALSE	P[response]	None	Viable	Alternate		Include		
	100	1.20	0.953	179.29	0.012	FALSE	P[response]	None	Viable	Recommende	Lowest AIC	Include		
	86.1	1.82	0.242	182.54	0.819	FALSE	P[response]	None	Viable	Alternate		Include		
	71.8	1.74	0.720	181.32	0.249	FALSE	P[response]	None	Viable	Alternate		Include		- 1
	30.6	1.86	0.0383	181.22	0.104	FALSE	P[response]	None	Viable	Alternate	Lowest BIVIDL	Include		-

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BMDS Wizard – Logic

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BMDS Wizard						
Model Recommendation Decision Logi	ic					
BMDL range doomed "sufficiently close	o" to uso lo					
instead of lowest BMDL in viable mod	e to use to els:	WestAIC	3			
				1		
Model Recommendation/Bin Placeme	nt Logic	T (0.10	rr.			
		Dichot-	Π	Test Threshold	Bin Placement if	
Test Description	Dichot- omous	omous Cancer	Continuous	(where appropriate)	Test is True	Notes to Show
BMD is not calculated	on	on	on	N/A	Unusable Bin	BMD not calculated
BMDL is not calculated	on	on	on	N/A	Unusable Bin	BMDL not calculated
BMDU is not calculated	off	off	off	N/A	Unusable Bin	BMDU not calculated
AIC is not calculated	on	on	on	N/A	Unusable Bin	AIC not calculated
VVrong variance model	off	off	on	0.1	Unusable Bin	Vvrong variance model (Test 2 p-value < 0.1)
Variance modeled poorly	σπ	011	on	0.1	Questionable Bin	Variances not well modeled (Test 3 p-value < 0.1)
Goodness of fit p-test	on	off	on	0.1	Questionable Bin	Goodness of fit p-value < 0.1
Goodness of fit p-test (cancer)	σπ	on	οπ	0.05	Questionable Bin	Goodness of fit p-value < 0.05
Ratio of BIVID/BIVIDL (serious)	on	on	on	20	Questionable Bin	BMD/BMDL ratio > 20
Ratio of BIVID/BIVIDL (caution)	on	on	on	5	No Bin Change (vvarning)	BIND/BINDL ratio > 5
Abs(Residual of Interest) too large	on	on	on	2	Questionable Bin	[Residual of Interest] > 2
BiviDS wodel warnings	on	on	on	N/A	No Bin Change (Warning)	DNDS output file included warning
BIVID nigher than nighest dose	on	on	on	1	No Bin Change (Warning)	DND higher than maximum dose
BNDL higher than highest dose	on	on	on	2	No Bin Change (Warning)	DMDL nigher than maximum dose
BIVID lower than lowest dose (warning)	on	on	on	3	No Bin Change (Warning)	DIVID 3X lower than lowest non-zero dose
BMD lower than lowest dose (warning)	on	on	on	3	Questionship Pin	PMD 10x lower than lowest non-zero dose
BMDL lower than lowest dose (serious)	OII	011	011	10	Questionable Din	PMDL 10x lower than lowest non-zero dose
Abc/Pasidual at control) too large	011	011	011	10	No Bin Change (Mersing)	Dividual at controll > 2
Aus(Residual at control) too large	off	off	on	15	No Bin Change (Warning)	Medeled control recording at day bit 51 petrol rec
Door control doco etd. dou	011	011	011	1.0	Questionable Rin	d f =0, acturated model (Geodpage of ft test connect
Poor control dose std. dev.	00					TO LEV SALUATED HOUSE ICTODUCESS OF ILLEST CANNOL
Poor control dose std. dev. d.f. equals 0	on	on	UII		adoutenable Bin	
Poor control dose std. dev. d.f. equals 0	on	on	UII			

EPA **BMDS Wizard – Results** 5-0-Ġ D ≠ XII dichotmous_example.xlsm - Excel ? 🗖 – 🗆 🗙 Davis, Allen 👻 🔍 FILE HOME INSERT PAGE LAYOUT FORMULAS DATA REVIEW VIEW ADD-INS AE12 Ŧ 1 \times \checkmark fx Include v R U Υ AA AB AC AD AE AF K Ν Ζ AI 🔺 1 Basis for 2 Clear View Output Recalculate Cre Model 3 Recommendation lesults Images Rep Selection 4 5 6 7 Scaled BMDS BMDS Parameter BMDS Include in Parameter Model BMD / p-value Residual for Wizard Wizard AIC BMDL Wizard Bin Summary User Notes Hit BMDL Test 4 Dose Group Summary Warnings Recommen Recommen near BMP Bound? Placement Table? dation dation Not-Ŧ -Ŧ -8 Ŧ 9 1.80 0.498 0.421 FALSE 73.2 181.64 P[response]=None Viable Alternate Include 10 107 1.22 0.885 179.44 0.053 FALSE P[response] None Viable Alternate Include 11 86.1 1.78 0.335 182.11 0.685 FALSE P[response] Viable Alternate Include None 12 100 1.20 0.953 179.29 0.012 FALSE Viable P[response] None Recommende Lowest AIC Include \mathbf{T} 13 86.1 0.242 182.54 FALSE Select 1.82 0.819 Viable P[response] None Alternate ection actude 14 1.74 0.720 181.32 0.249 FALSE Viable 71.8 P[response] None Alternate Don't Include elected model 15 P[response] None 63.4 1.86 0.857 181.22 0.104 FALSE Viable Alternate Lowest BMDL Incl "Include": print in 16 39.6 1.24 0.0383 186.25 -1.48 FALSE P[response] None Questionable Questionable Goodness of f Incl summary table 17 "Don't Include": don't 18 print in summary table 19 20 21 22 23 24 25 26 27 28 29 30 31 32 Main Data Results Ð -1 Startup Report Logic **Quick Start Guide** E 🔳 E F I READY + 100%

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BMDS Wizard – Automatic Report Generation

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	Show Report Being Created	FALSE				
	BMDS Reporting	Print BMDS Figure	Print BMDS Output File			
	Print Selected Model	TRUE	TRUE			
	Print Included Model	FALSE	FALSE			
	Template Location					
	Template Directory			Select MS Word		
	Template Filename			Template		
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BMDS Wizard – EPA Formated Report in Microsoft Word

BMDS WIZARD REPORT

1.1. BMDS Summary of Liver_hyper (Smith_2000)

Table 1. Model predictions for Liver_hyper (Smith_2000)

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

*Selected model in bold; scaled residuals for selected model for doses 0, 100, 300, and 600 ppm were -0.178, 0.012, 0.218, and -0.133, respectively.

^b No available degrees of freedom to calculate a goodness of fit value.

Data from Smith_2000



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

BMDS WIZARD REPORT

Probit Model. (Version: 3.3; Date: 2/28/2013)

The form of the probability function is: P[response] = CumNorm(Intercept+Slope*Dose), where CumNorm(.) is the cumulative normal distribution function Slope parameter is not restricted

Benchmark Dose Computation.

BMR = 10% Extra risk BMD = 120.676 BMDL at the 95% confidence level = 100.297

Parameter Estimates

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

+ Analysis of Deviance Table

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

AIC: = 179.287

Goodness of Fit Table

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

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



Dichotomous Data – Exercise #2

Set EPA

Dichotomous Exercise #2

- Open the default Wizard Template named "BMDS Wizarddichotomous.xlsm"
- Save as "Exercise_2.xlsm" (i.e., as a Macro Enabled Excel workbook)
- Select BMDS Installation Directory
- Select Output file directory (usually same directory as where you saved the Wizard template)
- Fill in Study & Year as "Exercise_2"
- Can fill out remaining Study and Modeling Inputs, but its not necessary for this exercise

Dichotomous Exercise #2

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

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

• On Main worksheet tab, click "AUTORUN"

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- **Results will automatically import to Results worksheet tab**
- Which model would you pick, and why?

Dichotomous Exercise #2

	\bullet : \times \checkmark f_x	View Output											
A	В	С	D	E	F	1	J	K	Ν	R	Т	U	Y
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						Import Result	t (s R	Clear esults			View C	Dutput	
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	OUT File Name	View Output File Update	Model Type (comment includes graph) ▼	Risk Type ▼	BMRF	Restricted Model	BMD	BMDL	BMD / BMDL	p-value Test 4	AIC	Scaled Residual for Dose Group near BMP	Paramet Hit Bound
	Exercise_2Gamma-10Pct-5d.out	View Output	Gamma	Extra	0.1	TRUE	66.0	57.6	1.15	0.745	361.61	0.632	FALSE
	Exercise_2Logistic-10Pct-5d.out	View Output	Logistic	Extra	0.1	TRUE	69.6	61.2	1.14	0.484	363.96	-0.416	FALSE
	Exercise_2LogLogistic-10Pct-5d.c	View Output	LogLogistic	Extra	0.1	TRUE	68.2	59.8	1.14	0.454	362.98	0.920	FALSE
Ŀ	Exercise_2Probit-10Pct-5d.out	View Output	Probit	Extra	0.1	TRUE	66.9	58.3	1.15	0.759	362.06	-0.272	FALSE
ŀ	Exercise_2LogProbit-10Pct-5d.ou	t <u>View Output</u>	LogProbit	Extra	0.1	FALSE	66.1	58.7	1.13	0.265	364.27	1.16	FALSE
ŀ	Exercise_2Weibull-10Pct-5d.out	View Output	Weibull	Extra	0.1	TRUE	64.2	55.2	1.16	0.999	360.40	-0.087	FALSE
ŀ	Exercise_2Multi2-10Pct-5d.out	View Output	Multistage 2°	Extra	0.1	TRUE	48.0	44.1	1.09	0.0855	367.74	-1.8/	IRUE
Ľ	Exercise_2Quantal-10Pct-5d.out	View Output	Quantal-Linear	Extra	0.1	TRUE	17.7	15.6	1.13	U	423.59	-4.75	FALSE