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Benchmark Dose Modeling – Nested Dichotomous Models

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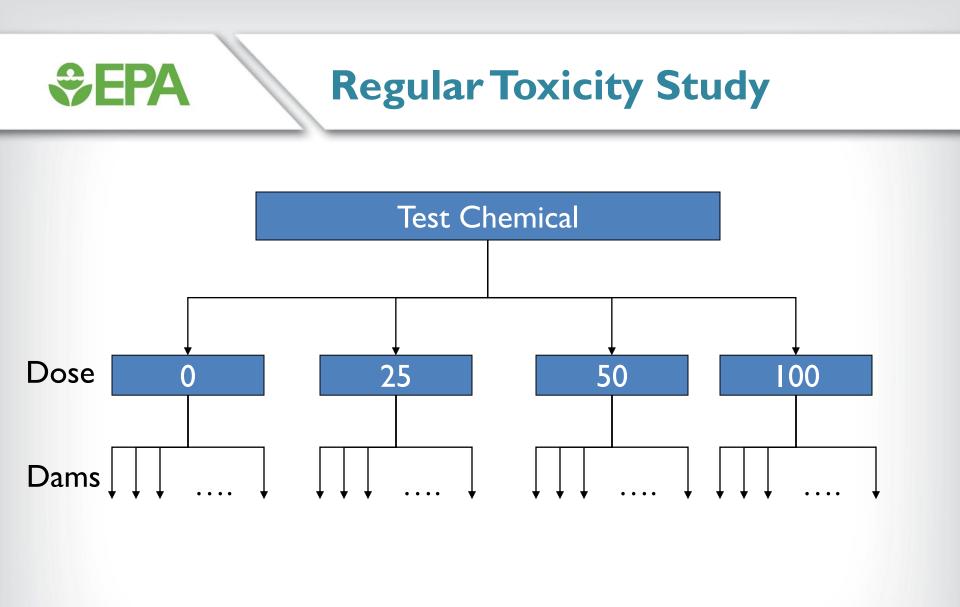


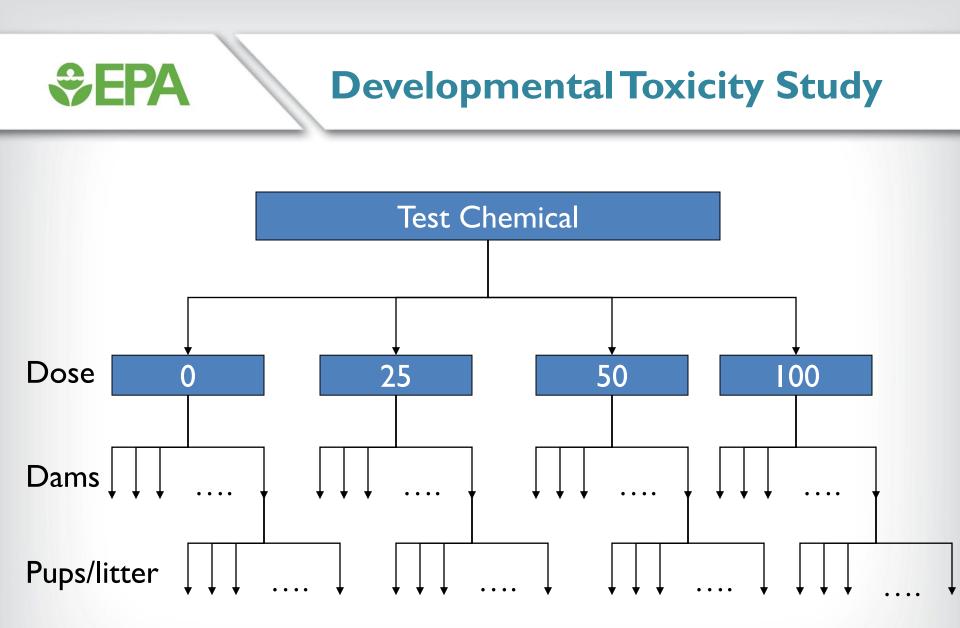
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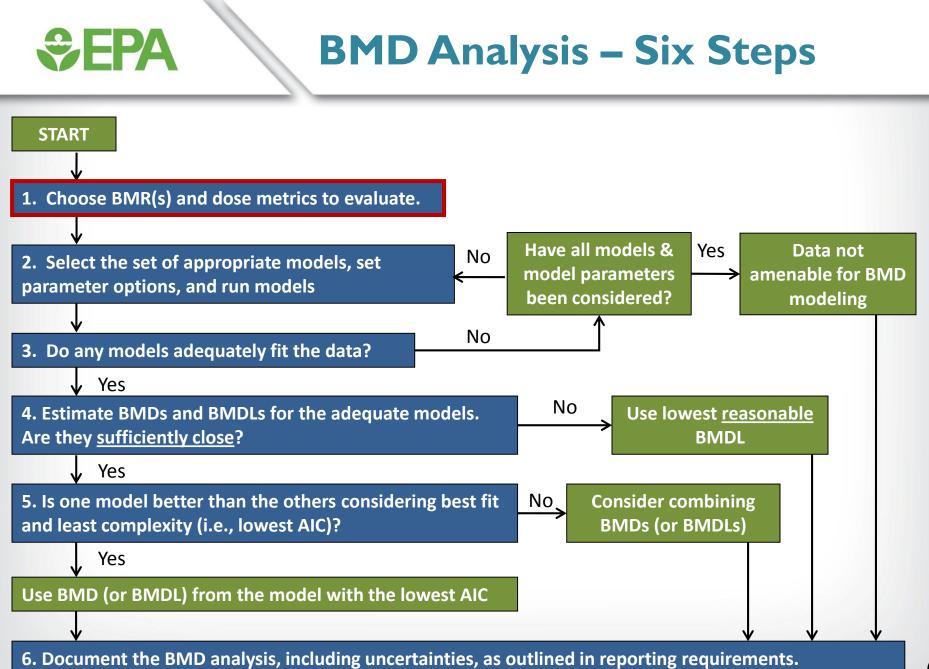
Nested Dichotomous Data

Description	 Response is measured as on/off or true/false Outcomes are measured in the offspring of exposed, pregnant animals BMDS can only model positive dose-response trends, where incidence increases with dose
Example Endpoints	 Structural abnormalities – malformations (e.g., cleft palate) or variations (ossification changes) Mortality – resorptions (early mortality) or fetal death (late mortality)
Model Inputs	 Dose Individual animal (i.e., dam) data – number of offspring experiencing the effect per exposed dam

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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.

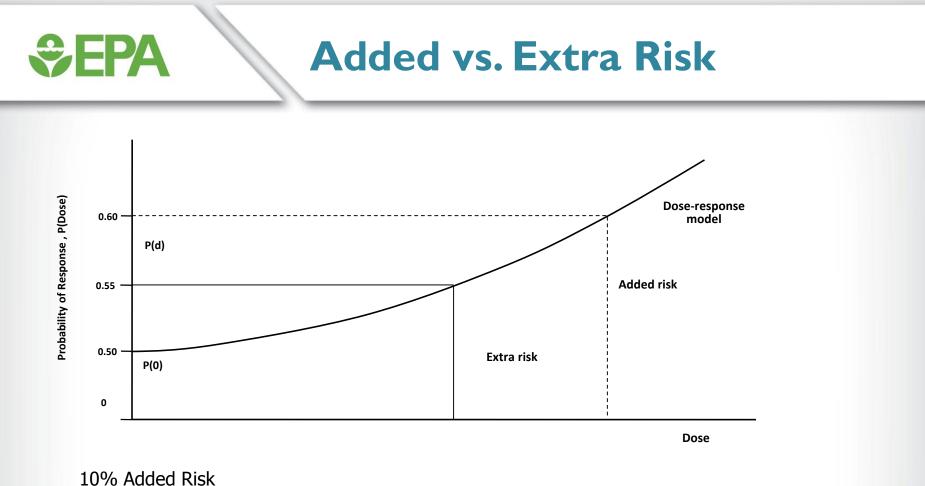
Select a Benchmark Response

- Although an excess risk of 10% is usually a standard BMR for dichotomous data, an excess risk of 5% approximates the NOAEL for most developmental studies.
- In a series of papers (Faustman et al., 1994; Allen et al., 1994a,b), it was shown that the BMDL for 5% extra risk corresponded on average with NOAELs identified from a large developmental toxicity database
- Support for using a BMR of 5% for developmental data
 - Developmental studies provide increased statistical power compared to regular toxicity studies due the increase in sample size (i.e., use of pups as the observational subject)
 - Developmental effects are often considered to be severe, or sometimes frank (i.e., fetal mortality)

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Measurement of Increased Risk

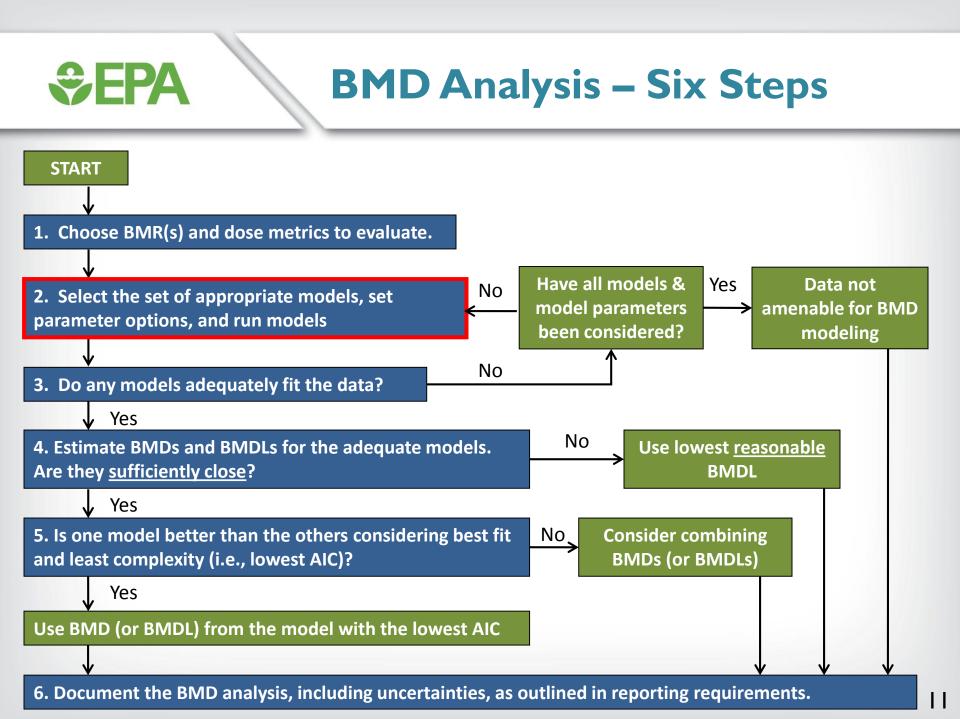
- For dichotomous data, BMRs are expressed as:
 - Added risk AR(d) = P(d) P(0)
 - Extra risk ER(d) = [P(d) P(0)]/[I P(0)]
- Extra risk is recommended by the IRIS, and is used in IRIS risk assessments.



 $\begin{array}{l} \text{Added Risk} \\ 0.10 = P(d) - P(0) \text{ ; if } P(0) = .50 \\ P(d) = 0.10 + P(0) = 0.10 + 0.50 = \textbf{0.60} \end{array}$

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



Nested Dichotomous Models

Model name	Functional form	Notes
Nested Logistic ^a	$\frac{\alpha + \theta_1 r_{ij} + \left[1 - \alpha - \theta_1 r_{ij}\right]}{\left(1 + \exp[-\beta - \theta_2 r_{ij} - \rho * \ln(X)]\right)}$	r_{ij} is the litter specific covariate for the j^th litter in the i^th dose group, there are g intra-litter correlation coefficients , 0 < Φ_i < 1 (i = 1,, g)
NCTR	$1 - \exp[-(\alpha + \theta_1[r_{ij} - r_m]) - (\beta + \theta_2[r_{ij} - r_m]) * dose_\rho]$	r_{ij} is the litter specific covariate for the j th litter in the i th dose group, and r_m is the overall mean for the litter-specific covariate, there are g intra-litter correlation coefficients , $0 < \Phi_i < 1$ (i = 1,, g)
Rai and van Ryzin	$[1 - \exp(-\alpha - \beta(dose_{\rho})] * \exp(-(\theta_1 + \theta_2 dose) * r_{ij})$	r_{ij} is the litter specific covariate for the j th litter in the i th dose group, there are g intra-litter correlation coefficients , $0 < \Phi_i < 1$ (i = 1,, g)

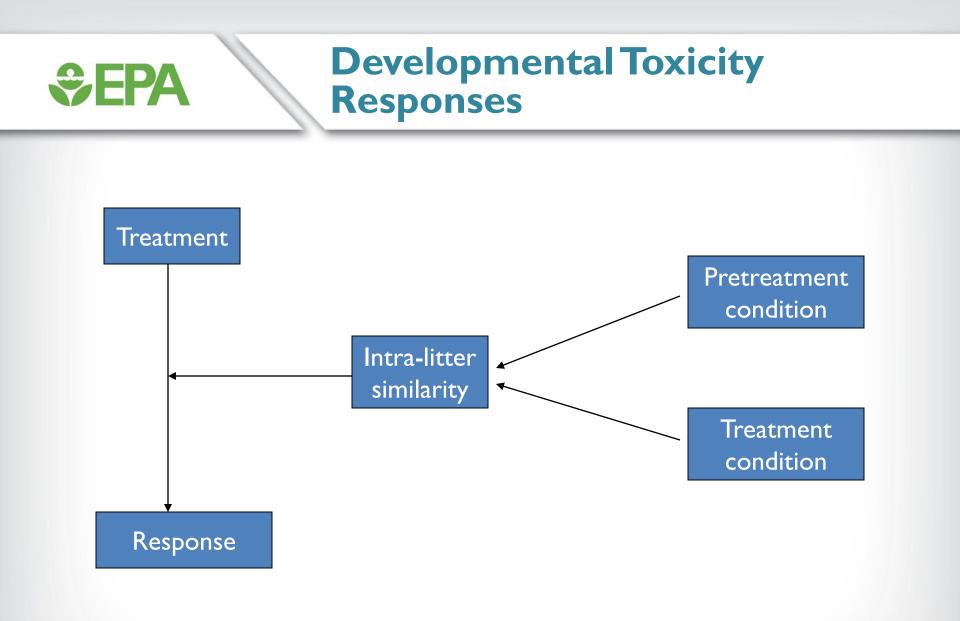
^a The nested Logistic model is the Log-logistic model modified to include a litter-specific covariate. Log-logistic model form: $\frac{\gamma + (1 - \gamma)}{1 + \exp\{-[\alpha + \beta \ln(X)]\}}$

Parameters Specific to the Nested Dichotomous Models

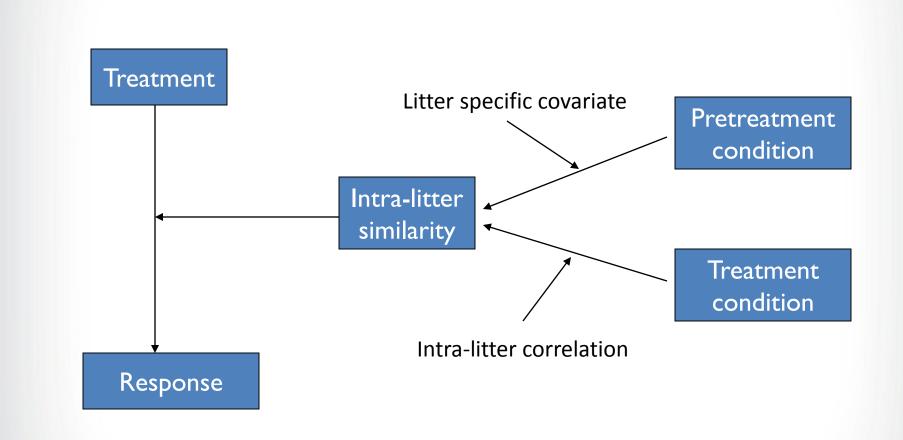
- It is usual for the responses of pups in the same litter to be more similar to each other than to the responses of pups in different litters
 - This is typically called "intra-litter similarity" or "litter effects"
- Models for nested dichotomous data incorporate two parameters to address this issue
 - Litter specific covariate (θ coefficients)

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Intra-litter correlation (Φ coefficients)

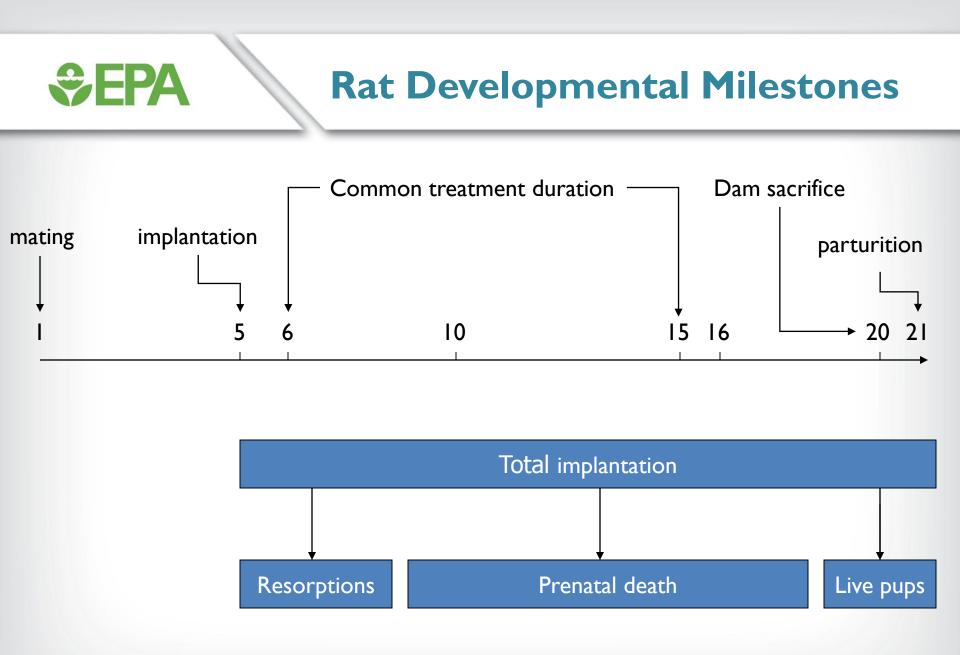


SEPA Developmental Toxicity Responses



Litter Specific Covariate

- A litter specific covariate (θ coefficients) takes into account the condition of the exposed dam prior to the onset of dosing/exposure.
- The pre-treatment condition of the dam should account for some of the observed "litter effect"
- The litter specific covariate should NOT be affected by treatment
- Commonly used litter specific covariates include:
 - Litter size
 - Dam weight
 - Implantation sites



Litter Specific Covariate

Implantation sites

- In a normal guideline developmental toxicity study, where dosing begins after implantation takes place, the number implantation sites is the preferred litter specific covariate
- However, these data are not reported in some toxicity studies

• Litter size

• Litter size is an appropriate litter specific covariate as long as there are not treatment-related resorptions or prenatal deaths

Use of Litter Specific Covariate

The litter specific covariate should only be used when ALL of the following 3 criteria are met:

- The chosen litter specific covariate is not affected by treatment
- θ coefficients are estimated by BMDS to be non-zero (currently, the software does not estimate coefficent standard errors, so some judgement is required when making this determination)
 - If the model estimates the θ coefficients to be EXACTLY 0, the modeling results (including AIC) should be the same as when running the model with the litter specific covariate turned off.
- When the litter specific covariate is included in the modeling scheme, the model fit becomes better (e.g., per AIC or scaled residual comparison)
- NOTE: regardless of whether an appropriate litter specific covariate can be identified, the modeled dataset MUST contain "covariate" data (even if it's dummy data)

Intra-litter Correlation

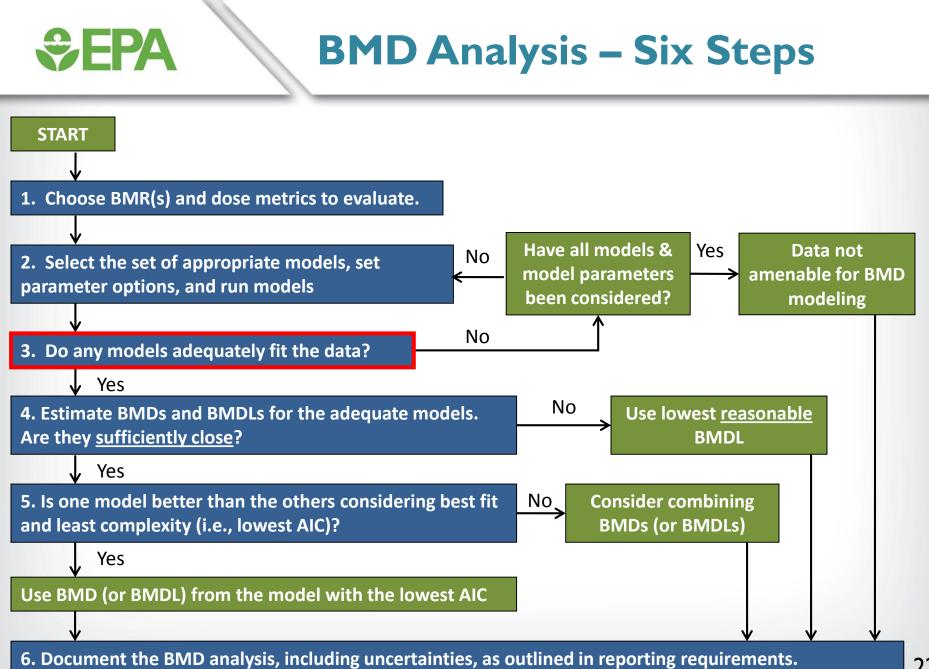
- The intra-litter correlation statistically describes the similarity of responses among pups in the same litter
- Intra-litter correlation should only be used when BOTH of the following 2 criteria are met:
 - Φ coefficients are estimated by BMDS to be non-zero (currently, the software does not estimate coefficent standard errors, so some judgement is required when making this determination)
 - When the intra-liter correlation is included in the modeling scheme, the model fit becomes better (e.g., per AIC or scaled residual comparison)
- When intra-litter correlation is used, if the range of the scaled residuals for the litters with the same litter specific covariate is not reduced, consult a statistician to determine a course of action

Model Parameter Selection for Nested Dichotomous Data

- For a single dataset, run the desired nested dichotomous model 4 times (assuming there is a covariate appropriate for the litter specific covariate):
 - Litter specific covariate = -, intra-litter covariate = +

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- Litter specific covariate = + intra-litter covariate = -
- Litter specific covariate = -, intra-litter covariate = +
- Litter specific covariate = +, intra-litter covariate = +
- Applying the criteria in the previous slides, final model selection can be made based on global goodness-of-fit p-value, scaled residuals, and AIC



Does the Model Fit the Data?

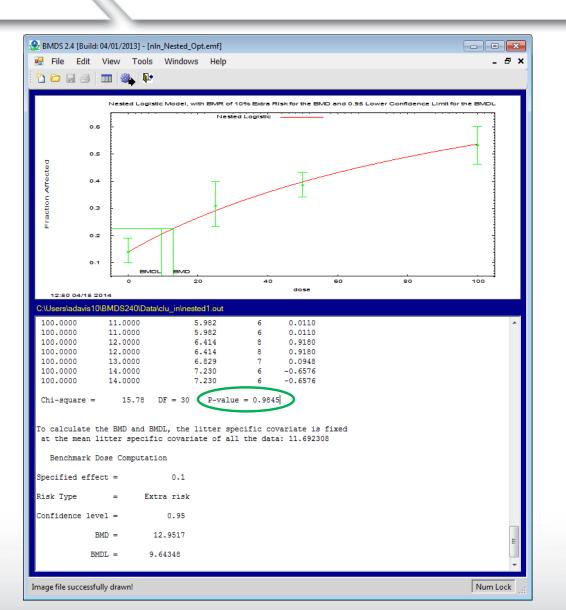
For dichotomous data:

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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



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Modeling Recommendations – Poor Global Goodness-of-Fit

- Consider dropping high dose group(s) that negatively impact low dose fit
- Use PBPK models if available to calculate internal dose metrics that may facilitate better model fitting
 - 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)

Log-transform doses

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)

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 nested 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

Scaled Residuals

Global goodness-of-fit p-values are not enough to assess local fit

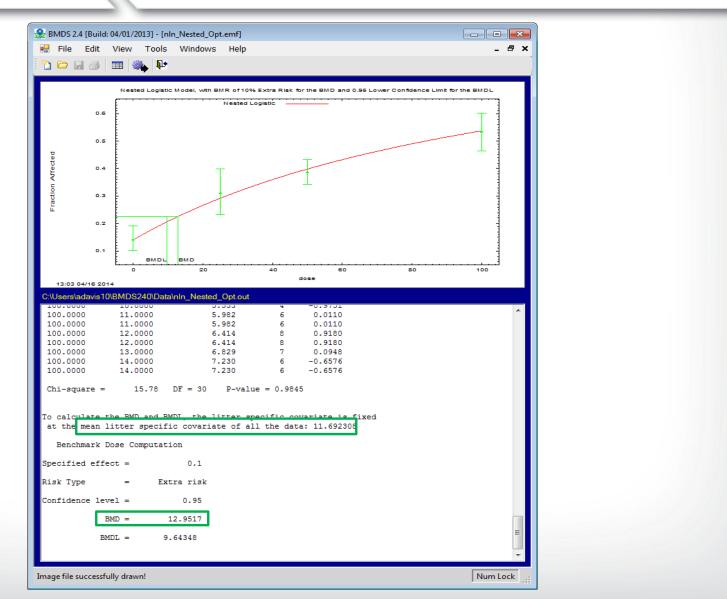
- Models with large p-values may consistently "miss the data" (e.g., always on one side of the dose-group means)
- Models may "fit" the wrong (e.g. high-dose) region of the dose-response curve.
- Scaled Residuals measure of how closely the model fits the data at each point; 0 = exact fit
 - Absolute values near the BMR should be lowest
 - Question scaled residuals with absolute value > 2

Scaled Residuals in Nested Dichotomous Models

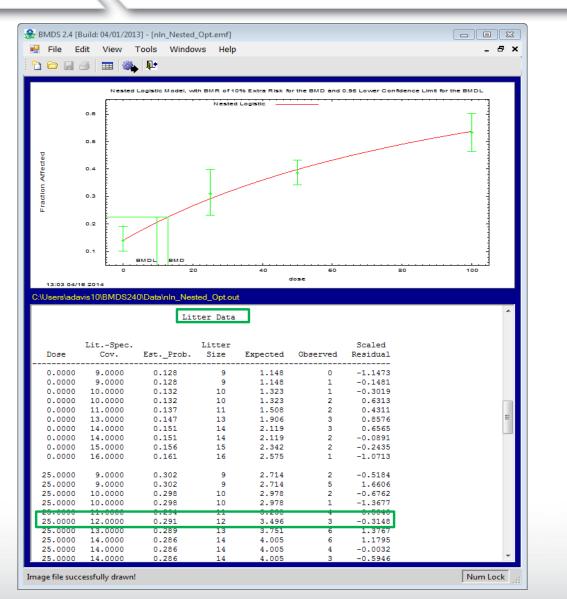
- The scaled residual of interest is estimated from the scaled residuals from the Litter Data for litters with a litter specific covariate value closest to the mean litter specific covariate of all the data
- When multiple scaled residuals are obtained from samples with the same litter specific covariate, there are a number of options for assessing local fit
 - Maximum (absolute) scaled residual value
 - Average (absolute) scaled residual value
 - Range of scaled residual values

Scaled Residuals in Nested Dichotomous Models

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Scaled Residuals in Nested Dichotomous Models



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Does the Model Fit the Data?

• For nested dichotomous data:

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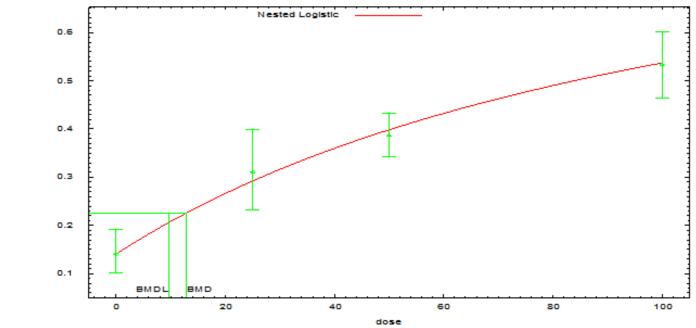
- Global measurement: goodness-of-fit p value (p > 0.1)
- Local measurement: Scaled residuals (absolute value < 2.0)
- Visual inspection of model fitting



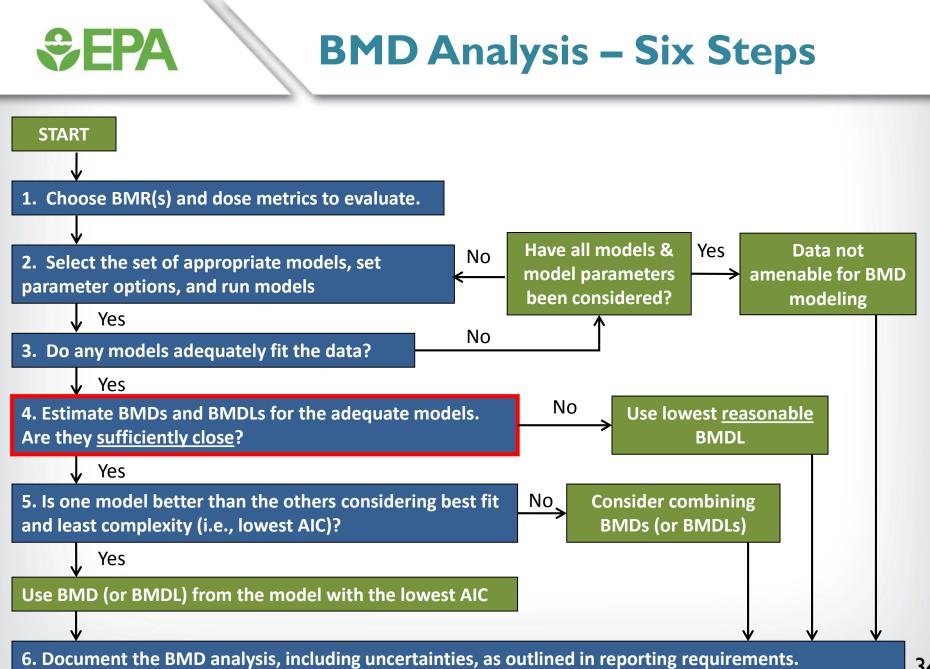
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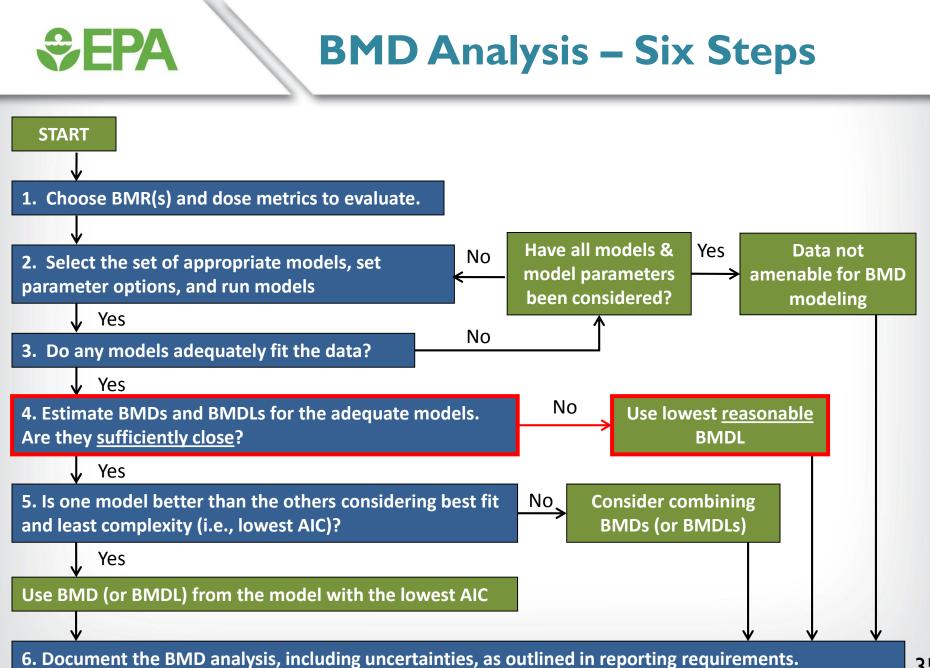
Visual Fit

Nested Logistic Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMDL



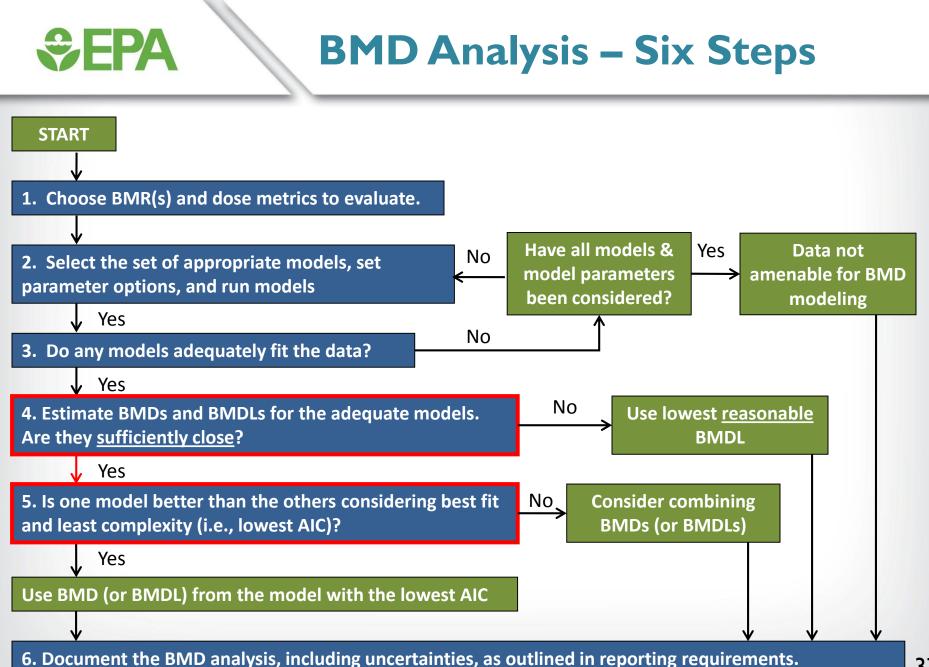
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Are BMDL Estimates "Sufficiently Close"?

- 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.

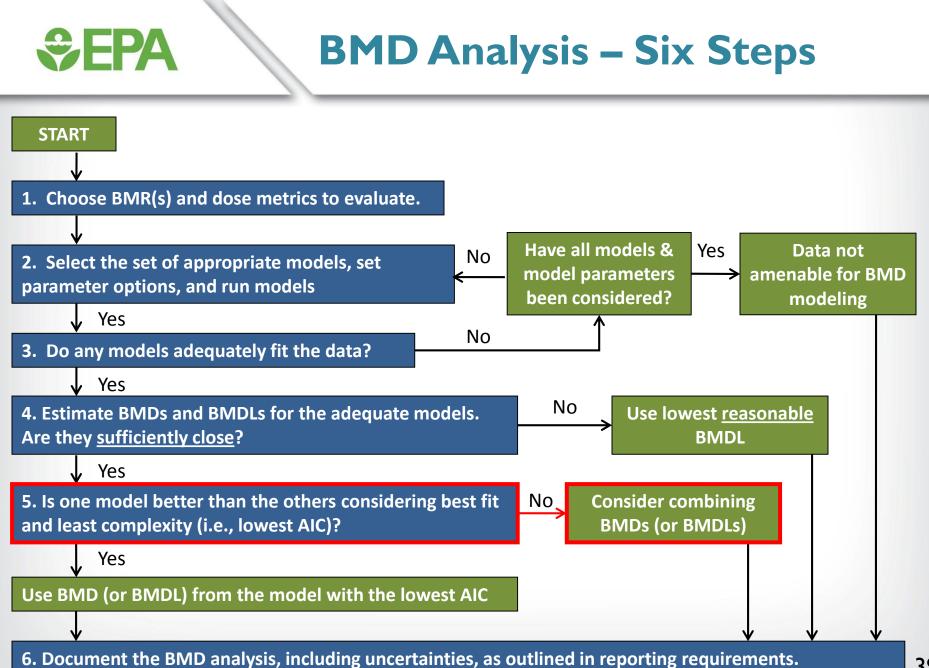


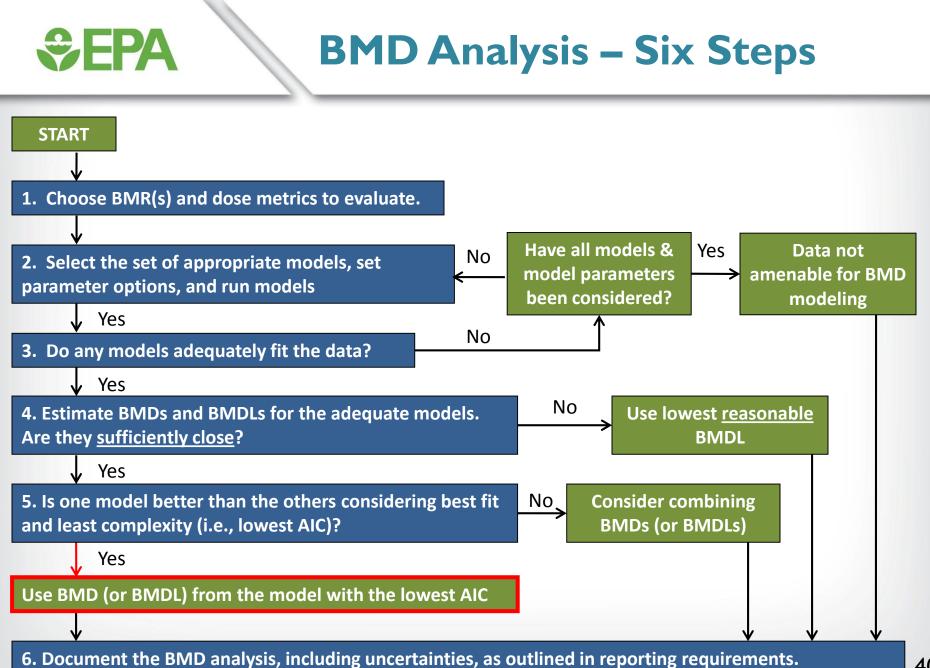
Akaike's Information Criterion (AIC)

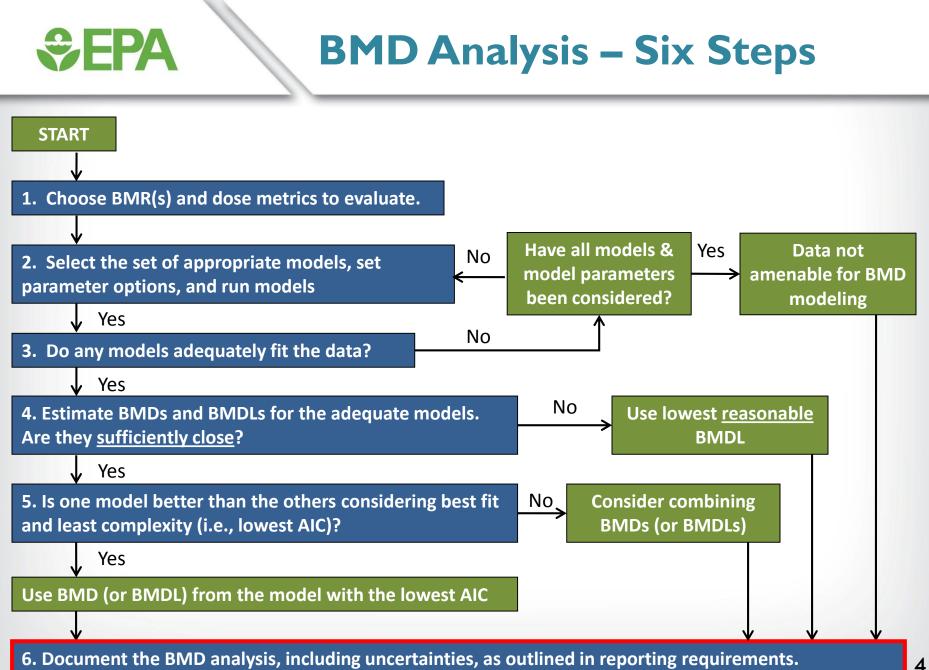
• AIC = $-2 \times LL + 2 \times p$

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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"



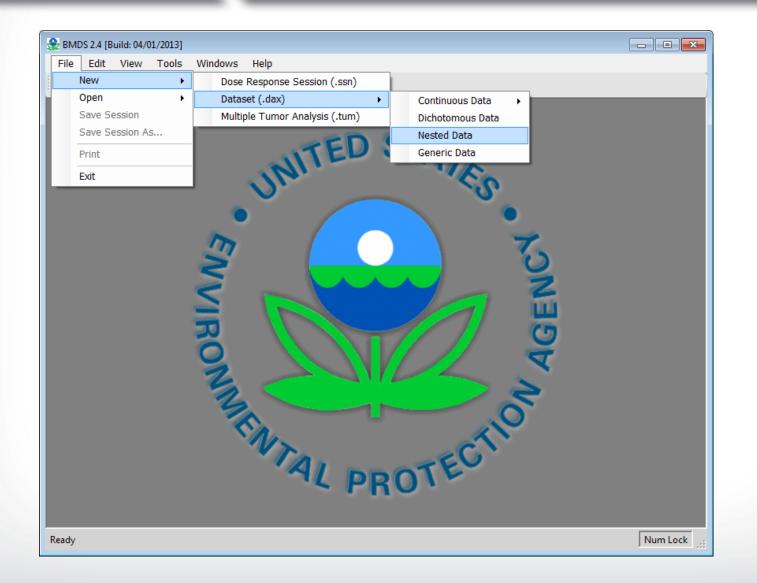






Nested Dichotomous Data – Running the models in BMDS

Creating a Dataset – Open New Nested Dataset



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Creating a Dataset – Open New Nested Dataset

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Creating a Dataset – Import an Existing 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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Selecting Model Options – Litter Specific Covariate

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Selecting Model Options – Intra-litter Correlation

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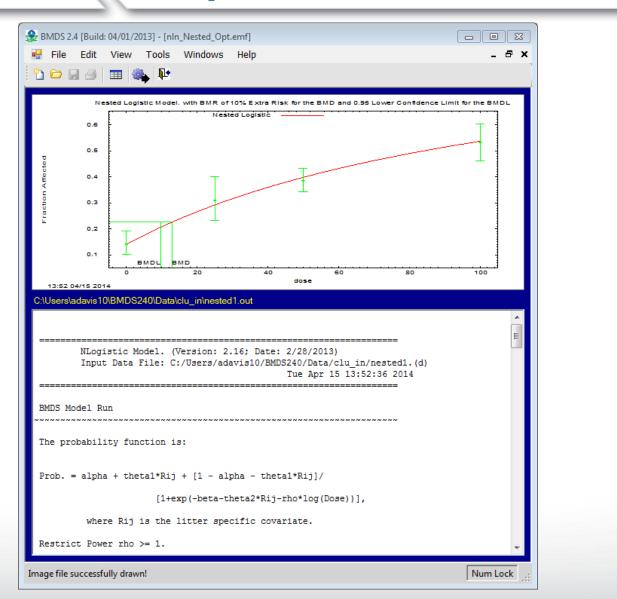
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Specifying Model Parameters

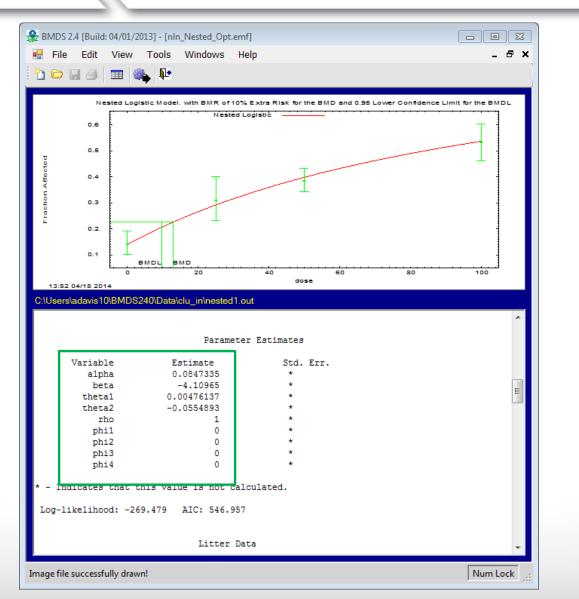
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Nested Dichotomous Plot and Output Files



Nested Dichotomous Model Parameter Estimates



*€***EPA**

Opening Output and Plot Files after Analysis



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Nested Dichotomous Data – Exercise

♦ EPA

Nested Dichotomous Exercise

- Open the provided dataset titled "Nested_Exercise.dax"
- Run the Nested Logistic model against the data with the following parameterizations
 - Litter Specific Covariate Use (select "Covariate" for the Litter Specific Covariate)
 - Intra-litter Correlation Estimate
 - BMR = 5% Extra risk
- Record the following data:
 - BMD and BMDL
 - p-value, AIC, and Scaled Residual of Interest (1. find "mean litter specific covariate"; 2. look at grouped data and dose group closest to BMD; 3. find individual rows for which reported mean litter specific covariate is closes to the value for all data; 4. average multiple values if necessary)
 - Parameter estimates for θ and Φ coefficients

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Nested Dichotomous Exercise

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Iteration	500	BMDL Curve. Calc.		
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Nested Dichotomous Exercise

	Litter Specific Covariate; Intralitter Correlation	No Litter Specific Covariate; Intralitter Correlation	Litter Specific Covariate; No Intralitter Correlation	No Litter Specific Covariate; No Intralitter Correlation
BMD ₀₅	505			
BMDL ₀₅	174.24			
AIC	1049.33			
p-value	0.2752			
Grouped Scaled residual (max value)	1.3312			
θ_1 estimate	0.0331164			
θ_2 estimate	-0.410957			
Φ_1 estimate	0.200123			
Φ_2 estimate	0.313042			
Φ_3 estimate	0.213544			
Φ_4 estimate	0.370267			

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♦ EPA

Nested Dichotomous Exercise

- Open the provided dataset titled "Nested_Exercise.dax"
- Run the Nested Logistic model against the data with the following parameterizations
 - Litter Specific Covariate Do Not Use
 - Intra-litter Correlation Estimate
 - BMR = 5% Extra risk
- Record the following data:
 - BMD and BMDL
 - p-value, AIC, and Scaled Residual of Interest (1. find "mean litter specific covariate"; 2. look at grouped data and dose group closest to BMD; 3. find individual rows for which reported mean litter specific covariate is closes to the value for all data; 4. average multiple values if necessary)
 - Parameter estimates for θ and Φ coefficients

Nested Dichotomous Exercise

	Litter Specific Covariate; Intralitter Correlation	No Litter Specific Covariate; Intralitter Correlation	Litter Specific Covariate; No Intralitter Correlation	No Litter Specific Covariate; No Intralitter Correlation
BMD ₀₅	505	658.131		
BMDL ₀₅	174.24	216.749		
AIC	1049.33	1053.46		
p-value	0.2752	0.1601		
Grouped Scaled residual	1.3312	1.3538		
θ_1 estimate	0.0331164			
θ_2 estimate	-0.410957			
Φ_1 estimate	0.200123	0.212445		
Φ_2 estimate	0.313042	0.312581		
Φ_3 estimate	0.213544	0.219964		
Φ_4 estimate	0.370267	0.371497		

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♦ EPA

Nested Dichotomous Exercise

- Open the provided dataset titled "Nested_Exercise.dax"
- Run the Nested Logistic model against the data with the following parameterizations
 - Litter Specific Covariate Use (select "Covariate" for the Litter Specific Covariate)
 - Intra-litter Correlation Assume Zero
 - BMR = 5% Extra risk

Record the following data:

- BMD and BMDL
- p-value, AIC, and Scaled Residual of Interest (1. find "mean litter specific covariate"; 2. look at grouped data and dose group closest to BMD; 3. find individual rows for which reported mean litter specific covariate is closes to the value for all data; 4. average multiple values if necessary)
- Parameter estimates for θ and Φ coefficients

Nested Dichotomous Exercise

	Litter Specific Covariate; Intralitter Correlation	No Litter Specific Covariate; Intralitter Correlation	Litter Specific Covariate; No Intralitter Correlation	No Litter Specific Covariate; No Intralitter Correlation
BMD ₀₅	505	658.131	526.799	
BMDL ₀₅	174.24	216.749	266.212	
AIC	1049.33	1053.46	1133.43	
p-value	0.2752	0.1601	0.00	
Grouped Scaled residual	1.3312	1.3538	2.0286	
θ_1 estimate	0.0331164		0.0340365	
θ_2 estimate	-0.410957		-0.431175	
Φ_1 estimate	0.200123	0.212445		
Φ_2 estimate	0.313042	0.312581		
Φ_3 estimate	0.213544	0.219964		
Φ_4 estimate	0.370267	0.371497		

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♦ EPA

Nested Dichotomous Exercise

- Open the provided dataset titled "Nested_Exercise.dax"
- Run the Nested Logistic model against the data with the following parameterizations
 - Litter Specific Covariate Do Not Use
 - Intra-litter Correlation Assume Zero
 - BMR = 5% Extra risk
- Record the following data:
 - BMD and BMDL
 - p-value, AIC, and Scaled Residual of Interest (1. find "mean litter specific covariate"; 2. look at grouped data and dose group closest to BMD; 3. find individual rows for which reported mean litter specific covariate is closes to the value for all data; 4. average multiple values if necessary)
 - Parameter estimates for θ and Φ coefficients

Nested Dichotomous Exercise

	Litter Specific Covariate; Intralitter Correlation	No Litter Specific Covariate; Intralitter Correlation	Litter Specific Covariate; No Intralitter Correlation	No Litter Specific Covariate; No Intralitter Correlation
BMD ₀₅	505	658.131	526.799	728.281
BMDL ₀₅	174.24	216.749	266.212	392.351
AIC	1049.33	1053.46	1133.43	1144.08
p-value	0.2752	0.1601	0.00	0.00
Grouped Scaled residual	1.3312	1.3538	2.0286	2.0499
θ_1 estimate	0.0331164		0.0340365	
θ_2 estimate	-0.410957		-0.431175	
Φ_1 estimate	0.200123	0.212445		
Φ_2 estimate	0.313042	0.312581		
Φ_3 estimate	0.213544	0.219964		
Φ_4 estimate	0.370267	0.371497		

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Nested Dichotomous Exercise

	Litter Specific Covariate; Intralitter Correlation	No Litter Specific Covariate; Intralitter Correlation	Litter Specific Covariate; No Intralitter Correlation	No Litter Specific Covariate; No Intralitter Correlation
BMD ₀₅	505	658.131	526.799	728.281
BMDL ₀₅	174.24	216.749	266.212	392.351
AIC	1049.33	1053.46	1133.43	1144.08
p-value	0.2752	0.1601	0.00	0.00
Grouped Scaled residual	-0.7259	-0.7061	-1.06127	-1.04193
θ_1 estimate	0.0331164		0.0340365	
θ_2 estimate	-0.410957		-0.431175	
Φ_1 estimate	0.200123	0.212445		
Φ_2 estimate	0.313042	0.312581		
Φ_3 estimate	0.213544	0.219964		
Φ_4 estimate	0.370267	0.371497		

Sepa



References

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- Allen, BC; Kavlock, RJ; Kimmel, CA; Faustman, EM. (1994a) Dose-response assessment for developmental toxicity: II. Comparison of generic benchmark dose estimates with NOAELs. Fundam Appl Toxicol 23:487-495.
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